Huntington's disease:

psychological aspects of predictive testing

De ziekte van Huntington:

psychologische aspecten

van het voorspellend testen

Reinier Timman

ISBN: 90-9019211-5

Cover design: Reinier Timman
Graph after: Hemelrijk J. Probability and statistics. In: Kuipers L, Timman R, editors. *Handbook of Mathematics.* Oxford: Pergamon, 1969.

Printed and bound in the Netherlands by FEBODRUK BV - Enschede

Financial support for the publication of this thesis has been provided by De Open Ankh, Stichting dienstverlening gezondheidszorg.

Huntington's disease: psychological aspects of predictive testing

Proefschrift

ter verkrijging van
de graad van Doctor
aan de Universiteit Leiden,
op gezag van de Rector Magnificus Dr. D.D. Breimer,
hoogleraar in de faculteit der Wiskunde en
Natuurwetenschappen en die der Geneeskunde,
volgens het besluit van het College voor Promoties
te verdedigen op woensdag 6 april 2005
klokke 14.15 uur

door

Reinier Timman
geboren te Delft in 1955

PROMOTIECOMMISSIE

Promotores
Prof.dr. A. Tibben
Prof.dr. R.A.C. Roos

Referent
Prof.dr. J. Passchier *(Erasmus MC)*

Overige leden
Prof.dr. J.C. van Houwelingen
Prof.dr. B. Kremer *(Universitair Medisch Centrum Nijmegen)*
Dr. M.N.W. Witjes-Ané

Aan Beer en Leeuw

Contents

CHAPTER 1
-
Introduction

1.1. HUNTINGTON'S DISEASE

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterised by involuntary choreatic and hypokinetic movements, and changes in mood and behaviour. The estimations of the mean age of onset range between 43.7[1] and 55.8[2] with standard deviations ranging from 10.9 to 13.5 respectively. Affected individuals slowly loose control over physical and mental functions. The disorder affects behaviour, emotions, thinking, social abilities and the motor functions needed to perform the activities of daily living. The occurrence of HD is estimated at 5-10 per 100.000 inhabitants.[3] The burden of HD affects about everything in the families involved.[4]

In 1983, the HD community experienced the discovery of a genetic marker that localised the HD gene on the fourth chromosome as a great break through.[5] A test was developed that provided information on the genetic status of many individuals at risk for HD. Depending on the informativeness of the DNA markers and the family structure of co-operating family members, the outcome of this test had a reliability of 90% to 99%. This finding gave a vista for a better future perspective and the hope became stronger that perhaps even a cure might become a reality. The discovery paved the way for predictive testing which was experienced by part of the HD community as a blessing, as a herald of better times in which the disease could be controlled, cured, and prevented. The test provided the opportunity to relieve the uncertainty, to have prenatal tests in order to have children free from the disorder, to make informed plans for the future regarding marriage, education, professional career, and finances. In 1993, the gene mutation for Huntington's Disease (HD) was identified.[6] Testing became possible with a reliability of more than 99%, without the need for co-operation of relatives. Even testing embryos, prior to implantation, became possible, providing couples with the opportunity to have a pregnancy without the burden of termination after an unfavourable prenatal test result.[7] In 2000 the first step towards cell therapy and neuronal transplantation was published.[8]

The spectacular advances in genetics also meant a novelty in medicine. The possibility of predictive testing for HD rang in a new era in which predictive testing for disorders with onset later in life would become available for many other -more or less rare- hereditary diseases with mendelian transmission. Moreover, increasing knowledge of the genetic factors in combination with environmental influences would inevitably open a new perspective for medicine. Individuals could get better information on their future health and the risk factors that might threaten a prosperous perspective. HD had the dubious honour to secede from the unknown rare diseases, and to become the paradigm that should provide the knowledge and experience to establish predictive testing programmes. This development has not only affected the medical field. The far-reaching consequences made predictive testing a matter of social, political and

economic forces[9] and made HD an important model on which the establishment of many other testing programmes could be based.

The studies described in this thesis address psychological and methodological issues that were encountered in 20 years experience with predictive testing for Huntington's disease.

1.2. PREDICTIVE GENETIC TESTING: HUNTINGTON'S DISEASE AS A MODEL

1.2.1. Anticipating predictive testing

In the mid-eighties of the previous century, the advent of predictive testing for HD was more or less a revolution in the world of science, health care, politics, insurance and companies. HD was regularly found at the front pages of prominent magazines and at prime time on television and radio. At the level of HD families, learning about the individuals' personal risk was expected to generate profound emotional responses that had to be acknowledged and dealt with. The risk of an adverse emotional response was considered the single greatest risk of predictive testing. Serious concerns were raised about the psychological consequences of results of predictive testing for HD, with the possibility of an increase in deaths by suicide among identified carriers of the gene. Suicide has long been recognized as a risk in families at risk for Huntington's disease.[10] In some instances, such as overt risk for suicide or other major depressive symptoms, it is appropriate to delay testing, initiate psychiatric treatment, and become emotionally stabilised before proceeding with the test. Although psychological evaluation of emotional stability became an important issue of the initial testing protocol, it should not be viewed as an obstacle to be jumped in order to get access to testing, but rather as a method of identifying persons likely to need greater emotional support after learning the test results.

This perspective highlighted the need for research to identify predictors of adjustment problems such as depression and suicidal intentions in those who would request for predictive testing. Previous studies of expectations of at-risk individuals had suggested that psychological effects of testing might include severe psychosocial problems such as overalertness for early symptoms, depression and suicidal behaviour in identified gene-carriers.[11-13] Between 40% and 79% of the individuals at risk reported their intention to take the test.[14] Interest in testing was found to be negatively associated with being married, and positively correlated with the number of affected relatives and earlier parental age of onset of HD. The most commonly given reasons in these surveys were craving for certainty, relieving uncertainty, planning for the future, planning a family, and the need to inform the children.[15-19]

With the outlook on the availability of DNA analysis for the HD gene, the Committee of International Huntington Association and the Working Group on Huntington's disease of the World Federation of Neurology gave consideration to the manner in which these tests should be carried out.[20]

The guidelines for protocols were first published in 1989 when the presymptomatic test made use of linkage analysis. After identification of the HD-gene in 1993, the guidelines were adjusted and published in 1994. In general the guidelines recommend that individuals at risk participating in presymptomatic testing programmes are seen for two to four counselling sessions, spread over a three month period before disclosure of the test results. Presymptomatic testing requires informed consent by the individual at risk, and the provision of psychological support. If the diagnosis is confirmed, counselling must be available for the family and others involved. The starting point is that presymptomatic tests should be offered only to individuals at risk who have had the appropriate counselling, are fully informed and wish to proceed.

Although HD can be considered as rare, the disease has proved to be a widely used model for research on psychological effects of genetic testing.

1.2.2. Predictive testing for disorders with late onset

After Huntington's disease, an increasing number of neurodegenerative diseases have been defined at the molecular level in the last decades, making it possible to determine precisely the genotype before the onset of symptoms. Predictive testing programmes are currently available for hereditary cerebral haemorrhage with amyloid-Dutch type (HCHWA-D),[21] myotonic dystrophy,[22] frontotemporal dementia, early onset Alzheimer disease,[23] spinocerebellar ataxia (SCA1-7),[24] and cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL).[25] No intervention is currently known to slow, stop, or reverse the progressive clinical deterioration or underlying neurodegeneration of these conditions. In contrast to these neurodegenerative diseases, several treatment or surveillance options are available for hereditary forms of cancer syndromes such breast/ovarian cancer and colon cancer. Susceptibility testing for several forms of cancer has been available since the early nineties. Women carrying a BRCA1/2 mutation, which causes breast and ovarian cancer, can opt for regular surveillance, prophylactic mastectomy, prophylactic bilateral salpingo-oophorectomy, and/or chemoprevention trials.[26] Genetic testing for hereditary non-polyposis colorectal cancer (HNPCC) provides carriers of the mismatch repair genes (MSH2, MSH6, MLH or PMS) with the possibility of improving survival through intensive focus on early detection, such as colonoscopy, and preventive strategies.[27]

There are fundamental differences between conditions for which testing is possible. Hereditary breast cancer affects predominantly women, and the proven absence of a mutation in the BRCA-genes does not relinquish the need of regular mammographic screening for breast cancer in women over the age 50. Identified carriers of the neurodegenerative disorders have to face a lack of treatment options and can only await the onset of the first symptoms. HD affects both men and women, and only symptomatic treatment is available. There is neither a cure nor a way to delay the progression. The level of penetrance -the probability that the disease will

manifest during a normal lifetime- differs in the various hereditary conditions. The trinucleotide repeat that causes HD (>39 repeats) has a complete penetrance. Women identified with a BRCA1/2 mutation have a cumulative lifetime risk of 39-85% for breast cancer and a 11-63% risk for ovarian cancer at the age of 70.[28-31] Furthermore, the life-time risk of contralateral breast cancer for genetically predisposed women after a history of breast cancer is 48-64%.[32]

Given the far-reaching psychosocial ramifications of test results, counselling and psychological follow-up studies have accompanied testing programmes to assess adjustment to genetic test outcomes and to identify factors that are associated with maladjustment.

1.3. ADJUSTMENT TO TEST RESULTS

It turned out that the actual uptake of the test for HD has been much lower than expected. The percentage of individuals at risk who requested testing when approached by registries or testing centres varied from 9% in Wales, 10% in Indiana, 16% in the Manchester area, to 20% in the Vancouver area.[14] In the Netherlands 752 out of 1032 individuals at risk, applying for predictive testing in the period 1987 to 1997, decided to be tested, which is 24% of the of the persons at risk registered in the Leiden Roster for HD.[33]

An important part of genetic counselling is preparing test candidates for adverse responses and helping them to cope. This requires an estimation of the resources of test candidates. There was a strong urge to obtain experience with predictive testing for late onset disorders. Worldwide, a number of groups started a psychological follow-up programme that accompanied the testing protocol for individuals who decided to undergo the predictive test.

A total of 100 centres in 21 countries have conducted follow-up studies on the test results and the psychosocial effects.[34] In general, the experiences are unambiguous over the years, and the studies published have shifted their attention. Understandably, the first concern was the newly identified mutation-carrier. However, a substantial minority of the non-carriers proved to experience adjustment problems after the test result. Partners and children received initially little attention, although some groups have addressed them in a number of studies.[35-37]

The initially designed studies used a variety of standardised psychological instruments and self-developed questionnaires. There was close contact between the study groups from the very beginning with regard to the instruments to be used, to allow cross-cultural comparison. The studies aimed to describe experiences with test results, to follow the course of adjustment over time, and to find factors that could help to identify those test candidates who might be at risk for extreme adverse reactions and adjustment problems. Studied were the reasons that were given to apply for the test and what the expectations were.

Three reviews were published on the psychological effects of testing for hereditary diseases.[14 38 39] The main cited reasons for taking a test were family planning, decrease uncertainty, and obtaining certainty. Partners

indicated that future planning was the most important reason. Test applicants expected generally few adverse psychological consequences of the test. No studies reported increased distress in mutation carriers or non-carriers at any point during 12 months after testing.[38] Both mutation carriers and non-carriers showed decreased distress after testing; this was greater and more rapid amongst non-carriers. Test result was rarely predictive of distress longer than one month after testing. Pre-test emotional state was predictive of subsequent distress in about half of the studies. Non-carriers and carriers differ significantly in their report of short term general psychological distress, but not in the long term.[14] Adjustment to results was found to depend more on psychological adjustment before testing than the test result itself. Few adverse events have been described and no obvious contraindications for testing people at risk have been identified. It must be noted that the psychological follow-up studies are all based on self-selected populations who have agreed to participate in psychological studies. There is some evidence that test applicants are more resourceful and emotionally more robust than others, thus outcomes are not to be extended to the whole population of persons at risk for HD.[40]

1.4. AIMS OF THE STUDY

The first aim of this thesis is to describe the psychological issues related to genetic testing for HD. These issues cover:

1. the psychological adaptation in the long term of individuals at risk for HD and their partners to the genetic test result (chapters 2, 3),
2. the methodology that is used in research to adaptation to genetic test results in general (chapter 4),
3. the characteristics of tested individuals who pursue a more accurate test (chapter 5),
4. the calculation of the risk for HD of individuals who are not tested (chapter 6).

The second aim is:

5. to develop a tool for registration of the progression of HD that is easy and quick to administer by nursing personnel (chapter 7).

1.4.1. Long term follow-up

After the initial effects, many studies revealed stability in time course of the psychological measures studied. However, these studies were limited in time and covered, according the initial study designs, a period of a few years at most. Participants in the studies had not been asked their consent to be approached after the studies had finished. Moreover, the ethical question was raised whether it is acceptable to burden tested individuals and their families after the book of testing was closed. A new confrontation with the genetic centre might recall the stressful experience of testing, reactivate negative emotions, or disturb the psychological adjustment to the test results. However, we decided to extend our follow-up study. The results of the follow-up studies, 3 years and 7-10 years after disclosure of the test, are described in Chapter 2 and 3 respectively.

1.4.2. Methodology of psychological studies

Psychological follow-up studies on the effects of predictive testing have provided important contributions to the improvement and refining of the testing programmes and counselling. The knowledge of the adjustments to test results and the insight into dynamics of families with a hereditary disease are based on reports of studies that have been published in peer-reviewed journals. In general, studies to the psychological effects of genetic testing have a longitudinal design that can be compared to a randomised condition design. Before the test, at baseline, the applicant fills out a number of questionnaires, for example on depression, general well-being and future expectations. Then the test is performed and the outcome is disclosed. The test outcome is comparable to random admission to an experimental condition. Missing time points are not easy to prevent in longitudinal research. Moreover, follow-up research is vulnerable to the problem of selectivity; persons who do not return for later follow-ups - dropouts- may have specific characteristics. As the analysis of findings of follow-up studies requires sound methodology and statistics, we reviewed all follow-up studies on effects of predictive testing for hereditary disorders with onset later in life that were carried out between 1988 and 2003 (Chapter 4).

1.4.3. Testing the test

Localisation of the gene responsible for HD in 1983 allowed the development of a genetic test based on linkage analysis. A structured predictive testing procedure for HD was introduced in 1987 in Leiden. The testing protocol, following the international guidelines, included, at least, two pretest and one post-test counselling session. Reliability of test results depended on cooperation of multiple, specified family members. About 24% of persons estimated to be at risk for HD in the Netherlands have applied for the test.[33] in this period, 245 individuals were tested with linkage analysis. Thirty-five did not receive an informative test outcome, 88 received an increased risk test outcome and 122 received a decreased outcome.

The detection in 1993 of the CAG repeat[6] made direct or mutation testing possible with more than 99% accuracy. Standardized analysis makes accurate CAG repeat size measurement possible (Losekoot et al., 1999). This new test could be performed without the need to test multiple family members. In the Netherlands, it was debated whether it was acceptable to inform linkage tested individuals that a more reliable test has become available and to offer them the accurate mutation test. The reluctance to inform them concerned the 'right not to know', and the risk that recalling the stressful events and reactivation of negative emotions would disturb the adjustments to the test results. The outcome of the debate, however, was that the tested individuals were informed on the mutation test and invited to discuss a re-test. This procedure allowed us to prolong the psychological follow-up study (Chapter 4). Furthermore, the psychological characteristics of individuals who were interested in the new test could be compared to individuals who were not (Chapter 5).

1.4.4. Risk refinement without a mutation test

At birth, children of a Huntington patient have a risk of 50% to have inherited the disease. Without being tested and on the condition that there are no symptoms, the risk decreases gradually in course of time, in particular at older ages. When genetic counsellors inform older test applicants, they often make use of the tables provided by Newcombe, to estimate the residual risk.[41 42] These tables were based on the age at onset or life-table analysis. Since the CAG repeat length is an important estimate for age at onset, we developed a model for an additional refinement of the residual risk, using information about the age at onset and test results of parents or other family members. The refined residual risk can contribute to the decision process of choosing to have the test performed, and to the process of adjusting to the test result. The systematic use of this calculation model can add to the quality of the information given by the genetic counsellor to the test applicants (Chapter 6).

1.4.5. The Behaviour Observation Scale Huntington (BOSH)

Preparing for the future is one of the main reasons to have a predictive test. Individuals, who received unfavourable test results, have to face new uncertainties with regard to the onset of the disease, and to the way the disease will manifest itself. The more specific information is available, the more identified carriers may be able to anticipate their future perspectives. HD is a disabling disease that progresses over time. Although no curative treatment is available yet, the increasing knowledge about HD has improved the caring and nursing considerably. The special wards for HD-patients in the Netherlands and Belgium (Katwijk aan Zee, Apeldoorn, Amsterdam, Geertruidenberg, Heist op den Berg) have much experience with HD-patients in the later stages of the disease. The perspective of good care in the later stages may comfort people, and may help them to distract from the appalling experiences with caring and nursing of relatives in the past. However, to better tailor the care and nursing of HD-patients, more insight is needed into the course and progress of the disorder at different stages of the disease. Shoulson & Fahn[43] made a categorisation of the progression on the basis of the capability to work, handle finances, domestic affairs, and activities of daily living. Patients are cared for at home until the care becomes too demanding or the patient becomes unmanageable. Admission to a nursing home is then inevitable. To monitor the disease progress, the Unified Huntington's Disease Rating Scale (UHDRS) was developed.[44] The UHDRS assesses four domains of functioning: motor performance, cognitive performance, behavioural abnormalities, and functional capacity. However, due to ceiling effects the UHDRS is less sensitive in later stages of the disease. In chapter 7, we describe the development of the Behaviour Observation Scale Huntington (BOSH). The BOSH should provide insight into the specific behaviours in the later stages of HD. The development of the BOSH benefited from 5 special wards for HD-patients that have been established in the Netherlands and Belgium.

1.5. REFERENCES

1. Adams P, Falek A, Arnold J. Huntington disease in Georgia: age at onset. *Am J Hum Genet* 1988;43(5):695-704.
2. Roos RA, Vegter - van der Vlis M, Van Ommen GJB, Bruyn GW. Duration of illness in Huntington's disease is not related to age of onset. *J Neurol Neurosur Ps* 1993;56:98-100.
3. Bates G, Harper PS, Jones L, eds. *Huntington's disease*. 3rd ed. Oxford: Oxford University Press, 2002.
4. Brouwer-Dudok de Wit AC, Savenije A, Zoeteweij MW, Maat-Kievit A, Tibben A. A hereditary disorder in the family and the family life cycle. Huntington disease as a paradigm. *Fam Process* 2002;41(4):677-692.
5. Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, et al. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 1983;306(5940):234-238.
6. Huntington Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72:971-983.
7. Evers-Kiebooms G, Nys K, Harper P, Zoeteweij M, Durr A, Jacopini G, et al. Predictive DNA-testing for Huntington's disease and reproductive decision making: a European collaborative study. *Eur J Hum Genet* 2002;10(3):167-176.
8. Bachoud-Levi AC, Remy P, Nguyen JP, Brugieres P, Lefaucheur JP, Bourdet C, et al. Motor and cognitive improvements in patients with Huntington's disease after neural transplantation. *Lancet* 2000;356(9246):1975-1979.
9. Harper PS, Gevers S, de Wert G, Creighton S, Bombard Y, Hayden MR. Genetic testing and Huntington's disease: issues of employment. *Lancet Neurol* 2004;3(4):249-252.
10. Farrer LA. Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. *Am J Med Genet* 1986;24(2):305-311.
11. Kessler S, Field T, Worth L, Mosbarger H. Attitudes of persons at risk for Huntington disease toward predictive testing. *Am J Med Genet* 1987;26:259-270.
12. Markel DS, Young AB, Penney JB. At risk persons' attitude toward presymptomatic and prenatal testing of Huntington disease in Michigan. *Am J Med Genet* 1987;26:295-305.
13. Meissen GJ, Berchek RL. Intentions to use predictive testing by those at risk for Huntington's disease: implications for prevention. *Am J Community Psychol* 1988;16(2):261-277.
14. Meiser B, Dunn S. Psychological impact of genetic testing for Huntington disease: an update of the literature. *J Neurol Neurosur Ps* 2000;69(5):574-578.
15. Craufurd D, Dodge A, Kerzin-Storrar L, Harris R. Uptake of presymptomatic predictive testing for Huntington's disease. *Lancet* 1989(September 9):603-605.

16. Bloch M, Fox S, Hayden MR. Predictive testing for Huntington disease: II. Demographic characteristics, life-style patterns, attitudes, and psychosocial assessments of the first fifty-one test candidates. *Am J Med Genet* 1989;32:217-224.
17. Meissen GJ, Mastromauro CA, Kiely DK, McNamara DS, Myers RH. Understanding the decision to take the predictive test for Huntington disease. *Am J Med Genet* 1991;39(4):404-410.
18. Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cassiman JJ, Cloostermans T, Demyttenaere K, et al. Predictive testing for Huntington's disease: risk perception, reasons for testing and psychological profile of test applicants. *Genet Couns* 1995;6(1):1-13.
19. Tibben A, Frets PG, Van De Kamp JJP, Niermeyer MF, Vegter-Van Der Vlis M, Roos RAC, et al. Presymptomatic DNA testing for HD: pretest attitudes and expectations of applicants and their partners in the Dutch program. *Am J Med Genet* 1993;48:10-16.
20. International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. *Neurology* 1994;44(8):1533-1536.
21. Bornebroek M, Haan J, Maat-Schieman ML, Van Duinen SG, Roos RAC. Hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D): I--A review of clinical, radiologic and genetic aspects. *Brain Pathol* 1996;6(2):111-114.
22. Suthers GK, Huson SM, Davies KE. Instability versus predictability: the molecular diagnosis of myotonic dystrophy. *J Med Genet* 1992;29(11):761-765.
23. Steinbart EJ, Smith CO, Poorkaj P, Bird TD. Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. *Arch Neurol-Chicago* 2001;58(11):1828-1831.
24. Nance MA, Sevenich EA, Schut LJ. Knowledge of genetics and ataxia and attitudes toward genetic testing in two hereditary ataxia (SCA1) kindreds. *Am J Med Genet* 1994;54:242-248.
25. Wang T, Sharma SD, Fox N, Rossor M, Brown MJ, Sharma P. Description of a simple test for CADASIL disease and determination of mutation frequencies in sporadic ischaemic stroke and dementia patients. *J Neurol Neurosur Ps* 2002;69(5):652-654.
26. Meijers-Heijboer EJ, Verhoog LC, Brekelmans CT, Seynaeve C, Tilanus-Linthorst MM, Wagner A, et al. Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. *Lancet* 2000;355(9220):2015-2020.
27. Lynch HT, Smyrk T. Hereditary nonpolyposis colorectal cancer (Lynch syndrome). An updated review. *Cancer* 1996;78(6):1149-1167.
28. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003;72(5):117-1130.

29. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 1998;62(3):676-689.
30. Meijers-Heijboer Hv, Geel Bv, Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *New Engl J Med* 2001;345(3):159-164.
31. Thorlacius S, Struewing JP, Hartge P, Olafsdottir GH, Sigvaldason H, Tryggvadottir L, et al. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. *Lancet* 1998;352(9137):1337-1339.
32. Verhoog LC, Brekelmans CT, Seynaeve C, Meijers-Heijboer EJ, Klijn JG. Contralateral breast cancer risk is influenced by the age at onset in BRCA1-associated breast cancer. *Brit J Cancer* 2000;83(3):384-386.
33. Maat-Kievit A, Vegter - van der Vlis M, Zoeteweij M, Losekoot M, Van Haeringen A, Roos R. Paradox of a better test for Huntington's disease. *J Neurol Neurosur Ps* 2000;69(5):579-583.
34. Almqvist EW, Bloch M, Brinkman R, D. C, R. HM. A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease. *Am J Hum Genet* 1999;64(5):1293-1304.
35. Tibben A, Timman R, Bannink EC, Duivenvoorden HJ. Three year follow up after presymptomatic testing for Huntington's disease in tested individuals and partners. *Health Psychol* 1997;16(1):20-35.
36. Decruyenaere M, Evers Kiebooms G, Cloostermans T, Boogaerts A, Demyttenaere K, Dom R, et al. Predictive testing for Huntington's disease: relationship with partners after testing. *Clin Genet* 2004;65:24-31.
37. Richards F, Williams K. Impact on couple relationships of predictive testing for Huntington disease: a longitudinal study. *Am J Med Genet* 2004;126A(2):161-169.
38. Broadstock M, Michie S, Marteau TM. The psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet* 2000;8(10):731-738.
39. Duisterhof M, Trijsburg RW, Niermeijer MF, Roos RAC, Tibben A. Psychological studies on Huntington's disease: making up the balance. *J Med Genet* 2001;38:852-861.
40. Van Der Steenstraten IM, Tibben A, Roos RAC, Van Der Kamp JJP, Niermeijer MF. Predictive testing for Huntington disease: nonparticipants compared with participants in the Dutch program. *Am J Hum Genet* 1994;55:618-625.
41. Newcombe RG. A life table for onset of Huntington's chorea. *Ann Hum Genet* 1981;45:375-385.
42. Harper PS, Newcombe RG. Age at onset and life table risks in genetic counseling for Huntington's disease. *J Med Genet* 1992;29:239-242.
43. Shoulson I, Fahn S. Huntington's disease: clinical care and evaluation. *Neurology* 1979;29:1-3.

44. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord* 1996;11(2):136-142.

CHAPTER 2
-
Three year follow up after presymptomatic testing for Huntington's disease in tested individuals and partners.

Aad Tibben [1,2], Reinier Timman [2], Erna C. Bannink [2], Hugo J. Duivenvoorden [2]

[1] University Hospital Dijkzigt, Department of Clinical Genetics, Rotterdam; [2] Erasmus University, Department of Medical Psychology and Psychotherapy, Rotterdam, the Netherlands
Health Psychol, 1997;16(1):20-35.

ABSTRACT

The 3-year psychological effects of presymptomatic DNA diagnosis for Huntington's disease are described in 20 identified carriers of the Huntington's disease gene (mean age = 31 years), 29 noncarriers (mean age = 32 years), and 37 partners. The Intrusion and Avoidance subscales of the Impact of Event Scale[1] and the Beck Hopelessness Scale[2 3] measured psychological distress at 4 time points: baseline (before disclosure of test results) and 1 week, 6 months, and 3 years after testing. Multivariate testing on course of distress revealed similar patterns of intrusive thoughts about Huntington's disease over the 3-year follow-up in carriers and noncarriers but showed opposite patterns of avoidance at the 6-month assessment. One week after disclosure, carriers had increased and noncarriers had decreased levels of hopelessness. These effects disappeared after 6 months and did not recur. Carrier partners followed the same course of distress as carriers. Carrier partners with children were significantly more distressed than those without offspring. Noncarrier partners were significantly less distressed than noncarriers after 3 years.

INTRODUCTION

Huntington's disease is a dominantly inherited, progressive neurodegenerative disorder, usually of adult onset, characterized by motor disability, often choreic in nature, a disturbance of affect, behavior and personality, and cognitive impairment.[4] Children of an affected parent are at 50% risk of being affected by Huntington's disease in later life. Although the mean age of onset is 40 years, with a range of 2 to 75 years,[5] at risk individuals will always remain at risk for Huntington's disease.

Presymptomatic DNA testing using genetic linkage analysis has been available since 1986. After identification of the Huntington's disease gene mutation in 1993, the laboratory aspect of testing was simplified.[6] In the overwhelming majority of cases, the test result is unequivocal; the detection of the gene mutation indicates that the individual will develop Huntington's disease at some time in the future, unless he or she dies of some other cause before the onset of early symptoms.

Previous studies of expectations of at risk individuals have suggested that psychological effects of testing might include severe psychosocial problems such as overalertness for early symptoms, depression, and suicidal behavior in identified gene carriers.[7-9] However, given that the most cited reasons to undergo testing were to seek relief from uncertainty, and to get some control over the future (particularly with a view to planning a family), we expected that a reduction of anxiety and gaining more certainty about one's risk could improve the test candidates' quality of life.[10]

Effects of testing on potential carriers

A number of recent studies have examined the psychological effects of DNA testing.[11-19] Generally, the results have indicated that tested individuals found relief from their prior psychological distress and that they benefited psychologically from testing. It appeared as though most carriers coped well up to this point, although this was largely based on strong psychological defenses and dependence on satisfactory relationships.[20] These studies also suggested that carriers tend to minimize the impact of their test results on their future. Although heightened distress was found in carriers, compared with noncarriers, this remained within normal limits.[16 19] The Baltimore Group[17] reported that identified carriers estimated that their risk after 6 months was much lower (60%) than was initially revealed at disclosure (>95%).

A substantial subgroup of noncarriers was found to have a lack of relief, survivor's guilt, and emotional numbing.[13 16] The Vancouver Group[14] found that, 6 months after test disclosure, psychological functioning in both carriers and noncarriers was significantly better than in individuals who had not been tested. In our study, carriers reported significantly more intrusive thoughts with respect to Huntington's disease than noncarriers in the 6-month follow-up, especially those who had suffered most from the burden before the test. Both carriers and noncarriers who tried to avoid thoughts about Huntington's disease before test disclosure did this also after the test

results. Posttest hopelessness in both carriers and noncarriers, 6 months after the test result, proved to be dependent on relative absence of avoidant thoughts and unsatisfactory supportive allies at baseline. High scores on avoidant thoughts in both groups at the 6-month follow-up were associated with low satisfaction with social support and low levels of hopelessness before disclosure.[20]

Severe adverse reactions in carriers have not been reported to date. However, at the 6-month follow-up, one quarter of the carriers were suspected of psychopathological states.[20] These carriers were characterized by increased avoidant thoughts and decreased intrusive feelings about Huntington's disease compared with baseline levels. Moreover, we have observed that carriers, who initially could cope satisfactory with the test result, showed disturbed functioning, depression, suicidal behavior, or all of these, after Huntington's disease diagnosis was confirmed. This was also reported by Quaid and Wesson.[19]

Effects of testing on partners

Huntington's disease is a family disease that inevitably will impose a direct imprint on the life of the partner.[21] Partners found the mental deterioration and the personality changes in the affected spouse or affected relatives to be the most difficult aspects to cope with, and the threat that their own children may later develop the same disease is one of the most dramatic aspects.[11] Partners have reacted to the clinical diagnosis with disbelief and denial but, after full awareness of the threat of transmission to the children, their responses changed to resentment and hostility.[21] In predictive testing programs, partners received little empirical attention.[11 16 19 22] Although Quaid and Wesson found that spouses of prospective carriers were more distressed about their marriage than partners of noncarriers at baseline, there were no differences at the follow-up measures. Spouses were more depressed than their at risk partners at baseline. In our study, partners of carriers reported the most difficulties in coming to terms with the impending burden.[16] Codori and Brandt[17] reported that the majority of carriers and noncarriers stated that the test result had no impact on their relationships. We found that satisfactory support of partners before test disclosure was associated with less feelings of hopelessness and avoidant thoughts at the 6-month follow-up in carriers and noncarriers, which emphasizes the important role of partners.[20]

Process of coping with DNA test results

The DNA test result can be considered as a psychologically distressing life event. Learning about a serious threat to the individual's wellbeing may have a profound impact on the future perspective of both the individual at risk and his or her intimate relationship. An unfavorable test result may be experienced with intense fear, terror, and helplessness, whereas a favorable may generate relief. Clinical and empirical evidence have consistently indicated that potentially traumatic events produce psychological symptomatology. The stress response theory of Horowitz

suggests that the central features of adjustment problems after a test result would involve (re) experiencing untoward intrusive feelings and thoughts and denial—avoidance of stimuli associated with Huntington's disease.[1 23]

Anticipating their future, some identified carriers may oscillate between facing the impending burden and distraction from the appalling future perspective. There may be a group that suffers from overwhelming fears and preoccupation with early signs of the disease and may have difficulty with the inevitable deterioration. Others may strongly deny any impact of Huntington's disease on their lives. Given that carriers approach the moment when the early signs of the disease may develop, an increase of both intrusive thoughts and avoidance may be expected. Noncarriers reported that the result had activated the past and that they were overwhelmed by early experiences with Huntington's disease in the affected parent. They also had difficulties coping with bad results in their relatives or facing the disease developing in their relatives.[13 20] The alternating phases of intrusions and avoidance in noncarriers apparently refer to working through the distressing events. Over time a reduction of both intrusive experiences and avoidant thoughts and an accommodation to new life perspectives would be expected.

The present study was a longitudinal study designed to follow up the course of responses of potential carriers and noncarriers and their partners over 3 years after the DNA test results. In the current research we measured psychological distress as indicated by intrusive feelings and thoughts, avoidant thoughts, and hopelessness at four points in time: one prior to the test and 1 week, 6 months, and 3 years after the test results. We examined whether the course of responses (as measured by intrusion, avoidance, and hopelessness) after the test result is different in carriers and noncarriers. We hypothesized that the psychological distress would show an increase for carriers—carrier partners and a decrease for noncarriers—noncarrier partners over the entire period after disclosure of test results. In addition, we investigated whether there were differences between carriers—noncarriers and their partners with regard to psychological responses over time.

METHOD

DNA testing program

In the Netherlands, 2,644 individuals at 50% risk were registered in 1991, belonging to 281 families that could be traced genealogically to at least two generations.[24] The presymptomatic test for Huntington's disease, in which DNA linkage analysis was used, has been available at the Clinical Genetics Center in Leiden since October 1987.[25] No official announcement was made by the Genetics Center, as a restrained policy was applied. Information about the availability of the test was given by the general practitioner, neurologist, clinical genetics service, relatives, or the patients organization. The counseling protocol included at least two sessions of pretest counseling and was undertaken along the lines of a structured protocol following the international guidelines. The testing protocol has previously been

described.[25] Inclusion criteria for the testing program included the following: age 18 years or older, absence of major mental illness or the intention to commit suicide after an unfavorable result, no neurological manifestations of Huntington's disease, and the ability to give informed consent. Results were disclosed about 3 months after the intake session.

Participants

In 1989, a psychological follow-up study on the effects of test results was added to the testing program. Previously, 18 individuals at risk had received results. Between 1989 and 1991, a total of 114 applicants who were at risk applied for the presymptomatic test. All applicants were requested to participate in the psychological follow-up study that included a series of in-depth interviews (6 weeks before disclosure and 1 week and 6 months after the test disclosure) and the completion of questionnaires. Applicants were informed of the follow-up study in the invitation letter for the first counseling session, and they were requested to consider participation. In addition to the first counseling session, they were further informed by the researcher. After they had consented, participants received the questionnaires for the baseline assessment. Partners were also requested to join in the study. No distinction was made between spouses and cohabitants because of the assumption that there are no differences.

Forty out of 114 individuals did not receive DNA test results for reasons described in detail elsewhere.[10] In brief, the main reasons for this were that the family structure was not informative, that applicants were already affected and clinically diagnosed, that applicants withdrew from the program after consideration of the possible effects of unfavorable test results, or that test candidates postponed testing. Seventy-three out of 74 individuals at risk, who eventually received test results, consented to participate in the follow-up study; 1 nonparticipant wished to maintain in contact with the researcher. Partners in seven couples who did not share a household, but who expressed their intention to marry or to live together in the future, were also asked to participate in the study. Three individuals out of the study group failed to complete most of the questionnaires, although they did not withdraw from the study and appreciated the follow-up contacts. At the 3-year follow-up assessment, 49 individuals of the initial study group participated in the present study. Two individuals who had consented to participate, but who did not complete the questionnaires, were considered as lost to follow-up.

Procedure

Individuals who applied for the presymptomatic test were informed by letter about the follow-up study and were encouraged to participate. At the initial counseling session, eligible male and female participants were given an introduction to the research protocol and were requested to take part in the long-term follow-up study on the psychosocial effects of the DNA test results. The research protocol was approved by the Medical Ethics Committee of the University Hospital of Leiden. The psychometric battery

included the Impact of Event Scale[1] and the Beck's Hopelessness Scale[2 3] as measures of psychological distress. Additionally, biographical data, including gender, age, marital status, number of children, and level of education, were assessed. The questionnaires were completed at the first meeting (before disclosure of results) and I week, 6 months, and 3 years after the disclosure of the DNA test results.

Measures

Huntington-specific distress. The Impact of Event Scale[1] is a reliable, self-report scale used to measure the current degree of subjective impact, experienced as a result of a specific life event, in this case, Huntington's disease. The Impact of Event Scale estimates the influence of a stressor on two dimensions: (a) intrusion of unwanted ideas and thoughts into consciousness and (b) avoidance of certain thoughts, feelings, or situations. This scale consists of seven items that form the Intrusion subscale (score range 0—35) and eight items that form the avoidance subscale (score range 0—40). The Impact of Event Scale has good internal consistency (Cronbach's a of .91 for total baseline and .88 and .83 for Intrusion and Avoidance subscales, respectively).

Hopelessness—future expectancies. The Beck Hopelessness Scale[2 3] consists of 20 true—false statements used to measure hopelessness or the pessimistic expectations one has for his or her future. A score of nine or greater (range 0—20) is indicative of depression and possible suicidal behavior (Cronbach's *a* — .97).

Sociodemographic factors. These factors include the following: age, marital status, education, number of children, and Huntington's disease awareness. An attitude questionnaire was used to assess the participant's experience with Huntington's disease in relatives, Huntington's disease awareness, reasons for taking the test, and the anticipated impact of either results. Huntington's disease awareness refers to the period that had elapsed since the participant first learned about his or her personal risk to get Huntington's disease. The question was, "How old were you when you first learned that you are at 50% risk to develop your parent's disease?"

Data analysis

All data analyses were carried out by using the *Statistical Package for the Social Sciences.*[26] Associations between participants and partners and the categorical biographical characteristics were investigated with chi-square tests. Baseline differences between the pairs of groups (carriers—noncarriers, carriers—carrier partners, noncarriers—noncarrier partners, and carrier partners—noncarrier partners), with respect to the psychological variables, were tested with a ***t*** test. In the analysis of the follow-up data, scores representing the difference between the follow-up scores and the baseline data were computed and compared by using a one-way analysis of variance.

To investigate the effect of the DNA test result over time, we performed a multivariate analysis of variance (MANOVA) for repeated measurements

with time point as the within-participant factor. Outcome measures (intrusion, avoidance, and hopelessness) were considered at four assessment occasions: baseline and 1 week, 6 months, and 3 years after disclosure of the DNA test results. Between-participants factors included DNA test result (carrier vs. noncarrier) and participant (test candidate vs. partner). The four time points were decomposed into the orthonormalized polynomial contrasts. Linear, quadratic, and cubic trends were examined in which effects could be demonstrated by two, three, and four measurement points, respectively. At least two measurement points are needed to demonstrate a linear trend (one line between two points, such as the course of carrier partners in Figure 1). To reveal a quadratic trend, at least three time points are needed (a curve through three points, such as the course of noncarriers in Figure 1), whereas four time points can disclose a cubic trend (two curves along four points, such as the course of carrier partners in Figure 2).

Partner scores were considered as not independent of the scores of the tested individual. We therefore considered the partner scores as scores of the test candidates in the repeated measurements analysis. Consequently, analyses were performed in a subsample that had a partner in order to determine interaction effects of the responses of partners. An interaction effect would reveal a different course of psychological responses over time.

First, we estimated the effects of the DNA test result, partner—spouse and their ‘interactions, in multivariate models. Second, we tested in step-down models whether the linear, the quadratic, or cubic trends were significant. A p value <. 05 (two-tailed) was considered significant.

The nature of the psychological tests caused skewness in the distributions (normal population scores zero or near zero, other scores were high). Therefore, raw scores were square root transformed in order to get normal distributions, which are paramount for MANOVAs.

RESULTS

Analysis of participation bias

Twenty-four individuals were lost to follow-up at 3 years after the test disclosure (33%). Six gene carriers had developed symptoms, 2 participants moved abroad, and 4 moved without leaving an address. Twelve noncarriers refused to cooperate for various reasons: three of them had experienced severe problems with coping with the test result and did not wish to share experiences for fear of reactivation of the burden, 2 individuals reported that Huntington’s disease was no longer an issue for them and felt no need for follow-up contacts, two had physical problems (bowel cancer and severe cardiac illness), 2 out of 3 noncarriers who had postponed the follow-up appointment several times were involved in care-taking of the affected parent or siblings, and 2 individuals responded to the invitation for follow-up but failed to complete the questionnaires. The group that was lost to follow-up did not differ significantly from the present study group on age, DNA test disclosure (carrier—noncarrier), time lag, gender or

marital status, or the scores on psychological measures at baseline and the 6-month follow-up (Table 1).

Baseline assessment

Table 2 presents the biographic characteristics of the initial study group at baseline (i.e., the first counseling session before disclosure of test results) in carriers, noncarriers, and partners. A significant difference was found regarding Huntington's disease awareness; that is, the period that had elapsed since the participants first learned about the personal risks to develop Huntington's disease.

The male: female ratio of the present study group was 16:33 (Table 1). Thirty-nine percent had at least one child. Sixty-three percent of the participants had completed a higher level of education than lower vocational school. Twenty participants had received an unfavorable test result (7 male and 13 female participants), and 29 had received a favorable result (9 male and 20 female participants). The male:female ratio did not differ significantly between carriers and non-carriers (chi-square, Yates corrected .20, *ns).* The carrier:noncarrier ratio was the same as in similar DNA studies for Huntington's disease testing.[14 19] With regard to the psychological variables, pairwise comparisons revealed no significant differences between the groups at baseline (Table 3).

Table 1. *Characteristics at baseline of participants in the present study compared with lost to follow-up after presymptomatic DNA testing for Huntington's disease*

	Participants (n = 49)			Participants lost to follow-up (n = 24)					
Characteristic	*M*	*sd*	*n*	*M*	*sd*	*n*	*df*	*F*	*p*
Age (years)	32.2	8.9	49	31.9	12.1	23	1,71	0.01	.91
HD awareness (years)	8.1	6.8	49	10.7	7.1	22	1,70	2.23	.14
Pretest									
IES-intrusion	10.6	7.7	45	12.5	10.6	21	1,64	0.68	.41
IES-avoidance	10.2	9.0	45	9.1	7.9	21	1,64	0.22	.64
BHS-hopelessness	4.9	3.8	45	4.2	3.9	20	1,63	0.40	.53
	n	*%*		*n*	*%*		*df*	χ^2	*p*
Sex									
male	16	33		11	46		1	1.20	.28
female	33	67		13	54				
Marital status									
single	12	24		8	33		1	0.36	.55
married-common-law	37	76		16	67				
Children									
0 children	30	61		16	67		1	0.20	.65
≥ 1 child	19	39		8	33				
Education									
< high school	18	37		8	33		1	0.08	.78
≥ high school	31	63		16	67				

Note. Pearson's chi-square tests were used to obtain data reported here. DNA = deoxyribonucleic acid; HD = Huntington's disease; IES = Impact of Event Scale; BHS = Beck Hopelessness Scale.

Follow-up assessments

The average changes of the psychological variables from baseline recorded at the follow-up assessments are summarized in Table 3. At the assessment 1 week after the disclosure of test results, pairwise comparisons showed that the decrease with regard to hopelessness in noncarriers differed significantly from the increased scores in carriers. The increased scores on intrusion and hopelessness in carrier partners differed significantly from the decreased scores in the noncarrier partners. No differences were found between the tested groups and partners.

At the 6-month follow-up, the increase from baseline in avoidant thoughts in carriers differed significantly from the decrease in noncarriers. The significant differences with regard to intrusion and hopelessness between the partner groups at the 1-week follow-up had sustained at the 6-months measurement. Also, the differences concerning avoidant thoughts were significant at this time point. Again, no differences were found between the tested groups and partners.

At the 3-years follow-up assessment, pairwise comparisons revealed no differences between carriers and noncarriers. However, noncarriers differed significantly from the noncarrier partners with regard to intrusion. The change from baseline in the partner groups differed significantly with regard to all psychological measures. Carrier partners were more hopeless and reported more intrusive feelings and avoidant thoughts, whereas noncarrier partners showed the reversed change.

Analysis of trend

Intrusive thoughts. A repeated measures MANOVA (Table 4) indicated no significant differences over time between the entire group of carriers and noncarriers. Similar results were found in the subgroup that had a partner. However, in the group that had a partner, a significant cubic interaction effect of DNA test result modified by time and partner scores was found, $F_{(1, 31)} = 8.52$; $p = .006$. With regard to the course over time, partners of carriers had a strong increase of intrusive thoughts I week after disclosure of the DNA test results, whereas partners of noncarriers showed a decline. Both groups had lower scores at the 6-month assessment. The significant change from baseline sustained for the next 3 years. No differences were found between the tested groups and partners, indicating that partners followed the same pattern as tested individuals, which can also be seen in Figure 2. At the 3-year follow-up assessment, the increase in noncarriers differed significantly from the decrease in their partners with regard to intrusive feelings.

Avoidance of thoughts. With regard to avoid-ant thoughts, a significant quadratic DNA test result modified by time effect was found (Table 4). The curving course of avoidant reactions over time for carriers was opposite to that of the noncarriers (see Figure 1). Six months after disclosure, the level of avoidant~ reactions was heightened for carriers compared with baseline levels, whereas it was reduced for noncarriers (Table 3). The significant change from baseline at the 6-month follow-up disappeared at the 3-year

assessment. There was significant evidence for a step-down linear trend for DNA test result modified by time in the subgroup that had a partner. In this subgroup, the carriers reported at the 3-year assessment occasion an increase in avoidant thoughts compared with the 6-month assessment, in which the pattern was similar to the course of carrier partners. Noncarriers with a partner showed the same course as the entire group of non-carriers. The slightly increased scores on avoid-ant thoughts at the 6-month and 3-year assessments in partners of carriers differed significantly from the decreased scores in partners of non-carriers. Partners followed the same pattern as the tested groups, as no interaction effect was found.

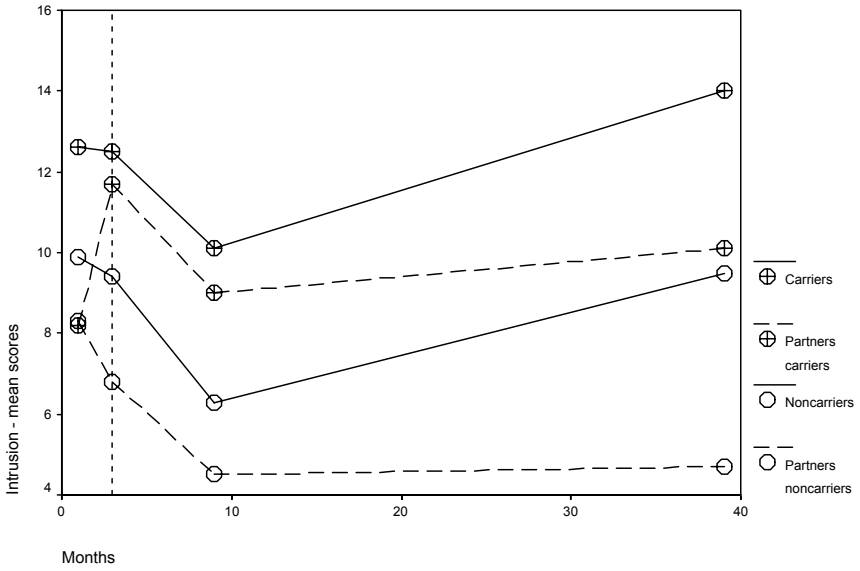

Figure 1. *Mean intrusion scores of gene carriers, noncarriers and partners*

Hopelessness. With regard to hopelessness (Beck's Hopelessness Scale), a significant multivariate DNA test result modified by time effect was found (Table 4). There was evidence for a step-down cubic DNA test result modified by time interaction effect on hopelessness. The decrease with regard to hopelessness in noncarriers differed significantly from the increased scores in the carriers at the 1-week follow-up assessment (Table 3 and Figure 3). Thereafter, the changes from baseline in both groups were no longer significant. Evidence for similar results was found when the analysis was conducted for the subgroup that had a partner. The increased hopelessness in carrier partners was significantly different from the decreased feelings hopelessness in non-carrier partners at all follow-up measurements. Noncarrier partners had a linear decline over the entire period, whereas carrier partners had a decline in the 6-month follow-up, followed by an increase of hopelessness. The course of hopelessness in partners could be considered as similar in the tested individuals, as no interaction effects were found.

