

What Is Knowledge But Grieving?

**On psychological effects of
presymptomatic DNA-testing for
Huntington's disease**

Rouwig Om Kennis.....?

Over de psychologische gevolgen van
presymptomatisch DNA-onderzoek voor
de ziekte van Huntington

PROEFSCHRIFT

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Cover painting: "Boulevard, Katwijk aan Zee", 1986 by Jeroen van Duijn (1937-1987), who suffered from Huntington's disease. He made the painting during his hospitalization in psychogeriatric centre "Overduin" at Katwijk aan Zee. Cover design: Joop de Kler. Photograph Pieter Vandermeer.

Title of the thesis from E.R.B. Lytton, earl of Lytton (1831-1891)

*Bel segreto taciuto
Tosto scoprir si può
Una sol volta detto
Celarlo non potrò*

Il ritorno d'Ulisse in Patria;
Monteverdi, 1567-1643

*Ter nagedachtenis aan Henk van den Beld
Voor Uta*

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Chapter 1

Introduction and Aim of the Study

1. General Introduction

George Huntington (1850-1916) could not foresee the enormous advances which genetic technology would make in the course of the next hundred years when he first described the inheritance of a disorder of movements (subsequently known as Huntington's disease (HD)) in a family with several affected patients in more than one generation (Huntington, 1872). However, he certainly was aware of the possibilities of how an hereditary characteristic could be passed on to the next generation: "When either or both the parents have shown manifestations of the disease and more especially when these manifestations have been of a serious nature, one or more of the offspring almost invariably suffer from the disease, if they live to adult age. *But if by any chance these children go through life without it, the thread is broken and the grandchildren and great-grandchildren of the original shakers may rest assured that they are free from the disease.*"

In another hundred years, the final decade of the twentieth century will probably be recalled as the period in which the human genome was comprehensively studied and catalogued and in which our genetic make-up became characterized (Galjaard, 1990). The dramatic progress in molecular genetics provided some individuals, at-risk for a variety of hereditary diseases, greater opportunities to comprehend their personal genetic make-up and, subsequently, their reproductive alternatives and future health prospects (Niermeijer, 1988). To date, there are approximately 4000 identified genetic loci or disorders (McKusick, 1990), including those responsible for some of mankind's most prevalent and burdensome diseases - such as cancer, forms of neuropsychiatric, degenerative and cardiovascular diseases and/or syndromes, developmental defects and many others. With increasing pace, these disorders have become susceptible to efficient diagnosis at the genetic level, either through characterization of mutant genes identified and isolated through devious metabolic pathways or through linkage with other mapped loci (Friedmann, 1990; Galjaard, 1990; Rona et al., 1992).

Obviously, people must gradually adapt themselves to an era in which genetic technology and, subsequently, personal genetic knowledge will become an essential and prominent part in their medical care as a result of novel medical science and practice, whether or not they will use the available technological options for themselves. Knowledge about one's genetic make-up is one of the most personal and private types of information one can possess about oneself (Shaw, 1987). The new options offered by molecular genetics are expected to have a deep impact on personal thoughts, feelings, behaviour and fantasies. As such, the experience of being identified as a carrier of an invalidating, devastating disorder like Huntington's disease might be regarded as "a potentially psychologically distressing event that is outside the range of usual human experience"

(DSM-III-R; American Psychiatric Association, 1987). Consequently, learning about one's increased risk for HD may be regarded as (learning about) a threat to one's life, to one's physical integrity, or to one's children, according to the DSM-III-R. Moreover, the potential threat of an increased risk may include social stigmatization, i.e. the extent to which knowledge of genetic status influences eligibility for gainful employment or life and health insurance. The privacy of an individual may be threatened when life and/or health insurance companies are allowed to request any information about genetic status (Frets et al., 1990; Chapman, 1992).

In addition, in the more commonplace, complex disorders, such as cancer, arteriosclerosis and major psychiatric syndromes (e.g. manic-depressive illness and schizophrenia), more ultimately will become known about the interaction of genetic and environmental factors; which could may lead to the identification of genetic risk factors for their effects on habits or life-styles. In both cases we, in the medical profession, will have to learn about motivation to utilize this knowledge and the need for support and understanding when people are confronted with such knowledge (Galjaard, 1990; Reiss et al., 1991).

The HD gene is a single-gene that when mutated causes a neurodegenerative disorder, associated with death of specific groups of brain cells (basal ganglia and cerebral cortex). The localization of the HD-gene on chromosome 4 (Gusella et al., 1983) made HD the first autosomal late-onset hereditary disorder which could be detected by linkage analysis in risk-carriers, preceding the manifestation of symptoms of the illness (presymptomatic or predictive diagnosis). As such, HD is regarded as a paradigm for late onset disorders (Jenkins and Conneally, 1989). Despite the breathtaking technological advances, however, this research has yet not led to identification of the gene itself nor to a breakthrough in the treatment of HD.

The subject of this thesis concerns the identification of characteristics of individuals at-risk for HD applying for presymptomatic DNA-diagnosis and of factors that predict the level and quality of their psychological adjustment after receiving a DNA-test result. The aim of this study is not only to identify factors that are related to subsequent psychological functioning and adjustment, thereby allowing early identification of those at-risk for later adjustment problems, but also to enable intervention, additional follow-up and aftercare. Furthermore, the study serves to tailor the genetic testing protocol and to develop strategies for the management of untoward psychological responses to the DNA-test results.

2.1. Huntington's Disease

"The hereditary chorea, as I shall call it, is confined to certain and fortunately a few families and has been transmitted to them, an heirloom from generations away back in the dim past. It is spoken of by those in whose veins the seeds of the disease are known to exist, with a kind of horror and not at all alluded to except through dire necessity when it is mentioned as 'that disorder'..... There are three marked peculiarities in the disease: 1. its hereditary nature; 2. a tendency to insanity and suicide; 3. it manifesting itself as a grave disease only in adult life" (Huntington, 1872). Huntington accurately defined the inheritance of the disorder, which was consistent with an autosomal dominant trait, giving the offspring of an affected parent a 50% risk to inherit the gene for HD. His description of the disorder was succinct and accurate and had the good fortune of being immediately translated into German, with the result that Huntington's name very quickly became attached to the disease in different parts of the world (Hayden, 1981).

With today's knowledge, extensive exchange of clinical experience and comprehensive reviews (Hayden, 1981; Folstein, 1991; Harper, 1991), Huntington's disease (HD) is currently defined as a late onset autosomal dominant heritable neurodegenerative disorder, characterized by 3 groups of clinical features:

A. *Motor abnormalities.*

A variety of spontaneous, involuntary movements are observed in HD patients. The most common, conspicuous and striking clinical feature is chorea, meaning "dance", characterized by excessive, sudden, quick, involuntary movements of almost any part of the body. In some patients the chorea may mainly affect the face, whilst others have hyperkinesia of the extremities. The frequency and pervasiveness of the movements increase with time. In the early phase, the involuntary movements can usually be suppressed by voluntary action. Although the pattern of the choreatic movements can obviously be different between affected individuals, they apparently persist in each patient in a stereotyped mode. Psychological distress might adversely affect the choreatic movements. Preceding the involuntary movements, many patients are restless and make a nervous impression on others. Often, patients themselves are unaware of their restlessness. Other characteristic abnormalities are dystonic posturing, tremors and, mostly later in the course of the disease, myoclonic jerks. Abnormalities of voluntary movement are eye movements, disturbance of fine motor coordination, speech disorders, dysphagia and disturbances of gait.

B. Cognitive impairment

Usually there is a decline of intellect, memory loss, reduced capacity for conceptual thinking, problems with attention and concentration and visuospatial ability. Early in the disease, these defects may be mildly expressed, but they gradually worsen over time. Unlike patients with Alzheimer's disease, HD patients do not have aphasia or agnosia and rarely apraxia. (Hayden, 1981; Folstein, 1991).

C. Changes in personality, mood and behaviour.

In some patients the premorbid personality becomes less differentiated during the illness, sometimes resulting in irritability, aggressive and violent behaviour. An increased risk for suicide or suicidal behaviour within the HD population, compared to the general population, was reported in a number of studies, reviewed by Harper (1991). Folstein (1991) did not find an excess of alcoholism in two separate studies, although this had been previously reported by others. However, detection of alcoholism can be difficult to establish because of the impaired judgement in HD patients.

HD patients frequently become easily neglectful and are often not able to organize their life. They may become irritable and aggressive, but also apathetic and increasingly self-centred. Whether these changes are due to specific brain damages or to a psychological reaction to the physical changes and/or to responses from the social environment, is still uncertain. It is highly likely that both these factors contribute to the observed personality changes.

Affective disorders, most commonly depression, are often seen in HD patients. From retrospective data, Folstein (1991) estimated that episodic depression began at an average of five years before motor symptoms. A few patients will develop a clear affective disorder without even subtle physical signs of HD. Folstein et al. (1991) found that affective disorders are more common in patients whose onset of motor symptoms occur later.

In the early phase, patients show often a dysphoric, low mood, change in self-attitude with feelings of self-depreciation, hopelessness and guilt, which may be causative factors for suicidal thoughts or actions. Furthermore, vegetative signs such as loss of interest, energy and appetite are characteristic for the early phase.

Although the symptoms worsen gradually, three stages in the course of HD are recognized (Harper, 1991). In the first stage, the HD patient is usually able to lead a largely independent life, without severe physical problems. The physical disability increases severely in the second stage, with the choreic movements often prominent. The dependency on others for many daily activities increases which often means a

psychological and physical burden for the family. In the third stage, the motor disability is generalized and the patient becomes completely dependent for all aspects of care.

2.2. HD: Age of Onset

The age at onset is usually between 30 and 50 years, although onset at 2 and 80 years has been reported (Hayden, 1981; Bruyn and Went, 1986). Roos et al. (1991) observed a mean age of onset of 40.0 years (sd 12.1) in 1084 HD patients from 201 Dutch pedigrees reaching back to the middle of the last century. An early onset (< 20 years) was found to be associated with an affected father (Bruyn and Went, 1986; Myers et al., 1982); late onset (> 50 years) was found to be associated with an affected mother (Myers et al., 1985). Roos et al. (1991) studied the data of all HD patients (n=1084) in the Leiden Register, of whom the age of onset was known and found an influence on the mean age of onset of the sex and the line of inheritance. The mean age of onset was higher for females than for males and higher for maternal than for paternal cases.

In a subsequent retrospective study on age of onset and duration of illness, Roos et al. (1992) found that the mean *duration of illness* was 15.6 years (range 2 - 45 years) and duration proved independent of age of onset. Twenty percent of the patients can be expected to have a duration of illness over 23.2 years.

The most common causes of death in HD patients from four states of America (Haines and Conneally, 1986) were pneumonia (37%), cardiovascular disease (24%) and infection (14%). Their low suicide rate (2%) is probably explained by the reluctance on the part of medical professionals to indicate suicide unless it is very clearly the cause.

Huntington already stated: 'No treatment seems to be of any avail and indeed nowadays its end is so well-known to the sufferer and his friends, that medical advice is seldom sought. It seems at least to be one of the incurables' (Huntington, 1872). A century later, Hayden (1981) states: 'at the present time there is still no cure for Huntington's chorea, nor is there any therapy which significantly alters the natural progression of this disease.' In 1991, Folstein reviewed: 'today there is still no treatment that can cure HD, delay its onset, or slow its course. However, a small amount of hope is offered: our ability to investigate the nervous system is improving rapidly and there is real hope that an effective treatment will be found.'

Although there is unfortunately still no cure for HD, much attention has been given to the improvement of the HD patient's quality of life. Pharmacological treatment can reduce both the mood disorders and the involuntary movements (Folstein, 1991). Psychological treatment may help affected individuals and their families to adjust to the changes in physical and psychic integrity and to deal with the resulting problems (Wexler, 1984).

Social welfare interventions may decrease the financial, legal and material set-backs, resulting from early withdrawal from a job (Folstein 1991; Wexler, 1984). In some countries, psychogeriatric departments have developed specialized wards, including day-treatment and ambulatory services to more fully accommodate the specific needs of HD patients and their families (Tibben et al., 1985).

Recently, advances in molecular genetics have increased the possibilities for those individuals at-risk to acknowledge their genetic status with more accuracy which might give them broader options that improve the quality of their life, including planning a family and acceptance of the impending disease (Bloch et al., 1989).

2.3. HD: Epidemiology of HD in the Netherlands

In the Netherlands, Beukers (1890) gave a first description and genealogical study of a HD family with four living patients and 61 affected ancestors, living between 1736 and 1794. Gezelle Meerburg (1923) described some large Dutch HD families and undertook a medical record study on 100 cases. He found differences among the pedigrees with respect to occurrence and age of onset of personality changes and movement disorders. He could not confirm Huntington's observations with respect to suicidal tendency and alcohol abuse. Frets (1943) described 15 patients and prudently discussed the issues of procreative decisions in affected individuals and those at-risk.

World-wide prevalence rates for HD in various regions and races have been calculated by many authors (see for review Folstein, 1991 and Harper, 1991). An approximation of 50 per million (Caucasian population) appears reasonable.

In the Netherlands the estimated prevalence is 676 (45 per million; 1:20.000), based on the number of living affected individuals, recorded at the Leiden Register for HD (M.Vegter-van der Vlis, personal communication, July 15, 1992). These affected individuals belong to 194 families which could be connected up genealogically to three generations (great-grand-parents). The Leiden Register furthermore contains 85 families without currently living affected individuals although in those families patients are recorded in at least two generations. Altogether, 2644 individuals at 50% risk are registered, out of which 657 are under 30 years, 1334 individuals are between 30 and 50 years and 653 individuals are between 50 and 65 years. We did not count individuals over 65 years because they are generally regarded as having a risk much lower than 50%, given the normal distribution of age of onset (Roos et al., 1991).

Finally, 142 single cases were registered, based on characteristic clinical features but in whom the diagnosis could not be confirmed genealogically. Although 279 families are registered, the number of patients and individuals at-risk certainly is an underestimation

since 9 new pedigrees were ascertained at the time of this study (in a 2-year period) as a consequence of newly identified individuals at 50% risk, who enrolled in the predictive testing programme and whose affected parents and other relatives were previously unknown at the Leiden Register.

3.1. HD: DNA-linkage analysis

The HD gene has been localized on the short arm of chromosome 4 by physical mapping, by linkage analyses of recombination events and linkage disequilibrium studies in two large families, one from the USA, the other from Venezuela (Gusella et al., 1983). The linkage was confirmed by studies in numerous other countries (Hayden et al., 1988; Meissen et al., 1988; Brock et al., 1989; Skraastad et al., 1989, 1991, 1992a). Its most likely location is between the loci D4S10 and D4S168 (reviewed by Skraastad et al., 1992b). Skraastad et al. (1992b) reported on a large series of 149 presymptomatically tested individuals from 77 Dutch HD families and stressed the need for extensive family haplotyping for chromosome 4 markers in available affected and non-affected relatives. Problems observed included non-paternity, recombination events between markers near the HD gene (crossing-over), unavailability of family material or an uninformative situation due to a too small or otherwise uninformative family structure. As the local protocol attempted to prevent undesired risk alterations in relatives who did not participate or request for risk assessment, we sought to test during prior family work-up only those individuals at-risk with a relative low a priori risk for HD. The test applicants requested their relatives to participate. Sometimes the informativity of the DNA test may be reduced, especially when the applicant had less than one or two closely related affected relatives. However, in most cases, these problems could be solved and, due to extensive use of markers, 140 out of 149 individuals (94%) could be informed on their genetic risk with a reliability of 92-99% (Skraastad et al., 1992b). Some of the many and varied problems in testing programmes have also been described by others (Morris et al., 1989; Huggins et al., 1990).

3.2. Attitudinal studies

Prior to the actual clinical application of the DNA-linkage test, a number of psychological studies were addressed to possible attitudes and intentions to utilize the test in individuals at-risk for HD (Kessler et al., 1987; Mastromauro et al., 1987; Meissen and Berchek, 1987; Markel et al., 1987; Evers-Kiebooms et al., 1987, 1989). Of a total of 376 individuals at-risk in the U.S.A., 73.1% were interested in taking the test when it would

become clinically available (Kessler et al., 1987). In Wales and Belgium, only 56% showed interest in the test, reflecting possible differences between Europe and the United States (Evers-Kiebooms et al., 1987). Two-third of the individuals at-risk surveyed in the USA (Kessler et al., 1987) believed that the greatest perceived impact of HD concerned the issue of children. About two-third would refrain from having children after an unfavourable test outcome, or would use prenatal diagnosis if a pregnancy occurred (Kessler et al., 1987). Of these, however, 29% would not terminate a pregnancy of an affected fetus. The majority of the subjects believed that they would experience depression and anxiety in response to an unfavourable test result. Suicidal thoughts were anticipated by 11% (Kessler et al., 1987) and 29% (Mastromauro et al., 1987). No suicidal tendency was reported by Meissen and Berchek (1987) and only 11% anticipated they would experience severe emotional difficulty. Becoming deterred from marriage after an unfavourable test outcome was mentioned by 11% (Markel et al., 1987).

The actual uptake of the presymptomatic DNA-test for HD is, since its introduction in 1987, significantly lower (12%-20%) than was predicted by these prior attitudinal studies (Craufurd et al., 1989; Quaid et al., 1989; Tyler et al., 1992a). Apparently, many persons at-risk have found an acceptable mode of living without knowing their risk status precisely. They do not need or do not want to know. Many of them may have succeeded in minimizing the conscious jeopardy of HD, without being tested. However, fear of finding out that one is likely to develop HD in the future might be a paramount reason to avoid the test. It has also been suggested that reluctance to undergo the test in those who have considered application, might be due to the nature of the current linkage test, which leaves a remaining uncertainty of $\pm 35\%$ to up to a few percent (Quaid et al., 1989). A third reason might be the necessary involvement of relatives for obtaining blood samples from both affected and unaffected relatives, which might exclude those who are reluctant to ask their family members for cooperation. Fourth, potential problems with access to health and life insurances or jobs might be reasons to postpone testing. Doubts about confidentiality and protection of information might be a related reason to feel reluctant to undergo the test.

3.3. Studies on Presymptomatic DNA-testing

Since its introduction, most reports on presymptomatic testing contained information on the genetic technology of DNA-testing, numbers of individuals tested (review: Skraastad, 1992c), discussion of the ethical problems raised by the use of testing (review: Terrenoire, 1992) and some biographical data of applicants (Table 1). Some authors have

extensively described their clinical experience with tested individuals (Bloch et al., 1992; Huggins et al., 1992; Tyler et al., 1992a,b).

Two studies have reported on psychometric follow-up data thus far (Brandt et al., 1989; Wiggins et al., 1992). In both studies neither psychological nor biographical baseline differences were found between prospective gene-carriers and non-carriers, with the exception that in the study of Wiggins et al. (1992) the non-carriers group was significantly older than the carriers group. During follow-up, Brandt et al. (1989) reported a slight elevation of distress in carriers after 3 months and 12 months, due to higher scores on depression and anxiety scales, though the scores remained well within normal limits. No differences were found between both carriers and non-carriers with regard to possible social consequences. In the Vancouver study (Wiggins et al., 1992), the identified carriers and non-carriers differed significantly with regard to depression, general well being and psychological distress, about one week after disclosure of the test results. After 6 months both groups only differed on the well-being scale, although the 12 month- follow-up showed again significant differences on all three outcome measures. However, a considerable number were lost to follow-up (24% of the carriers, 9% of the non-carriers). Carriers reported less depression and a greater sense of well-being at the 12-month follow-up assessment, as compared to those individuals who could not be informed on their genetic risk.

4.1. Development of DNA-testing for HD in the Netherlands: the Genetic Counselling Protocol

In the Netherlands, DNA-diagnosis of genetic diseases, was introduced in 1985. Four clinical genetic services (at Groningen, Leiden, Nijmegen and Rotterdam) received financial support through the Law for extraordinary medical expenses (AWBZ). It is expected, that the three other clinical genetic centres will receive similar support from 1993. From October, 1987 onwards, presymptomatic DNA-testing for HD was centralized at the Clinical Genetics Centre, Leiden. The protocol for presymptomatic DNA-testing was approved by the Medical Ethics Committee of the University Hospital, Leiden (April, 1987).

It was generally felt that, compared to other genetic diseases for which carrier detection or diagnosis became available, like cystic fibrosis or Duchenne muscular dystrophy, HD needed to be handled differently (Smurl and Weaver, 1987). Firstly, HD is irreversible and no specific treatment is known.

Table 1. Presymptomatic DNA-testing for Huntington's Disease: Reported experiences in Different Programmes

	Country	Individuals Tested	Mean Age	Male/Female Ratio	Increased/Decreased Risk/ Uninformative	Biographical Data	Psychometric Data
Meissen et al. 1988	USA	15	34.1	1:2.6	4/7/5	few ¹	-
Brandt et al. 1989	USA	55	35.4	1:1.1	12/30/13	+	+
Craufurd et al. 1989	England	43	²	1:1.6	15/15/3	few	-
Brock et al. 1989	Scotland	44	-	-	19/25/-	-	-
Tibben et al. 1990a,b	Netherlands	18	34.5	1.6:1	9/9/-	few	-
Nance et al. 1991	USA	19	-	-	7/10/2	-	-
Bloch et al. 1992	Canada	4	-	1:1	4/-/-	+	+
Huggins et al. 1992	Canada	6	-	1:5	-/6/-	+	+
Wiggins et al. 1992 ³	Canada	135	37.5	1:2.3	37/58/40	+	+
Tyler et al. 1992a ⁴	UK	248	32.5	1:1.5	97/151/-	few	-
Tyler et al. 1992b	Wales	38	-	-	11/23/4	few	-
Simpson et al. 1992	Scotland	45	33.1	1:1.1	16/26/3	few	-
Tibben et al. 1992 ⁵	Netherlands	76	32.2	1:1.8	29/45/2	+	+

¹ few = e.g. age, male/female ratio, motivational data and/or clinical description of reactions

² - = no data were reported

³ this study includes the data from Bloch et al. (1992) and Huggins et al. (1992)

⁴ the UK data include the data from Wales (Tyler et al., 1992b), England (Craufurd et al., 1989) and Scotland (Brock et al., 1989; Simpson et al., 1992)

⁵ this study

Secondly, it is widely known that HD adversely affects the future prospects of relatives as well as those of the affected patients. Thirdly, the test requires the cooperation of two or more generations in the family and reliable data on the diagnosis of index patients, as available in the Leiden Register, were essential in many of the families requesting testing. Fourthly, symptoms usually do not become manifest until the affected individuals are adults and have often started their families. There was wide international agreement on the necessity for careful psychological support, follow-up and research on the psychosocial effects of presymptomatic HD testing. Hence, a research protocol was developed to this purpose, shortly after the start of the Leiden programme, and funded by the Prinses Beatrix Fonds.

The DNA-test can be applied for *presymptomatic* or *predictive testing* in individuals who are at 50% risk (in case of an affected parent), or 25% (in case of an affected grand-parent) and for *prenatal testing*, when the prospective parent is at high risk or already affected. In addition, the test can be used for *exclusion testing*, i.e. excluding whether or not a fetus has received a chromosome-4 of the affected grand-parent. That option was originally suggested for candidates from small families where DNA is unavailable from some crucial relatives (Quarell et al., 1987). However, exclusion testing is mostly requested by individuals at-risk who do not wish to learn of their own HD status, but only want to exclude the risk of having an affected fetus, accepting the decision to terminate a pregnancy when the fetus has the same risk as the at risk parent (50%). Fahy et al. (1989) described the option of the *guided exclusion testing*, i.e. a stepwise combination of exclusion testing and presymptomatic testing. The first step is exclusion testing. If the fetus is found to be at low risk, the at risk parent remains uninformed on his/her own risk and the pregnancy may become completed. However, if the fetus is found to have a 50% risk like its parent, the parental status of the marker segregating with HD may be determined. Of course, in this way both the genetic status of the parent at risk and of the fetus relative to HD, become known. However, pregnancy termination of a fetus unlikely to have inherited the gene for HD can be avoided.

Whilst the principal of parental and individual autonomy and freedom of decision to take the test should always be respected, there are certain occasions when testing should not be applied. The policy that was adopted was not to apply the test when the applicant at-risk for HD was under 18 years, had major mental illness, had suicidal plans when identified as gene-carrier, had attempted suicide in the preceding 10 years, had early clinical signs of HD, or was not able to give informed consent.

Table 2
Presymptomatic DNA-Testing For Huntington's Disease
Leiden Clinical Genetics Centre

session	PREPARATION FOR TEST
1	exploration test demand and motivation - information about HD, inheritance, DNA-test - drawing the pedigree - medical records/ neurological examination <i>- introduction to follow-up study on psychosocial aspects by psychologist</i> <i>- completion of questionnaires*</i>
2	additional information about DNA-testing - exploration of consequences of disclosure alternatives - contact with General Practitioner (GP) - blood sampling <i>- 1st in-depth interview of psychologist, separately with applicant and partner</i> <i>- completion of questionnaires</i>
3	DISCLOSURE OF TEST RESULTS - communication to GP - contact with psychologist FOLLOW-UP AFTER DISCLOSURE
4	within 24 hours telephone contact with psychologist
5	after 1 week <i>- second in-depth interview of psychologist with applicant and partner</i> <i>- completion of questionnaires</i>
6	after 6 months <i>- 3rd in-depth interview of psychologist with applicant and partner</i> <i>- completion of questionnaires</i>
7	after 18 months <i>- 4th in-depth interview of psychologist with applicant and partner</i> <i>- completion of questionnaires</i>

* data sampling for psychological follow-up study *in italics*

The counselling protocol we use follows the guidelines of the Research Group on Huntington's Chorea, World Federation of Neurology (1990). The ethics of genetic prediction of HD address potential difficulties such as adverse psychological effects on tested individuals, their partners and their relatives as well as the likelihood of discrimination in such matters as employment and insurance (Craufurd and Harris, 1986; Chapman, 1990; Huggins et al., 1990; Terrenoire, 1992).

Information about the availability of the test was given by either the general practitioner, neurologist, clinical genetics service, relatives or patients organization. No official announcement was made by the Genetics Centre as a restrained policy was applied. Television broadcasts and articles in magazines about HD and DNA-testing had been an incentive to apply for the test in few instances. The counselling protocol (see table 2) includes at least two sessions of pre-test counselling.

Initially, a brief neurological examination was conducted in the first session. However, some individuals at-risk did not want to learn about possible early symptoms but only about their current genetic risk status. In their view, being diagnosed as an HD-patient is obviously not the same as being identified as a gene-carrier. Consequently, when applicants and their partners, after profound counselling, persisted in their denial of possible early signs of the illness, these psychological reactions were appreciated and the DNA-test was still carried out. If applicants are suspected of early signs for HD and willing to acknowledge this possibility, they were referred to the department of neurology for confirmation.

Right at the outset of presymptomatic DNA-testing for HD at the Clinical Genetics Centre and the Human Genetics Department (1987), both professionals and the Dutch patient organization, acknowledged that the identification of being a carrier for HD might have adverse effects on the individual tested and his/her family. Hence, in a collaboration between the Clinical Genetics Centre, the departments of Neurology and Psychiatry and the Human Genetics Department of the University Hospital and State University Leiden and the departments of Medical Psychology and Psychotherapy and Clinical Genetics of the Erasmus University and University Hospital Dijkzigt Rotterdam, a psychological research protocol was developed in 1989. The Medical Ethics Committee of the University Hospital, Leiden, approved of the protocol on both pre- and post-test psychological evaluation.

4.2. Aims of the Psychological Follow-Up Study

A. Main Questions

The identification of factors predicting the psychological responses to presymptomatic testing for HD is the main question in this study. How does the knowledge about a modified genetic status becomes integrated into daily life? How adequately can applicants and their partners adjust to the new situation and more specifically: does early detection of the disorder lead to preoccupation with symptoms of the future disease? If so, will this impair normal development of the personality? What impact does the test outcome have on relationships with the partner, children and relatives. How do tested individuals adapt to and evaluate their experiences and can they formulate expectancies for the future?

B. Need for Assistance

Another main objective of this study was to establish the needs of test candidates, whilst adjusting to the objective changes in their lives. Additional services might include physical adjustments, vocational adaptation and subsequent training, to encourage participation in (sometimes difficult) adjustment programmes and assistance in obtaining access to available social services and benefits.

C. Developing improved strategies for counselling and support

The aim was to develop a counselling protocol providing optimal pre- and post-test support and management of untoward psychological reactions in test candidates.

4.3. Methodology

Seventy-three individuals at-risk for HD and their partners, who applied for the test between April 1989 and April 1991 and who received a DNA-test result, participated in the prospective follow-up study. Those who had an uninformative family, or who withdrew from DNA-testing, or who showed early symptoms or who opted for exclusion testing, were excluded (chapter 3a). Test candidates gave a separate consent for the psychological follow-up study, provided that they could understand the questionnaires.

The measurement points for the study are presented in table 2. The measurement methodology addressing the main questions were identical to other studies so that a comparison of our data with those of other research groups could be made (Fox et al.,

1989; Brandt et al., 1989; Meissen et al., 1991). The rationale for the selection was based on the assumption that an important event, such as presymptomatic diagnosis, induces distress that can cause depression and reduce one's sense of well-being.

The measures selected for this study included an Attitude Questionnaire (AQ) (Appendix C), completed at baseline (session 1) and 6 months after disclosure of the test result (session 6). The AQ was adapted from other studies on presymptomatic testing for HD and modified to accommodate at-risks and partners (Mastromauro et al., 1987; Fox et al., 1989).

Standardized psychometric instruments considered as the most appropriate for answering the specific questions in our study population were used. The psychometric battery included the Impact of Event Scale, the Beck Hopelessness Scale, the General Health Questionnaire and the Multi Health Locus of Control Scale (completed at session 1, 2, 4, 6 and 7), the Social Support Questionnaire (completed at session 1 and 6) and the Defense Mechanisms Inventory (completed at session 1).

The qualitative part of the study was designed to gather intensive and comprehensive information about the defense and coping activity and about the adequacy of psychological adjustment of this very specific group with a specific potential burden. Hence, an in-depth interview was held by a psychotherapist (A.T.), 6 weeks after application (the first counselling session). The content of the interview was derived from a review of the literature, our own clinical experience and pilot interviews with the first 18 consecutively tested individuals and their partners (chapter 2 and Tibben et al., 1992a). Although the interviews were semi-structured, a checklist served to ensure that the following areas were covered: personal development, coping with stressing events, experience and coping with HD and personal risk, intimate relationships and anticipating the test-outcome. The interviews lasted 1-2 hours and the first 45 minutes were audio-taped. The average period between the first interview and disclosure of the test results was 4 months.

The audio-tapes were judged at-random by independent pairs of 9 psychotherapists (judges). A specifically-designed semistructured questionnaire was used which allowed judges to develop vignettes of salient reactions to anticipation of the test outcome. Next, a panel of three experienced psychoanalysts (raters) categorized both groups of these vignettes into specific coping/defense strategies of anticipating the disclosure of test results.

To obtain more information on the motives and characteristics of those knowledgeable about but not utilizing the test (non-participants), we recently (August 1992) did an anonymous questionnaire study among 50 members of the Dutch Huntington patients association.

5.1. Outline of this Study (chapter 2-9)

Until quite recently there was a noticeable paucity of available data about psychological effects of presymptomatic DNA-testing for hereditary late onset disorders. In 1989, we evaluated 18 individuals and their partners, who had received presymptomatic testing for HD in Leiden between 1987 and 1989, one year after disclosure of the results. In-depth interviews were held and supplemented with a psychometric test battery. Findings in carriers were analyzed separately and demonstrated that carriers adapted rather well, whereas non-carriers had problems in the early adaptation to their new genetic status. These descriptive data helped to generate hypotheses for the prospective study (**chapter 2**).

In the prospective part of the study, the pre-test attitudinal profile of 70 test candidates and their partners was established, as this might eventually be related to the life-long and overshadowing effect of the presence of HD in the family (**chapter 3A**). To establish the relevance of any specific patterns a comparison was made with non-participants.

In **chapter 3B** we present the data of the questionnaire study amongst a sample ($n=28$) of members of the patient organization (having a 50% risk), who have considered taking the test but who have not done so yet.

The possible effect of the test outcome on the individual's attitudes with respect to different areas of life, prenatal testing and testing children, as compared with their pre-test attitudes was analyzed. In **chapter 4**, we report on the post-test attitudes in 67 individuals, 6 months after disclosure. The results were compared with the data of the pre-test attitude study. Special emphasis was given to the problems of those with increased risk, decreased risk and the effects upon their partners.