Table 2. *Characteristics of initial study group of individuals and partners that underwent presymptomatic DNA testing for HD*

	Carriers (*n* = 29)			Noncarriers (*n* = 44)			Carrier partners (*n* = 21)			Noncarrier partners (*n* = 36)					
Characteristic	*M*	*sd*	*n*	*M*	*sd*	*n*	*M*	*sd*	*n*	*M*	*sd*	*n*	*df*	*F*	*p*
Age (in years)	31.2	9.8	29	32.6	10.1	44	34.8	9.3	21	33.7	9.5	36	3,126	0.62	.60
HD awareness [a]	6.5	5.2	29	10.6	7.5	44	5.8	7.8	21	6.8	6.5	32	3,122	3.56	.02 [b]
	n	%		*n*	%		*n*	%		*n*	%		*df*	χ^2	*p*
Sex															
Male	9	31		18	41		13	62		23	64		3	0.75	.86 [c]
Female	20	69		26	59		8	38		13	36				
Marital status															
Single	10	34		11	25		3	14		4	11		3	6.16	.10
Married-common law	19	66		33	75		18	86		32	89				
Children															
0 children	16	55		30	68		10	48		25	69		3	3.99	.26
≥ 1 child	13	45		14	32		11	52		11	31				

Note. Pearson chi-square tests were used to obtain data reported here.
[a] Time period that had elapsed since participants learned about personal risk for HD. [b] Significant because of noncarriers. [c] Sex of partners was reversed for Pearson's chi-square test.

Table 3. *Means and standard deviations on psychological variables in individuals tested for HD and partners*

	Carriers			Noncarriers			Carrier partners			Noncarrier partners		
Variable	*M*	*sd*	*n*	*M*	*sd*	*n*	*M*	*sd*	*n*	*M*	*sd*	*n*
IES-intrusion												
Baseline	12.6	10.2	29	9.9	7.1	37	8.2	7.2	20	8.3	6.3	30
1 week [a]	-0.1	8.0	29	-0.5	5.9	37	3.5	8.0	20	-1.5	5.2	29
> 6 months [b]	-2.5	7.5	27	-3.6	5.4	36	0.8	8.5	18	-3.8	5.5	29
> 3 years [c]	1.4	4.0	19	0.04	7.0	26	1.9	7.2	14	-3.6	4.2	23
IES-avoidance												
Baseline	9.2	9.3	29	10.3	8.2	37	8.3	10.2	20	8.8	9.7	30
1 week	-0.1	7.7	29	-2.2	8.3	36	0.3	8.4	20	-2.9	6.1	29
> 6 months [d]	1.3	6.7	27	-4.3	8.6	36	0.8	5.7	18	-4.2	8.7	29
> 3 years [e]	0.4	5.1	18	-1.4	8.8	27	1.2	10.1	14	-5.5	8.7	23
BHS												
Baseline	5.0	4.3	25	4.4	3.5	40	3.7	1.8	21	4.2	3.4	35
1 week [f]	1.7	4.3	23	-1.3	3.6	39	1.5	2.8	20	-1.0	2.2	34
> 6 months [g]	1.2	4.3	20	-0.3	4.0	35	1.0	3.5	17	-1.3	2.7	32
> 3 years [h]	1.1	5.0	17	-0.4	4.3	28	1.9	5.0	14	-2.1	2.8	23

Note: Values shown for follow-up intervals were calculated on the basis of the change from baseline scores; groups were pairwise compared at each follow-up with regard to change from baseline. IES = Impact of Event Scale; BHS = Beck Hopelessness Scale.
[a] after disclosure; $p = .01$, partners of carriers versus partners of noncarriers. [b] $p = .03$, partners of carriers versus partners of noncarriers. [c] $p = .04$, noncarriers versus partners of noncarriers; $p = .007$, partners of carriers versus partners of noncarriers. [d] $p = .008$, carriers versus noncarriers; $p = .03$, partners of carriers versus partners of noncarriers. [e] $p = .04$, partners of carriers versus partners of noncarriers. [f] $p = .005$, carriers versus noncarriers; $p = .0007$, partners of carriers versus partners of noncarriers. [g] $p = .01$, partners of carriers versus partners of noncarriers. [h] $p = .004$, partners of carriers versus partners of noncarriers.

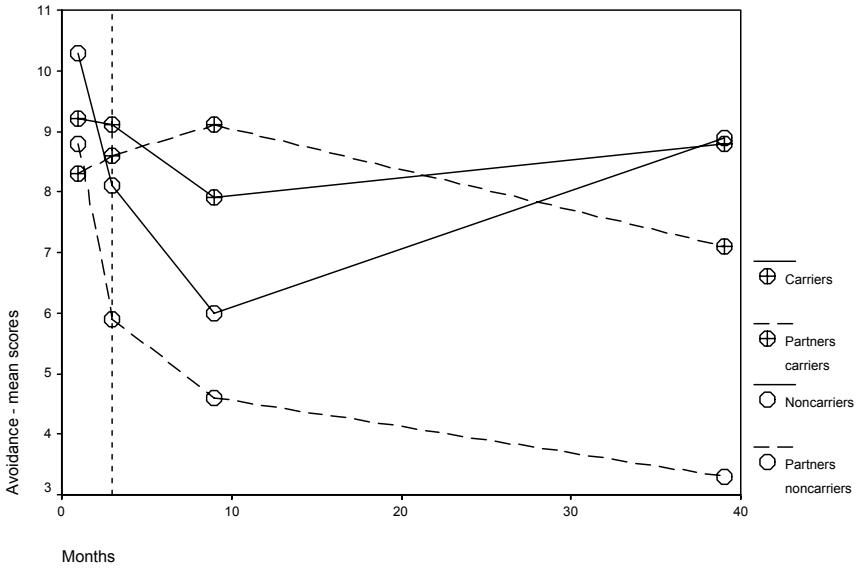

Figure 2. *Mean avoidance scores of gene carriers, noncarriers and partners*

Table 4. *Multivariate testing on course of psychological variables for carriers and noncarriers with additional analysis of effect of course in partners in subgroups of couples*

	DNA test result in total study group X time point			DNA test result in those who have partner X time point			DNA test result X partner X time point		
Variable	*df*	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
IES-intrusion									
Multivariate [a]	3,42	1.55	.22	3,31	2.02	.13	3,31	5.37	.004
Step-down									
linear trend	1,44	1.15	.29	1,33	2.75	.11	1,33	3.14	.09
quadratic trend	1,43	1.87	.18	1,32	1.27	.27	1,32	2.83	.10
cubic trend	1,42	1.54	.22	1,31	1.91	.18	1,31	8.52	.01
IES-avoidance									
Multivariate [a]	3,42	2.77	.05	3,31	5.14	.005	3,31	0.93	.44
Step-down									
linear trend	1,44	1.52	.22	1,33	9.91	.003	1,33	1.94	.17
quadratic trend	1,43	6.29	.02	1,32	4.84	.04	1,32	0.01	.92
cubic trend	1,42	0.42	.52	1,31	0.02	.90	1,31	0.90	.35
BHS									
Multivariate [a]	3,39	4.63	.01	3,30	3.16	.04	3,30	0.37	.77
Step-down									
linear trend	1,41	2.30	.14	1,32	2.99	.09	1,32	0.51	.48
quadratic trend	1,40	2.45	.13	1,31	1.95	.17	1,31	0.56	.46
cubic trend	1,39	8.17	.01	1,30	3.97	.06	1,30	0.09	.77

Note. IES = Impact of Event Scale; BHS = Beck Hopelessness Scale.
[a] Pillai's multivariate repeated measures test.

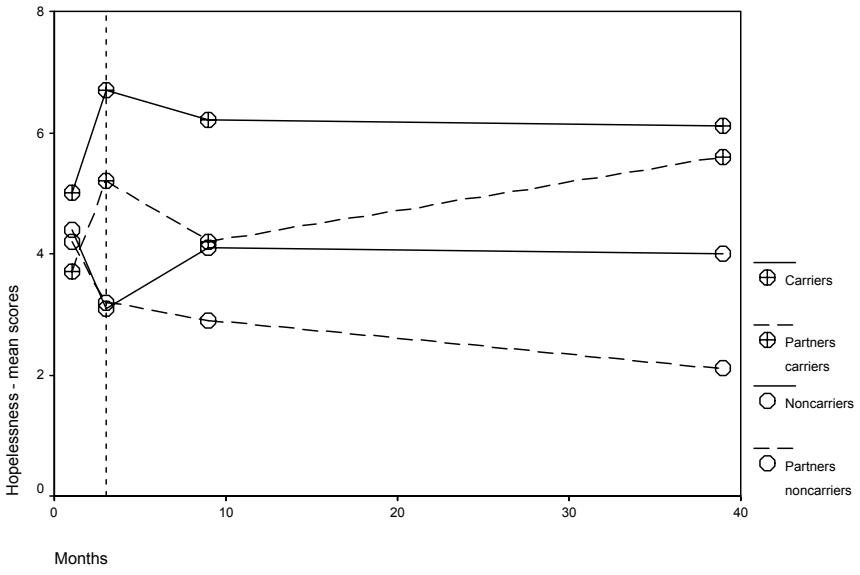

Figure 3. *Mean hopelessness scores of gene carriers, noncarriers and partners*

Table 5. *Means and standard deviations on psychological variables in partners of individuals tested for HD (distinguished by having children)*

	Partners of carriers without children			Partners of carriers with children					
Variable	*M*	*sd*	*n*	*M*	*sd*	*n*	*df*	*F*	*p*
IES-intrusion									
Baseline	7.3	6.1	9	8.2	7.2	11	1,18	0.20	.66
1 week [a]	7.1	5.2	9	11.3	4.9	11	1,18	13.10	.002
> 6 months	3.9	4.4	7	11.3	9.2	10	1,15	4.03	.06
> 3 years	7.8	6.4	9	13.0	2.3	7	1,14	4.18	.06
IES-avoidance									
Baseline	6.8	11.8	9	8.3	9.1	11	1,18	0.33	.57
1 week [a]	5.0	5.8	9	8.6	3.2	11	1,18	10.01	.005
> 6 months	3.1	4.2	7	11.3	8.5	10	1,15	5.46	.03
> 3 years	7.8	6.2	9	14.1	4.9	7	1,14	5.15	.04
BHS									
Baseline	3.7	1.7	9	3.8	1.9	11	1,18	0.03	.86
1 week [a]	3.7	2.4	9	6.5	2.8	11	1,18	5.46	.03
> 6 month	3.7	1.8	7	5.8	4.1	10	1,15	1.59	.23
> 3 years	5.4	3.5	9	6.1	5.8	7	1,14	0.36	.56

Note. IES = Impact of Event Scale; BHS = Beck Hopelessness Scale.

The presence of children. As an unfavorable test result increases the risk of children to 50%, the presence of offspring may affect the psychological distress. Hence, we performed an additional exploratory analysis on the effect of having children on the psychological variables. No differences were found between carriers and noncarriers at baseline or at any of the follow-up assessments with regard to the psychological variables. Partners of noncarriers who had children showed significantly higher hopelessness scores than those without children, $F_{(1, 28)} = 5.17$, $p = .03$, in which the effect disappeared after the test disclosure. Table 5 presents the psychological measures in partners of carriers distinguished by the presence of children. At 1 week after disclosure, partners with children had significantly higher scores on all three variables, in which the difference was sustained for avoidance thoughts over the 3-year period and approached significance for the Intrusion subscale.

DISCUSSION

Our expectation that carriers would show an increase and noncarriers would show a decrease in psychological stress responses over time was not confirmed. In both groups, only slight changes from baseline were observed at the 3-year assessment regarding intrusion and avoidance. The shock of the test result in carriers and the relief of the test result in noncarriers were only reflected by their respective hopelessness scores 1 week after disclosure of the test results. After 6 months, subsequently, carriers had more avoidant thoughts about Huntington's disease than noncarriers. Both groups did not differ significantly in the long term with regard to change from baseline on the psychological variables. Although this finding is consistent with the results of the Vancouver Group,[14] it is contrary to our expectations, given the prognosis for carriers and the clinical features of Huntington's

disease and the improved life perspective for noncarriers. This observation needs clarification. One explanation is that the dropouts have caused this result. On the one hand, noncarriers for whom Huntington's disease was no longer an actual problem in their lives and who felt relieved were not motivated to participate in the 3-year follow-up. This may have caused an overrepresentation of noncarriers who were still burdened by the presence of Huntington's disease in their family and who perceived participation in the study as psychological support. On the other hand, some carriers were lost to follow-up after the Huntington's disease diagnosis was confirmed in them—they had reacted with severe depression and suicidal behavior, although they had previously coped well (as was personally communicated by their partner or relatives). Therefore, relatively well-functioning carriers may be overrepresented in our study group. A second explanation is that the reactions in carriers, who have continued their participation in the study, reflect denial, relief from uncertainty, or both. Although the dropout group did not differ on any of the baseline variables, we have no insight in their psychological functioning at the consecutive assessment occasions. This limits the generalizability of the findings.

We investigated whether the course of psychological distress over time differed in tested individuals. Carriers and noncarriers showed a similar course over the entire period with regard to intrusion. However, carriers evidenced an increase in avoidant thoughts, and noncarriers evidenced a decrease at the 6-month follow-up. High positive correlations between both subscales were found at the 1-week and 6-month assessments[20] and at the 3-year follow-up measurement (r = .57 for noncarriers and r = .83 for carriers). These correlations were also reported by others, reflecting a single, general dimension of stress.[27-29] However, the opposed cubic courses of avoidance and the similar course of intrusion (Figures 1 and 2) may reflect qualitatively different trajectories of intrusion and avoidance over time, such as low intrusion—high avoidance or high intrusion—low avoidance.[1 27]

Intrusion and avoidance in noncarriers showed the similar course. Most noncarriers were still entangled in family issues regarding Huntington's disease, which may explain the increase in intrusion and avoidant thoughts about Huntington's disease in the long term. The decline in the first 6 months after disclosure may reflect the release from the personal risk to get Huntington's disease; thereafter it is apparently Huntington's disease in the family and guilt feelings that cause the specific distress.

Carriers had a different trajectory over time. The decrease in intrusion and the increase in avoidance at the 6-month assessment were significant with regard to change from baseline (p = .007), whereas after 3 years the reverse pattern approached significance (p = .073). This might indicate that carriers are frozen in avoidant states of mind regarding the implications of the disease in the first 6 months after disclosure of test results. Thereafter, carriers dose themselves with tolerable levels of intrusive thoughts so that effective processing of the personal meaning of Huntington's disease can proceed.[27] This is the nonpathological pattern according to Zilberg et al.[27] We have not observed pathological intensifications of reactions[30] to the test

results in the study group. Further investigation of the different patterns in carriers and noncarriers may uncover the dynamic interplay of intrusion and avoidance and may also indicate which stress patterns are associated with adjustment disorders.

The significant change at the 1-week follow-up assessment between carriers and noncarriers with regard to hopelessness was less at the 6-month follow-up and had disappeared at the 3-year measurement. This finding is in concordance with the clinical experience as reported in prior studies.[12 16] The relatively stable estimation of perspectives regarding their future underlines the assumption that carriers minimize the full impact of the test result on their personal future and the ramifications for their families. Given the finding that the intrusive feelings have increased and avoidant thoughts decreased after 3 years, we suggest that carriers may have succeeded in finding a balance between facing reality (and preparing for the future) and continuing their current life without full awareness of the future disease. This in line with Wiggins et al.[14] who have concluded that testing has maintained or even improved the psychological well-being of carriers. An unresolved question is how the foreknowledge of becoming a patient will affect carriers as they approach the impending onset of Huntington's disease.

The pattern of hopelessness over time in noncarriers also needs attention. Over the long term they had an unchanged outlook with regard to their future. Presumably, the test result has not brought the expected effect on their life perspective, which is how lack of relief has previously been described.[13 16] Contrary to their expectations, the favorable result has apparently not conferred new mental resources to make decisions or solve personal problems. This might explain the return to baseline levels of the intrusive and avoidant thoughts. Moreover, non-carriers may have realized that being identified as a noncarrier is not a release from the shadow of Huntington's disease in the family.

The second issue that was investigated in the current study concerned the comparison of the course of psychological responses in tested individuals and their partners. Partners of both groups did not differ at baseline. Quaid and Wesson[19] however, found that partners of prospective carriers were more distressed about their marriage at baseline than partners of prospective noncarriers, which might indicate that the group of partners of prospective carriers contained some individuals who had reasons to anticipate unfavorable test results because of early signs of Huntington's disease such as clumsiness or changes in mood. We also found no differences between the tested groups and the respective partner groups, which is different from the findings of Quaid and Wesson who reported that spouses were more depressed at baseline than individuals at risk.

The results reveal that, generally, partners showed similar patterns over the first 6-month follow-up compared with the tested individuals, which were sustained for the carriers—carrier partners group over the period that followed. Interestingly, noncarriers reported at the 3-year follow-up similar intrusion levels and slightly lower avoidant thoughts as in the pretest period, whereas their partners had significantly lower levels on both dimensions.

The better prospects of noncarrier partners reflect obviously the relief that Huntington's disease has disappeared from their life and that the future was now open for them, with the inclusion of planning a family. The different course of psychological distress has led to marital discord in some couples that can be explained by the partners' inability to appreciate the reactions in noncarriers.[16] Quaid and Wesson[19] have found that carrier couples were more distressed about their marriage than noncarrier couples at the follow-up assessments. However, they have analyzed the distress in partners as independent of the tested individuals. In the present study, the similar course of avoidant thoughts and hopelessness in tested individuals and partners have confirmed that their scores should not be treated as independent. The increase on all psychological variables in carrier partners differed significantly from the decrease in noncarrier partners over the 3-year follow-up— this finding emphasizes the completely different future prospects for either partner group. Further investigation is needed on the relationship of avoidance—intrusion patterns in marital couples and marital functioning.

Having children proved to be an additional stress factor for partners. Partners of prospective noncarriers with children were significantly more hopeless than those without children at baseline. Understandably, this effect disappeared after the test result. Partners of carriers who had children had significantly higher scores on all three variables at the 1-week follow-up than partners without children, and this difference sustained for avoidant thoughts and intrusive feelings over the 3-year period. Besides all of the problems with the future disease in the carrier, carrier partners with children have also the difficult task of informing the children about their risk and helping them cope with the problems raised by their at risk status. The threat that their own children may develop Huntington's disease as well is one of the most dramatic aspects of their life and may cause feelings of anxiety and hopelessness, but also feelings of resentment and hostility.[11 21]

The meaning of quadratic and cubic trends may seem difficult to understand for those who are unfamiliar with these statistical methods. We chose this approach to data analysis because the process of psychological responses is not merely a linear process.[31 32] The trends in this study have demonstrated that the psychological process of coping with being at risk, receiving test results, and facing new life perspectives is very complex. However, whether the patterns found in this study were real or were due to chance must be further evidenced by follow-up studies in other samples with other late-onset inherited disorders.

The major limitation of this study was the relatively small number of participants and, subsequently, the quarter of the initial study group that was lost to follow-up—as was also found in the Vancouver Study.[14] Systematic evaluation of this group is necessary for interpretation of the results. In addition, the study group was overrepresented by female individuals. Interaction effects with regard to gender were not found, perhaps because of small groups. This issue should be addressed in future studies when larger samples are available. Another bias may have been caused by a number of siblings in the study: Eleven individuals belonged to four

different families. The numbers were too small to investigate the possible effect on outcome, but this must be considered as a potentially strong bias in every study. Furthermore, the duration of marriage or relationship might mediate the psychological conditions in tested individuals. Some relationships were ended before test disclosure, others in the 3-year period after the test. Some individuals had started a new relationship; these partners were not involved in the study. The effects of these confounders were not investigated in the current study, as no complete data were available. As was suggested by Wiggins et al.,[14] the studied group may not be representative of the entire population at risk for Huntington's disease. Moreover, the results may have been biased by the extensive psychological attention the researchers had given the participants. An important limitation is that the data were obtained by means of self-report. The disadvantages of self-report data are well-known and include possible social desirability bias. Therefore, case studies conducted by individuals who are able to objectively observe tested individuals and marital functioning can improve the understanding of the observations that will consequently increase the clinical significance.[33] Yet, although the limitations of the study restrict the generalizability of the results, they generally are consistent with the findings of other groups.

After a decade of monogenic disorders, the current focus is on multifactorial disorders with more complex transmission patterns and a variety of therapeutic options for some disorders, but with no prospects of treatment for others. This development will have a tremendous impact on health care because people are offered new options that will influence their life perspectives— they are challenged to cope with these risks. The psychological impact of prediction of genetic diseases should be further studied with the emphasis on risk perception and on the ramifications for intimate relationships and the family system.

REFERENCES

1. Horowitz MJ, Wilner N, Alvarez W. Impact of event scale: A measure of subjective stress. *Psychosom Med* 1979;41:209-218.
2. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: The hopelessness scale. *J Consult Clin Psychol* 1974;42:861-865.
3. Beck AT. Hopelessness as a predictor of eventual suicide. In: Mann JJ, Stanley M, editors. *Psychology of suicidal behavior*. New York: Academy of Sciences, 1986:90-96.
4. Harper PS, ed. *Huntington's disease*. London: Saunders, 1991.
5. Roos RA, Vegter-van der Vlis M, Hermans J, Elshove HM, Moll AC, van de Kamp JJ, et al. Age at onset in Huntington's disease: effect of line of inheritance and patient's sex. *J Med Genet* 1991;28(8):515-519.
6. Huntington Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72:971-983.

7. Kessler S, Field T, Worth L, Mosbarger H. Attitudes of persons at risk for Huntington disease toward predictive testing. *Am J Med Genet* 1987;26:259-270.
8. Markel DS, Young AB, Penney JB. At risk persons' attitude toward presymptomatic and prenatal testing of Huntington disease in Michigan. *Am J Med Genet* 1987;26:295-305.
9. Meissen GJ, Berchek RL. Intended use of predictive testing by those at risk for Huntington disease. *Am J Med Genet* 1987;26:283-293.
10. Tibben A, Frets PG, Van De Kamp JJP, Niermeyer MF, Vegter-Van Der Vlis M, Roos RAC, et al. Presymptomatic DNA testing for HD: pretest attitudes and expectations of applicants and their partners in the Dutch program. *Am J Med Genet* 1993;48:10-16.
11. Evers-Kiebooms G, Swerts A, Van den Berghe H. Partners of Huntington patients: Implications of the disease and opinions about predictive testing and prenatal diagnosis. *Genet Couns* 1990;1(2):151-159.
12. Bloch M, Adam S, Wiggins S, Huggins M, Hayden MR. Predictive testing for Huntington disease in Canada: the experience of those receiving an increased risk. *Am J Med Genet* 1992;42:499-507.
13. Huggins M, Bloch M, Wiggins S, Adam S, Suchowersky O, Trew M, et al. Predictive testing for Huntington disease in Canada: adverse effects and unexpected results in those receiving a decreased risk. *Am J Med Genet* 1992;42:508-515.
14. Wiggins S, Whyte P, Huggins M, Adam S, Theilmann J, Bloch M, et al. The psychological consequences of predictive testing for Huntington's disease. *New Engl J Med* 1992;327(20):1401-1405.
15. Quaid KA. Presymptomatic testing for Huntington disease in the United States. *Am J Hum Genet* 1993;53(3):785-787.
16. Tibben A, Frets PG, van de Kamp JJ, Niermeijer MF, Vegtervan der Vlis M, Roos RA, et al. On attitudes and appreciation 6 months after predictive DNA testing for Huntington disease in the Dutch program. *Am J Med Genet* 1993;48(2):103-11.
17. Codori A-M, Brandt J. Psychological costs and benefits of predictive testing for Huntington's disease. *Am J Med Genet* 1994;54:174-184.
18. Tibben A, Duivenvoorden HJ, Niermeijer MF, Vegter-van der Vlis M, Roos RAC, Verhage F. Psychological effects of presymptomatic DNA testing for Huntington's disease in the Dutch program. *Psychosom Med* 1994;56(6):526-532.
19. Quaid KA, Wesson MK. Exploration of the effects of predictive testing for Huntington Disease on intimate relationships. *Am J Med Genet* 1995;57:46-51.
20. Tibben A, Duivenvoorden HJ, Vegter-van der Vlis M, Niermeijer MF, Frets pG, van de Kamp JJP, et al. Presymptomatic DNA testing for Huntington Disease: Identifying the need for psychological intervention. *Am J Med Genet* 1993;48:137-144.
21. Hans MB, Koeppen AH. Huntington's chorea: Its impact on the spouse. *J Nerv Ment Dis* 1980;168(4):209-214.

22. Kessler S. Forgotten person in the Huntington disease family. *Am J Med Genet* 1993;48(3):145-50.
23. Horowitz MJ, Field NP, Clasen CC. *Stress response syndromes and their treatment*. New York: Free Press, 1993.
24. Tibben A. What is knowledge but grieving? On the psychological effects of presymptomatic DNA-testing for Huntington's disease Unpublished doctoral dissertation, Erasmus University, Rotterdam, the Netherlands, 1993.
25. Skraastad MI, Verwest A, Bakker E, Vegter - van der Vlis M, van Leeuwen - Cornelisse I, Roos RAC, et al. Presymptomatic, prenatal and exclusion testing for Huntington disease using seven closely linked DNA markers. *Am J Med Genet* 1991;39:217-222.
26. Statistical package for the Social Sciences (program). 5.01 version. Chicago, 1993.
27. Zilberg NJ, Weis DS, Horowitz MJ. Impact of Event Scale: A cross-validation study and some empirical evidence supporting a conceptual model of stress response syndromes. *J Consult Clin Psychol* 1982;50(3):407-414.
28. Schwarzwald J, Solomon Z, Weisenberg M, Mikulincer M. Validation of the Impact of Event Scale for psychological sequelae of combat. *J Consult Clin Psychol* 1987;55(2):251-256.
29. Solomon Z. Psychological Sequelae of war: A 3-year prospective study of Israeli combat stress reaction casualties. *J Nerv Ment Dis* 1989;177(6):342-346.
30. Horowitz MJ, Bonanno GA, Holen A. Pathological grief: Diagnosis and explanation. *Psychosom Med* 1993;55:260-273.
31. Janis IL, Mahl GF, Kagan J, Holt RR. *Personality: Dynamics, development, and assessment*. New York: Harcourt, Brace & World, 1969.
32. Horowitz MJ. A model of mourning: Change in schemas of self and other. *J Am Psychoanal Assoc* 1990;38(2):297-324.
33. Shedler J, Mayman M, Manis M. The illusion of mental health. *Am Psychol* 1993;48(11):1117-31.

CHAPTER 3
-
Adverse effects of predictive testing for Huntington disease underestimated: Long term effects 7-10 years after the test.

Reinier Timman [1,2], Raymund Roos [1], Anneke Maat-Kievit [3], Aad Tibben [1,4]

[1] Leiden University Medical Center, Department of Neurology; [2] Erasmus University Medical Center Rotterdam, Department of Medical Psychology and Psychotherapy; [3] Erasmus University Medical Center Rotterdam, Department of Clinical Genetics; [4] Leiden University Medical Center, Department of Clinical Genetics, the Netherlands.
Health Psychol, 2004;23(2):189-197.

ABSTRACT

The 7-10 year psychological effects of presymptomatic testing for Huntington disease are described in 142 individuals and 104 partners. Questionnaires included the Beck Hopelessness Scale,[1] the Impact of Event Scale[2] and the General Health Questionnaire.[3] Carriers and their partners were more distressed immediately after the test result, although their outlooks improved somewhat in the 2-3 year posttest period. However, they became more pessimistic thereafter, when approaching the age of onset. Carriers, who were lost to follow-up after disclosure of test results, reported pretest more distress than did retained carriers. This demonstrates that studies that report few harmful effects, may have underestimated the real impact. Moreover, follow-up studies need to investigate time effects for longer than a few years.

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease, characterized by involuntary movements (chorea), progressive dementia, and affective disturbances.[4] Children of an affected parent are at 50% risk of inheriting the disease. A linkage-based test was developed in 1983.[5] The gene was identified in 1993,[6] which made a direct test for pre-symptomatic diagnosis possible. Because it was expected that people who received a high risk test result would develop severe adverse psychological consequences,[7-9] extensive psychological support was offered,[10] and world-wide follow-up studies were started.[11-13]

Effects of testing on identified carriers and noncarriers

In a study by Tibben et al.,[14] increased scores on feelings of hopelessness were found following high risk test results, and reduced scores were found for those who tested out as low risks. In both cases, the scores returned to baseline levels after 6 months. Unwanted intrusive thoughts about HD decreased in both groups after 6 months. Carriers showed an increase in denial-avoidance behavior, whereas noncarriers showed a clear decrease. A later follow-up study by Tibben, Timman, Bannink, and Duivenvoorden[15] showed that hopelessness scores remained stable after 3 years.

In general, past studies on the psychological effects of predictive testing for HD have revealed temporary effects on psychological measures taken, although no long-term adverse emotional consequences have been observed.[11-13] It has been concluded that tested individuals benefit psychologically from testing.[16] Carriers seemed to minimize the impact of the test results on their future.[17 18]

Effects of testing and parenthood on people at risk and their partners

HD imposes a considerable burden on the family, especially on the spouse. Tibben et al.[15] observed that partners of carriers followed the same course of distress as the carriers themselves. In addition, partners of carriers with children were significantly more distressed than those without offspring, whereas partners of noncarriers were significantly less distressed than noncarriers after 3 years, regardless of whether they had children. Codori et al.[19] observed that carriers without children were more hopeless than noncarriers without children throughout the 12 months of their investigation. In this respect, one can pose the question of how important children are as a determinant of distress, and whether there are other or more important determinants that will surface 4 to 7 years later.

The first goal of this study was to asses whether psychological effects of testing are mainly short-time effects and whether tested individuals and their partners benefit psychologically from testing in the long term, 7– 10 years after the disclosure of the test result. Second, we examined whether the course of the responses (as measured by intrusion, avoidance, and hopelessness) changed with the age of onset approaching for carriers. We hypothesized that the distress and hopelessness would show an increase

over the long term for identified carriers and their partners, and a decrease for noncarriers and their partners.

We finally address the issue of dropout, one of the vulnerabilities of long-term longitudinal studies. In course of time, participants are lost to follow-up due to mortality, moving to an unknown address, refusing to participate further, exclusion from the study because of early symptoms of HD, or due to other reasons. Dropout is never at random but systematic.[20]

METHOD

Subjects

Between October 1987 and October 1993, 209 at-risk individuals were offered an informative test result obtained by linkage analysis at the Clinical Genetics Center in Leiden, the Netherlands. individuals who came for the test were encouraged to be accompanied by their spouse or a close family member. Twenty-eight individuals at risk were tested before the start of the psychological follow-up study, of whom 18 were evaluated retrospectively.[21] The other 181 individuals were included at the start of this evaluation program and were accompanied by 134 spouses. A structured predictive testing procedure for HD was introduced in 1987 in Leiden.[17] The testing protocol followed the international guidelines,[22 23] with the inclusion of two pretest and up to five posttest counseling sessions. All participants gave their informed consent. The Medical Ethics Committee of Leiden University Medical Center approved the protocol. For inclusion in the longitudinal analyses, participants required to have participated in at least one of the pretest and one of the posttest counseling sessions. Ten individuals were excluded from further follow-up sessions when they were clinically diagnosed as having HD; the other individuals had not yet exhibited signs of HD and thus remained included in the study.

After identification of the mutation,[6] people who had had a linkage test with a residual risk of 1% to 9 % were informed about the mutation test. In addition, they were offered the mutation test and were requested to cooperate with the last follow-up of this study. Of those who had a mutation retest performed (30%), no risk reversals were revealed.[24]

Measures

At each counseling session, the Beck Hopelessness Scale (BHS), the Impact of Events Scale (IES), and the General Health Questionnaire (GHQ) were administered.

Hopelessness-future expectancies. The BHS is a reliable 20-item scale. Subjects are requested to indicate whether they agree with these items, resulting in a hopelessness score between 0 and 20.[1] A score of 9 or higher is a possible predictor of suicidal behavior.[25]

Huntington specific distress. The IES is a reliable 15-item, four-answer category, Likert-type self-report scale that can be linked to a certain disease or a distressing event, in this case HD.[2] It estimates the current degree of subjective impact, experienced as a result of HD. This subjective impact is

estimated on two dimensions: intrusion of unwanted ideas and thoughts into consciousness and avoidance of certain thoughts, feelings, or situations. The Intrusion subscale contains seven items, ranging in scores from 0 to 35, and the Avoidance subscale contains eight items, ranging in scores from 0 to 40.

General well-being. The GHQ-60 is a reliable estimator of psychopathological states, such as depression, anxiety, somatic complaints and social dysfunction.[3] A general score can be computed, with a range of 0 to 60.

Data analysis

In contrast to repeated measure analysis of variance, which is often used for longitudinal data, we used linear mixed models, using the PROC MIXED procedure in SAS.[26] This analysis method allows the use of incomplete cases. In these models, parameters can be random or fixed. A random intercept allows a different baseline measure. A random time parameter allows shorter or longer courses. Whether parameters should be random or fixed is determined by examining the covariance structure. First, a model is postulated with a saturated fixed part, including all interaction effects between relevant independent variables, and a large-as-possible random part with an unstructured covariance matrix. Then, the covariance model is simplified step by step without significant loss of information. This loss of information is estimated with the restricted maximum likelihood (REML) test. If a simpler model is not significantly different, that is, the difference in the maximum likelihood estimations is not significant, then the model is assumed to be more parsimonious than the more elaborate model, without evident loss of information.

Hereafter, the fixed part of the model is simplified by using the ordinary likelihood ratio test until a model is obtained that is as parsimonious as possible. The final model can include regression loadings on relevant independent variables, such as gender, age, DNA-test outcome, and time. Linear, quadratic, cubic, and higher order time effects can be revealed. For a linear effect at least 2 time points are needed, 3 time points for a quadratic effect, 4 for a cubic effect, and so forth. The resulting regression parameters can be used in a graph to make the significant effects visible, as an aid to interpretation.

RESULTS

Description of the sample, participants and nonparticipants

Of the 181 test applicants who were included at the start of the study, 142 (78%) returned for follow-up and additional counseling and hence were included in the longitudinal analyses. Of 134 partners, 104 (78%) were included. This sample for longitudinal analyses was composed of 81 noncarriers and 61 carriers, accompanied by 59 and 45 partners respectively (Table 1). No significant differences in age were found between carriers, noncarriers and partners. Note that there is a trend that gene

carriers are older than noncarriers, $F_{(54, 1)} = 3.73$, $p = .06$. This is in contrast to other studies,[19 27] in which the group of carriers has a lower mean age, because symptomatic -and thus older- carriers are excluded from the study. In our study, we have information on 9 carriers with a mean age of 34.9 years at baseline, who were excluded because they had HD symptoms. However, we have also information on a group of 7 carriers who returned for prenatal testing but who dropped out of the study. The dropout of this young group of carriers (mean age = 24.7 years) may be an important reason for the high mean age of the remaining group of carriers.

At the last time point, 56 (31%) carriers and noncarriers participated in the study (Table 1). At Time Point 5 (1½ years after the test) fewer respondents (n = 40, 22%) participated. The project was temporarily called off at the time, with the consequence that only the first half of the consecutively tested participants (those who had the test before October 1990) were contacted for follow-up. This selection can be considered random. In previous analyses this time-point was unusable because we had used repeated measure multivariate analyses of variance (MANOVAs). For this study, the data of this time-point were added to the database to make use of as much information as possible.

Thirty-nine of 181 individuals at risk who had come for the predictive test and of whom we had pretest measures did not return for follow-up and additional counseling. No significant differences regarding gender, marital status, having children, and education were found between participants and

Table 1. *Number, mean age (in years), and gender ratio of participants in the follow-up study at different time-points*

	At risk						Partners					
	Gender [a]		Non-carriers		Carriers		Non-carriers		Carriers		Total	
Time point	Men	Women	*n*	age *(M)*	*n*	age *(M)*	*n*	age *(M)*	*n*	age *(M)*	*n*	age *(M)*
Intake	66	102	95	32	73	33	73	34	53	34	294	33
Blood taking	54	86	75	33	65	33	56	34	47	33	243	34
Test disclosure	52	83	78	33	57	34	57	35	42	34	234	34
½ year	26	50	42	33	34	32	32	33	21	32	129	33
1½ years	12	28	27	35	13	29	21	36	6	33	67	34
3 years	14	36	30	35	20	34	23	35	14	34	87	35
7-10 years	18	38	32	39	24	44	21	43	20	45	97	43
All participants at baseline	66	107	98	32	75	33	74	33	55	33	302	33

[a] There was no significant difference between time points, $\chi^2_{(6)} = 3.93$, $p = .69$.

non-participants (Table 2). However, individuals who turned out to be carriers and who did not return for follow-up scored at pretest significantly higher on hopelessness, intrusion, avoidance, and lower general well-being than did individuals who turned out to be carriers and who did return for follow-up. No significant pretest differences in hopelessness, intrusion, avoidance, and general well-being were found between noncarriers who returned for follow-up and noncarriers who did not.

Reliability coefficients of the measures turned out to be satisfactory: Cronbach's alpha was .82 for the BHS, .87 for the Intrusion sub-scale of the IES, .83 for the Avoidance sub-scale, and .95 for the GHQ. A large correlation between the intrusion and avoidance sub-scales of the IES was found: r = .71 over all time points. The BHS has a very skewed and peaked distribution because many respondents have scores at the lower end of the scale. Therefore, a log transformation was performed on the BHS scores. In addition, because the first time intervals were much shorter than the later time intervals, the square root of time was used for analyses.

Table 2. *Differences in baseline characteristics of people who did and did not return for follow-up, for people who turned out to be a noncarrier or a carrier*

	Noncarriers					Carriers				
Baseline	Retained (*n* = 81)		Dropouts (*n* = 21)			Retained (*n* = 61)		Dropouts (*n* = 18)		
characteristic	*n*	%	*n*	%	*p* [a]	*n*	%	*n*	%	*p* [a]
Gender					.21					.10
Men	32	40	11	52		22	36	3	17	
Women	49	60	10	48		39	64	15	83	
Marital status [b]					.58					.28
Single	28	35	6	33		15	25	6	35	
Married [c]	53	65	12	67		46	75	11	65	
Children [d]					.56					.45
No children	52	65	12	67		29	48	9	53	
One or more	28	35	6	33		32	52	8	47	
Education [e]					.20					.40
< vocational	42	53	7	39		36	60	9	53	
≥ vocational	37	47	11	61		24	40	8	47	

	Noncarriers				Carriers			
	Retained *(M)*	Dropouts *(M)*	$F_{(1,94)}$	*p*	Retained *(M)*	Dropouts *(M)*	$F_{(1,94)}$	*p*
Age (years)	32.4	28.2	3.27	.07	33.6	32.6	0.08	.77
BHS	4.6	5.2	0.60	.44	5.2	7.6	5.86	.02
Intrusion	10.7	11.9	0.73	.40	12.0	17.9	11.61	.00
Avoidance	9.8	8.9	0.44	.51	9.9	16.2	8.05	.01
GHQ-60	9.4	11.2	0.33	.57	10.2	18.2	7.50	.01

Note. BHS = Beck Hopelessness Scale; GHQ-60 = General Health Questionnaire.
[a] Significance was determined with Fisher's exact test. [b] For 4 persons, no data on marital status were available. [c] This included participants in common-law marriages. [d] At intake, for 4 persons no data on number of children were available. [e] For 7 persons no data on education were available.

The final model

There were two pretest measures: at intake and about 3-6 weeks later when blood was taken. No significant differences were found between scores at intake and scores at blood sampling in participants who filled out questionnaires on both occasions. Therefore, these measures were taken together as one baseline measure. If a respondent had filled out questionnaires at intake as well as at blood taking, the mean of these two was used; otherwise, either the intake or the blood taking measure was used as the pretest measure. This resulted in more parsimonious models.

Using the restricted maximum likelihood function (REML),[26] it appeared that models with time as a fixed parameter were to be preferred over models with time as a random parameter, $\chi^2_{(3, N = 492)} = 1037.2$ versus $\chi^2_{(1, N = 492)} = 1032.3$, $p = .09$). This means that there was no indication that there were differences in the time course by which people cope with the test results. The intercept was maintained as a random parameter, which means that the model was better if it was taken into account that individuals differ at baseline. We do not report on models with the GHQ as an outcome variable, because no significant test-outcome interaction effects remained in these models.

Hopelessness

Because a considerable proportion (27%) of at-risk individuals did not have a partner, it was not possible to use people at risk and partners in combined analyses. For establishing the final model, we used the at-risk sample. Although for partners a somewhat more parsimonious model was appropriate because there were no interactions with gender, we estimated the parameters of the models equivalent to the solution for participants at risk, for means of comparability.

Table 3. *Beck Hopelessness Scale (BHS) parameter estimates, and standard errors for the final at-risk and partner models*

	At risk			Partners		
Effect	Estimate	*SE*	*p*	Estimate	*SE*	*p*
Intercept	1.44	0.22	.0001	1.24	0.32	.0002
			Main effects			
DNA	- 0.03	0.30	.92	- 0.44	0.54	.42
Gender	- 0.01	0.32	.99	- 0.06	0.42	.90
Age	0.01	0.01	.35	0.01	0.01	.14
Linear time trend	- 0.47	0.12	.0001	- 0.58	0.14	.0001
Quadratic time trend	0.21	0.07	.01	0.28	0.08	.001
Cubic time trend	- 0.03	0.01	.02	- 0.05	0.02	.003
Quaternary time trend	0.002	0.001	.03	0.002	0.001	.004
			Interaction effects			
DNA X gender	- 1.12	0.51	.03	0.12	0.67	.86
DNA X age	0.003	0.01	.69	0.01	0.02	.47
Gender X age	- 0.003	0.01	.77	- 0.01	0.01	.66
DNA X linear time trend	0.85	0.19	.0001	0.86	0.23	.0002
DNA X quadratic time trend	- 0.41	0.12	.001	- 0.41	0.15	.01
DNA X cubic time trend	0.07	0.02	.003	0.07	0.03	.01
DNA X quaternary time trend	- 0.003	0.01	.01	- 0.004	0.001	.01
DNA X gender X age	0.03	0.01	.04	0.001	0.02	.97

Note. Regression coefficients are based on the logarithm of the BHS and on the square root of time in months. Proportion of variance accounted for was in the at risk solution: .46, and .53 in the partner solution.

No significant main effects on hopelessness were found for test result, gender, and age (Table 3). Significant time effects were found for the whole

group: carriers, noncarriers and their respective partners. The weak test outcome-gender interaction effect was caused by female carriers who had higher hopelessness scores than did male carriers throughout the study. Among noncarriers, no gender differences were found. The test outcome-gender-age interaction effect reflected a larger correlation between age and BHS for carriers, especially male carriers, than for noncarriers. Linear, quadratic, cubic, and quaternary interaction effects of test outcome with time were found for at-risk people and their partners. One week after the test outcome, carriers reported more hopelessness (Figure 1). After that, the level of hopelessness decreased dramatically to a lowest level 1½ year after the test, and then increased again. Seven to 10 years after the test, hopelessness level was higher than at baseline.

Partners followed the same pattern. However, noncarriers reported extremely reduced feelings of hopelessness after disclosure of the test results; levels return towards baseline after that. Their partners followed the same pattern.

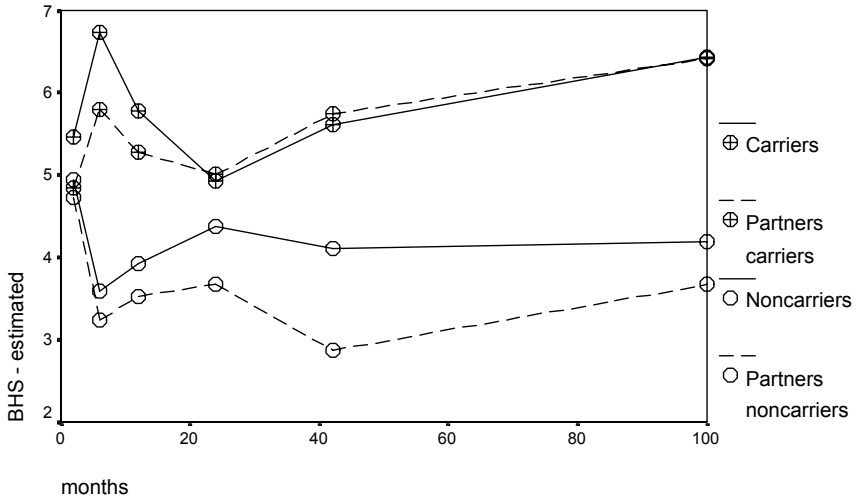

Figure 1. *Hopelessness for carriers, noncarriers and partners based on final model parameters*

Intrusion

Female carriers and noncarriers reported more intrusive thoughts than did men. For their partners, no significant gender effect was found (Table 4). Older participants, those tested, as well as their partners, reported more intrusive thoughts. Significant main effects over time were found for intrusion. Generally, participants scored higher 1
week after the test results; thereafter, scores decreased to a lowest level 1½ years after the test disclosure, returned to baseline 3 years after the test, and decreased eventually 7-10 years later (Figure 2). The pattern of the significant interaction effects between test outcome and time was similar

to the more significant avoidance pattern described below. The linear time-test result interaction effect for partners means that partners of carriers had higher intrusion scores after the test than did partners of noncarriers.

Table 4. *Intrusion parameter estimates, and standard errors for the final at-risk and partner models*

	At risk			Partners		
Effect	Estimate	*SE*	*p*	Estimate	*SE*	*p*
Intercept	8.59	1.88	.0001	3.16	2.20	.16
			Main effects			
DNA	0.85	1.24	.50	0.60	1.26	.63
Gender	- 4.03	1.08	.0001	- 1.23	1.09	.26
Age	0.11	0.05	.02	0.17	0.05	.002
Linear time trend	4.29	1.26	.001	4.73	1.27	.0002
Quadratic time trend	- 3.26	0.75	.0001	- 3.30	0.75	.0001
Cubic time trend	0.64	0.14	.0001	0.60	0.14	.0001
Quaternary time trend	- 0.04	0.01	.0001	- 0.03	0.01	.0001
			Interaction effects			
DNA X linear time trend	1.93	0.94	.04	2.10	0.93	.02
DNA X quadratic time trend	- 0.54	0.28	.05	- 0.38	0.28	.17
DNA X cubic time trend	0.04	0.02	.06	0.02	0.02	.32

Note. Regression coefficients are based on the square root of time in months. Proportion of variance accounted for in at was .57 in the at risk solution, and .60 in the partner solution.

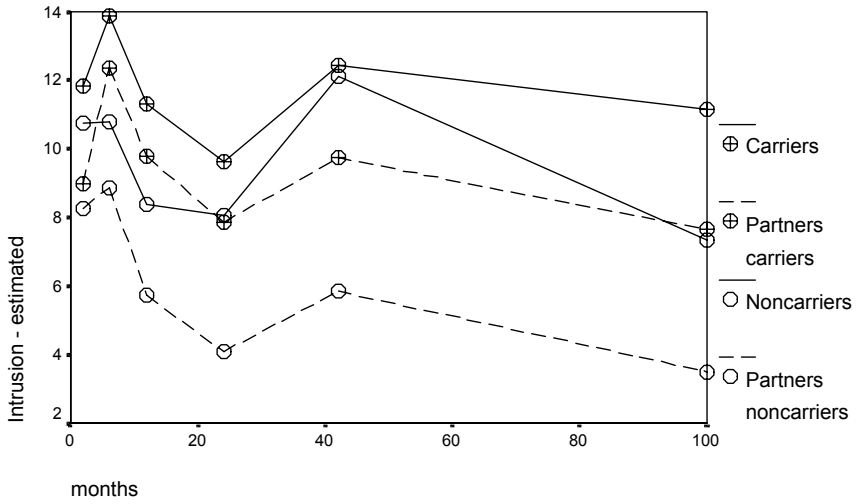

Figure 2. *Intrusion for carriers, noncarriers and partners based on final model parameters*

Table 5. *Avoidance parameter estimates and standard errors for the final at risk and partner models*

	At risk			Partners		
Effect	Estimate	*SE*	*p*	Estimate	*SE*	*p*
Intercept	7.67	2.09	.0004	5.54	2.37	.02
		Main effects				
DNA	- 0.40	1.39	.77	0.34	1.38	.81
Gender	- 2.43	1.19	.04	- 0.51	1.69	.66
Age	0.10	0.06	.07	0.09	0.06	.14
Linear time trend	1.84	1.43	.20	2.66	1.47	.07
Quadratic time trend	- 1.81	0.85	.03	- 2.21	0.87	.01
Cubic time trend	0.39	0.16	.01	0.41	0.16	.01
Quaternary time trend	- 0.02	0.01	.01	- 0.02	0.01	.01
		Interaction effects				
DNA X linear time trend	3.33	1.07	.002	0.84	1.07	.43
DNA X quadratic time trend	- 0.91	0.32	.004	0.12	0.32	.71
DNA X cubic time trend	0.06	0.02	.007	- 0.02	0.02	.45

Note. Time trend regression coefficients are based on the square root of time in months. Proportion of variance accounted for was .55 in the at risk solution and .55 in the partner solution.

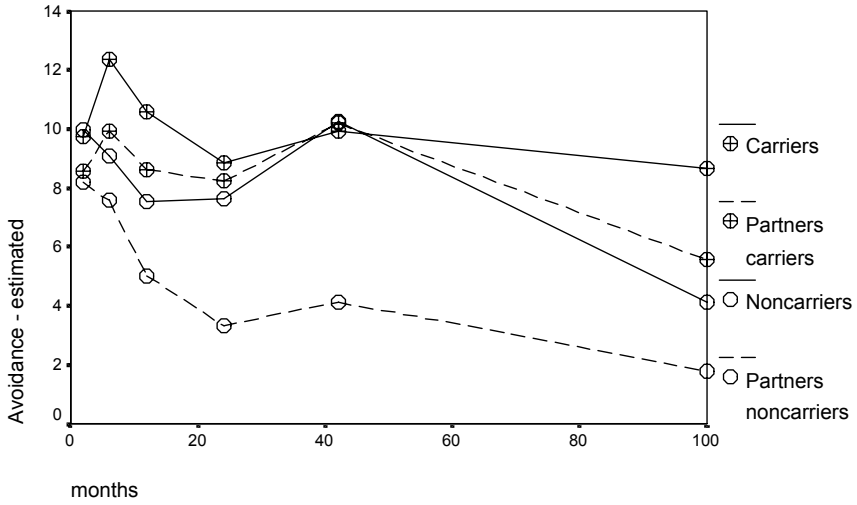

Figure 3. *Avoidance for carriers, noncarriers and partners based on final model parameters*

Avoidance-denial

Female carriers and noncarriers also reported more avoidance behavior than did men; there was no such difference among partners. About the same significant main time effects were found for avoidance as for intrusion (Table 5). In general, participants score higher 1 week after the test

outcome. The scores decreased to a lowest level 1½ years after the test outcome, rose again 3 years after the test, and decreased eventually 7-10 years after the test (Figure 3). Carriers reported more avoidance behavior 1 week after the test outcome than did noncarriers. One and a half years later this difference disappeared, but after 7-10 years noncarriers again had lower avoidance scores than carriers.

Effects of parenthood on people at risk and their partners

Initially, parenthood was included in the regression models. However, as parenthood is highly related with age (mean age of at risk parents = 40.1 years, mean age of people without children = 26.5 years, $F_{(1, 188)} = 163$, Cohen's $d = 1.83$, $p = .00$), problems of multicollinearity arose. Multicollinearity in regression analysis makes it impossible to distinguish which independent variable explains the variance in the dependent variable. If the shared variance is large, only a small part of the non-shared variance of the dependent variables can be allocated. One of the solutions to this problem is to remove the collineated independent variable with the weakest predictive qualities. Comparing a model that includes having children with a model that includes age, the fit measure is in favor of the model with age (at-risk model for BHS: $\chi^2_{(16, N = 492)} = 633.8$ vs. $\chi^2_{(16, N = 492)} = 645.1$). Consequently, parenthood is not included as a variable in the model.

DISCUSSION

In general, few harmful effects of predictive testing for HD have been reported in previous studies,[11-13] which led to the suggestion that tested individuals have benefited from testing.[16] This study, however, demonstrates that such a conclusion must be made with caution. Test candidates who reported less hope for the future, had more intrusive thoughts, reported more avoidance reactions, and had a worse sense of well-being at pretest returned significantly less often for follow-up and for additional counseling after they received an unfavorable test result than did distressed people who received a favorable test outcome. Intrusive thoughts are, and to a lesser extent avoidance behavior is, more frequent directly after the test and gradually become less frequent in course of time - this is in accordance with the findings of Horowitz et al.[28] There is a temporal peak a few years after the test. We found different patterns of avoidance behavior and intrusive thoughts in carriers and noncarriers. Noncarriers reported less avoidance and intrusion shortly after the test, and although they also had a maximum, or peak in reporting of avoidance and intrusion, after a few years, they reported less avoidance and intrusion in the long run. It can be inferred that the test did not change the level of intrusion and avoidance for carriers eventually, but it revealed that noncarriers benefited from the test in this respect. Some carriers were lost to follow-up after they were diagnosed with HD. They reacted to the diagnosis with severe depression and suicidal behavior, although they had previously coped well, as was personally communicated by their partners or relatives.[15] In addition, we speculate that individuals who had pessimistic future expectancies, had many intrusive

thoughts, reported much avoidance behavior, and had a worse sense of well-being may have reacted with extreme avoidance behavior and denial to an unfavorable test outcome. This reaction was also directed at everything that is associated with testing, including the messengers of the bad news (geneticists) and their associates (psychologists-researchers). Psychological functioning in the past has been regarded as the best predictor of psychological functioning.[29] If one assumes that the effect of an unfavorable test outcome has the same effect on these people as on the people in our study group, there is cause to be concerned about the level of psychological functioning in these people.

The sample dropout in this and other studies was not random. Therefore dropouts need to be carefully examined. Tibben et al.[15] studied differences between participants and those lost to follow-up and found no differences. However, they did not distinguish between identified carriers and noncarriers. A serious problem in long-term clinical follow-up studies is the dropout over time. The longer a follow-up study is maintained, the more people will drop out of the study. After a number of years a dropout rate of 40% to 60% is not uncommon.[20] The dropout rate after 10 years in this study is 69%. A relatively high proportion is expected to drop out because of the onset and clinical diagnosis of HD. Because of this selective dropout, the mean age of the group of carriers is lower than the mean age of the group of noncarriers in some other studies.[19 27] In this study, no significant difference in age is found. This discrepancy can be explained by the higher age of onset as established in the Dutch study group.[30 31] Because the age of onset is established as about 10 years higher in the Netherlands, this selective dropout effect is much weaker in our study.

From a dropout analysis, differences between dropouts and follow-up participants can be made, but results must be regarded with caution, in particular when data are not missing at random.[32] In this study, missing data were not random at all, but dependent on outcome (e.g., BHS) and input (test outcome) measures. Missing data are not only responsible for loss of information, but they bias the findings and interpretations.[26] The use of linear mixed models is an advantage over repeated measure MANOVA for analyzing incomplete cases, but there is, up to now, no method to compensate for dropout immediately after disclosure of a DNA test result. The only way to cope with this problem is to try to find ways to improve the participation of individuals and their partners. Another reason to reconsider former conclusions that predictive testing for HD does not have harmful consequences in the long run[16] is that feelings of hopelessness rose again for carriers, 7-10 years after the test outcome. Feelings of hopelessness in carriers were increased immediately after the test result, reduced thereafter, but eventually rose again. For carriers themselves, this effect could have been caused by the disease itself. Although in principle participants who received a clinical diagnosis of HD were excluded from the follow-up, it is difficult to determine the exact point at which symptoms emerge. No formal neurological and neuropsychological examinations were performed. Nevertheless, 10 persons showed signs of HD and were excluded from further follow-up analyses. A high hopelessness score may be suggestive of

the first symptoms. This cannot hold for the partners, however, and they have similar hopelessness scores 7-10 years after the test. For this reason it is likely that the test outcome, the approaching age of onset, the onset of HD in relatives, loss experiences, and so forth are responsible for their enhanced feelings of hopelessness, Because the mean age of carriers at the last measurement was 45 years (range 27-73), many of these participants will probably develop HD in the near future, because the mean age of onset is 47 years in the Dutch cohort.[31]

Follow-up studies on predictive testing and the reviews have not comprehensively reported on the issue of dropouts.[13 33] Hence, we would suggest that other groups also have a close look at their data over time, with the inclusion of those lost to follow-up, in order to better understand the well-being of all who were involved in predictive testing programs.

Testing for fatal inherited diseases creates a long term, life long stress reflected by gradually increasing levels of hopelessness as the onset of the disease approaches. This pattern may have implications for follow-up of cases. Increased avoidance behaviors may signal difficulties in returning to see those who performed the test and may warrant instituting alternative sources of follow-up care.

ACKNOWLEDGEMENTS

We thank Mrs. Vicky Kleinman for her corrections on our use of the English language.

REFERENCES

1. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: The hopelessness scale. *J Consult Clin Psychol* 1974;42:861-865.
2. Horowitz MJ, Wilner N, Alvarez W. Impact of event scale: A measure of subjective stress. *Psychosom Med* 1979;41:209-218.
3. Goldberg DP. *The detection of psychiatric illness by questionnaire*. London: Oxford University Press, 1972.
4. Harper PS, ed. *Huntington's disease*. London: Saunders, 1996.
5. Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, et al. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 1983;306(5940):234-238.
6. Huntington Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72:971-983.
7. Kessler S, Field T, Worth L, Mosbarger H. Attitudes of persons at risk for Huntington disease toward predictive testing. *Am J Med Genet* 1987;26:259-270.
8. Markel DS, Young AB, Penney JB. At risk persons' attitude toward presymptomatic and prenatal testing of Huntington disease in Michigan. *Am J Med Genet* 1987;26:295-305.
9. Meissen GJ, Berchek RL. Intended use of predictive testing by those at risk for Huntington disease. *Am J Med Genet* 1987;26:283-293.

10. Tibben A. *What is knowledge but grieving? On the psychological effects of presymptomatic DNA-testing for Huntington's disease* Unpublished doctoral dissertation, Erasmus University, Rotterdam, the Netherlands, 1993.
11. Broadstock M, Michie S, Marteau TM. The psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet* 2000;8(10):731-738.
12. Meiser B, Dunn S. Psychological impact of genetic testing for Huntington disease: An update of the literature. *J Neurol Neurosur Ps* 2000;69(5):574-578.
13. Duisterhof M, Trijsburg RW, Niermeijer MF, Roos RAC, Tibben A. Psychological studies on Huntington's disease: Making up the balance. *J Med Genet* 2001;38:852-861.
14. Tibben A, Duivenvoorden HJ, Niermeijer MF, Vegter-van der Vlis M, Roos RAC, Verhage F. Psychological effects of presymptomatic DNA testing for Huntington's disease in the Dutch program. *Psychosom Med* 1994;56(6):526-532.
15. Tibben A, Timman R, Bannink EC, Duivenvoorden HJ. Three year follow up after presymptomatic testing for Huntington's disease in tested individuals and partners. *Health Psychol* 1997;16(1):20-35.
16. Bundey S. Few psychological consequences of presymptomatic testing for Huntington disease. *Lancet* 1997;349(9044):4.
17. Tibben A, Frets PG, Van De Kamp JJP, Niermeyer MF, Vegter-Van Der Vlis M, Roos RAC, et al. Presymptomatic DNA testing for HD: pretest attitudes and expectations of applicants and their partners in the Dutch program. *Am J Med Genet* 1993;48:10-16.
18. Quaid KA, Wesson MK. Exploration of the effects of predictive testing for Huntington Disease on intimate relationships. *Am J Med Genet* 1995;57:46-51.
19. Codori A-M, Slavney PR, Young C, Miglioretti DL, Brandt J. Predictors of psychological adjustment to genetic testing for Huntington's disease. *Health Psychol* 1997;16(1):36-50.
20. Bijleveld CCJH, van der Kamp LT, Mooijaart A, van der Kloot WA, van der Leeden R, van der Burg E, eds. *Longitudinal data analysis: Designs, models and methods*. London: Sage, 1999.
21. Tibben A, Vegter - van der Vlis M, Skraastad MI, Frets PG, Van de Kamp JJP, Niermeijer MF, et al. DNA-testing for Huntington's disease in the Netherlands; a retrospective study on psychosocial effects. *Am J Med Genet* 1992;44:94-99.
22. International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea. Ethical issues policy statement on Huntington's disease molecular genetics predictive test. *J Med Genet* 1990;27:34-38.
23. International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. *Neurology* 1994;44(8):1533-1536.

24. Timman R, Maat-Kievit A, Brouwer-DudokdeWit C, Zoeteweij M, Breuning MH, Tibben A. Testing the test - why pursue a better test for Huntington disease? *Am J Med Genet* 2003;117B:79-85.
25. Beck AT, Brown G, Steer RA. Prediction of eventual suicide in psychiatric inpatients by clinical ratings of hopelessness. *J Consult Clin Psychol* 1989;57(2):309-10.
26. Verbeke G, Molenberghs G, eds. *Linear mixed models in practice - A SAS oriented approach*. New York: Springer, 1997.
27. Lawson K, Wiggins S, Green T, Adam S, Bloch M, Hayden M, et al. Adverse psychological events occurring in the first year after predictive testing for Huntington's disease. *J Med Genet* 1996;3:856-862.
28. Horowitz MJ, Field NP, Zanko A, Donnelly EF, Epstein C, Longo F. Psychological impact of news of genetic risk for Huntington disease. *Am J Med Genet* 2001;103(3):188-192.
29. Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cassiman JJ, Cloostermans T, Demyttenaere K, et al. Prediction of psychological functioning one year after the predictive test for Huntington's disease and impact of the test result on reproductive decision making. *J Med Genet* 1996;33(9):737-743.
30. Brinkman RR, Mezei MM, Theilmann J, Almqvist E, Hayden MR. The likelihood of being affected with Huntington disease by a particular age, for a specific CAG repeat. *Am J Hum Genet* 1997;60:1202-1210.
31. Maat-Kievit A, Losekoot M, Zwinderman K, Vegter - van der Vlis M, Belfroid R, Lopez F, et al. Predictability of age at onset in Huntington disease in the Dutch population. *Medicine* 2002;81(4):251-259.
32. Little RJA, Rubin DB. *Statistical analysis with missing data*. New York: John Wiley and Sons, 1987.
33. Meiser B, Gleeson MA, Tucker KM. Psychological impact of genetic testing for adult-onset disorders. An update for clinicians. *Med J Australia* 2000;172(3):126-129.

CHAPTER 4
-
Methodology in longitudinal studies on effects of predictive DNA-testing for late onset disorders: A review.

Reinier Timman [1,2], Theo Stijnen [3], Aad Tibben [1,4]

[1] Leiden University Medical Center, Department of Neurology; [2] Erasmus University Medical Center Rotterdam, Department of Medical Psychology and Psychotherapy; [3] Erasmus University Medical Center Rotterdam, Department Epidemiology; [4] Leiden University Medical Center, Department of Clinical Genetics, the Netherlands.
J Med Genet, 2004;41:e100.

ABSTRACT

In the last two decades predictive testing programs have become available for various hereditary diseases, often accompanied by follow-up studies on the psychological effects of test outcomes. The aim of this systematic literature review is to describe and evaluate the statistical methods that were used in these follow-up studies. A literature search revealed 40 longitudinal quantitative studies that met the selection criteria for the review. Fifteen studies (38%) applied adequate statistical methods. The majority, 25 studies, applied less suitable statistical techniques. Nine studies (23%) did not report on dropout rate, and 18 studies provided no characteristics of the dropouts. Thirteen out of 22 studies that should have provided data on missing values, actually reported on missing values. It is concluded that many studies could have yielded more and better results if more appropriate methodology had been used.

INTRODUCTION

Fifteen years ago, predictive genetic testing became available for hereditary diseases with onset later in life. Since then, quantitative and qualitative psychological follow-up studies have shown that predictive testing offers several benefits. Although most psychological research on genetic testing has focused on the tests for Huntington's disease (HD) and the BRCA1 and BRCA2 mutations, clinical experience has provided evidence that the findings can be extrapolated to other diseases with similar inheritance patterns. Research included the characteristics of tested individuals, why they make certain choices, their understanding of the information conveyed by the test, and how they adjust after the test results. Generally, people are able to make informed decisions and they can cope with the test results. However, little is known about those who did not apply for predictive testing, or those who withdrew from the follow-up studies.[1] The latter individuals who drop out of studies may bias the findings. Obviously, careful statistical modelling is required to provide reliable conclusions, but also to make optimal use of the data. This has led to growing interest in the methodological quality of the studies. Although sophisticated software enables almost everyone to carry out the most exotic of statistical and epidemiological analyses, the methodological implications are too often incompletely understood.[2] This review aims to investigate the statistical methods used in the studies of psychological effects of DNA testing for genetic diseases.

METHODS

Search methods and inclusion criteria

First, the reviews of Broadstock et al.,[3] Meiser & Dunn[4] and Duisterhof et al.[5] provided insight into the studies that have been published. In addition, we used the databases MEDLINE and PsycLIT from 1988 onwards. The key words used for the searches were: Huntington* disease, HBOC, BRCA*, FAP, familial adenomatous polyposis, HNPCC, colon cancer, SCA or spinocerebellar ataxia.

Follow-up studies encompass the prediction of psychological adjustment or the course of adjustment over time. Firstly, studies are included if they analyse quantified measures statistically. Secondly, studies should have investigated the psychological effects of a genetic test outcome for hereditary diseases. Thirdly, studies should have a longitudinal, not a cross-sectional or retrospective design.

Categorisation strategy for longitudinal research methods

This review categorises and discusses articles according to the longitudinal methods that are used. Methods that could be valuable for longitudinal research such as structural equation models were not observed and hence are not discussed. For a more complete overview of longitudinal research

we refer to Bijleveld et al.[6] Statistical methods can be classified as less adequate for two reasons. First, when the measurement level of the variable does not correspond with the level that is required for the method that is used. Second, when the study includes more than three waves, but the method used is only suitable for two waves at most. We distinguished in this review five issues of interest: (1) the measurement level of the variables, (2) the number of measurement moments (waves), (3) dropout handling, (4) missing value handling, and (5) the groups and subgroups that are studied. For classifying the studies we considered the measurement level (continuous or discrete) and the number of waves (two wave or multiple wave studies).

A longitudinal effect study must contain a pre-test baseline measure, and one or more post-test measures. Depending on the number of waves, several effects can emerge over the course of time. With two waves, a linear effect can be found. With multiple waves a quadratic effect can be found, which implies that the linear effect between baseline and first post-test follow-up is not continued at a later follow-up. In studies with more than three waves, cubic effects can be found, analogous to a third power polynomial. We will categorise firstly according to measurement level: continuous and discrete; and secondly to longitudinal capabilities: higher order time effects, only linear time effects, and no time effects.

Dropout analyses and reporting

Dropout, caused by subjects who do not return for follow-up measurements, is a serious problem in virtually all longitudinal research. Dropout can invalidate the findings of a study when dropouts have characteristics or psychological outcomes different from the persons who remain in the study.

Missing value handling and reporting

Related to the dropout problem, but different in nature, is the handling of missing measurement points. Dropouts are subjects who participated at the start of the study, but do not return for follow-up after a certain time-point, for instance after the disclosure of a test result. We refer to missing values when subjects did not complete questionnaires at a certain time point, but did return for follow-up at other time points. It should be noted that this problem emerges only in longitudinal studies with multiple waves.

RESULTS

The search was carried out in November 2003. The first search resulted in 41840 references. This search was then combined with the keywords: genetic* and psychol*, which decreased the number of references to 585. From the abstracts it was concluded that 86 of these could be useful for this study.

Table 1. *Studies categorized by measurement level and number of waves, diseases, psychological outcome variables and statistical methods*

Study	Disease †	Outcome variables ‡	Statistical method	§
Continuous variables, more than two waves				
Codori (1997) [60]	HD	BDI, BHS	GLMM	+
Meiser (2002) [82]	BRCA	IES, BDI, STAI, MBSS	GLMM	+
Codori (2003) [85]	FAP	SCL-90, BDI	GLMM	+
Almqvist (2003) [84]	HD	SCL-90, BDI, GWB	GLMM	~
Timman (2004) [1]	HD	IES, BHS	GLMM	+
Wiggins (1992) [51]	HD	SCL-90, BDI, GWB	Repeated measures MANOVA	~
Tibben (1994) [52]	HD	IES, BHS, GHQ	Repeated measures MANOVA	+
Campodonico (1996) [54]	HD	SCL-90, BDI, WAIS-R, HVLT, SCWT, WCST, QNE	Repeated measures ANOVA	~
Tibben (1997) [64]	HD	IES, BHS	Repeated measures MANOVA	+
DudokdeWit (1998) [65]	HD, FAP, HBOC	IES	Repeated measures MANOVA	+
Aktan-Collan (2001) [75]	HNPCC	STAI, IAS	Repeated measures ANOVA	~
Lodder (2002) [81]	BRCA	IES, SCL-90, HADS, BIS	Repeated measures ANOVA	+
Decruyenaere (2003) [86]	HD	STAI, BDI, SCL-90, IES, HOS, MMPI	Repeated measures ANOVA	~
Tercyak (2001) [79]	BRCA	STAI	Regression	~
Schwartz (2002) [83]	BRCA	IES, HSCL	Regression, ANOVA	~
Decruyenaere (1996) [56]	HD	STAI, BDI, MMPI, UCL	Paired t-test, regression	~
Dorval (2000) [71]	BRCA-LF	SCL-90, BSI-53	Paired t-test, regression	~
Friedman (1999) [68]	BRCA	IES, POMS-SF	Logistic regression	~
Oostrom (2003) [87]	BRCA	HADS, IES, CWS, ODCFS	Logistic regression	~
Horowitz (2001) [76]	HD	IES, BDI	ANCOVA	~
Brandt (1989) [50]	HD	STAI, SCL-90, BDI, BHS	T-test for independent samples	+
Lerman (1998) [66]	BRCA	IES, CES-D	Logistic regression	~
Michie (2001) [78]	FAP	IES, STAI, HADS, RCBS, HOS, LOT	Friedman's test for ordinal data	~
Broadstock (2000) [70]	HBOC	IES, STAI, GHQ, CWS	Friedman's test for ordinal data	~
Abe (1997) [59]	SCA	STAI, SDS	Kruskal-Wallis	~
Quaid (1995) [53]	HD	SCL-90, BDI, BHS, MSI	Mann-Whitney U test	~
Lawson (1996) [57]	HD	SCL-90, BDI, SSQ, adverse events	No longitudinal analyses performed	~
Continuous variables, two waves				
Codori (1996) [55]	FAP	SCL-90, BDI, CDI, RADS, RCMAS, CBCL	Repeated measures ANOVA	+
Lodder (2001) [77]	BRCA	IES, HADS	Repeated measures ANOVA	+
Kirkwood (2002) [80]	HD	MMPI	Repeated measures ANOVA	+
Marteau (1997) [62]	CF	STAI, GHQ, 12 dichotomous questions	Regression, logistic regression	+
Croyle (1997) [61]	BRCA	IES, STAI	Regression	~
Decruyenaere (1999) [67]	HD	STAI, BDI, MMPI	Regression	+
Smith (1999) [69]	BRCA	IES, STAI	Regression	~
Ritvo (2000) [73]	BRCA	STAI, CES-D, LOT, MOSS	Regression	~
Grosfeld (2000) [72]	MEN	IES, STAI, SCL-90	Paired t-test	~
Lerman (1996) [58]	BRCA	IES, CES-D	ANOVA on difference scores, regression	~
Wood (2000) [74]	BRCA	IES, HSCL	Wilcoxon's sign rank/rank sum	+
Taylor (1997) [63]	HD	SCL-90, BDI, BHS	Fisher's exact test	~
Discrete variables, more than two waves				
Aktan-Collan (2000) [90]	HNPCC	5-answer categories questions	Repeated Measurements ANOVA, paired sample t-tests	~

Note: † BRCA - Breast Cancer (BRCA1 and BRCA2); CF - Cystic Fibrosis; FAP - Familial Adenomatuous Polyposis; HBOC - Hereditary Breast and Ovary Cancer; HD - Huntington Disease; HNPCC - Hereditary Non-Polyposis Colon Cancer; MEN - Multiple Endocrine Neoplasia; LF - Li-Fraumeni cancer syndrome; SCA - Spino Cerebellar Ataxia.
§ - + adequate; ~ less adequate

Forty-six articles did not meet our inclusion criteria as:

- fourteen were qualitative studies. Although some of these studies used quantitative measures, the data were not statistically analysed and thus the studies were classified as qualitative for our purpose.[7-20]
- ten studied psychological effects, but not of a genetic test outcome.[21-30]
- thirteen studies were not longitudinal but cross-sectional or retrospective.[31-43]
- three did not investigate psychological outcomes of genetic testing.[44-46]
- six were reviews on effects of (genetic) testing.[3-5 47-49]

Studies that could be classified in more than one category were mentioned in the first of the exclusion criteria involved. Forty articles met the inclusion criteria[1 50-87] (Table 1).

Categorisation of methods

Methods for continuous outcome variables and three or more waves. General linear mixed models (GLMM), also referred to as random effect modelling, random coefficient regression modelling, mixed models or multilevel regression analysis. This method, used in five studies,[1 60 82 84 85] has three advantages: (1) incomplete cases can be analysed, (2) different time spans for individuals between the waves can be handled, and (3) the method allows control for confounding variables, for example age or the number of children, by entering these as covariates into the model equation. Missing data that are dependent on the observed outcome variables and other observed characteristics can be dealt with by including these in the analysis.[88 89]

Repeated Measures Analysis of Variance. Eight studies used repeated measures analysis of variance on continuous data with multiple waves.[51 52 54 64 65 75 81 86] Repeated measures analysis of variance has three main advantages: (1) it is relatively easy to perform, (2) several outcome variables can be analysed simultaneously, and (3) confounding variables can be included as covariates. The disadvantage, that only complete cases can be analysed, can be reduced by imputing the missing values of incomplete cases. A second, but less serious problem is that the time spans between the waves must be equal for each participant.

Five studies did not report on quadratic or higher order time effects, which suggests that they have not made optimal use of repeated measure analysis.[51 54 75 81 86] Three studies have used missing value imputation,[51 65 81] which is discussed in the section on missing data. One study,[90] used SPSS MANOVA on discrete variables, which must be considered as less adequate.

Methods for continuous outcome variables and two waves. Repeated measures analysis of variance. Three studies[55 77 80] used this highly appropriate method for analyses on two waves.

Regression analysis,(multiple) linear regression analysis, sequential or hierarchical regression analysis. The follow-up outcome variable is defined as the dependent variable in the regression equation. The baseline scores,

DNA test outcome, and other variables (gender, age education) are defined as independent variables. Two studies[58 67] used this method adequately on two waves. Four studies,[61 62 69 73] did not include the baseline measure in the analysis, which is less adequate when there are baseline differences. One of these[62] did not include the baseline measure because of missing baseline data. Four studies[56 71 79 83] used this analysis for multiple waves, which is less adequate, because only two by two comparisons can be made.

Analysis of variance or covariance of change scores. In principle this method is the same as regression analysis. Two studies[76 83] used it to analyse multiple waves, which is not optimal. One of these[83] did not use the baseline score as a covariate, and differences were analysed at baseline in separate t-tests.

Logistic regression. By using the DNA test outcome as the dependent variable, logistic regression can be used for analysing continuous outcome variables. Baseline, follow-up scores and confounding variables can be entered as independent variables. This method is unconventional since the role of determinant (DNA test outcome) and outcome (psychological test) are interchanged. The advantage of this method is that very few requirements are posed on the independent variables. Two studies,[68 87] used logistic regression in this way for their multiple wave study.

Paired samples t-test. With two time points, the paired samples t-test yields the same solution as a repeated measure ANOVA. However, no comparisons for change in course of time between groups can be made. One study[72] used it for two time points, and they analysed the differences between groups separately. It is better to use one integrative method, so that interaction effects can be revealed. Two studies[56 71] used this technique less adequately for multiple waves and for more than one group.

Methods for continuous outcome variables that are not longitudinal. T-test for independent samples. Brandt et al.[50] used this method for their study comprising of eight waves. Probably because the sample size was relatively small compared to the number of waves, repeated measures analysis of variance would yielded invalid results. As more advanced methods were not common in 1989, there is no reason to object to this method. Lawson et al.[57] used this test to analyse baseline characteristics of persons who had an adverse event after the prediagnostic test for HD.

Methods for discrete outcome variables and three or more waves. Friedman's test for ordinal data. This test is regarded as the non-parametric equivalent of a one sample repeated measures design. It neither reveals differences between groups, nor can it reveal quadratic, cubic or higher order time effects. If a significant time effect within a group is revealed, pair-wise comparisons between waves must be analysed separately for significance. Two studies used this procedure[70 78] for their continuous data. This could be adequate if the variables could not be successfully transformed to normality. Neither study reported on the distribution of the variables.

Methods for discrete outcome variables and two waves. Logistic regression. Logistic regression is an appropriate analysis when the outcome variable is dichotomous. One study,[66] dichotomised the continuous outcome variable, and performed logistic regression analysis which is less efficient. The authors also report that measures were taken at three time points, but they barely touched on the third wave in the result section.

Wilcoxon signed ranks test in combination with Wilcoxon rank sum test. These are non-parametric equivalents to a paired samples t-test and a t-test for independent samples. One study[74] used these tests for one group and two waves, on continuous variables that were not normally distributed. This is a reasonable alternative when variables cannot be transformed to normality, though no interactions can be analysed.

Methods for discrete outcome variables that are not longitudinal. Kruskal-Wallis H test. This is a non-parametric equivalent to one-way ANOVA. One study[59] seem to have used this test to compare three groups with respect to differences between the follow-up measure and baseline. Analyses for each of the three follow-up measurements were performed separately.

Mann-Whitney U test. This test is equivalent to a Kruskal-Wallis H test, but restricted to compare only two groups. One study[53] used this test on continuous data for multiple waves, because of a small sample size. Carriers were compared with non-carriers, at each time point separately. Another study[57] used this test to analyse baseline characteristics of persons who had an adverse event after the prediagnostic test for HD.

Fisher's exact test. One study[63] used Fisher's exact test for analysing the difference between the number of people who had an increase and those who had a decrease since baseline with regard to certain outcome variables. When continuous variables are treated in this way, much information may be lost.

Dropout analysis and reporting

In this review we differentiate between individuals lost to follow-up (that is, dropouts) and those for whom data are incomplete as a consequence of missing time points. Incompleteness of data within questionnaires because participants did not answer all questions is not discussed here. In general, questionnaire manuals provide rules for handling this problem. Moreover, this is not a specific issue of longitudinal designs.

We divided the studies into four groups; (1) baseline differences analysed and found, (2) baseline differences analysed but not found, (3) dropout rate reported, but no analysis for differences reported, and (4) no mention of dropout (Table 2).

(1). Thirteen studies reported differences between dropouts and participants who returned for follow-up questionnaires.[1 53 58 63 65 66 68 78 83-86 90].

(2). Ten studies reported that differences between dropouts and persons participating with follow-up were analysed, but no differences were found.[51 60 64 71 75-77 81 82 87].

(3). Eight studies reported the dropout rate, but did not analyse possible characteristics of dropouts.[50 54 56 59 61 67 70 72].

(4). Nine studies reported neither on dropout analyses, nor on dropout rate.[52 55 62 69 73 74 79] One study[57] seemed to claim that there were no dropouts at all, though from the text it can be inferred that there must have been between one and 18 dropouts. And one study[80] reported that unfortunately no baseline records of dropouts were kept.

Missing value handling and reporting

Twenty-eight studies included three or more waves, which made these studies vulnerable to missing values. Five studies used GLMM for analysis, and one study performed no longitudinal analysis.[57] From the remaining 22 studies information is needed about how they dealt with missing values. Three studies imputed missing values before performing repeated measures analysis of variance. One[77] used singular regression imputation, which is considered inferior to multiple imputation,[88 91] one[65] used mean substitution, which is generally insufficient, and one[51] did not report which method they used. In 10 studies participants with missing time points were excluded from the analyses[54 56 66 68 70 71 75 78 86 90] and nine studies did not report on the handling of missing time points at all.[50 52 53 59 64 76 79 83 87]

The groups and subgroups that are studied

In 35 studies carriers were compared to non-carriers. Several of these studies also included other groups; people with an uninformative test outcome,[50 51 57 82 83 85] people who refrained from testing,[57 58 66] partners,[1 64 81] parents of individuals tested for FAP,[85] and people who had had a spinocerebellar attack.[59] One study compared unaffected Li-Fraumeni, unaffected BRCA1 tested individuals and women who were carriers of BRCA1 mutations.[71] One study[68] compared high and average risk groups of BRCA 1/2 mutation negatives. One study[72] compared parents with children tested for the MEN2 gene: all children positive, all negative and mixed. Two studies included only one group.[70 73]

Accuracy of reporting

Some studies reported in an incomplete or unclear fashion. Sometimes the size of the study group and inclusion criteria remained unclear, or no actual p-values were reported. In other studies the presented p-values were different from values that could be calculated from the tables. Sometimes, the number of participants inferred from *df* or χ^2-values was not in accordance with the reported number of participants.

Table 2. *Sample sizes, dropout, missing values, study length, number of waves, compared groups and accuracy of reporting*

Study	Sample size	Dropout rate	Dropout analysis	Missing value handling	Time span in months	Waves	Within group	Groups	Between group
Continuous variables, more than two waves									
Codori (1997) [60]	160	4%	no difference	NA	12	5	Y	2; C/NC	Y
Meiser (2002) [82]	143	20%	no difference	NA	12	4	Y	3: C/NC, no test	Y
Codori (2003) [85]	48	27%	differences	NA	55	4	Y	4; C/NC, ditto parents 3; C/NC, mixed families	Y
Almqvist (2003) [84]	202	48%	differences	NA	60	7	Y	2; C/NC	Y
Timman (2004) [1]	302	22%	differences	NA	120	6	Y	4; C/NC, partners	Y
Wiggins (1992) [51]	135	26%	no difference	imputed	12	4	Y	3; C/NC, uninformative	Y
Tibben (1994) [52]	73	?	none	?	6	3	Y	2; C/NC	Y
Campodonico(1996) [54]	59	75%	none	excluded	24	3	Y	2; C/NC	Y
Tibben (1997) [64]	86	33%	no difference	?	36	4	Y	4; C/NC, partners	Y
DudokdeWit(1998) [65]	58	36%	differences	imputed	6	3	Y	2; C/NC	Y
Aktan-Collan(2001) [75]	271	19%	no difference	excluded	12	4	Y	2; C/NC	Y
Lodder (2002) [81]	102	50%	no difference	imputed	12	4	Y	4; C/NC, partners	Y
Decruyenaere(2003) [86]	57	25%	differences	excluded	60	3	Y	2; C/NC	Y
Tercyak (2001) [79]	107?	?	none	?	2	3	Y	2; C/NC	Y
Schwartz (2002) [83]	279	20%	differences	?	6	3	Y	3; C/NC, uninformative	Y
Decruyenaere(1996) [56]	53	7%	none	excluded	12	3	Y	2; C/NC	Y
Dorval (2000) [71]	65	9%	no difference	excluded	6	3	Y	3;unaffected LF, BRCA1 affected BRCA1	Y
Friedman (1999) [68]	289	31%	differences	excluded	6	3	Y	2; non-carriers: in- / decreased risk	Y
Oostrom (2003) [87]	65	24%	no difference	?	60	5	Y	2; C/NC	Y
Horowitz (2001) [76]	79	47%	no difference	?	12	4	Y	2; C/NC	Y
Brandt (1989) [50]	55	75%	none	?	24	8	N	3; C/NC, uninformative	N
Lerman (1998) [66]	327	18%	differences	excluded	6	3	Y	3; C/NC, not tested	Y
Michie (2001) [78]	19?	39%	differences	excluded	18	3	Y	2; C/NC	N
Broadstock (2000) [70]	21	36%	none	excluded	12	4	Y	1; unaffected at risk	NA
Abe (1997) [59]	62	5%	none	?	12	4	Y	3; C/NC, affected	N
Quaid (1995) [53]	19	24%	differences	?	12	5	N	2; C/NC	Y
Lawson (1996) [57]	135	?	none	NA	12	4	N	4; C/NC, uninform., not tested	Y
Continuous variables, two waves									
Codori (1996) [55]	41	?	none	NA	3	2	Y	2; C/NC	Y
Lodder (2001) [77]	78	16%	no difference	NA	1	2	Y	2; C/NC	Y
Kirkwood (2002) [80]	43	?	none	NA	44	2	Y	2; C/NC	Y
Marteau (1997) [62]	743	?	none	NA	36	2	N	2; C/NC	Y
Croyle (1997) [61]	60	3%	none	NA	1	2	N	2; C/NC	Y
Decruyenaere(1999) [67]	69	27%	none	NA	12	2	Y	2; C/NC	Y
Smith (1999) [69]	212	?	none	NA	1	2	N	2; C/NC	Y
Ritvo (2000) [73]	60	?	none	NA	12	2	N	1; tested women	NA
Grosfeld (2000) [72]	25	4%	none	NA	1	2	Y	3; parents with: C/NC child(ren), both	Y
Lerman (1996) [58]	192	31%	differences	NA	1	2	Y	3; C/NC, not tested	Y
Wood (2000) [74]	35	?	none	NA	1	2	Y	2; C/NC	Y
Taylor (1997) [63]	16	20%	description	NA	108	2	Y	2; C/NC	Y
Discrete variables, more than two waves									
Aktan-Collan (2000) [90]	334	19%	differences	excluded	12	3	Y	2; C/NC	?

Note: N - No NA - Not applicable Y - Yes ? - Unknown C/NC - carriers and non-carriers

DISCUSSION

The aim of this review was to describe the methodology and statistics of psychological follow-up studies on effects of predictive genetic testing. Fifteen studies were found to have applied more or less adequate statistical methods. The majority of the studies, however, applied statistical techniques that were less suitable or less efficient for the data that were available to the researchers. We evaluated studies on five issues; (1) the measurement level of the variables, (2) the number of waves, (3) dropout handling, (4) missing value handling, and (5) the groups and subgroups that are studied.

The measurement level of the variables

Generally, most studies used variables with a continuous measurement level. Many statistical methods that are appropriate for this measurement level require normal distribution. If not, an attempt can be made to transform it to normality.[92 93] If transformation is not successful, a non-parametric test should be used, as is prescribed for discrete variables. Generally, parametric tests are more efficient than non-parametric tests.[94] For this reason it is recommended that a parametric test is used whenever permitted. Thirty-one studies used a parametric test on continuous data, seven studies used a non-parametric test on continuous data, one study used a parametric test on discrete data, and one study did not perform any longitudinal analysis.

Dropout analyses and reporting

Eighteen studies gave no evidence of having performed any analysis on the characteristics of dropouts. These differences should include outcome variables and all biographical measures that have been assessed. We favour the suggestion of Moher[95] who reports that a flow diagram should be provided with the number of participants in any condition and any moment, and that reasons for these numbers should be given. Only two studies in this review actually provided such a flow chart.[58 90]

Sample size

An important characteristic of a study is the number of participants. The costs and efforts needed to conduct a large sample study will be higher than a small sample study. Obviously, a study with a large sample will reveal more (significant) effects. Although sample size issues are not within the scope of this review, it should be noted that a minimum sample size is needed to perform quantitative analyses. Our scope is to review the effectiveness and correctness of the methodology used, which is an issue independent of the sample size.

A model for study design and analysis

The type of study for examining the effects of testing for late onset genetic diseases is a longitudinal design in which one or more post-test measures are compared with a pre-test measure. Admitted, there is not one ideal study design, as it depends on the resources the researcher have access to, the subjects who can and want to participate, and the questions that are to be answered. We provide some recommendations. The study should include a baseline measure, an intervention such as a genetic test outcome, and follow-up measures. Generally it is concluded from previous research[5] that test results have a large impact directly after the test, but measures stabilise some time after baseline measurement. Timman et al.[1] suggested that the genetic test outcome does have long term effects. For this reason it is recommended that a study be continued over several years. For an initial study report, for example when baseline and the first follow-up are undertaken, analysis can be done with repeated measures analysis of variance. For reports on subsequent follow-ups, GLMM is recommended. Although GLMM can handle incomplete cases, all efforts should be made to avoid missing values and retain as many participants in the study as possible.

In many articles no rationale was given for the analytic approach used. Sometimes the method used for the analysis was not clearly described, and we had to infer the analysis from the reported results. In some cases this may have meant that a different procedure was used than we inferred.

The use of an inadequate method can result in incorrect conclusions, but more often it can result in a failure to find a significant effect. To determine whether studies would have produced different findings if a more adequate method had been used, one needs to reanalyse the data. In a number of circumstances we performed the method described on our own data, and we compared the results of the various analyses. It is beyond the scope of this article to report on this extensively. Often the use of a non-parametric test where a parametric test could be used, does not lead to a dramatic loss of power efficiency. Mostly the power of a non-parametric test is about 95% compared to a F-test when conditions for this test are met. In some circumstances however, for example when distributions are dichotomised before analysing, this power can drop dramatically to a lower 63%.[94]

In this review, we found a number of studies that used sound methods and reported their findings and dropout handling in an excellent way. Our purpose is to present these methods and ways of reporting to all researchers in the field of psychological effects of genetic testing. Using an inadequate technique can cause loss of information, for example when a technique excludes incomplete cases. If more up-to-date and sophisticated techniques are included in one's statistical package, these should be used. In hindsight it can be said that some of our own new findings were already present in our previous data, but the statistical packages available to us at the time did not reveal these. We hope that this study can be of help to other researchers for finding more, and better founded results.

ACKNOWLEDGEMENTS

We thank Vicky Kraver for correcting our use of the English language.

REFERENCES

1. Timman R, Roos RAC, Maat-Kievit A, Tibben A. Adverse Effects of Predictive Testing for Huntington Disease Underestimated: Long Term Effects 7-10 years after the test. *Health Psychol* 2004;23(2).
2. Bouter LM, Rosendaal FR, editors. *Dwalingen in de methodologie*. Amsterdam: Nederlands Tijdschrift voor Geneeskunde, 2002.
3. Broadstock M, Michie S, Marteau TM. The psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet* 2000;8(10):731-738.
4. Meiser B, Dunn S. Psychological impact of genetic testing for Huntington disease: An update of the literature. *J Neurol Neurosur Ps* 2000;69(5):574-578.
5. Duisterhof M, Trijsburg RW, Niermeijer MF, Roos RAC, Tibben A. Psychological studies on Huntington's disease: Making up the balance. *J Med Genet* 2001;38:852-861.
6. Bijleveld CCJH, van der Kamp LT, Mooijaart A, van der Kloot WA, van der Leeden R, van der Burg E, editors. *Longitudinal data analysis: Designs, models and methods*. London: Sage, 1999.
7. Evers-Kiebooms G, Fryns J-P, Cassiman JJ, Van den Berghe H. *Psychosocial aspects of genetic counseling*. New York, NY, US: Wiley-Liss, 1992.
8. Bloch M, Adam S, Wiggins S, Huggins M, Hayden MR. Predictive testing for Huntington disease in Canada: the experience of those receiving an increased risk. *Am J Med Genet* 1992;42:499-507.
9. Huggins M, Bloch M, Wiggins S, Adam S, Suchowersky O, Trew M, et al. Predictive testing for Huntington disease in Canada: adverse effects and unexpected results in those receiving a decreased risk. *Am J Med Genet* 1992;42:508-515.
10. Petersen GM, Boyd PA. Gene tests and counseling for colorectal cancer risk: lessons from Familial polyposis. *J Nat Cancer Inst M* 1995;17:67-71.
11. Hayden MR, Bloch M, Wiggins S. Psychological effects of predictive testing for Huntington's disease. In: Weiner WJ, Lang AE, editors. *Behavioral neurology of movement disorders. Advances in neurology*. New York, NY: Raven Press, 1995:201-210.
12. Michie S, McDonald V, Bobrow M, McKeown C, Marteau T. Parents' responses to predictive genetic testing in their children: report of a single case study. *J Med Genet* 1996;33(4):313-8.
13. Grosfeld FJM, Lips CJM, Kroode ten HFJ, Beemer FA, Spijker van HG, Brouwers-Smalbraak GJ. Psychosocial consequences of DNA analysis for MEN Type2. *Oncology* 1996;10(2):141-146.
14. Lynch HT, Lemon SJ, Durham C, Tinley ST, Connolly C, Lynch JF, et al. A descriptive study of BRCA1 testing and reactions to diclosure of test results. *Cancer* 1997;79(11):2219-2228.