The pre-test psychological functioning of defence activity and control beliefs of 70 individuals at-risk were specifically studied (**chapter 5**). We questioned whether the higher uptake of testing by women at-risk for HD in most programmes might be related to their pre-test adjustment to the distress of being at-risk. It was expected that the expectancy of a specific test outcome is associated with specific personality characteristics or mood states. These expectancies might be major predictors of abilities to pursue their goals in life after an unfavourable test outcome or otherwise induce a premature assumption of the role of an HD patient. These data are important to identify persons, at pre-test, who are vulnerable for the outcome of the test.

Predicting the working through process following the presymptomatic test may be improved by using the model of alternating phases of intrusive emotions and avoidance behaviour, which, if unbalanced, might lead to adjustment problems. Intrusion is usually most severe shortly after the stressing events (Horowitz, 1990). As time passes, the

frequency and intensity of the alternating phases decreases until the intrusive thoughts are diminished and avoidance behaviour is no longer necessary to escape the confrontation with painful experiences or its sources. This model proved to be meaningful in that 73 individuals, examined 6 months after the disclosure of the test, revealed that their working through process was still incomplete in many of them (**chapter 6**).

Identifying those individuals, who are at a high risk for adverse reactions, is important since they might need additional support because of these adjustment problems. Adverse reactions might be reflected by the expectancies about their future life, suffering from feelings and thoughts about HD and by avoidance behaviour. Patterns of these parameters may reflect the specific processes of working through and individual coping styles. In **chapter 7**, we show which predictor variables could identify the level of hopelessness and degree of intrusive ideas and avoidance behaviour, 6 months after disclosure of the test results.

Being identified as either a gene-carrier or a non-carrier can be seen as an unfamiliar shift in the reality, which has changed more rapidly than people themselves are apparently able to adapt to. Familiar shifts in reality elicit conscious coping strategies and social supports, whereas unfamiliar shifts in reality evoke involuntary coping strategies, i.e. defense mechanisms (Vaillant, 1992). In **chapter 8** we analyzed the pre-test defense styles of 20 tested individuals based upon in-depth interviews and categorization of specific coping mechanisms. Significant correlations were found between pre-test anxiety and self-reported hopelessness, intrusive thoughts and denial-avoidance behaviour. In those individuals, rated as most anxious, significantly more immature defenses were observed. More insight in defense mechanisms may improve the pre-test and post-test counselling and additional support.

In **chapter 9** we discuss the general conclusions and provide suggestions for further prospective research on a. follow-up of those tested for HD and b. DNA-testing for other late-onset inherited disorders such as various cancer syndromes (like polyposis coli and other colonic carcinomas), hereditary cerebral haemorrhage with amyloid-Dutch type, polycystic kidney disease, neurofibromatosis (M.Recklinghausen), myotonic dystrophy (M.Steinert).

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Chapter 2

Presymptomatic DNA-Testing for Huntington's Disease in The Netherlands; a Retrospective Study on Psychological Effects

DNA-Testing for Huntington's Disease in The Netherlands; a Retrospective Study on Psychosocial Effects

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ABSTRACT

Presymptomatic DNA-testing for Huntington's disease has made it possible to predict whether or not at-risk individuals are gene-carriers with a reliability of about 98%.

In our retrospective study of 18 tested individuals, most of the newly identified carriers function apparently well. They use avoidance and repression of affect as psychological defense strategies. However, 8 out of 9 non-carriers do not experience the expected relief about their test results. They experience survivor guilt and emotional numbness and find it difficult to cope with the effects of the test results on the family system. The partners of gene-carriers are at risk of becoming emotionally isolated by putting aside their own feelings for fear of seeming self-centered. Appreciation of these effects on tested individuals is important and professional support is needed to prevent post-traumatic stress disorders. Whatever the test result may be, the working through process may take years rather than months. These findings have important implications for patient care and necessitate an extended period of observation after presymptomatic testing.

INTRODUCTION

Huntington's disease (HD) is a progressive, autosomal dominant heritable disease characterized by involuntary movements, and changes in behavior and personality with

cognitive impairment (Hayden, 1981). Although the average age of onset is between 30 and 50 years, at-risk individuals can never be sure of having escaped HD. Hence persons at-risk of HD often have children before the first symptoms appear.

When DNA probes linked to the HD gene became available, the door was opened for genetic counselling and thereby helped people make fundamental individual determinations (Gusella et al., 1983; Hayden et al., 1988). The primary objective of presymptomatic testing of at-risk individuals is to support them and help them make personal decisions based on their subjective judgement and made in their own interest and to provide options that may generally improve the quality of their lives (Bloch et al., 1989).

Before the test became available, a number of studies had already assessed its acceptability to at-risk individuals and their attitudes towards it (Evers-Kiebooms et al., 1987; Kessler et al., 1987; Markel et al., 1987; Mastromauro et al., 1987). About two thirds of these individuals intended to seek presymptomatic testing. Unfavorable results were expected to lead to major psychological and social difficulties, including depression, psychiatric morbidity and suicidal tendencies.

To a large extent, ethical guidelines and exclusion criteria for presymptomatic testing have been based largely upon these expected reactions in newly identified gene-carriers (Ethical Issues Policy Statement, 1990).

We present follow-up results of a group of 18 individuals in the Dutch presymptomatic testing program before a structured psychosocial research protocol had been established. We evaluated the effects of the results on these people and their partners one year after disclosure. This investigation will serve as a pilot project for a larger longitudinal prospective study.

PARTICIPANTS AND METHODS

Participants

Presymptomatic testing for HD within a structured protocol was started in Leiden, The Netherlands, in October 1987. All of the participants in the current study were at 50% risk of inheriting the HD gene and decided to apply for a test at the Clinical Genetics Center in Leiden in the period from August 1987 until December 1988. The participants were the first consecutive applicants who received a result. Minimum age for application was 18 years and applicants had to be free of psychiatric disorders and clinical signs of HD. One year after disclosure of the results they were requested to participate in a study of the psychosocial effects of their DNA test.

Methods

Since a further protocol for research into the psychosocial impact on presymptomatic testing was only started in April 1989, i.e. subsequent to the original interviews, neither baseline data nor psychological assessment were available at the moment of disclosure.

One year after disclosure, the applicants and partners were separately interviewed by a psychotherapist (A.T.). The extensive in-depth interviews lasted from one to two hours each and were recorded on audiotape. Feelings, cognition, defense mechanisms, coping and family dynamics were evaluated. After the interviews each participant completed several questionnaires to test the hypothesis that the impact of the test-results would vary depending on personality characteristics, coping-style, psychological symptoms and family-history. The parameters used were identical to other studies (Fox et al., 1989; Brandt et al., 1989) and included the Attitude Questionnaire (AQ), the Beck Hopelessness Scale (BHS), the General Health Questionnaire (GHQ), the Multi Health Locus of Control (MHLC) and the Defense Mechanisms Inventory (DMI). The AQ, as used in a similar study by Mastromauro et al. (1987) and Fox et al. (1989), assesses the subject's attitude towards presymptomatic and prenatal testing and the impact of the test result. The BHS consists of 20 true-false statements which measure negative expectation concerning oneself and one's future life. Hopelessness is identified as a core symptom of depression and is considered as a possible important predictor of suicidal behavior (Beck et al., 1985). The GHQ is a self-report questionnaire and a measure of minor psychiatric disturbance (Tarnapolsky et al., 1979). The MHLC is an 18-item questionnaire, examining the perceptions of the factors influencing health (Wallston et al., 1976). The DMI measures five groups of defense mechanisms (Passchier and Verhage, 1986).

DNA Analysis

In order to guarantee a maximum of informative results, the decision about which family members should cooperate was made on the basis of the pedigree in consultation with the laboratory. DNA was isolated from lymphocytes or fibroblasts. DNA probes used for analysis were D4S10 (Gusella, Boston; Pearson, Leiden), D4S81 (Collins, Ann Arbor), D4S125 (Nakamura, Salt Lake City), D4S43 (Gusella, Boston), D4S95 (Wasmuth, Irvine) and D4S111 (Frischauf, London). The method according to Lathrop and Ott was used for linkage analysis (Lathrop et al., 1984). The distance between the DNA markers and the HD gene determines the risk of an undetected recombination and thus the reliability of the test result. The probes used have a recombination frequency of 2-4% which translates into a diagnostic reliability of 96-98% in fully informative pedigrees. Occasionally, due to the

pedigree structure, a lower practical reliability is obtained (but in our pedigrees so far was not less than 92%). The risk assessment was carried out by computer analysis, using the program Mlink v5.03 (J Ott, Colombia University, New York). The scoring of marker alleles was carried out by at least 2 experienced individuals independently, and paternity analysis was performed in parallel using a variety of unrelated hypervariable probes. In parallel to computer analysis, the haplotype determination was also carried out manually by at least three experienced individuals independently (Skraastad et al., 1991).

RESULTS AND DISCUSSION

Out of the 18 individuals who were tested and had definitive test results, 9 were at increased risk for having inherited the HD gene (7 men and 2 women) and 9 were at decreased risk (4 men and 5 women). All tested individuals were counselled to expect that the result would be conclusive with the proviso that the result may not be definitive due to the possibility of a recombination event. We will use the words gene-carrier and non-carrier to refer to an increased risk and a decreased risk, respectively. All individuals but 2 had stable relationships. The male-female ratio in this reported part of our study (11:7) differs from other studies (Meissen et al., 1988; Craufurd et al., 1989; Brandt et al., 1989). This is most probably a chance observation since actually about 60% of the participants in our program are female, as observed by others. Three carriers and 8 non-carriers had children (Table I).

When invited for a follow-up, one gene-carrier did not respond, another came alone because "his wife's feelings and thoughts were the same as his". Neither of these 2 completed the questionnaires. Participation in the follow-up study was 88%.

Probably because of the small sample size and low power of the statistical tests, no significant differences were found among the 4 groups (gene-carriers, non-carriers, partners of gene carriers, and of non-carriers respectively) for the GHQ, the MHLC and the DMI. The data of the BHS and the AQ will be reported here. Data from the other questionnaires will be used in the ongoing study in our Center and for international comparisons at a later date.

Table 1. Age, Sex, Marital Status, Family Size, and Results of 18 Individuals Undergoing Presymptomatic Testing for HD

Characteristics	Applicants	
	Male (n=11)	Female (n=7)
Age	35.9 (22-45)	33.0 (24-43)
Marital Status		
Single	0	1
Married	10	6
Divorced	1	0
No. of children		
0	4	4
≥ 1	7	3
Results		
Decreased risk	4	5
Increased risk	7	2

Interviews and Attitude Questionnaire

Reasons for Testing

Planning for the future, the desire to have children, relief from uncertainty, and the wish to be prepared for a future disease had been the most common reasons for wanting to undergo the test (Table II). These reasons were restated one year after presymptomatic diagnosis for HD. Out of the 14 couples that completed the questionnaires, 7 (50%) indicated that, before having been tested, they had wanted to base their reproductive decisions on the results. This is a much higher percentage as reported by others (Meissen et al., 1988 (13%); Craufurd et al., 1989 (25%)). In addition to the reasons for wanting the test, 5 non-carriers and 2 carriers gave reasons for not wanting it. Fear of an unfavorable result was mentioned by 2 carriers and 3 non-carriers. Two carriers felt uncertain about their partner's ability to cope with an unfavorable result. However, nobody regretted applying for the test.

*Table II. Follow-up at One Year After Presymptomatic Testing for HD: Summary of Reasons Given by Participants for Taking the Test**

	c (n=7)	non-c (n=9)	p-c (n=6)	p-non-c (n=8)
1. Planning for the future	5	6	5	6
2. Desire to have children	4	5	4	5
3. Relieve the uncertainty	4	3	2	3
4. Anticipate HD	3	2		
5. Others				
To help the research		2		
To inform children	2	2		3

* *c*, gene-carrier; *p*, partner

Adaptation in Gene-Carriers

Though reported in retrospect, all carriers had expected to be carrier of the HD gene. One carrier felt cheated because she had been "selected" as potentially healthy by her family. Six newly identified carriers reported that their problems had not increased and that they did not find their lives less valuable.

Like others, we found that gene-carriers apparently bore their new knowledge well (Meissen et al., 1988; Craufurd et al., 1989; Brandt et al., 1989). Within a week after disclosure, a fairly remarkable resilience followed the initial shock. No psychiatric morbidity, severe depression or suicidal tendency has been reported as a reaction to the result. However, one carrier showed increasing neurological signs of HD, which led to diagnosis 2 weeks before the follow-up interview. He decided to leave his job. He has feelings of extreme guilt and dreads becoming increasingly dependent on his wife and children. He is also afraid that his partner will leave him, which had happened to his mother. He has elected to undergo psychotherapy.

Over the long term, gene-carriers denied having had depressive periods, but this was contradicted by some of their partners. It may be a matter of putting on a brave face but gene-carriers are more likely to deny these feelings at an unconscious level. Gene-carriers did not want to discuss the result with family members, close friends, or professionals. The result meant relief from uncertainty and they were less pre-occupied with the possible development of involuntary movements. They felt that nothing had actually changed.

Three carriers had not expected to cope so well and wondered whether they did so by means of repression or denial of feelings. Three of the carriers put their hopes on progress in medical technology and an eventual cure for HD. Two carriers said that they felt too good to be true. Three carriers experienced a strengthening of the bonds between themselves and the affected parent. One of these has even decided to take care of the (divorced) affected parent.

Only one carrier occasionally questioned the reliability of the test.

Carriers appeared to take their new genetic status rather lightly with little show of emotion. However, they all felt strong emotions in the week preceding the follow-up with an upsurge of negative feelings when visiting the Genetics Center, which is similar to other reports (Meissen et al., 1988; Craufurd et al., 1989). These feelings were not specifically associated with the Center or the counsellors who had delivered the unfavorable news.

Four carriers thought that their partner's problems had increased. Most carriers thought that there was no reason for their partners to worry, as long as they themselves had no problems with the result. Although recognizing that eventually they would be a burden, gene-carriers showed little ability to appreciate their partner's feelings.

Carriers may also repress or isolate those emotions which would normally be expected following an unfavorable result. They also feel relief that the uncertainty is over.

Suicidal Ideation in Gene-Carriers

The incidence of suicide among people with HD is believed to be 5-11 times higher than the population average (Kessler et al., 1987). Newly identified gene-carriers have not yet shown an increase in suicidal behavior (Meissen et al., 1988; Brandt et al., 1989). The latter also reported no difference in the pretest scores on the BHS between identified carriers and non-carriers. In our study, the scores on the BHS (Table III) show a significant difference between gene-carriers and non-gene-carriers, and between their respective partners.

Three carriers and two carrier-partners perceived their future as moderately hopeless and two carriers saw it as severely hopeless. All carriers said that it were not the symptoms of HD, but the increasing dependence on others, that frightened them. During the interviews, most carriers stated that euthanasia or suicide would be a genuine option in the later stages of HD. The carrier who received a clinical diagnosis of HD shortly before the follow-up has become depressed and has had suicidal fantasies. Our impression is that newly-identified carriers do not immediately consider suicide, but only after the clinical symptoms appear.

*Table III. Follow-up at One Year After Presymptomatic Diagnosis for HD: Degree of Hopelessness as Measured by the Beck Hopelessness Scale (BHS)**

	Normal	Mild	Moderate	Severe
Gene-carriers (n=7)	2	0	3	2
Non-carriers (n=9)	7	2	0	0
Partners-carriers (n=6)	3	1	2	0
Partners-non-carriers (n=8)	7	1	0	0

* BHS= 0-3 (normal), 4-8 (mild), 9-14 (moderate), >14 (severe). Between gene-carriers and non-carriers significant difference ($p=.0081$); between partner-gene-carriers and partner-non-carriers significant difference ($p=.05$) (Mann-Whitney U-Wilcoxon Rank Sum W Test)

For this reason, carriers should be regularly followed up over a long period of time, or at least until they have become aware of the first symptoms.

In carriers, we found a contradiction between the way they experience their current life-situation and their future. Though recognizing their future burden, this does not seem to affect their feelings and behavior. One could argue that their identity, which has merely been built upon a future disease, has not yet been distorted. It has even become more structured than ever before. Moreover, by warding off unbearable feelings and thoughts, they are able to pick up the threads of their lives.

Partners of Gene-Carriers

Partners of gene-carriers found great relief in being able to talk about their feelings during the interviews. After disclosure of the result, they experienced a short period of intense sorrow, anger and despair about a future that would be totally overshadowed by HD. They all felt neglected by relatives, friends and professionals alike. At first they concealed these feelings, because all attention was focussed on the newly-identified gene-carrier. They did not reveal their emotions to their partners due to feelings of guilt. Some felt the need to talk to other professionals (e.g. general practitioner and/or social worker), but they were reluctant to do so, for fear of hurting the carrier's feelings. Partners found it hard to understand and accept that carriers seem able to cope so well whilst they themselves did not feel relief from uncertainty. This may lead to marital conflicts. However, partners who knew about the risk for HD in their partner from the onset of

their relationship, appeared to have fewer problems than those who became aware at a later stage, such as after their marriage. This may be due to spouse selection. People seek a partner who best serves to substitute for some unattained ego ideal. Once established, marital partners have an implicit "contract" to continue to gratify these needs throughout their marriage (O'Leary and Smith, 1991). The burden of a future, devastating disease may consciously or unconsciously create and structure a "marital scenario". The way marital conflicts are resolved and marital adjustment is established should be given more attention.

Future Family Planning

Four carriers did not think it justifiable to have (more) children. Three carriers wished to have (more) children, even though they had earlier indicated that they would base their decision about family planning on the test results; their desire to have children proved to be too strong. When their opinion was asked about prenatal testing, one female carrier considered this as an option, whereas 2 male carriers rejected it. All 7 carriers who approved of prenatal testing found termination of the pregnancy acceptable should the fetus be found to have the HD gene, whereas 4 carrier-partners did not. This attitude is contrary to earlier findings in surveys of prenatal testing for HD. A considerable number (30%-70%) of untested at-risk individuals indicated that they would wish to continue a pregnancy, irrespective of their own test result or that of the fetus (Kessler et al., 1987; Meissen and Berchek, 1987; Markel et al., 1987). Reproductive decisions prove to be very complex and are not merely determined by the 'rational' assumption that an identified HD carrier will automatically abstain from (further) procreation (Frets et al., 1990). We believe therefore that there is an obvious need for more data on the effects of presymptomatic diagnosis on reproductive decisions. In answer to the question whether children under 18 should be allowed to have tests, 5 carriers, 5 non-carriers and 5 non-carrier-partners responded positively, whilst 4 of the 6 carrier-partners did not. This tendency was also found in other studies of attitudes of at-risk individuals (Meissen and Berchek, 1987; Markel et. al., 1987). Most geneticists advocate strongly against the idea of testing children for late onset disorders (Bloch and Hayden, 1990; Harper and Clarke, 1990). However, some respondents realized that children might not be aware of the emotional impact of the procedure and argued that children might be more open-minded to the test. All agreed that comprehensive expert support would be required. The issue of testing children requires extensive discussion both among professionals and the wider public (Harper and Clarke, 1990).

Reactions of Non-Carriers

Little attention has been paid to the reactions created by favorable results. Incidentally some non-gene carriers reported negative reactions upon the favorable outcome in the form of hostility or resentment from affected or untested siblings (Meissen et al., 1988; Craufurd et al., 1989).

In 8 non-carriers the expected relief was short-lived and was soon replaced by persistent guilt feelings (survivor's guilt), depression and emotional numbness (Lifton, 1979; Tibben et al., 1990). Six of them have avoided contact with their sibs. The relatives of the non-carriers seemed to be indifferent to the results. Two non-carriers did not even tell their sibs about the results for fear of giving the impression that they (the non-carriers) wanted them to have tests too. Five non-carriers remained preoccupied with possible development of any involuntary movements and the threat of the disease. Five non-carriers displayed strong aggressive feelings of resentment towards parents and grand-parents for having denied the existence of HD in the family. Four out of these 5 came up against exclusion from family affairs. Their relatives reacted to their "privileged" position by "banning" them from the family because the HD tie had been severed. Communication in a family is affected by the threat of HD, often for more than one generation. It either induces close scrutiny for early symptoms ('symptom search') or denial of these in relatives (Kessler and Bloch, 1989). A conspiracy of silence functions as a strictly guarded code in order to ward off the burden of the disease. This code is broken once a relative applies for a presymptomatic test. Conversely, a family might unconsciously seek to break the family strategy by selecting and persuading one of its members to have a test. If the result is unfavorable, this member will then remain part of the family. It is an enormous challenge for a family to adjust to the idea of having a non-gene-carrier in their midst.

For several non-carriers, the question why they had escaped HD appeared difficult to answer. Some thought that their sibs were more at risk because they themselves had not inherited the gene. All non-carriers experienced feelings of guilt towards their affected or at-risk relatives. They felt an obligation to be continuously available to bolster affected or at-risk members of the family. Some of their spouses were unable to appreciate the rather long-lasting process that the non-carriers went through.

Eight non-carriers reported numbed feelings lasting for more than 6 months ($n=3$) or persisting for over a year ($n=5$). This emotional numbness may be seen as an adjustment mechanism to the sudden removal of the HD-carrier scenario. Four non-carriers occasionally questioned the reliability of the test. Two female non-carriers delivered a child, one before and one 6 months after the interview.

Many of those at risk of HD had lived for years with the fear of onset of the disease and had a continuous struggle to master the threat. They had shaped their lives against a background burden of HD. Our findings suggest that most non-carriers were neither emotionally nor cognitively equipped to assimilate the notion that their adaptation to the threat of HD had, after all, been totally unnecessary.

All partners of non-carriers were relieved, particularly those who wanted to plan a family. However, 2 of them (male), who knew about their partner being at 50% risk before they got married, had reckoned with an eventual disease: and the result had altered their perspective. They had to "give up" a future with a devastating disease. Now they felt no longer restrained from developing their careers further. The impact of testing on marital adjustment and spouse selection should be further explored.

Practical Implications of the Working Through Process

Coping with the test results should be seen as a traumatic experience and requires adequate defense activity against threatening feelings and thoughts. The ability to anticipate the consequences of the test might facilitate the working through process. While working through, acknowledgement of traumatic experiences alternates with denial until a new balance is struck. Positive development and differentiation of emotions are characteristic of good working through. As a result a person will be able to make decisions, take an interest in other people and things and can look forward to new experiences (Horowitz, 1976; Brett and Ostroff, 1985). According to our findings, this process may take years rather than months. If the process becomes blocked, a post-traumatic stress disorder may develop. Therefore, there is a risk of under-diagnosis and under-treatment of newly-identified gene-carriers who seem to be coping well. They may isolate and deny their affect which may be their way of adjusting to reality. On the other hand, absence of intrusive images of a future determined by HD, may reflect inadequate defense activity. All this calls for careful observation.

Our observations clearly suggest that attention should also be paid to the needs of partners of newly identified gene-carriers. They tend not to ask for help, seeing it as disloyal and selfish to do so (Tibben et al., 1990). This point has not been appreciated in other HD presymptomatic diagnosis programs. It underlines the need for long-term evaluation of both HD-carriers and their partners. Moreover, appreciation of the effects of a distorted perspective of non-carriers should obtain professional attention. Applicants do not need to be alarmed when they experience the foregoing effects: they may even be encouraged to face them because it is all part of coming to term with the result.

The data may be an incentive for patient organizations to further explore possibilities of forming support groups for partners.

After disclosure, many tested individuals may seek support from their general practitioners (Mennie et al., 1990). We recommend that people working in the health sector be informed about reactions typical of the working through process.

The current protocol of the testing program is comparable with the programs in Vancouver and Manchester (Bloch et al., 1989; Craufurd et al., 1989). There should be every opportunity for all parties involved to explore and anticipate potential responses to favorable, unfavorable or non-informative test results. The significance of presymptomatic testing for close relatives should also be examined, for, although at-risk individuals maintain their freedom to undergo the test, they also show strong commitment to their families. On being given the test results, all persons are requested to telephone the psychologist at the Center after 24 hours. A first follow-up session is arranged for the following week.

It is extremely important to keep in touch with gene-carriers, their partners and the non-gene carriers. However, the tendency of some carriers and partners to associate the burden of the testing process with the Genetic Center may make support by other health workers more appropriate for some of them. There is an important role for the family physician (the general practitioner) in the first line of the health care system to serve as a neutral point for support as is important in the process of coping.

These data have important implications for the scope and objectives of psychological support during presymptomatic test programs for HD and other late onset genetic diseases.

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Chapter 2

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Chapter 3a

Presymptomatic DNA-Testing for Huntington Disease: Pretest Attitudes and Expectations of Applicants and Their Partners in the Dutch Program.

Presymptomatic DNA-Testing for Huntington Disease: Pretest Attitudes and Expectations of Applicants and Their Partners in the Dutch Program

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ABSTRACT

We studied the baseline attitudes, prior to testing, of 70 applicants at risk for Huntington disease (HD) and their partners in the Dutch presymptomatic DNA-testing program. Two thirds of the applicants were female; 36% already had children. The main reason (60%) for undertaking the test was for family planning. Other reasons were either to reduce uncertainty (43%) or to obtain certainty (38%). Partners of applicants stated that planning for the future was for them the most important reason (76%). Significantly more at-risk females (42%) than males (16%) anticipated an unfavorable test outcome. Quite remarkably, most applicants and partners denied that a positive result might have adverse effects on either personal mood, quality of life, or marriage. Only a few did not expect that a favorable result would induce relief. The eventual outcome of the test was expected to enable applicants to gain control over their future, whatever the result. Hence, we propose that the applicants form a self-selected group, based on their expectation that they will not be emotionally affected by either result.

INTRODUCTION

Huntington disease (HD) is a late onset, progressive, autosomal dominant heritable disorder characterized by involuntary movements, changes in behavior and personality, and cognitive impairment (Hayden, 1981). Although the average age at onset is 40 (\pm 12) years with a range of 2-75 years, at-risk individuals can never be sure of having escaped HD (Roos et al., 1991). Hence, persons at-risk often have children by the time the first symptoms appear.

The localization of the HD gene on chromosome 4 using linked probes (Gusella et al., 1983) has widened the scope for genetic counselling. Clinical application of linkage

analysis started in 1986, often associated with research programs on the psychosocial effects (Bloch et al., 1989; Brandt et al., 1989). Before introduction of this presymptomatic test, about two thirds of HD risk-carriers interviewed intended to seek presymptomatic testing. Also, they expected an increased risk for major psychological and social difficulties including depression and suicidal plans (Evers-Kiebooms et al., 1987; Kessler et al., 1987; Markel et al., 1987; Mastromauro et al., 1987; Meissen and Berchek, 1987). Obviously, genetic centers should only offer the test following guidelines for careful psychological support and follow-up (World Federation of Neurology, 1989). Only a few studies have reported on psychological data of tested individuals (Bloch et al., 1989; Brandt et al., 1989, 1992; Craufurd et al., 1989; Tibben et al., 1990, 1992; Meissen et al., 1991; Huggins et al., 1992).

In a prospective study in The Netherlands, including self-report questionnaires and a series of in-depth interviews, we assessed the psychosocial effects of presymptomatic testing and the need for support of applicants and their partners. The pretest attitudes of at-risk individuals and their partners are presented in this paper.

PARTICIPANTS AND METHODS

Genetic Counselling

Presymptomatic testing for HD was offered at the Clinical Genetics Center, Leiden, The Netherlands, from October 1987, after approval by the Medical Ethics Committee of the University Hospital, Leiden. In 1989, the same committee approved the protocol on both pre- and posttest psychological evaluation. Information about the availability of the test was given by either general practitioner, neurologist, clinical genetics service, relatives, or the patient organization. No official announcement was made by the Genetics Center as a restrained policy was applied. Television broadcasts about HD and testing had been an incentive to apply for the test in few instances. The protocol includes several sessions of pretest counselling and a brief neurological examination. Testing is offered provided that applicants meet the inclusion criteria, i.e., age over 18 years, absence of major mental illness, suicidal plans, or early clinical signs of HD, and ability to give informed consent. Applicants are usually referred to the neurologist when they suspect that they are already affected.

The DNA-test is currently informative in >90% of the applicants when sufficient data on affected and unaffected relatives are available. The reliability is often higher than 96%. In each family, the clinical geneticist and the molecular geneticist indicated which relatives are essential for obtaining the most informative result. The linkage analyses have been

presented separately (Skraastad et al., 1991).

Participants

Between April 1, 1989, and March 31, 1991, a total of 114 at-risk individuals entered the program. Criteria for enrollment in the psychological follow up study were: 1) a suitable family structure and availability of blood samples of those affected and unaffected individuals that would enable an informative result; 2) absence of language barriers or other inability to understand questionnaires; 3) informed consent for participation.

This study reports on 70 at-risk individuals and 55 partners who were informed about risk modification and who participated in the attitude questionnaire study. Characteristics of the study population are shown in Table I. The male/female ratio was 1:2, 36% already had children. Eight applicants reported as being single, although they had an intimate partnership. These partners also participated in the study.

Forty-four other individuals entered the program in the 1989-1991 period but were excluded from the psychological study. Four of them received test results but decided not to complete participation in the follow-up study.

Forty applicants did not fulfil the requirements necessary for inclusion in this study (see Table II).

Six applicants eventually requested exclusion testing in the event of a future pregnancy. Three of them did not want to burden their future offspring with the knowledge of a higher risk for HD because they could cope well with their being at 50% risk. Two individuals learned about exclusion testing during the first counselling session. One applicant first wanted presymptomatic testing only for herself, but changed her mind and asked for the guided-exclusion test (Fahy et al., 1989). In her first pregnancy the fetus received a normal chromosome 4 from the unaffected grandparent.

Five applicants asked for testing to confirm their own suspicion that they were affected, despite "normal" clinical findings by their neurologist or general practitioner. Neurological examination by the neurologist in the team (R.R.) confirmed the diagnosis in the 5 cases and DNA-testing was no longer necessary. The patients have been referred for aftercare.

Three applicants withdrew from the study because of lack of cooperation by their relatives.

Table 1. Pretest Characteristics of At-Risk Individuals Before Presymptomatic DNA-Testing for Huntington Disease (Period 1989-1991)

	Male (N=25)	Female (N=45)
Mean age years (range)	32.7 (19-61)	31.0 (18-59)
	N (%)	N (%)
Marital status		
Single	8 (32)	11 (24)
Married	10 (40)	21 (47)
Common-law	6 (24)	10 (22)
Divorced	1 (24)	3 (7)
Children		
0 children	18 (72)	27 (60)
1 child	1 (4)	4 (9)
≥ 2 children	6 (24)	14 (31)
Siblings		
0 sibs	1 (4)	2 (4)
1 sib	7 (28)	14 (31)
2 sibs	9 (36)	14 (31)
≥ 3 sibs	8 (32)	15 (33)
Highest level of education		
Elementary school	0 (0)	3 (7)
Lower vocational school	11 (44)	11 (24)
High school or secondary vocational school	9 (36)	18 (40)
Secondary school	2 (8)	6 (13)
Higher vocational school, university or college	3 (12)	7 (16)
Employment status		
Employed	22 (88)	28 (62)
Unemployed	1 (4)	2 (4)
Housewife/man	1 (4)	10 (22)
Other	1 (4)	5 (11)
Religious practice		
Yes	2 (8)	8 (18)
No	23 (92)	37 (82)

Table II. Reasons for not Performing Presymptomatic Diagnosis In 40 At-Risk Individuals

	N
1. Family structure not informative for DNA-testing	16
2. Opting for exclusion testing in future pregnancy	6
3. Early symptoms	5
4. At-risk individuals delayed testing after one or more counselling sessions	5
5. No cooperation by relatives	3
6. Uninformative DNA markers	2
7. Withdrawal for unknown reasons	2
8. Under age (< 18 years)	1

Methods

An attitude questionnaire (AQ) was used consisting of 31 questions covering the following areas: the subject's reasons for taking the test; the anticipated impact of either test results; the people with whom applicants discussed the test and to whom they would tell either result; expected outcome of the test; attitudes toward testing offspring under 18; attitudes toward prenatal testing and terminating a pregnancy in different circumstances. Eleven questions were open-ended. Twenty questions were multiple choice. Respondents could comment on all questions.

The questionnaire was adapted from other studies on presymptomatic testing for HD and modified to accommodate at-risks and partners (Mastromauro et al., 1987; Bloch et al., 1989). Additionally, biographic data, including gender, age, marital status, employment status, number of children, number of sibs, level of education, and religious practice were assessed.

Here we present the 95% confidence intervals (95% CI) of proportions. Difference between groups was regarded as significant when intervals do not overlap. The statistical significance of differences between groups was assessed by means of the Chi square test for categorical data. When the data were dichotomous, a correction for continuity was applied.

RESULTS

Hearing About HD in the Family

Applicants learned about HD in the family at a mean age of 22.7 years (sd 9.3) and about their own risk status at a mean age of 23.8 years (sd 10.1). This latter information was most often given by their parents (49%), or otherwise by sibs (17%), other relatives (16%) or the general practitioner or medical specialist (37%). Additional and ongoing information about HD was received from the patient organization (59%), relatives (44%), and the media (24%).

Male partners learned most often (69%) from their partners about their partner's risk for HD. The female partners were informed by their male at-risk partner (31%), by their parents-in-law or the grandparents of the at-risk partner (35%).

All applicants and partners, except 5 out of 12 female partners, were familiar with persons with HD and with symptoms of HD.

Impact of HD on Life

Twenty applicants (29%) denied an influence of HD on their lives so far. However, most (n=50) reported restrictions such as the inability to make choices for the future, career planning, starting a family, or having an intimate relation. Seven at-risk individuals also indicated a positive influence, feeling more independent and self-assured. Four at-risk persons experienced an overwhelmingly paralysing influence of HD. Whereas only 3 at-risk individuals explicitly mentioned refraining from having children as an important influence, half of the female partners reported this as a paramount impact of HD on their lives.

The most significant symptoms of HD in the affected parent, as perceived by the at risk individual and partner, are presented in Table III. Individuals at-risk were more apprehensive about the personality changes than their partners, whereas the latter were more anxious about the depression.

Reasons For or Against Taking the Test

The 3 main reasons for applicants to take the test (Table IV) were planning a family and either relieving uncertainty or obtaining certainty. We differentiated between those who wished to relieve uncertainty and those who yearned to obtain certainty because both statements could have a different psychological meaning.

*Table III. The Affected Parent's Most Significant Symptoms of Huntington Disease as Perceived and Experienced by Applicants and Their Partners**

	At-risks (N=68)	Partners (N=48)	
	% (95% CI)	% (95% CI)	P
Involuntary movements	71 (58-81)	74 (60-86)	ns
Aggression/personality disorders	31 (20-43)	15 (06-28)	.05
Speech disorders	16 (08-27)	6 (01-17)	ns
Depression	15 (07-25)	35 (22-50)	.05
Denial/negation	12 (05-22)	10 (03-23)	ns
Cognitive disturbances	7 (02-16)	12 (05-25)	ns

* This was an open-ended question; more than one symptom could be given.

Less frequent reasons for taking the test were: to help others, help the family cope, to take preventive measures, need to know whether physical complaints were due to HD, and to relieve personal stress because of those physical complaints.

Partners mentioned planning for the future and planning a family as most important. Other reasons were to reduce fear, to take a positive step to happiness, to determine reasons for physical complaints, to accommodate to the future disease, to improve acceptance of potential early symptoms.

Within either group, no significant differences were found between males and females.

Reasons against taking the test had been considered by 33 applicants (47%) and 29 partners (53%). Fear of adverse effects after an unfavorable result was mentioned by 21 applicants. Other reasons were the fear that an early diagnosis would prematurely lead to a life with the role of a patient, "symptom search" and accordingly, restriction in different areas of life. Thirteen partners mentioned fear of an adverse effect after an unfavorable result. Six partners doubted whether they would be able to support their spouses when the test indicated a high risk for HD. The need to involve relatives and deprivation of hope after an unfavorable result were among other reasons given against the test.

The decision to take the test is the sole responsibility of an at-risk individual, as 91% of the respondents agree. Most (78%) stated that the partner must participate in this decision before it is discussed with professionals (65%). Two thirds (69%) discussed the decision to apply for the test with one or more sibs.

Table IV. Reasons for Taking the Presymptomatic DNA-Test for Huntington Disease*

	At-risks (N=68)	Partners (N=55)	P
	% (95% CI)	% (95% CI)	
1. To plan a family	60 (47-72)	55 (41-68)	ns
2. To relieve uncertainty	43 (31-55)	2 (00-10)	.001
3. To obtain certainty	38 (27-51)	16 (08-29)	.05
4. To stop the disease	18 (09-29)	18 (09-29)	
5. To prepare for the future (anticipating the disease)	9 (03-18)	9 (03-18)	
6. For the sake of children/ clarify risk to children	4 (01-12)	18 (09-31)	.05
7. General planning for the future	3 (00-10)	76 (63-87)	.001
8. To help research	2 (00-08)	5 (01-15)	ns

* This was an open-ended question in all studies; more than one reason could be given.

Expected Effects of an Increased or Decreased Risk for HD

Prior feelings about the test outcome were studied with questions like "I'm certain/I often think that the test will show an increased/decreased risk." Four male (16%) and 19 female applicants (42%) anticipated a high risk for HD (Chi square 3.89, df 1, $P < .05$). Seven males (28%) and 11 females (24%) often thought that the risk would decrease for them. Males more often (56%) answered "I don't know" than females (33%).

The areas of life which were anticipated as being affected by receiving an increased risk at testing are presented in Table V.

Most at-risk individuals expected that an increased risk might allow them better planning of their future. Both at-risk individuals and partners thought that an increased risk would raise more problems for the spouses than it would for themselves. About half thought that the problems for their children would increase. Few respondents anticipated becoming depressed. None of the partners anticipated an adverse effect on their relationship. Twenty-two percent of at-risk persons thought that an increased risk would influence their jobs in the short term, i.e., less than one year after disclosure. The anticipated impact of an increased risk was equal for male and female at-risk individuals.

Table V. The Anticipated Impact of Receiving an Increased Risk at Testing

An increased risk:	At-risks (N=68)	Partners (N=55)	<i>P</i>
	% (95% CI)	% (95% CI)	
a. Will allow me to better plan the future of my family	75 (64-85)	59 (44-71)	ns
b. Will allow me to better plan my own future	70 (58-80)	49 (35-63)	.05
c. Will increase the problems of my partner	65 (53-77)	52 (39-66)	ns
d. Will increase the problems of my children	51 (39-64)	61 (48-75)	ns
e. Will increase my problems	36 (25-48)	36 (24-50)	ns
f. Will adversely affect my marriage/relationship	11 (05-21)	0 (00-06)	ns
g. Will decrease the quality of my life	9 (03-18)	4 (00-13)	ns
h. Will cause me to become depressed	4 (01-12)	7 (02-18)	ns

The anticipated impact of receiving a reduced risk (Table VI) shows that at-risk individuals expected significantly more often than their partners, that the planning of their future would be improved. Most respondents agreed that the problems of their spouses would decline. A few thought that it would increase the quality of their lives and few people thought that it would enhance their relationship.

Pretest Ideas About Sharing Test Results With Others

Most at-risk individuals and their partners would like to discuss an increased risk outcome with their general practitioner (71%). A support group was mentioned by 36% of all respondents, a social worker by 30%, and a psychologist by 56%. About 85% of all at-risk individuals would tell their sibs about the results.

Ideas About Presymptomatic Testing of Minors

Forty-one per cent of all respondents had the opinion that children under 18 should be allowed to have the test. Males at risk (52%) agreed with this, significantly more than females at risk (26%) (Chi square 8.49, df 1, $P < .05$).

Table VI. The Anticipated Impact of Receiving a Decreased Risk at Testing

A decreased risk:	At-risks (N=68)	Partners (N=55)	<i>P</i>
	% (95% CI)	% (95% CI)	
a. Will decrease the problems of my partner	70 (58-80)	71 (57-82)	ns
b. Will allow me to better plan the future of my family	64 (52-75)	51 (37-65)	ns
c. Will decrease the problems of my children	63 (51-74)	76 (63-87)	ns
d. Will allow me to better plan my own future	60 (48-72)	42 (29-56)	ns
e. Will decrease my problems	59 (46-70)	51 (37-65)	ns
f. Will cause my mood to improve	46 (34-58)	40 (27-54)	ns
g. Will increase the quality of my life	33 (22-45)	20 (10-33)	ns
h. Will enhance my marriage/ relationship	15 (08-26)	13 (05-25)	ns

Expected Impact on Family Planning

Thirty-eight applicants wished to have (more) children. Ten already had completed their family. Another 3 females stated that due to the impact of HD on their lives and irrespective of the result, they already had decided to refrain from having children. Two applicants opted for sterilization because of the risk for HD. Seven individuals at risk were unsure and their reproductive choice was dependent on a reduced risk outcome of the test. In the event of a pregnancy, 13 candidates wished to continue this pregnancy, irrespective of the test results. Two thirds of all individuals would use prenatal testing for HD, while only a few (10%) in the whole cohort would refuse.

The acceptance of pregnancy termination in case of prenatal detection of an increased risk for HD showed that half of the respondents would make such a decision (Table VII). A similar proportion of all respondents expected to decide for pregnancy termination if the fetus has Down syndrome. However, female partners found abortion of a fetus at risk for HD more often acceptable (61%) than of a fetus with Down syndrome (39%).

Table VII. Pretest Attitude of Applicants and Partners Towards Abortion in Different Circumstances

I think abortion is acceptable if:	At-risk (N=68)	Partners (N=54)	<i>P</i>
	% (95% CI)	% (95% CI)	
a. Health of mother is in danger because of pregnancy	94 (86-98)	92 (82-98)	ns
b. Prenatal diagnosis shows a serious disease	84 (73-92)	83 (71-92)	ns
c. Prenatal diagnosis shows Down syndrome	57 (45-69)	48 (34-62)	ns
d. Prenatal diagnosis shows increased risk for Huntington disease	52 (39-64)	52 (38-66)	ns
e. The baby is unwanted (for other than medical reasons)	16 (08-27)	17 (08-29)	ns

DISCUSSION

General Characteristics

The male/female ratio (1:2) and the relatively high mean age of applicants in our study are comparable to other reports (Meissen et al., 1988; Brandt et al., 1989; Craufurd et al., 1989). Most ($\pm 70\%$) applicants had, as in the other studies, a stable relationship. About one third already had children whereas in the forementioned studies most ($>60\%$) had at least one child. Almost all applicants had at least one sib.

Female applicants had a significantly higher level of education than the general female population (Chi square 70.44, df 4, $P < .001$) (Dutch Office for Statistics, Voorburg) as was found in other series of presymptomatic testing (Meissen et al., 1988; Bloch et al.; 1989; Brandt et al., 1989), or subjects visiting a genetic clinic (Frets et al., 1990). Seven percent had only elementary school compared with 26% of the general population. However, male applicants had a significantly lower educational level than the general male population (Chi square 59.65, df 4, $P < .001$). Forty-four percent completed lower vocational school compared with 17% of the general population. Educational level of male partners was representative for the male general population (Chi square 3.42, df 4, ns). Mean level of schooling of female partners was above that of the mean general

population (Chi square 35.57, df 4, $P < .001$). Fewer applicants reported a religious belief compared with the general population (Chi square 4.14, df 1, $P < .05$).

Reasons for Having the Test

A paramount reason for wanting the test, expressed by at risks and partners ($\pm 60\%$), was to plan a family, which was much higher than reported in other studies (Craufurd et al., 1989; Bloch et al., 1989; Meissen et al., 1991). In these studies, more than 40% took the test in order to inform their children vs only 4% in our sample; also there were more families without children in our study (Table I).

For the partners in our study, the main reason (75%) was planning for the future whereas only 2 at-risk individuals mentioned this. Obviously, partners are more involved with thoughts about a future overshadowed by HD, whereas at-risk individuals apparently suffered more from the present uncertainty.

Relieving uncertainty and obtaining certainty were the second and third main motivations for individuals at risk in our study. Both reflect psychic conflicts which they attempt to solve. We propose that there is a subtle difference between these motivations. Suffering from uncertainty might reflect the incapacity to defend against threatening feelings and thoughts whereas the wish to get certainty might reveal a rather cognitive and intellectual way of coping with the threat of inheriting or developing HD.

The uncertainty of the at-risk individuals might be induced by the partner's wish to have children thus influencing the at-risk individual to opt for the test so as to meet the (usually unspoken) expectations of the partner. Some female partners refused to have children without complete knowledge of the at-risk's genetic status. We hypothesize that these mechanisms induced at-risk individuals to seek information that they would otherwise not have sought. Moreover, this might have long-term effects on the relationship.

Reasons Against Testing

About half of the applicants listed reasons against taking the test. This is considerably more than the 14% reported by Craufurd et al. (1989). However, one could also argue that most applicants were extremely determined after having gone through a serious process of consideration.

Pretest Counselling: Discussing the Motivation

In the first pretest counselling session, many applicants were unwilling to repeat the motivations for their decision. They may have been anxious about the possibility of reopening the consideration process that might produce ambivalence towards the test. The counsellor approaches applicants with full respect for their opinions but is often perceived as the devil's advocate when trying to discuss the pros and cons of testing. Hence, it takes some time to establish a satisfactory "working alliance," so that an open discussion of potential and conceivable ambivalence towards the test is possible.

Expected Effects on Relatives

Undertaking the test is bound to affect the extended family, particularly because participation of specific relatives to donate blood samples is essential. Yet, a notable group (31%) did not discuss their decision to take the test with their sibs. Some people feared that, by telling them, their sibs might be induced to also take the test, making the applicants responsible for the possible consequences of an unfavorable result. Others only wanted to disclose a favorable result because they feared stigmatization after having received an increased risk. Most of them were fully aware of deliberately keeping their test participation a secret. Yet, some people decided to discuss this with their sibs after profound exploration of their motives during the pretest counselling sessions.

Pretest Expectation to be Affected (Increased Risk) or Not

Female applicants thought the test would show an increased risk significantly more often than males. In the report of Meissen et al. (1991), 32% of all individuals at-risk anticipated an increased risk, vs 25% who thought it unlikely. Our findings may support the hypothesis (Bloch et al., 1989) that women have a greater capacity to acknowledge the consequences of unfavorable messages. Men on the contrary may be more able to circumvent or deny threatening circumstances.

Pretest Anticipation of Effect of Risk Modification

Most at-risk individuals thought that an increased risk would enable them to better plan their future (Tables V, VI). This might reflect the applicants' urge to gain control over their personal prospects and fears for the future. This hypothesis is supported by their wish to relieve uncertainty which is given as an important reason to take the test. Gaining

control might thus lead to reduction of uncertainty and anxiety (Meissen et al., 1991). This could also explain why most people did not expect adverse effects of an increased risk on personal mood, quality of life, or mutual relationship. After all, recognizing these effects would imply loss of control.

One might expect that a decreased risk would be expected to have a paramount positive influence on general mood and quality of life. However, less than half of the respondents agreed with this (Table VI). This might reveal anticipation of numbed emotions after a favorable result. Actually, absence of relief after a decreased risk has been reported previously (Tibben et al., 1990, 1992; Huggins et al., 1992). Respondents may be reluctant to imagine these favorable effects because they want to be prepared for the worst. Thus, looking forward to a possible disappointment might bring about control.

Another signal of warding off threatening feelings and thoughts and consequently gaining control, is that more respondents thought that either result would, respectively, increase or decrease the problems of their spouses than that it would affect their own problems. This hierarchy of anticipated impact on areas in life (Tables V, VI) is comparable with the findings of Bloch et al. (1989).

Sharing Information and Seeking Support

About two third of all respondents expect to discuss an increased risk result with their family physician (the general practitioner), whose support may be sought as the most knowledgeable professional on personal and family circumstances. It is our impression that there is an important role here for the general practitioner. The rather high number of respondents who would like to further discuss an increased risk with a psychologist may reflect the profound involvement in this study of the psychologist during testing and the psychological research protocol. A support group as a safety net was mentioned by 36% of all respondents which is less than in the Vancouver study (51%; Bloch et al., 1989).

Testing Minors: Views at Pretest

As 41% of the respondents were prepared to allow the testing of minors, this is in concordance with other reports (Meissen and Berchek, 1987; Markel et al., 1987; Bloch et al., 1989; Tibben et al., 1992). However, most geneticists advocate strongly against testing children for late-onset disorders for nonmedical indications (Bloch and Hayden, 1990; Harper and Clarke, 1990). From the medical-ethical viewpoint, this would deny the right of a minor at risk to make personal and autonomous decisions, and would not be

beneficial to the child. These contradictory views between professionals and parents call for further information and discussion in order to reach a consensus of opinion.

Pretest Expectations on Reproductive Planning

Two thirds of the respondents would use prenatal testing for HD if there was a pregnancy in their family (compared to 29.4% in the Vancouver study; Bloch et al., 1989). Half of the respondents considered abortion of a fetus with the HD gene acceptable. This appears to indicate important reproductive uncertainties amongst at-risk individuals. This is also reflected in the high percentage of applicants predominantly motivated for the test because of planning a family. Yet, this was also confirmed by 13 at-risk individuals accepting a pregnancy irrespective of the outcome of the test. As a comparison, a study on adult polycystic kidney disease (APKD) in the United Kingdom showed that a few would undergo prenatal testing, although in general half of the participants agreed with termination of an APKD fetus (Hodgkinson et al., 1990). In the Northern American APKD study by Sujansky et al. (1990), 8% of their at-risk individuals agreed with terminating a pregnancy for APKD, compared with 16% who would terminate other serious medical problems. Apparently, the attitude towards prenatal testing and abortion may depend on cross-cultural differences, the perception of the burden of the disorder, the availability of therapeutic prospects, and the personal motives for undergoing either presymptomatic or prenatal testing.

CONCLUDING REMARKS

In The Netherlands, there are about 3,000 individuals at 50% risk for HD. About 7% of these have applied for the test to date. Though a restrained policy to inform about the availability of the test was applied, a notable number still found their way to the genetics center. The general impression is that the current group of candidates is self-selected, highly motivated, well educated, and mentally resourceful (Bloch et al., 1989). Though applicants in our study were extremely determined to take the test, still many of them denied potential personal adverse effects when the test outcome would be unfavorable. Moreover, a favorable result was not expected to induce relief. Apparently, control over future prospects and worry for the spouse were the main concerns of applicants and their partners. Hence, we hypothesize that self-selection of applicants may be based on the applicants' expectation that they will not be emotionally affected by either result. Many candidates appear already to be psychologically adjusted to the new genetic status. The paramount question is whether this adjustment will prove to be adequate. Hence, we need

further insight in the psychological makeup of applicants and their partners in order to offer them appropriate support when needed.

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Chapter 3b

Understanding the Low Uptake of Presymptomatic DNA-Testing for Huntington's Disease

Understanding the Low Uptake of Presymptomatic DNA-Testing for Huntington's Disease

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The uptake of the presymptomatic DNA-test for Huntington's disease (HD) is lower¹⁻² than was predicted by prior attitudinal studies³. Test participants form a highly educated, self-selected group with large mental resources⁴. In the Dutch HD testing programme, most participants anticipated that they would not be emotionally affected by either test outcome⁵, but expected that the test result would allow them to gain more control over their future, including planning a family⁶.

To obtain more information on the motives and characteristics of those knowledgeable about but not taking the test (non-participants), we did an anonymous questionnaire study among 50 members of the Dutch Huntington association (membership 875) who had been addressed through a notice in their periodical. The sample was between 18-50 years, and at 50% risk of HD. The questionnaire was similar to that completed by participants at the first, pre-test counselling⁵. 28 questionnaires (54%) were returned to date.

The participants were similar to non-participants in age (31 years), frequency of stable relationship, offspring, and male/female ratio (1:3)⁵.

All non-participants indicated that HD has had a negative influence in their lives (feeling restricted in important choices, feeling burdened), whereas 20% of the participants denied a burden from HD before the test result. After an unfavourable test result, non-participants expected worse planning of their life and/or family and more often a depressive reaction (table). Non-participants thought that a favourable result would reduce the problems of their partners and children more often than the participants.

Non-participants gave the usual reasons for testing, but the reasons against (fear of unfavourable result, 60%; unable to cope with an unfavourable result, 70%) reflect their difference in general attitude and (realistic) fear for HD and its effects on their life. This contrasts with the more subdued expectations participants had of either test result⁵.

Most non-participants (71%) had heard or read about the effects of testing, half noticed the good coping, the other half mentioned depressive feelings in carriers.

The Anticipated Impact of Results of DNA-testing for Huntington's Disease

	Participants (N=68)	Non-Participants (N=27)
An unfavourable result:	% (95 % CI*)	% (95 % CI)
Increases partner's/children's problems	65 (53-77)	89 (71-98)
Increases own problems	36 (25-48)	63 (42-81)
Better planning life/family	75 (64-85)	48 (29-68)
Decreases quality of life	9 (03-18)	30 (14-50)
Causes depression	4 (01-12)	30 (14-50)
Adversely affects marriage	10 (04-20)	26 (11-46)
A favourable result:		
Decreases partner's/children's problems	63 (51-74)	94 (76-99)
Decreases own problems	59 (46-70)	71 (50-86)
Better planning life/family	60 (48-72)	56 (35-75)
Increases quality of life	33 (22-45)	29 (14-50)
Enhances marriage	15 (08-26)	17 (06-38)

* 95% Confidence Intervals

88% of non-participants with incidental information on the test mentioned negative consequences of a favourable test result, such as depression, survivor's guilt, and being banned from the family. 29% mentioned positive effects, such as the ability to make new plans. None mentioned relief from uncertainty.

The presymptomatic DNA-test does not seem a realistic option to non-participants to improve their quality life since they anticipate pessimistic reactions to an unfavourable result.

Another explanation for not taking the presymptomatic test is, that individuals at-risk and their partners may be reluctant because of incomplete information about advantages and disadvantages. Half of the non-participants reported that carriers have reacted with depression to the bad news in the short term, which is contradictory to current experiences^{5,8}, and might be seen as selective perception. The positive reactions have surprised both professionals and lay people^{6,7}. Follow-up studies are awaited to throw light on the reactions to an unfavourable result in the long term.

Non-participants tended to overemphasize the negative consequences of the test, such as

depression and guilt in non-carriers, which they may find difficult to appreciate since more than two-thirds expected a decline of problems after a favourable result. Health professionals and patients' organisations must realize that these negative effects are normal and necessary for psychological adjustment. This process takes time, often more than a year⁶.

Since DNA-testing is becoming available for an increasing number of hereditary late onset disorders, our findings are an incentive for clinical genetics services and patients' organisations to provide lay people and health professionals with updated information about presymptomatic DNA-testing and its consequences.

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Note: a similar study was recently reported by Quaid and Morris (1993). Important reasons not to be tested included the lack of treatment and impact of an unfavourable result on relatives. Other reasons for reluctance to take the test were fear of losing one's health insurance and financial costs of testing, which demonstrate the difference between the US and European/Dutch health care systems.

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Chapter 4

On Attitudes and Appreciation, 6 Months after Predictive DNA-testing for Huntington Disease in the Dutch Program

On Attitudes and Appreciation, 6 Months after Predictive DNA-Testing for Huntington Disease in the Dutch Program

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ABSTRACT

We have studied the 6-month follow-up attitudes of 63 individuals, after predictive testing for Huntington disease (HD). Reducing uncertainty (81%) and family-planning (60%) were the major reasons for taking the test. Twenty-four individuals were diagnosed as having an increased risk ($\pm 98\%$), and 39 a decreased risk ($\pm 2\%$).

Among those with an increased risk, denial or minimisation of the ultimate impact of the increased risk result was observed. Most of them (84%) rated their current life situation at the very least as being good. Twenty-one per cent of individuals with an increased risk who originally planned to have a family, decided to refrain from having children. Sixty per cent of those with increased risk who still wished to have children, would choose to have prenatal testing. In most individuals with increased risk, the test result did not increase the previously expected control over their own future.

Half of the partners of persons with increased risk acknowledged the burden of the future disease. Half had no one in whom they could confide. They showed loyalty to the denial and avoidance reactions of their spouses.

Half of the individuals with decreased risk denied the impact of the result, as reflected by absence of relief, and emotional numbness. A third of persons with decreased risk experienced involvement with problems of affected relatives.

We found that 20% of all participants were discontented with the support given by their general practitioner, who is normally regarded as being the most significant professional for aftercare.

Our findings suggest that the perpetuation of psychological defenses, which may temporarily be adequate, may ultimately prevent an individual from taking advantage of being informed. These questions should be further addressed in long term follow-up studies.

INTRODUCTION

Huntington disease (HD) is an autosomal dominant inherited disease, characterized by involuntary movements, behavioral and personality changes, dementia and cachexia (Hayden, 1981; Harper, 1991). Although the mean age at onset is 40 (\pm 12) years, a wide range of 2-75 years has been recorded (Roos et al., 1991). Therefore, at-risk individuals are never sure of having escaped HD.

The Huntington gene is localized on the short arm of chromosome 4 (Gusella et al., 1983). The use of DNA probes improved the accuracy of risk determination by linkage analysis. This might provide some individuals at-risk with options that could generally improve the quality of their lives (Bloch et al., 1989). Although an increased risk test result was expected to lead to major psychological and social difficulties (Kessler et al., 1987; Markel et al., 1987; Meissen and Berchek, 1987), no alarming adverse consequences have currently been reported (Meissen et al., 1988; Brandt et al., 1989; Craufurd et al., 1989; Bloch et al., 1992; Tibben et al., 1990 and 1992a).

Pre-test attitudes of most test candidates studied in our center, showed that no possible adverse effects were expected of an increased test result on either personal mood, quality of life or marriage. Only a minority expected that a decreased risk result would induce relief. The outcome of either test result was expected to enable applicants to gain control over their future (Tibben et al., 1992b). Furthermore, female test candidates tended to turn their unacceptable feelings against themselves and had the opinion that health and future prospects depended on themselves, whereas males turned their unacceptable feelings to the outer world and tended to base their health and future prospects on chance. The anticipation of a specific test-outcome was reflected in the permutations of adaptive styles (Tibben et al., 1992c).

Here we report on the post-test attitudes of tested individuals and their partners, 6 months after disclosure of test results.

PARTICIPANTS AND METHODS

Participants

Predictive testing for HD has been offered by the Clinical Genetics Center, Leiden, The Netherlands, from October, 1987. The inclusion criteria were: age over 18 years, absence of major mental illness, of suicidal plans after an increased risk result, or of early clinical signs of HD and ability to give informed consent.

The counselling protocol and linkage analyses were presented separately (Skraastad et al.,

1991). The DNA-test is currently informative in >90% of the applicants when sufficient data on affected and unaffected relatives are available. The distance between the DNA-markers and the HD-gene determines the risk of an undetected recombination and thus the reliability of the test result. The probes used have a recombination frequency of 2-4% which translates into a diagnostic reliability of 96-98% in fully informative pedigrees. Occasionally, due to the pedigree structure, a lower practical reliability is obtained (in our pedigrees to date was not less than 92%). We will further use the words gene-carrier and non-carrier to refer to an increased risk and a decreased risk, respectively.

This study reports on 63 out of 73 originally at-risk individuals who were informed about risk modification between April 1, 1989, and March 31, 1991, and who participated in all phases of the study (Table I). The male-female ratio was $\pm 1:2$. There were 39 females (mean age 31.0 years) and 24 males (mean age 32.7 years) in the study. Two third of the test candidates had a stable relationship. Thirty-five per cent had at least one child. With respect to educational level, 56% of the males, and 69% of the females had more than lower vocational school. The majority of the male (88%) and female (62%) candidates were employed. Major reasons for undertaking the test were to relieve uncertainty (80%), and family planning (60%). A more detailed description of the test candidates at baseline is reported elsewhere (Tibben et al., 1992b). Twenty-four individuals received an increased risk modification of up to $\pm 98\%$; whilst for 39 other individuals, the risk was decreased to $\pm 2\%$.

Criteria for enrollment in the psychological follow up study were: 1. DNA-testing was potentially possible as evidenced by a suitable family structure and availability of DNA samples from relevant affected and non-affected relatives; 2. Ability to understand the questionnaires; 3. Informed consent.

The research protocol was approved by the Medical Ethics Committee of the University Hospital of Leiden.

Methods

At baseline (first counselling session), test candidates and their partners were asked for their consent to participate in a follow-up study on the psychosocial consequences of the test outcome. The qualitative part of the study involved a series of one pre-test and two post-test in-depth interviews. Test candidates and their partners were interviewed separately, so that they could communicate feelings and thoughts they found difficult to tell their partner. One candidate and her partner objected to this procedure and were consequently interviewed together.

Table 1. General Characteristics of Individuals, Presymptomatically Tested for HD

	Carriers N=24 (38%)		Non-carriers N=39 (62%)	
	Male 9 (38%)	Female 15 (62%)	Male 15 (39%)	Female 24 (61%)
Age Mean	30.7	31.6	34.1	31.8
Range	19-46	18-59	20-61	19-46
Marital Status				
Single	4	5	4	4
Married	3	5	6	12
Common-law	2	4	4	6
Divorced	0	1	1	2
Children				
0 children	5	9	12	15
1 child	1	0	0	1
> 2 children	3	6	3	8

The average period between the first and the second interview (disclosure of the test results) was 4 months. The third interview was held 6 months after receiving the test results.

The quantitative part of the study involved completion of a psychometric battery including an attitude questionnaire, and questionnaires measuring stress-specific signs, general signs and symptoms and personality characteristics. Here we report on the results of the attitude questionnaire (AQ), administered 6 months after test disclosure. The questionnaire was adapted from the pretest questionnaire, as used in other studies on predictive testing for HD and modified to accommodate to the posttest situation (Bloch et al., 1989; Tibben et al., 1992b). The AQ is a descriptive instrument and was used to generate hypotheses about the impact of the test results.

The AQ consisted of 30 questions covering the following areas: the subject's reasons for taking the test; the impact of HD and the test results in the short and long term; the people with whom applicants discussed the test results; attitudes toward testing offspring under 18; attitudes towards prenatal testing and terminating a pregnancy in different circumstances. Seven questions were open ended. Twenty-three questions were multiple choice. Respondents could comment on all questions.

In this paper, we present the 95% confidence intervals (95% CI) of proportions of carriers, non-carriers, and their partners. Difference between groups was regarded as

significant when intervals did not overlap.

RESULTS

Originally, 73 test candidates had consented to participate in the psychological follow-up study. Ten were lost to follow-up for the following reasons: two did not complete either the pre- or post-test attitude questionnaires, one female non-carrier because of depression, two without reason, and five because of not completing the post-test attitude questionnaire.

Prior feelings about the test outcome were studied with the question "I'm certain/I often think that the test will show an increased/decreased risk" (Tibben et al., 1992b). Formerly, 40 test candidates (57%) had prior notions about the likely test outcome. Twelve carriers and sixteen non-carriers had their prior expectations confirmed, whereas two carriers and ten non-carriers received the reverse of what they had expected. Of those, who did not anticipate a specific test outcome, 47% were informed of an increased risk and 53%, of a decreased risk result. None of the tested individuals has expressed any regret about having undergone the test.

GENE-CARRIERS AND THEIR PARTNERS

Impact upon areas of life

A quarter of the carriers stated in an open ended format, that the test result has not influenced their lives thus far, whereas another 25% labelled the influence positively with statements like "relief from uncertainty", "I feel more independent", and "I appreciate life more". Twenty-one per cent stated that the previous uncertainty has been replaced by the intrusive question about onset of HD. Other individual statements concerned anticipation of the disease, anxiety, early death, family problems, and refraining from an intimate relationship.

Half of the carriers mentioned that they were uncertain whether the test result would seriously influence their life in the immediate future or they hoped that the onset of symptoms would occur in the distant future (Table II).

Table II. Impact of HD in the Future in Carriers and their Partners

	Carriers (N=24)		Partners (N=17)	
	N	(%)	N	(%)
In the Near Future*:				
- "HD will not influence my life"	8	(33)	3	(18)
- "I hope few influence, hard to say"	7	(30)	5	(29)
- "we'll have to decide about planning a family"	4	(17)	1	(13)
- "we'll make the most of life"	3		2	
- "how to tell our children"	1		1	
- "it's always present"	1		2	
- "it will disturb contact with parents"			2	
- "my partner needs me now"			3	(18)
In the Far Future*:				
- "I don't know"	11	(46)	5	(29)
- "HD will not influence my life"	4	(17)	2	
- "how will my children cope with it?"	2		1	
- "I'm afraid of personality changes"	2		2	
- "I'll become completely dependent"	4	(17)		
- "Let's hope it won't be so bad"	2			
- "Look at the affected parent!"	1		1	
- "no children/family"	2			
- "take care of my partner/nursing"			6	(35)
- "no career"			1	
- "depends on when the disease appears"			3	(18)

* more than one statement could be given

Two carriers wished to fully enjoy life in the immediate future. Four carriers (17%) mentioned that, in the short term, they have to come to a decision about planning a family. Three carrier-partners denied experiencing any current effects, and five hoped that there would be little effect. Two partners intended to make the most of life. Generally, they anticipated possible effects of the disease in the future and its far-reaching effects on family life. About half (46%) of the carriers and 29% of the partners could not say what effect the disease would have upon them in the distant future. Forty per cent of the

carriers and their partners were highly and actively interested in general developments with respect to HD, like pharmacological treatment, search for the HD gene, insurance issues, etc.