15. DudokdeWit AC, Tibben A, Frets PG, Meijers-Heijboer EJ, Devilee P, Klijn JGM, et al. BRCA1 in the family: A case description of the psychological implications. *Am J Med Genet* 1997;71:63-71.
16. Robins Wahlin T-B, Lundin A, Bäckman L, Almqvist E, Haegermark A, Winblad B, et al. Reactions to predictive testing in Huntington disease, Case reports of coping with a new genetic status. *Am J Med Genet* 1997;73:356-365.
17. Marteau TM, Croyle RT. The new genetics: Psychological responses to genetic testing. *Brit Med J* 1998;316:693-696.
18. Shoda Y, Mischel W, Miller SM, Diefenbach M, Daly MB, Engstrom PF. Psychological interventions and genetic testing: Facilitating informed decisions about BRCA!/2 cancer susceptibility. *J Clin Psychol Med S* 1998;5(1):3-17.
19. Chapman PD, Burn J. Genetic predictive testing for bowel cancer predisposition: the impact on the individual. *Cytogenet Cell Genet* 1999;86(2):118-124.
20. Claes E, Evers Kiebooms G, Boogaerts A, Decruyenaere M, Denayer L, Legius E. Communication with close and distant relatives in the context of genetic testing for hereditary breast and ovarian cancer in cancer patients. *Am J Med Genet* 2003;116A(1):11-19.
21. Bloch M, Fox S, Hayden MR. Predictive testing for Huntington disease: II. Demographic characteristics, life-style patterns, attitudes, and psychosocial assessments of the first fifty-one test candidates. *Am J Med Genet* 1989;32:217-224.
22. Adam S, Wiggins S, Whyte P, Bloch M, Shokeir MHK, Soltan H, et al. Five year study of prenatal testing for Huntington's disease: demand, attitudes, and psychological assessment. *J Med Genet* 1993;30(7):549-556.
23. Wroe AL, Salkovskis PM. Factors influencing anticipated decisions about genetic testing: experimental studies. *Brit J Health Psych* 1999;4:19-40.
24. Julian-Reynier C, Eisinger F, Chabal F, Lasset C, Nogues C, Stoppa-Lyonnet D, et al. Disclosure to the family of breast/ovarian cancer genetic test results: patient's willingness and associated factors. *Am J Med Genet* 2000;94(1):13-8.
25. Kinney AY, Choi Y, DeVellis BM, Millikan R, Kobetz E, Sandler RS. Attitudes toward genetic testing in patients with colorectal cancer. *Cancer Pract* 2000;8(4):178-186.
26. Kinney AY, Choi YA, DeVellis B, Kobetz E, Millikan RC, Sandler RS. Interest in genetic testing among first-degree relatives of colorectal cancer patients. *Am J Prev Med* 2000;18(3):249-52.
27. Biesecker BB, Ishibe N, Hadley DW, Giambarresi TR, Kase RG, Lerman C, et al. Psychological factors predicting BRCA1/BRCA2 testing decisions in members of hereditary breast and ovarian cancer families. *Am J Med Genet* 2000;93:257-263.
28. Schwartz MD, Hughes C, Roth J, Main D, Peshkin BN, Isaacs C, et al. Spiritual faith and genetic testing decisions among high risk breast cancer probands. *Cancer Epidemiol Biomarkers Prev* 2000;9:381-385.

29. Di Prospero LS, Seminsky M, Honeyford J, Doan B, Franssen E, Meschino W, et al. Psychosocial issues following a positive result of genetic testing for BRCA1 and BRCA2 mutations: findings from a focus group and a needs- assessment survey. *Can Med Assoc J* 2001;164(7):1005-9.
30. Meiser B, Butow PN, Barratt AL, Schnieden V, Gattas M, Kirk J, et al. Long-term outcomes of genetic counseling in women at increased risk of developing hereditary breast cancer. *Patient Educ Couns* 2001;44(3):215-25.
31. Codori A-M, Brandt J. Psychological costs and benefits of predictive testing for Huntington's disease. *Am J Med Genet* 1994;54:174-184.
32. Codori A-M, Hanson R, Brandt J. Self-selection in predictive testing for Huntington's disease. *Am J Med Genet* 1994;54:167-173.
33. Van Der Steenstraten IM, Tibben A, Roos RAC, Van Der Kamp JJP, Niermeijer MF. Predictive testing for Huntington disease: Nonparticipants compared with participants in the Dutch program. *Am J Hum Genet* 1994;55:618-625.
34. Robinson GE, Rosen BP, Bradley LN, Rockert WG, Carr ML, Cole DE, et al. Psychological impact of screening for familial ovarian cancer: reactions to initial assessment. *Gynecol Oncol* 1997;65:197-205.
35. De Villiers C, Weskamp K, Bryer A. The sword of Damocles: the psychosocial impact of familial spinocerebellar ataxia in South Africa. *Am J Med Genet* 1997;74(3):270-274.
36. Vernon SW, Perz CA, Gritz ER, Peterson SK, Amos CI, Baile WF, et al. Correlates of psychological distress in colorectal cancer patients undergoing genetic testing for hereditary colon cancer. *Health Psychol* 1997;16:73-86.
37. Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cloostermans T, Cassiman J-J, Demyttenaere K, et al. Non-participation in predictive testing for Huntington's disease: Individual decision making, personality and avoidant behavior in the family. *Eur J Hum Genet* 1997;5:351-363.
38. DudokdeWit AC, Tibben A, Duivenvoorden HJ, Frets PG, Zoeteweij MW, Losekoot M, et al. Psychological distress in applicants for predictive DNA testing for autosomal dominant, heritable, late onset disorders. *J Med Genet* 1997;34(5):382-390.
39. Williams JK, Schutte DL, Holkup PA, Evers C, Muilenburg A. Psychosocial impact of predictive testing for Huntington disease on support persons. *Am J Med Genet* 2000;96(3):353-359.
40. Robins Wahlin T-B, Backman L, Lundin A, Haegermark A, Winblad B, Anvret M. High suicidal ideation in persons testing for Huntington's disease. *Acta Neurol Scand* 2000;102(3):150-161.
41. Bonadonna V, Saltel P, Desseigne F, Mignotte H, Saurin J-C, Wang Q, et al. Cancer patients who experienced diagnostic genetic testing for cancer susceptibility: Reactions and behavior after the disclosure of a positive test result. *Cancer Epidem Biomar* 2002;11:97-104.
42. Michie S, French DP, Marteau TM. Predictive genetic testing: Mediators and moderators of anxiety. *Int J Behav Med* 2002;9(4):309-321.

43. Kirkwood SC, Siemers E, Viken RJ, Hodes ME, Conneally PM, Christian JC, et al. Evaluation of psychological symptoms among presymptomatic HD gene carriers as measured by selected MMPI scales. *J Psychiatr Res* 2002;36(6):377-382.
44. Kirkwood SC, Siemers E, Stout JC, Hodes ME, Conneally PM, Christian JC, et al. Longitudinal cognitive and motor changes among presymptomatic Huntington disease gene carriers. *Arch Neurol-Chicago* 1999;56(5):563-568.
45. Harper PS, Lim C, Craufurd D. Ten years of presymptomatic testing for Huntington's disease: the experience of the UK Huntington's Disease Prediction Consortium. *J Med Genet* 2000;37(8):567-571.
46. Cannella M, Simonelli M, D'Alessio C, Pierelli F, Ruggieri S, Squitieri F. Presymptomatic tests in Huntington's disease and dominant ataxias. *Neurol Sci* 2001;22(1):55-56.
47. Shaw C, Abrams K, Marteau TM. Psychological impact of predicting individual's risk of illness: a systematic review. *Soc Sci Med* 1999;49(12):1571-1598.
48. Evers-Kiebooms G, Welkenhuysen M, Claes E, Decruyenaere M, Denayer L. The psychological complexity of predictive testing for late onset neurogenetic diseases and hereditary cancers: implications for multidisciplinary counselling and for genetic education. *Soc Sci Med* 2000;51(6):831-41.
49. Meiser B, Gleeson MA, Tucker KM. Psychological impact of genetic testing for adult-onset disorders. An update for clinicians. *Med J Australia* 2000;172(3):126-129.
50. Brandt J, Quaid KA, Folstein SE, Garber P, Maestri NE, Abbott MH, et al. Presymptomatic diagnosis of delayed-onset disease with linked DNA markers. The experience in Huntington's disease. *JAMA* 1989;261(21):3108-14.
51. Wiggins S, Whyte P, Huggins M, Adam S, Theilmann J, Bloch M, et al. The psychological consequences of predictive testing for Huntington's disease. *New Engl J Med* 1992;327(20):1401-1405.
52. Tibben A, Duivenvoorden HJ, Niermeijer MF, Vegter-van der Vlis M, Roos RAC, Verhage F. Psychological effects of presymptomatic DNA testing for Huntington's disease in the Dutch program. *Psychosom Med* 1994;56(6):526-532.
53. Quaid KA, Wesson MK. Exploration of the effects of predictive testing for Huntington Disease on intimate relationships. *Am J Med Genet* 1995;57:46-51.
54. Campodonico JR, Codori AM, Brandt J. Neuropsychological stability over two years in asymptomatic carriers of the Huntington's disease mutation. *J Neurol Neurosur Ps* 1996;61(6):621-624.
55. Codori AM, Petersen GM, Boyd PA, Brandt J, Giardiello FM. Genetic testing for cancer in children. Short-term psychological effect. *Arch Pediatr Adolesc Med* 1996;150:1131-1138.

56. Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cassiman JJ, Cloostermans T, Demyttenaere K, et al. Prediction of psychological functioning one year after the predictive test for Huntington's disease and impact of the test result on reproductive decision making. *J Med Genet* 1996;33(9):737-743.
57. Lawson K, Wiggins S, Green T, Adam S, Bloch M, Hayden M, et al. Adverse psychological events occurring in the first year after predictive testing for Huntington's disease. *J Med Genet* 1996;3:856-862.
58. Lerman C, Narod S, Schulman K, Hughes C, Gomez-caminero A, Bonney G, et al. BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. *JAMA* 1996;275:1885-1892.
59. Abe K, Itoyama Y. Psychological consequences of genetic testing for spinocerebellar ataxia in the Japanese. *Eur J Neurol* 1997;4(6):593-600.
60. Codori A-M, Slavney PR, Young C, Miglioretti DL, Brandt J. Predictors of psychological adjustment to genetic testing for Huntington's disease. *Health Psychol* 1997;16(1):36-50.
61. Croyle RT, Smith KR, Botkin JR, Baty B, Nash J. Psychological responses to BRCA1 mutation testing: preliminary findings. *Health Psychol* 1997;16(1):63-72.
62. Marteau T-M, Dundas R, Axworthy D. Long-term cognitive and emotional impact of genetic testing for carriers of cystic fibrosis: The effects of test result and gender. *Health Psychol* 1997;16(1):51-62.
63. Taylor CA, Myers RH. Long-term impact of Huntington disease linkage testing. *Am J Med Genet* 1997;70:365-370.
64. Tibben A, Timman R, Bannink EC, Duivenvoorden HJ. Three year follow up after presymptomatic testing for Huntington's disease in tested individuals and partners. *Health Psychol* 1997;16(1):20-35.
65. DudokdeWit AC, Duivenvoorden HJ, Passchier J, Niermeijer MF, Tibben A. A Course of distress experienced by persons at risk for an autosomal dominant inheritable disorder participating in a predictive testing program: an explorative study. Rotterdam/Leiden Genetics Workgroup. *Psychosom Med* 1998;60(5):543-549.
66. Lerman C, Hughes C, Lemon SJ, Main D, Snyder C, Durham C, et al. What you don't know can hurt you: adverse psychologic effects in members of BRCA1- linked and BRCA2- linked families who decline genetic testing. *J Clin Oncol* 1998;16:1650-1654.
67. Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cassiman JJ, Cloostermans T, Demyttenaere K, et al. 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* 1999;36(12):897-905.
68. Friedman LC, Webb JA, Richards CS, Lynch GR, Kaplan AL, Brunicardi FC, et al. Psychological impact of receiving negative BRCA1 mutation test results in Ashkenazim. *Genet Med* 1999;1(3):74-79.

69. Smith KR, West JA, Croyle RT, Botkin JR. Familial context of genetic testing for cancer susceptibility: Moderating effect of siblings' test results on psychological distress one to two weeks after BRCA1 mutation testing. *Cancer Epidem Biomar* 1999;8:385-392.
70. Broadstock M, Michie S, Gray J, Mackay J, Marteau TM. The psychological consequences of offering mutation searching in the family for those at risk of hereditary breast and ovarian cancer--a pilot study. *Psycho-oncol* 2000;9(6):537-48.
71. Dorval M, Patenaude AF, Schneider KA, Kieffer SA, DiGianni L, Kalkbrenner KJ, et al. Anticipated versus actual emotional reactions to disclosure of results of genetic tests for cancer susceptibility: findings from p53 and BRCA1 testing programs. *J Clin Oncol* 2000;18:2135-2142.
72. Grosfeld FJ, Beemer FA, Lips CJ, Hendriks KS, ten Kroode HF. Parents' responses to disclosure of genetic test results of their children. *Am J Med Genet* 2000;94(4):316-23.
73. Ritvo P, Robinson G, Irvine J, Brown L, Matthew A, Murphy KJ, et al. Psychological adjustment to familial genetic risk assessment: differences in two longitudinal samples. *Patient Educ Couns* 2000;40(2):163-72.
74. Wood ME, Mullineaux L, Rahm AK, Fairclough D, Wenzel L. Impact of BRCA1 testing on women with cancer: a pilot study. *Genet Test* 2000;4(3):265-72.
75. Aktan-Collan K, Haukkala A, Mecklin JP, Uutela A, Kaariainen H. Psychological consequences of predictive genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): a prospective follow-up study. *Int J Cancer* 2001;93(4):608-611.
76. Horowitz MJ, Field NP, Zanko A, Donnelly EF, Epstein C, Longo F. Psychological impact of news of genetic risk for Huntington disease. *Am J Med Genet* 2001;103(3):188-192.
77. Lodder L, Frets PG, Trijsburg W, Meijers-Heijboer EJ, Klijn JGM, Duivenvoorden HJ, et al. Psychological impact of receiving a BRCA1/BRCA2 test result. *Am J Med Genet* 2001;98:15-24.
78. Michie S, Bobrow M, Marteau TM. Predictive genetic testing in children and adults: a study of emotional impact. *J Med Genet* 2001;38(8):519-26.
79. Tercyak K-P, Lerman C, Peshkin B-N, Hughes C, Main D, Isaacs C, et al. Effects of coping style and BRCA1 and BRCA2 test results on anxiety among women participating in genetic counseling and testing for breast and ovarian cancer risk. *Health Psychol* 2001;20(3):217-222.
80. Kirkwood SC, Siemers E, Viken R, Hodes ME, Conneally PM, Christian JC, et al. Longitudinal personality changes among presymptomatic Huntington disease gene carriers. *Neuropsychiat Neuropsychol Beh Neurol* 2002;15(3):192-197.

81. Lodder LN, Frets PG, Trijsburg RW, Meijers-Heijboer EJ, Klijn JGM, Seynaeve C, et al. One year follow-up of women opting for presymptomatic testing for BRCA1 and BRCA2: Emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery). *Breast Cancer Res Tr* 2002;73:97-112.
82. Meiser B, Butow P, Friedlander M, Barratt A, Schnieden V, Watson M, et al. Psychological impact of genetic testing in women from high-risk breast cancer families. *Eur J Cancer* 2002;38(15):2025-2031.
83. Schwartz MD, Peshkin BN, Hughes C, Main D, Isaacs C, Lerman C. Impact of BRCA1/BRCA2 mutation testing on psychologic distress in a clinic-based sample. *J Clin Oncol* 2002;20(2):514-520.
84. Almqvist EW, Brinkman RR, Wiggins S, Hayden MR. Psychological consequences and predictors of adverse events in the first 5 years after predictive testing for Huntington's disease. *Clin Genet* 2003;64(4):300-309.
85. Codori A-M, Zawacki KL, Petersen GM, Miglioretti DL, Bacon JA, Trimbath JD, et al. Genetic testing for hereditary colorectal cancer in children: Long-term psychological effects. *Am J Med Genet* 2003;116A(2):117-128.
86. Decruyenaere M, Evers Kiebooms G, Cloostermans T, Boogaerts A, Demyttenaere K, Dom R, et al. Psychological distress in the 5 year period after predictive testing for Huntington's disease. *Eur J Hum Genet* 2003;11(1):30-38.
87. Oostrom Iv, Meijers-Heijboer H, Lodder LN, Duivenvoorden HJ, Gool ARv, Seynaeve C, et al. Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study. *J Clin Oncol* 2003;21(20):3867-3874.
88. Little RJA, Rubin DB. *Statistical analysis with missing data*. New York: John Wiley and Sons, 1987.
89. Molenberghs G, Bijnens L, Shaw D. Linear mixed models and missing data. In: Verbeke G, Molenberghs G, editors. *Linear mixed models in practice - A SAS oriented approach*. New York etc.: Springer, 1997:191-274.
90. Aktan-Collan K, Mecklin JP, Jarvinen H, Nystrom-Lahti M, Peltomaki P, Soderling I, et al. Predictive genetic testing for hereditary non-polyposis colorectal cancer: uptake and long-term satisfaction. *Int J Cancer* 2000;89(1):44-50.
91. Schafer JL. *Analysis of incomplete multivariate data*. London: Chapman & Hall, 1997.
92. Tabachnick BG, Fidell LS. *Using multivariate statistics - third edition*. New York: HarperCollins, 1996.
93. Stevens J. *Applied multivariate statistics for the social sciences - third edition*. 3rd ed. Hillsdale, New Jersey: Erlbaum, 1996.
94. Siegel S, Castellan NJJ. *Nonparametric statistics for the behavioral sciences*. 2nd ed. ed. New York: McGraw-Hill, 1988.
95. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357(9263):1191-1194.

CHAPTER 5
-
Testing the test - why pursue a better test for Huntington disease?

Reinier Timman[1, 2], Anneke Maat-Kievit [3], Christine Brouwer-DudokdeWit [4], Moniek Zoeteweij [5], Martijn H. Breuning [5], Aad Tibben[1, 2, 3, 5]

[1] Leiden University Medical Center, Department of Neurology; [2] Erasmus University Medical Center Rotterdam, Department of Medical Psychology and Psychotherapy; [3] Erasmus University Medical Center, Department of Clinical Genetics; [4] The Bosgroup, Center for Psychotherapy, Research and Counseling, Amsterdam; [5] Leiden University Medical Center, Department of Clinical Genetics, The Netherlands.

Am J Med Genet, 2003;117B:79-85

ABSTRACT

In 1993, the gene mutation for Huntington Disease (HD) was identified and testing became possible with a reliability of >99%, without the need for co-operation of relatives. In 1997 a systematic information program offered the mutation retest to individuals who had earlier received a linkage test result for Huntington disease, which has a residual uncertainty of 1 to 9%. The characteristics of 129 individuals tested by linkage analysis for HD are reported on, as well as the reasons for their reassessment by mutation testing. Three groups were compared: (1) people who were retested between 1993 and 1997, before this study had started, (2) people who were retested after we provided information, and (3) persons who refrained from retesting. Nearly half of the linkage-tested individuals were retested, with the exception of noncarriers with a residual risk of 1 or 2%. Of them, less than one out of five were retested. Carriers with a hopeful view on the future (BHS) and a better sense of well being (GHQ) were more likely to have the retest. Female carriers were also more likely to have the retest before we contacted them. Noncarriers who were retested were more anxious (HADS) than noncarriers who refrained from the retest. Retestees were younger at the time of testing. No risk reversals were revealed by this study.

INTRODUCTION

Huntington disease (HD) is an autosomal, progressive neuropsychiatric disorder. Since the mean age of onset in the Dutch population is 47 years [1], the risk to a person with an affected parent is still approximately 50%, when decisions about future- and family planning are being made in early adult life.[2]

After localization of the HD gene to the chromosome band 4p16.3 in 1983, predictive testing using linkage analysis became available.[3] For linkage analysis, the co-operation of crucial family members is required. Once the gene causing HD was identified in 1993,[4] a number of technical testing problems were solved, such as: cases of non-paternity, recombination, unavailability of family material, residual risk (1-9%) or an uninformative family structure because of too few co-operating family members.

The primary objective of predictive testing is to bring an end to uncertainty about the genetic status of people at risk from a genetic disease. At-risk individuals, who received a linkage test result with residual risks of 1-9%, could benefit by a reduction of this uncertainty level to less than 1%. Before the mutation test became available, Babul et al.,[5] investigated whether linkage tested people were interested in a hypothetically more certain (99%) test, for which co-operation of relatives was still required, and a hypothetically 100% certain test, for which co-operation was not required. They reported that 58% of people who had received an informative linkage test outcome were interested in the more certain test, and 72% were interested in the certain test. Of the linkage testees who had not received a test result, because of unavailability of DNA from crucial family members or uninformativeness of DNA markers, 87% were interested in a certain test. More individuals with an increased risk in their study were interested in the certain test than individuals with a decreased risk (82% vs. 64%). To gain in conciseness and readability, we will refer to these people as carriers and noncarriers. It was inferred by Babul et al.[5] that carriers have less to lose with a retest than noncarriers. Reasons for reluctance to have a more certain retest performed might be that individuals have accepted living with the residual risk, that they could be frightened of being found to be a carrier after all, that they do not understand the implications of the test result, that they deny the residual risk or that they were just not aware of the new test.

The aim of this study was to gain more insight into the need and the reasons for reassessment of the risk obtained by linkage analysis by use of the mutation retest, and also to gain more insight into the psychological characteristics of retestees and individuals who refrained from retesting. Based on the findings of Babul et al.[5] and Benjamin et al.[6] we hypothesized firstly that more carriers will opt for the retest (before and after our information) than noncarriers. Secondly, we hypothesized that linkage testees with a high residual risk will opt more often for the retest than linkage testees with a low residual risk. For those with a high residual risk it

is probably more important to relieve dissonance caused by uncertainty. For noncarriers with a residual risk of 1% or 2 % there is not much gain in having the retest with a residual risk of 1% or less, but there is much to lose in case of a risk reversal. Thirdly, we hypothesized that those who opt for the retest will be younger. In general, for younger people it is more important to be certain of the test result in order to plan for the future and family. Moreover, the probability that an asymptomatic at-risk individual has a disease-causing mutation gradually decreases with increasing age.[7] Fourthly, we inferred that more optimistic carriers, in a better state of well being, will choose more often to have the retest. Optimistic carriers will clutch more at this piece of straw than pessimistic carriers. Also, just as the way of adapting to the linkage test result will be different for noncarriers, we predict that the psychological characteristics of noncarriers that opt for the retest will also be different.

METHODS AND PARTICIPANTS

Participants

In The Netherlands the estimated prevalence of HD is 6.5:100.000, based on the number of living affected individuals, recorded at the Leiden Roster for HD. At least 3115 individuals at 50% risk are registered.[8]

Pre-symptomatic DNA testing for HD has been performed in The Netherlands by linkage analysis since 1987. When the mutation test became available in 1993, the people who had received an informative linkage test result, were not immediately informed. An active policy was not applied because it could be interpreted as if the linkage test had been unreliable, according to the Medical Ethics Committee of Leiden University Medical Center. Life important decisions were based on it, and people might become upset. Moreover, people had the right not to know. Only 35 individuals who previously could not be given an informative linkage test outcome were actively approached by letter in 1993. They were offered the new test, to have an appointment with a clinical geneticist for more information and additional psychological counseling. Eventually, in 1997 the Department of Genetics was allowed to start a systematic information program to inform and offer retesting to those who had received linkage test results. Prior to this program, a number of linkage testees opted for more certainty regarding their at-risk status for HD by making use of the retest. Three groups are compared in this study: (1) the group that had the retest in the period from 1994 to 1997 before our information program started, (2) the group of linkage testees who were retested after our information, and (3) the group of linkage testees who were not retested.

Twelve out of the 35 individuals who could not receive an informative test outcome did not receive it due to uninformativeness of markers. The other 23 could not be tested because of an uninformative family structure. Those at-risk individuals who did not receive a linkage test result were contacted and informed by our department about the new test in 1993. Eleven individuals (92%) who received no test result due to uninformative

markers and 7 (30%) who could not be tested because of their family structure then decided to be tested by mutation analysis. Taken together, 18 (51%) out of these 35 individuals who did not receive a linkage test result at the time, had the mutation test performed in 1993.

Procedures

Two letters were sent together to 210 individuals who had received an informative linkage test outcome and who were eligible for this investigation. Before they were contacted, their addresses were checked with great care in order to ensure that letters would be delivered accurately. This was carried out using the address database of the Dutch telecom and the registry office. If a person was no longer listed in these databases, the family practitioner was contacted, on the condition that he or she had been informed about the linkage test results.

In the first letter, they were reminded of their personal residual risk percentage, and they were informed about the possibility of reassessment with a much higher accuracy by mutation testing. They were offered an appointment with a clinical geneticist for more information, and they were offered additional psychological counseling. In the second letter, their co-operation was requested for a psychological follow-up investigation on the long-term effects of predictive testing for HD. A reminder was sent after 6 weeks if there was no response.

Eighty-one out of the 210 eligible individuals could not participate in this study. Eight individuals already had received a mutation test in combination with the linkage test in 1993, three were deceased (not due to HD), 15 had developed symptoms, 15 had come for prenatal testing and a retest was automatically performed, three did not want to receive the test outcome at the time, (they had only co-operated to enlarge the reliability of their children's test result), one wished to have no further contact, for one the physician advised against contact, two had moved abroad, for seven the addresses were unknown, one was retested because a family member had received a reversed outcome and 25 did not react to either of the two letters and they had not been retested in The Netherlands. A total of 129 respondents remained as the retest study group.

Questionnaires

Sixty-four of the 129 respondents also participated in the psychological follow-up investigation. Questionnaires, administered **before** respondents were retested, included: the Beck Hopelessness Scale (BHS),[9] the Impact of Events Scale (IES),[10] the General Health Questionnaire (GHQ-12),[11] and the Hospital Anxiety and Depression Scale (HADS).[12] The BHS is a twenty-item scale. Subjects are requested to indicate whether they agree or not with the items, resulting in a feeling of hopelessness score between zero and twenty. A score of nine or higher is indicative of suicidal danger.[13] The IES is a fifteen item four-answer categories likert type scale with two sub-scales: intrusion and avoidance. It can be linked to a certain disease or a (traumatic) event. The intrusion sub-scale contains seven items that indicate

whether thoughts about HD come in to one's mind involuntarily. The avoidance sub-scale contains eight items that indicate whether one tries to avoid these intrusive thoughts. The GHQ-12 is a four-answer categories likert type questionnaire with 12 items that is used to measure well being. The HADS is also a four-answer categories likert type questionnaire with 14 items. It has a sub-scale with 7 items for depression and a sub-scale with 7 items for anxiety.

Table 1. *Number and mean age of noncarriers and carriers by gender and retest decision*

	Noncarriers	Carriers	Total
	n (mean age)	*n* (mean age)	*n* (mean age)
Gender			
Men	34 (42.4)	13 (45.9)	47 (43.4)
Woman	54 (40.5)	28 (40.8)	82 (40.6)
Retest decision			
No retest	61 (42.3)	21 (43.0)	82 (42.5)
Retest after info	21 (39.3)	8 (38.0)	29 (39.0)
Retest before info	6 (37.2)	12 (44.3)	18 (41.9)
Total	88 (41.3)	41 (42.4)	129 (41.6)

Statistical Analysis

Statistical analysis was carried out with SPSS. Differences between the number of participants who opted for the retest and the number of participants who did not, were analyzed with Pearson's chi-square test or Fisher's exact test, differences in age or in psychological variables between groups were determined with analysis of variance.

RESULTS

Description of the Sample

The retest study group consisted of 129 respondents; 34 male and 54 female noncarriers, and 13 male and 28 female carriers (Table 1). No risk reversals were revealed. Eighteen subjects who had received a linkage test result, were retested before our information between 1994 and 1997, 29 subjects were retested after our information, and 82 others refrained from having the retest. If the 129 linkage testees included in the investigation are compared with the 81 who were not included, fewer carriers were in than out of the study sample (32% vs. 58%; $p < .0002$). The reasons are obvious; people who already have a clinical diagnosis of HD, have no need for a better test, and people who were excluded because they were retested when they came for prenatal diagnosis, are carriers. There were no gender differences, 59% of the men and 63% of the women were included ($p = .315$). There were also no age differences between participants and non-participants (mean 42.0 vs. 41.9 years, $F_{1, 208} = 0.01$; $p = .94$). In the study group, there was no significant age difference found between carriers and

noncarriers, and men were older than women (Table 1). People who opted for the retest after our information, participated more often in the psychological part of the investigation (76%) than people who were retested before our information (56%), and people who refrained from the retest (39%; $\chi^2_{(2)}$ = 11.93; p = .003). One interaction effect for age was found; carriers who were retested before our information were significantly older than carriers who were retested after our information.

Differences in reassessment

The first hypothesis, that more carriers would have the retest than noncarriers, was confirmed (49% vs. 31%). More carriers were retested before our information than noncarriers (29% vs. 7%, Table 2). Differences were also found between male and female carriers. Of the female carriers 39% were retested and 8% of the male carriers were retested before our information. Male carriers were more often retested after our information than female carriers were (46% vs. 7%).

The second hypothesis, that more people with a high residual risk would have the retest, was confirmed for noncarriers, but not for carriers. For analysis of the residual risk, the linkage test receivers were divided into two groups of equal magnitude, that is, a low (≤ 2%) and a high residual risk (=3%) group. While there was no significant difference in uptake of the test among carriers, there was a significant difference among noncarriers. Of the noncarriers with a low residual risk, 9 out of 48 (19%) were retested, and in the high residual risk group 18 out of 40 (45%) were retested (figure 1). Noncarriers with a low residual risk had the retest significantly less often than noncarriers with a high residual risk.

Table 2. *Relation of genetic status, sex and magnitude of residual risk on the choice for the retest*

	No retest	Retest after information	Retest before information		
	n (%)	*n* (%)	*n* (%)	χ^2 (2)	*p*
Noncarriers	61 (69)	21 (24)	6 (7)		
Carriers	21 (51)	8 (20)	12 (29)	11.8	.003
Men	27 (57)	16 (34)	4 (9)		
Women	55 (67)	13 (16)	14 (17)	6.4	.041
Residual risk ≤ 2%	49 (73)	10 (15)	8 (12)		
Residual risk ≥ 3%	33 (53)	19 (31)	10 (16)	6.0	.051
Noncarriers					
Men	21 (62)	10 (29)	3 (9)		
Women	40 (74)	11 (20)	3 (6)	1.5	.473
Residual risk ≤ 2%	39 (81)	7 (15)	2 (4)		
Residual risk ≥ 3%	22 (55)	14 (35)	4 (10)	7.1	.029
Carriers					
Men	6 (46)	6 (46)	1 (8)		
Women	15 (54)	2 (7)	11 (39)	10.0	.007
Residual risk ≤ 2%	10 (53)	3 (16)	6 (32)		
Residual risk ≥ 3%	11 (50)	5 (23)	6 (27)	0.3	.848

The third hypothesis, that younger people would have a retest more often, was confirmed for those people who were retested after our information. Individuals who were retested after our information, had a mean age of 39.0 years and people who were not retested had a mean age

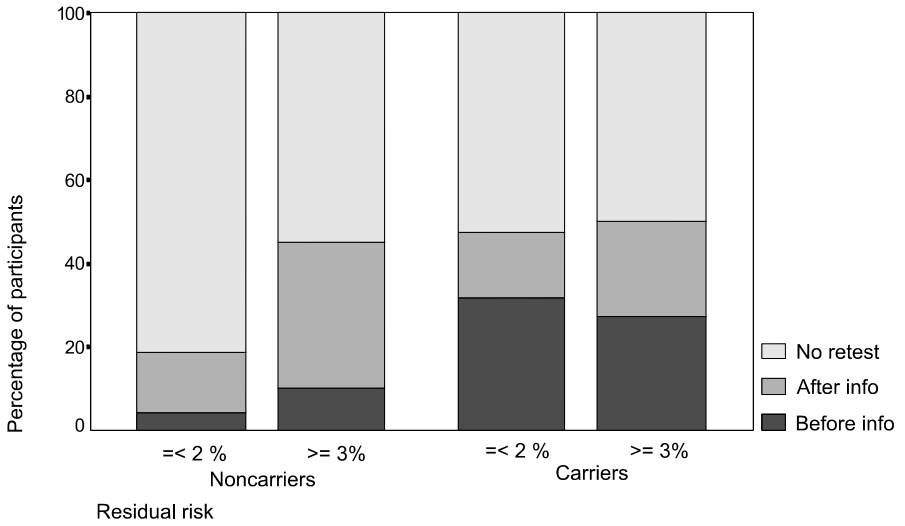

Figure 1. *Percentage of carriers and noncarriers, with a low and high residual risk opting for retest*

of 42.5. There were no significant interactions with test outcome and gender. Carriers who were retested before our information were older than carriers who were retested after our information.

Table 3. *Differences in psychological indicators between carriers and noncarriers*

	Noncarriers (*n* = 42)	Carriers (*n* = 22)	*F*	*p*
Multivariate			2.88	.016
BHS	3.5	6.7	15.53	.000
IES-intrusion	7.0	11.6	6.39	.014
IES-avoidance	3.9	8.5	7.54	.008
GHQ-12	1.2	2.4	2.30	.134
HADS-anxiety	3.2	5.2	4.61	.036
HADS-depression	1.8	3.3	4.01	.050

In general, carriers had higher hopelessness scores (BHS), reported more intrusion and avoidance (IES) and scored higher on anxiety and depression (HADS) than noncarriers (Table 3). The fourth hypothesis, that carriers with a better psychological state will be more likely to choose to have the retest was confirmed for hopelessness (BHS) and well being (GHQ, Table 4). Carriers who were not retested had significantly higher scores on the BHS and GHQ than carriers who were retested (before and

after our information taken together). For noncarriers there were no significant differences in hopelessness and well being, but those who were retested (before and after our information) had higher HADS-anxiety scores than noncarriers who refrained from the retest.

Table 4. *Differences in psychological indicators between retestees and non-retestees by test outcome*

	Noncarriers				Carriers			
	No retest (*n* = 20)	Retest (*n* = 22)	*F*	*p*	No retest (*n* = 12)	Retest (*n* = 10)	*F*	*p*
Multivariate			3.55	.01			2.92	.04
BHS	3.0	4.1	2.06	.16	8.3	4.8	5.76	.03
IES-intrusion	7.6	6.5	0.30	.59	12.4	10.6	0.28	.60
IES-avoidance	4.6	3.4	0.52	.48	10.1	6.6	1.05	.32
GHQ-12	0.7	1.8	2.61	.11	4.1	0.4	6.08	.02
HADS-anxiety	1.8	4.5	7.82	.01	6.1	4.2	1.29	.27
HADS-depression	1.5	2.1	0.85	.36	3.9	2.6	0.68	.42

Missing hopelessness data

Twenty-two out of the 41 carriers in our sample have filled out psychological questionnaires. Five of them had a hopelessness score of 9 or higher, which is indicative of suicidal risk.[13] None of the carriers with such a high score choose for reassessment, while 10 of the 17 with a low hopelessness score did (Fisher's $p = .03$). We studied the possibility of extrapolating this to the carriers who did not fill out questionnaires. We reasoned that the best predictor of the present hopelessness is the hopelessness score in the past,[14-17] and therefore we examined the scores one week after disclosure of the linkage test 7 to 10 years ago. For 10 out of 19 carriers for whom we did not have recent hopelessness scores, scores of one week after the linkage test were available. Three of them were in the range of 9 or higher. None of these individuals choose for reassessment either. If we combine these hopelessness scores, none of the 8 high scoring carriers choose for reassessment, while 14 of the 24 carriers with a low hopelessness scores did ($p = .004$).

DISCUSSION

HD carriers, as identified by linkage analysis (with a residual risk uncertainty of 1-9%) were more likely than noncarriers to have the linkage test confirmed by mutation testing. This is in agreement with the expectation, which was based on the findings of Babul et al.[5] Their reasoning was that carriers have less to lose. However, Babul et al. did not differentiate between levels of residual risk, and this can be a motive too. Nearly half of linkage tested individuals wanted to have more certainty and eventually had the mutation retest carried out (figure 1). There is one exception however; only a minority of the group of noncarriers with a residual risk of 1 to 2% had the retest. Probably they did not feel the need to reduce their residual risk any further. Noncarriers with a residual risk of 3% or more, on the other

hand, and, in particular, anxious noncarriers, chose to retest as often as carriers.

Carriers had the retest more often carried out before we contacted them. This holds especially for female carriers and carriers with a positive view on the future. It can be inferred that for them the need for certainty was strongest. Also, carriers may have more contacts with other carriers, family members, or members of the Huntington Association, they might be more eager for information about HD in general, and they may have had more knowledge of innovation in the field of testing for HD than noncarriers.

People who were not retested were older than people who were retested after our information. Reasons that were mentioned by them to have the test, were planning for the future and the family. Another reason for a lower age of the retest group is that the probability that an a-symptomatic at risk person has a disease causing mutation gradually decreases with increasing age.[7] For example, if someone with a decreased linkage based test result, is over 70 years of age, the chance of developing HD has become minimal, and there will be hardly any motivation to have the retest.

In general, identified carriers had more feelings of hopelessness, were more anxious, had more intruding thoughts, and reported more avoidance behavior than noncarriers, which may reflect the depressing, frightening and intrusive impact of a perspective overshadowed by the disease. These feelings however, could also be a result or symptom of HD in an early stage. Interestingly, carriers who decided to have a retest had fewer hopeless feelings and had a better sense of well being than carriers who refrained from the retest. A possible explanation for this is that those carriers with a relatively positive view on the future are more inclined to have the retest in the (slight) hope of a low risk test outcome. None of the persons with a high score on hopelessness who had received a high-risk linkage test outcome chose to have the retest. Noncarriers who had the retest were more anxious than noncarriers who did not have it. The anxious noncarriers may have opted for the retest as an attempt to reduce their anxiety, while less anxious noncarriers may not have a need to reduce anxiety.

We observed a gender difference for carriers who were retested before our information and the carriers who were retested after our information. Female carriers were more often retested before our information than men were, and men were more often retested after our information. Women may be more inclined to be actively sure of their genetic status, this may reflect the more intimate involvement of women with the process of reproduction and child rearing, both biologically and emotionally.[18] Moreover, if women wish to have children, most would like to have them before they reach a critical age. An indication of this is the fact that women in our sample are younger than men.

Remarkably, 92% of the at risk people, who had not received a linkage test result because of uninformative DNA markers, opted for the retest, and only 30% who had not received it because of an uninformative family structure were retested. We reasoned that individuals who did not receive a linkage test outcome because of uninformative DNA markers had gone

through the whole process of counseling testing, giving blood etc. They may have been more involved in the process of testing, and much more eager to receive eventually a test outcome. The people at risk who were not tested because of an uninformative family structure had not gone through that whole process, and the testing procedure was terminated at a much earlier stage. They may have had family members who objected, they may have found it too troublesome to ask co-operation of relatives, or they may have found a way to cope with this uncertainty.

Fifty-one percent of the people at risk who did not receive a linkage test outcome, either due to an uninformative family structure, or due to uninformative markers, were retested. This is considerably lower than the 87% that Babul et al.[5] found for a hypothetically certain test. Also, in their study, a much larger proportion of linkage testees with an informative outcome indicated that they would have a certain test carried out, than in our study. It is obvious that there is a discrepancy between the hypothetical option of a more certain test and actual behavior. An analogous discrepancy was observed between interest in a predictive test before such a test was available and actual participation after the linkage test was introduced. Before the predictive test became available, 57% to 84% of the at-risk individuals, indicated interest in the predictive test.[19-21] Since its introduction in 1987 the uptake (2-24%), has fallen significantly behind expectation.[8 18 22-24]

Most studies show that the rate of retesting is low; Benjamin et al.[6] reports a rate of 10.4%, Holloway et al.[25] a rate of 6% and Maat-Kievit et al.[8] a rate of 7%. The retest rate in our study group is larger than the retest rate mentioned in a study from Maat-Kievit et al.[8] due to selection of the study group; people whose addresses were unknown and those who did not react to the invitation letter for example, were not included in our study. Also, in our study a number of people were discovered to have had a retest in another center for clinical genetics in The Netherlands. Our study showed that the retest rate was enlarged by the information program from 14% to 36% retests. Although this information program enlarged the number of re-assessments, the majority of the linkage testees did not have the retest, even after our information. It seems that the residual risk of the linkage test is not seen by most as a burden that must be extinguished. It is also possible that the group who had gained more certainty about their genetic status with the linkage test, did not want to risk that certainty with a new test procedure and they did not want to disturb the subject of HD in their minds, which a retest would inevitably do.

ACKNOWLEDGEMENTS

This study was supported by the Prinses Beatrix Fonds grant 94-1111.
We thank Adrian Greeman and the reviewers for correcting our use of the English language.

REFERENCES

1. Maat-Kievit A, Losekoot M, Zwinderman K, Vegter - van der Vlis M, Belfroid R, Lopez F, et al. Predictability of age at onset in Huntington disease in the Dutch population. *Medicine* 2002;81(4):251-259.
2. Harper PS, editor. *Huntington's disease*. London: Saunders, 1996.
3. Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, et al. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 1983;306(5940):234-238.
4. HD Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72:971-983.
5. Babul R, Adam S, Kremer B, Dufrasne S, Wiggins S, Marlene H, et al. Attitudes toward direct predictive testing for the Huntington disease gene. Relevance for other adult-onset disorders. *JAMA* 1993;270(19):2321-2325.
6. Benjamin CM, Adam S, Wiggins S, Theilmann JL, Copley TT, Bloch M, et al. Proceed with care: direct testing for Huntington Disease. *Am J Hum Genet* 1994;55:606-617.
7. Harper PS, Newcombe RG. Age at onset and life table risks in genetic counseling for Huntington's disease. *J Med Genet* 1992;29:239-242.
8. Maat-Kievit A, Vegter - van der Vlis M, Zoeteweij M, Losekoot M, Van Haeringen A, Roos R. Paradox of a better test for Huntington's disease. *J Neurol Neurosur Ps* 2000;69(5):579-583.
9. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: The hopelessness scale. *J Consult Clin Psychol* 1974;42:861-865.
10. Horowitz MJ, Wilner N, Alvarez W. Impact of event scale: A measure of subjective stress. *Psychosom Med* 1979;41:209-218.
11. Goldberg DP. *The detection of psychiatric illness by questionnaire*. London: Oxford University Press, 1972.
12. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiat Scand* 1983;67(6):361-370.
13. Beck AT, Steer RA. Clinical predictors of eventual suicide: a 5- to 10-year prospective study of suicide attempters. *J Affect Disorders* 1989;17:203-209.
14. Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cassiman JJ, Cloostermans T, Demyttenaere K, et al. Prediction of psychological functioning one year after the predictive test for Huntington's disease and impact of the test result on reproductive decision making. *J Med Genet* 1996;33(9):737-743.
15. Broadstock M, Michie S, Marteau TM. The psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet* 2000;8(10):731-738.
16. Meiser B, Dunn S. Psychological impact of genetic testing for Huntington disease: An update of the literature. *J Neurol Neurosur Ps* 2000;69(5):574-578.

17. Duisterhof M, Trijsburg RW, Niermeijer MF, Roos RAC, Tibben A. Psychological studies on Huntington's disease: Making up the balance. *J Med Genet* 2001;38:852-861.
18. Bloch M, Fox S, Hayden MR. Predictive testing for Huntington disease: II. Demographic characteristics, life-style patterns, attitudes, and psychosocial assessments of the first fifty-one test candidates. *Am J Med Genet* 1989;32:217-224.
19. Teltscher B, Polgar S. Objective knowledge about Huntington's disease and attitudes towards predictive tests of persons at risk. *J Med Genet* 1981;18:31-39.
20. Evers-Kiebooms G, Swerts A, Cassiman JJ, Van den Berghe H. The motivation of at-risk individuals and their partners in deciding for or against predictive testing for Huntington's disease. *Clin Genet* 1989;35(1):29-40.
21. Kessler S, Field T, Worth L, Mosbarger H. Attitudes of persons at risk for Huntington disease toward predictive testing. *Am J Med Genet* 1987;26:259-270.
22. Craufurd D, Dodge A, Kerzin-Storrar L, Harris R. Uptake of presymptomatic predictive testing for Huntington's disease. *Lancet* 1989(September 9):603-605.
23. Tyler A, Ball D, Craufurd D. Presymptomatic testing for Huntington's disease in the United Kingdom. *Brit Med J* 1992;304:1593-1596.
24. The World Federation of Neurology Research Group on Huntington's Disease. Presymptomatic testing for Huntington's disease: a world survey. *J Med Genet* 1993;30:1020-1022.
25. Holloway SM, Porteous ME, Fitzpatrick DR, Crosbie AE, Cetnarskyj R, Warner J, et al. Presymptomatic testing for Huntington's disease by linkage and by direct mutation analysis: comparison of uptake of testing and characteristics of test applicants. *Genet Couns* 1998;9(2):103-111.

CHAPTER 6
-
Decreased risk estimation for Huntington's disease without a test

Reinier Timman [1 2], Benno Bonke [2], Theo Stijnen [3], Aad Tibben [1 4], Anneke Maat-Kievit [5]

[1] Leiden University Medical Centre, Department of Neurology; [2] Erasmus University Medical Center Rotterdam, Department of Medical Psychology and Psychotherapy; [3] Erasmus University Medical Center Rotterdam, Department of Epidemiology; [4] Leiden University Medical Centre, Centre for Human and Clinical Genetics; [5] Erasmus University Medical Center Rotterdam, Department of Clinical Genetics, the Netherlands.
Submitted

ABSTRACT

Background and objective: The majority of individuals at risk for Huntington's disease (HD) is reluctant to learn more precisely about the risk of becoming affected, as is suggested by the low uptake of the predictive test for HD. Subsequently, the future expectancies of individuals at risk are often based on rough risk estimates such as 50% (child of a patient) or 25% (grandchild of a patient). Individuals at risk can be offered a better risk estimate based on their current age, length of the disease causing CAG-repeat in close relatives, information on the age at onset (AO), or test results of family members.

Method: Regression modelling and Cox regression determined relations between ages at onset and CAG repeat length in a sample of 755 tested individuals.

Results: A model for calculating the adjusted residual risk status was constructed. This model is implemented in a spreadsheet that can be used in genetic counselling.

Conclusions: This model and accompanying spreadsheet broadens the information clinical geneticists and genetic counsellors can offer. They will be able to provide a best estimation of the residual risk status for individuals in their circumstances. This might help in the decision to be tested and the preparation for the test result.

INTRODUCTION

As an exemplary autosomal dominant hereditary late-onset disorder, Huntington disease (HD) shows a wide variability in age at onset (AO), with a mean between 38.6 and 55.8 years for proven carriers of the HD-gene, and a range of 2 to 80 years.[1] HD is caused by a CAG expansion mutation, coding for an expanded polyglutamine stretch in the cognate protein. Affected individuals have CAG repeat lengths between 36 and 250 in the HD gene[2-4] with some overlap between normal and disease ranges, because reduced penetrance is observed in the lower range of the CAG repeat length (36-39).[5] CAG repeat length is the major determinant of, and inversely related to AO.[5 6] Other modifiers for AO than the expanded CAG repeat are GluR6 gene polymorphism,[7] the normal CAG repeat length,[8 9] UCHL1 gene polymorphism,[10] the adjacent CCG repeat,[11-14] a Δ2642 deletion codon,[14-17] apolioprotein E with genotype ε2ε3,[18] possibly other, yet unknown genes at 4p16, 6p21-23 and 6q24-26,[19] and also the gender of the affected parent and grandparent.[20-24]

Boundaries of the CAG repeat length have been defined for HD: < 27 is normal, 27-35 intermediate, 36-39 disease with reduced penetrance, and > 39 regular disease.[25] Not all carriers of the HD-gene with a CAG repeat length in the reduced penetrance range will develop HD-symptoms during an average life-span of 75 years, whereas few with a CAG repeat length of more than 48 remain symptom free beyond the age of 40. Two research groups[5 6 26] have calculated ages at HD-onset for various CAG repeat lengths, based on large sample sizes, though with substantial differences. For the expanded repeats studied, Maat-Kievit et al.[5] reported a 10 years higher median AO than Brinkman et al.[6] did. Perhaps, this difference is due to the sampling strategies used or to the ways in which the age of first HD-symptomatology, or lack thereof, were defined and determined.

Predictive testing is possible since 1983, though the majority of the individuals at-risk (76-98%) do not wish to be tested.[27-31] The fear of being unable to cope with the personal diagnosis of a future disease is the main reason for reluctance.[27 32-40] Other reasons for refraining from having the predictive test are concern for the possible risk increase for their children, absence of treatment for HD, potential problems with insurance, financial costs of testing, and the definite nature of the results.[27 28 31-33 35 41-46] The low uptake of the predictive test may reflect that the majority of the individuals at risk is reluctant to learn more precisely about their risks of becoming affected. Future expectancies of individuals are mostly based on rough lay risk estimates such as 50% (child of a patient) or 25% (grandchild of a patient). When age advances without signs of the disease, the risk of being a mutation carrier decreases.[47] Indeed, each child of an affected patient has an a priory probability of 50%, regardless of the sex of parent or child. The actual risk, however, may differ considerably and is critically dependent on the age of the individual. Harper and Newcombe[47] provided tables with the actual residual risk at a certain age. The probability that an asymptomatic person at risk has a disease-causing mutation remains close to 50% during

childhood and young adulthood, but gradually decreases with increasing age. At the age of 55, the risk, based on these tables, of being a carrier of the gene is about 25%. Consequently, the children at 50% risk for HD will often have to make reproductive decisions before there is any substantial decrease in risk. The Harper and Newcombe tables[47] are useful in older age groups, where the question often is the age at which one can reasonably be sure of having escaped the disease. It turns out however, that the risk at older ages remains higher than expected.

Some individuals from large families with a considerable number of patients over two generations or more refer to the age of onset in their affected relatives. There is often hope for a relatively late onset when the affected relatives became ill at higher age, but also despair when the mean age at onset is relatively low. A number of studies, however, reported a wide range of variation in AO within families, which can now mainly be explained by the instability of the CAG repeat.[48] Another situation in which one could depart from the Harper and Newcombe tables,[47] was when a sibling had already developed juvenile HD.

Prior to considering a predictive test, individuals at risk may wish to learn about their residual risk status (RRS), that is, their risk of being an HD-carrier given their present age and unaffected state. In addition, if they remain symptom-free, they may wish to learn what their expected RRS will be in the years to come. As part of the predictive testing process, a more precise residual risk estimate could broaden the genetic counsellor's repertoire of tools for informing test applicants in a pre-test situation or counselling session. Moreover, informing a test candidate about the RRS can help him or her to prepare for the test result or to withdraw from the test. Consider, for instance, an individual with a prior risk of 50% who has reached the age at which the mother displayed the first symptoms. The mother's CAG repeat length is a straightforward estimate of his or her own CAG repeat length given that he or she is a carrier. Likewise, because AO is related to repeat length, the best estimate of one's own AO is one's mother's AO. Therefore, if this individual has inherited the mutation with the same length, the probability of developing symptoms is 50% both before and after this age. Given the fact that he or she is symptom free at this age, it can be shown that the prior risk of 50% has been reduced to 0.5/(1+0.5) = 33%. Assume further that this individual has an adult child who is hesitant to start a family because of the risk of HD for his or her offspring. Then the risk of this child has decreased from the prior risk of 25% to 33% / 2 = 16.7%. Generally, if the relevant RRS is disclosed to the adult child, he or she is then —without being tested— optimally informed of the changed risk for any future children, which has, under these circumstances, diminished from a prior risk of 12.5% to approximately 8%. In conclusion, determining the RRS for asymptomatic individuals at risk, whose ages are beyond the AO of the affected parents, is clearly important for themselves and for their (future) offspring.

In order to estimate the RRS, one must first verify, preferably by neurological examination, that the proband is asymptomatic, if the at risk person wants to be informed about his or her neurological status. Secondly,

the CAG repeat length, in case the proband inherited the HD-gene, must be estimated, by using the CAG repeat length of the parent. If the parent did not have a mutation test, the repeat length of the parent can be estimated from the parent's AO. Also, the gender of the affected parent is critical, as has been shown in several studies.[20-22 24] Paternal transmission frequently results in a larger CAG repeat length than maternal inheritance. Thirdly, the probability that he or she is still without symptoms must be determined, given the estimated repeat length. Finally, the RRS can be calculated. To improve RRS-accuracy of asymptomatic target individuals even further, counsellors must also take into account any close family members who have been tested mutation negative.[49]

The aim of this study is to estimate the RRS of a proband as a risk refinement to broaden the information possibilities of the genetic counsellor. The robustness of this estimate, as indicated by confidence intervals (CI), can be of importance for the clinical value. There is a difference between a RRS with a large CI and one with a small CI. The former has less clinical value than the latter. Nevertheless, the best estimate of the RRS is independent of the CI.

For practical purposes we will provide a spreadsheet in which the age of the proband, the CAG repeat length or AO of the affected parent, and the number of negatively tested family members can be entered, resulting in the best estimate of the RRS. The more data will become available, the more precise RRS estimates can be effectuated using this method.

METHODS

Subjects

Data from all 755 individuals enrolled in the Dutch cohort study, tested between 1993 and 2000, with a CAG repeat length of more than 35, were included. Our subjects came from 344 different HD families, 614 were affected, and 141 were asymptomatic gene carriers. More details have been described elsewhere.[5] Data were available in two sets (I and II), including 755 cases with CAG repeat lengths, AOs, and information on clinical status (I), and a subset of 127 individuals for whom CAG repeat length of the affected parent was also available (II).

Data Analysis

Relations between CAG repeat length of the affected parent and the child were analysed with regression modelling in data set II. Relations between AO and CAG repeat length and the probabilities that carriers were still asymptomatic were analysed with Cox regression in data set I. Dependent on the pedigree, favourable test outcomes of family members can decrease the RRS. This influence was determined with Bayes' theorem.

RESULTS

Estimation of Repeat Length.

Regression modelling, with CAG repeat length of the proband as the dependent variable, and CAG repeat length and gender of the affected parent as the independent variable resulted in a regression equation with significant linear and quadratic CAG components for the parent. This model accounted for 71% of the total variance of the CAG repeat length of the child, and has the following equation:

$$CAG_{child} = 44.3 + 0.88*(CAG_{parent} - 44.8) + 0.04*(CAG_{parent} - 44.8)^2 + 2.16*gender_{parent} \quad (1)$$

with $gender_{parent}$ = 0 for an affected mother, and $gender_{parent}$ = 1 for an affected father.

If the CAG repeat length of the affected parent is not known, but the CAG of a sibling is, then the parent's CAG can be estimated from the siblings CAG using equation (1). In a second step the proband's CAG can be estimated, resulting in an CAG estimate that is equal to the sibling's. Thus the best estimate for the proband's CAG is the CAG of the sibling.

Estimation of being unaffected.

Let the probability that an individual is without symptoms, given that he or she is a carrier, equal q. The proportional Cox regression model from AO and CAG repeat length in the data set I resulted in the following equation:

$$q = S^{e^{0.305*(CAG-45.8)}} \quad (2)$$

In this equation, S is the survival function at the mean of the covariates (Appendix 1). The probability that an individual has developed symptoms before the estimated AO is 50%. Consequently, the probability that the first symptoms emerge thereafter is also 50%. To estimate the CAG repeat length of the parent from the AO of the parent, the CAG repeat length corresponding to a q of 0.5 must be estimated. Thus, if one substitutes 0.5 for q in equation (2), this can be converted into:

$$CAG = \frac{\ln(-\ln(0.5)) - \ln(-\ln(S))}{0.305} + 45.8 \quad (3)$$

To illustrate the procedure, we will compute the RRS of a proband without symptoms at age 40, in a case where the father had his first symptoms at age 40. The probability of being without symptoms at age 40 is .710, given that one has inherited the gene (Appendix 1). From (3) we can estimate the CAG repeat length of the father:

$$CAG = \frac{\ln(-\ln(0.5) - \ln(-\ln(0.710))}{0.305} + 45.8 \approx 48$$

Substitution in (1) gives the estimate of the repeat length of the proband:

$$CAG_{child} = 44.3 + 0.88 * (CAG_{parent} - 44.8) + 0.04 * (CAG_{parent} - 44.8)^2 + 2.16 * gender_{parent} \approx 50$$

Finally, substitution in (2) gives the estimate of q, i.e. the probability that the proband is without symptoms at age 40 and a father who had the first symptoms at age 40:

$$q = 0.71^{e^{0.305*(50-45.8)}} \approx 0.30$$

Calculation of Residual Risks.

We used Bayes' theorem as follows. Let the prior risk Pr(C) of an individual being a carrier of the HD-gene at a given age, based on the family pedigree, equal p and the probability that this individual is without symptoms at this age Pr(NS|C) equal q. Let Pr(C|NS) denote the probability that the individual is a carrier of the HD-gene, given that he or she is without symptoms, Pr(NC) the probability that an individual is a non-carrier, and Pr(NS) the prior probability of being without symptoms, then Bayes' theorem states that:

$$\begin{aligned} Pr(C|NS) &= [Pr(NS|C)*Pr(C)]/Pr(NS) \\ &= [Pr(NS|C)*Pr(C)]/[Pr(NS|C)*Pr(C) + Pr(NS|NC)*Pr(NC)] \\ &= (q*p)/\{(q*p)+[1*(1-p)]\} \\ &= p*q/[p*(q-1)+1] \end{aligned} \quad (4)$$

For individuals at a prior risk of 50% (p=0.5), this formula (4) reduces to:

$$\begin{aligned} Pr(C|NS) &= 0.5q/(0.5q-0.5+1) \\ &= q/(q+1) \end{aligned} \quad (5)$$

And:

$$\begin{aligned} Pr(NC|NS) &= 1 - [q/(q+1)] \\ &= 1/(q+1) \end{aligned} \quad (6)$$

Consider, the foregoing example of an asymptomatic individual with a prior risk of 50%, who has a 0.30 probability of being without symptoms if he or she is a carrier, based on age and AO of the affected parent. Then the estimated risk of being a carrier Pr(C|NS), following formula (6), equals 0.30/1.30= 0.23.

Now let us also take into account any children of the asymptomatic individual who have been tested mutation negative. Let Pr(C|NS;n) be the probability that an individual is a carrier, given that he or she is without clinical signs or symptoms and has n children tested mutation negative. It can then be shown[49] that:

$$RRS = Pr(C|NS;n) = q/(q+2^n) \quad (7)$$

This holds on the condition that no child has been tested positive. As an aid for calculating the RRS, we provide an MS-Excel spreadsheet that can be downloaded from our website (see correspondence information).

Further information about calculating risk changes in more complicated pedigrees is available upon request, including a general formula that can be used for all situations.

DISCUSSION

The increased number of data on CAG-repeats and ages at onset within families allowed us to develop the presented model. This model provides new alternatives for risk refinement that can be offered to individuals at risk who have not (yet) been tested. Applying this model can only lead to an estimation of decreased risk, while the mutation test can yield the irreversible outcome that one carries the HD gene. Nevertheless, this model is not primarily aimed at individuals who do not wish to be tested for a variety of reasons. Our model is aimed at broadening the information that genetic counsellors can offer, based on absence of symptoms. Establishing early HD signs is difficult. Self-reports of the individuals at risk with regard to being unaffected are not sufficient to rely on, and neurological examination remains the most accessible, reliable, and cost-effective means of determining onset of clinical disease.[50] However, De Boo et al.[51] reported considerable disagreement amongst HD-experienced neurologists with regard to neurological examinations in the earliest phase of the disease. Neuropsychological motor assessment proved to be more sensitive to early changes than neurological judgments. Obviously, the first HD-symptoms are hard to recognize, and not all individuals show the same first symptoms[52] Some individuals display motor symptoms first, whereas in others first symptoms are psychiatric. Further studies may reveal the extent to which hereditary components contribute to these differences.

It must be noted that all our estimates are based on empirical data, and hence all values contain some uncertainty: the estimate of CAG repeat length of an affected or at-risk individual depends to some extent on the techniques used in the mutation test and all regression analyses put confidence limits to the coefficients in the equations. This means that all calculations are based on the best possible estimates of a parameter, and consequently all values of the CAG of a proband and the Residual Risk Status (RRS) must be considered as best possible estimates too. Given this uncertainty, counselees will generally be interested to learn whether the original (prior) risk of the target individual has substantially changed with

increasing age, and what the best possible estimate of the RRS would be, given their situation. This might help in their decision to be tested and their preparation for the test result. This decision can depend on the actual RRS and the RRS in the near future. From the CAG repeat length estimated with our model and the tables published by Langbehn et al.[26] it can be determined whether the individual is at a critical age regarding onset. During this critical period the decrease in RRS is most prominent, which can affect the decision to be tested soon or to postpone the test for a few years.

Recently, concern has arisen for individuals at risk for HD regarding employment.[53] Burgermeister described how a teacher at risk was refused a job because of a family history of HD.[54] In fact this topic is an extension of insurance problems that have been raised previously.[38 55] Assuming that many will hold on the a priori risk, all those involved should be better informed about the actual risk to develop HD. A refinement of the actual risk for HD without actually performing a test can help to make judgements that are more adequate. Moreover, this is always beneficial for individuals at risk because the RRS is always lower than the a priori risk.

With our model and the accompanying spreadsheet, clinical geneticists and genetic counsellors will be able to provide a best estimation of the residual risk status for individuals in their circumstances. The model also allows establishing the slope of decline in risk status for the years to come by determining the changed risks for future ages, given that the individual at risk remains symptom-free.

ACKNOWLEDGEMENTS AND AFFILIATIONS

We thank Vicky Kraver for correcting our use of the English language.

REFERENCES

1. Kremer B. Clinical neurology of Huntington's disease - Diversity in unity, unity in diversity. In: Bates G, Harper PS, Jones L, editors. *Huntington's disease*. 3rd ed. Oxford: Oxford University Press, 2002:28-61.
2. Kremer B, Squitieri F, Telenius H, Andrew SE, Theilmann J, Spence N, et al. Molecular analysis of late onset Huntington's disease. *J Med Genet* 1993;30(12):991-995.
3. Nance MA, Mathias-Hagen V, Breningstall G, Wick MJ, McGlennen RC. Analysis of a very large trinucleotide repeat in a patient with juvenile Huntington's disease. *Neurology* 1999;52(2):392-394.
4. Rubinsztein DC, Leggo J, Coles R, Almqvist E, Biancalana V, Cassiman JJ, et al. Phenotypic characterization of individuals with 30-40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36-39 repeats. *Am J Hum Genet* 1996;59(1):16-22.
5. Maat-Kievit A, Losekoot M, Zwinderman K, Vegter - van der Vlis M, Belfroid R, Lopez F, et al. Predictability of age at onset in Huntington disease in the Dutch population. *Medicine* 2002;81(4):251-259.

6. Brinkman RR, Mezei MM, Theilmann J, Almqvist E, Hayden MR. The likelihood of being affected with Huntington disease by a particular age, for a specific CAG repeat. *Am J Hum Genet* 1997;60:1202-1210.
7. MacDonald ME, Vonsattel JP, Shrinidhi J, Couropmitree NN, Cupples LA, Bird ED, et al. Evidence for the GluR6 gene associated with younger onset age of Huntington's disease. *Neurology* 1999;53(6):1330-1332.
8. Farrer LA, Cupples LA, Wiater P, Conneally PM, Gusella JF, Myers RH. The normal HD allele, or a closely linked gene, influences age at onset of Huntington's disease. *Am J Hum Genet* 1993;53:125-130.
9. Djousse L, Knowlton B, Hayden M, Almqvist EW, Brinkman R, Ross C, et al. Interaction of normal and expanded CAG repeat sizes influences age at onset of Huntington disease. *Am J Med Genet* 2003;119A(3):279-282.
10. Nazé P, Vuillaume I, Destée A, Pasquier F, Sablonnière B. Mutation analysis and association studies of the ubiquitin carboxy-terminal hydrolase L1 gene in Huntington's disease. *Neurosci Lett* 2002;328(1):1-4.
11. Andrew SE, Goldberg YP, Kremer B, Telenius H, Theilmann J, Adam S, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nat Genet* 1993;4(4):398-403.
12. Andrew SE, Goldberg YP, Theilmann J, Zeisler J, Hayden MR. A CCG repeat polymorphism adjacent to the CAG repeat in the Huntington disease gene: implications for diagnostic accuracy and predictive testing. *Hum Mol Genet* 1994;3(1):65-67.
13. Rubinsztein DC, Barton DE, Davison BC, Ferguson-Smith MA. Analysis of the huntingtin gene reveals a trinucleotide-length polymorphism in the region of the gene that contains two CCG-rich stretches and a correlation between decreased age of onset of Huntington's disease and CAG repeat number. *Hum Mol Genet* 1993;2(10):1713-1715.
14. Vuillaume I, Vermersch P, Destee A, Petit H, Sablonniere B. Genetic polymorphism to the CAG repeat influence clinical features at onset in Huntington diseases. *J Neurol Neurosur Ps* 1998;64:758-762.
15. Almqvist E, Spence N, Nichol K, Andrew SE, Vesa J, Peltonen L, et al. Ancestral differences in the distribution of the delta 2642 glutamic acid polymorphism is associated with varying CAG repeat lengths on normal chromosomes: insights into the genetic evolution of Huntington disease. *Hum Mol Genet* 1995;4(2):207-214.
16. Ambrose CM, Duyao MP, Barnes G, Bates GP, Lin CS, Srinidhi J, et al. Structure and expression of the Huntington's disease gene: evidence against simple inactivation due to an expanded CAG repeat. *Somat Cell Mol Genet* 1994;20(1):27-38.
17. Lucotte G, Gerard N, Roubertoux P, Schmitt I, Riess O. Relationships of the 2642 deletion polymorphism (delta 2642) in the huntingtin gene with the CAG repeat expansion length and age at onset of the disease. *Genet Couns* 1996;7(4):297-302.

18. Kehoe P, Krawczak M, Harper P, Owen MJ, Jones AL. Age of onset in Huntington disease: sex specific influence of apolipoprotein E genotype and normal CAG repeat length. *J Med Genet* 1999;36(2):108-111.
19. Li J-L, Hayden MR, Almqvist EW, Brinkman RR, Durr A, Dodé C, et al. A genome scan for modifiers of age at onset in Huntington disease: the HD MAPS study. *Am J Med Genet* 2003;73:682-687.
20. Farrer LA, Conneally PM. A genetic model for age at onset in Huntington disease. *Am J Hum Genet* 1985;37(2):350-357.
21. Krawczak M, Bockel B, Sandkuijl L, Thies U, Fenton I, Harper PS. Covariate-dependent age-at-onset distributions for Huntington disease. *Am J Hum Genet* 1991;49(4):735-745.
22. Ridley RM, Frith CD, Crow TJ, Conneally PM. Anticipation in Huntington's disease is inherited through the male line but may originate in the female. *J Med Genet* 1988;25(9):589-595.
23. Ridley RM, Frith CD, Farrer LA, Conneally PM. Patterns of inheritance of the symptoms of Huntington's disease suggestive of an effect of genomic imprinting. *J Med Genet* 1991;28(4):224-231.
24. Roos RA, Vegter-van der Vlis M, Hermans J, Elshove HM, Moll AC, van de Kamp JJ, et al. Age at onset in Huntington's disease: effect of line of inheritance and patient's sex. *J Med Genet* 1991;28(8):515-519.
25. American College of Medical Genetics, American Society of Human Genetics, Group HDGTW. Laboratory guidelines for Huntington disease genetic testing. *Am J Hum Genet* 1998;62(1243-1247).
26. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR, International Huntington's Disease Collaborative Group. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin Genet* 2004;65(4):267-277.
27. Bloch M, Fox S, Hayden MR. Predictive testing for Huntington disease: II. Demographic characteristics, life-style patterns, attitudes, and psychosocial assessments of the first fifty-one test candidates. *Am J Med Genet* 1989;32:217-224.
28. Tyler A, Ball D, Craufurd D. Presymptomatic testing for Huntington's disease in the United Kingdom. *Brit Med J* 1992;304:1593-1596.
29. International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. *J Med Genet* 1994;31:555-559.
30. Laccone F, Engel U, Holinski-Feder E, Weigell-Weber M, Marczinek K, Nolte D, et al. DNA analysis of Huntington's disease: five years of experience in Germany, Austria, and Switzerland. *Neurology* 1999;53(4):801-806.
31. Maat-Kievit A, Vegter - van der Vlis M, Zoeteweij M, Losekoot M, Van Haeringen A, Roos R. Paradox of a better test for Huntington's disease. *J Neurol Neurosur Ps* 2000;69(5):579-583.
32. Evers-Kiebooms G, Cassiman JJ, Van den Berghe H. Attitudes towards predictive testing in Huntington's disease: a recent survey in Belgium. *J Med Genet* 1987;24:275-279.

33. Evers-Kiebooms G, Swerts A, Cassiman JJ, Van den Berghe H. The motivation of at-risk individuals and their partners in deciding for or against predictive testing for Huntington's disease. *Clin Genet* 1989;35(1):29-40.
34. Meissen GJ, Myers RH, Mastromauro CA, Koroshetz WJ, al. e. Predictive testing for Huntington's disease with use of a linked DNA marker. *New Engl J Med* 1988;318(9):535-542.
35. Craufurd D, Dodge A, Kerzin-Storrar L, Harris R. Uptake of presymptomatic predictive testing for Huntington's disease. *Lancet* 1989(September 9):603-605.
36. Morris MJ, Tyler A, Lazarou L, Meredith L, Harper PS. Problems in genetic prediction for Huntington's disease. *Lancet* 1989;2(8663):601-603.
37. Tibben A, Frets PG, Van De Kamp JJP, Niermeyer MF, Vegter-Van Der Vlis M, Roos RAC, et al. Presymptomatic DNA testing for HD: pretest attitudes and expectations of applicants and their partners in the Dutch program. *Am J Med Genet* 1993;48:10-16.
38. Quaid KA, Morris M. Reluctance to undergo predictive testing: the case of Huntington disease. *Am J Med Genet* 1993;45(1):41-45.
39. Codori A-M, Hanson R, Brandt J. Self-selection in predictive testing for Huntington's disease. *Am J Med Genet* 1994;54:167-173.
40. Van Der Steenstraten IM, Tibben A, Roos RAC, Van Der Kamp JJP, Niermeijer MF. Predictive testing for Huntington disease: nonparticipants compared with participants in the Dutch program. *Am J Hum Genet* 1994;55:618-625.
41. Teltscher B, Polgar S. Objective knowledge about Huntington's disease and attitudes towards predictive tests of persons at risk. *J Med Genet* 1981;18:31-39.
42. Schoenfeld M, Berkman B, Myers RH, Clark E. Attitudes toward marriage and childbearing of individuals at risk for Huntington's disease. *Soc Work Health Care* 1984;9(4):73-81.
43. Kessler S, Field T, Worth L, Mosbarger H. Attitudes of persons at risk for Huntington disease toward predictive testing. *Am J Med Genet* 1987;26:259-270.
44. Mastromauro C, Myers RH, Berkman B. Attitudes toward presymptomatic testing in Huntington disease. *Am J Med Genet* 1987;26:271-282.
45. Meissen GJ, Berchek RL. Intended use of predictive testing by those at risk for Huntington disease. *Am J Med Genet* 1987;26:283-293.
46. Markel DS, Young AB, Penney JB. At risk persons' attitude toward presymptomatic and prenatal testing of Huntington disease in Michigan. *Am J Med Genet* 1987;26:295-305.
47. Harper PS, Newcombe RG. Age at onset and life table risks in genetic counseling for Huntington's disease. *J Med Genet* 1992;29:239-242.
48. Wexler NS, Lorimer J, Porter J, Gomez F, Moskowitz C, Shackell E, et al. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *Proc Natl Acad Sci U S A* 2004;101(10):3498-3503.

49. Bonke B, Tibben A, Lindhout D, Stijnen T. Favourable mutation test outcomes for individuals at risk for Huntington disease change the perspectives of first-degree relatives. *Hum Genet* 2002;111:297-298.
50. McCusker E, Richards F, Sillence D, Wilson M, Trent RJ. Huntington's disease: neurological assessment of potential gene carriers presenting for predictive DNA testing. *J Clin Neurosc* 2000;7(1):38-41.
51. De Boo G, Tibben A, Hermans J, Maat A, Roos RA. Subtle involuntary movements are not reliable indicators of incipient Huntington's disease. *Mov Disord* 1998;31(1):96-99.
52. Witjes-Ané MN, Vegter-van der Vlis M, van Vugt JP, Lanser JB, Hermans J, Zwinderman AH, et al. Cognitive and motor functioning in gene carriers for Huntington's disease: a baseline study. *J Neuropsychiatry Clin Neurosci* 2003;15(1):7-16.
53. Harper PS, Gevers S, de Wert G, Creighton S, Bombard Y, Hayden MR. Genetic testing and Huntington's disease: issues of employment. *Lancet Neurol* 2004;3(4):249-252.
54. Burgermeister J. Teacher was refused job because relatives have Huntington's disease. *Brit Med J* 2003;327:827.
55. Burgess MM, Adam S, Bloch M, Hayden MR. Dilemmas of anonymous predictive testing for Huntington disease: privacy vs. optimal care. *Am J Med Genet* 1997;71:197-201.

APPENDIX 1.

Survival function at the mean of covariates.

Age in years	Survival	Age in years	Survival	Age in years	Survival
4	0,9998648296	32	0,9211905093	60	0,0629806062
5	0,9998648296	33	0,9078111164	61	0,0602230337
6	0,9998648296	34	0,8983660080	62	0,0498256866
7	0,9995683096	35	0,8725536578	63	0,0359824731
8	0,9993674982	36	0,8511427002	64	0,0279641391
9	0,9993674982	37	0,8256689172	65	0,0209831443
10	0,9988069390	38	0,7992705745	66	0,0137979672
11	0,9988069390	39	0,7737601077	67	0,0102777203
12	0,9984927618	40	0,7102701388	68	0,0061011707
13	0,9984927618	41	0,6872908368	69	0,0046470872
14	0,9984927618	42	0,6479470703	70	0,0024215613
15	0,9984927618	43	0,5865683119	71	0,0018075845
16	0,9978580841	44	0,5543537282	72	0,0011619988
17	0,9972068868	45	0,5093739451	73	0,0011619988
18	0,9965294999	46	0,4714799104	74	0,0010279425
19	0,9965294999	47	0,4484252329	75	0,0004266614
20	0,9945680373	48	0,4043457776	76	0,0002448453
21	0,9908924474	49	0,3804504242	77	0,0001586526
22	0,9884457913	50	0,3126109815	78	0,0000512595
23	0,9845913076	51	0,2924192908	79	0,0000094335
24	0,9821489122	52	0,2650219915	80	0,0000023917
25	0,9773467405	53	0,2289791507	81	0,0000008359
26	0,9733702412	54	0,2037671950	82	0,0000001716
27	0,9679857532	55	0,1714190410	83	0,0000000063
28	0,9634262994	56	0,1390389326	84	0,0000000063
29	0,9574896216	57	0,1163949018	85	0,0000000063
30	0,9434607655	58	0,0937128217	86	0,0000000000
31	0,9407665592	59	0,0854611583		

CHAPTER 7a
-
Nature and Development of Huntington Disease in a Nursing Home Population: The BOSH Rating Scale

Reinier Timman [1 2], Hans Claus [3], Henk Slingerland [4], Marijanne van der Schalk [5], Saskia Demeulenaere [6], Raymund Roos [7], Aad Tibben [1 7]

[1] Leiden University Medical Centre, Department of Neurology; [2] Erasmus Medical Center Rotterdam, Department of Medical Psychology and Psychotherapy, Rotterdam, the Netherlands; [3] Stichting Duyn & Rhyn, location Overduin, Katwijk, The Netherlands; [4] Atlant Zorggroep, location Heemhof, Apeldoorn, The Netherlands; [5] R.K. Zorgcentrum Sint Jacob, Amsterdam, The Netherlands; [6] Home Marjorie, Heist-op-den-berg, Belgium; [7] Leiden University Medical Centre - Centre for Human and Clinical Genetics, Leiden, The Netherlands

Submitted

ABSTRACT

Objective: The Behavior Observation Scale Huntington (BOSH) was developed to obtain a detailed description of the manifestation of Huntington's disease in the final stages in a nursing home.

Background: The Unified Huntington's Disease Rating Scale (UHDRS), developed to assess Huntington's patients' clinical capacities, does not differentiate adequately in later stages of the disease. A scale easy to administer by nursing personnel for progression of the disease in later stages was needed.

Method: Two pilot questionnaires preceded the final version of the BOSH. Observers administered the final version twice independently on 91 patients in four nursing homes.

Results: The BOSH contains 32 items in three subscales: 1) Activities of daily living (ADL), 2) social-cognitive functioning, and 3) mental rigidity and aggression. Internal and inter-rater reliabilities were between .83 and .95.

Conclusions: A linear relation was found between disease duration and deterioration of ADL. Non-linear relations were found between 1) ADL and rigidity-aggression, and 2) ADL and social-cognitive capabilities. Rigidity and aggression become more frequent as the disease progresses, later on this behavior diminishes. Social-cognitive capabilities deteriorate more rapidly in later stages.

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease, characterized by disturbance of movements (chorea and hypokinesia), progressive dementia and affective disturbances.[1] The end stages of the disease often warrant admission in a nursing home. The mean age at onset is between 30 and 50 years and the specific features of the disease have justified the establishment of specialized wards. Since the mid eighties of the previous century much experience and knowledge has been acquired in caring for HD patients. In later stages of the disease, the patient can hardly perform any action without help, and communication is difficult or impossible. In these stages, there is a lack of insight in the nature and course of the clinical manifestations of the disease. This lack of insight hardly allows an individually tailored caring program.

Shoulson & Fahn[2] described a categorization of the course of the disease in five stages according to engagement in occupation, capacity to handle financial affairs, capacity to manage domestic problems, capacities to perform activities of daily living (ADL), and the place where care can be provided. They proposed this categorization for functional designations of patients for care evaluation, and it was to be confirmed by further investigation. However, Shoulson and Fahn indicated that the broad assessment of functional capacities is probably not sufficiently sensitive to register marginal clinical effects,[2] and it seems not to be adequately sensitive to cognitive and psychiatric symptoms.[3]

The Huntington Study Group[4] developed the Unified Huntington's Disease Rating Scale (UHDRS) to assess four domains of clinical performance and capacities in Huntington's disease: motor, cognitive, behavioral and functional assessment. A word fluency test, the Symbol Digit Modalities Test and the Stroop Color Interference Test assess cognitive abilities These tests can hardly be administered in the later stages of HD, when speech or write capacities have deteriorated too far. Functional capacities are administered by 25 dichotomous (yes/no) items. In later disease stages, all functional capacity items are scored as "no". For these reasons, differentiation of the UHDRS is limited in the later stages of the disease. For administration of the UHDRS more than an hour is needed, requiring a skilled neurologist and a physician or psychologist familiar to the patient. We developed the Behavior Observation Scale Huntington (BOSH) as a quicker and easier instrument. The BOSH should allow repeated monitoring for longitudinal assessment, and it is meant to make an inventory of the behavior in the later stages of the disease.

SUBJECTS AND METHODS

Two pilot questionnaires preceded the final version of the BOSH. The first pilot was constructed in two Dutch nursing homes (Overduin in Katwijk, Heemhof in Beekbergen). We developed the second pilot and the final version also in two other nursing homes (St. Jacob in Amsterdam, The Netherlands, Home Marjorie in Heist-op-den-Berg, Belgium). The pilot and

final version of the BOSH were administered for all but two patients. The latter were admitted to a psychiatric hospital, one patient because of extreme aggressive behavior, the other because of extreme anxiety and delusions. The clinical details of the participants are given in Table 1.

Table 1. *Number of participants, age and years of care in pilots and final questionnaire*

		n			mean age (years)			mean years of admission		
	Nursing Home	♂	♀	total	♂	♀	total	♂	♀	total
1st pilot	Overduin [a]	11	11	22	48	48	48	2.4	2.7	2.5
	day-treatment	5	1	6	52	55	53	1.2	0.2	1.0
	Heemhof	11	10	21	40	41	41	3.2	1.3[b]	2.3
	Total	27	22	49	45	45	45	2.5	1.8	2.2
2nd pilot	Overduin [a]	9	17	26	46	51	50	3.3	3.2	3.9
	day-treatment	4	1	6	55	45	53	2.8	0.8	2.0
	Heemhof	14	17	31	46	50	48	3.6	3.8	3.7
	St. Jacob	4	7	11	59	51	54	1.8	3.3	2.7
	Marjorie	6	4	10	43	43	43	1.2	1.8	1.4
	Total	38	46	84	48	50	49	2.8	3.2	3.0
Final version	Overduin [a]	10	18	28	47	55	52	3.1	4.4	3.9
	day-treatment	4	3	7	56	50	53	3.5	0.8	2.0
	Heemhof [a]	15	17	32	48	49	49	3.8	3.6	3.7
	day-treatment	1	6	7	49	53	53	0.5	0.3	0.3
	St. Jacob	5	3	8	50	54	52	1.8	4.3	2.8
	Marjorie	6	3	9	45	38	42	1.8	2.7	2.1
	Total	41	50	91	49	51	50	3.0	3.2	3.1

Note. [a] Clinic only; [b] $F_{(1,18)} = 4.87$; $p = .04$. No other differences are below $p = .05$ level for gender.

The first pilot questionnaire was based on 11 characteristics of the HD-patient, according to the observations of the staff of the nursing homes: 1) inflexible behavior, 2) need for social care, 3) need for mental care, 4) need for physical care, 5) communication problems, 6) choking problems, 7) uncontrolled eating and drinking behavior, 8) self-orientated behavior, 9) repetitive behavior, 10) aggressive behavior, and 11) inability to perform complex actions. The pilot questionnaire contained 32 four-answer-category items and was administered by nursing personnel to 49 patients. Nursing personnel were given written instructions for filling in the rating scale. Principal component analysis (PCA) revealed 6 designated components; speech capability, mental rigidity-aggression, social-cognitive capacities, obsessive-compulsive behavior, voraciousness and deterioration of ADL.

For the construction of the second version we restructured the items in line with the 6 components that emerged from the first pilot. Twenty-four items with the highest loadings on each component were selected, on the premise that these did not have too large a conceptual overlap. The inclusion of items with a high conceptual overlap, such as "choking while eating" and "choking while drinking" would unduly raise the internal consistency measure. Four items with lower component loadings, which were considered as clinically essential aspects of HD, were added. Four

items from the functional assessment sub-scale of the UHDRS[4] were included because they were also considered essential to the manifestation of HD. Infrequently scored response categories were reformulated. Behavior such as "the patient bolts every portion of food at once, and cannot be controlled" was not observed. We toned this response category down to "tends to bolt food and cannot be corrected". Ambiguous items, double questions and items with an overlap in the response possibilities, as well as items with gaps between answer possibilities were reformulated. The layout was made uniform for all items and carefully arranged after the recommendations of Dillman.[5] The second version was administered to 84 patients in one Belgian and three Dutch nursing homes. For each patient different nurses in charge of the daily care of the patients administered the scale twice independently. Instructions were printed on the questionnaire.

For the third and final version, we reformulated the 32 items again to avoid overlap and gaps. Ambiguousness was reduced and items were rearranged in a more logical order. Routings for outpatients and for tube fed patients were introduced. The final version was administered in Dutch to 91 patients in the 4 nursing homes.

Factor or principal component analysis requires that the number of cases is at least 5 times the number of items,[6] which meant that at least 160 cases were needed. For the third version of the BOSH, 91 patients were available, largely the same population as was included in the second version. The required number of cases was achieved by having the scale completed for the 91 patients twice, independently by different observers. Two data sets were created in this way and single measure intraclass correlation coefficients (ICC's) could be computed.

Missing values were imputed using the singular Expectation Maximization procedure (EM)[7] in the SPSS missing value module. EM is an algorithm that estimates the means, covariances, and the Pearson correlations of quantitative variables. It is an iterative process, which uses two steps for each iteration. The E step computes expected values conditional on the observed data and the current estimates of the parameters. The M step calculates maximum likelihood estimates of the parameters based on values computed in the E step.[8] This imputation procedure was performed in both samples separately before performing PCA. The component structures in both data sets should be comparable.

Duration of care was computed from the administered date of admission to the nursing home or start of the day treatment. Disease duration was computed from medical information on age at onset. We determined the age at onset from the first neurological or psychiatric signs that could be attributed to HD. Relations between principle components among each other and with disease and nursing duration were analyzed with regression modeling.

RESULTS

Administration of the questionnaires took 10 to 15 minutes, with a mean of 14 minutes. The 91 patients included 41 men (mean age 48.5 years, sd 9.5) and 50 women (mean age 51.2 years, sd 11.1), 77 inpatients and 14 outpatients.

Principal components

A three-component PCA solution was found in both samples. After a VARIMAX rotation, these components could be labeled as ADL, social-cognitive capabilities, and rigidity-aggression. Principal component loadings of the individual items are summarized in Table 2. Characteristics of the subscales are summarized in Table 3. The statistics for all three scales suggest an acceptable level of internal consistency.[9]

Table 2. *Principal component loadings for 3 factors of 32 BOSH items*

Component / item	loading
ADL	
4. Going to the toilet	.84
2. Going to bed	.83
5. Mobility	.82
9. Comprehensibility through nonverbal communication	.81
7. Voice control and articulation	.79
30. Eating and drinking	.78
1. Washing and getting dressed	.77
8. Intelligibility	.74
29. Choking while eating or drinking	.57
Social-cognitive	
18. Seeking contact and receptiveness	.78
12. Recollection of recent events important to patient	.77
15. Patient knows staff members and fellow inpatients by name	.73
10. Ability to understand verbal communication	.73
16. Emotionalism	.70
13. Remembering appointments	.69
14. Ability to occupy himself/herself and participate in organised activities	.66
17. Awareness of being ill	.65
6. Ability to understand complex actions	.61
19. Contact with family, friends or fellow inpatients	.61
11. Ability to understand nonverbal communication	.58
Rigid-aggressive	
26. Patient is open to correction	.81
25. Patient accepts what you say	.80
21. Degree to which verbal and physical aggression can be corrected	.77
24. Patient causes problems if a fixed routine is not adhered to	.72
22. Tendency towards verbal and physical aggression	.72
23. Patient tries to exceed the limits of standing agreements or house rules	.72
20. Showing consideration for fellow inpatients	.67
27. Performance of specific activities is impeded	.59
28. Patient performs stereotypical, apparently aimless activities	.42
32. Bolting food	.42
31. Voracity and insatiability	.40
3. Going to bed on time	.25

Table 3. *Characteristics of the subscales*

Scale	number of items	% variance sample 1-2	α sample 1-2	ICC	mean (sd)
ADL	9	23-20	.94-.94	.95	2.25 (0.88)
Social and cognitive abilities	11	18-20	.92-.91	.90	2.10 (0.79)
Rigidity and aggression	12	16-16	.83-.86	.85	1.63 (0.48)

Note. ICC = intraclass correlation coefficient; ADL = activities of daily living

Individual sub-scale scores were computed by dividing the total score by the number of valid items of the subscale involved. In this way, the original clinical meaning of the values was preserved (Table 4).

Table 4. Scale values and clinical denotation

	1	2	3	4
ADL	self-supporting	guidance needed	care needed	nursing required
Social-cognitive	unaffected	first signs of decay	contact still possible	contact not possible
Rigidity-aggression	never	sometimes	often	always

Note. ADL = activities of daily living

Relations with disease and care duration

A linear relation was found between ADL deterioration and duration of care (Table 5). Patients had higher ADL deterioration scores when they had been longer institutionalized or had been in day treatment for a longer period. Women tended to have (p = .04) worse ADL scores than men, means 2.45 and 2.00 respectively.

Table 5. *Regression modeling of principal components on duration illness, of institutional care, gender and age.*

	ADL (R^2 = 0.38)		Social-cognitive (R^2 = 0.35)		Rigid-aggressive (R^2 = 0.24)	
Independent variables	β	*p*	β	*p*	β	*p*
Duration of illness	.10	.48	-.07	.63	-.34	.03
Squared duration of illness	.12	.37	.27	.04	.14	.32
Duration of care	.50	.001	.14	.34	-.05	.77
Squared duration of care	-.14	.31	.14	.34	-.11	.49
Gender (men=1; women=2)	.21	.04	.03	.74	.00	1.00
Clinic / day care	-.19	.07	-.32	.004	-.30	.01
Age	-.07	.54	.21	.07	-.11	.34

Note. ADL = activities of daily living

For 74 patients, an indication for the age of onset of HD was found. A weak significant quadratic relation of social-cognitive deterioration with duration of illness was found. Social-cognitive abilities decline more rapidly

in the later stages of the disease. A weak significant linear relation between duration of illness and the rigid-aggressive component indicates that patients who are affected for a longer period display less rigid and aggressive behavior. Outpatients had significantly lower social-cognitive deterioration and rigidity-aggression scores than institutionalized patients.

Table 6. *Regression modeling of social-cognitive and rigid-aggressive components on ADL*

	Social-cognitive (R^2 = 0.59)		Rigid-aggressive (R^2 = 0.35)	
Independent variables	β	*p*	β	*p*
ADL	.56	.000	.10	.32
Squared ADL	.22	.004	-.50	.000
Gender (men=1; women=2)	-.04	.64	-.07	.46
Clinic / day care	-.16	.03	-.31	.002
Age	.23	.002	-.10	.27

Note. ADL = activities of daily living

Relations between components

Regression modeling of the social-cognitive component on the ADL component revealed significant linear and quadratic relations (Figure 1, Table 6). The interpretation of the linear relation is that as ADL declines (higher ADL deterioration scores), social-cognitive abilities also decline (higher disability scores). The positive quadratic relation implies that social-cognitive abilities deteriorated faster in more advanced stages of HD.

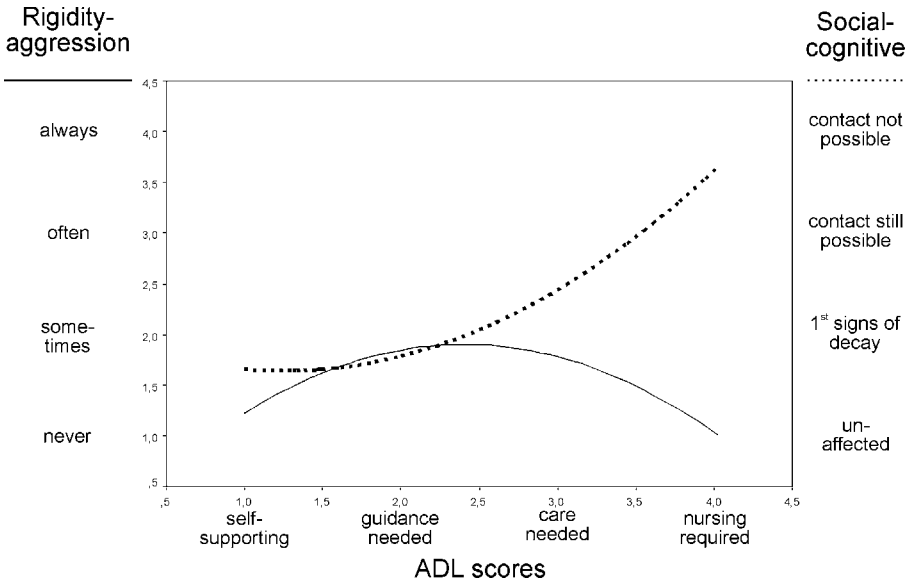

Fig 1. *Regression model of social-cognitive and rigidity-aggression on ADL*

A significant, negative quadratic effect was found between ADL and rigid-aggressive behavior, reflecting that aggressive behavior was most frequent in the intermediate stages.

The significant clinic/day care effects can be interpreted as outpatients having better social-cognitive competence and displaying less rigid-aggressive behavior. The significant age effect implies that older patients had worse social-cognitive abilities.

Missing values

For 14 outpatients (15% of the total number of patients) the three items regarding washing, dressing and going to bed (items 1 - 3) could not be administered. The items related to washing and dressing (item 1) and going to bed (item 2) for these outpatients were imputed with values between 2 and 4, with means of 2.8 and 2.6 respectively. The values of the estimates indicate that these patients needed assistance from their spouse or caregiver, but were able to cooperate. Going to bed in time (item 3, was imputed for outpatients with values between 0.4 and 3.4 (mean 1.7), which indicated that most outpatients needed not too much persuasion to get them to bed.

For the 3 tube fed patients (3% of the total number of patients) the 3 items concerning consuming food were not applicable. For these patients the eating ability item (30) was imputed with values higher than 4, indicating complete assistance. The items on voracity (item 31) and bolting of food (item 32) were imputed with values below 1.5, which indicates that these patients caused hardly any problems. In addition to these structural missing values, there were totally 21 other missing values (0.4% of the total number of items in all administered questionnaires).

DISCUSSION

Main findings

The final version of the BOSH contains 32 items. A principal component analysis with varimax rotation revealed 3 designated components: 1) deterioration of ADL, 2) deterioration of social and cognitive abilities and 3) mental rigidity and aggressive behavior. Internal reliabilities and inter-rater reliabilities were acceptable. Non-linear relations were found between these components.

Relations with duration of disease and care

Weak relations between disease duration and deterioration of social-cognitive abilities and rigid-aggressive behavior were found. The weakness of these relationships may be caused by the less precise way in which the age at onset, and thus disease duration, were determined retrospectively.[10] The insidious course of the disease in the first stages makes it very difficult, if not impossible, to determine the exact onset. If the age at onset was inferred from the first psychiatric signs, obtained from medical information,

there are two possibilities. On the one hand, the age at onset was estimated too high if the first psychiatric signs were indeed clinical signs of HD. On the other hand, the age at onset was estimated too low if the first psychiatric signs were not a clinical manifestation. Hence disease duration was estimated too short or too long respectively. The problem may be solved in the future by the results of current studies in the USA, Australia, and Europe, which address the transition from health to HD in persons at risk for developing HD (http://www.euro-hd.net). The intent of these studies is to learn more about the beginning changes in thinking skills, emotional regulation, brain structure and brain function as a person begins the transition from health to HD.

A significant linear relation between the care period and deterioration of ADL was found. We argue that the institutional care period is a biased indicator for the progression of the disease. Though impairment of motor functioning is important in the decision for placement in a nursing home, the decision of placement in a nursing home is principally dependent on the absence of a caring spouse or other person.

Relations between components

Nehl et al.[3] did not find a significant relation between aggression, and obsessive/compulsive behavior with the total functional capacity scale (TFC) of the UHDRS. They argue that TFC scale may not be a particular good indicator of a person's cognitive and psychiatric difficulties. Another reason might be that they only analyzed linear relations. We found a strong significant quadratic relation between rigidity-aggression and the ADL level. This can be interpreted as rigid and aggressive behavior becomes more frequent at first, and less frequent later. A similar relation, between inflexibility and disease duration was observed in the study of Craufurd et al.[11] but it was not clear whether that relation was significant.[12]

Strong significant linear and quadratic relations are also found between social-cognitive functioning and ADL level. Again applying ADL deterioration as an operationalization of disease duration, the interpretation of these relations is that the deterioration of social-cognitive capabilities progresses more rapidly in later stages of the disease, when rigid and aggressive behavior is decreasing. In other words, the decline of ADL precedes the decline of social-cognitive behavior. This is consistent with the observation of Bamford et al.[13] that memory did not deteriorate until patients reached advanced stages of the disease.