The areas of life which were most affected in carriers and their partners, as rated on a multiple choice inquiry, are presented in Table III and IV, but no significant differences were found, probably due to the small sample size. However, compared with pre-test opinions, fewer carriers and partners thought that the result allowed them to better plan their own life and their family in the future.

Only a few carriers-partners (17%) stated that their own problems had increased. Neither quality of life, nor their personal relationships seem to be affected in most carriers and partners, which is in accordance with pre-test opinions. In comparison to their pre-test attitude, five carriers thought differently about the impact of the test result on planning a family: the result enabled three of them to better plan a family, whereas two felt less capable of this. Four carriers changed their pre-test attitude and now thought that they could better plan their own future. Two other carriers changed in the opposite direction.

Table III. The Impact of an Increased Risk for HD in Gene-Carriers

The Test Result:	Post-Test (N=24)		Pre-Test (N=27)	
	%	(95% CI)	%	(95% CI)
a. has allowed me to better plan the future of my family	33	(14-62)	53	(32-77)
b. has allowed me to better plan my own future	29	(10-56)	50	(27-73)
c. has increased the problems of my partner	47	(23-72)	55	(32-77)
d. has increased the problems of my children	36	(14-62)	58	(36-81)
e. has increased my own problems	35	(14-62)	40	(19-64)
f. has adversely affected my marriage/relationship	6	(1-29)	0	(1-17)
g. has decreased the quality of my life	6	(1-29)	5	(1-25)

Impact on work and insurance

Two carriers have experienced problems at their work place, because of general weariness and intrusive thoughts about HD. One thought that the result would certainly

influence his/her work conditions in the coming year. In addition, eight carriers (35%) anticipated that the increased risk result would influence their work in the distant future, whereas five stated that it would not. None has experienced any problems with insurance companies since disclosure.

What has changed in your life?

One carrier dreaded the onset of the disease in the future, two mentioned relief from uncertainty, whilst six carriers felt that nothing had changed (25%). The majority (67%), stated that they enjoyed life to the hilt, and they felt more self-confident. Two partners ended their relationship within a week after disclosure, and one after 2 months. Three carriers have started a new intimate relationship. For half of the partners nothing had changed in 6 months, whereas 25% tried to get the best out of life.

Certainty about result

Almost all carriers stated that they did not doubt the accuracy of the test result. Three commented that the test had confirmed their suspicions. Most of them affirmed that it did not make sense to doubt. One carrier often felt uncertain about the result, commenting that it was difficult to accept that she might develop the illness in the future. Two carrier-partners have questioned the test result. They commented that the test gives no 100% certainty. Another stated "every laboratory can make mistakes...".

Discussion of carriers and partners with others

Twenty-six per cent of the carriers did not discuss the results with their sibs, which is about the same number that did not discuss the undertaking of the test. Fear of stigmatization was mentioned, but the main reason was to prevent unwanted sympathy and subsequently, finding themselves in the family's limelight. Most carriers (75%) discussed the result with their general practitioner as against 68% who initially intended to do so. However, about 20% were not satisfied about the availability and support given by their general practitioner.

More than half (57%) talked with a psychologist (usually the psychologist of the genetics center). Four carriers (17%) actually participated in a support group, as against 40% who initially planned to do so.

Half of the carriers preferred the general practitioner as the primary person for support, whilst 40% favored a psychologist. Seventy-six per cent of their partners on the other

hand, preferred the general practitioner, with 53% choosing a psychologist as second choice. About 20% of the carriers indicated a lack of confidence or an inability to feel comfortable either with or when discussing test results with others. About half of the partners (47%) missed the support of others with whom they could share their feelings. Twenty per cent were discontented about the readiness of their relatives to provide necessary support.

Twenty-five per cent of carriers who discussed the result with their colleagues or employer, appreciated the support given by them.

Twenty-nine per cent of the tested individuals have had supportive contacts with representatives of the Dutch patient organization.

Table IV. The Impact of an Increased Risk for HD in Carrier-Partners

The Test Result:	Post-Test (N=17)		Pre-Test (N=20)	
	%	(95% CI)	%	(95% CI)
a. has allowed me to better plan the future of my family	53	(29-71)	58	(39-78)
b. has allowed me to better plan my own future	38	(19-59)	57	(39-78)
c. has increased the problems of my partner	40	(22-63)	64	(42-81)
d. has increased the problems of my children	42	(22-63)	31	(14-50)
e. has increased my own problems	17	(5-37)	36	(19-58)
f. has adversely affected my marriage/relationship	18	(5-37)	4	(1-19)
g. has decreased the quality of my life	8	(1-27)	11	(2-29)

Reflection of carriers and partners on the testing procedure

The most stressful periods for the carriers were the pre-test period (for 46%) during which time they experienced the impending fear of having reached a point of no return, and the first week after disclosure of the test results (for 33%). The second most often mentioned periods were the first month (40%), and the pre-test period (25%). Their partners rated the first week after disclosure (76%) as most distressing, and the first post-test month (71%) as the second most difficult time. Two carriers and three partners

mentioned the period of the 6-month follow-up as the most distressing.

Most carriers (83%) rated their current life situation as good to extremely good, which is much higher in comparison to their partners (58%). Seventeen per cent of the carriers, and 30% of the partners were modestly contented. One partner judged the present situation as extremely bad. About half of the carriers (46%) mentioned that they thought of HD between once a week and once a month. Twenty-nine percent of the carriers stated that they thought of HD at least once a day. Twenty-five percent of the carriers think of HD less than once a month. Nobody has regretted the decision to undergo the test.

Appreciation of the counseling procedure

Generally, both the tested individuals and their partners were contented with the testing procedure. Three individuals were a little dissatisfied with the support given by the genetics center. Generally, carriers and partners appreciated the way the results were given. Four carriers reported that they have found the period between application and learning about the results too long. However, we found no correlation between the time-lag and degree of satisfaction. Some individuals, who had to wait over 6 months, were still contented although they did comment that the waiting time was too long. Others were dissatisfied, even though they were informed about their genetic risk within 3 months after application.

Generally, the aftercare given by the genetics center was appreciated. Only one carrier was dissatisfied: "your overwhelming attention gives me the feeling that I've already died...".

Half of the carriers found it important that the decision to take the test is discussed with a professional familiar with HD, which is 10% less in comparison to the pre-test opinion.

Testing minors

Twenty-nine percent of the identified carriers (pre-test 25%) and 41% of the partners thought that minors should be free to take the test. Two carriers and two partners became more reluctant about the idea after the test, but another three carriers and four partners felt exactly the opposite. Eight of the carriers (33%) stressed the autonomy of the child, whilst four thought that children might cope more easily with the distress of the procedure and could adapt faster to an increased risk, in comparison to adults. Half of the carriers stated that children are too young to shoulder the burden of an increased risk.

Prenatal testing

Seven carriers did not wish to have more children since their family was already complete. Twelve carriers (50%) wished to have (more) children. Seven of them (58%) would opt for prenatal testing, whilst five were unsure about this. The carrier-partners, however, were more in favor of prenatal testing (71%). Eight of those, who opted for more children (67%), considered termination of a pregnancy acceptable when the fetus was found to be at high risk, whereas four were unsure. Five carriers (21%), who previously wished to start a family or have more children, said that they had refrained from having children as a consequence of the test result.

Eighteen months after the test, three carriers have produced children since learning about their increased risk status. One of them had undergone prenatal testing with a decreased risk result. In one carrier who did not wish to undergo prenatal testing, the general practitioner had tried in vain to persuade her to terminate the pregnancy. One female carrier had a pregnancy terminated after an increased risk result.

More than half of the carriers and their partners considered abortion of a fetus at high risk for HD acceptable. The test result has not influenced that attitude.

NON-CARRIERS AND THEIR PARTNERS

Impact upon areas of life

One-third of the non-carriers valued the current influence of the test results positively. With respect to the influence of the test in the immediate future, 28% stressed the problems with affected relatives, 41% denied any such influence and 18% listed relief. Forty-nine per cent thought that the influence of HD will diminish in the distant future, 33% expected to remain involved with the problems with relatives and 18% mentioned that their (future) children will be free of the HD burden. Their attitudes towards abortion have not significantly changed.

What has changed in your life?

In response to the open-ended question, "what changes has the result brought about in your life", 41% mentioned that nothing has changed, 26% have felt relieved and more self-assured and 23% stressed their attitude to family planning as the most important change in life.

Table V. The Impact of a Decreased Risk for HD in Non-Carriers

		Post-Test (N=39)		Pre-Test (N=44)	
The Test Result:		%	(95% CI)	%	(95% CI)
a.	has allowed to better plan the future of my family	79	(64-91)	85	(70-93)
b.	has allowed me to better plan my own future	72	(55-85)	83	(70-93)

Table VI. The Impact of a Decreased Risk for HD in Non-Carrier-Partners

		Post-Test (N=31)		Pre-Test (N=35)	
The Test Result:		%	(95% CI)	%	(95% CI)
a.	has allowed to better plan the future of my family	82	(63-93)	85	(70-95)
b.	has allowed me to better plan my own future	71	(52-86)	49	(31-67)

Most non-carriers felt that the test result facilitated family planning and were of the opinion that they could now exercise more control in planning (Table V).

Although not significant, partners tended to perceive more control over their own future, in comparison with their pre-test ideas (Table VI).

One non-carrier withdrew from the study, shortly after disclosure because she had become severely depressed. Although the general practitioner had been informed by the genetics center about the possibility of this type of reaction and the need for psychological treatment, she received only anti-depressants.

Half of the partners stated that nothing had actually changed. Others have felt relieved, more self-confident and have thought about the future, including family planning.

Within 18 months after disclosure, six non-carriers produced children and three female non-carriers terminated their relationships. Four non-carriers received additional psychotherapy. One non-carrier has started an intrusive campaign to have other relatives tested as well.

Ten non-carriers (23%) have sometimes doubted the result. One commented that she could not accept having escaped HD. Only 1 emphasized the remaining 5% risk. One-third have extensively followed the scientific and treatment developments with respect to HD.

Discussion of test results of non-carriers and their partners with others

Almost all non-carriers (92%) have discussed the test results with their sibs, which is considerably more than before disclosure. Fifty-nine per cent have further discussed the result with their general practitioner and 51% with a psychologist. About half (46%), mentioned a psychologist as most appropriate in giving support, as second and third most appropriate, the general practitioner (26%) and a social worker (13%) respectively. About 20% of both non-carriers and partners, have few or no individuals, with whom they can feel comfortable. Thirteen per cent was not satisfied about the support given by their general practitioner. One-fifth (22%) was disappointed with the reactions of relatives.

Appreciation of the counseling procedure

Most non-carriers and their partners have expressed their appreciation of the testing procedure. Three individuals were discontented with the support given by the genetics center. Five non-carriers and eight partners complained about the length of the waiting period prior to disclosure. Generally, the aftercare, given by the genetics center was appreciated.

Testing minors

Non-carriers (46%) and their partners (51%) maintained their pre-test attitude with respect to testing minors. The right of the child to choose to undergo testing was their major reason (56%) in favor of testing minors, whereas 39% thought that children might be able to cope well with the distress of the testing program, and of an increased risk result.

Reflection of non-carriers on procedure

Most non-carriers considered the pre-test period (79%) and the first week (64%) after disclosure as most distressing. However, 10 per cent indicated the period 6 months after the test as the most stressful. None of the partners experienced distress later than two months after disclosure.

Satisfaction about support

Most non-carriers (85%) found their life situation good to excellent, whereas 13% rated it as reasonable to modest. One non-carrier ascribed the life situation as bad.

Eighteen per cent of the non-carriers stated that they thought of HD at least once a day. About half of them (44%) mentioned that they thought of HD once a week or at least once a month.

DISCUSSION

The most remarkable finding that emerged from our study concerns firstly the extensive denial in carriers and the underestimation of the impact of knowing that one has a high statistical probability of developing HD. This became even more apparent after the test outcome. Secondly, it was found that half of the non-carriers found no relief at all ("nothing has changed in my life..."). Our findings confirm previous reports that in the short term, carriers have not shown alarming adverse reactions to the increased risk modification (Meissen et al., 1988; Brandt et al., 1989; Bloch et al., 1992; Tibben et al., 1992a). Furthermore, the reactions in non-carriers were not unexpected since these reactions have already been reported (Tibben et al., 1990; Huggins et al., 1992; Tibben et al., 1992a).

Although the distribution of test outcome expectancies (31% increased risk, 26% decreased risk and 43% did not know) was the same as in the report of Meissen et al. (1991), the real outcome showed a different figure. About half of those who anticipated an increased risk, found their expectancy confirmed ($n=12$; 55%) (Meissen: 25%). Quite remarkably, most of those who expected a decreased risk result, proved to be free of the gene ($n=16$; 89%) (Meissen: 40%). Two of them were above 45 years, two were at 25% risk. After correction for this group, 67% had their expectancy confirmed. In the 'no expectancy' group, 47% received an increased and 53%, a decreased risk result. Most tested individuals have not applied for further professional support, although this might be influenced by the available support of the genetics center. Some individuals, mostly non-carriers, requested for additional contacts with the center.

Denial

Half of the carriers stated that the test results have not, thus far, influenced their lives either one way or the other, and 84% of them even rated their present life situation as, at least good. The majority stated that the result had not increased their problems or

diminished the quality of life. After 6 months, half of the carriers rarely thought of the result. In our opinion, this attitude apparently reflects denial and underestimation of the impact of the test result, which can be seen as an important psychological adaptive defense against the threat. It reflects a capacity of carriers to be able to ward off the threat of the new genetic reality and to adjust to an ominous reality. Such denial may allow the carriers the opportunity to unconsciously work through this painful information. However, this way of adjustment might be maladaptive when the actuality of the increased result is ultimately avoided and is not integrated into daily life. The warding off of the threatening reality may be recognized as being useful in the short term. However, there is always the hazard that carriers exclude both themselves and subsequently their family, from follow-up and support when the test result is enduringly denied or minimized, even when the early signs become clearly visible.

Control

Feelings of powerlessness and lack of control of events was a primary source of uncertainty and a major reason for seeking the test (Bloch et al., 1989; Meissen et al., 1991; Tibben et al., 1992ab). Not surprisingly, the pre-test period was recalled as the most distressing. However, in comparison with the pre-test experience, fewer carriers had the opinion that the result enabled them to regain control. However, they did experience another uncertainty, which concerned when and how the disease and its symptoms would manifest themselves. The majority of carriers experienced fears in the early post-test phase (first week after disclosure), where intrusive ideas or thoughts about HD might prevent a carrier experiencing a retrieval of control. Psychological defenses such as denial or minimisation might enable carriers to regain their control. However, since their partners have suffered the anticipation of ultimately having the burden of a devastating illness, the carriers' defenses might result in marital conflicts.

Discussion with others

Fear of stigmatization and confrontation at unexpected moments might have been the main reason why a third of the carriers did not discuss their result with their sibs. Many carriers indicated in the interviews that the result had affected their family, more than they previously had expected. This might explain the subsequent decline in sense of control, in comparison with the pre-test ideas (see also Bloch et al., 1992; Tibben et al., 1992a).

Most non-carriers have talked about their results with their sibs. Survivor-guilt was not

identified as a major experience in the AQ, but was frequently mentioned in the follow-up contacts. Since we were aware, early in the DNA-program, of the possible adverse effects in individuals with a decreased risk, these emotions were extensively discussed in the pre-test counselling sessions (Tibben et al., 1990; Huggins et al., 1992). Non-carriers might have warded off their guilt feelings by defenses such as intellectualization or rationalization. Absence of relief reflects that guilt might be unconsciously worked through.

Carrier-partners

Carrier-partners obviously anticipate a future, totally overshadowed by HD. Half of them affirmed that they have no one with whom they could share their feelings. Also, less than half was actively interested in developments in HD. A considerably greater number of partners than carriers found the first week after disclosure the most distressing, possibly due to their reluctance to trouble the carrier, for fear of hurting his/her feelings. Moreover, the carrier-partner perhaps felt embarrassed to talk about his/her spouse to a third party, which might give the feeling of betrayal. When the partner adapts to the carrier's defenses, the reality of the increased risk is avoided. When the partner explicitly faces the truth and, consequently seeks help, he/she might risk open marital conflicts. Carrier-partners generally tend to choose the first option, i.e. loyalty to the spouse and, consequently, denial and minimisation. This is also reflected by the observation that fewer partners thought that the result had increased their own and the carrier's problems. In the long term, this loyalty might prove counter productive. A further study should be undertaken to see how couples could be helped to cope with this issue. The impact of test results on marital relationships should be further addressed in long term follow-up studies on psychosocial effects.

Non-carriers

Planning for the future was experienced by most non-carriers as an important effect of the test result. This is in accordance with their pre-test expectation (Meissen et al., 1991; Tibben et al., 1992). About half of the non-carriers denied the impact of the test result, which was reflected by absence of relief and sustained emotional numbness. These adverse emotions may be seen as an adjustment mechanism to the sudden removal of the HD-carrier-scenario. Although the absence of relief was found peculiar by non-carriers and their partners, many were not aware of the significance of this reaction. A third tended to become heavily involved in the personal lives of affected or at risk relatives,

which may be seen as reaction formation, whereby unacceptable guilt feelings ("I have deserted my family") were transformed into exaggerated attention. Moreover, the unconscious anger towards the sources of all problems, i.e. parents and grand-parents as the HD gene transmitters, might be warded off by a variety of psychological defenses (Martindale, 1987). Non-carriers and their partners should be encouraged to work through their reactions. Emotional insight might enable them to acknowledge the relief and cope in accordance with a decreased risk.

General Practitioners

The significance of the general practitioner was confirmed (Tibben et al., 1992b; Mennie et al., 1990; Thomassen et al., 1992). However, a considerable number of tested individuals was not contented with the given support. General practitioners may not be sufficiently knowledgeable about predictive testing for late onset disorders and the far reaching consequences of either test result (Thomassen et al., 1992). However, we should take into account that general practitioners may also be anxious to acknowledge the painful reality of a prospective, incurable and devastating illness within a family. They may unconsciously play a perpetuating part in the avoidance and denial strategies.

Non-carriers rated a psychologist as the most appropriate person to give further support. This could imply that non-carriers had accurately estimated that adverse feelings such as depression and survivor guilt could be psychologically worked through. They should be encouraged by the genetic counsellor as well as their general practitioner to further explore their feelings and actions.

Testing minors

Experiencing the distress of the testing procedure and the disclosure, has not led to any change in attitude to the approval of testing minors. Some carriers stated that the increased risk result turned out to be less distressing than expected. Hence, referring to their own experience, they may think that this also applies to minors. They may also wish to "undo" their fate by the certainty of having a healthy child, i.e. free of the HD gene.

It is difficult to reconcile the attitude of many carrier-partners on this subject (41% pro testing) to their obvious acknowledgment of the threat of HD. It might apply to the same feelings of powerlessness: either test result might induce the sense of control over future life. Another explanation might be that carrier-partners would like to resolve the avoidance and denial in their family. Partners might think that marital dialogue will be opened when their children are tested and that their anger or worry might be compensated

for by the certainty of having a child, free of HD. However, the risk of stigmatization and early 'symptom search' in a child, identified as gene-carrier, might have adverse psychological effects and subsequently, restrict the child in its personality development. Moreover, the child's right to opt for the test in the future (at the age of 18 years or older) should be safeguarded. We hypothesize that when parents go deeper into the pros and cons of DNA testing of minors, they might develop a more balanced point of view.

Family planning

Family planning was a paramount reason for undertaking the test. Our experiences differ strongly from other programs, which reported family planning as a rather unimportant reason (Craufurd et al., 1989; Bloch et al., 1989; Meissen et al., 1991). Although some carriers said previously that their reproductive plans would depend on the test result, only few have eventually decided to refrain from children. Most carriers would like a family, and most of them would opt for prenatal testing. The far reaching consequences of their child having an affected parent was taken into account in only a few cases.

However, the partners were obviously more inclined to anticipate a future overshadowed by HD. Yet despite this, two carriers have had a child without prenatal testing, notwithstanding their earlier decision to utilize it. This again shows the complexity of reproductive decisions since they are not merely determined by the rational assumption that a carrier will abstain from (further) procreation (Frets et al., 1990; Tibben et al., 1992a). In a Dutch study on general practitioners' attitudes on predictive testing for HD, most GP's approved of prenatal testing and terminating a high risk pregnancy.

Concluding remark

Early follow-up has shown that predictive testing has generally fulfilled the expectations of the test candidates. We recommend that further study be undertaken to compare whether candidates who received an increased risk and their family members anticipate the illness differently from those who have not been informed of their risk status. In addition, follow-up studies on long-term effects are needed, since denial and underestimation of the impact in carriers might have adverse effects on individual and family development. We also recommend that clinical genetics centers further inform general practitioners and other professionals in health care, about the possible reactions to either test result.

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Chapter 5

Presymptomatic DNA-Testing for Huntington's Disease: Defence Activity and Control Beliefs of Test Candidates at 50% Risk

Presymptomatic DNA-Testing for Huntington's Disease: Defence Activity and Control Beliefs of Test Candidates at 50% Risk.

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ABSTRACT

Presymptomatic DNA-testing is becoming available for an increasing number of late onset heritable disorders. Little data is available about the impact of test results. In the Dutch presymptomatic DNA-testing program for Huntington's disease (HD), long term follow-up psychological effects are studied since an increased risk for HD may be regarded as (learning about) a serious threat to one's physical integrity. In this report it was studied whether specific psychological characteristics could be identified in dealing with the pre-test distress. In the first genetic counselling session, defence activities (DMI), control beliefs (MHLC), general health (GHQ) and level of pessimism (BHS) were assessed in 25 males and 45 females at risk who were tested consecutively. Females at-risk turned their threatening feelings against themselves and showed internal control beliefs. Males turned unacceptable feelings against the outer world and depended their health on fate. Anticipation of a specific test outcome was reflected in the permutations of adaptive styles: optimistic individuals dealt with the distress by denial and avoidance; pessimists showed less defence activity and more health complaints; individuals without an outspoken expectation anticipated pessimistic prospects but tended to isolate their feelings. Control beliefs and defence activity enables the individual at-risk to deal with the distress of an awaited threatening event like the outcome of DNA-testing. It is important in genetic counselling to correctly identify these individuals, who are vulnerable for the outcome of presymptomatic testing.

INTRODUCTION

Huntington's disease (HD) is an incurable late onset, progressive, autosomal dominant heritable disorder characterized by involuntary movements, changes in behavior and in personality, and cognitive impairment (Hayden, 1981). Children of an affected parent are at 50% risk to inherit the gene for HD. The average age of onset is 40 (\pm 12) years

Roos et al., 1991).

The localization of the Huntington gene to the short arm of chromosome 4 using DNA-probes (Gusella et al., 1983) has introduced the possibility of risk modification by linkage analysis to either an increased risk ($\pm 98\%$) or to a decreased risk ($\pm 2\%$) in informative families. Presymptomatic diagnosis was expected to lead to preoccupation with symptoms of HD, depression, and suicidal ideation (Markel et al., 1987; Meissen and Berchek, 1987; Kessler et al., 1987). An increased risk might be regarded as (learning about) a threat to one's life, to one's physical integrity, or to one's children, and thus induce a post traumatic stress or adjustment disorder (American Psychiatric Association, 1987). Methods for linkage or mutation analysis are becoming available for an increasing number of late onset inherited disorders such as various cancer syndromes, neurofibromatosis, myotonic dystrophy and for some cases of Alzheimer disease. Introduction of such programmes requires careful consideration of the psychological effects on tested individuals. Testing for HD is regarded as a paradigm for other late onset disorders (Jenkins and Conneally, 1989).

About 80% of the test candidates in our program were preoccupied with the potential deterioration of their physical integrity (Tibben et al., 1993). The majority (71%) reported an inability to make choices for the future, including to start a family or to undertake an intimate relationship (Tibben et al., 1993).

Like others, we too have found that about two-thirds of test candidates expected that either test outcome would enable them to gain control over their future (Tibben et al., 1990, 1993; Meissen et al., 1991). Most test candidates denied that an unfavorable result could have adverse effects on themselves. Only a minority expected that a favorable result would induce relief.

We report here the pre-test functioning of defence activity and control beliefs of test candidates. Since more female than male at-risk individuals are participating in most HD-programmes (Meissen et al., 1988; Craufurd et al., 1989; Bloch et al., 1989), we posed the question whether they differed from males in their psychological adjustment to the distress undertaking the DNA-test. Furthermore, we wanted to ascertain whether the expectancy of either test outcome is associated with personality characteristics. The underlying assumption is that outcome expectancies are a major predictor of whether test candidates are able to persist in their goals in life after an unfavorable test outcome or instead exert a premature patient role (Scheier et al., 1986).

PARTICIPANTS AND PROCEDURE

Participants

Presymptomatic DNA-testing for HD is offered at the Clinical Genetics Center in Leiden, The Netherlands, provided that test-candidates fulfill the inclusion criteria, i.e. age over 18 years, absence of major mental illness, or early clinical signs of HD and ability to give informed consent.

The counselling protocol and linkage analyses have been presented separately (Skraastad et al., 1991). The DNA-linkage analysis is currently informative in >90% of the test candidates when sufficient data on affected and unaffected relatives are available. The psychological evaluation of the programme involves administration of self-report questionnaires and a series of pre- and post-test in-depth interviews. Criteria for enrolment in the psychological study were: 1. absence of language barriers or other inability to understand questionnaires; 2. informed consent. The study protocol was approved by the Medical Ethics Committee of the University Hospital Leiden.

Females (n=45, mean age 31.0) were more represented in the study population than males (n=25, mean age 32.7). Two third of the test candidates had a stable relationship. Thirty-six per cent had at least one child. With respect to educational level, 56% of the males, and 69% of the females had more than lower vocational school. The majority of the males (88%) and 62% of the female candidates was employed. Major reasons for undertaking the test were to relief uncertainty (80%), and to plan a family (60%). More detailed description of the test candidates is reported elsewhere (Tibben et al., 1993).

Procedure

In the first counselling session, test candidates were asked for their consent to participate in a psychological follow-up study. Subsequently, participants completed the following questionnaires:

The Beck Hopelessness Scale (BHS) focusses on pessimistic expectations concerning oneself and one's future and might predict depression and suicidal behavior (Beck et al., 1990).

The 60-item General Health Questionnaire (GHQ) measures minor psychiatric disturbance and is sensitive to changes in the psychopathological states, like depression, anxiety, somatic complaints and social dysfunctioning (Tarnapolsky et al., 1979).

The Defense Mechanisms Inventory (DMI) measures five defence mechanisms: 1. turning aggression against object (TAO), including displacement and identification with the

aggressor; 2. projection (PRO); 3. principalization (PRN), including intellectualization and isolation; 4. turning aggression against self (TAS); and 5. reversal (REV), i.e. responding in a positive or neutral fashion to a frustrating object including negation, denial, reaction formation and repression. The DMI measures personality structure rather than mood states such as anxiety or depression (Gleser and Ihilevich, 1969; Tauschke et al., 1991).

The Multi Health Locus of Control (MHLC) examines the perceptions of three factors that influence health (Wallston et al., 1976): Internal locus of control (MHLC-I), indicating that thoughts and actions can directly affect health; External locus of control (MHLC-P), indicating that health depends upon the actions of powerful others (eg doctors); Chance locus of control (MHLC-C), indicating that health is dependent on fate.

In an attempt to measure prior feelings about the test outcome, we have categorized 'pessimism' by the statement "I'm certain/I often think that I will get HD", and 'optimism' by the statement "I'm certain/I often think that I will not get HD". Having 'no expectancy' was categorized by: "I don't know whether or not I will get HD". The anticipated impact of either test result was measured by means of an attitude questionnaire which has been described elsewhere (Tibben et al., 1993).

Statistical analyses

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS). Stepwise backwards logistic regression analyses were used to assess the main effect of the psychological variables. We took also into account the possible effect of the covariates age, gender and time-lag (i.e. the time a participant had been familiar with HD in the family), given that our study sample is not randomized. The dichotomous dependent variable in the first analysis is gender (female coded as 1; male coded as 0). In the second analysis we created the following subsamples with respect to expected DNA-test outcome: optimism (coded as 0) versus pessimism (coded as 1); optimism (coded as 0) versus 'no expectation' (coded as 1); pessimism (coded as 0) versus 'no expectation' (coded as 1).

RESULTS

Psychological Variables and Gender

Mean values and standard deviations of the psychological scales are presented in Table I. Firstly, we conducted a logistic regression analysis with gender as dependent variable

and, independently entered, the scores in the psychological variables as predictor variables, both adjusted and unadjusted for age and time-lag. The DMI-scale TAS was significantly related to females at risk ($\beta = .21$; 95% CI .07 to .35; $p = .01$), whereas TAO was identified as significantly related to males at risk ($\beta = -.07$; 95% CI -.13 to -.01; $p = .04$). A high MHLC-C was significantly related to males at risk ($\beta = -.17$; 95% CI -.34 to -.01; $p = .05$).

In addition, we employed a backwards logistic regression analysis with gender as dependent variable and all psychological variables as predictor variables, adjusted for age and time-lag. Females could be identified by TAS ($\beta = .22$; 95% CI .08 to .37; $p = .0025$) and males by MHLC-C ($\beta = -.20$; 95% CI -.39 to -.01; $p = .04$).

Table 1. Means and Standard Deviations of Individuals At-Risk for Huntington Disease on DMI, BHS, GHQ and MHLC.

	Males At-Risk (N=25)		Females At-Risk (N=45)		t (df=67)	p
	Mean	SD	Mean	SD		
DMI-TAO	38.7	(8.6)	34.3	(8.1)	2.11	.04
DMI-PRO	39.1	(6.0)	37.7	(5.8)	.91	ns
DMI-PRN	46.7	(5.9)	47.9	(6.0)	-.77	ns
DMI-TAS	33.7	(6.1)	38.7	(5.4)	-3.53	.01
DMI-REV	41.8	(7.0)	41.7	(7.5)	.05	ns
BHS	4.3	(4.3)	4.8	(3.3)	-.63	ns
GHQ	6.7	(7.4)	11.7	(13.8)	-1.68	ns
MHLC Internal	11.8	(3.3)	13.5	(3.7)	-1.83	ns
Powerful O.	16.4	(4.0)	16.3	(3.7)	.10	ns
Chance	14.4	(3.3)	12.6	(3.3)	2.22	.03

*Note: TAO=Turning against Others; PRO=Projection;
PRN=Principalization; TAS=Turning against Self; REV=Reversal;
BHS=Beck Hopelessness Scale; GHQ= General Health Questionnaire; MHLC=Multi Health Locus of Control*

Psychological Variables and Expected Outcome

Test candidates were asked about prior expectancies on the DNA-test outcome. Significantly more females (42%) than males at risk (16%) expected an unfavorable test result i.e. identifying them as carrier of the HD gene. We conducted a backwards logistic regression analysis on three sets of subsamples drawn from the total sample on the basis

of the expected test outcome, after adjustment for the covariates of age, gender and time-lag. No differences were found between pessimists and optimists, when adjusted for the covariates (Table II-A).

Table II-A. Final Model after Backwards Logistic Regression Analysis of Expected Outcome with DMI-scales, BHS, GHQ and MHLC (0=Optimism N=18; 1=Pessimism N=22)

Variable	β	95% CI	p
TAO	-.50	-.84;-.15	.01
REV	-.39	-.70;-.08	.01
BHS	.43	.08;. 79	.02

Note: TAO=Turning against Others; REV=Reversal; BHS=Beck Hopelessness Scale

However, when unadjusted, optimists could be identified by TAO and REV, whereas pessimists could be identified by hopelessness (BHS).