Influence of medication

The level of aggression is moderated, because nursing homes try to reduce this behavior by several means. Firstly, this includes psychological and pharmacological interventions, though a restrictive policy is maintained for sedating medication. Secondly, patients are referred to a psychiatric hospital in extreme cases when these interventions fail to reduce the risk of aggressive outbursts that may be dangerous for staff personnel, fellow

patients, or the patient himself. These moderating effects may reduce relations with the rigid-aggressive component.

Relation to the UHDRS

The UHDRS rates four domains of clinical performance and capacities in HD: motor function, cognitive function, behavioral abnormalities, and functional capacity. In later stages of HD, the cognitive function and functional capacity cannot be assessed adequately. Motor function is assessed by a trained neurologist. Cognitive functioning is assessed by a neurologist or psychologist with a word fluency test, the Symbol Digit Modalities Test and the Stroop Color Interference Test. Behavioral abnormalities and functional capacity is assesses by a physician or psychologist. In short, the UHDRS is to be assessed by qualified personnel, and assessment takes more than one hour. The BOSH covers more or less the same domains and is administered within a quarter of an hour by nursing personnel who are in charge of the daily care of the patients. The UHDRS can be used adequately for longitudinal studies,[14] but is more laborious to assess. We expect that the BOSH is also sensitive to small changes in behavior, and is thus suitable for detecting changes in relatively small time spans, which is advantageous in longitudinal studies.

Implications for further research

We developed the BOSH in order to gain detailed insight into the progress of the disease and to distinguish individual differences between patients. A more detailed insight into these differences will facilitate a study of the relation of the phenotypic expression of HD with the pre-morbid personality and social support system. A better insight into this relation can be of help in better tailoring treatment to individual patients. The relation of the BOSH with other relevant scales will be determined thoroughly in an extensive study to the syndrome description of HD. Finally, the BOSH can be used as outcome measure in addition to functional measures in clinical trials.

ACKNOWLEDGEMENTS

The authors are very grateful to the nursing personnel, who filled in the questionnaires on which this study is based, and the cooperation of the nursing homes, these are:
Stichting Duyn & Rhyn, location Overduin, Katwijk, The Netherlands,
Atlant Zorggroep, location Heemhof, Apeldoorn, The Netherlands,
R.K. Zorgcentrum Sint Jacob, Amsterdam, The Netherlands,
Home Marjorie, Heist-op-den-berg, Belgium.
We also thank Vicky Kraver for correcting our use of the English language.

REFERENCES

1. Harper PS. *Huntington's disease*. London: Saunders, 2002.
2. Shoulson I, Fahn S. Huntington's disease: clinical care and evaluation. *Neurology* 1979;29:1-3.
3. Nehl C, Paulsen JS, The Huntington Study Group. Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. *J Nerv Ment Dis* 2004;192(1):72-74.
4. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord* 1996;11(2):136-142.
5. Dillman DA. *Mail and telephone surveys: the total design method*. New York; Chicester: Wiley, 1978.
6. Gorsuch RL. *Factor analysis*. Philadelphia etc.: W.B. Saunders Company, 1974.
7. Dempster A, Laird NM, Rubin D. Maximum likelihood from incomplete data via the EM algorithm. *J Roy Stat Soc B* 1977;39(1):174-194.
8. Hill M. *SPSS Missing value analysis 7.5*. Chicago, Ill: SPSS, 1997.
9. Nunnally JC. *Psychometric theory*. 2nd ed. New York: McGraw-Hill, 1978.
10. Maat-Kievit A, Losekoot M, Zwinderman K, Vegter - van der Vlis M, Belfroid R, Lopez F, et al. Predictability of age at onset in Huntington disease in the Dutch population. *Medicine* 2002;81(4):251-259.
11. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington disease. *Neuropsychiatr Neuropsychol Behav Neurol* 2001;14(4):219-226.
12. Timman R, Roos RAC, Tibben A. Nonlinear effects in behavioral changes in Huntington disease. *Cogn Behav Neurol* 2003;16(1):82.
13. Bamford KA, Caine ED, Kido DK, Cox C, Shoulson I. A prospective evaluation of cognitive decline in early Huntington's disease: functional and radiographic correlates. *Neurology* 1995;45(10):1867-1873.
14. Siesling S, Van Vugt JP, Zwinderman KA, Kieburtz K, Roos RA. Unified Huntington's disease rating scale: a follow up. *Mov Disord* 1998;13(6):915-919.

APPENDIX - THE BOSH

BEHAVIOUR OBSERVATION SCALE HUNTINGTON

(BOSH)

George Huntington
at the time he presented his classic
article in 1872

Patient (name): .....

BEHAVIOUR OBSERVATION SCALE HUNTINGTON (BOSH)

INSTRUCTION

The aim of this questionnaire is to describe the behaviour of a patient suffering from Huntington's Disease. The questionnaire applies to inpatients or outpatients.

The assessment covers your observation of the patient's behaviour in the **past two weeks.**

If an inpatient/outpatient displays changeable behaviour, you should base your assessment on the behaviour which you thought most prominent during the assessment period. Please tick the answer that, in your opinion, matches the inpatient's/outpatient's behaviour. If more than one answer is appropriate, please tick the one that best describes your observation of the patient's behaviour in the past two weeks.

If you find none of the answers appropriate, please tick the answer that most approximates the patient's behaviour. Please answer all the questions, unless it is explicitly stated that this is not necessary.

Patient number: .....

Sex: ❑ male ❑ female

Date of birth: ..... - ..... - .....

Team: .....

Completed by: .....

On: ..... - ..... - .....

Date of admission: ..... - ..... - .....

Outpatient treatment: ❑ no ❑ yes (start at question 4)

1. Washing and getting dressed:
   - ❑ Independently (if necessary under supervision)
   - ❑ Needs some assistance
   - ❑ Needs full assistance, but does cooperate
   - ❑ Completely dependent, cooperates hardly or not at all

2. Going to bed:
   - ❑ Independently (if necessary under supervision)
   - ❑ Needs some assistance
   - ❑ Needs assistance, but does cooperate
   - ❑ Cooperates hardly or not at all

3. Going to bed on time:
   - ❑ Causes no problems (not too early, not too late)
   - ❑ Has to be reminded
   - ❑ Has to be persuaded to go to bed on time
   - ❑ Difficult or impossible to get to bed on time

4. Going to the toilet:
   - ❑ Completely independently
   - ❑ Needs some assistance
   - ❑ Needs almost full assistance
   - ❑ No longer able to go to the toilet

5. Mobility:
   - ❑ Independent for short distances, if necessary using wheelchair or walker
   - ❑ Needs assistance, can move independently with difficulty
   - ❑ Can no longer move independently, but is capable of calling for assistance
   - ❑ Is completely dependent

6. Ability to understand complex actions, such as operating an electric wheelchair, a communicator, other electrical appliances, etc.:
   - ❑ Poses no problems (besides restrictions resulting from motor dysfunction)
   - ❑ Rough explanation and/or encouragement are necessary
   - ❑ Intensive step-by-step assistance is necessary
   - ❑ Patient is no longer capable of understanding complex actions

7. Voice control (control of sound and volume) and articulation:
   - ❑ Normal or almost normal
   - ❑ Affected
   - ❑ Bad
   - ❑ Voice is used for little more than uncontrolled cries

8. Intelligibility:
   - ❑ Is intelligible to everyone, perhaps with some difficulty
   - ❑ Is intelligible only to those who know patient well
   - ❑ Tries to say things, but is hardly intelligible or not at all, even for those who know patient well. Utterances consist mainly of making noises and crying out
   - ❑ Hardly or no longer uses voice for communication

9. Comprehensibility through nonverbal communication:
   - ❑ Patient is verbally clear to the extent that nonverbal communication is usually unnecessary
   - ❑ Capable of often making himself/herself clear by using gestures or communication aids
   - ❑ Uses gestures and aids to express himself/herself, but it is often necessary to inquire what he/she means
   - ❑ Can no longer make functional use of nonverbal communication

10. Ability to understand verbal communication:
   - ❑ Patient usually understands what is said in immediate vicinity
   - ❑ Patient only understands what is said if addressed personally
   - ❑ Limited, understands simple information
   - ❑ It is no longer clear if anything is understood

11. Ability to understand nonverbal communication:
   - ❑ Nonverbal support is not necessary
   - ❑ Nonverbal support is sometimes necessary
   - ❑ Understanding is difficult even with use of nonverbal support
   - ❑ It is no longer clear if anything is understood

12. Recollection of recent events important to patient (birthdays, trips, weddings):
   - ❑ Patient usually refers to the event himself/herself
   - ❑ Patient sometimes refers to the event himself/herself
   - ❑ Patient only shows signs of recognition or recollection when others refer to the event
   - ❑ Patient never shows signs of recognition or recollection

13. Remembering appointments:
   - ❑ Remembers appointments himself/herself, if necessary using a diary
   - ❑ Tries to remember appointments himself/herself, but usually forgets them
   - ❑ Always needs to be reminded of an appointment
   - ❑ It is no longer possible to make appointments

14. Ability to occupy himself/herself and participate in organised activities:
    - ❑ Generally reasonable to good
    - ❑ Needs assistance, encouragement and guidance
    - ❑ Hardly shows any initiative, or fills time with passive activities
    - ❑ No longer occupies himself/herself

15. Patient knows staff members and fellow inpatients by name:
    - ❑ All or almost all
    - ❑ Most
    - ❑ Some
    - ❑ None, or there is no way of telling

16. Emotionalism:
    - ❑ Emotions are appropriate and understandable
    - ❑ Strong mood swings, little control of emotions
    - ❑ Mood is flat, sometimes emotional distress or great restlessness, not always for an explicable reason
    - ❑ Emotions are hardly observable or difficult to recognise

17. Awareness of being ill:
    - ❑ Sufficient or reasonably sufficient awareness of being ill
    - ❑ Awareness of being ill, but has no real understanding of the seriousness and consequences
    - ❑ Seems to lack awareness of being ill because of incomprehension or denial
    - ❑ No longer speaks, utterances are hard to interpret

18. Seeking contact and receptiveness:
    - ❑ Usually seeks contact himself/herself, or is receptive
    - ❑ Often avoids contact, or contact is difficult because of demanding or attention-seeking behaviour
    - ❑ Passive, but responds briefly to attention and acquaintances
    - ❑ Contact practically impossible, does not respond to acquaintances

19. Contact with family, friends or fellow inpatients:
    - ❑ Usually goes well, or there is no contact, but that is not a problem
    - ❑ Frequent tension because of contact (or the lack of it)
    - ❑ Response usually flat, sometimes more responsive to certain persons
    - ❑ Little or no contact possible

20. Showing consideration for fellow inpatients:
    - ❑ There are few problems regarding contact with fellow inpatients
    - ❑ Patient does not show enough consideration, but does accept correction or rejection
    - ❑ Contact with fellow inpatients may lead to arguments, but the team can resolve the matter verbally
    - ❑ Patient is obtrusive to such an extent that arguments often cannot be prevented

21. Degree to which verbal and physical aggression can be corrected:
    - ❑ Aggression occurs hardly or not at all
    - ❑ Patient can be corrected verbally
    - ❑ Patient can only be corrected physically
    - ❑ Cannot be corrected with the means usually available on the ward

22. Tendency towards verbal and physical aggression:
    - ❑ Aggression occurs hardly or not at all
    - ❑ Tends to react evasively to frustrations and setbacks
    - ❑ Tends to react aggressively to frustrations and setbacks
    - ❑ Displays aggression at unpredictable moments

23. Patient tries to exceed the limits of standing agreements or house rules:
    - ❑ Never or n/a
    - ❑ Sometimes
    - ❑ Often
    - ❑ Always

24. Patient causes problems if a fixed routine is not adhered to:
    - ❑ Never
    - ❑ Sometimes
    - ❑ Often
    - ❑ Always

25. Patient accepts what you say:
    - ❑ Always, at least does not contradict it
    - ❑ Usually, sometimes with difficulty
    - ❑ Only if much cogency is used
    - ❑ Hardly ever, does completely what he/she wants

26. Patient is open to correction:
    - ❑ Always
    - ❑ Often
    - ❑ Sometimes
    - ❑ Never

27. Performance of specific activities is impeded because patient cannot dissociate from subjects or events that are not or are no longer relevant:
    - ❑ Never or n/a
    - ❑ Sometimes
    - ❑ Often
    - ❑ Almost always

28. Patient performs stereotypical, apparently aimless activities (such as walking and then sitting down again immediately), which take precedence over everything:
    - ❑ This never happens
    - ❑ This is only noticeable if you pay special attention to it
    - ❑ This happens remarkably often
    - ❑ This happens all the time

29. Choking while eating or drinking:
    - ❑ Patient does not choke often
    - ❑ Regularly, but can easily cough it up
    - ❑ Regularly and cannot easily cough it up
    - ❑ No longer capable of taking in food or liquids orally. (If this is the case you do not need to answer questions 30, 31 and 32)

30. Eating and drinking:
    - ❑ Completely independently
    - ❑ Independently, using special equipment
    - ❑ Needs supervision and partial assistance
    - ❑ Needs to be assisted completely

31. Voracity and insatiability:
    - ❑ Usually finds quantity satisfactory
    - ❑ Often asks for more, but accepts refusal
    - ❑ Eats or drinks everything he/she comes across, but does not go looking for it
    - ❑ Is constantly looking for something to eat or drink

32. Bolting food:
    - ❑ Patiently finishes one bite before taking the next
    - ❑ Tends to bolt food but can be corrected verbally
    - ❑ Tends to bolt food and can only be corrected physically
    - ❑ Tends to bolt food and cannot be corrected

Developed jointly by:
Psychogeriatrisch Centrum Overduin - Katwijk
Verpleeghuis Hullenoord - Beekbergen
Verpleeg en verzorginstelling St. Jacob - Amsterdam
Verzorginstelling Home Marjorie - Heist-op-den-Berg
Erasmus University Medical Center - Medical Psychology & Psychotherapy
Leiden University Medical Centre - Neurology

October 2004

CHAPTER 7b
-
Nonlinear effects in behavioral changes in Huntington disease

Reinier Timman [1 2], Aad Tibben [2], Raymund A.C. Roos [2]

[1] Erasmus University Medical Center Rotterdam, Department of Medical Psychology and Psychotherapy, the Netherlands; [2] Department of Neurology, Leiden University Medical Center, the Netherlands.
Cogn Behav Neurol, 2003;16(1):82.

Sir,

Craufurd et al.[1] found three factors in their study of the behavioral changes in Huntington disease (HD): Apathy, Depression and Irritability. The 'Apathy' factor was highly correlated with duration of illness, whereas no such relationship was observed for 'Depression' and 'Irritability'. However, in our opinion they have underestimated their findings due to inappropriate statistical methodology.

In figure 1(B) of their article all variables in factor 2, labeled as irritability, have a peak in the middle of the progression of the disease. The overall range of illness duration the authors monitored was 1 to 23 years. The peak in the figure suggests a non-linear relationship in their data. Although they did mention that there was a tendency for factor 2 symptoms to occur more frequently in subjects with illness duration between 6 and 11 years, they did not report whether they tested the significance of this tendency. Dividing duration of illness into 7 equal groups has the consequence that the measurement level is reduced from continuous to categorical. The authors have used Spearman rank-order correlations for analyzing the relationship of behavioral symptoms to disease duration. Generally, the efficiency of Spearman correlations are 91% relative to Pearson correlations.[2 3] It is less efficient to categorize data and use Spearman correlations than it is to use Pearson correlations on the original continuous data. Much information is lost by categorizing the continuous variable.

In a similar study on developing a 32 four-answer items rating scale for Huntington patients in the final stages of the disease (Behavior Observation Scale Huntington), we found five principal components in two clusters.[4] The first cluster includes activities of daily living, social-cognition and speech capacity, representing the progression of the disease. The other cluster contains inflexibility and obsessive-compulsive behavior, representing unmanageability of the patient. Using regression analysis, we found a significant non-linear relation between these two clusters ($F_{(2, 81)} = 6.56$; $p = .0023$). Unmanageability was found to be highest half way through the progression of the disease. Although it is possible to find a quadratic relation by correlating the square of the progression with the unmanageability, it is less effective to find non-linear effects, such as quadratic, cubic or logarithmic effects. Commonly used statistical packages, such as SPSS[5] provide a curve-fitting module, based on regression, that facilitates the finding of nonlinear relations. If our data would have been analyzed with Spearman rank order correlations, after categorization into 7 equal groups, the effect would not have been significant ($p = .185$), which is particularly due to unnecessary loss of information. This loss of information may disguise clinical reality. Therefore, regression analysis on the continuous data is more suitable here and we suggest that Craufurd et al. reanalyze their data.

REFERENCES

1. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington disease. *Neuropsychiat Neuropsychol Beh Neurol* 2001;14(4):219-226.
2. Siegel S. *Nonparametric statistics for the behavioral sciences*. Tokyo (etc.): McGraw-Hill Kogakusha, 1956.
3. Hotelling H, Pabst MR. Rank correlation and tests of significance involving no assumption of normality. *Ann Math Stat* 1936;7:29-43.
4. Nature and development of HD in a nursing home population: The development of the GOSH rating scale. 19th International Meeting of the World Federation of Neurology Research Group on Huntington's Disease; 2001 August 25 - 28, 2001; Copenhagen.
5. SPSS for Windows: Release 10.0. Chicago: SPSS, 2000.

CHAPTER 8a
-
Summary and discussion

8a.1. GENERAL INTRODUCTION

Huntington's disease (HD) is an autosomal dominant inheritable disease characterised by involuntary movements, cognitive deterioration, and psychiatric problems. The onset is usually in middle age. The mean age at onset ranges from 43.7 to 55.8 years,[1-3] with standard deviations of 10.9 and 13.5 years respectively.[2 3] The median duration of HD is about 16.2 years,[3] and eventually the patient deceases by causes associated with the disease.[1] The occurrence rate in people of Western European descent is estimated at 5-10 per 100.000 inhabitants,[4] though there are indications that this rate is higher.[5] The specific symptoms and progression of HD can be related to its neuropathology, which is characterised by loss of specific neuronal populations, most strikingly in the basal ganglia of the brain.[6] HD is caused by a CAG repeat on the short arm of chromosome 4.[7-10] Affected subjects have repeats from 36 to over 100.[8-10] The limits of the CAG repeat size in the HD gene have been defined: the normal allele with 26 repeats at most, the intermediate allele with 27-35 repeats, the disease allele with reduced penetrance with 36-39 repeats, and the disease allele with 40 repeats or more.[11] The age on which the first symptoms emerge is negatively associated with the repeat length,[12] whereas the duration is not.[13]

Individuals with a HD parent have a 50% chance of having inherited the disease themselves. Since the late eighties of the last century, a predictive DNA-test became available. This test was carefully introduced because severe consequences of the test were anticipated, especially for persons receiving an increased risk outcome. In the Netherlands 24% of people at risk for HD choose to have the test.[14]

8a.2. BACKGROUND OF THE STUDY

Since the advent of predictive testing a variety of psychological issues have been encountered that deserved close attention. Disclosure of an unfavourable test result was found to cause a temporal psychological distress, which reduced toward pre-test levels 6 months to a few years after the test. Individuals who received a favourable test result found a short-term relief of the burden, but also returned to pre-test levels in the medium-term.[15-17] The Dutch programme addressed the psychological effects in the long-term.

In 1993, the detection of the CAG-repeat allowed direct mutation testing with more than 99% certainty. After an extensive debate whether the individuals who received previous test results from linkage testing should be informed and offered the mutation test, the test was offered in 1997. This provided the opportunity to study the uptake of the retest and to assess the long-term psychological effects.

The findings of follow-up studies have had profound impact on psychosocial support and the quality of predictive testing programmes for a variety of genetic disorders with onset later in life. These studies ought to use reliable and effective methodology. The methodology of virtually all

follow-up studies on psychosocial effects of genetic testing, published between 1988 and 2003, was investigated.

Genetic counselling aims to offer precise risk estimation. The predictive test based on linkage analysis provided risk estimation, whereas the mutation test reached optimal certainty. The increasing knowledge on age of onset, its relationship with the CAG-repeat length, and the repeat length in close relatives allows more precise risk estimation before mutation testing.

Preparing for the future is one of the main reasons to have a predictive test. Individuals, who will receive unfavourable test results, have to face new uncertainties with regard to the onset of the disease, and to the way, the disease will manifest itself. The more specific information is available, the more identified carriers may be able to anticipate their future perspectives. HD is a disabling disease that progresses over time. Although no curative treatment is available yet, the increasing knowledge about HD has improved the caring and nursing considerably. Special wards for HD-patients in the Netherlands and Belgium have developed much experience with HD-patients in the later stages of the disease. The perspective of good care in the later stages may comfort people, and may help them to distract from the appalling experiences with caring and nursing of relatives in the past. However, to better tailor the care and nursing of HD-patients, more insight is needed into the course and progress of the disorder at different stages of the disease. The Unified Huntington's Disease Rating Scale (UHDRS) was developed as a clinical rating scale to assess four domains of clinical performance and capacity in HD: motor function, cognitive function, behavioural abnormalities, and functional capacity.[18] The UHDRS allows monitoring the patients' disease course over time, although the instrument is not very sensitive in the later stages of the disease. There was a need for a scale that is more directed to the later stages of HD. Also needed was a better indicator of a patient's cognitive and psychiatric aspects.[19] The Behaviour Observation Scale for Huntington's disease was developed to provide an observational instrument for monitoring the behavioural aspects of the patient in later stages of HD.

8a.3. AIMS OF THE STUDY

In this thesis the following psychological issues related to genetic testing for HD are described:

- the psychological adaptation in the long term of individuals at risk for HD and their partners to the genetic test result,
- the methodology that is used in research to adaptation to genetic test results in general,
- the characteristics of tested individuals who pursue a more accurate test,
- the calculation of the risk for HD of individuals who are not tested.

Also, a tool was developed for registration of the progression of HD that is easy and quick to administer by nursing personnel.

8a.4. RESULTS

In **chapter 2**, the 3-year psychological effects of the predictive test for HD on tested individuals and their partners are described. The intrusion and avoidance subscales of the Impact of Event Scale (IES),[20] measuring HD specific distress, and the Beck Hopelessness Scale (BHS)[21] measuring future expectations, were administered pre-test, 1 week, 6 months and 3 years after the test. Repeated measures analysis of variance revealed similar intrusion patterns for carriers and non-carriers, but opposite patterns for avoidance after 6 months. One week after the test outcome, carriers had increased and non-carriers had decreased levels of hopelessness. These effects were reduced after 6 months, and remained stable thereafter. Partners of carriers followed the same course. Partners of carriers with children were more distressed then those without offspring.

In **chapter 3**, the effects of the test after 7-10 years on tested individuals and their partners are presented. Worldwide this study covers the longest time-span on psychological effects of testing for hereditary diseases with onset later in life. Carriers and their partners were temporarily more distressed immediately after the test results, although their outlooks improved somewhat in the 2-3 year post-test period. However, they became more pessimistic in the long term, when they approached the mean age of onset of HD. Non-carriers reported strong relief after the test result, but eventually returned towards pre-test distress levels. Carriers, who did not return questionnaires after they had received their test results, had reported more distress at baseline than carriers who returned questionnaires and came back for additional counselling. Given that pre-test distress has been found to be a strong predictor for post-test distress, we need to consider how it can be provoked counsellors keep in touch with individuals who have high distress scores. Moreover, this observation might reveal that studies reporting few harmful effects among people, who had received an unfavourable test result, have underestimated the real impact.

In the study of the long-term effects of testing, the importance of an adequate statistical technique and the attention to dropout became apparent. This led to an investigation on dropout and adequacy of techniques used in other longitudinal studies in the field of psychological effects of genetic testing. The results are described in **chapter 4**. The aim of this systematic literature review is to describe and evaluate the statistical methods that were used in the follow-up studies. A literature search revealed 40 longitudinal quantitative studies that met the selection criteria for the review. Fifteen studies (38%) applied adequate statistical methods. The majority, 25 studies, applied less suitable or less efficient statistical techniques. Nine studies (23%) did not report on dropout rate at all, and 18 studies provided no characteristics of the dropouts. Thirteen out of 22 multi-wave studies that should have provided data on missing values actually reported these. It is concluded that many studies could have yielded more and better results if a more appropriate methodology was used. The most common shortcoming was that multi-wave studies used a statistical method suited for a two-wave study (14 out of 28). In these studies the analysis is

broken down into sub-analyses, which results in a less complete overview, and hence a loss of insight in the total course.

Dropout is a serious problem in longitudinal follow-up studies. Though every effort must be taken to prevent subjects from dropping out of the study, it can hardly be prevented completely. Dropout can have various reasons. In case of an unknown address or death, the effect is generally not very disrupting. However, loss to follow up due to lack of interest or disturbed mood distorts the results of the study considerably. Such a selectivity of dropout can be detrimental to the generalization of the results of the study. For example, the conclusion that a genetic test does not have serious harmful psychological effects cannot be generalised to the whole group of tested individuals when it is based on individuals who are less likely to develop a depression. Indeed, in our study[22] the group of individuals that could develop adverse consequences is selectively expelled from the study. Several studies have demonstrated that pre-test scores are highly predictive for post-test levels.[23 24] This indicates that this group is vulnerable to psychological problems. Hence, this group that has lost all contact with the counsellors is probably in need of extra attention and support. In only one other study[25] such a selective dropout was reported. All other studies have not reported on selective drop out. Nearly half of the studies (18) did not report anything on dropout.

Chapter 5 focuses on the uptake of a more than 99% accurate test. In 1987 the linkage test for HD was introduced in the Netherlands.[26 27] This test had a residual risk of 1-10% and the cooperation of relatives was needed. In the Netherlands, 245 individuals were tested with linkage analysis. Due to a lack of informative markers, 12 did not receive a test outcome, and 23 did not receive an outcome because of an uninformative family structure. Eighty-eight individuals were identified as carriers and 122 as noncarriers. Six years later, the gene mutation for HD was identified and testing became possible with a reliability of more than 99%,[7] without the need for testing of multiple family members. In 1997, the new mutation retest was offered to the 210 individuals who had received a linkage test result for HD. Eighty-one individuals could not participate in the study. The most important reasons were that they had been offered the mutation test previously in combination with prenatal testing or had already developed symptoms. Others were deceased, had moved and were not traceable any more, or did not react. This resulted in a study group of 129 individuals. Three groups were compared: (1) 18 individuals who were retested between 1993 and 1997, before the study had started, (2) 29 individuals who were retested after information was provided, and (3) 82 individuals who refrained from retesting. Nearly half of the linkage-tested individuals choose to be retested, with the exception of noncarriers who previously received a residual risk of 2% or lower. Of the latter group, less than 20% choose to be retested. Carriers who were more confident in the future (BHS)[21] and had a better sense of well being (GHQ)[28] were more likely to opt for a confirmatory test. Noncarriers who were retested were more anxious (HADS)[29] than noncarriers who refrained from retesting. Female carriers were also more likely to have the retest before the information

campaign had started. Retestees were younger at the time of testing. No risk reversals were revealed by this study.

In the Netherlands, a minority of the individuals at risk (24%), who have opted for predictive testing since 1987, received precise information about their risk status. The study reported in **chapter 6** focuses on the residual risk status of those who have not (yet) undergone the predictive test. This residual risk is often lower then the a priori risk of 50% (children) or 25% (grandchildren). A model for calculating the reduced residual risk was developed on basis of a data set with CAG repeat lengths and ages of onset (AO) of HD patients, and a subset with CAG repeat lengths of parents and their children. In this model, the parents' CAG repeat length is estimated from the AO in a first step. Secondly, the parents' CAG repeat length is used for estimating the CAG repeat length of the proband, considering the parents' gender. Thirdly, the probability that the proband has not yet symptoms given that he or she is a carrier is estimated. Finally, after inclusion of information on favourably tested siblings (non-mutation carriers), the residual risk of the proband is calculated. One application is that genetic counsellors can offer residual risks as part of the pre-test procedure. The provision of a spreadsheet allows genetic counsellors to calculate the residual risk relatively easy. In this spreadsheet the age of the applicant, the AO, or CAG repeat length of the relative and number of favourably tested children can be entered, and estimates of CAG repeat length and RRS percentage will be provided. The spreadsheet is available on request.

HD is a disabling disease that progresses over time, and no curative treatment is available yet. One of the main cited reasons to have a predictive test was preparing for the future. Individuals, who receive unfavourable test results, face new uncertainties with regard to the onset of the disease, and to the way the disease will manifest itself. Identified carriers may be able to anticipate better their future perspectives when they are informed more specifically about the course and progress of the disease. The management of HD, the caring, and nursing options have been improved by the increasing knowledge about HD. The neurological outpatient clinics, the special Huntington Support Centre (Huntington Steunpunt), and the special wards for HD-patients in the Netherlands and Belgium have developed much experience with HD-patients in the different stages of the disease. The perspective of good care in the later stages may comfort people, and may help them to distract from the appalling experiences with caring and nursing of relatives in the past. However, to better tailor the care and nursing of HD-patients, more insight is needed into the course and progress of the disorder at different stages of the disease. In **chapter 7**, the development of the Behaviour Observation Scale Huntington (BOSH) is reported. In 1996 the Unified Huntington's Disease Rating Scale (UHDRS)[18] was introduced to assess clinical performance and capacities in HD. However, due to ceiling effects, the UHDRS does not differentiate in later stages of HD. The BOSH was developed to obtain a detailed description of the patients' behaviour in the final phases of the disease. The scale contains 32 four-answer category items. From principal component

analysis three subscales emerged: (1) degeneration of activities of daily living (ADL), (2) social-cognitive degeneration and (3) mental rigidity and aggression. The scale was validated in four nursing homes with a specialised ward for HD-patients. For 91 patients nursing personnel administered the BOSH twice independently. Internal reliabilities of the three subscales were between .83 and .94 and inter-rater reliabilities were between .85 and .95. A linear relation was found between disease duration and deterioration of ADL. Non-linear relations were found between (1) degeneration of ADL and rigidity-aggression, and (2) degeneration of ADL and of social-cognitive capabilities. Rigidity and aggression become more frequent as the disease progresses, later on this behaviour diminishes. Social-cognitive capabilities deteriorate more rapidly in later stages of the disease

8a.5. DISCUSSION

8a.5.1. Psychological adaptation to the test outcome

It was generally accepted that, when outweighing the psychological ramifications of testing for HD, there were more positive than negative consequences.[15-17] This has led to the suggestion that tested individuals have benefited from testing.[30] However, such a conclusion must be made with caution. Up to 2003, there were no studies reported that encompassed a period longer than 3 years after the test. In the study 7-10 years after the test outcome, feelings of hopelessness rose again for carriers. Feelings of hopelessness or depression, as the first symptoms of HD, could cause this effect for the carriers. However, this cannot hold for their partners, who reported similar levels of hopelessness. For this reason, it is likely that the test outcome, the approaching age of onset, the onset of HD in relatives, loss experiences, and HD-related life events are responsible for their enhanced feelings of hopelessness. Because the mean age of carriers at the last measurement was 45 years (range 27-73), for many of them the first symptoms of HD will probably become apparent in the very near future.

These results are based on a selection of individuals who had the predictive test performed. The study did not include a control group with individuals who were not tested. Van der Steenstraten et al.[31] noted differences between tested and not tested individuals. Untested individuals felt more vulnerable and saw themselves as less able to cope with an unfavourable test outcome. It should be noted too, that the study group of Van der Steenstraten was recruited from volunteer members of the Dutch Huntington Association. It is conceivable that even these volunteers belong to a selective group of psychologically more stable individuals. For conclusions that are more decisive, it would be interesting to study individuals at risk at the age of about forty, who were not tested.

8a.5.2. Dropout analysis

The dropout problem in longitudinal research is inevitable. There are various reasons for persons to be lost to follow-up. People can move and

their addresses become unknown. They can decease from a cause unrelated to HD. They can develop symptoms and hence be excluded from further analysis. Alternatively, they may just not want to cooperate any more. In general, when there is no response to the request to complete questionnaires, the reasons for non-response remain unknown. It should be noticed that non-response is generally not random. Dropouts often have special characteristics that can invalidate a longitudinal study.[32] Therefore, longitudinal research requires the inclusion of dropout analyses. Dropouts need to be compared with persons who remained in the study on every biographic and outcome measure. Generally, it is reasoned that if no differences are found, there is no need to conclude that selective dropout has invalidated the study. Although selective dropout is often considered as a threat to the validity of a study, a thorough dropout analysis can reveal very interesting insights. In Tibben et al.[33] no significant differences between dropouts and the remaining participants in the study were found. A significant difference was present however, and was observed many years later, when the effects after 7-10 years were analysed. The key to the problem was the insight that individuals who had received an unfavourable test outcome will have to adjust to the test outcome completely different from individuals who received a negative outcome. When dropout analyses were performed on these groups separately, it emerged that dropout carriers had a much worse view on the future at pre-test, had much more intrusive thoughts, reported more avoidant behaviour and had worse general well-being scores. These differences were highly significant and the effect sizes ranged from above medium to very large (0.6 to 1.0). Thus, it was not only found that carriers had a worse view on the future than noncarriers in the long term, but this finding was also based on a selection of carriers who were less anxious and distressed. When we add this observation to the issue of selectivity of the study group at baseline, it is likely that the effects of an unfavourable test outcome are even worse than was implied from the longitudinal analyses alone. Geneticists and psychosocial workers estimate whether the applicant can adapt adequately to an unfavourable result. Nevertheless, individuals, who are very anxious, depressed or who have pessimistic views on a future after an unfavourable test result should be given professional attention in the long term. Follow up appointments should be scheduled, and if needed referral to appropriate additional caregivers should be arranged. Yet, we must account for the possibility that the offer of further support is rejected because the confrontation with the future perspectives is unbearable.

8a.5.3. Importance of an adequate statistical technique

Analyses for the study 7-10 years after the test were carried out with General Linear Mixed Models (GLMM) that can handle cases with missing measurements at one or more time points. This allowed the optimal use of data, subjects, and waves. A rather incomplete time-point, 1½ year after the test, could also be used. The collection of data of this time-point was stopped because the project had been called of at the time. If the technique

of GLMM had been used at the time of the 3-year follow-up study, it could have been observed by then that carriers were already losing their prospect on the future.

Another consequence of using an inadequate technique may be that it will fail to notice narrowly significant differences. This may happen, for example, when a non-parametric test is used instead of a parametric test. Often this does not lead to a dramatic loss of power efficiency. Generally, the power of a non-parametric test is about 95% compared with an F-test when conditions for the latter are met. In some circumstances however, such as dichotomising distributions before analysing, the power can drop dramatically. When a technique for dichotomous data is used for continuous data, efficiency for finding significant results can drop to 63%.[34]

8a.5.4. Presenting a more accurate DNA test

The uptake of the test has been considerably higher in the Netherlands than in other countries.[14] The main reason to have the test was relief from unbearable uncertainty, reflecting the strong need for reassurance. Yet, it was debated whether individuals tested by linkage analysis should be informed on the mutation test. The Clinical Genetics Centre Leiden had the opinion that the new test should be offered to everyone who had taken the old linkage test, in order to allow obtaining optimal certainty. However, the Leiden Medical Ethical Committee questioned whether individuals should be approached after so many years with the chance that they are burdened unasked. The committee reasoned that tested individuals may have adjusted to their test outcome and have found a new balance in their life. This balance could be distorted by the perception of the message that the linkage test outcome was uncertain or even wrong. People may conclude that the old test was not good at all.

On the other hand, people had applied for the test to receive optimal certainty in order to make life arrangements in accordance with the test outcome, with the inclusion of planning a family. In addition, from a non-directive and non-paternalistic point of view, it was considered important to leave the decision to have a mutation test to the tested individual. Moreover, the patient organisation had published information on the direct mutation test in its quarterly magazine. After some years of debate and outweighing the pros and cons, it was concluded that the test could be offered to those who had received the linkage test.

Before the >99% reliable mutation test was introduced, Babul et al.[35] questioned linkage-tested individuals whether they were interested in a hypothetical 100% certain test. They reported that 72% would be interested in such a test. Actually, the uptake of the test was much lower after the introduction (42%).[36] A similar observation was made before the introduction of the linkage test. Than, 40% to 84% individuals at risk reported an intention to be tested,[16 37-39] but since its introduction in 1987 the uptake (2-24%), has fallen considerably below expectation.[14 40-43] It is obvious that there is a discrepancy between the intention to be tested and actual behaviour. As was expected, the residual risk of the linkage test was

of influence, but only for individuals who had received a decreased risk test outcome. Noncarrriers with a low residual risk seemed to feel no need to reduce that risk any further. To our knowledge, informing tested individuals on the mutation test has not led to adverse effects.

8a.5.5. Additional risk information for counsellors and counselees

Generally, persons at risk are considered to be at 50% risk, as he or she has a probability of 50% of having inherited the disease. This probability, however, decreases with increasing age. The increased number of data on CAG-repeats and ages at onset within families allowed us to develop a model that estimates the reduced risk for HD regarding an individual's age, the parent's repeat length or age of onset, and other favourably tested family members. This model can be offered to individuals at risk who have not (yet) been tested and who do not have any symptoms. The model can only lead to a decreased risk estimation, while the mutation test can yield the irreversible outcome that one certainly will get HD. Nevertheless, this model is not primarily aimed at persons who do not whish to be tested for a variety of reasons. Generally, we speculate that these persons are not interested in their precise risk estimation. Our model and the accompanying spreadsheet are meant to broaden the range of information that clinical geneticists and genetic counsellors will be able to provide to persons who come for a genetic test and have no symptoms. They can offer them a best estimation of the residual risk in their specific circumstances.

All calculations are based on the best possible estimates of parameters and consequently all values of the CAG of a proband and Residual Risk Status (RRS) must be considered as best possible estimates too. A certain amount of uncertainty exists in this model, which will be reduced in the future when more data on CAG repeat lengths of parents and offspring, and more data on ages of onset will become available.

Counselees will generally be interested to learn whether their prior risk has substantially changed with increasing age, and what the best possible estimate of the RRS would be, given their situation. This might help in the decision to be tested and to be better prepared for the test result. This decision can depend on the actual RRS and the RRS in the near future. From the CAG repeat length estimated with our model and the tables published by Langbehn et al.[44] it can be determined whether the individual is at a critical age regarding onset. During this critical period, the decrease of the RRS is most substantial, which can influence the decision to be tested soon or to postpone the test for a few years.

Persons at risk have encountered problems with insurance companies and employment.[45-48] As it is ethically disputed to require a genetic test when persons apply for a job or a health or life insurance, a refinement of the actual risk for HD without actually performing a test can be a benefit for third parties such as insurance companies and employers. If we assume that third parties apply an estimation of 50% for offspring of HD patients, this model is also beneficial for individuals at risk, as the actual risk is virtually always lower.

8a.5.6. Structure of the Behaviour Observation Scale Huntington (BOSH)

In the development of the BOSH, three principal components were found: deterioration of activities of daily living (ADL), deterioration of social and cognitive abilities, and mental rigidity and aggression. A good indicator for disease duration was not available because the age at onset was often determined retrospectively. In some cases, for instance, the age at onset was estimated by the date of admittance to a psychiatric hospital. If this admittance was indeed the result of disturbances caused by HD, then the age at onset was estimated too late. If not, then the age at onset was estimated too early. This resulted in a weak though significant relation between disease duration and deterioration of social-cognitive abilities. The institutional care period did not serve as a better indicator for disease duration either. On the one hand, impairment of motor functioning is important in the decision for placement in a nursing home. Patients can also have obsessions, compulsions, delusions, and auditory hallucinations. These behaviours may have been the compelling reason for admission in an institution.[49] On the other hand, the decision to be placed in a nursing home is principally dependent on the presence of a caring spouse or other person, and less dependent on the capabilities of the patient and severity of HD. In the Belgian nursing home in this study, the absence of a caretaker is even a prerequisite for admission. Nevertheless, a significant linear relation between the care period and ADL was found.

A strong significant quadratic relation between rigidity-aggression and the ADL level was found. This can be interpreted as rigid and aggressive behaviour becoming more frequent at first, and less frequent later. It must be noted that the level of aggression is moderated, as the nursing homes try to reduce the aggression by psychological and pharmacological interventions. Future research should take into account sedative medicines. A similar relation, between inflexibility and disease duration was observed in the study of Craufurd et al.[50 51]

A second significant quadratic relation was found between social-cognitive functioning and ADL level. Again, applying ADL level as an operationalization of disease progression, this indicates that the deterioration of social-cognitive capabilities progresses in later stages of the disease, when rigid and aggressive behaviour is decreasing. In other words, the decline of ADL and rigid and aggressive behaviour precedes the decline of social-cognitive behaviour. This is consistent with the observation of Bamford et al.[52] that memory did not deteriorate until patients reached advanced stages of the disease.

The external validity of the BOSH needs to be assessed more extensively. In a subsequent study the BOSH in combination with the Unified Huntington Disease Rating Scale (UHDRS) will be administered. The UHDRS was developed by the US-based Huntington Study Group in 1994[18] to provide a comprehensive assessment of motor performance, cognitive functioning, behavioural and psychiatric problems, and functional status of an individual. The UHDRS was not intended to provide an all-encompassing description of every possible manifestation of HD.[1] Though

the UHDRS does not differentiate in later stages of HD, a comparison of the BOSH with the UHDRS is needed.

The BOSH was developed in order to gain detailed insight into the progress of the disease and to distinguish individual differences between patients. A more detailed insight into these differences will facilitate a study of the relation of the phenotypic expression of HD with the pre-morbid personality and social support system. Finally, a better insight into this relation can be of help in better tailoring treatment to individual patients.

To date, there still is no cure for HD, and treatment for patients is limited to palliative aspects. The specific manifestations of HD justify nursing in specialised wards that have been established in many countries. There is an increasing knowledge of the clinical expressions of the disease in the mid-stages.[50 53] To enable the development of tailored support programmes in the final stages, there is a need for a detailed description of the course of the disease that can help to improve the care of patients.

8a.5.7. Concluding remarks

The future perspectives of HD patients, mutation-carriers and individuals at risk are extremely difficult to cope with. Yet, compared with their affected parents they can perceive slight rays of hope. Thanks to the co-operation of patients, family members, and patient associations with scientific investigations, a lot of insight has been gained. Predictive tests have been developed, psychological counselling is offered, much has been revealed of psychological and psychosocial effects of testing. Genetic predictive testing have allowed studies on the onset of symptoms and improvement of the diagnostic process at an earlier stage. Nursing homes with specialised wards for HD patients have been established. Palliative treatment is available, and the first hints to the direction of finding a cure for HD emerge.

HD is a rather rare disease. For this reason, much more progression can be made when information and studies are brought together. An interventional trial, testing Riluzole in 450 patients in early stages of HD in 9 countries throughout Europe, demonstrated that large scale studies on HD can be done in Europe. To allow a long-term observation period of HD-patients and to create an appropriate infrastructure for clinical trials on HD in Europe, the Euro-HD Network was established in 2003. The Predict Study, one of the activities of the network, aims to assess the early clinical changes paralleling the onset of HD, using sophisticated and standardised measures of cognitive performance and volumetric assessment of serial brain magnetic resonance imaging.[54] The database can be used to get more insight into the onset of symptoms in unaffected identified mutation carriers, to study the course of the disease after onset, and to investigate therapies meant to influence the course of HD or to delay the onset.

The Euro-HD Network provides a platform for professionals, people affected by HD and their relatives to facilitate working together throughout Europe. The Euro-HD Network facilitates natural history studies and interventional trials meeting high standards ('Good Clinical Practice' = GCP) thus helping on the road towards a cure of HD (http://www.euro-hd.net). The

Euro-HD Network aims to be a true network in that all participants involved can take a lead and propose, conduct and publish studies. The network provides an infrastructure for large-scale clinical trials on HD throughout Europe (database, IT-tools, monitoring personal etc.). An IT platform for communication tools (in the respective native languages) and e-trials. A forum for close cooperation of basic scientists and clinicians. Low threshold (native language!) support for study sites by language group coordinators.

The Euro-HD network encourages long-term investigations and stimulates the development of instruments that are used in the studies of HD. These instruments -tests, questionnaires, rating scales - are unified and translated in the languages of the participating countries.

There is no cure for HD yet. It is promising that the joint efforts and collaborations of the patients, their families, the Huntington associations, the physicians and the scientific researchers have contributed to make the burden of the disease and the future perspective more bearable for all individuals involved.

8a.6. REFERENCES

1. Kremer B. Clinical neurology of Huntington's disease - Diversity in unity, unity in diversity. In: Bates G, Harper PS, Jones L, editors. *Huntington's disease*. 3rd ed. Oxford: Oxford University Press, 2002:28-61.
2. Adams P, Falek A, Arnold J. Huntington disease in Georgia: age at onset. *Am J Hum Genet* 1988;43(5):695-704.
3. Roos RA, Vegter - van der Vlis M, Van Ommen GJB, Bruyn GW. Duration of illness in Huntington's disease is not related to age of onset. *J Neurol Neurosur Ps* 1993;56:98-100.
4. Bates G, Harper PS, Jones L, eds. *Huntington's disease*. 3rd ed. Oxford: Oxford University Press, 2002.
5. Siesling S, Vegter-van de Vlis M, Losekoot M, Belfroid RD, Maat-Kievit JA, Kremer HP, et al. Family history and DNA analysis in patients with suspected Huntington's disease. *J Neurol Neurosur Ps* 2000;69(1):54-59.
6. Gutekunst CA, Norflus F, Hersch SM. The neuropathology of Huntington's disease. In: Bates G, Harper PS, Jones L, editors. *Huntington's disease*. 3rd ed. Oxford: Oxford University Press, 2002:251-275.
7. Huntington Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72:971-983.
8. Kremer B, Goldberg P, Andrew SE, Theilmann J, Telenius H, Zeisler J, et al. A worldwide study of the Huntington's disease mutation. The sensitivity and specificity of measuring CAG repeats. *New Engl J Med* 1994;330(20):1401-1406.
9. Nance MA, Mathias-Hagen V, Breningstall G, Wick MJ, McGlennen RC. Analysis of a very large trinucleotide repeat in a patient with juvenile Huntington's disease. *Neurology* 1999;52(2):392-394.