When optimism was compared to 'no expectation', after adjustment for gender, age and time-lag, this showed that only hopelessness could identify 'no expectation' ($\beta = .41$; 95% CI .04 to .79; $p = .03$).

With respect to pessimism versus 'no expectation', TAO and TAS were related to 'no expectation' and general health (GHQ) with pessimism (Table II-B).

Table II-B. Final Model after Backwards Logistic Regression Analysis of Expected Outcome with DMI-scales, BHS, GHQ and MHLC (0=Pessimism N=22; 1=No Expectation N=30)

Variable	Unadjusted			Adjusted*		
	β	95% CI	p	β	95% CI	p
TAO	.26	.06; .46	.01	.25	.06; .44	.01
TAS	.19	.01; .37	.05	.18	.01; .36	.05
MHLC-P	-.25	-.49;-.01	.05			
GHQ	-.10	-.18;-.02	.02	-.11	-.19;-.33	.01

*Note: TAO=Turning against Others; TAS=Turning against Self; MHLC=Multi Health Locus of Control (Powerful Others) * adjusted for Gender, Age and Time-lag; MHLC-P was removed from the model*

As is shown in Table III-A, current feelings of hopelessness and health complaints are significantly related with the anticipated impact of test outcomes. Candidates with health problems (GHQ) and feelings of hopelessness (BHS) expected adverse effects after an unfavorable test result. Individuals with health complaints expected that a decreased risk would induce relief.

Table III-A. Significant Correlations of The Anticipated Impact Of Receiving Testing Results, and Hopelessness (BHS), General Health (GHQ)

An Increased Risk:	BHS	GHQ
1. Will allow me to better plan the future of my family		-.23*
2. Will increase my problems		.21*
3. Will make me avoid my relatives	.24*	.35**
4. Will decrease the quality of my life	.24*	.35**
5. Will cause me to become depressed	.33**	.23*
A Decreased Risk:	BHS	GHQ
1. Will decrease my problems		-.24*
2. Will cause my mood to improve		-.23*
3. Will increase the quality of my life		-.24*

* $P < .05$; ** $P < .01$

PRO was correlated with the expectation that an increased risk will increase the partners' problems (see Table III-B). Anticipation of increased problems for the children was correlated to TAO and inversely correlated with TAS. REV, including denial and repression, is inversely correlated to expected depression after an increased risk result.

Table III-B. Significant Correlations of the Anticipated Impact of Receiving an Increased Risk At Testing, and DMI-subcales

An Increased Risk:	DMI				
	TAO	PRO	PRN	TAS	REV
1. Will allow me to better plan my own future			.20*		
2. Will increase the problems of my partner		.23*			
3. Will increase the problems of my children	.22*			-.21*	
4. Will cause me to become depressed					-.20*

*Note: TAO=Turning against Others; PRO=Projection; PRN= Principalization; TAS=Turning against Self; REV=Reversal; * $p < .05$*

DISCUSSION

Psychological Variables and Gender

Male test candidates turned their anger and anxiety significantly more against the outer world, whereas females turned those feelings against themselves. However, this gender difference is not specific for individuals at-risk for HD (Cramer, 1988). Social role patterns may account for this difference.

Males believed that their health is dependent on chance, which reveals that they neither rely on health care professionals nor on themselves with respect to their future. Although this might be realistic given in awareness that there is no cure for HD, they might also exclude themselves from professional support.

Females showed a trend, though not significant, towards relying on themselves with respect to their health and prospects. With respect to HD, however, this might be an illusion since they may become subject to an incurable disorder. Relative adjustment may be undermined when there is no congruence between control beliefs and objective circumstances in a progressive illness such as HD (Christensen et al., 1991).

We found that more females than males informed their intimate partner about the risk of HD, and more readily acknowledge the impact of their genetic risk on their relationship (Tibben et al., 1993). Moreover, since women are more involved with the reproductive process, they might experience more often the far-reaching consequences of their being at-risk and, consequently, of a test outcome.

Psychological Variables and Expected Outcome

After adjusting for the covariates, the psychological variables failed to differentiate between pessimists and optimists (Table II-A). Unadjusted, however, optimistic candidates could be identified by two defence mechanisms, TAO (avoidance) and REV (denial). Optimists based their expectations (unjustified!) most often on absence of early signs, and differences with affected parent with respect to personality and behaviour. They seem to be more concerned about their children than about themselves, since TAO was significantly correlated with an expected increase of problems for their children and REV was inversely correlated with depression. Hence, it might be concluded that TAO and REV enable the optimistic candidate to cope with the pre-test distress and adequately overcome the distress of the awaited test results (Scheier et al., 1986; Mahl, 1971). Too strong a reliance on reversal, however, has generally been found to be associated with poor coping capacities and restriction of personality in the long term. Moreover, extreme

and externally expressed anger towards others might even result in psychosocial maladjustment (Gleser and Ihilevich, 1969).

Pessimistic candidates could be identified by hopelessness, which was correlated with adverse effects upon quality of life after an increased risk was diagnosed, and was also expected to lead to avoidance of relatives. They mentioned preparing for the worst, identification and comparison with the affected parent, and preoccupation with early signs as the most significant reasons to expect an unfavorable result. They apparently face the burden of an increased risk for HD by allowing threatening feelings to arise more than optimists. This defensive pessimism might enable them to gradually adjust to the potential distress that a positive HD-diagnosis might bring. However, too much avoidance on the long term might be inadequate and could lead to exerting a premature patient-role with subsequent adjustment disorders and marital conflicts (Mahl, 1971).

The 'no expectation' group could be identified by hopelessness, when compared to optimists. We hypothesize therefore that candidates with 'no expectation' adapt to the distress by cognitively acknowledging the threat but also temporarily isolating their feelings. This might enable them to feel less overwhelmed by an unfavorable test result and subsequently, to be better prepared to accept the outcome.

TAO and TAS, readily identified the 'no expectation' group (Table II-B), when compared to the pessimistic individuals, who could be identified by current health complaints (GHQ). Less specific defence activity might reveal that pessimists suffer more from anxiety, general health complaints and preoccupation with early signs of HD. This might also explain why pessimists tend to more rely their health on 'powerful others' like doctors (MHLC-P).

Many of the test candidates stated that they had no prior expectancy about either a positive or a negative test outcome. However, it is hardly conceivable that individuals at-risk never fear or think about the test outcome. Compared with pessimistic individuals, the 'no expectation' group could be identified by TAO and TAS. Therefore, we hypothesize that the 'no expectation' group negated a possible test result in order to ward off the accompanying anxiety.

Defenses can temporarily relieve a person of his untoward feelings; as such these too are adaptive. Extensive use of defenses is expected to be highly maladaptive when the reality of either a decreased or an increased risk is ultimately avoided. On the other hand, relative lack of defence activity, and the subsequent overwhelming fears or anger might prevent an individual from taking part in life. Control beliefs may be dependent on the perceived, or absence of treatment prospects. Whether or not these defenses and control beliefs will enable an adequate adjustment after disclosure of the test results, remains to be studied. These data will be important in genetic counseling to identify those individuals

that may have special vulnerabilities for the outcome of predictive testing.

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Chapter 6

On Prediction of Psychological Distress after Presymptomatic DNA-Testing for Huntington's Disease

On Prediction of Psychological Distress after Presymptomatic DNA-Testing for Huntington's Disease

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ABSTRACT

Since 1987, individuals at 50% risk for the heritable Huntington's disease (HD), can be identified as either gene-carrier or non-carrier, using linked DNA-probes. Learning to be a carrier was expected to induce intrusive emotions and avoidance behavior and subsequent adjustment problems. This study examined 6-month follow-up distress in 29 carriers and 44 non-carriers, using the Impact of Event Scale. The most important finding was that high distress, 6 months after learning about the result, could not significantly be explained by an unfavorable test outcome. The total distress effect could be best predicted by the stress level, experienced 1 week after disclosure, in both HD-carriers and non-carriers. Intrusion and avoidance remained high after 6 months in some of the test candidates, indicating a working through process. Others denied the impact of the test results. It appears that the working through process after receiving a test result takes longer than 6 months.

INTRODUCTION

Huntington's disease (HD) is a late onset inherited neurodegenerative disorder, characterized by involuntary movements, changes in behavior, personality and cognitive impairment (Hayden, 1981; Harper, 1991). Children of an affected parent are at 50% risk of being affected in later life by HD. Although the average age of onset is 40 (\pm 12) years with a range of 2-75 years (Roos et al., 1991), at-risk individuals can never be sure of having escaped HD.

Recently, new developments in presymptomatic DNA-testing for an increasing number of heritable disorders mean that it is now possible to detect the genetic status in relation to a defined disorder. Thus, individuals at 50% risk for HD might have their risk modified to \pm 98% (gene-carriers) or \pm 2% (non-carriers). This more accurate risk determination might give at-risk individuals options that could generally improve the quality of their

lives (Bloch et al., 1989). On the other hand, presymptomatic diagnosis could also lead to major psychological and social difficulties, including preoccupation with symptoms of the future disease, depression, and suicidal ideation (Markel et al., 1987; Meissen and Berchek, 1987; Kessler et al., 1987). Identification as a gene-carrier can be regarded as a threat to one's life, to one's physical integrity, or to one's children, according to the DSM-III-R (American Psychiatric Association, 1987).

The link between traumatic life events and subsequent psychological symptomatology has been regarded earlier (Freud, 1916; Lindemann, 1944, Horowitz, 1976). Systematic research has been carried out for a variety of traumatic events like natural disasters, wars and diseases, which are generally not predictable (Horowitz et al., 1979; Horowitz et al., 1984; Schwarzwald et al., 1987; Landsmann et al., 1990). Consequently, most studies have been retrospective. Since the development of DNA-technology enabled accurate prediction of late onset genetic diseases, a number of prospective studies have been carried out on the impact of testing for HD (Brandt et al., 1989; Craufurd et al., 1989; Meissen et al., 1991; Bloch et al., 1992; Tibben et al., 1992a).

Recently, we have reported that, preceding the disclosure of DNA-test results, most test candidates denied or minimized the possible adverse effects of an unfavorable test result. Moreover, test candidates sought, above all, control over their future (Tibben et al., 1992b). Furthermore, female candidates tended to turn their unacceptable feelings against themselves and had the opinion that health and future prospects depend on themselves, whereas males turned their unacceptable feelings to the outer world and tended to base their future prospects on chance (Tibben et al., 1992c).

In order to more fully evaluate the presymptomatic testing program, we studied the psychological effects of receiving test results. The main emphasis was addressed to the psychological adjustment of being either a gene-carrier or a non-carrier. Using the stress response theory of Horowitz (1976; 1990), our conclusions lead us to believe that tested individuals may experience intrusive emotions, both prior and subsequent to the DNA-test, but they may also consciously attempt to avoid these emotions. The long term psychological adjustment may depend on the patterns of intrusion and avoidance. Here we report on the stress reactions of 73 consecutively tested applicants, one week and 6 months after having received the test results.

TABLE 1. General Characteristics of the Survey Population

	Gene-Carriers				Non-Gene-Carriers			
	Male N=9 (31%)		Female N=20 (69%)		Male N=18 (42%)		Female N=26 (59%)	
Age (range)	30.7 (19-46)		31.6 (18-59)		34.1 (20-61)		31.8 (19-46)	
	N	(%)	N	(%)	N	(%)	N	(%)
Marital Status	4	(44)	6	(30)	5	(28)	5	(19)
Single	3	(33)	8	(40)	8	(44)	13	(50)
Married	2	(22)	4	(20)	4	(22)	6	(23)
Common-law	0		2	(10)	1	(6)	2	(8)
Divorced								
Children								
0 children	5	(56)	10	(50)	13	(72)	17	(65)
≥ 1 child	4	(44)	10	(50)	5	(28)	9	(35)
Sibs								
0 sibs	1	(11)	1	(5)	0		1	(4)
1 sib	2	(22)	6	(30)	5	(28)	8	(31)
≥ 2 sibs	6	(67)	13	(65)	13	(72)	17	(65)
Education Level								
Elementary school/ Lower vocat. school	4	(44)	8	(40)	7	(39)	7	(27)
≥ High school	5	(56)	12	(60)	11	(61)	19	(73)
Reasons for Testing*								
Preparation for future	5	(56)			1	(6)	3	(12)
Relief uncertainty	4	(44)	19	(95)	14	(78)	17	(65)
Family planning	4	(44)	13	(65)	10	(56)	11	(42)
Informing children	1	(11)	5	(25)	1	(6)	5	(19)
Assisting research			3	(12)	2	(11)	2	(8)

* more than 1 reason could be given

PARTICIPANTS AND METHODS

Participants

Presymptomatic testing for HD was offered at the Clinical Genetics Center in Leiden, The Netherlands, from October, 1987. Inclusion criteria were: age over 18 years, absence

of major mental illness or suicidal plans following an unfavorable result, no clinical signs of HD and the ability to give informed consent.

The counselling protocol and linkage analyses have been presented elsewhere (Skraastad et al., 1991). The DNA-test is currently informative in >90% of the applicants provided that sufficient data on affected and unaffected relatives is available. The reliability is often higher than 96%.

This study reports on 73 at-risk individuals who were informed about risk modification between April 1, 1989, and March 31, 1991. Characteristics of the study population are shown in Table I. The male/female ratio was 1:2. Twenty-nine individuals received an increased risk result ($\pm 98\%$), identifying them as gene-carriers; 44 individuals were identified as non-carriers (decreased risk to $\pm 2\%$). Criteria for enrolment in the psychological follow-up study were: 1. DNA-testing was potentially possible as evidenced by a suitable family structure and availability of DNA samples from affected and non-affected relatives; 2. Ability to understand the questionnaires; 3. Informed consent. A more detailed description of the test candidates is reported elsewhere (Tibben et al., 1992b). The research protocol was approved by the Medical Ethics Committee of the University Hospital of Leiden.

Procedure

At the first counselling session, the test candidates were given an introduction to the research protocol and asked for their consent to participate in a follow-up study on the psychosocial consequences of the test outcome. The quantitative part of the study involved completion of a psychometric battery, including the Impact of Event Scale (IES). In this article, we report on the levels of psychological distress, as measured by the IES. The IES was administered at baseline, one week and 6 months after disclosure of the DNA-test results.

The IES is a reliable, self-report scale for measuring the current degree of subjective impact experienced as a result of a specific event (Horowitz et al. 1979; Zilberg et al., 1982; Schwarzwald et al., 1987). Horowitz has suggested that the 15 items of the IES should be coupled to the specific stress factor, i.e. Huntington's disease. The IES summarizes the influence of HD on two major dimensions, i.e. 1. *intrusion* into consciousness of unwanted ideas and feelings, and 2. consciously recognized *denial-avoidance*. The two subscales indicate symptoms on the dimensions that are characteristic for the DSM-III diagnosis of post-traumatic stress disorder (Horowitz et al., 1979; Horowitz et al., 1984). Originally, the IES contained 7 items forming an Intrusion subscale, and 8 items forming an Avoidance subscale. The IES was chosen for its

suitability in assessing test candidates over time, and comparison of the degree of distress among subgroups (e.g. male/female, gene-carrier/non-carrier).

Statistical analyses

All data analyses were obtained using the Statistical Package for the Social Sciences (SPSSPC). Pearson product-moment correlations were calculated for the biographical variables, i.e. gender (male=0, female=1), age and timelag (years that had elapsed since the test candidate learned about HD in the family), the DNA-test outcome (carrier=1; non-carrier=0) and the levels of pre- and post-test psychological stress, as measured by the IES (Stress). We defined Stress as the highest score on either the *intrusion* or the *avoidance* subscale (see further: Results: structure of IES).

The contribution of the single prognostic stress variables, biographical variables and DNA-test outcome was studied in relation to stress, 6 months after disclosure of the test results. We employed multiple regression analyses with long term stress (Stress3, 6 months after disclosure) as outcome variable and the pre-test (Stress1), short term post stress (Stress2, 1 week after disclosure), the DNA-test outcome, and the first order interaction terms, as prognostic variables. We adjusted for gender, age and timelag, since these variables might confound the relationships of the significant prognostic variables with the outcome measure. In addition, all candidate prognostic variables and the interactions were entered in regression analyses, both backward and stepwise, with Stress3 as outcome variable. After the prognostic variables ($P < 0.10$) were identified, they were entered in multiple regression analyses in 3 stages: (1) Stress1 and biographical variables; (2) Stress1 and biographical variables, added with the DNA-test outcome; (3) the pre-test variables and DNA-test result, added with Stress2. Models were thus fitted using stepwise and backward approach. The identified final model had to meet stronger criteria (P for entry < 0.05 , P for removal > 0.055).

RESULTS

Structure of the IES

Since the IES has not previously been used in presymptomatic testing programs, we performed a principal factor analysis followed by oblimin rotation, in order to determine the structure of the scale for use in our specific population at-risk for HD.

Table II. Results Factor Loadings for Two-Factor Forced Solution of the Items of the Impact of Event Scale: Items Selected for the Intrusion (1) and Avoidance Subscale (2)

	Factor ¹⁾	
	1	2
<u>Selected Intrusion Items</u>		
1. I thought about Huntington's Disease (HD) when I didn't meant to	.80*	-.04
2. I avoided letting myself get upset when I thought about HD or was reminded of it	.78*	-.15
4. I had difficulty falling or staying asleep because of images or thoughts related to HD	.63*	.19
5. I had waves of strong feelings about HD	.72*	.17
10. Images about HD popped into my mind	.84*	-.04
11. Things I saw or heard suddenly reminded me of HD	.65*	.12
14. Any reminder of HD brought back feelings about HD	.76*	.10
<u>Selected Avoidance Items</u>		
12. I knew that I still have a lot of feelings about HD, but I didn't want to think about it	.24	.64*
13. I tried not to think about HD	.10	.78*
15. My feelings about HD were kind of numb	.13	.63*
<u>Not Selected Items</u>		
3. I tried to remove HD from my memory	.56	.33
6. I had dreams about HD	.57	-.04
7. I stayed away from things or situations that might remind me of HD	.14	.41
8. I felt so unrealistic about it, as if nothing had happened	-.23	.74*
9. I tried not to talk about HD	.12	.47

¹⁾ factor 1=Intrusion; factor 2=Avoidance; *) selected items

Items were selected if they met the criterion of a loading ≥ 0.60 on one factor (either intrusion or avoidance) on the one hand, whilst the loading on the other factor was lower than 0.25, and vice-versa. The resulting two-factor forced solution yielded two factors (see Table II): an Intrusion factor (items 1,2,4,5,10,11 and 14), and an Avoidance factor (items 8,12,13 and 15). Loadings of the intrusion factor ranged from 0.62 to 0.84, whereas loadings on the avoidance factor ranged from 0.63 to 0.78.

Coefficients of internal consistency (Cronbach's alpha) for the 7 items of the intrusion factor and the 3 items of the avoidance factor were 0.89 and 0.81, respectively. The intercorrelation (Spearman's rank correlation) of both factors were 0.58 (pre-test), 0.67 (1 week after disclosure) and 0.67 (6 months after disclosure), indicating that both factors are substantially interrelated, and hence reflect a single dimension of general stress.

Despite the satisfactory loading, item 8 was removed because the content of the item differed basically from the other 3 avoidance items. The internal consistency (Cronbach's alpha) proved highest when this item was deleted.

We postulate that the highest score on either the intrusion or the avoidance subscale indicates the subjective impact of HD. Thus, we have considered the highest of both scores as the lower limit of the level of stress as response to the disclosure of the test results. Subsequently, we decided to take the highest Z-scores of either the intrusion or the avoidance subscale. Thus, Stress1 was the highest individual score at pre-test, Stress2 was the highest score 1 week after disclosure, and Stress3 the highest score, 6 months after the test.

Descriptive analyses

The means and standard deviations for each of the prognostic and outcome variables in the carriers and in the non-carriers are presented in Table III. Carriers of HD showed a significantly shorter timelag (years that had elapsed since the test candidate learned about HD in the family) than non-carriers. Intercorrelations of the outcome variable and prognostic variables for the whole sample are presented in table IV. Both intrusion and avoidance, were pre- and post-test significantly correlated. Both dimensions proved to be independent of the biographical variables and the DNA-test result.

Predictability of Post-test Stress

We studied the predictive value of the biographical variables, the level of Stress1 and Stress2, and the DNA-test outcome. Hence, we firstly conducted a regression analysis with Stress3 as outcome variable and, independently entered the prognostic variables, adjusted for age, gender and timelag (See Table V for the highest standardized coefficients). Both Stress1 and Stress2 significantly predicted the level of stress after 6 months. Females showed a significant higher level of long term stress than males. The stress level after 6 months could not be predicted by the DNA-test outcome. Test results and gender had only predictive value in interaction with high pre-test stress and high stress, 1 week after disclosure. Age and timelag were not related to stress.

Table III. Means and Standard Deviations of Outcome Measures and Prognostic Variables

Variable	Gene-carriers N=29		Non-Carriers N=44		t (df)
	Mean	Sd	Mean	Sd	
Age	31.3	9.8	32.6	10.1	.55 (71)
Timelag (years)	6.3	5.1	10.8	7.5	2.73 (67) ¹⁾
<u>Pre-test</u>					
Intrusion1 ²⁾	16.4	6.6	14.8	5.1	1.10 (64)
Avoidance1	5.1	2.7	5.8	2.7	1.09 (63)
<u>Post-test</u>					
<i>(after 1 week)</i>					
Intrusion2	16.2	6.2	14.3	5.4	1.37 (70)
Avoidance2	5.2	2.5	4.9	2.5	.45 (70)
<i>(after 6 months)</i>					
Intrusion3	15.0	6.0	12.5	5.0	1.92 (68)
Avoidance3	5.4	3.1	4.6	2.2	1.36 (68)

¹⁾ $p < 0.01$; ²⁾ scores were based on 7 items for Intrusion (range 7 - 28), and 3 items for Avoidance (range 3 - 12)

In addition, we conducted a stepwise and backwards regression analysis with Stress1, Stress2, the biographical variables and their mutual first order interactions as prognostic variables (Table VI). The final solution yielded one variable: the interaction of Stress1 and gender. A high stress level in the long term could be predicted for female test candidates with a high level of stress.

Table IV. Intercorrelations between the Prognostic Variables and Outcome Measures

Prognostic Variables	IES3		DNA-Test Result
	Intrusion	Avoidance	
<u>Pre-Test</u>			
Gender (0= male; 1 =female)	.22	.13	.12
Age	.06	.05	-.07
Timelag	.01	.05	.15
Intrusion	.65*	.47*	.14
Avoidance	.54*	.45*	-.14
DNA-test			
(0=non-carrier; 1=carrier)	.23	.16	-
<u>Post-Test</u>			
Intrusion (after 1 week)	.72*	.50*	.16
Avoidance	.58*	.73*	.05
Intrusion (after 6 months)	-	.67*	-
Avoidance	-	-	-

*Note: IES=Impact of Event Scale; * $P < 0.001$*

The gender effect disappeared when we added the DNA-test outcome as prognostic variable. This resulted in two variables, Stress1 and the DNA-test outcome, which accounted for the variance in the Stress3. The significant increase in the R^2 indicates that the DNA-test outcome has significantly improved the fit of the equation predicting the Stress3 level.

Finally, we added Stress2 and its interactions with the stage 2 variables. After accounting for the Stress1 level and the DNA-test results, Stress2 explained the additional variance in Stress3.

Table V. Predictability of Long Term Stress (6 months after disclosure of DNA-test Results) by Single Multiple Regression Analysis

Prognostic variables	Adjusted ¹⁾		
	β^2	95% CI ³	P ⁴
DNA-test (0=non-carrier; 1=carrier)	.21	-.03;.45	.09
Stress1(pre-test) ⁵⁾	.61	.43;.79	.001
Stress2(1 week after disclosure)	.75	.59;.91	.001
Stress1xDNA	.46	.26;.66	.001
Stress1xGender (male=0,female=1)	.50	.30;.70	.001
Stress2xDNA	.57	.37;.77	.001
Stress2xGender	.52	.32;.72	.001
Stress12xDNA ⁶⁾	.23	-.01;.47	.06

¹⁾ adjusted for gender, age and timelag; ²⁾ standardized regression coefficient; ³⁾ 95% Confidence Interval; ⁴⁾ significance level; ⁵⁾ Stress1 and Stress2: highest score on either Intrusion or Avoidance; ⁶⁾ Stress12: highest score on either Stress1 or Stress2

The DNA-test outcome, was only modestly related with high Stress3. Female carriers with a high Stress1 were found to have a higher Stress3. Timelag was inversely associated with Stress3: the shorter a test candidate was familiar with HD, the higher Stress3.

Table VI. Predictability of Long Term Stress3 by Multiple Regression Analysis for the joint prognostic variables

Prognostic Variables	$\beta^{1)}$	95% CI ²⁾	P ³⁾
Stage 1:			
Stress1xGender ⁴⁾ (males=0; females=1)	.52	.32;.84	.001
MR = .52			
MR ² = .27			
MR ² adj = .26			
Stage 2:			
Stress1	.62	.44;.80	.001
DNA-test result (non-carrier=0; carrier=1)	.20	.02;.38	.03
MR = .66			
MR ² = .43			
MR ² adj = .42			
Stage 3:			
Stress2	.59	.41;.77	.001
DNA-test result	.17	.02;.32	.03
Stress1xDNA	.17	.01;.33	.04
Stress1xGender	.16	-.01;.33	.08
Stress2xTimelag	-.13	-.27;.01	.10
MR = .80			
MR ² = .64			
MR ² adj = .62			

¹⁾ standardized regression coefficient; ²⁾ 95% Confidence Interval; ³⁾ significance level;

⁴⁾ Stress1, Stress2 and Stress3: highest Z-score on either Intrusion or Avoidance

DISCUSSION

The structure of the IES

Generally, the IES proved to be appropriate for the measurement of the impact of Huntington's disease in HD carriers and non-carriers. We have found that the factors of intrusion and avoidance played a significant role in pre- and post-test stress. These observations have already been reported by others when measuring stress caused by a variety of other events (Horowitz et al., 1979; Zilberg et al., 1982; Weissenberg et al., 1987; Schwarzwald et al., 1987; Solomon and Mikulincer, 1988). There were, however, some discrepancies between our findings and these reports. In some studies, all items of the IES were included in one or the other of both factors, regardless of the magnitude of the loading (Horowitz et al., 1979; Zilberg et al., 1982). Like others, we removed some items (Table II) because of insufficient loading (Schwarzwald et al., 1987).

Horowitz et al. (1979) found a correlation of 0.42 between the intrusion and avoidance factor, reflecting that the two variables are associated but do not measure identical constructs. In this current study, we have found correlations on the consecutive measurement points of 0.58 (pre-test), and 0.67 (post-test) respectively. Other studies have also reported two factors with high correlations (0.53 - 0.78), reflecting a single dimension of psychological distress (Solomon and Mikulincer, 1988; Schwarzwald et al., 1987; Zilberg et al., 1982).

Experimental studies, which were mostly retrospective, have confirmed that the working through of a serious life event, is often characterized by alternating phases of intrusive thoughts and feelings and of ideational denial and emotional numbing (Horowitz et al., 1979; Horowitz et al., 1980; Horowitz et al., 1984). We expected that these effects would also occur in both carriers and non-carriers of HD and our results confirmed our expectations for individuals with moderate or high levels of stress. Individuals with low levels of both intrusion and avoidance might manifest denial, and their working through of the test results, i.e. experiencing the oscillating process between intrusion and avoidance, might be postponed until some future date.

In most test candidates, the levels of intrusion and avoidance, both pre- and post-test, proved to be equally high. Similar observations were noted after other recently experienced stressful events (Solomon and Mikulincer, 1988; Schwarzwald et al., 1987; Zilberg et al., 1982). We therefore propose that after a long period (> 1 year), different patterns of intrusion and avoidance may be observed, e.g. low intrusion/high avoidance or high intrusion/low avoidance. Extended longitudinal follow-up after testing for HD may elucidate this important point, and also indicate whether the stress patterns associated with

pathological reactions, might eventually lead to post traumatic stress or adjustment disorders. These data will enable to determine stress level and patterns and thereby indicate a need for psychological intervention. The psychological functioning of individuals with different IES scores will be addressed in a separate study.

Predictability of distress

The most important finding from this study is that the DNA-test outcome did not significantly contribute to the amount of stress after 6 months. This corroborates the current experience that gene-carriers generally cope well with the test outcome (Brandt et al., 1989; Craufurd et al., 1989; Huggins et al., 1992; Tibben et al., 1992a). However, carriers also denied or minimized the implications of the test outcome, which might explain the absence of distress in some of them (Tibben et al., 1992d). Moreover, non-carriers reported not only relief from uncertainty, but also guilt feelings and depressive reactions. Half of the non-carriers found no relief after the test outcome, and a third sublimated their guilt feelings by exaggerated overattention for at-risk or affected relatives (Tibben et al., 1990; Tibben et al., 1992b,d; Huggins et al., 1992).

Another important finding is that the level of distress related to HD, as measured 1 week after the disclosure of the DNA-test, accounted for most of the variance in the distress after 6 months. This indicates that test candidates who were extremely affected by the test result (high stress level) still suffer from the burden of HD, irrespective of the outcome of the test. Six months may actually be too short a period to reach a point of psychological adjustment. This supports our earlier suggestion that tested individuals may need years, rather than months, to adapt to their new genetic status and that this applies both to identified HD carriers and non-carriers. The need for adaptation in the latter group has been previously indicated (Tibben et al., 1992a) and is substantiated by the present results.

Individuals who were less distressed 1 week after disclosure, remained at that level for the ensuing 6 months. The absence of either intrusion or avoidance, may reflect denial or minimisation of the test result and its impact. This could indicate a (temporary) postponement of working through the test result and its consequences. Adequate as that may be, on a short term basis, it has yet to be determined whether long term absence of the working through process does not restrict the personal capacities and development, and eventually lead to inadequate psychological adjustment (Mahl, 1971).

Test candidates who were highly distressed in the first counselling session (pre-test) and who would eventually prove to be gene-carrier, reported much stress 6 months thereafter. They may have been very uncertain and preoccupied with early symptoms which

prompted them to seek certainty and hoping for a favorable result. The bad outcome has confronted them more than ever with the devastating illness.

Female test candidates were more distressed, 6 months after receiving the test result than males. Females more often discussed HD and the test with their partners than males did (Tibben et al., 1992a). Prior to the test, females turned their unacceptable feelings against themselves and suffered from health complaints, whereas males turned these feelings toward others. Furthermore, females tended to rely their health and future prospects on themselves, whereas males relied on chance. These findings may indicate that, female test candidates may be more able to face their fear and to acknowledge the implications of testing (Bloch et al., 1989; Tibben et al., 1992a,b). Men may have a greater capacity to deny their feelings. Moreover, women may rather experience a double burden: their personal being at-risk and the possible consequences for their (prospective) offspring.

Finally, the shorter test candidates were familiar with HD and their being at-risk, the more distress was experienced, 6 months after test disclosure. A number of test candidates applied for the test soon after they had first learned about HD in their family. They might not have had the opportunity to accommodate slowly to the full implications of HD in their life, like others who grew up in the knowledge of HD. They may have underestimated the impact of testing and its outcome when they, perhaps impulsively, applied for the test. Tyler et al. (1992) have suggested that people who only recently learned about their being at-risk, should be advised to postpone DNA-testing, at least for one year, in order to fully comprehend the implications of either result.

In conclusion, our findings indicate that, irrespective of the test results, in some tested individuals distress may be present for periods longer than 6 months. Longer observation periods (> 6 months after disclosure) are required to study changes of distress over time.

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Chapter 7

Presymptomatic DNA-Testing for Huntington's Disease: Identifying the Need for Psychological Intervention

Presymptomatic DNA-Testing for Huntington's Disease: Identifying the Need for Psychological Intervention

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ABSTRACT

In the Dutch predictive DNA-testing program for Huntington disease, 73 individuals (29 gene-carriers, 44 non-carriers) were followed-up 6 months after receiving test results. Psychological adjustments were measured with the Impact of Event Scale, the Beck Hopelessness Scale, the General Health Questionnaire and the Social Support Questionnaire. The strength and uniqueness of this study is that we have built a prognostic model aimed at identifying individuals at risk for psychological maladjustment. It was found that: 1. the more that applicants suffered from intrusive feelings about HD and tried strongly to avoid HD-related situations, prior to the test, the greater the chance that they will experience this 6 months after the test if they subsequently proved to be carrier; 2. the more that both carriers and non-carriers who suffered from the potential threat of having HD tried to avoid HD-related situations prior to the test and the less contented they were with available support, the greater the chance that they will show avoidance behavior after the test; 3. the more pessimistic that carriers as well as non-carriers were about their future when they applied for the test, the more they avoided situations that might confront them with HD and the more dissatisfied they were about their available support (pre-test), the greater the chance that they will become depressive and suicidal.