10. Rubinsztein DC, Leggo J, Coles R, Almqvist E, Biancalana V, Cassiman JJ, et al. Phenotypic characterization of individuals with 30-40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36-39 repeats. *Am J Hum Genet* 1996;59(1):16-22.
11. American College of Medical Genetics, American Society of Human Genetics, Group HDGTW. Laboratory guidelines for Huntington disease genetic testing. *Am J Hum Genet* 1998;62(1243-1247).
12. Maat-Kievit A, Losekoot M, Zwinderman K, Vegter - van der Vlis M, Belfroid R, Lopez F, et al. Predictability of age at onset in Huntington disease in the Dutch population. *Medicine* 2002;81(4):251-259.
13. Harper PS, Jones L. Huntington's disease: genetic and molecular studies. In: Bates G, Harper PS, Jones L, editors. *Huntington's disease*. 3rd ed. Oxford: Oxford University Press, 2002:113-158.
14. Maat-Kievit A, Vegter - van der Vlis M, Zoeteweij M, Losekoot M, Van Haeringen A, Roos R. Paradox of a better test for Huntington's disease. *J Neurol Neurosur Ps* 2000;69(5):579-583.
15. Broadstock M, Michie S, Marteau TM. The psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet* 2000;8(10):731-738.
16. Meiser B, Dunn S. Psychological impact of genetic testing for Huntington disease: an update of the literature. *J Neurol Neurosur Ps* 2000;69(5):574-578.
17. Duisterhof M, Trijsburg RW, Niermeijer MF, Roos RAC, Tibben A. Psychological studies on Huntington's disease: making up the balance. *J Med Genet* 2001;38:852-861.
18. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord* 1996;11(2):136-142.
19. Nehl C, Paulsen JS, The Huntington Study Group. Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. *J Nerv Ment Dis* 2004;192(1):72-74.
20. Horowitz MJ, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. *Psychosom Med* 1979;41:209-218.
21. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. *J Consult Clin Psychol* 1974;42:861-865.
22. Timman R, Roos RAC, Maat-Kievit A, Tibben A. Adverse effects of predictive testing for Huntington disease underestimated: long term effects 7-10 years after the test. *Health Psychol* 2004;23(2):189-197.
23. Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cassiman JJ, Cloostermans T, Demyttenaere K, et al. Prediction of psychological functioning one year after the predictive test for Huntington's disease and impact of the test result on reproductive decision making. *J Med Genet* 1996;33(9):737-743.
24. Marteau T-M, Dundas R, Axworthy D. Long-term cognitive and emotional impact of genetic testing for carriers of cystic fibrosis: the effects of test result and gender. *Health Psychol* 1997;16(1):51-62.

25. Quaid KA, Wesson MK. Exploration of the effects of predictive testing for Huntington Disease on intimate relationships. *Am J Med Genet* 1995;57:46-51.
26. Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, et al. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 1983;306(5940):234-238.
27. Skraastad MI, Verwest A, Bakker E, Vegter - van der Vlis M, van Leeuwen - Cornelisse I, Roos RAC, et al. Presymptomatic, prenatal and exclusion testing for Huntington disease using seven closely linked DNA markers. *Am J Med Genet* 1991;39:217-222.
28. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. *Psychological Medicine* 1979;9:139-145.
29. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiat Scand* 1983;67(6):361-370.
30. Bundey S. Few psychological consequences of presymptomatic testing for Huntington disease. *Lancet* 1997;349(9044):4.
31. Van Der Steenstraten IM, Tibben A, Roos RAC, Van Der Kamp JJP, Niermeijer MF. Predictive testing for Huntington disease: nonparticipants compared with participants in the Dutch program. *Am J Hum Genet* 1994;55:618-625.
32. Bijleveld CCJH, van der Kamp LT, Mooijaart A, van der Kloot WA, van der Leeden R, van der Burg E, eds. *Longitudinal data analysis: designs, models and methods*. London: Sage, 1999.
33. Tibben A, Timman R, Bannink EC, Duivenvoorden HJ. Three year follow up after presymptomatic testing for Huntington's disease in tested individuals and partners. *Health Psychol* 1997;16(1):20-35.
34. Siegel S, Castellan NJJ. *Nonparametric statistics for the behavioral sciences*. 2nd ed. ed. New York: McGraw-Hill, 1988.
35. Babul R, Adam S, Kremer B, Dufrasne S, Wiggins S, Marlene H, et al. Attitudes toward direct predictive testing for the Huntington disease gene. Relevance for other adult-onset disorders. *JAMA* 1993;270(19):2321-2325.
36. Timman R, Maat-Kievit A, Brouwer-DudokdeWit C, Zoeteweij M, Breuning MH, Tibben A. Testing the test - why pursue a better test for Huntington disease? *Am J Med Genet* 2003;117B:79-85.
37. Teltscher B, Polgar S. Objective knowledge about Huntington's disease and attitudes towards predictive tests of persons at risk. *J Med Genet* 1981;18:31-39.
38. Evers-Kiebooms G, Cassiman JJ, Van den Berghe H. Attitudes towards predictive testing in Huntington's disease: a recent survey in Belgium. *J Med Genet* 1987;24:275-279.
39. Kessler S, Field T, Worth L, Mosbarger H. Attitudes of persons at risk for Huntington disease toward predictive testing. *Am J Med Genet* 1987;26:259-270.
40. Bloch M, Fox S, Hayden MR. Predictive testing for Huntington disease: II. Demographic characteristics, life-style patterns, attitudes, and psychosocial assessments of the first fifty-one test candidates. *Am J Med Genet* 1989;32:217-224.

41. Craufurd D, Dodge A, Kerzin-Storrar L, Harris R. Uptake of presymptomatic predictive testing for Huntington's disease. *Lancet* 1989(September 9):603-605.
42. Tyler A, Ball D, Craufurd D. Presymptomatic testing for Huntington's disease in the United Kingdom. *Brit Med J* 1992;304:1593-1596.
43. The World Federation of Neurology Research Group on Huntington's Disease. Presymptomatic testing for Huntington's disease: a world survey. *J Med Genet* 1993;30:1020-1022.
44. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR, International Huntington's Disease Collaborative Group. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin Genet* 2004;65(4):267-277.
45. Quaid KA, Morris M. Reluctance to undergo predictive testing: the case of Huntington disease. *Am J Med Genet* 1993;45(1):41-45.
46. Burgess MM, Adam S, Bloch M, Hayden MR. Dilemmas of anonymous predictive testing for Huntington disease: privacy vs. optimal care. *Am J Med Genet* 1997;71:197-201.
47. Burgermeister J. Teacher was refused job because relatives have Huntington's disease. *Brit Med J* 2003;327:827.
48. Harper PS, Gevers S, de Wert G, Creighton S, Bombard Y, Hayden MR. Genetic testing and Huntington's disease: issues of employment. *Lancet Neurol* 2004;3(4):249-252.
49. Wheelock VL, Tempkin T, Marder K, Nance M, Myers RH, Zhao H, et al. Predictors of nursing home placement in Huntington disease. *Neurology* 2003;60(6):998-1001.
50. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington disease. *Neuropsychiatr Neuropsychol Behav Neurol* 2001;14(4):219-226.
51. Timman R, Roos RAC, Tibben A. Nonlinear effects in behavioral changes in Huntington disease. *Cogn Behav Neurol* 2003;16(1):82.
52. Bamford KA, Caine ED, Kido DK, Cox C, Shoulson I. A prospective evaluation of cognitive decline in early Huntington's disease: functional and radiographic correlates. *Neurology* 1995;45(10):1867-1873.
53. Shoulson I, Fahn S. Huntington's disease: clinical care and evaluation. *Neurology* 1979;29:1-3.
54. Kieburtz K, Shoulson I. Therapeutic trials in Huntington's disease. In: Bates G, Harper PS, Jones L, editors. *Huntington's disease*. 3rd ed. Oxford: Oxford University Press, 2002:501-511.

HOOFDSTUK 8b
-
Samenvatting en discussie

8b.1. ALGEMENE INLEIDING

De ziekte van Huntington is een autosomaal dominante erfelijke ziekte die wordt gekenmerkt door onwillekeurige bewegingen, cognitieve achteruitgang, en psychiatrische problemen. De eerste verschijnselen openbaren zich meestal op middelbare leeftijd. Gemiddeld begint de ziekte tussen 43,7 en 55,8 jaar,[1-3] met standaardafwijkingen van respectievelijk 10,9 en 13,5 jaar.[2 3] De mediaan van de ziekteduur is ongeveer 16,2 jaar[3] en uiteindelijk overlijdt de patiënt door complicaties ten gevolge van de ziekte.[1] De ziekte komt naar schatting voor bij 5 - 10 per 100.000 personen van West-Europese afkomst,[4] hoewel er aanwijzingen zijn dat het er meer zijn.[5] De specifieke symptomen en beloop van de ziekte kunnen in verband worden gebracht met de neuropathologie, die gekenmerkt wordt door een verlies van bepaalde neuronengroepen, in het bijzonder in de basale ganglia van de hersenen.[6] De ziekte wordt veroorzaakt door een CAG herhaling op de korte arm van het vierde chromosoom.[7-10] Aangedane personen hebben herhalingen van 36 tot meer dan 100.[8-10] De grenzen van deze herhalingen zijn als volgt vastgesteld: een normaal allel heeft ten hoogste 26 herhalingen, een intermediair allel heeft 27-35 herhalingen, ziekte met beperkte penetrantie heeft 36-39 herhalingen en een ziekte allel heeft tenminste 40 herhalingen.[11] De aanvangsleeftijd is omgekeerd evenredig met het aantal CAG's,[12] terwijl er geen samenhang is met de ziekteduur.[13]

Personen die één ouder met de ziekte van Huntington hebben, hebben 50% kans om de ziekte te hebben geërfd. Aan het eind van de tachtiger jaren van de vorige eeuw kwam de voorspellende test beschikbaar. Deze test werd met enige terughoudendheid geïntroduceerd omdat een ongunstige uitslag verstrekkende gevolgen zou kunnen hebben. In Nederland heeft 24% van de risicodragers zich laten testen.[14]

8b.2. ACHTERGROND VAN HET ONDERZOEK

De introductie van de voorspellende test heeft een aantal psychologische vragen opgeroepen die een bijzondere aandacht verdienen. Het bleek dat de schok na een ongunstige testuitslag slechts van tijdelijke aard was. Zes maanden tot een paar jaar na de test was de stress weer tot pre-test niveau gedaald. Personen die een gunstige testuitslag kregen voelden een kortstondige opluchting na de test, maar ook zij keerden naar pre-test niveaus terug.[15-17] Het Nederlandse onderzoeksprogramma richtte zich op de psychologische effecten op de lange termijn.

Aanvankelijk werd de test met koppelingsonderzoek uitgevoerd en had een betrouwbaarheid van 90-99%. In 1993 maakte de ontdekking van de CAG herhaling een directe mutatietest met een zekerheid van meer dan 99% mogelijk. Er volgde in Nederland een uitgebreide discussie over de wenselijkheid om personen, die eerder waren getest met DNA-koppelingsonderzoek, te informeren over de mutatietest. In 1997 werd hen aangeboden om zich opnieuw te laten testen. De belangstelling voor de

nieuwe zekere test en de lange termijn psychologische effecten werden toen systematisch onderzocht.

De bevindingen van de vervolgstudies hebben een diepgaande invloed gehad op de psychosociale ondersteuning en de kwaliteit van de voorspellende testprogramma's voor diverse erfelijke aandoeningen die op latere leeftijd optreden. Deze psychologische vervolgstudies dienen betrouwbare en effectieve methodologie te gebruiken. De methodologie van alle gepubliceerde vervolgstudies op het gebied van psychosociale effecten van voorspellend genetisch testen tussen 1988 en 2003 zijn onderzocht.

Erfelijkheidsadvisering heeft onder meer als doel een precieze risicoschatting te geven. De op DNA-koppelingsonderzoek gebaseerde voorspellende test gaf een schatting van het verhoogde of verlaagde risico, terwijl de mutatietest optimale zekerheid bood. De toenemende kennis over de aanvangsleeftijd en de relatie met het aantal CAG's, alsmede het aantal CAG's in nabije familieleden laten, voorafgaand aan de mutatietest, meer precieze risicoschattingen toe.

De voorbereiding op de toekomst is een van de belangrijkste redenen om zich te laten testen. Personen die een ongunstige testuitslag ontvangen, zullen naast nieuwe onzekerheden met betrekking tot de aanvang van de ziekte, ook de manier waarop de ziekte zich precies zal uiten onder ogen moeten zien. Hoe meer specifieke informatie beschikbaar is, hoe meer bewezen gendragers in staat zullen zijn om rekening te houden met hun toekomstperspectieven. De ontwikkeling van de ziekte is momenteel niet te vertragen, noch te stoppen. En hoewel er nog geen genezing mogelijk is, heeft de toegenomen kennis over de ziekte de verzorging en verpleging aanzienlijk verbeterd. Speciale Huntington afdelingen in verpleeghuizen in Nederland en België hebben veel ervaring opgedaan in de latere stadia van de ziekte. Het vooruitzicht van een goede verzorging in de latere stadia kan een geruststelling zijn en kan er aan bijdragen dat de negatieve ervaringen met de zorg voor familieleden in het verleden niet langer het eigen toekomstperspectief bepalen. Om de verzorging van de patiënten nog beter op maat te maken, is nog meer inzicht nodig in het beloop en voortgang van de ziekte in de verschillende stadia. De Unified Huntington's Disease Rating Scale (UHDRS) is een beschrijvende schaal, waarmee het motorisch functioneren, en de cognitieve-, gedrags- en functionele capaciteiten vastgelegd kunnen worden.[18] De UHDRS maakt het mogelijk het beloop van de ziekte in de tijd te volgen, hoewel het instrument niet erg gevoelig is in de latere stadia van de ziekte. Er was behoefte aan een schaal waarmee de beperkingen van de ziekte in de latere stadia konden worden vastgesteld. Bovendien was er behoefte aan een betere indicator van de cognitieve en psychiatrische aspecten van de patiënt.[19] De Gedrags Observatie Schaal Huntington (GOSH) is ontwikkeld als observatie instrument om de gedragsaspecten in de latere stadia te volgen.

8b.3. DOEL VAN HET ONDERZOEK

In dit proefschrift worden de volgende aspecten behandeld die met het voorspellend genetisch testen voor de ziekte van Huntington samenhangen:

- de lange termijn psychologische aanpassing na de testuitslag bij risicodragers en hun partners,
- de gebruikte methodologie in vervolgonderzoek naar aanpassing aan genetische testuitslagen in het algemeen,
- de kenmerken van personen die zich opnieuw hebben laten testen,
- de berekening van het risico van personen die zich niet hebben laten testen.

Daarnaast is een instrument ontwikkeld om het beloop van de ziekte vast te stellen, dat gemakkelijk en snel door verplegend personeel is in te vullen.

8b.4. RESULTATEN

In **hoofdstuk 2** zijn de psychologische effecten 3 jaar na de test op geteste personen en hun partners beschreven. De intrusie- en vermijdingssubschalen van de Impact of Event Scale (IES)[20] die ziektespecifieke stress meet, en de Beck Hopelessness Scale (BHS),[21] die iemands toekomstverwachtingen meet, zijn voorafgaand aan de test, 1 week, 6 maanden en 3 jaar na de test afgenomen. Variantie analyse met herhaalde metingen toonde gelijksoortige intrusiepatronen voor gendragers en niet-dragers, maar tegenovergestelde patronen voor vermijdingsgedrag na 6 maanden. Een week na de testuitslag rapporteerden gendragers een slechter toekomstperspectief en niet-dragers een beter toekomstperspectief. Deze effecten waren 6 maanden na de test verminderd en bleven daarna op hetzelfde niveau. Partners van de gendragers volgden hetzelfde beloop. Partners met kinderen waren psychisch meer aangedaan dan partners zonder kinderen.

In **hoofdstuk 3** worden de effecten 7 tot 10 jaar na de test op geteste personen en hun partners gepresenteerd. Dit onderzoek omvat wereldwijd gezien de langste periode waarover psychologische effecten van genetisch testen van op latere leeftijd optredende erfelijke ziekten zijn onderzocht. Gendragers en hun partners waren direct na de test tijdelijk geschokt en meer aangeslagen, daarna, in de periode van 2 tot 3 jaar na de test werd hun toekomstvisie enigszins beter. Zij werden echter op de langere termijn, bij het naderen van de aanvangsleeftijd, weer pessimistischer. Niet-dragers rapporteerden grote opluchting na de testuitslag, maar keerden op termijn weer naar pre-test niveaus terug. Gendragers die na de uitslag geen vragenlijsten meer invulden, rapporteerden pre-test meer stress dan gendragers die de vragenlijsten wel invulden en terugkwamen voor vervolggesprekken. Gegeven dat de beste voorspeller voor psychologische stress na de testuitslag de stress voor de test is, verdient het aanbeveling na te denken hoe in de toekomst hulpverleners contact kunnen blijven houden met personen met hoge stress. Het lijkt erop dat onderzoeken, die weinig nadelige effecten rapporteren over personen met een ongunstig testresultaat, de werkelijke invloed onderschat hebben.

In het onderzoek naar de lange termijn effecten van testen kwam het belang van een adequate statistische techniek en de aandacht voor uitval van deelnemers naar voren. Dit leidde tot een onderzoek naar rapportage over uitval en de adequaatheid van technieken die in psychologische

vervolgstudies naar effecten van voorspellend testen werden gebruikt. De resultaten worden in **hoofdstuk 4** beschreven. Het doel van dit systematische literatuuronderzoek is om de in dit soort vervolgonderzoek gebruikte statistische methoden te beschrijven en te beoordelen. Een literatuurzoektocht resulteerde in 40 longitudinale kwantitatieve onderzoeken, die aan de selectiecriteria voor dit literatuuronderzoek voldeden. Vijftien onderzoeken (38%) pasten adequate statistische technieken toe. De meerderheid, 25 onderzoeken, gebruikten minder geschikte of minder efficiënte statistische technieken. Negen onderzoeken (23%) rapporteerden in het geheel niet over uitval van respondenten, en 18 (45%) onderzoeken deden geen mededelingen over de kenmerken van uitvallers. Dertien van de 22 onderzoeken met tenminste 3 meetmomenten, die over missende waarden gerapporteerd zouden behoren te hebben, deden dat daadwerkelijk. De conclusie is dat veel onderzoeken meer en betere resultaten zouden kunnen hebben als een meer adequate techniek was gebruikt. De meest voorkomende zwakheid was dat een statistische methode, geschikt voor hoogstens twee meetmomenten, werd gebruikt voor een onderzoek met meer meetmomenten. Dit was het geval in 14 van de 28 betroffen studies. In veel van deze onderzoeken werden de analyses in deelanalyses uitgevoerd, met daardoor een minder compleet overzicht en minder inzicht in het totale beloop.

Uitval van deelnemers is een ernstig probleem in longitudinale onderzoeken. Hoewel zoveel mogelijk voorkomen moet worden dat personen zich aan het onderzoek onttrekken, zal er altijd om diverse redenen uitval zijn. Bij een onbekend adres of bij overlijden is het effect in het algemeen niet erg verstorend. Als de uitval echter wordt veroorzaakt door ongeïnteresseerdheid van de respondent, of door psychische problemen, dan kan dat het onderzoek wel ernstig verstoren. Selectieve uitval is met name beperkend voor de generalisatie van de onderzoeksresultaten. De conclusie bijvoorbeeld, dat een voorspellende test geen ernstige ongewenste psychologische gevolgen heeft, geldt niet voor de hele groep geteste personen als die conclusie gebaseerd is op personen die minder depressief zijn. In ons onderzoek[22] is de groep, die gemakkelijker nadelige gevolgen kan ondervinden, inderdaad selectief uit het onderzoek verdwenen. Diverse onderzoeken hebben uitgewezen dat pre-test scores goede voorspellers zijn voor post-test scores.[23 24] De groep met een pessimistischer toekomstperspectief en met hoge vermijdingsscores vóór de test is dus vatbaarder voor psychologische problemen na de test. In de toekomst moet door extra aandacht en steun voorkomen worden dat er een groep ontstaat die alle contact met de hulpverleners verliest. In slechts één ander onderzoek[25] werd ook een selectieve uitval gemeld. Geen enkel ander onderzoek rapporteerde een selectieve uitval en bijna de helft (18) van de onderzoeken beschreef in het geheel niets over uitval.

Hoofdstuk 5 is gericht op de interesse voor een meer dan 99% zekere voorspellende test. In 1987 kwam de koppelingstest in Nederland beschikbaar.[26 27] Deze test had een restrisico van 1-10% waarbij de medewerking van familieleden vereist was. In Nederland hebben 245

personen de koppelingstest laten uitvoeren. Twaalf van hen kregen geen testuitslag omdat de markeerpunten niet voldoende informatief waren, en 23 personen kregen geen uitslag omdat de familiestructuur niet voldoende informatief was. Van de anderen bleken 88 personen gendragers en 122 niet-dragers te zijn. Zes jaar later werd de genmutatie van de ziekte van Huntington gevonden en werd voorspellend testen met een zekerheid van meer dan 99% mogelijk.[7] De medewerking van familieleden was toen niet meer nodig. In 1997 werd deze nieuwe mutatietest aangeboden aan de 210 personen die een koppelingstestuitslag hadden ontvangen. Eenentachtig personen konden niet aan het onderzoek deelnemen. De belangrijkste redenen waren dat de mutatietest al eerder was uitgevoerd in combinatie met prenatale diagnostiek of dat inmiddels de diagnose Huntington was vastgesteld. Anderen waren overleden, waren verhuisd, waren om andere redenen niet meer te achterhalen of zij reageerden niet. Een onderzoeksgroep van 129 personen bleef over. Drie groepen werden vergeleken: (1) 18 personen die met mutatieanalyse waren getest tussen 1993 en 1997 voor dit onderzoek was begonnen, (2) 29 personen die opnieuw getest werden nadat wij hun hadden geïnformeerd en (3) 82 personen die de niet opnieuw wilden worden getest. Bijna de helft van de personen, die met koppelinganalyse waren getest, wilde opnieuw worden getest, met als uitzondering de personen die eerder een gunstige testuitslag hadden gekregen met een restrisico van 2% of minder. In deze laatste groep heeft minder dan 20% zich opnieuw laten testen. Gendragers die meer vertrouwen hadden in de toekomst (BHS)[21] en een betere algemene gezondheid (GHQ)[28] aangaven, kozen vaker voor de nieuwe, meer betrouwbare test. Niet-dragers, die hun eerdere uitslag lieten bevestigen, waren angstiger (HADS)[29] dan niet-dragers die dat niet lieten doen. Vrouwelijke gendragers hadden vaker de voorspellende test laten bevestigen voordat onze informatiecampagne begon. Personen, die zich opnieuw lieten testen, waren jonger dan personen die dat niet lieten doen. Er zijn geen foutieve koppelingstestuitslagen aan het licht gekomen bij dit onderzoek.

In Nederland heeft een minderheid van de risicodragers (24%), zich sinds 1987 laten testen. Zij hebben daarmee precieze informatie over hun risicostatus. Het onderzoek in **hoofdstuk 6** is gericht op het restrisico van risicodragers die zich (nog) niet hebben laten testen. Dit restrisico is vaak lager dan het a priori risico van 50% voor kinderen, of 25% voor kleinkinderen van gendragers. Wij hebben een model ontwikkeld om het verminderde risico te berekenen. Daarvoor hebben wij een gegevensset met aantallen CAG's en aanvangsleeftijden gebruikt, deze bevatte ook een deelgegevensset met CAG's van ouders en hun kinderen. In dit model wordt eerst de CAG van de ouder uit zijn of haar aanvangsleeftijd geschat. In een tweede stap wordt de CAG van de adviesvrager uit de CAG van de aangedane ouder geschat, waarbij rekening met het geslacht van die ouder wordt gehouden. Als derde stap wordt de kans bepaald dat de adviesvrager nog geen symptomen heeft, gegeven dat hij of zij gendrager zou zijn. Tenslotte wordt daaruit het restrisico berekend, waarbij ook rekening wordt gehouden met eventuele gunstige geteste kinderen. Dit model kan door

klinisch genetici worden gebruikt om het restrisico van een adviesvrager te bepalen. Doordat een spreadsheet beschikbaar is gesteld, is het voor de adviesgever betrekkelijk eenvoudig om dit restrisico te berekenen. In deze spreadsheet kan de leeftijd van de adviesvrager, de aanvangsleeftijd of de CAG van het aangedane familielid en het aantal gunstig geteste kinderen worden ingevoerd. Schattingen van de CAG en het restrisico worden dan als uitkomst gegeven.

De achteruitgang bij de ziekte van Huntington is niet te stoppen en ook niet te vertragen. Genezing is niet mogelijk. Een van de meest genoemde motieven om zich te laten testen was een betere voorbereiding op de toekomst. Personen met een ongunstige uitslag moeten nieuwe onzekerheden onder ogen zien. Daarbij gaat het om het begin van de ziekte en hoe deze zich zal openbaren. Bewezen gendragers zullen zich beter op hun toekomst kunnen voorbereiden als zij adequater over de bijzonderheden van het beloop van de ziekte worden ingelicht. De behandeling, de verzorging en de zorgmogelijkheden zijn verbeterd door meer kennis over de ziekte. De neurologische poliklinieken, het Huntington Steunpunt, en de speciale verpleegafdelingen voor Huntington patiënten in Nederland en België hebben veel ervaring opgedaan met Huntington patiënten in de verschillende stadia van de ziekte. Het vooruitzicht op een goede verzorging in de latere stadia kan een geruststelling zijn en kan er aan bijdragen dat de negatieve ervaringen met de zorg voor familieleden in het verleden niet langer het eigen toekomstperspectief bepalen. Om deze zorg verder te verbeteren is nog meer inzicht nodig in het beloop van de ziekte. In **hoofdstuk 7** wordt de ontwikkeling van de Gedrags Observatie Schaal Huntington (GOSH) beschreven. In 1996 werd de UHDRS[18] geïntroduceerd om het klinisch beeld en functionele beperkingen bij de ziekte van Huntington te bepalen. Door plafondeffecten onderscheidt de UHDRS echter niet in latere stadia van de ziekte. De GOSH werd ontwikkeld om een gedetailleerde beschrijving van het gedrag van de patiënten in de laatste fasen van de ziekte te geven. De schaal bevat 32 vragen met ieder vier antwoordcategorieën. Principale componenten analyse leverde drie subschalen op: (1) achteruitgang van activiteiten van het dagelijks leven (ADL), (2) sociaal-cognitieve achteruitgang en (3) mentale rigiditeit en agressie. De schaal is gevalideerd in vier verzorgingshuizen met een speciale Huntington afdeling. Verpleegkundigen hebben voor 91 patiënten de GOSH twee maal onafhankelijk van elkaar ingevuld. Interne betrouwbaarheden van de drie subschalen lagen tussen .83 en .94 en tussen-beoordelaar betrouwbaarheden lagen tussen .85 en .95. Er werden zwak significante verhoudingen gevonden tussen ziekteduur en vermindering van sociaal-cognitieve vermogens en rigide en agressief gedrag. Tussen componenten onderling werden sterkere significante verhoudingen gevonden. Non-lineaire verhoudingen bestonden tussen (1) achteruitgang van ADL en rigiditeit-agressie en (2) achteruitgang van ADL en sociaal-cognitieve achteruitgang. Rigide en agressief gedrag kwam bij de ontwikkeling van de ziekte steeds vaker voor, later verminderde dit gedrag weer. Sociaal-cognitieve vermogens gingen vooral in de laatste stadia van de ziekte achteruit.

8b.5. DISCUSSIE

8b.5.1. Psychologische aanpassing aan de testuitslag

De algemeen heersende opvatting was dat de gevolgen van voorspellend testen voor de ziekte van Huntington meer positief dan negatief waren.[15-17] Aangenomen werd dat men baat had bij het testen.[30] Deze conclusie kan echter niet zonder meer worden getrokken. Tot 2003 waren er geen publicaties over een periode langer dan drie jaar na de test. In het onderzoek zeven tot tien jaar na de test gaven de gendragers aan slechtere toekomstperspectieven te hebben gekregen. Depressieve gevoelens en pessimistische toekomstverwachtingen kunnen eerste symptomen van de ziekte van Huntington zijn en derhalve de hogere scores verklaren. Echter, bij hun partners werd een zelfde verandering in toekomstperspectief waargenomen. Waarschijnlijker is dat de testuitslag, de naderende aanvangsleeftijd, het begin van de ziekte bij familieleden, verlieservaringen en andere Huntington gerelateerde levensgebeurtenissen deze verslechtering van het toekomstperspectief veroorzaakt hebben. Omdat de gemiddelde leeftijd op het laatste meetmoment 45 jaar was, uiteenlopend van 27 tot 73, zullen de eerste verschijnselen zich in de nabije toekomst gaan voordoen.

Deze resultaten zijn gebaseerd op een selectie van personen die zich hebben laten testen. Er was geen controlegroep van personen die dat niet hebben laten doen. Van der Steenstraten et al.[31] bemerkten verschillen tussen wel en niet geteste personen. Personen die zich niet hebben laten testen voelden zich kwetsbaarder en minder goed in staat een slechte testuitslag te verwerken. Maar ook bij dat onderzoek moet worden opgemerkt, dat de onderzoeksgroep een selectie was, geworven uit leden van de Vereniging van Huntington. Het is denkbaar dat ook deze personen psychologisch stabieler waren. Voor meer definitieve conclusies is het aangewezen om niet-geteste risicodragers van rond de veertig jaar in een onderzoek te betrekken.

8b.5.2. Uitvalanalyse

Uitvallers in longitudinaal onderzoek zijn onvermijdelijk. Er bestaan diverse redenen waarom men niet meer aan het vervolgonderzoek deelneemt. Dit kunnen verhuizingen of niet te achterhalen adressen zijn. Men kan overlijden aan een ziekte of oorzaak die geen verband met de ziekte van Huntington heeft. Men kan voor de ziekte kenmerkende symptomen krijgen en daardoor van verdere analyses uitgesloten worden. In een aantal gevallen is de reden niet bekend. Één van die redenen kan zijn dat men niet meer wìl meewerken. Non-response is meestal niet toevallig. Uitvallers hebben vaak bepaalde kenmerken die een longitudinaal onderzoek kunnen ontkrachten.[32] Bij longitudinaal onderzoek moet daarom een uitvalanalyse uitgevoerd worden. Uitvallers behoren vergeleken te worden met personen die in de studie behouden blijven op alle aanwezige biografische en psychologische uitkomstmaten. Daarbij kan geredeneerd worden dat als zulke verschillen niet worden gevonden, dat er dan ook geen reden is om

aan te nemen dat het onderzoek door selectieve uitval ontkracht wordt. Selectieve uitval wordt vaak gezien als een bedreiging voor de validiteit van het onderzoek. Een goede uitvalanalyse kan daarentegen juist zeer interessante inzichten bieden. In Tibben et al.[33] werden geen significante verschillen tussen uitvallers en de andere deelnemers aan het onderzoek gevonden. Er bleek echter wel degelijk een significant verschil aanwezig. Dit werd pas vele jaren later gevonden, toen de effecten zeven tot tien jaar na de test geanalyseerd werden. De sleutel tot het probleem was het inzicht dat een gunstige testuitslag geheel anders verwerkt wordt dan een ongunstige uitslag. Toen uitvalanalyses op deze groepen afzonderlijk uitgevoerd werden, kwam naar voren dat uitgevallen gendragers, voorafgaand aan de test, meer vermijdend gedrag vertoonden, aanmerkelijk slechtere toekomstverwachtingen, meer intrusieve gedachten, en slechtere algemene gezondheidsscores hadden. Deze verschillen waren hoogst significant en effectgrootten varieerden van middelgroot tot zeer groot (0.6 - 1.0). Daarmee werd dus niet alleen gevonden dat gendragers op lange termijn een slechter toekomstperspectief aangaven dan niet-dragers, maar deze bevinding was bovendien gebaseerd op een selectie van gendragers die psychologisch stabieler waren. Het is dus waarschijnlijk dat de effecten van een ongunstige testuitslag nog sterker zijn dan uit de longitudinale analyses alleen was af te leiden.

Genetici en psychosociale medewerkers schatten in of iemand een ongunstig testresultaat goed zal kunnen verwerken. Niettemin zouden meer angstige, depressieve of pessimistische personen, die een ongunstige testuitslag krijgen, op lange termijn extra professionele aandacht verdienen. Er zouden lange termijn vervolgafspraken geregeld moeten worden en zonodig zou naar additionele hulpverleners moeten worden verwezen. Ondanks al dit soort inspanningen moeten we er rekening mee blijven houden dat het aanbod van verdere steun wordt geweigerd, omdat elke confrontatie met de ziekte en de toekomst uit de weg wordt gegaan.

8b.5.3. Het belang van een adequate statistische techniek

Voor de analyse van het lange termijn onderzoek zeven tot tien jaar na de voorspellende test werd General Linear Mixed Modeling (GLMM) gebruikt. Deze methode is geschikt voor longitudinaal onderzoek met ontbrekende waarnemingen. Dit maakt een optimaal gebruik van de gegevens, deelnemers en meetmomenten mogelijk. Zo konden de vragenlijsten, die anderhalf jaar na de test afgenomen waren, ook verwerkt worden. Van dat meetmoment waren weinig gegevens, omdat het project toen tijdelijk onderbroken was. Als GLMM voor het onderzoek drie jaar na de test was gebruikt, en daarbij het anderhalf jaar meetmoment was geïncludeerd, dan had toen al aan het licht kunnen komen dat het toekomstperspectief van de gendragers zich minder gunstig ontwikkelde.

Een minder adequate techniek kan er ook toe leiden dat zwak significante verschillen niet worden opgemerkt. Dit kan optreden als een non-parametrische test gebruikt wordt waar een parametrische op zijn plaats is. Meestal leidt dit niet tot een ernstig powerverlies, want gewoonlijk

is de power van een non-parametrische test ongeveer 95% vergeleken met bijvoorbeeld die van een F-test. Soms kan de power echter wel drastisch verminderen. Als een analyse voor dichotome gegevens gebruikt wordt voor continue gegevens kan de efficiëntie dalen tot 63%.[34]

8b.5.4. De introductie van een meer accurate DNA test

In Nederland hebben aanzienlijk meer risicodragers zich laten testen dan in andere landen.[14] De voornaamste reden om zich te laten testen was om verlost te worden van de ondragelijke onzekerheid. De grote noodzaak om zekerheid en geruststelling te krijgen wordt hiermee duidelijk. Toen de nieuwe, zekere mutatietest beschikbaar werd, ontstond er niettemin toch een discussie of de personen die met koppelingsanalyse getest waren, wel ingelicht moesten worden. Het Klinisch Genetisch Centrum Leiden wilde de nieuwe test aan iedereen aanbieden, die met koppelingsanalyse was getest. De Leidse Commissie Medische Ethiek (CME) vroeg zich echter af of men wel na zoveel jaar nog benaderd zou mogen worden, met het risico dat men daarmee ongevraagd problemen zou oprakelen. De CME redeneerde dat geteste personen zich aan hun testuitslag zouden hebben aangepast en een nieuwe balans in hun leven zouden hebben gevonden. Deze balans zou kunnen worden verstoord. Men zou de indruk kunnen krijgen dat de koppelingstestuitslag onzeker of misschien zelfs onjuist was. Zelfs de conclusie dat de test in het geheel niet goed geweest zou zijn, zou kunnen worden getrokken.

Aan de andere kant had men zich laten testen om optimale zekerheid te krijgen en daarmee het leven in te richten. Als een nieuwe techniek meer zekerheid geeft, dan moet die techniek ook worden aangeboden. Bovendien, vanuit een niet-directief en niet-paternalistisch oogpunt zou de beslissing voor een zekere test aan het geteste individu moeten worden overgelaten. Daar komt nog bij dat de Vereniging van Huntington al informatie over de directe test in hun kwartaalblad had gepubliceerd. Na enige jaren discussie, waarin de argumenten voor en tegen werden afgewogen, werd de conclusie getrokken dat de test mocht worden aangeboden aan allen die met koppelingsanalyse waren getest.

Voordat de mutatietest, die een betrouwbaarheid van praktisch 100% heeft, beschikbaar kwam, enquêteerden Babul et al.[35] personen, die met koppelinganalyse getest waren. Er werd hun gevraagd of zij in een, toen nog hypothetische, 100% zekere test geïnteresseerd waren. Het bleek dat 72% aangaf zich dan opnieuw te willen laten testen. Toen de test daadwerkelijk uitkwam, bleek in het Nederlandse onderzoek, dat het percentage personen dat zich opnieuw liet testen slechts 42% was.[36] Een soortgelijke waarneming werd gedaan voorafgaand aan de koppelingstest in de jaren 1984-1987. Toen gaf 40% tot 84% van de risicodragers aan getest te willen worden.[16 37-39] Het percentage dat zich sinds de introductie van de test daadwerkelijk heeft laten testen (2%-24%) viel echter beduidend lager uit.[14 40-43] Het is duidelijk dat er een discrepantie bestaat tussen het voornemen om getest te worden en het daadwerkelijk laten uitvoeren ervan.

Zoals verwacht, was het restrisico van de koppelingstest van invloed op de beslissing om zich opnieuw te laten testen, maar dat gold alleen voor personen die een gunstige uitslag hadden gekregen. Niet-dragers met een laag restrisico schenen minder noodzaak te voelen om dat risico nog verder te verlagen. Voor zover wij weten heeft het informeren van geteste personen over de mutatietest niet tot nadelige effecten geleid.

8b.5.5. Additionele risico informatie voor hulpvragers en hulpverleners

Algemeen wordt een risicodrager voor de ziekte van Huntington beschouwd als iemand met 50% kans om de ziekte te krijgen. Hij heeft immers een kans van 50% om de erfelijke eigenschap van de aangedane ouder bij zich te dragen. De kans neemt echter af bij het toenemen van de leeftijd.[44] De hoeveelheid gegevens over CAG en aanvangsleeftijden binnen families maakte het mogelijk een model te ontwikkelen waarmee het risico nauwkeuriger kan worden ingeschat van iemand die (nog) niet getest is en symptoomvrij is. Dit gebeurt aan de hand van iemands leeftijd, de CAG of de aanvangsleeftijd van de ouder en van eventuele geteste familieleden met een gunstige testuitslag. Het model leidt alleen tot een lagere risicoschatting, terwijl de mutatietest tot een onomkeerbare uitkomst leidt. Het model is niet in de eerste plaats gericht op personen voor wie, om welke reden dan ook, de test geen optie is. Ons model en bijbehorende spreadsheet kunnen het repertoire van klinisch genetici uitbreiden. Klinisch genetici kunnen hiermee een meer precieze actuele risicoschatting van de adviesvrager bepalen. Een risico lager dan 50% kan de beleving van het persoonlijke risico beïnvloeden en een ander licht werpen op de motieven om meer zekerheid te wensen.

Alle berekeningen zijn gebaseerd op de best mogelijke parameterschattingen en zodoende dienen ook de restrisico's en CAG's van de adviesvrager als de beste schattingen beschouwd te worden. Deze schattingen hebben een zekere betrouwbaarheidsmarge. Als in de toekomst meer gegevens over CAG's, aanvangsleeftijden en de betreffende relaties tussen ouders en hun kinderen beschikbaar komen, kunnen deze marges kleiner worden en zullen de schattingen preciezer worden.

Adviesvragers willen vaak weten hoe groot hun risico is en hoe dat risico in de toekomst zal veranderen. Dit kan hen van dienst zijn bij de keuze om zich te laten testen en om zich beter op de uitslag voor te bereiden. Deze beslissing kan afhankelijk zijn van het actuele restrisico en het restrisico in de nabije toekomst. Aan de hand van ons model en de tabellen die door Langbehn et al.[44] zijn gepubliceerd, kan worden bepaald of de adviesvrager betreffende de aanvangsleeftijd in een kritische periode is. In deze kritische periode is de afname van het restrisico het grootst en dat kan van invloed zijn op de beslissing om in korte termijn getest te willen worden of de test enige jaren uit te stellen.

Risicodragers kunnen problemen met verzekeringsmaatschappijen en het verkrijgen van werk ondervinden.[45-48] Voor derden kan een nadere nuancering van het actuele risico nuttig zijn, zonder dat een genetische test wordt uitgevoerd. Aangenomen dat deze derden meestal een

risicoschatting van 50% voor kinderen van Huntington patiënten hanteren, biedt dit model ook voordelen voor de risicodragers, want het actuele risico is altijd lager dan het a priori risico.

8b.5.6. Structuur van de Gedrags Observatie Schaal Huntington (GOSH)

Bij de ontwikkeling van de GOSH werden drie principale componenten gevonden: achteruitgang van activiteiten van het dagelijks leven (ADL), achteruitgang van sociale en cognitieve vermogens, en mentale rigiditeit en agressie. Er was geen goede indicator voor ziekteduur beschikbaar omdat de aanvangsleeftijd vaak retrospectief bepaald was. Zo was in een aantal gevallen de aanvangsleeftijd bepaald aan de hand van de opname in een psychiatrisch ziekenhuis. Indien deze opname inderdaad het gevolg was van een stoornis die door de ziekte van Huntington was veroorzaakt, dan was de aanvangsleeftijd te laat ingeschat. Als dat niet het geval was, dan was de aanvangsleeftijd juist te vroeg ingeschat. Dit leidde tot een slechts zwak significante samenhang tussen ziekteduur en sociaal-cognitieve achteruitgang. De verplegingsduur was geen betere indicatie van de ziekteduur. De achteruitgang van motorische functies kan doorslaggevend geweest zijn in de beslissing tot plaatsing in een verpleeghuis. Bij andere patiënten kon de psychiatrische problematiek op de voorgrond staan waardoor opname in een verpleeginrichting noodzakelijk werd.[49] De beslissing om opgenomen te worden kon ook afhankelijk zijn van de aanwezigheid van een verzorgende partner of een andere verzorger en in mindere mate van de beperkingen van de patiënt en ernst van de ziekte. In het Belgische verzorgingstehuis is het ontbreken van een verzorger zelfs de belangrijkste indicatie voor opname. Niettemin is er een zwak significante lineaire samenhang tussen de verzorgingsperiode en achteruitgang van ADL gevonden.

Er wel is een hoogst significante kwadratische relatie tussen rigiditeit-agressie en ADL gevonden. Een verklaring is dat rigide en agressief gedrag aanvankelijk toeneemt en later weer afneemt. Een soortgelijke relatie tussen rigide gedrag en ziekteduur is beschreven in het onderzoek van Craufurd et al.[50 51] Opgemerkt moet worden dat het agressieniveau beperkt wordt. In verpleeginrichtingen wordt agressie met psychologische behandeling en farmacotherapie bestreden. Toekomstig onderzoek zou rekening moeten houden met de aard en effecten van deze interventies.

Een tweede significante kwadratische relatie is gevonden tussen sociaal-cognitief functioneren en ADL niveau. Als wederom het ADL niveau als operationalisatie van ziektevoortgang genomen wordt, dan duidt dit erop dat de achteruitgang van sociaal-cognitieve vermogens vooral in de latere stadia van de ziekte toeneemt, als rigide en agressief gedrag afnemen. Met andere woorden: de achteruitgang van ADL en rigide en agressief gedrag gaat vooraf aan de achteruitgang van sociaal-cognitief gedrag. Dit is in overeenstemming met de waarneming van Bamford et al.[52] dat het geheugen pas in de laatste stadia van de ziekte verslechtert.

De externe validiteit van de GOSH kan nog beter bepaald worden. In een vervolgonderzoek zal de GOSH tezamen met de UHDRS afgenomen

worden. De UHDRS is door de Amerikaanse Huntington Study Group in 1994 ontwikkeld voor een ruimere bepaling van iemands motorische, cognitieve en functionele vaardigheden, alsmede van de gedrags en psychiatrische problemen.[18] Het was niet de bedoeling dat de UHDRS een alomvattende beschrijving van elke mogelijke uiting van de ziekte van Huntington zou geven.[1] Hoewel de UHDRS niet goed in latere stadia van de ziekte differentieert, is een vergelijking tussen de GOSH en de UHDRS wel gewenst.

De GOSH is ontwikkeld om een gedetailleerd inzicht in het beloop van de ziekte te krijgen, en om individuele verschillen tussen patiënten te onderscheiden. Een meer gedetailleerd inzicht in deze verschillen is van belang voor een lopende studie naar de relatie tussen de fenotypische expressie van de ziekte van Huntington en de pre-morbide persoonlijkheid en het sociale ondersteuningssysteem. Uiteindelijk kan een beter inzicht in deze verhouding de begeleiding van patiënten verbeteren.

Tot op heden bestaat er geen genezing voor de ziekte van Huntington, de behandeling blijft beperkt tot palliatieve ondersteuning. De kenmerken van de ziekte rechtvaardigen verzorging in speciale verpleegafdelingen die in een toenemend aantal landen zijn ingericht. Er is een groeiende hoeveelheid kennis over de klinische expressie van de ziekte in de middenstadia.[50] [53] Om de ontwikkeling van toegespitste begeleidingsprogramma's in de laatste stadia mogelijk te maken, is er een nauwkeurige beschrijving van het ziektebeloop nodig. Daarmee kan de zorg voor de patiënten toegesneden en verbeterd worden.

8b.5.7. Slotopmerkingen

Het toekomstperspectief van patiënten met de ziekte van Huntington, gendragers en risicodragers is moeilijk in te schatten. Toch lijkt voor hen meer hoop gerechtvaardigd in vergelijking met hun aangedane ouders en voorouders. Dankzij de medewerking van patiënten, familieleden en de Vereniging van Huntington aan wetenschappelijk onderzoek naar de effecten van de voorspellende test is in de afgelopen 15 jaar veel inzicht verkregen in de beleving van de ziekte bij alle betrokkenen. Psychologische ondersteuning kan steeds beter toegesneden worden aangeboden. Met de mutatietest kan de ziekte in een eerder stadium worden vastgesteld of bevestigd. De mutatietest maakt ook wetenschappelijk onderzoek naar de eerste symptomen in een vroeger stadium mogelijk. Verpleeghuizen hebben speciale afdelingen opgericht waar goede verzorging op basis van kennis en ervaring met deze bijzondere ziekte kan worden aangeboden. De eerste aanwijzingen in de richting van het vinden van genezing dienen zich aan.

De ziekte van Huntington is een zeldzame ziekte. Er kan veel meer vooruitgang geboekt worden als kennis, informatie, en wetenschappelijk onderzoek gebundeld worden. Zo heeft er een interventiestudie plaatsgevonden met 450 patiënten in negen Europese landen waarin Riluzole in vroege stadia van de ziekte getest werd. Dit toonde aan dat grootschalig onderzoek in Europa mogelijk is. In 2003 werd het Euro-HD

netwerk opgericht. Dit netwerk beoogt een lange termijn observatieperiode van patiënten met de ziekte van Huntington, en het creëren van een passende infrastructuur voor klinisch onderzoek in Europa (http://www.euro-hd.net). Met het Predict onderzoek, een van de activiteiten van het netwerk, wil men de klinische veranderingen bij het eerste begin van de ziekte vaststellen. Daarbij gebruikt men verfijnde en gestandaardiseerde cognitieve prestatiematen en wordt met seriële MRI (Magnetic Resonance Imaging) scans de omvang van de hersenen bepaald.[54] Het gegevensbestand kan ook gebruikt worden om meer inzicht te krijgen in de allereerste symptomen bij nog niet aangedane gendragers. Ook kan het beloop van de ziekte na het begin worden bestudeerd en kunnen therapieën worden onderzocht die bedoeld zijn om het beloop van de ziekte te beïnvloeden. Het Euro-HD netwerk dient als een spreekbuis voor professionals, aangedane personen en hun familie om de samenwerking in Europa gemakkelijker te maken. Het Euro-HD netwerk bevordert ook biologisch en interventie onderzoek dat aan hoge standaarden voldoet, waarmee de weg naar genezing voor de ziekte van Huntington wordt vrijgemaakt. Het netwerk is erop gericht een echt netwerk te zijn, in die zin dat iedereen die zich met de ziekte van Huntington bezig houdt kan participeren in de ontwikkeling van onderzoeksvoorstellen en de uitvoering van onderzoek.