The relevance of contentment with the (marital) relationship is discussed.

Psychological adjustment was also studied as a function of a. intrusion/denial-avoidance pattern over time and b. healthy mental functioning/future expectancies. Most carriers (86%) seem to cope well thus far, although this was based largely on strong psychological defenses and dependent on satisfactory relationships. Five carriers (17%) had either health complaints and/or extreme pessimistic expectancies. They were not able to face the consequences of the test result and showed an increase of denial-avoidance behavior thereafter.

Most non-carriers (80%) appear to have worked through the test result. Seven out of 9

non-carriers, identified as possible psychopathological cases with pessimistic expectancies, had less intrusive feelings than prior to the test. This group could later develop severe problems with detachment from their previous life style and also with adapting to their new genetic status.

We conclude that DNA-testing has shown benefits for most tested individuals. However, a considerable number are at-risk for maladjustment and should be offered additional help. Further studies as to whether the strong defenses in carriers safeguard adequate adjustment in the long term should be undertaken.

INTRODUCTION

Huntington's disease (HD) is an incurable, late onset, autosomal dominant inherited neurodegenerative illness, characterized by unintended choreatic movements, changes in behavior, personality and cognitive impairment (Harper, 1991). Children of an affected parent are at 50% risk of becoming affected in later life by HD. The average age of onset is 40 (\pm 12) years (Roos et al., 1991).

The localization of the Huntington gene to the short arm of chromosome 4 using DNA-probes has introduced the possibility of risk modification by linkage analysis to either an increased risk (\pm 98%; gene-carriers) or to a decreased risk (\pm 2%; non-carriers) in informative families (Gusella et al., 1983). This more accurate risk determination might give at-risk individuals options that could generally improve the quality of their lives (Bloch et al., 1989). On the other hand, presymptomatic diagnosis has been also expected to lead to major psychological and social difficulties, including preoccupation with impending symptoms, depression and suicidal ideation as evidenced from inventories in risk carriers before the actual introduction of the test (Markel et al., 1987; Meissen and Berchek, 1987; Kessler et al., 1987). Identification as a gene-carrier can be considered as a threat to one's (future) life, or to one's children and might therefore lead to adjustment disorders.

Since the development of DNA-technology has enabled accurate prediction of HD, a number of prospective studies have been carried out on the impact of testing (Brandt et al., 1989; Craufurd et al., 1989; Meissen et al., 1991; Fox et al., 1989; Wiggins et al., 1992; Tibben et al., 1993a).

Prior to the disclosure of DNA-test results, most test candidates denied or minimized the possible adverse effects of an unfavorable test result. Moreover, test candidates sought, above all, control over their future (Meissen et al., 1991; Tibben et al., 1993a). Six months after the test, no differences could be found between carriers and non-carriers with regard to the amount of stress (Tibben et al., 1993b), although the causes for any

particular type of distress were obviously different.

Using the stress response theory of Horowitz (1979; 1990), our observations made us suppose that tested individuals may experience intrusive emotions, both prior and subsequent to the DNA-test, but they may also consciously attempt to deny and/or avoid these emotions. In addition, since 80% of the test candidates suffered severely from a future overshadowed by HD, we expected that identified gene-carriers would show an increase of feelings of hopelessness after the result, whereas non-carriers would perceive their future more optimistically. We hypothesized that these variables (intrusion, denial-avoidance and future expectancies) were indicators for the process of working through the test results and psychological adjustment to the new genetic status.

Here we report on the predictability of intrusion, denial-avoidance and perception of the future in 73 consecutively tested applicants, 6 months after having received the test results.

Subsequently, the interrelation of intrusion and denial-avoidance is interpreted on basis of potentially psychopathological states.

PARTICIPANTS AND METHODS

Participants

Presymptomatic testing for HD was offered at the Clinical Genetics Center in Leiden, The Netherlands, from October, 1987. Inclusion criteria were: age over 18 years, absence of major mental illness or suicidal plans following an unfavorable result, no clinical signs of HD and the ability to give informed consent. The counselling protocol and linkage analyses have been presented elsewhere (Skraastad et al., 1991). The DNA-test is currently informative in >90% of the applicants provided that sufficient data on affected and unaffected relatives is available. The reliability is often higher than 96%.

This study reports on 73 at-risk individuals who received DNA-test results between April 1, 1989 and March 31, 1991. Characteristics of the study population are shown in Table I. The male/female ratio was 1:3. Twenty-nine individuals received an increased risk result ($\pm 98\%$), identifying them as gene-carriers; 44 individuals were identified as non-carriers (decreased risk to $\pm 2\%$). Criteria for enrolment in the psychological follow-up study were: 1. Ability to understand the questionnaires; 2. Informed consent. A more detailed description of the test candidates is reported elsewhere (Tibben et al., 1993a). The research protocol was approved by the Medical Ethics Committee of the University Hospital of Leiden.

Procedure

At the first counselling session (pre-test), the test candidates were given an introduction to the research protocol and asked for their consent to participate in a follow-up study on the psychosocial consequences of the test outcome. At the first counselling session and 6 months after disclosure of the test results (post-test), a psychometric battery comprised of the Impact of Event Scale (IES), the Beck Hopelessness Scale (BHS), the General Health Questionnaire (GHQ) and the Social Support Questionnaire (SSQ) was implemented.

The IES measures the current degree of subjective impact experienced as a result of a specific event (Horowitz et al. 1979; Zilberg et al., 1982; Schwarzwald et al., 1987). We coupled the 15 items of the IES to the specific stress factor, i.e. Huntington's disease, as was suggested by Horowitz et al. (1979). The IES summarizes the influence of HD on two major dimensions, i.e. 1. involuntary *intrusion* into consciousness of unwanted ideas and feelings and 2. consciously recognized *denial-avoidance*. Intrusion and denial-avoidance reflect the alternating phases in the process of working through a stressing event (Horowitz, 1990). In a separate study the structure of the IES was determined for use in our specific study population (Tibben et al., 1993b).

The BHS consists of 20 true-false statements which focus on pessimistic expectations concerning oneself and one's future. The scale was considered appropriate for our population, given questions like "I have enough time to accomplish the things I most want to do" and "The future seems vague and uncertain to me". A score (range=0-20) of 9 or more is regarded as a possible predictor of depression and suicidal behavior (Beck and Weissman, 1974; Beck and Steer, 1989; Beck et al., 1990).

The 60-item GHQ is a reliable estimator of psychopathological states, such as depression, anxiety, somatic complaints and social dysfunctioning. A score of 12 or more positive items means a possible psychiatric condition (Goldberg, 1972; Tarnapolsky et al., 1979; Koeter and Ormel, 1992).

We considered the test candidate's access to supportive allies to be of great influence on the psychological and social adjustment after either result. To assess this, we used the 6-item Social Support Questionnaire (SSQ), developed by Sarason et al.(1987). The SSQ consists of 6 items, each with two parts. The first part of each item (SSQM) assesses the *number* of other persons that are available in times of need and includes questions like "Whom can you really count on to be dependable when you need help?" and "Who accepts you totally, including both your worst and your best points?". The second part of each item measures the degree of *satisfaction* with the perceived support (SSQS).

TABLE 1. General Characteristics of the Survey Population

	Gene-Carriers				Non-Gene-Carriers			
	Male N=9 (31%)		Female N=20 (69%)		Male N=18 (42%)		Female N=26 (59%)	
Age (range)	30.7 (19-46)		31.6 (18-59)		34.1 (20-61)		31.8 (19-46)	
	N	(%)	N	(%)	N	(%)	N	(%)
<i>Marital Status</i>								
Single	4	(44)	6	(30)	5	(28)	5	(19)
Married	3	(33)	8	(40)	8	(44)	13	(50)
Common-law	2	(22)	4	(20)	4	(22)	6	(23)
Divorced	0		2	(10)	1	(6)	2	(8)
<i>Children</i>								
0 children	5	(56)	10	(50)	13	(72)	17	(65)
≥ 1 child	4	(44)	10	(50)	5	(28)	9	(35)
<i>Sibs</i>								
0 sibs	1	(11)	1	(5)	0		1	(4)
1 sib	2	(22)	6	(30)	5	(28)	8	(31)
≥ 2 sibs	6	(67)	13	(65)	13	(72)	17	(65)
<i>Education Level</i>								
Elementary school/ Lower vocat. school	4	(44)	8	(40)	7	(39)	7	(27)
≥ High school	5	(56)	12	(60)	11	(61)	19	(73)
<i>Reasons for Testing*</i>								
Preparation for future	5	(56)			1	(6)	3	(12)
Relief uncertainty	4	(44)	19	(95)	14	(78)	17	(65)
Family planning	4	(44)	13	(65)	10	(56)	11	(42)
Informing children	1	(11)	5	(25)	1	(6)	5	(19)
Assisting research			3	(12)	2	(11)	2	(8)

* more than 1 reason could be given

The interrelation between *intrusion* and *avoidance* may reflect the process of working through the test result (Zilberg et al., 1982). According to the theory of Horowitz (1990), it might be expected that the magnitude of oscillations between painful and unwanted intrusions and denial-avoidance decrease over time as the implications of the test result are worked through, leading to relative adjustment to the new genetic status. However, the interpretation of this interrelation in both carriers and non-carriers may depend on both healthy psychological functioning (as measured by the GHQ), the test outcome and perception of the future (BHS). Hence, we distinguished between individuals with high post-test scores (≥ 12) on the GHQ, reflecting possible psychopathology and low (< 12) scores. We also distinguished between high post-test scores (≥ 9) on the BHS, predicting a risk for depression and suicidal behavior and low scores (< 9).

To analyze the interrelation between intrusion and denial-avoidance we took the percentage of change over time in both intrusion and avoidance with the formula: $(score_{pre-test} - score_{post-test}) / (score_{pre-test} - lower\ scale\ limit) \times 100$. A positive change means a decrease in either intrusion or denial-avoidance, a negative change an increase on both dimensions. Hence, in both the figures 1 and 2, four quadrants can be distinguished, e.g. an individual's position in the first quadrant means a decrease of intrusion and an increase of avoidance behavior.

Statistical analyses

All data analyses were obtained using the Statistical Package for the Social Sciences (Norusis, 1990). With regression analyses, the association of the DNA-test outcome with the three outcome measures (intrusion, denial-avoidance and hopelessness) was investigated, adjusted for gender, age and timelag (years that had elapsed since the test candidate learned about HD in the family).

The procedure of predicting the outcome variables was as follows:

Firstly, a regression analysis was performed in order to find out whether the single pre-test psychological variables (intrusion, denial-avoidance, BHS, GHQ, SSQS and SSQN) and the biographical data could predict the outcome variables. Subsequently, the significant single prognostic variables and the first order interaction terms of the psychological baseline variables and the DNA-test outcome were entered in a backward regression analysis. We adjusted for gender, age and timelag, since these variables might confound the relationships of the significant prognostic variables with the outcome measures. These results will be summarized.

Finally, all candidate prognostic variables and the first order interactions were entered in backward regression analyses for all 3 outcome measures (intrusion, denial-avoidance and

hopelessness).

A measure of relative importance is the standardized partial regression coefficient, symbolized by β . This implies that the data were standardized with a mean of 0 and variance of 1. β indicates that e.g. a change of one unit in the predictor variable yields an expected change of β in the outcome variable. The 95% confidence intervals for β indicate that a same population standardized partial regression coefficient are probably (95%) situated within this range. The multiple correlation coefficient (MR) is the correlation between the predictor variable on the one hand and the outcome variables on the other. The higher the MR, the better the prediction of the outcome variable. The range lies between 0.0 (not predictable at all) and 1.0 (perfectly predictable). The squared multiple correlation coefficient (MR^2) equals the variance of the outcome variable, explained by the predictor variable(s). The adjusted MR^2 is an MR^2 statistic adjusted for both the number of predictor variables and the number of patients in the study and an unbiased estimate of the explained variance in the population. The F-test is the significance level for MR^2 .

RESULTS

Prospective gene-carriers and non-carriers did not differ significantly on the psychological and biographical variables at baseline, i.e. the first genetic counselling pre-test session, except that non-carriers had a significantly longer awareness about HD in their family than carriers (timelag) ($t=2.73$, $df\ 67$; $p<0.01$). The DNA-test outcome was not significantly associated with either of the single outcome variables: intrusion, denial-avoidance and hopelessness, indicating that carriers and non-carriers did not differ in this respect (Table II).

Analysis by backward multiple regression of combinations of factors yielded however a final model for **Intrusion**, as presented in Table III. Post-test Intrusion was related to a high degree of pre-test denial-avoidance and intrusion and to an unfavorable result ($F = 17.7$; $p < .001$).

Table II. Predictability of Post-Test¹⁾ Intrusion, Denial-Avoidance and Hopelessness by DNA-Test Outcome (0=Non-Carrier; 1=Gene-Carrier)

<i>Post-Test:</i>	Unadjusted			Adjusted ²⁾		
	β^3	95 % CI ⁴⁾	P	β	95 % CI	P
Intrusion	.18	-.08; .44	.16	.23	-.05; .51	.10
Denial-Avoidance	.19	-.07; .45	.13	.23	-.05; .51	.09
Hopelessness	.20	-.04; .46	.11	.12	-.14; .39	.38

¹⁾ 6 months after receiving the DNA-test results; ²⁾ adjusted for gender, age and timelag; ³⁾ standardized regression coefficient; ⁴⁾ 95% confidence intervals

This means that, the more that a test candidate had suffered from intrusive feelings and ideas prior to the test and the more he avoided HD-related situations, the more likely he/she will suffer from intrusive ideas if he/she proves to be carrying the HD gene, 6 months after receiving the test results.

Table III. Predictability of Post-Test Intrusion (IES), 6 months after disclosure of DNA-test results, by multiple regression analysis

	β^1	95 % CI ²⁾
<i>Pre-test:</i>		
Denial-Avoidance (IES)	.28	.06; .50
DNA-test outcome (carrier=1; non-carrier=0)	.20	.02; .38
Intrusion (IES)	.42	.20; .64
MR	= .66	
MR ²	= .44	
MR ² adjusted	= .41	

¹⁾ standardized regression coefficient; ²⁾ 95% confidence intervals

Post-test **denial-avoidance** (Table IV) could be predicted by pre-test denial-avoidance and pre-test intrusion. High scores on post-test denial-avoidance were also associated with low satisfaction with social support and with the combination of (low) hopelessness and a short timelag ($F = 9.90$; $p < .001$).

Table IV. Predictability of Post-Test Denial-Avoidance (IES), 6 months after disclosure of DNA-test results, by multiple regression analysis

	$\beta^{1)}$	95% CI ²⁾
<i>Pre-test:</i>		
Denial-Avoidance (IES)	.23	.00; .35
Intrusion (IES)	.33	.09; .57
SSQS	-.24	-.42; -.06
Timelag x Hopelessness (BHS)	-.27	-.45; -.09
MR	= .61	
MR ²	= .37	
MR ² adjusted	= .33	

¹⁾ standardized regression coefficient; ²⁾ 95% confidence intervals

This means that if, prior to the test, an individual (prospective carrier or non-carrier) reported that he/she suffered a lot from the burden of HD (intrusive feelings) and tried to deny and escape (avoid) his/her anguish and if he/she was also discontented with the available support and had only recently learned about HD in his/her family, combined with a rather optimistic view, then he/she will probably try hard to abandon HD and avoid HD-related situations, 6 months after disclosure.

The perception of the future (**hopelessness**) could best be predicted by pre-test expectancies about the future. A pessimistic view proved also to be dependent on relative absence of denial-avoidance behavior and unsatisfactory supportive allies (Table V) ($F = 13.1$; $p < .001$). This indicates that the more an individual at-risk was pessimistic when he/she applied for the test and the more he/she could face the burden (low denial-avoidance) and the more he/she was dissatisfied with supportive persons, the more likely he/she will be pessimistic about the future.

Table V. Predictability of Post-Test Hopelessness (BHS), 6 months after disclosure of DNA-test results, by multiple regression analysis

	$\beta^{1)}$	95 % CI ²⁾
<i>Pre-test:</i>		
Denial-Avoidance (IES)	-.21	-.41; -.01
Hopelessness (BHS)	.55	.35; .75
SSQS	-.27	-.45; -.09
MR	= .60	
MR ²	= .36	
MR ² adjusted	= .34	

¹⁾ standardized regression coefficient; ²⁾ 95 % confidence intervals

DISCUSSION

Intrusion

The only difference that was found between gene-carriers and non-carriers in the 6-month follow-up, concerned more unwanted intrusive thoughts and feelings with respect to HD in carriers, especially in those who suffered most from the burden prior to the test and who found it difficult to face their fate (Table III).

Once identified, carriers may experience that the test give them less control over their future than they initially had expected (Tibben et al., in press). Moreover, they could become concerned about when and how the disease will manifest itself. They may also find that the result affected their partner and/or family more strongly than they originally expected. Further studies should be undertaken to see whether these states of intrusion and avoidance decrease over time and whether these carriers will find a reasonable adjustment to the knowledge of developing HD. Carriers who experienced less intrusive feelings and who showed less denial-avoidance, may cope well in the short term, but may have numbed their emotions and may underestimate reality. Only long term follow-up will give the answer whether the working through process in these carriers is delayed or whether denial persists. Some carriers experienced an upsurge of negative feelings when they are confronted with the test-result, such as shortly before a follow-up visit. However, none has regretted taking the test thusfar (Tibben et al., 1993a).

In comparison to carriers, non-carriers reported less intrusive feelings about HD. This

could lead to the false suggestion that they may have worked through the meaning of the non-carrier status and integrated it in daily life. However, relative absence of intrusion might also be explained by the observation that some non-carriers did not fully appreciate the impact of the test result, as was reflected by sustained emotional numbness (Tibben et al., 1990, 1992; Huggins et al., 1992). This numbness may reflect warding off a variety of guilt feelings, anger, resentments and hostility towards the family and its HD history and the inability to create new life perspectives that may withhold non-carriers from encountering the expected relief.

Denial-Avoidance

Both carriers and non-carriers who previously avoided situations which might confront them with HD, continued to do so this also in the 6 months after the test (Table IV). This was also related to high pre-test intrusion levels, which might mean that they have neither succeeded in escaping the burden of HD nor in integrating HD in their daily life. Apparently, the working through process takes longer than expected and pre-test problems and expectations are often exchanged for new problems that may burden a personality.

Individuals who had optimistic future expectancies (table IV) and who only recently learned about HD in the family, showed more avoidance behavior with regard to HD. They were apparently shocked after the test results and only after its disclosure they realized the full impact of their decision to undergo the test. They may have previously underestimated the devastating illness and the impact of the DNA-test and its consequences. Tyler et al. (1992) suggested that these people, i.e. those who had only recently learnt about HD in their family, rather might postpone testing at least one year until they are better prepared to face all the consequences of a test result.

Those individuals, who have long been familiar with HD and who had previously pessimistic expectancies, may have shaped their psychological make-up against the background of HD and may have learned to face, or to cope with, the burden of HD without getting too upset. They may be emotionally numbed and feel resigned to becoming a HD patient. These individuals were perhaps strongly interwoven with the family and the HD burden.

Hence, for identified carriers it is important not to adopt the role of patient too prematurely. For non-carriers it is obviously a challenge to detach themselves from their HD scenario and build a new life. Apparently, the relationship between discontentment with support and denial-avoidance behavior emphasizes the relevance of paying close attention to the interrelational impact of HD and a test result.

Hopelessness

The perception of the future was not significantly associated with the test outcome as such. Moreover, a pessimistic attitude proved to be dependent on the previous unwillingness to face the impact of HD and on the perception of unsatisfactory support (table V). This observation has obviously a different meaning for carriers and non-carriers.

Carriers with a pessimistic attitude are apparently able to acknowledge their fate and their feelings about HD. They may feel resigned to the confirmation of developing HD and to their life perspectives. Their pre-test pessimistic attitude had enabled them to prepare for the test outcome and the post-test adjustment (Janis et al., 1969). Absence of denial-avoidance may also indicate that there was less necessity to escape the continuous burden than to obtain a relief from uncertainty. The waiting seems over. This is in concordance with the observation of Wiggins et al. (1992), who found that identified carriers felt better after one year than those who were not informed.

However, carriers with high denial-avoidance were relatively optimistic (Table V). This obviously indicates underestimation or minimization of the implication of the test result (Tibben et al., 1993c). They may apply psychological defenses such as feeling inviolable, i.e. they reversed their vulnerability into imperviousness. Some carriers demonstrated 'identification with the aggressor' i.e. they identified strongly with the affected HD parent or other relatives, thus warding off adverse emotions like anger, resentments and grief. E.g., 3 carriers in our study group became intensively involved in the care for their affected parent. If effective in the short term, these defenses might, over time, lead to overestimation of their capacity to bear the HD-burden. Also, the long term impact of HD on the relationship must be appraised, as satisfaction with a supportive companion seems to be a *sine qua non* for a bearable perspective.

In non-carriers, a pessimistic attitude might reflect problems with expressing their relief towards relatives at-risk and with building a new life scenario. They may have felt that they have squandered their life options. This confirms previous reports on the effects of being identified as a non-carrier, resulting in survivor's guilt and numbed emotions (Tibben et al., 1990, 1992; Huggins et al., 1992). They neither experienced an emotional effect on their lives nor the expected relief from uncertainty, within 6 months after the test. They may have ascribed their pre-test problems to the anticipated feeling of being at-risk for HD and may subsequently become disappointed that the outcome did not automatically lead to the expected relief. It certainly takes more effort (both in terms of psychological adjustment and time) to wrench oneself free from the previous HD-shadow.

However, being able to think and be emotionally involved about HD and having a satisfactory supportive ally seems to safeguard a positive attitude (table V).

Social support by allies

Sarason et al. (1987), found that low social support was generally associated with excessive worry, self-preoccupation and less adequate coping behavior in periods of high distress. As expected, satisfaction with the perceived quality (rather than the number) of supportive others was associated with low avoidance of HD-related situations (Table IV) and with hopeful expectancies about the future (Table V).

Tested individuals mentioned their spouse/partner as the most important source for support. Interestingly, answering the SSQ was found to be very upsetting, especially questions on "possible future dependency" and "acceptance by others of worst points". They obviously associated these items as implicit to becoming an HD patient and reflected on the expected reactions of their partners/friends. However, in a previous attitudinal study, we found that most individuals denied at pre-test that the result could have adverse effects on their relationship, although the potential influences on a spouse were appreciated (Tibben et al., 1993c).

These individuals may have felt a kind of resignation about the huge burden of HD and its impact on the spouse, but on the other hand did not wish to perceive the consequences for their marital relationship.

This observation probably reflects ambivalent feelings in test candidates such as fear, guilt, the need for safety and dependency, but probably also hostility and doubts about the spouse's loyalty and faith (Hans and Koeppen, 1980). They may find it difficult to appraise their partnership, both prior to the test as well as thereafter.

We propose that spouse selection may be (un-)consciously influenced by the knowledge of being at risk for HD and induce some at-risk persons to find a partner that seems capable of accepting the (final phase of the) disease (Vandenberg, 1972). A partner, on the other hand, may be attracted by the at-risk's dependency and need for affirmation and adopt the role of the ultimate rescuer. This might result in a double narcissistic companionship substituting for some unattainable ego ideal (O'Leary and Smith, 1991). The objective test result may confront both partners with the inevitable reality of either being free from HD, or the necessity to prepare for the real tragedy of the illness. In either situation, these couples will have to cope with the unfamiliar shifts in reality, as they affect their (marital) relationship. Accordingly, some (marital) partners rather wish to continue along their expected beliefs in their relationship. Others (when the test result is contrary to their expectations), may experience an outcome completely contrasting with the pre-test marital

scenario and, consequently, may become at risk for relational conflicts and divorce. Test candidates content with their perceived support, showed less hopelessness after the test result. However, in 10 cases (4 carriers and 6 non-carriers), the partner-relationship broke up, in three non-carriers shortly before disclosure and in 4 carriers and 1 non-carrier within 6 months after the test disclosure. In all cases, the partners knew about the risk for HD in the testee from the onset of their relationship. Generally, post-stress data indicated a substantial increase in family stress, divorce, with related adjustment problems (Adams and Adams, 1984; Ryn, 1990; Rae-Grant and Robson, 1988; Stellman et al., 1988). This supports the view that the partner-relationship, rather than the individual at-risk who seeks testing, is really the patient (Kessler and Bloch, 1989).

Identifying the need for intervention

Carriers

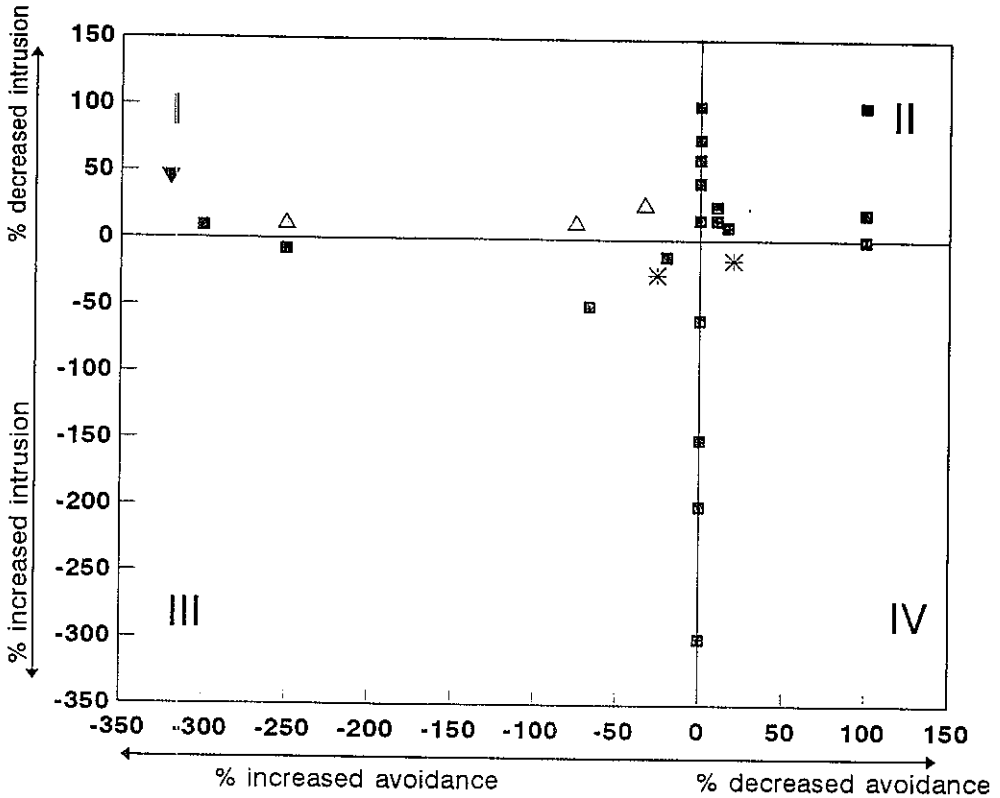
Although the immediate response to the unfavorable result was a shock, most carriers felt remarkably well and showed a remarkable resilience within a week, which persisted for 6 months at least (Tibben et al., 1993b). Generally, carriers did not express any need for additional help within the 6 months after disclosure. Many individuals experienced relief from the previous uncertainty and returned to their customary forms of life. Some stated that it was as if nothing had changed. Most of them were aware that they were possibly denying their feelings. The combination of increased avoidance responses and decreased intrusive activity might reflect denial or minimization of the impact of the result.

As can be seen in the first and third quadrant in fig.1, 9 carriers responded with more denial-avoidance behavior with respect to HD, indicating that they might have severe difficulties with facing the consequences of the outcome.

The 4 carriers among them with high GHQ scores suffered less from intrusive feelings and thoughts (quadrant I), reflecting possible maladaptation. They may use premature defenses such as somatization or hypochondriasis (Vaillant et al., 1986). These individuals may be helped by giving them insight in their specific ways of coping and defenses against threatening feelings.

Those with an increase of intrusive feelings (n=9, quadrant III) might more consciously suffer from the test results and its consequences. Although they are not inclined to psychopathology (according to their GHQ scores), they may need help to face the consequences of the test result.

Figure 1. Change in intrusion and denial-avoidance in gene-carriers 6 months after the DNA-test outcome. A positive change indicates a decrease in intrusion and/or denial-avoidance, a negative change an increase, in comparison to the pre-test situation. A high score on the GHQ (≥ 12) indicates potentially psychopathological states. A high score on the BHS (≥ 9) indicates a risk for depression and suicidal behavior.



- = low on GHQ (< 12), low on BHS (< 9)
- * = low on GHQ (< 12), high on BHS (≥ 9)
- △ = high on GHQ (≥ 12), low on BHS (< 9)
- ▼ = high on GHQ (≥ 12), high on BHS (≥ 9)

Those with high BHS-scores ($n=3$), indicating a risk for depression and suicidal behavior (Beck et al., 1990), deserve close attention, not least because they belong to the group with social support perceived as insufficient (Table V). Two of them did not change much with respect to coping with HD. For them, the test result may have confirmed their expectancies of getting HD. They may have already adopted their patient role.

Five carriers (21%) showed a decline in both intrusive feelings and avoidance behavior (2nd quadrant), which might indicate they could cope reasonably well with the test result. They may experience relief from uncertainty and for some it may mean a confirmation of previous expectations (Tibben et al., 1993c; Bloch et al., 1992; Wiggins et al., 1992). Since only 4 carriers report current health complaints, this might reflect strong ego-functioning in most carriers and a satisfactory psychological adjustment. However, long term follow-up is essential to verify whether this apparent adequate response is rather a deficient anticipation to the invalidating disorder and might eventually result into maladaptive behavior (Janis et al., 1969). Moreover, these reactions are in strong contrast with the great worries of their partners, who subsequently tended to exclude themselves from needed support for fear of seeming selfish (Tibben et al., 1993c).

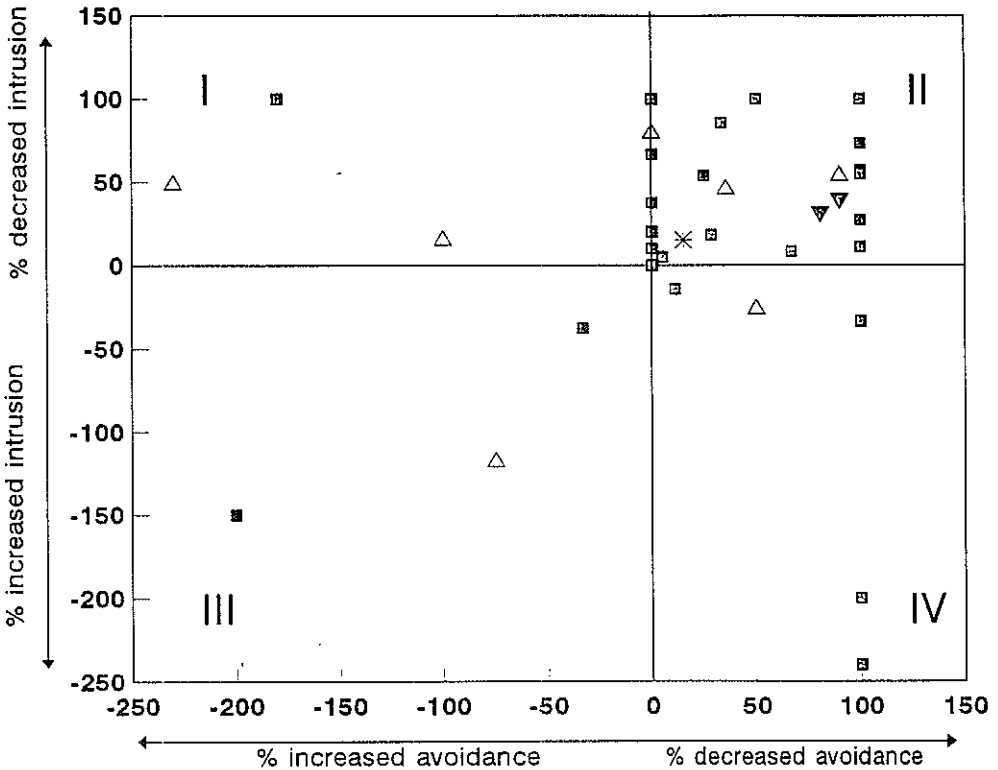
Non-carriers

In most non-carriers (second quadrant of fig.2) the intensity of intrusive thoughts was reduced and avoidance responses were less necessary. However, 6 non-carriers (3 of them with high GHQ scores) tried harder than before to avoid facing HD (1st and 3rd quadrant). Three of them reported that they suffered more from unwanted intrusive feelings, in comparison to their pre-test situation (3rd quadrant). Five non-carriers suffered more than previously from unwanted feelings with regard to HD (4th quadrant) but needed to avoid HD much less.

The observation that most non-carriers reported a reduction of intrusive thoughts and avoidance responses (second quadrant of fig.2), might reflect that the test result has been worked through and integrated into daily life. Yet, 9 non-carriers (20%) were at risk for psychopathological disorders (high GHQ scores), 5 of them showing a decrease in both avoidance behavior and intrusive feelings.

This might reflect inadequate unconscious defensive activity against the ambivalent feelings like anger, resentment and hostility resulting in reactions like survivor's guilt, emotional numbness and restriction of life. These persons might need additional professional support in order integrate their new perspective in life.

Figure 2. Change in intrusion and denial-avoidance in *non-carriers*, 6 months after the DNA-test outcome. A positive change indicates a decrease in intrusion and/or denial-avoidance, a negative change an increase, in comparison to the pre-test situation. A high score on the GHQ (≥ 12) indicates potentially psychopathological states. A high score on the BHS (≥ 9) indicates a risk for depression and suicidal behavior.



- = low on GHQ (< 12), low on BHS (< 9)
- * = low on GHQ (< 12), high on BHS (≥ 9)
- △ = high on GHQ (≥ 12), low on BHS (< 9)
- ▼ = high on GHQ (≥ 12), high on BHS (≥ 9)

Generally, those non-carriers who have not experienced a decline in either intrusive feelings or in denial-avoidance (quadrants I, III and IV) deserve close attention, together with those with either high GHQ or high BHS scores, or both, since they might have problems with adopting their new genetic status or finding a new role amid their relatives.

CONCLUDING REMARK

Our findings suggest that more follow-up on the process of working through the test results is needed both in carriers and non-carriers. Apart from their participation in the research program, close attention should be given to those individuals who are at-risk for maladaptive functioning. Specific attention should be given to the impact of testing on partner relationships in the psychological research program as well as in the pre-test and post-test genetic counselling.

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Chapter 8

Defense and Presymptomatic DNA-Testing for Huntington's Disease

Defense and Presymptomatic DNA-Testing for Huntington's Disease

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submitted

ABSTRACT

In the Dutch presymptomatic DNA-testing program for Huntington's disease, 10 gene-carriers and 10 non-carriers were followed up, 6 months after disclosure of the result. Nine psychotherapists rated pre-test interviews on anxiety and listed salient examples of anticipating the test outcome, which were subsequently categorized into defense mechanisms by 3 expert psychoanalysts.

Significant correlations were found between pre-test anxiety and self reported hopelessness, intrusive thoughts and avoidance behavior. In those individuals, rated as most anxious, significantly more immature defenses were observed. Highly anxious carriers showed increased avoidance behavior and decline of hopelessness over time, which means an increased risk for maladaptive functioning. Highly anxious non-carriers reported slightly decreased feelings of hopelessness, reflecting difficulties in adopting a new life scenario. These findings may have implications for DNA-testing programs related to other inheritable late onset disorders.

INTRODUCTION

Huntington's disease (HD) is a late onset autosomal dominant heritable neurodegenerative disorder, characterized by involuntary movements, changes in behavior and in personality, and cognitive impairment^{1,2}. Children of affected parents have a 50% risk to inherit the gene for HD. Although the average age of onset is 40 (\pm 12) years with a range of 2-75 years³, at-risk individuals can never be sure of having escaped HD, even at a late age.

Recent developments in presymptomatic DNA-testing for an increasing number of inherited disorders has widened the choice available for individuals at risk for HD upon the HD-gene localization. Since then, individuals at 50% risk for HD can now opt for a risk modification from \pm 98% (gene-carriers) to \pm 2% (non-carriers)⁴. Individuals at-risk could use this option to improve the quality of their lives⁵. Conversely, an unfavorable

test result might lead to major psychological and social problems, including preoccupation with symptoms of the future disease, depression, and suicidal ideation⁶.

After clinical introduction of the test, most applicants indicated planning for the future, and a family as the major reasons for participation. Most applicants also wished to relieve uncertainty^{7,8}. Prior to the test disclosure, most applicants were found to deny any possible adverse effects resulting from an unfavorable test result. Moreover, a favorable test outcome was not expected to induce relief from uncertainty⁷. They sought, above all, control over their future.

Reactions to DNA-testing, however, have proved to be much more complicated than was previously expected^{9,10,11}. Gene-carriers seemed to cope well in the short term and pick up the thread of daily life quite quickly. Non-carriers experienced guilt and depression, or numbed emotions^{8,9,11}. Neither the amount of stress, nor the level of hopelessness were significantly associated with an unfavorable test outcome¹². Our findings compelled us to assume that the real reason for undertaking the test might have originated from inner psychological conflicts and ambivalent feelings, which might not later be solved by a mere test result, e.g. a favorable test result would relieve more than just ambivalent feelings, whilst an unfavorable result would not be expected to have only adverse effects. We have therefore studied the psychological defenses against ambivalent feelings since they were considered as being very important in the way people deal with the threats to their physical and psychological well-being.

Here we report on 20 out of 72 consecutively tested applicants, 10 carriers and 10 non-carriers. In each group, 5 were judged at baseline (pre-test) as most anxious, and 5 as least anxious. The aim of the study is to improve the counselling protocol by enabling professionals a. to identify specific anticipation or defense mechanisms in test candidates at risk for HD and other late onset disorders, and, subsequently, b. to improve their support.

METHODS AND PARTICIPANTS

The testing protocol and linkage analyses have been reported separately¹³. The DNA-test is currently informative in >90% (reliability > 96%) of the applicants when sufficient data on affected and unaffected relatives are available.

Individuals at-risk could enter the testing program if they met the inclusion criteria for the testing program, i.e. age over 18 years, absence of major mental illness, absence of suicidal plans, or clearly visible signs of HD. This study reports on 20 out of 72 at-risk individuals who were informed about their risk modification between April 1, 1989, and March 31, 1991. The study sample was selected on basis of level of anxiety, as rated by

expert judges, from semistructured interviews. Characteristics of the sample are shown in Table I. The male/female ratio was 2:3. The majority had a stable relationship and no children. Relieving uncertainty and planning for the future, including family planning, were the most cited reasons for wanting to take the test.

Individuals entering the HD testing program, gave a separate consent for the psychological follow-up study, provided that they could understand the questionnaires. The psychological follow-up included at baseline (first counselling session) the Impact of Event Scale (IES), and the Beck Hopelessness Scale (BHS). The IES summarizes the influence of HD on two major dimensions, i.e. 1. *intrusion* into consciousness of unwanted ideas and feelings, and 2. consciously recognized *denial-avoidance*¹⁴. The Beck Hopelessness Scale (BHS) focusses on pessimistic expectations concerning oneself and one's future and is capable of predicting depression and suicidal behavior¹⁵. An Attitude Questionnaire was used in order to measure feelings prior to the test outcome and its impact on different areas of life.

The qualitative part of the study involved a series of interviews by a psychotherapist (A.T.). The first being six weeks after application (pre-test). The content of the interview was derived from a review of the literature, our own clinical experience, and pilot interviews with the first 18 consecutively tested individuals and their partners⁸. Although the interviews were semi-structured, a checklist was used to make sure that the following areas were covered: personal development, coping with stressing events, experience and coping with HD and personal risk, intimate relationships, and anticipating the test-outcome.

The interviews lasted 1-2 hours and the first 45 minutes were audio-taped. In addition, the IES, and the BHS were completed. The average period between the first interview and disclosure of the test results was 4 months.

The audio-tapes were judged at-random by independent pairs of 9 psychotherapists (judges). A specifically-designed semistructured questionnaire was used which had been tested in two sessions with all judges. Judges were asked:

- a. to find interviewee's most salient statements (vignettes) which reflect modes of anticipating the disclosure of DNA-test results, up to a maximum of five;
- b. to rate, on 3 visual analogue scales, interviewees level of anxiety (low-high), the adequacy of dealing with anxiety (not at all-highly) and interviewees ability to withstand the distress of the DNA-test disclosure (low-high);

Next, a panel of three experienced psychoanalysts (raters) categorized both groups of the above mentioned vignettes into specific coping/defense strategies of anticipating the disclosure of test results. A label 'defense mechanism' was only assigned to the vignettes if it had the consensus of these three raters.

Table 1. Characteristics of 20 Individuals At-risk, Tested Presymptomatically for Huntington's Disease, selected for high/low level of pre-test anxiety

	Gene-Carriers Anxiety		Non-Carriers Anxiety	
	High*	Low	High	Low
Sex				
Male	2	2	3	1
Female	3	3	2	4
Mean Age (s.d.)	36.6 (8.9)	32.0 (16.0)	32.2 (6.8)	32.4 (7.8)
Marital Status				
Single	2	-	-	1
Married	2	2	1	4
Common-law	1	2	3	-
Divorced	-	1	1	-
Children				
0 children	4	3	2	4
≥ child	1	2	3	1

* All groups N=5

RESULTS

Seventy-two individuals were judged on the 3 visual analogue scales (range 1-8): (1) anxiety, (2) on dealing with anxiety, and (3) on level of stress tolerance. In addition, they were ranked on basis of the sum of scores of pairs of judges. No sumscore was calculated if judges disagreed more than 3 points (total 14% disagreements). Seven patients were removed from the analysis since judges disagreed on more than 1 statement out of 3 (total 7 patients). Subsequently, in both the carriers and the non-carriers group we selected 5 individuals with the highest pre-test level of anxiety, and 5 with the lowest level. The mean levels of anxiety did neither differ significantly in both groups with lowest anxiety, nor in those with highest anxiety.

Descriptives

The 4 groups did not differ in demographical characteristics, as can be seen in Table I. The mean age in the high anxiety/carriers was higher but was not significant. Significant correlations (Pearson product moment) between the outcome variables and the psychological 'state' variables are presented in Table II. No significant correlations were found between the outcome variables, and both the biographical variables (age, gender, children).

Table II. Significant Pearson Product Moment Correlations between Psychological Variables, and Pre-Test Level of Stress and Anxiety as Rated by Judges

Variable	Anxiety ¹	Coping ²	Resistance ³	Total ⁴
Pre-Test				
BHS	.33*	.33*	.37*	.39*
IES				
Intrusion	.55**		.40*	.44**
Avoidance	.39*			.32*
Post-Test				
(1 week)				
BHS			.28*	
Post-Test				
(6 months)				
IES				
Intrusion	.43**		.32*	.35*
Avoidance	.39*		.32*	.32*

¹) "in what degree does itee suffer from anxiety?" (not at all-highly)

²) "how do you estimate itee's ability to cope with anxiety" (high-low)

³) "how do you estimate itee's ability to resist the stress of a test result?" (high-low)

⁴) sumscore of anxiety, coping, and resistance

* $p < .01$; ** $p < .001$

In figures 1-3, the scores on Hopelessness, Intrusion, and Avoidance are presented. No differences in baseline values of the BHS ($t=.13$; $df=18$; ns), Intrusion ($t=.63$; $df=18$; ns), and Avoidance ($t=1.94$; $df=18$; ns) were found between prospective carriers and non-carriers.

A MANOVA for repeated measures (Statistical Package of Social Sciences) was then performed with the scores on the BHS, Intrusion, and Avoidance as the dependent variables, and the DNA-test outcome and level of anxiety as the grouping variables.

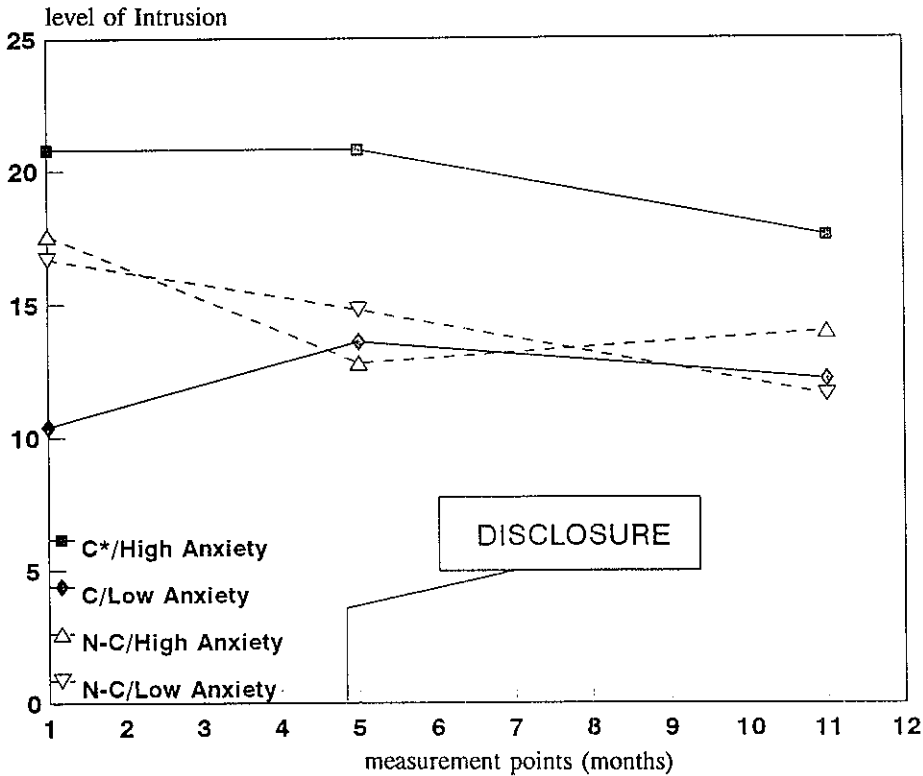


Figure 1. Intrusion in 20 Individuals, DNA-Tested for HD, by Pre-Test Level of Anxiety and DNA-Test Results; Intrusion, as measured by the Impact of Event Scale; *C=Gene-Carriers; N-C=Non-Carriers; all groups N=5

Unequal time intervals between the measurement points were taken into account. The DNA-test outcome proved to be significantly related to post-test intrusion ($F=9.87$; $p=.007$), which means that carriers suffered more from intrusive ideas and feelings about HD, 6 months after disclosure, than non-carriers (Figure 1). For the DNA-test outcome \times Anxiety interaction, the level of intrusion fluctuated significantly ($F=5.04$; $p=0.02$) between the 4 groups. Level of anxiety could not differentiate between low and high anxious test candidates ($F=2.41$; $p=.13$). The linear decrease of intrusion within individuals over time was significant ($F=13.64$; $p=.002$).

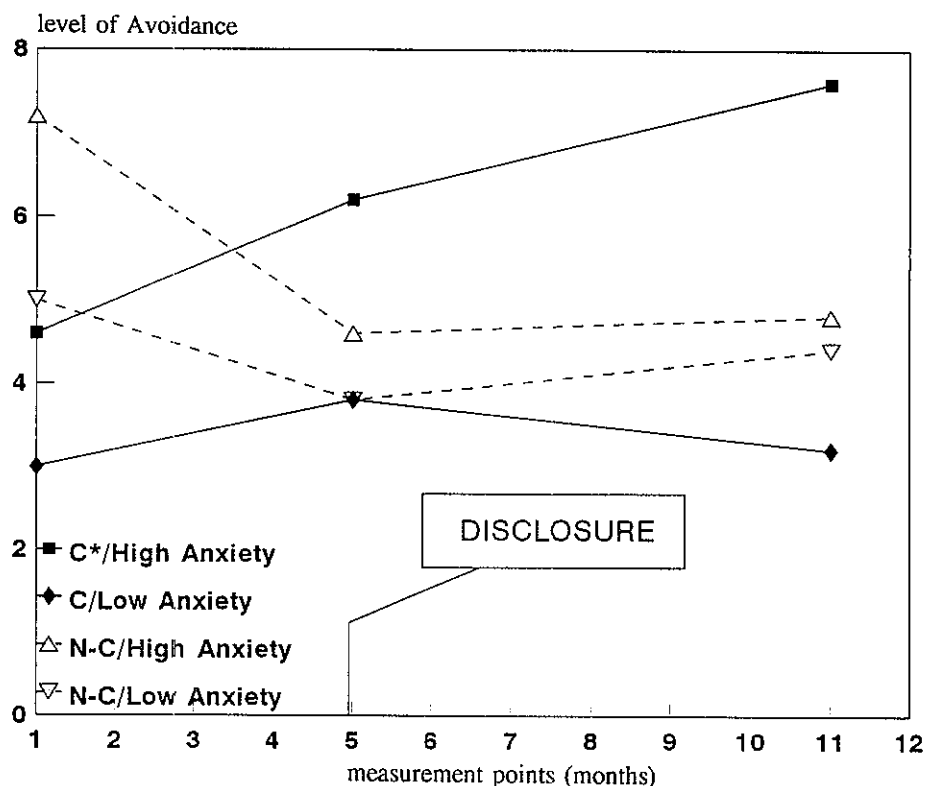


Figure 2. Avoidance in 20 Individuals, DNA-Tested for HD, by Pre-Test Level of Anxiety and DNA-Test Results; Avoidance, as measured by the Impact of Event Scale; *C=Gene-Carriers; N-C=Non-Carriers; all groups N=5

For avoidance (Figure 2), no significant change was observed. However, the DNA-test outcome seemed to induce a difference between subgroups ($F=3.69$; $p=.08$). High anxious gene-carriers showed an increase in avoidance behavior, soon after they were informed on the result, whereas low-anxiety carriers showed a decrease in avoidance behavior.

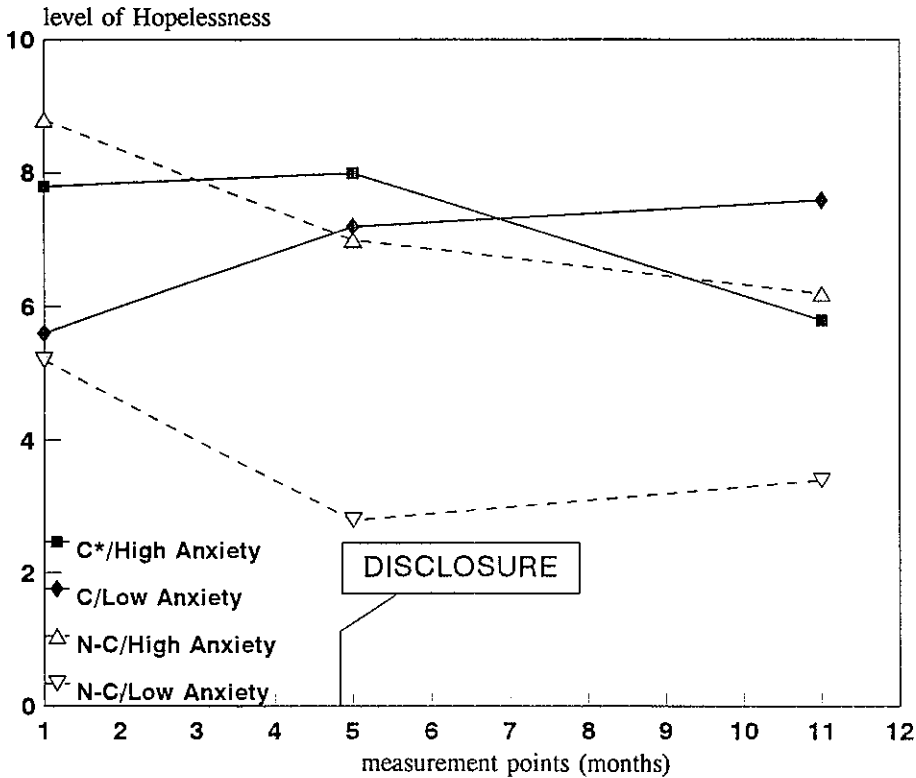


Figure 3. Hopelessness in 20 Individuals, DNA-Tested for HD, by Pre-Test Level of Anxiety and DNA-Test Results; Hopelessness, as measured by the Beck Hopelessness Scale; *C=Carriers; N-C=Non-Carriers; all groups N=5

With hopelessness as the dependent variable (Figure 3), no significant changes could be found neither among, nor within the test candidates themselves, although there was a trend for the grouping variable anxiety ($F=3.46$; $p=.08$), i.e. low anxious individuals showed a slight increase of feelings of hopelessness, whereas high anxious persons showed the reverse. The unfavorable test result did not immediately affect the expectancies with respect to the future (BHS) in high-anxious carriers (Figure 3). They were even less hopeless after 6 months.

Anticipating disclosure of DNA-test results

The most characteristic conscious representations of coping/defensive behavior prior to the disclosure of the DNA-test outcome were listed by the judges, whilst the 3 raters identified 10 unconscious coping mechanisms (see Table III for labels and their conscious representations). The high anxiety group was characterized by using significantly more immature mechanisms (χ^2 11.6, $df=3$, $p<.01$). No significant difference was found between prospective gene-carriers and non-carriers.

There were 5 **immature** adaptation mechanisms that could be recognized:

- a. *denial in fantasy*; this was found in 9 individuals. This label was used for cognitions or behavior that covered control over the future, such as being convinced about the eventual test outcome. Believing that the DNA-test result will prove either positive or negative might enable individuals to anticipate disappointment. As such, they devaluated the effect of the test result. The individual is capable of mastering the threat by fantasies of omniscience.
- b. *Obsessive preoccupation*, reflected by a preoccupation with early symptoms, prolonged sleep disturbances or a variety of somatic complaints was found in 2 high anxious individuals.
- c. *Turning against self* (passive aggression) was observed in 5 individuals who turned their unconscious hostility inwardly. They tended to put themselves aside and affirmed that others might more deserve or need the attention, given by friends, relatives or professionals. This behavior is correlated with the provocation of aggression in potential allies.
- d. *Avoidance or withdrawal* was observed in 5 individuals who did not consciously worry about the result, had no alternative scenario's for the outcome, or avoided any discussion of the matter actively. They did not mobilize social support, or inform their friends that they had applied for the test.
- e. *Acting out* involves the uninhibited expression of impulses in order to circumvent the associated affect; this was found in 6 individuals, 5 of them were rated as extremely anxious. Some individuals expressed their intention to attempt suicide after an unfavorable result whilst others had already made arrangements for the end phase of the disease. The shock or worry, elicited in others by the anticipatory warning, might be seen as acting out. An individual who signals to his/her spouse that he/she may become depressive after an unfavorable result may also be interpreted as acting out.

The **neurotic defense mechanisms** that were observed were:

a. *Minimisation* or rationalizing (n=13): the test candidate cognitively reduced the threat. "One can die of many more diseases" reflects that reality is deformed. Another example is seen in those individuals who stated that, if they should be identified as a carrier, they would not worry and would think and act positively. Thus, they anticipated the denial of the unfavorable message and therefore minimized it. This differs from denial in fantasy, as minimisation does not imply exaggeration or distortion, but merely a reduction of the meaning of reality.

b. *Denial in action* means that test candidates (n=5) worked hard in order not to feel or think about the test result. They did not want to think about the possible threats. Consequently, they acted as if the threat did not exist. This defense differs from denial in fantasy because denial in actions depends on interaction with the external world.

The **mature coping mechanisms** that were observed were:

a. *work of worrying*, which was observed in 6 high anxious and 2 low anxious individuals. As soon as the individual at-risk becomes aware of signs of the impending danger that might affect him personally, he/she begins to worry in advance. Work of worrying is characterized by voluntary and involuntary intrusions of threatening feelings and a relative lack of avoidance behavior. Individuals read, talked and thought about the threat of the test result and were able to think of the different outcome scenario's, which may eventually lead to a better adjustment to either test result.

b. The most mature coping strategy was *anticipation* (control through realistic thinking and planning), reflecting a balance between acknowledging the threat and the capacity to adapt adequately, i.e. do the things of normal life, including conscious and realistic planning. Different outcome scenario's were discussed and the consequences of each outcome considered. In addition, specific confidants were chosen to talk to. The most important difference with work of worrying is that it has intrusive aspects. Six of the individuals in our series actually fulfilled anticipation.

DISCUSSION

Descriptives

Like others¹⁶, we did not find any baseline personality differences between prospective gene-carriers and non-carriers. In previous reports on presymptomatic testing for HD, it was shown that, until now, carriers have not shown catastrophic reactions^{9,10,16-19}. Moreover, an unfavorable DNA-test result did not significantly contribute to the amount of stress, 6 months after disclosure¹⁹.

Table III. Defense and Coping Mechanisms in 20 Individuals At-Risk for Huntington's Disease, Anticipating Disclosure of Presymptomatic DNA-Testing

Defense or Coping Mechanism	Conscious Representation
<i>Immature Mechanisms</i>	
1. Denial in Fantasy	I know that I'll prove to be gene-carrier
2. Obsessive Preoccupation	I'm anxious that I'll get HD because I often let things fall out my hands
3. Turning against Self	Nobody knows that I'm always worrying about my future
4. Avoidance	I don't go to my parents because I just don't want to think or talk about HD
5. Acting Out	If the test shows that I'm a gene-carrier I'll kill myself
<i>Neurotic Mechanisms</i>	
6. Minimisation	I don't think that a positive result will have a paramount influence on my life
7. Denial in Action	My work does not allow me to think about HD; I just don't have the time to ponder over HD because I'm too busy
<i>Mature Mechanisms</i>	
8. Work of Worrying	I talk and read a lot about the things that could happen to me after the disclosure of the test results
9. Anticipation	If I prove to be gene-carrier, than I'll only tell some specific friends I can trust

The results of the current study support these findings. The level of anxiety (including stress tolerance and adequacy of preparing for the outcome), however, had a greater discriminating power than the test result itself. Intrusive feelings and thoughts were significantly correlated with high anxiety level.

When we consider the change over time (Figure 1), we may conclude that high anxious

gene-carriers show a decrease of intrusive feelings, apparently due to a strong increase of avoidance behavior (figure 2). This observation might also explain the decrease of feelings of hopelessness (figure 3). The low anxiety carriers showed the least avoidance behavior of all groups. However, they also showed the highest level of hopelessness, 6 months after being informed on the DNA-test result. Moreover, their intrusion level apparently did not change. This may reflect that they could fully acknowledge the impact of HD on their future, but it may also indicate that they are able to cope adequately with the result and to integrate it in daily life.

Non-carriers with high anxiety showed a decline on all aspects. This obviously reflects relief (Figures 1-3).

Defenses as Preparation Mechanisms

Defenses are defined as intrapsychic coping mechanisms that have the function of keeping anxiety within manageable limits. In contrast to coping skills, deployment of defense mechanisms is involuntary and more or less unconscious. Defense mechanisms can be considered as pathological when they are so extensive or rigid that they prevent the test candidate from gradually coming to terms with the possible implications of HD in their own and their family's lives^{20,21}.

The relation between the use of mature defenses and the individual's successful adaptation to daily life, including stressful events has been emphasized repeatedly²²⁻²⁴. Using the criteria of Bond et al.²³, we grouped the rated preparation mechanisms into defense styles, indicating the adequacy of preparation to a test result. A defense style might also give information about the individual's ego-functioning.

The 'maladaptive action' pattern includes acting out, obsessive preoccupation, turning against self and avoidance. These defenses were predominantly observed in high anxious individuals (80% versus 20% in low anxious individuals) and indicate the individual's inability to deal with his/her behavior by taking constructive action on his/her own behalf²⁴. They make the test candidate direct his feelings and actions toward others, as if the latter was able to solve all problems²⁵. Awareness of internal conflicts is hardly or never acknowledged. Accordingly, internal and external problems remain unsolved and raise adverse responses in potential companions. Test candidates with the least mature defense styles may develop serious behavior problems, including maladaptive behavior after the DNA-test outcome.

Another pattern involves the 'self-sacrificing' defenses, including the neurotic defenses like minimisation and denial in action. The 'self-sacrificing' individuals may become incapacitated for their creative potential upon an unfavorable test outcome. Neurotic

defenses were, however, observed in all test candidates, which confirms observations by Perry and Cooper²⁵. They found that individuals from different study populations and at all levels of psychological functioning, used these defenses. Individuals who have defective mature adaptive defenses, might suffer intense fears and anger over time. This may be due to lack of anticipatory fear, preceding the test result, and absence of mental rehearsal of the threat of an unfavorable result. Despair and helplessness may result when the threat becomes reality. This will make them extremely vulnerable. Due to overextended, unrealistic expectations, they are prone to disappointment in friends or protective authorities.

On the other hand, the 'adaptive' defense style, including anticipation and work of worrying can be observed. Individuals with adaptive defenses may achieve creative self-expression without restrictions in personal development after a unfavorable test outcome. Also, they may be able to experience relief after a favorable test result.

Since major mental illness was an exclusion criterion for the DNA-testing program, the present sample is restricted to individuals without psychiatric disorders and, consequently, no psychotic defenses were expected.

Clinical Relevance of the Study

Understanding the dynamics of defense and adaptive coping mechanisms might enable the clinician to better respond to the problems of individuals undergoing genetic testing for late onset genetic diseases. Using the scheme of Vaillant²⁶, defense mechanisms were categorized for their effect on mental functioning (Table IV). An individual can deal with external or internal threats by a variety of defenses, which are considered to be produced by the interaction of innate determinants and environmental influences²⁰.

Defense mechanisms allow (un-)conscious denial or distortion of a (combination of) subject, idea or affect that otherwise threatens well-being. For example, a test candidate who strongly believes that the test result will identify him as a gene-carrier, denies in his fantasy the possibility of a favorable result (alteration of idea). He acts as if that first result is a reality. In his fantasy, he controls the threat (omnipotence), so that it will not cause any disabling anxieties (minimization). He has fantasies about other people reacting to this outcome (distortion). He is the omnipotent creator and master of the future. Obviously, the reality is distorted and the reality-testing out of order, but the accompanying fears are minimized and under control. This defense might be adaptive in the short term, and prevent the person from experiencing overwhelming fears if his belief would become true. In the long term, this defense might be less appropriate as it may cause social conflicts. Two identified gene-carriers, who used this defense, decided to

have children without using prenatal diagnosis, even though they had previously decided to opt for prenatal testing. This change in attitude might reflect prolonged omnipotent fantasies and denial of the severity of the test result. However, if he/she proves to be non-carrier, the omnipotence is severely thwarted, which may result in adverse affects like depression or numbed emotions^{8,11}. Adverse reactions may be expected when either the test candidate has become accustomed to suppress the anticipatory fear by means of immature or neurotic defenses, or by avoiding signals that would stimulate the work of worrying or anticipation. In the pre-test counselling, a test candidate may be helped to achieve a more realistic appraisal of his future. In order to anticipate the eventual test outcome and its consequences, it seems advisable that each potential source of stress be anticipated and worked through in advance as much as possible²⁰. These findings have far reaching consequences for current and future presymptomatic DNA-testing programs.

Studies on defense mechanisms

A study on defense and adaptive mechanisms is an enterprise fraught with methodological issues like inter-rater reliability, the predictive validity of defenses, the different labels used for defense mechanisms and, consequently, problems with cross-cultural comparisons. Defenses are studied in a broad variety of samples. Yet, the findings from our study support data on other predictive programs for HD^{5,16-18}, case reports⁸⁻¹¹, and studies on the relationship between defenses and healthy functioning of the personality in other populations^{22,25}. The combination of qualitative and quantitative research techniques provide promising opportunities to obtain further insight into the psychological functioning of those who are at-risk for late onset heritable disorders and who wish to be informed on their genetic risk. It might also help professionals to improve the pre- and post-test counselling and additional support.