Het Euro-HD netwerk stimuleert de ontwikkeling van instrumenten die in de Huntington studies gebruikt worden. Deze instrumenten (testen, vragenlijsten en beoordelingsschalen) worden gestandaardiseerd en vertaald in de talen van de deelnemende landen.

De ziekte van Huntington is nog niet te genezen. Maar door de gezamenlijke inspanningen van patiënten en hun families, de Vereniging van Huntington, de bij de ziekte betrokken (para)medici, en de wetenschappelijk onderzoekers kunnen patiënten en hun families geholpen worden allerlei aspecten van de ziekte, hun leven en hun levensperspectief beter te leren verdragen.

8b.6. REFERENTIES

Voor referenties zie p. 143.

KAPITEL 8c
-
Zusammenfassung
und Schlussfolgerungen

8c.1. ALLGEMEINE EINLEITUNG

Die Huntingtonsche Krankheit ist eine autosomal dominante Erbkrankheit, die durch unwillkürliche Bewegungen, kognitive Degeneration und psychiatrische Probleme charakterisiert wird. Die ersten Anzeichen treten normalerweise im mittleren Lebensalter auf. Durchschnittlich beginnt die Krankheit zwischen dem 43,7 und dem 55,8 Lebensjahr,[1-3] (Standardabweichungen 10,9 beziehungsweise 13,5 Jahre).[2 3] Die Krankheit dauert im Median etwa 16,2 Jahre[3]; der Patient stirbt schließlich an Ursachen, die mit der Krankheit in Verbindung stehen.[1] Die Prävalenz bei Menschen westeuropäischer Herkunft wird auf 5 - 10 pro 100.000 Einwohner geschätzt,[4] obwohl es Hinweise gibt, dass die Häufigkeit höher ist.[5] Die kennzeichnenden Symptome und der Fortschritt der Krankheit beziehen sich auf die Neuropathologie, die von einem Verlust spezifischer Neuronen, insbesondere in den Oberschlundganglien, gekennzeichnet ist.[6] Die Krankheit wird von einer CAG-Wiederholung auf dem kurzen Arm des vierten Chromosoms verursacht.[7-10] Erkrankte Personen haben Wiederholungen von 36 bis über 100.[8-10] Die Grenzen dieser Wiederholungen sind folgendermaßen bestimmt: ein normales Allel hat höchstens 26 Wiederholungen, ein intermediäres Allel hat 27-35 Wiederholungen, eine Erkrankung mit eingeschränkter Penetranz hat 36-39 Wiederholungen und ein krankes Allel hat mindestens 40 Wiederholungen.[11] Das Anfangsalter steht in einem umgekehrten Zusammenhang mit der Wiederholungslänge,[12] während es keinen Zusammenhang mit der Krankheitsdauer gibt.[13]

Kinder eines Huntingtonpatienten haben eine 50% Chance, die Erkrankung selbst geerbt zu haben. Seit dem Ende der Achtziger Jahre des letzten Jahrhunderts steht ein prädiktiver DNA-Test zur Verfügung. Die Einführung des Tests wurde behutsam vorgenommen, da schwerwiegende Konsequenzen, insbesondere für Personen mit einem erhöhten Risiko, erwartet wurden. In den Niederlanden sind bereits 24% der Risikoträger getestet.[14]

8c.2. HINTERGUND DER FORSCHUNG

Die Einführung des prädiktiven Tests warf eine Vielzahl psychologischer Fragen auf, die besonderer Aufmerksamkeit bedürfen. Es zeigte sich, dass ein ungünstiges Testergebnis vorübergehend psychische Beschwerden verursachte, welche sich sechs Monate bis ein paar Jahre nach dem Test wieder auf Prä-Test Niveau verringerten. Teilnehmer, die ein günstiges Ergebnis erhielten, erlebten eine kurzfristige Erleichterung, kehrten aber mittelfristig ebenfalls auf das Prä-Test Niveau zurück.[15-17] Das Niederländische Forschungsprogramm hatte die Untersuchung der langfristigen psychologischen Effekte zum Ziel.

1993 ermöglichte die Entdeckung der CAG-Wiederholung einen direkten Mutationstest mit einer Sicherheit von über 99%. Nach einer ausführlichen Diskussion, ob zuvor getestete Personen über den Mutationstest informiert und diesen angeboten bekommen sollten, wurde dieser Test 1997

angeboten. Dies ermöglichte die Untersuchung des Interesses am neuen Test und die langfristigen psychologischen Effekte.

Die Ergebnisse der Follow-up Studien hatten einen starken Einfluss auf die psychosoziale Unterstützung und die Qualität des prädiktiven Testprogramms bei mehreren Erbkrankheiten, die in fortgeschrittenem Lebensalter auftreten. Es wird angenommen, dass diese Studien zuverlässige und effektive Methoden anwenden. Die Methodologie nahezu aller zwischen 1988 und 2003 publizierten Follow-up Studien über die psychosozialen Effekte von Gentests wurde von uns untersucht.

Genetische Beratung zielt unter anderem auf eine genaue Risikobewertung. Der auf Kopplungsanalyse basierende prädiktive Test resultiert in der Einschätzung eines erhöhten oder verminderten Risikos, während der Mutationstest eine optimale Sicherheit gibt. Die zunehmende Kenntnis über das Erkrankungsalter, dessen Beziehung zur CAG-Wiederholungslänge, und die CAG-Wiederholungslänge bei nahen Verwandten ermöglichen genauere Risikoabschätzungen vor dem Mutationstest.

Die Vorbereitung auf die Zukunft ist einer der wichtigsten Gründe, einen prädiktiven Test durchführen zu lassen. Personen, die ein ungünstiges Testresultat empfangen, werden neuen Unsicherheiten bezüglich des Ausbruchs der Krankheit und der Weise, wie die Krankheit sich manifestieren wird, gegenübertreten müssen. Je mehr spezifische Information verfügbar sein wird, desto mehr identifizierte Genträger werden imstande sein, ihren Zukunftsaussichten entgegenzusehen. Die Huntingtonsche Krankheit schreitet über die Zeit hinweg fort. Obwohl Heilung noch unmöglich ist, hat die zunehmende Kenntnis über die Krankheit die Versorgung und die Pflege bedeutend verbessert. Spezialabteilungen in den Niederlanden und Belgien haben umfangreiche Erfahrung mit Huntingtonpatienten in späteren Erkrankungsphasen gesammelt. Die Aussicht auf eine gute Versorgung in späteren Phasen kann beruhigend wirken und einen Beitrag leisten, die entsetzlichen Erlebnisse mit der Pflege von Verwandten in der Vergangenheit zu vergessen. Jedoch ist mehr Einblick in den Verlauf und den Fortschritt der Krankheit in verschiedenen Phasen nötig, um die Versorgung besser anzupassen. Die Unified Huntington's Disease Rating Scale (UHDRS) wurde als eine klinische Beurteilungsskala entwickelt, um die vier Leistungsbereiche, die von der Krankheit betroffen sind, zu bestimmen: das motorische Funktionsniveau, das kognitive Funktionsniveau, Verhaltensstörungen und die funktionale Kapazität.[18] Die UHDRS ermöglicht die Beobachtung des Krankheitsverlaufes, obwohl das Instrument in späteren Phasen der Krankheit nicht sehr sensitiv ist. Daher fehlte eine Skala, die stärker auf spätere Phasen der Krankheit gerichtet ist. Darüber hinaus war ein besserer Indikator für die kognitiven und psychischen Aspekte des Patienten nötig.[19] Die Behaviour Observation Scale Huntington (BOSH) wurde als Beobachtungsinstrument entwickelt, um die Verhaltensaspekte in späteren Phasen der Erkrankung zu betrachten.

8c.3. ZIEL DER FORSCHUNG

In dieser Arbeit werden folgende, mit dem Gentest bei der Hungtington-Erkrankung zusammenhängende psychologische Aspekte behandelt:

- langfristige psychologische Anpassung von Risikoträgern und ihren Partnern an das Testresultat
- in der Forschung angewendete Methoden zur Untersuchung der Anpassung an die Ergebnisse von Gentests im Allgemeinen
- die Merkmale getesteter Personen mit einem sicheren Testergebnis
- die Risikoberechnung nicht getesteter Personen

Zudem wurde ein Instrument zur Erfassung des Fortschreitens der Krankheit entwickelt, das einfach und schnell vom Pflegepersonal angewendet werden kann.

8c.4. ERGEBNISSE

In **Kapitel 2** werden die psychologischen Effekte des prädiktiven Tests bei Getesteten und ihren Partnern nach drei Jahren beschrieben. Die Intrusions- und Vermeidungssubskalen der Impact of Event Scale (IES)[20], die krankheitsspezifisches Verhalten misst, und die Beck Hopelessness Scale (BHS),[21] die Zukunftserwartungen erfasst, wurden vor dem Test sowie eine Woche, sechs Monate und drei Jahre nach dem Test erhoben. Varianzanalysen mit wiederholten Messungen zeigten gleichartige Intrusionspatterns für Genträger und Nichtträger, jedoch entgegengesetzte Vermeidungsmuster nach sechs Monaten. Eine Woche nach dem Test berichteten Genträger schlechtere und Nichtträger bessere Zukunftserwartungen. Diese Effekte verminderten sich sechs Monate nach dem Test und blieben danach stabil. Die Partner von Genträgern hatten denselben Verlauf. Partner mit Kindern waren psychisch stärker beeinträchtigt als Partner ohne Kinder.

In **Kapitel 3** werden die Effekte, die sieben bis acht Jahre nach dem Test auftreten, dargestellt. Diese Studie untersucht mit der weltweit längsten Zeitspanne die psychologischen Effekte von Gentests für im mittleren Erwachsenenalter auftretende Erbkrankheiten. Genträger und ihre Partner waren unmittelbar nach dem Test vorübergehend beeinträchtigt, jedoch verbesserten sich ihre Erwartungen zwei bis drei Jahre nach dem Test. Sie wurden aber langfristig, mit Näherrücken des prognostizierten Krankheitsbeginns, wieder pessimistischer. Nichtträger berichteten große Erleichterung nach dem Testergebnis, kehrten aber langfristig wieder auf das Prä-Test Niveau zurück. Genträger, die nach dem Testergebnis keine Fragebögen mehr ausfüllten, berichteten vor dem Test mehr psychologischen Stress als solche, die die folgenden Fragebögen ausgefüllt hatten und weitere Beratungen in Anspruch nahmen. Für den Fall, dass sich die Prä-Test Beeinträchtigung als der beste Prädiktor für Post-Test Beeinträchtigung erweisen sollte, ist den zuständigen Beratern zu empfehlen, zukünftig Kontakt mit stärker beeinträchtigten Testpersonen zu halten. Studien, die bei Testpersonen mit einem ungünstigen Testergebnis kaum schädliche Effekte berichten, scheinen den wirklichen Einfluss des Testergebisses unterschätzt zu haben.

Bei der Untersuchung langfristiger Effekte des Gentests sind adäquate statistische Methoden von großer Bedeutung. Daher wurden die statistischen Methoden, die in anderen Langzeitstudien über die psychologischen Folgen des prädiktiven Testens angewendet werden, auf ihre Angemessenheit hin untersucht. Die Ergebnisse werden in **Kapitel 4** beschrieben. Das Ziel dieses systematischen Literatur-Reviews ist die Beschreibung und Beurteilung der statistischen Methoden, die in den Follow-up Studien verwendet werden. Eine Literaturrecherche ergab 40 longitudinale quantitative Studien, die den gestellten Selektionskriterien entsprachen. Fünfzehn Studien (38%) wendeten adäquate statistische Methoden an. Die Mehrheit (25 Studien) verwendeten weniger geeignete oder weniger effiziente Methoden. Neun Studien (23%) berichteten keine Dropout-Rate und in 18 Studien (45%) wurden keine Merkmale der Dropouts beschrieben In dreizehn der 22 Studien mit mindestens drei Messzeitpunkten wurden wie erwartet die fehlenden Werte über die Zeit hinweg beschrieben. Daraus ist zu schließen, dass viele Studien mehr und bessere Ergebnisse gebracht hätten, wenn angemessenere Methoden angewendet worden wären. Die häufigste methodische Schwäche war die Anwendung von statistischen Methoden, die für höchstens zwei Zeitpunkte geeignet sind, in Studien mit mehr als zwei Zeitpunkten. Dies war bei 14 von 28 Studien der Fall. In vielen dieser Studien wurden die Analysen in Teilanalysen unterteilt, was zu einem weniger vollständigen Überblick und einem geringeren Einblick in den Gesamtverlauf führt.

Dropout ist ein wichtiges Problem in longitudinalen Follow-up-Studien. Obwohl jede Möglichkeit, den Dropout von Teilnehmern zu vermeiden, ausgeschöpft werden muss, ist Dropout nicht vollständig zu verhindern. Dropout kann mehrere Ursachen haben. Falls eine unbekannte Adresse oder ein Todesfall vorliegt, ist der Einfluss auf die Forschungsergebnisse in der Regel weniger bedeutsam. Falls Dropout jedoch auf mangelndes Interesse oder psychische Probleme des Teilnehmers zurückzuführen ist, kann das Ergebnis erheblich verzerrt werden. Selektiver Dropout kann insbesondere die Generalisierung der Forschungsergebnisse verhindern. Beispielsweise kann die Folgerung, dass Gentests keine bedeutsamen schädlichen psychologischen Konsequenzen haben, nicht auf die Gesamtgruppe getesteter Personen verallgemeinert werden, wenn das Ergebnis nur für Personen mit einem geringen Risiko, eine Depression zu entwickeln, gilt. In unsere Studie[22] ist die Personengruppe, die mit höherer Wahrscheinlichkeit schädliche Konsequenzen erleben könnte, tatsächlich selektiv aus der Studie ausgeschieden. Mehrere Studien haben gezeigt, dass Prä-Test Werte sehr gute Prädiktoren für Post-Test Werte sind.[23] [24] Personen mit negativen Zukunftserwartungen und hohen Vermeidungsscores leiden also mit höherer Wahrscheinlichkeit nach dem Test unter psychologischen Problemen. Deswegen benötigt diese Gruppe, die jeden Kontakt mit den Beratern verloren hat, besondere Aufmerksamkeit und Unterstützung. Nur in einer anderen Studie[25] wurde ein selektiver Dropout berichtet. Keine andere Studie berichtet einen selektiven Dropout und in fast der Hälfte (18) der Studien wurde kein Dropout beschrieben.

In **Kapitel 5** wird die Akzeptanz eines zu mehr als 99% sicheren prädiktiven Tests dargestellt. 1987 wurde der prädiktive Kopplungstest verfügbar.[26 27] Dieser Test, bei dem die Mithilfe von Verwandten erforderlich ist, hat ein Restrisiko von 1-10%. In den Niederlande hatten sich 245 Personen dem Kopplungstest unterzogen. Zwölf von ihnen hatten kein Testergebnis bekommen, weil die Marker nicht genügend Informationen enthielten. Weitere 23 Personen hatten wegen ungenügender Information zu ihrer Familienstruktur kein Testergebnis erhalten. 88 der übrigen Personen waren Genträger und 122 waren Nichtträger. Sechs Jahre später wurde die Genmutation der Huntington-Krankheit identifiziert und damit ein Test mit einer Sicherheit von mehr als 99% möglich. Das Testen von Verwandten war nicht mehr erforderlich.[7] 1997 wurde dieser neue Mutationstest den 210 Personen, die das Ergebnis des Kopplungstests erhalten hatten, angeboten. 81 Personen konnten nicht an der Studie teilnehmen. Die Hauptgründe dafür waren, dass bereits ein Mutationstest durchgeführt worden war oder bereits die ersten Krankheitsanzeichen vorlagen. Andere Personen waren gestorben, umgezogen, wegen anderer Gründe nicht auffindbar oder reagierten nicht. Daraus resultierte ein Untersuchungssample von 129 Personen. Es wurden drei Gruppen miteinander verglichen: (1) 18 Personen, die sich zwischen 1993 und 1997, vor dem Beginn dieser Studie, mit der Mutationsanalyse hatten testen lassen, (2) 29 Personen, die wieder getestet wurden, nachdem wir sie informiert hatten und (3) 82 Personen, die sich nicht noch einmal testen lassen wollten. Fast die Hälfte der Personen, die mit der Kopplungsanalyse getestet worden waren, ließ sich wieder testen. Eine Ausnahme bildeten Personen mit einem günstigen Ergebnis (Nichtträger) und einem sehr geringen Restrisiko im Kopplungstest, von denen sich weniger als 20% wieder testen ließ. Optimistischere Genträger (BHS)[21] mit besserem Wohlbefinden (GHQ)[28] ließen häufiger den neuen Test durchführen. Nichtträger, die ihr früheres Testergebnis durch den neuen Test bestätigen lassen wollten, waren ängstlicher (HADS)[29] als Nichtträger, die sich nicht wieder testen ließen. Weibliche Genträger hatten sich häufiger erneut testen lassen, noch bevor unsere Informationskampagne gestartet war. Personen, die sich erneut testen ließen, waren zum Testzeitpunkt jünger. In dieser Studie konnten alle Ergebnisse des Kopplungstests bestätigt werden.

In den Niederlanden hat sich eine Minderheit (24%) der Risikoträger seit 1987 testen lassen. Damit sind sie genau über ihr Risiko informiert. Die Studie, die in **Kapitel 6** dargestellt wird, beschäftigt sich mit dem Restrisiko von Personen, die sich (noch) nicht haben testen lassen. Dieses Restrisiko ist oft niedriger als das a priori Risiko für Kinder (50%) oder für Enkelkinder (25%) von Genträgern. Wir haben ein Modell zur Berechnung des verminderten Restrisikos entwickelt. Dafür verwendeten wir eine Datenbank mit CAG-Zahlen und dem Alter bei Krankheitsbeginn und eine Teildatenbank mit CAG-Zahlen von Eltern und ihren Kindern. Im ersten Schritt dieses Modells wird die CAG-Wiederholungslänge des Elternteils aus dem Alter bei Krankheitsbeginn geschätzt. Im zweiten Schritt wird hieraus die CAG-Länge des Probanden geschätzt, wobei das Geschlecht des betroffenen Elternteils berücksichtigt wird. Im dritten Schritt wird die

Wahrscheinlichkeit, dass der Proband – vorausgesetzt, er oder sie sei Genträger - noch keine Krankheitssymptome aufweist, bestimmt. Schließlich wird daraus das Restrisiko des Probanden berechnet, wobei die Information über eventuell getestete Geschwister (Nichtträger) berücksichtigt wird. Dieses Modell kann von Mitarbeitern in der genetischen Beratung angewendet werden, um das Restrisiko eines Probanden zu bestimmen. Dank einer dafür zur Verfügung gestellten Kalkulationstabelle ist die Berechnung dieses Restrisiko relativ einfach. In diese Kalkulationstabelle wird das Alter des Probanden, das Alter bei Krankheitsbeginn oder die CAG-Wiederholungslänge des erkrankten Verwandten und die Anzahl eventueller als Nichtträger getesteter Kinder eingetragen. Als Ergebnis erhält man die Schätzung der CAG-Wiederholungslänge und des reduzierten Restrisikos.

Chorea Huntington ist eine Krankheit mit progressivem Verlauf, für die es bisher keine Heilung gibt. Einer der meist genannten Beweggründe, sich testen zu lassen, ist eine bessere Vorbereitung auf die Zukunft. Als Genträger getestete Personen sehen sich neuen Unsicherheiten in bezug auf den Krankheitsbeginn und die Art der Krankheitsmanifestation gegenüber. Als Genträger identifizierte Personen werden sich besser auf die Zukunft vorbereiten können, wenn sie besser über die Besonderheiten des Krankheitsverlaufs informiert werden. Die Behandlung der Krankheit und die Versorgung der Erkrankten haben sich mit zunehmender Kenntnis über die Huntingtonsche Krankheit verbessert. Die neurologischen Tageskliniken, das Spezialzentrum für Huntington (Huntington Steunpunt) und die Spezialabteilungen für Huntington-Patienten in den Niederlanden und in Belgien haben viel Erfahrung mit Huntington-Patienten in verschiedenen Krankheitsphasen gesammelt. Die Aussicht auf eine gute Versorgung in späteren Krankheitsphasen kann beruhigend wirken und dazu beitragen, die negativen Erfahrungen mit der Pflege erkrankter Verwandter in der Vergangenheit zu vergessen. Um die Versorgung und Pflege besser den Bedürfnissen der Hungtinton-Patienten anzupassen, ist jedoch mehr Einblick in den Verlauf der Krankheit notwendig. In **Kapitel 7** wird die Entwicklung der BOSH (Behaviour Observation Scale Huntington - Verhaltensbeobachtungsskala bei Huntington) beschrieben. 1996 war die UHDRS[18] (Unified Huntingtons Disease Rating Scale) eingeführt worden, um klinische Leistungs- und Kapazitätsparameter der Huntingtonschen Krankheit zu bestimmen. Aufgrund von Deckeneffekten differenzierte die UHDRS jedoch nicht in späteren Krankheitsphasen. Die BOSH wurde entwickelt, um eine detaillierte Beschreibung des Verhaltens in späteren Phasen der Krankheit zu erhalten. Der Fragebogen enthält 32 Items mit vier Antwortmöglichkeiten. Eine Hauptkomponentenanalyse führte zu drei Subskalen: (1) Abnahme von Aktivitäten des täglichen Lebens (Activities of Daily Living, ADL), (2) Abnahme des sozial-kognitiven Funktionsniveaus und (3) mentale Rigidität und Aggression. Der Fragebogen wurde in vier Pflegeheimen mit Spezialabteilungen für Huntington-Patienten validiert. Bei 91 Patienten wurde die BOSH von zwei Krankenpflegern unabhängig voneinander ausgefüllt. Die internen Konsistenzen der drei Subskalen lagen zwischen .83 und .94, die Interrater-Übereinstimmungen zwischen .85 und

.95. Es wurde eine lineare Beziehung zwischen der Krankheitsdauer und der Abnahme der ADL gefunden. Nicht-lineare Beziehungen wurden gefunden zwischen (1) Abnahme der ADL und Rigidität-Aggression und (2) Abnahme der ADL und sozial-kognitiver Fähigkeiten. Rigides und aggressives Verhalten trat zunächst mit zunehmendem Krankheitsverlauf häufiger auf, nahm aber in späten Krankheitsphasen wieder ab. Sozial-kognitive Fähigkeiten verschlechterten sich vor allem in den letzten Krankheitsphasen.

8c.5. DISKUSSION

8c.5.1. Psychologische Adaptation infolge des Testergebnisses

Es war allgemein herrschende Meinung, dass der prädiktive Gentest bei Chorea Huntington mehr positive als negative Konsequenzen nach sich zieht.[15-17] Dies führte zu der Annahme, dass getestete Personen vom Test profitierten.[30] Diese Schlussfolgerung kann allerdings nicht ohne Einschränkungen getroffen werden. Bis 2003 wurden keine Studien veröffentlicht, die eine Zeitspanne von mehr als drei Jahren nach dem Test eingeschlossen hatten. In der Studie verschlimmerten sich sieben bis zehn Jahre nach dem Testergebnis die Hoffnungslosigkeitsgefühle bei den Genträgern. Die ersten Krankheitssymptome können Gefühle von Hoffnungslosigkeit oder Depression sein, was die höheren Werte bei Genträgern verursacht haben könnte. Dies gilt jedoch nicht für die Partner der Genträger, die ähnlich starke Hoffnungslosigkeitsgefühle berichteten. Daher ist anzunehmen, dass das Testergebnis, das nahende Alter des Krankheitsbeginns, der Ausbruch der Krankheit bei Verwandten, Verlusterfahrungen und Huntington-spezifische Lebenserfahrungen die Verschlechterung der Zukunftserwartungen verursachten. Da das Durchschnittsalter der Genträger beim letzten Messzeitpunkt 45 Jahre betrug (Range: 27 bis 73 Jahre), werden bei vielen von ihnen die ersten Symptome der Krankheit in naher Zukunft auftreten.

Diese Ergebnisse beziehen sich auf eine Auswahl von Personen, die den prädiktiven Test durchführen ließen. Es gab keine Kontrollgruppe mit nicht getesteten Personen. Van der Steenstraten et al.[31] berichten Unterschiede zwischen getesteten und nicht getesteten Personen. Nicht getestete Personen fühlten sich verletzbarer und weniger gut in der Lage, ein ungünstiges Testergebnis zu bewältigen. Allerdings muss berücksichtigt werden, dass bei dieser Studie das Untersuchungssample aus Freiwilligen der Niederländischen Huntington Vereinigung rekrutiert worden war. Diese Freiwilligen könnten einer selektiven Gruppe von psychisch stabileren Personen angehören. Für definitive Schlussfolgerungen wäre es interessant, nicht getestete Risikoträger im Alter von etwa 40 Jahren zu untersuchen.

8c.5.2. Dropout-Analyse

Das Dropout-Problem ist in longitudinalen Studien unvermeidbar. Es gibt verschiedene Gründe, warum Probanden nicht mehr an der Studie

teilnehmen. Manche ziehen um und ihre Adresse ist nicht mehr auffindbar. Manche sterben an einer Krankheit, die nichts mit Huntington zu tun hat, oder entwickeln die ersten Symptome der Huntington-Krankheit und sind daher von weiteren Analysen ausgeschlossen. Auf der anderen Seite gibt es Personen, die einfach nicht mehr teilnehmen möchten. Wenn auf die Bitte hin, Fragebögen auszufüllen, gar nicht reagiert wird, bleiben die Gründe für den Non-Response im allgemeinen unbekannt. Dabei ist anzumerken, dass Non-Response in der Regel nicht zufällig auftritt. Dropouts weisen oft bestimmte Charakteristika auf, die die Validität einer Langzeitstudie infrage stellen können.[32] Bei longitudinalen Studien sollte deshalb eine Dropout-Analyse durchgeführt werden. Dropouts sollten mit Personen, die die Studie beenden, bezüglich aller biografischen und ergebnisbezogenen Variablen verglichen werden. Falls keine Unterschiede gefunden werden, gibt es keinen Grund anzunehmen, die Validität der Studie sei durch selektiven Dropout geschwächt. Selektiver Dropout wird oft als eine Bedrohung der Validität der Studie angesehen. Eine gründliche Dropout-Analyse kann allerdings sehr interessante Einblicke bieten. Tibben et al.[33] fanden keine signifikanten Unterschiede zwischen Dropouts und Personen, die in der Studie verblieben waren. Jedoch wurde Jahre später, als die Effekte sieben bis zehn Jahre nach dem Test analysiert wurden, ein Unterschied gefunden. Der Schüssel für dieses Problem war die Erkenntnis, dass sich Personen mit einem positiven Testergebnis ganz anders an das Ergebnis anpassen als Personen mit einem negativen Ergebnis. Als für diese Gruppen getrennte Dropout-Analysen durchgeführt wurden, wiesen Genträger, die die Studie abgebrochen hatten, vor dem Test bedeutend schlechtere Zukunftserwartungen, ein schlechteres allgemeines Wohlbefinden, mehr Intrusionsgedanken und mehr Vermeidungsverhalten auf. Diese Unterschiede waren hoch signifikant und die Effektgrößen variierten von mittelgroß bis sehr groß (0.6 - 1.0). Demnach wurde nicht nur gefunden, dass Genträger langfristig schlechtere Zukunftserwartungen zeigten als Nichtträger, sondern auch, dass dieses Ergebnis auf einer selektiven Gruppe von Genträgern, die weniger psychologisch beeinträchtigt waren, basierte. Vermutlich sind die Effekte eines ungünstigen Testergebnisses noch schlimmer als aus den longitudinalen Analysen allein hervorgegangen war.

Genetiker und Mitarbeiter im psychosozialen Bereich schätzen ab, ob eine Person ein ungünstiges Testergebnis adäquat verarbeiten kann. Dennoch sollten besonders ängstliche, depressive oder pessimistische Personen die ein ungünstiges Testergebnis bekommen, langfristig besondere Aufmerksamkeit von professioneller Seite erhalten. Es sollten Follow-up Termine angesetzt werden und bei Bedarf zu anderen Personen oder Einrichtungen im Gesundheitssystem überwiesen werden. Dennoch müssen wir damit rechnen, dass das Angebot weiterer Unterstützung zurückgewiesen wird, da die Konfrontation mit der Zukunft vermieden werden soll.

8c.5.3. Die Bedeutung adäquater statistischer Methoden

Für die Analyse der longitudinalen Daten sieben bis zehn Jahre nach dem prädiktiven Test wurden allgemeine gemischt-lineare Modelle (General Linear Mixed Modeling, GLMM) angewendet. Diese Methode ist für Langzeitstudien mit fehlenden Werten zu einem oder mehreren Erhebungszeitpunkten geeignet und ermöglicht den optimalen Umgang mit Daten, Probanden und Messzeitpunkten. Daher konnten auch die Daten, die 1½ Jahre nach dem Test erhoben worden waren, verwendet werden. Zu diesem Messzeitpunkt liegen unvollständige Daten vor, da das Projekt damals vorübergehend unterbrochen worden war. Mit Hilfe von GLMM hätte sich, bei Berücksichtigung des Messzeitpunkts nach 1½ Jahren, bereits drei Jahre nach dem Test gezeigt, dass sich die Zukunftserwartungen von Genträgern verschlechtern.

Auch können als Folge einer weniger geeigneten Methode kleine, aber signifikante Unterschiede unbemerkt bleiben. Dies kann z.B. auftreten, wenn ein nicht parametrischer Test angewendet wird, obwohl ein parametrischer Test geeignet wäre. Häufig führt dies nicht zu einem folgenreichen Verlust an Power, da die Power eines nicht parametrischen Tests ungefähr 95% im Vergleich zu einem F-Test beträgt – vorausgesetzt, die Bedingungen für den parametrischen Test sind erfüllt. Unter bestimmten Umständen kann die Power aber drastisch absinken. Wenn eine Methode, die für dichotome Daten bestimmt ist, auf kontinuierliche Daten angewendet wird, kann die Effizienz bis auf 63% fallen.[34]

8c.5.4. Die Einführung eines präziseren DNA-Tests

In den Niederlanden wurden bedeutend mehr Risikoträger getestet als in anderen Ländern.[14] Der wichtigste Grund, sich testen zu lassen, ist das Ende der unerträglichen Ungewissheit, was ein starkes Bedürfnis nach Sicherheit ausdrückt. Dennoch wurde darüber diskutiert, ob der zu über 99% sichere Mutationstest Personen, die mit der Kopplungsanalyse getestet worden waren, angeboten werden soll. Das Zentrum für Klinische Genetik in Leiden wollte den neuen Test jedem anbieten, der mit der Kopplungsanalyse getestet worden war. Allerdings stellte die Medizinische Ethik-Kommission in Leiden (MEK) infrage, ob nach so vielen Jahren noch an Personen herangetreten werden dürfe mit dem Risiko, dass sie damit ungefragt belastet werden könnten. Das MEK war der Meinung, dass sich die getesteten Personen mit ihrem Testergebnis abgefunden und ein neues Gleichgewicht in ihrem Leben gefunden hätten. Dieses Gleichgewicht könnte durch den Eindruck, das Ergebnis des Kopplungstests sei unsicher oder sogar falsch, gestört werden. Es könnte die Schlussfolgerung, der alte Test sei ganz und gar nutzlos gewesen, gezogen werden.

Andererseits hatten sich die Personen testen lassen, um die bestmögliche Gewissheit zu erhalten und damit ihre Lebensplanung, einschließlich der Familienplanung, zu gestalten. Wenn eine neue Methode mehr Sicherheit bietet, dann sollte diese auch angeboten werden. Von einem nicht-direktiven und nicht-paternalistischen Standpunkt aus ist es außerdem wichtig, die Entscheidung über die Durchführung des sicheren

Mutationstests den Betroffenen selbst zu überlassen. Darüber hinaus hatte die Niederländische Huntington Vereinigung bereits Informationen über den Mutationstest in ihrer vierteljährlich erscheinenden Zeitschrift veröffentlicht. Nachdem einige Jahre über die Vor- und Nachteile diskutiert worden war, wurde beschlossen, den Test allen anzubieten, die mit der Kopplungsanalyse getestet worden waren.

Bevor der Mutationstest entwickelt wurde, fragten Babul et al.[35] mit Kopplungsanalyse getestete Personen, ob sie sich einem, damals hypothetischen, zu 100% sicheren Test unterziehen würden. 72% gaben an, sich unter diesen Umständen testen zu lassen. Als der Test tatsächlich eingeführt wurde, ließen sich allerdings nur 42% der Betroffenen testen.[36] Vor der Einführung des Kopplungstests war eine ähnliche Beobachtung gemacht worden. Damals gaben 40% bis 84% der Risikoträger an, sich testen lassen zu wollen.[16 37-39] Der Prozentsatz an Personen, die sich seit der Verfügbarkeit des Tests tatsächlich haben testen lassen, ist mit 2% bis 24% aber deutlich geringer.[14 40-43] Es herrscht eine offensichtliche Diskrepanz zwischen der Intention und dem tatsächlichen Verhalten.

Wie erwartet, beeinflusste das Restrisiko die Entscheidung, sich wieder testen zu lassen - allerdings nur bei Personen mit einem günstigen Testergebnis. Genträger mit einem niedrigen Restrisiko hatten bei einem neuen Test offenbar nichts zu verlieren und ließen sich häufiger testen als Nichtträger mit einem niedrigen Restrisiko. Nichtträger mit niedrigem Restrisiko sahen es wohl nicht als notwendig an, das Risiko noch weiter zu reduzieren. Unseres Wissens hatte es keinerlei nachteilige Konsequenzen, bereits getestete Personen über den Mutationstest zu informieren.

8c.5.5. Zusätzliche Risikoaufklärung für Berater und ihre Klienten

Die Datenmenge zu CAG-Wiederholungen und dem Alter bei Krankheitsbeginn innerhalb von Familien ermöglichte es uns, ein Modell zur Einschätzung des reduzierten Restrisikos zu entwickeln. Dafür wird das Alter der Person selbst, die CAG-Länge oder das Auftrittsalter des erkrankten Elternteils und eventuell Verwandte, die als Nichtträger getestet wurden, berücksichtigt. Dieses Modell richtet sich an (noch) nicht getestete Risikopersonen, die noch keine Symptome haben. Das Modell kann nur eine Abnahme der Risikoeinschätzung zur Folge haben, während der Mutationstest zu dem unwiderruflichen Ergebnis führen kann, dass man erkranken wird. Dennoch richtet sich das Modell nicht in erster Linie an Personen, die sich, aus welchen Gründen auch immer, nicht testen lassen wollen. Wir nehmen an, dass diese Personen nicht an einer präzisen Risikoeinschätzung interessiert sind. Unser Modell und die von uns entwickelte Kalkulationstabelle sollen das Repertoire von klinischen Genetikern und Beratern erweitern. Damit können sie bei Personen, die wegen eines Gentests kommen und keine Symptome haben, das Restrisiko am besten einschätzen. Mit Hilfe dieses Modells kann auch die Abnahme des Restrisikos in den Folgejahren bestimmt werden. Diese Information kann die Entscheidung, den Test sofort durchführen zu lassen oder zu verschieben, unterstützen.

Alle Berechnungen basieren auf den bestmöglichen Parameterschätzungen und deshalb sollen auch die Werte des Restrisikos und der CAG-Wiederholungslängen des Probanden als bestmögliche Schätzungen betrachtet werden. Wenn zukünftig mehr Daten über das Onset-Alter der Krankheit und über die CAG-Wiederholungslängen von Eltern und ihren Kindern verfügbar sein werden, werden die Schätzungen genauer werden.

Probanden fragen sich oft, wie groß ihr Risiko ist und wie sich das Risiko in Zukunft ändern wird. Das kann hilfreich sein für die Entscheidung, sich testen zu lassen und um sich besser auf den Test vorzubereiten. Diese Entscheidung kann vom aktuellen Restrisiko und dem Risiko in der nahen Zukunft abhängen. Anhand unseres Modells und der Tabellen, die von Langbehn et al.[44] publiziert wurden, kann festgestellt werden, ob sich der Proband in einem für den Ausbruch der Krankheit kritischen Alter befindet. In diesem kritischen Zeitraum ist die Reduktion des Restrisikos von besonderer Bedeutung und kann die Entscheidung beeinflussen, sich kurzfristig testen zu lassen, oder noch einige Jahre zu warten.

Risikoträger können Probleme mit Versicherungsgesellschaften und Arbeitgebern bekommen.[45-48] Da es vom ethischen Standpunkt aus umstritten ist, bei der Bewerbung um eine Arbeitsstelle oder dem Antrag auf eine Lebensversicherung einen Gentest zu verlangen, kann eine genauere Risikoeinschätzung, ohne dass ein Test durchgeführt wird, für diese dritten Parteien sinnvoll sein. Angenommen, dritte Parteien geben bei Kindern von Huntingtonpatienten eine Risikoeinschätzung von 50% an, dann ist die Anwendung dieses Modells auch für die Risikoträger selbst vorteilhaft, da das tatsächliche Risiko nahezu immer niedriger ist als das a priori Risiko.

8c.5.6. Struktur der Verhaltensbeobachtungsskala Huntington (Behaviour Observation Scale Huntington - BOSH)

Bei der Entwicklung der BOSH wurden drei Hauptkomponenten gefunden: Abnahme der Aktivitäten des täglichen Lebens (ADL), Rückgang sozialer und kognitiver Fähigkeiten, mentale Rigidität und Aggression. Es ergab sich kein guter Indikator für die Krankheitsdauer, da das Auftrittsalter der Krankheit oft retrospektiv bestimmt wurde. In einigen Fällen wurde das Auftrittsalter aus dem Aufnahmedatum in ein psychiatrisches Krankenhaus geschätzt. Falls die Aufnahme tatsächlich aufgrund einer von Huntington verursachten Störung erfolgte, wurde das Auftrittsalter zu spät eingeschätzt. Falls dies nicht der Fall war, wurde das Auftrittsalter zu früh geschätzt. Dies führte zu einem nur schwachen, aber signifikanten Zusammenhang zwischen der Krankheitsdauer und der Abnahme sozial-kognitiver Fähigkeiten. Die Zeitspanne, seit der sich eine Person in stationärer Betreuung befindet, erwies sich ebenfalls als kein guter Indikator für die Krankheitsdauer. Einerseits ist der Rückgang motorischer Funktionen für die Entscheidung, jemanden in ein Pflegeheim einzuweisen, von Bedeutung. Patienten können auch unter Zwangsgedanken, Wahnvorstellungen oder akustischen Halluzinationen leiden, die zur Aufnahme in ein Pflegeheim führen.[49] Andererseits hängt die Entscheidung, den Betroffenen in einem Pflegeheim unterzubringen, weniger von dessen

Fähigkeiten und dem Schweregrad der Erkrankung ab, als vielmehr davon, ob Ehepartner oder Angehörige die Pflege übernehmen. Für die Aufnahme in belgischen Pflegeheimen ist es sogar Voraussetzung, dass im persönlichen Umfeld niemand die Pflege übernehmen kann. Dennoch wurde ein schwacher linearer Zusammenhang zwischen der Pflegedauer und dem Rückgang der Aktivitäten des täglichen Lebens festgestellt.

Demgegenüber wurde ein hochsignifikanter Zusammenhang zwischen Rigidität/Aggression und dem ADL-Index festgestellt. Dies kann als eine Zunahme von rigidem und aggressivem Verhalten, das später wieder abnimmt, interpretiert werden. Ein ähnlicher Zusammenhang zwischen unflexiblem Verhalten und Krankheitsdauer wird in der Studie von Craufurd et al.[50] [51] beschrieben. Allerdings muss angemerkt werden, dass in Pflegeheimen das Aggressionsniveau durch psychologische und pharmakologische Maßnahmen eingeschränkt wird. Zukünftige Studien sollten daher die Wirkung von Sedativa berücksichtigen.

Ein weiterer signifikanter Zusammenhang wurde zwischen dem sozial-kognitiven Funktionsniveau und dem ADL-Index festgestellt. Wenn der ADL-Index als Indikator für die Entwicklung der Krankheit herangezogen wird, dann weist dies darauf hin, dass sich die sozial-kognitiven Fähigkeiten besonders in späteren Phasen der Krankheit, wenn rigides und aggressives Verhalten abnimmt, verschlechtern. In anderen Worten: der Rückgang des rigiden und aggressiven Verhaltens und die Abnahme der Aktivitäten des täglichen Lebens gehen dem Rückgang sozial-kognitiver Fähigkeiten voraus. Dies stimmt mit der Beobachtung von Bamford et al.[52] überein, dass sich das Erinnerungsvermögen erst in den letzten Phasen der Krankheit verschlechtert.

Die externe Validität der BOSH bedarf noch intensiverer Untersuchung. In einer künftigen Studie wird die BOSH zusammen mit der UHDRS (Unified Huntington Disease Rating Scale) verwendet werden. Die UHDRS wurde von der amerikanischen Huntington Study Group 1994 entwickelt, um motorische und kognitive Fähigkeiten, Verhaltensauffälligkeiten, psychiatrische Probleme sowie das allgemeine Funktionsnivau umfangreicher zu erfassen.[18] Die UHDRS sollte keine allumfassende Beschreibung aller denkbaren Ausprägungen der Huntington-Erkrankung enthalten.[1] Da die UHDRS in späteren Phasen der Krankheit nicht gut differenziert, ist ein Vergleich zwischen der BOSH und der UHDRS nötig.

Die BOSH wurde entwickelt, um einen detaillierten Einblick in den Fortschritt der Krankheit und die individuellen Differenzen zwischen Patienten zu gewinnen. Ein besserer Einblick in diese Unterschiede wird die Untersuchung des Zusammenhangs zwischen dem phänotypischen Ausdruck der Erkrankung einerseits und der prämorbiden Persönlichkeit und dem Netzwerk an sozialer Unterstützung andererseits erleichtern. Schließlich kann eine genauere Kenntnis dieses Zusammenhangs dazu beitragen, die Behandlung besser auf die Bedürfnisse der Patienten abzustimmen.

Bis jetzt ist die Huntingtonsche Krankheit nicht heilbar; die Behandlung beschränkt sich auf palliative Maßnahmen. Die spezifischen Krankheitssymptome rechtfertigen die Behandlung in Spezialabteilungen,

die in vielen Ländern eingerichtet wurden. Die Kenntnis der klinischen Erscheinungsformen in den mittleren Krankheitsphasen hat zugenommen.[50] [53] Um die Entwicklung spezieller Unterstützungsprogramme für die letzten Krankheitsphasen und damit eine Verbesserung der Pflege zu ermöglichen, ist eine genauere Beschreibung des Krankheitsverlaufs nötig.

8c.5.7. Abschließende Bemerkungen

Für Huntington-Patienten, Genträger und Risikoträger ist es außerordentlich schwierig, mit den Zukunftsperspektiven zurecht zu kommen. Dennoch gibt es für sie verglichen mit ihren erkrankten Elternteilen einen Funken Hoffnung Dank der Mitarbeit von Patienten, Verwandten und Patientenvereinen an wissenschaftlichen Untersuchungen wurden viele Einsichten gewonnen. Prädiktive Test wurden entwickelt, psychologische Unterstützung wird angeboten und psychologische und psychosoziale Effekte des Tests wurden erforscht. Prädiktive Gentests bieten frühzeitige Diagnosemöglichkeiten und ermöglichten Studien über die Erstmanifestation von Symptomen in frühen Phasen. Pflegeheime mit Spezialabteilungen für Huntington-Patienten wurden eingerichtet. Es stehen palliative Behandlungsmöglichkeiten zur Verfügung und erste Hinweise, dass in Zukunft eine Heilung möglich sein könnte, werden sichtbar.

Chorea Huntington ist eine ziemlich seltene Krankheit. Daher kann mehr Fortschritt erzielt werden, wenn Information und Forschung Hand in Hand gehen. Beispielsweise wurde eine Interventionsstudie mit 450 Patienten in neun europäischen Ländern durchgeführt, in der Riluzol in den frühen Phasen der Krankheit getestet wurde. Dies zeigt, dass bedeutende Huntington-Forschung in Europa möglich ist. Um Langzeitbeobachtungen von Huntington-Patienten zu ermöglichen und eine angemessene Infrastruktur für klinische Forschung in Europa zu schaffen, wurde 2003 das Euro-HD Netzwerk eingerichtet (http://www.euro-hd.net). Mit der "Predict"-Studie, einer der Aktivitäten des Netzwerks, sollen die ersten klinischen Veränderungen in der frühen Krankheitsphase festgestellt werden. Dazu werden verbesserte Standardinstrumente zur Erfassung der kognitiven Leistung und serielles MRI (Magnetic Resonance Imaging) zur Bestimmung des Gehirnvolumens eingesetzt.[54] Die Datenbank kann auch verwendet werden, um die Erstmanifestation von Symptomen bei noch nicht erkrankten Genträgern und den Krankheitsverlauf zu untersuchen. Auch können Therapien untersucht werden, die den Krankheitsverlauf beeinflussen oder den Beginn der Krankheit verzögern sollen. Das Euro-HD Netzwerk stellt eine gemeinsame Plattform für Professionals, Huntington-Erkrankte und ihre Angehörigen dar, um die Zusammenarbeit über ganz Europa hinweg zu erleichtern. Das Netzwerk fördert auch biologische Studien und Interventionsstudien, die hohen Maßstäben entsprechen (good clinical practice, GCP), womit die Suche nach Heilungsmöglichkeiten vorangebracht wird. In diesem Netzwerk kann sich jeder Teilnehmer zu Wort melden, Forschungsthemen vorschlagen, Studien durchführen und publizieren. Das Netzwerk stellt eine Infrastruktur für groß angelegte klinische Studien über Huntington in ganz Europa zur Verfügung: Eine IT-

Plattform für Kommunikations-Tools und e-trials in der jeweiligen Muttersprache und ein Forum, das die enge Zusammenarbeit von Grundlagenforschern und Klinikern ermöglicht.

Das Euro-HD Netzwerk unterstützt Langzeitstudien und fördert die Entwicklung von Instrumenten die in der Huntington-Forschung verwendet werden. Diese Instrumente (Tests, Fragebögen und Beurteilungsskalen) werden standardisiert und in die Sprachen der teilnehmenden Länder übersetzt.

8c.6. LITERATURHINWEISE

Für Literaturhinweise bitte sehe Seite 143.

Appendices

APPENDIX A ACKNOWLEDGEMENTS

I thank all Huntington patients, individuals at risk and their partners who participated in this study.

I thank Vicky Kraver and Adrian Greeman for correcting the use of the English language, and Christine Gallas for correcting my use of the German language.

APPENDIX B CURRICULUM VITAE

Reinier Timman was born in Delft on the 17th of June 1955. He completed HAVO in 1973 and Atheneum β in 1975. In 1982 he obtained his bachelors degree at the University of Amsterdam. In 1982 he set up a firm producing camper vans until 1992. In 1996 he graduated as a master of psychology, subject methodology, at the University of Leiden.

After graduation he worked at Erasmus University Rotterdam, and from 1997 he worked at the Netherlands Institute of Criminality and Law Enforcement in Leiden. Since 1999 he investigates psychological aspects of Huntington's disease for the Leiden University Medical Centre (departments of Clinical Genetics and Neurology). From 2000 on he also studies the effectiveness of clinical psychotherapy in the Standard Evaluation Project (STEP) for the Erasmus University Medical Centre Rotterdam.