ACKNOWLEDGMENTS

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Table IV. Differential Identification of Defenses (after Vaillant, 1992)

Style of Anticipation	Expression of Impulse			
	Self/Subject	Idea	Affect	Object
Failing Defenses	Distorted	Distorted	Exaggerated	Distorted
Denial in Fantasy	Omnipotent	Altered	Minimized	Distorted
Obsessive Preoccupation	Made Object	Altered	Anger becomes displaced	
Turning against Self	Made Object	-	-	Ignored
Avoidance	-	Minimized	Devalued	Ignored
Acting Out	Omnipotent	Ignored	Ignored	Generalized
Minimisation	-	Minimized	Minimized	Minimized
Denial in Action	-	Minimized	Ignored	Ignored
Work of Worrying	-	Exaggerated	Exaggerated	-
Anticipation	-	Diminished	Diminished	-

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Chapter 9

General Discussion and Conclusions

Introduction

Analysis of the human genome will provide an increasingly large proportion of mankind with information about their genetic make-up. One of the ensuing questions is whether this will provide any benefit and prevent any harm in individuals at-risk for late onset genetic diseases. The benefit may depend on factors such as the reduction of uncertainty, preventive treatment and general planning for the future. The harm may depend on the inability to cope with unfavourable results, a lack of treatment prospects and the possible misuse of genetic information by employers and (life) insurance companies. Hence, the initial reluctance to start with a presymptomatic programme for Huntington's disease (HD) was understandable, given the lack of experience with such medical technology. In addition, prior to its actual introduction, attitudinal studies in HD at-risk individuals on the expectations and acceptability of presymptomatic DNA-testing had predicted a high rate of depression and suicidal ideation in case of unfavourable test results (Kessler et al., 1987). However, initiating a testing programme for HD was also a challenge because it might be used as a paradigm for other late onset genetic disorders (Jenkins and Conneally, 1989).

In Leiden, presymptomatic DNA-testing for HD was introduced in 1987. A psychological follow-up programme, funded by the Prinses Beatrix Fonds, was added in 1989. Seventy-three individuals at-risk for HD and their partners, who applied for the test between April 1989 and April 1991 and who received a DNA-test result, participated in the prospective follow-up study. The main question concerned the identification of factors predicting the psychological responses of tested individuals to the outcome of the test.

Results of the Present Study in Comparison with Other Follow-up Studies

At this moment, only two other psychological studies on presymptomatic programmes for HD are available (Brandt et al., 1989; Wiggins et al., 1992). Furthermore, less specific reports on clinical experiences with HD-testing (Meissen et al., 1988; Craufurd et al., 1989; Meissen et al., 1991; Bloch et al., 1992; Huggins et al., 1992; Tyler et al., 1992a; Tyler et al., 1992b) and on presymptomatic programmes for other diseases such as breast cancer (Lynch and Watson, 1992) and adult polycystic kidney diseases (Sujansky et al., 1990) are available.

Pre-Test Results

In the present study, most participants at-risk for HD wished to reduce their unbearable uncertainty (chapter 3a), this being one of the main reasons in most reports thus far (Meissen et al., 1988; Brandt et al., 1989; Bloch et al., 1989; Craufurd et al., 1989; Tyler et al., 1992a,b; Simpson et al., 1992). However, it is difficult to compare the data on the "uncertainty" of being at-risk. Some studies reported on 'relieve uncertainty' (Tyler et al., 1992b; Simpson et al., 1992; Bloch et al., 1989), others mentioned 'need to know' (Meissen et al., 1991), 'eliminate/reduce uncertainty' (Meissen et al., 1988, 1991), 'just to know' (Meissen et al., 1991), 'reduce prevalence of HD' (Tyler et al., 1992a), 'need or want to know' (Meissen et al., 1988), or 'relieve personal stress' (Bloch et al., 1989). Most studies used an open ended format for assessing the motives for testing. Hence, the different answers possibly indicate the same motive/emotion, i.e. anxiety induced by uncertainty. The conscious representation may reflect a variety of psychological coping strategies. In chapter 3a we have made the theoretical difference between obtaining certainty and relieving uncertainty.

More than half of our study group wished to undergo testing with regard to reproductive decisions (60%), which is much more than the 12%-25% in other reports (Meissen et al., 1988; Bloch et al., 1989; Craufurd et al., 1989; Meissen et al., 1991; Simpson et al., 1992; Tyler et al., 1992a). On the other hand, in these reports, 23%-45% sought testing in order to clarify the risk to children compared to only 4% in our study who wished to do so.

As reported by others, gaining control over one's future life was considered as an important effect of either test outcome (Bloch et al., 1989; Meissen et al., 1991). Remarkably, participants tended to trivialize the impact of unfavourable results on their quality of life and their intimate relationships (Bloch et al., 1989; Meissen et al., 1991; chapter 3a).

Females (42%) in our study anticipated significantly more than males (16%) that they would be likely to receive unfavourable test results. Meissen et al. (1991) found the same distribution of test outcome expectancies.

We have studied whether any specific psychological characteristics could be identified in dealing with the pre-test distress (chapter 5). It was found that females were more inclined to turn their threatening feelings against themselves, which is not specifically related to being at-risk for HD and at the same time showed internal control beliefs. Males turned their unacceptable feelings against the outer world and placed dependence for their health prospects on fate. Furthermore, it was found that those individuals

expecting a favourable test result, showed more denial-avoidance, whereas pessimistic at-risk applicants suffered more from HD and reported more health complaints. Those who did not anticipate a specific outcome, could generally face the HD burden, but isolated their feelings about it.

A substantial number of attitudinal studies on the presymptomatic test, carried out prior to its introduction, have shown that approximately two-thirds of at-risk individuals would wish to undergo the test (Mastromauro et al., 1987; Kessler et al., 1987; Meissen and Berchek, 1987). However, the proportion of those at-risk who have requested testing when approached by genetics centres and/or patient organizations has varied from 12.5% to 15.5%. Indeed many of these and others who referred themselves, changed their minds after counselling (Quaid et al., 1987; Meissen et al., 1988; Craufurd et al., 1989; Wiggins et al., 1992; Tyler et al., 1992b). This in contrast to our experience. Only 7 (6%) out of 114 applicants in the study period have postponed testing after one or more counselling sessions ($n=5$) or have withdrawn from the protocol for unknown reasons ($n=2$) (chapter 3a). Hence, most individuals who were extremely determined to take the test yet were still anxious about the possibility of reopening the consideration process that might produce ambivalence towards the test. However, after a detailed counselling process and participation in the follow-up study, the majority continued to go through the testing process.

In the first study on those individuals at-risk, who did not originally apply for the test, we have shown that they anticipated more adverse effects following an unfavourable test result in comparison to those applicants who actually undertook the test. Non-participants' reasons against the test included fear of an unfavourable result and an inability to cope with this result. Moreover, non-participants did not believe that a test result would give them more control over their future (chapter 3b). Three non-participants stated that they would like to take the test but their spouse objected. These findings demonstrate that attitudinal research prior to introduction of the test may not give sufficient insight into the actual attitude of at-risk individuals at the time the test is available. Moreover, our findings emphasize the importance of intensive psychological follow-up research at the moment a new technology is available. Furthermore, this supports our view that more research is needed into how at-risk individuals, suffering from uncertainty about a genetic familial disorder, can be helped.

The in-depth interviews with applicants and their partners gave us a deeper insight into the processes they experienced (chapter 8). The protocol for analysis of the interviews by a group of judges was added in the course of this study. Here we report only the initial

results of this complex analysis with a sample of the participants ($n=20$), that has already provided us with more insight. The first observation being that the pre-test defense style in highly anxious participants, involved more immature defense mechanisms, such as denial in fantasy, acting out and turning against self, in comparison with low anxiety participants. No differences could be found between prospective gene-carriers and non-carriers. We hypothesize that immature defense styles might lead to post-test maladaptive functioning, whereas mature pre-test defense styles safeguard adequate post-test mental functioning and adaptation to the new genetic status (Janis et al., 1969; Boeke et al., 1991).

General Post-Test Results

Initially, most attention of research groups was given to which impact a presymptomatic test result would have on those identified as gene-carriers. However, in the early phase of our programme we observed unexpected adverse reactions in non-carriers and carrier-partners. These findings concerned the experience, at one-year follow-up, of 18 tested individuals who were tested prior to the start of the psychological study (chapter 2). These observations were presented in 1989 (Working Group on Huntington's Chorea, World Federation of Neurology, Vancouver) and published in 1990 (Tibben et al., 1990a,b). Subsequently, the first report of other groups on these reactions was published in 1992 without citation of our observations (Huggins et al., 1992).

We found a similar biographical profile at baseline in eventual gene-carriers and non-carriers as reported by Brandt et al. (1989) and Wiggins et al. (1992) (chapter 3a). The females in our study group were, as were all applicants in the Vancouver study (Bloch et al., 1989), higher educated than the general population. Males in our study were lower educated than the general male population (chapter 3a). The only pre-test difference in our sample was that identified non-carriers had a significantly longer familiarity with HD but this could not be related to their having an older mean age. Wiggins et al. (1992) found that non-carriers were significantly older than carriers.

We considered the psychological adjustment to the new genetic status as a function of the presence of intrusive thoughts and feelings about HD, denial-avoidance behaviour and perception of the future. The strength and uniqueness of this study, in comparison with others (Brandt et al., 1989; Wiggins et al., 1992), is that we applied a predictive model in our statistical analyses (multiple regression analyses) which enabled us to identify those who are at-risk for e.g. the amount of suffering from HD, denial-avoidance behaviour and

depression/suicidal ideation. The second important finding that emerged from our study was that our observations are in accordance with the 'working through' model, reflected by the alternating phases of unwanted intrusive thoughts and denial-avoidance behaviour (Horowitz et al., 1979; Horowitz, 1990).

In a first analysis (chapter 6), it was found that the best predictor for the amount of post-test distress (after 6 months) in both carriers and non-carriers, was the level of distress, one week after disclosure of the test results. If females had severely suffered from HD prior to the test, than they were at higher risk for post-test distress in comparison to male applicants. Identified gene-carriers who had high pre-test distress, were found to be more at-risk for post-test distress than non-carriers. Individuals who experienced low stress shortly after disclosure and were long familiar with HD in the family, reported low stress after 6 months.

In addition, post-test unwanted intrusive feelings could be predicted by being identified as a carrier, pre-test denial-avoidance behaviour and pre-test intrusive thoughts and feelings about HD (chapter 7). Denial-avoidance behaviour could be predicted by the pre-test factors denial-avoidance, high intrusion, discontentment with partner's support and pessimistic future expectancies. Perception of the future proved to be dependent on pre-test denial-avoidance, pessimism and dissatisfaction with the partner's support.

Other pre-test personality characteristics such as defense style and control beliefs were neither associated with the DNA-test outcome, nor with the post-test outcome measures, i.e. unwanted intrusive ideas and feelings, conscious denial-avoidance behaviour and future expectancies (chapter 6 and 7). This is in concordance with the other studies (Brandt et al., 1989; Wiggins et al., 1992). We conclude that in some of the participants, the working through process has not yet been completed, whereas others showed denial or minimization of the test results. As is often found in recently experienced stressful events (Schwarzwald et al., 1987), the levels of intrusion and denial-avoidance proved to be equally high in most applicants. After a long period (> 1 year), different patterns of intrusion and denial-avoidance may be observed, which may reflect the specific individual style of working through. Subsequently, these patterns may provide points of application for additional support when needed. Long term follow-up should provide more insight in how these coping processes develop and in which individuals this leads to inadequate psychological functioning.

Like other reports (Brandt et al., 1989; Wiggins et al., 1992), short term (6 months) post-test adaptation seemed, at first sight, rather appropriate both in carriers (86%) and non-carriers (80%), given the outcome measures intrusion, denial-avoidance and perception of the future (chapter 7). Only a few individuals expressed their need for additional contacts

with their genetics centre. Need for other professional support was not requested. Wiggins et al. (1992) found that both carriers and non-carriers functioned better than those who could not be informed on their genetic risk. The reservation about these findings concern the possibility of a self selected group. Moreover, a rather large number of the carriers (24%) were lost to follow-up in the Vancouver study which may have biased their results. We have excluded the 'uninformative' individuals (n=2) in the analyses of our study. However, our clinical experience with one of them shows that she reacted to the uninformative result with prolonged depression and severe suicidal ideation.

As expected from our clinical experience (the pre-test and post-test in-depth interviews), the reported pre-test contentment with a supportive companion was highly important with respect to the ability to face the new genetic reality (chapter 7). However, 10 out of 48 couples (5 carriers and 5 non-carriers) have terminated their relationship. They were unable to cope with the shift in their marital contract, induced by taking the test (pre-test) or by the test result itself. Only one non-carrier has sought professional support elsewhere other than was offered by the genetics centre, but this was only after she had been divorced.

Early follow-up in all studies have, thus far, shown that presymptomatic testing has fulfilled the expectations of the test candidates, given that testing is performed in a clinical context that includes profound pre-test counselling, psychological support and regular follow-up. No one in our study and only a few in the Vancouver study (Bloch et al., 1992) has regretted testing thus far. The combination of psychological inventory by questionnaires and in-depth interviews gave many applicants and their partners, the additional incentive of work of worrying (pre-test) and working through (post-test). This may have facilitated their thinking, feeling and sharing their experiences.

The test outcome certainly has far reaching consequences for the future, though many participants denied these.

Identified Carriers/Non-Carriers Ratio

The ratio of carriers to non-carriers in our study was 1:1.5, which is comparable with most other reports. Brandt et al. (1989) had a 1:2.5 ratio, probably due to their policy of excluding test applicants who were found to have minor motor abnormalities and/or mental disturbances. Brandt et al. (1989) reported that the differences in number of carriers and non-carriers was unlikely to be due to chance. Prospective non-carriers may, as a group, function better and be more interested in scientific advances. Non-carriers

also assigned a lower subjective risk for HD than carriers, prior to the test (Brandt et al., 1989).

Tyler et al. (1992b) hypothesized that some at-risk individuals correctly expect to be eventually freed from the anxiety of perceiving subtle abnormalities becoming evident in their siblings and are thus encouraged to undertake testing in the expectation of a favourable result. In addition, some presymptomatic carriers may be less likely to seek testing because early cognitive and/or personality changes, in fact, made them *less* worried about the possibility of inheriting the disease (Tyler et al., 1992b). In our study, half of those who thought it likely that they would eventually prove to be a carrier, actually had this confirmed, which is twice as frequent as Meissen et al. (1991) reported. Most individuals (89%) who had anticipated a favourable result proved to be free of the gene (Meissen: 40%). However, after correction for two individuals over 45 years of age and two applicants at 25% risk, 67% had their expectancy confirmed.

Over a period of time, we adapted our policy so as to include these applicants, who were suspected of having early signs of HD, but who were not (consciously) aware of it, as became obvious after profound counselling on these aspects. Applicants were asked whether they would wish to know about possible early signs for the illness when they proved to be gene-carrier. Learning to be a carrier might serve as the first step in accepting the future illness.

Post-Test Effects in Identified Gene-Carriers and Their Partners

Most identified carriers have generally recuperated within a week after hearing the outcome of the test. This was generally observed by others (Meissen et al., 1988; Brandt et al., 1989; Wiggins et al., 1992; Tyler et al., 1992a). Carriers in our study have tended subsequently to deny the meaning of the test result and have avoided talking about it (chapter 2 and 4). They rated their current life situation as good. Bloch et al. (1992) reported that carriers suffered from anxiety and depression up to two months after disclosure, but generally felt better after one year although experiencing a heightened perception of the present. They also experienced difficulties in sharing their feelings with others and the impact of testing for their families. In our study, carriers seemed disappointed about the quality of control and greater difficulty in making plans for the future, 6 months after disclosure (chapter 4). This may be due to new doubts about their prior opinions on having a family, the underestimated reactions of others to the unfavourable results and the impact on their spouses.

Yet, the impact on quality of life and relationship was denied or minimized. Denial and minimizing the test result might be not realistic but adequate in the short term, indicating

resilience, ego-strength and well functioning psychological defences. Taylor (1983) mentioned amongst the basic illusions or involuntary ways of coping with stressful events: self-enhancement, exaggerated belief in one's personal control and unrealistic optimism. Self-enhancement involves the perception of one's self, one's past behaviour and one's enduring attributes as more positive than is actually the case. Exaggerated belief in one's personal control involves the perception that one is invulnerable. Unrealistic optimism involves an unrealistic array of opportunities in the future and absence of adverse events. Hence, it is uncertain whether these defences are adequate in the long term. When defences are not flexible, but rather rigid, then maladaptive functioning may be expected, all the more since strong denial of the disease and overestimation of oneself is often observed in HD patients (Martindale, 1987).

The coping capabilities of carriers is difficult to reconcile with the significance of the outcome for their partners, of whom the latter have indicated their need to discuss the implications of the result but did not dare to effectuate this. This certainly has profound effects on the marital relationship, in the short term as well as in the long term. Some partners have contacted the centre after the 6-month follow-up with their concern about possible early signs for HD in their spouse. Psychological intervention should be carefully applied as to not adversely interfere with the relationship.

In 4 carriers (14%) indicators for post-test psychopathological dysfunctioning were found, which could not be predicted from the pre-test personality characteristics measured (chapter 5 and 7). These individuals reported that they suffered less from intrusive thoughts, but showed more denial-avoidance behaviour. Three of them proved to be at-risk for depression and future suicidal behaviour. This pattern of coping with their fate might justify psychological intervention.

Preliminary findings of the long-term follow-up (> 6 months) showed that 2 out of 4 identified carriers in our study, in whom the HD disease became clinically manifest one year after the test, attempted suicide and all 4 had depressive feelings. These carriers coped well shortly after the test results until the 6 month follow-up. However, they had trivialized the meaning of the test results. Two other carriers requested psychiatric hospitalization after one year. Hence, it is important that the short term defences in carriers are appreciated but should be treated with caution. Further investigations should be undertaken of how carriers, their partners and their family can find a balance between fully utilizing their current capacities to fulfil their life expectancies and slowly adjusting to their future burden.

Post-Test Effects in Non-Carriers and Their Partners

Identified non-carriers showed absence or lack of relief at least within the first six months after the test. Most of them experienced emotional and/or social problems, including problems with affected relatives. However, they saw their previous ideas confirmed with regard to gaining control in the future, including having a family (chapter 4). Non-carriers who were highly distressed prior to the test outcome, were more at risk to be distressed after 6 months. Female non-carriers were more at risk of experiencing post-test distress about HD-related matters (chapter 6).

The initial absence of relief was not unexpected since we have observed this in the first 18 consecutive tested applicants (Tibben et al., 1990a,b). Moreover, similar effects were, for example, seen in survivors from concentration camps (Lifton, 1979). Most applicants had based their early life scenario's on the belief that they will probably get HD.

Therefore, non-carriers are suddenly deprived of this concept and their life prospects, including relationships with (affected) parents, (affected) siblings and other relatives. They are challenged to adapt to their new role in the intrafamilial network. Depression and survivor's guilt can adequately describe some of the associated feelings.

Moreover, since their choice of partner has often been established against the background of HD, non-carriers and/or their partners may feel the need to re-evaluate their partnership. The long lasting effect of the HD-expectancy in eventual non-carriers might also have (unconsciously) influenced their partner choice. For example, they might ask a partner to either accept or exclude the risk for progeny as a condition for a continuous partnership. If the test outcome refutes the necessity for such limitative conditions, the partnership may lose its basis.

Our first report on these observations in non-carriers (Tibben et al., 1990, 1992) have been confirmed by the Vancouver group (Huggins et al., 1992). Nine non-carriers in our study (20%) showed indicators for post-test psychopathological dysfunctioning which could not be predicted from the pre-test personality characteristics measured (chapter 5 and 7). Two non-carriers proved to be at-risk for depression and future suicidal behaviour. Huggins et al. (1992) reported that 10% of the non-carriers had psychological difficulties coping with the new genetic status. Difficulties included the making of irreversible decisions based on the belief that one would get HD and having too optimistic expectations of the positive effects of being identified as non-carrier. Generally, non-carriers may be most vulnerable between 2 and 12 months after disclosure of the test results.

Post-Test Effects in Partners

In this study we gave much attention to the partners of applicants for the test (chapter 2, 3a and 4), which has not been appreciated in other presymptomatic HD testing programmes, with the exception of the study by Meissen et al. (1991), who reported on the pre-test attitudes and expectations in both applicants and their companions.

Generally, partners found great relief in being able to talk about their feelings during the interviews and appreciated completing the questionnaires.

Carrier-partners experienced a short period of intense sorrow and anger and saw their future as being even more overshadowed by the illness. However, they minimized the impact of the test result on their present quality of life, probably as a result of their perception of their partners' ability to cope. They often found it difficult to understand why in fact, carriers coped so well. Partners were able to face the possible effects of the disease and its far-reaching consequences and wished to share their feelings, although half of them missed the support of others, including relatives. This certainly has profound effects on the marital relationship, in the short as well as in the long term. Some partners have contacted the centre after the 6-month follow-up with their concern about possible early signs for HD in their spouse. Psychological intervention should be carefully applied so as to not adversely interfere in the relationship.

Half of the non-carrier-partners stated that nothing had changed, compared to the pre-test situation, with the exception that they perceived more control over their own future. The other half found relief: the option to having children free of HD being finally open for them.

Methodological Issues

The research protocol described in this study was developed so as to be more comparable to that used in other studies (Meissen et al., 1988; Brandt et al., 1989; Fox et al., 1989; Craufurd et al., 1989; Tyler et al., 1992a,b). This concept was also supported by the regular discussions of their working groups at the biannual meetings of the Working Group on Huntington's Chorea of the World Federation of Neurology. Over time, however, some differentiation developed in the choice of measurement instruments depending on their psychometric qualities (validity, reliability), appropriateness in the specific population and local research interests. Furthermore, methods for statistical analyses of the data may show group-specific preferences (e.g. non-parametrical versus parametric models; descriptive versus predictive analyses) (Brandt et al., 1989; Wiggins et al., 1992; Kreiner, 1989; Schafer and Fals-Stewart, 1991).

Longitudinal follow-up studies afford a perspective that is based on measurements obtained at discrete time-points. The measurement points in our programme were chosen for pragmatic reasons (simultaneously with the counselling sessions) and based on previous experience with the first consecutively tested persons (Tibben et al., 1992). In the future, time-points should also be theory based (Schafer and Fals-Stewart, 1991).

The study samples were small and necessarily self-selected (self-chosen participants only). A control-group would have facilitated differentiation between predictor and outcome variables. However, obtaining a meaningful control group in this and other studies was unattainable. Firstly, a call for participation in the Netherlands for a prospective control group, in 1989, via the HD patient organization gave no response. Secondly, using those who applied for the test but who could not be informed about their genetic status for different reasons, would be an invalid group since they would not eventually be in the actual situation of experiencing the impact of a test result. The next best solution therefore was to study at-risk individuals during the actual period of HD testing and then to compare these non-participants with participants (chapter 3b). In this way, the changes within individuals, or between subgroups in the programme e.g. between carriers and non-carriers become more meaningful. Although generalizations towards other potential participants must be guarded, the results may, nevertheless, serve to generate hypotheses. Individuals tested, but lost to follow-up (although in our study there only two at the 6-month follow-up), may be of some concern, since they may be most vulnerable. Follow-up data on them should be made available as much as possible. If necessary, information could be obtained from the general practitioner, with the assumption that participants have previously given consent. In one case, a non-carrier withdrew from the study after she became depressed for a prolonged period due to guilt feelings towards her siblings and affected parent. After 18 months, she was able to accept her new status and felt relieved. A carrier with previous phobic symptoms was lost for follow-up at the 6-month visit. Although her spouse tried to persuade her, she did not want to complete the questionnaires. She started behavioral therapy with favourable results.

Another source of bias might be that the conceptional framework of the follow-up study was partly based upon experiences from the first groups of applicants who went through presymptomatic testing with supportive care, but who only had post-test psychological evaluation. That "founding" group might have special characteristics and mental resources of being able to go through the testing procedure which might have induced self-selection of individuals with strong coping capabilities (Bloch et al., 1989). In the follow-up programme, the dual role of the psychologist (being the follow-up observer and the person available for support), might have biased the results on the objective needs in a follow-up programme. In practice, support varied from additional contacts with

participants, (rare) referrals to other professionals in mental health care and informing and supporting general practitioners. Even if applicants might have had a feeling of dependency upon the primarily investigative effort in the genetic testing programme, most of them could discriminate between the primarily investigative (and accordingly supportive) nature of the follow-up programme and the need for specific referrals whenever their coping mechanisms were apparently inadequate to answer actual problems. In fact, it was foreseen that the inherent therapeutic qualities of an inventory follow-up programme might partly fulfil therapeutical needs in the post-test period and that a request for additional support might be even more meaningful as evidence of psychological maladjustment or essential needs for more personally directed help.

In addition, the research experience was soon implemented in genetic counselling. Prior to the release of the test results, applicants were informed on, for example, the survivor syndrome, effects on partner relationships and modes of preparing for disclosure. This might have influenced the cognitive schema's which enabled applicants to cope better (Horowitz, 1990). Moreover, retrospective observations on the first group of individuals going through presymptomatic testing (chapter 2), were introduced into the pre- and post test counselling of individuals during the second phase, including preparing for unexpected feelings of grief and sorrow about being identified as a non-carrier. Although people did not give it profound attention, many could recall the pre-test counselling information on psychological effects and found it helpful thereafter, e.g. "Because you told me of the possible effects, I knew that I was not the only one that felt numb...".

The interview study was added in the course of the programme (chapter 8). It enabled us to obtain deeper insight into the defences and coping mechanisms of applicants and their partners. Although the use of professional judges of the interviews is expensive and the analysis of the qualitative data elaborate, it is nevertheless a promising approach given the complicated psychological processes present in samples of this study group. They did provide a unique opportunity (as compared with other studies, Brandt et al., 1989; Bloch et al., 1989; Wiggins et al., 1992) to give access to the deeper psychodynamics of participants.

Practical Implications of the Results

What have we learned thus far? For many participants, the test result has ended a period of anxiety and uncertainty, which was often characterized by squandering a variety of life options. The knowledge of either being a carrier or a non-carrier is an enormous shift in reality which needs adjustment and integration into daily life. This is characterized by

denial and minimization in carriers in the short term, loyalty problems in their partners and absence of relief in non-carriers. This study supports the view that the partner-relationship or family, rather than the individual who seeks testing, is really "the patient" in medical genetics (Kessler and Bloch, 1989). This study enabled us to gain deeper insight into the participants' motives and the short term psychological processes they went through. Applicants should be aware of this prior to receiving the results. They should be offered the full opportunity to consider the advantages and disadvantages of testing.

The Genetic Counselling

The genetic counselling process could be improved by introducing concepts from the growing experience on presymptomatic testing for HD and other late onset diseases. Comprehensive semi-structured pre-test and post-test interviews should be developed that enable participants to reflect on their psychological processes and to increase their introspective capacities. These could include the exploration of emotions and discussion of themes such as: understanding the conscious and underlying motives to take the test, anticipating and discussing the impact of either result for the mutual partners, discussing the impact on marriage/relationship, the impact of having an affected parent, sharing the information of the test, discussing sources and persons for help/support when needed, current feelings towards affected (grand)parents. The characteristic ways of coping with distressing events such as being at-risk, or typical defense strategies are to be thoroughly explored, e.g. is the participant more inclined to face his/her problems, or does he/she rather show denial-avoidance behaviour.

The international guidelines for presymptomatic testing (Ethical issues, 1990) should emphasize the need for profound exploration of the consequences for the partner-relationship and the family system with respect to interaction and communication (section 5.3. of the guidelines). The process of working through the test results, the psychodynamics of the motives must be familiar to the applicants, their partners and the genetic counsellor.

Follow-through and follow-up after the counselling and testing procedure.

We ask applicants and their partners not to make a final decision about taking the test until after the second counselling session so as to ensure insight into the possible relevant effects for themselves. All available information, not only on technology, but also on social and psychological effects of either result should be profoundly discussed. We also encourage test applicants and their partners to discuss the test and its consequences with

chosen relatives or friends. Applicants are asked to indicate their preference for the most suitable moment and method of disclosure of the test results, in order to heighten their sense of control. This will not prevent emotions. It may mean, for example, that if an applicant tells his/her friends or relatives when the moment of disclosure is to take place, then these friends may themselves seek contact with the tested individual about the test result.

Knowledge about the various ways that tested individuals and their partners cope, may help the genetic counsellor to avoid any prejudgment about the reactions of a participant towards the test results. The counsellor's role is to inform the participant as comprehensively as possible not only about all the potential consequences, but also about subsequent decisions based upon the test results.

Contraindications for presymptomatic testing?

Early clinical signs of HD and/or the symptoms of a current or previous psychiatric disease in an applicant have been held as contraindications for presymptomatic testing (Brandt et al., 1989; Craufurd et al., 1989; Nance et al., 1992; Tyler et al., 1992a,b). During our study, 3 persons with a previous history of anxiety disorders were tested (and identified as gene-carriers). The short term effects on their quality of life, their social relationships and the psychiatric treatment were favourable. Careful consideration is indicated to balance risks and benefits for individuals with a psychiatric condition, which may have possibly originated from the knowledge of being at-risk and from problems in personality development in early childhood due to traumatic experiences with HD in the affected parent. Here, again, the possibility of giving a realistic appraisal of the actual situation as a basis for further psychotherapy must not be interfered with by dogmatic restrictions.

Informing and Training Health Care Providers

DNA-testing for late onset genetic disorders is a rather new discipline for clinical genetic services, when compared to the already established syndrome diagnosis, chromosomal, metabolic and DNA diagnosis, risk determination, prenatal diagnosis etc.

Apart from other developments in genetic technology, the number of late onset genetic disorders that can be predicted will increase substantially. This may also create situations where decisions by young adults may result in undesired information to their parents and other relatives (Galjaard, 1990). The problem of risk modification in individuals not directly involved in a study or seeking information for themselves is inherent in any

linkage study, but may also be present in studies applying direct mutation analysis, for example in the children of a healthy parent originating from a family with myotonic dystrophy or the fragile X-syndrome (Verkerk et al., 1991; Brown et al., 1991; Harper et al., 1992; Follette and Laird, 1992).

One of the ethical questions is, especially if direct mutation analysis can be applied, whether a parent can prevent an adult son or daughter obtaining such information. Hence, the clinical geneticist is then confronted with a new type of confidentiality problem towards an indirectly tested parent of a consultant.

At the level of genetic/medical health care, many medical disciplines and non-medical professionals in health care, e.g. psychologists and social workers, will become involved in the issues raised by this development, since follow-up and information on these options and their effects will become more generalized. Clinical genetic services will thus have to meet an increasing work load, emphasizing the need for high standards within the genetics services (Galjaard, 1990; Chapman, 1992). Clinical geneticists are trained and qualified to give information to individuals at-risk and to encourage exploration of their motives for taking the test. This requires accuracy, specific knowledge, empathy and a code of ethics. It may be questioned whether the actual clinical genetics services have sufficient capability to meet the present and future service demands of presymptomatic testing programmes. Moreover, the presymptomatic detection of an increasing number of late onset genetic disorders will make simplification of the pre-test and post-test counselling procedures unavoidable (Tyler et al., 1992b). However, the quality and acceptability of an entire testing procedure might be safeguarded and improved by a closer involvement of the applicant's general practitioner (Mennie et al., 1990; Thomassen et al., in press). In a study amongst general practitioners in this country, it was recently shown that general practitioners are highly interested in such testing programmes and that over 70% wished to assume an important role in the counselling and support during and after decision making (Thomassen et al., in press). In such a way, genetics may become more integrated into primary health care. However, during the actual developmental phase, extensive pre-test counselling and release of the test results will remain the responsibility of the clinical geneticist until sufficient knowledge and experience has been obtained and introduced into general practice (including post-graduate training). General practitioners and other health care professionals may take pivotal roles in preparing and supporting patients going through presymptomatic testing. In particular the supportive aspects towards partners, patients and non-carriers might be safeguarded in this way.

Clinical geneticists may familiarize themselves with the specific problems of applicants for presymptomatic testing, train new geneticists and develop their organization to adapt to the growing interest in this field. Clinical genetic centres, as related to academic

institutes, may have an unique task to perform research not only on the information transfer and decision processes, but also on the psychodynamic and social consequences of the implications of the "new" genetics.

Research Funding Strategies

The future development of our understanding of the psychosocial effects of presymptomatic testing and needs for psychological support systems will be severely dependent on research funding strategies. Funding of this type of research is essential to develop standards of care and to introduce them into the (genetic) health care of individuals and their families. In the future it will be necessary to see which type of funding is needed for clinical genetic services and other health care providers so as to guarantee an optimize this and other types of predictive testing for late onset genetic diseases in the population.

Psychological Follow-up Research on HD and Other Late Onset Genetic Diseases

Since the actual follow-up reported in this study is 6 months after test disclosure and various observations indicate long term effects after this period that might be of profound significance, continuation and long term observation are mandatory. Long term coping of identified carriers, their potential suicidal ideation and eventual adaptation of non-carriers are only two fields of unresolved questions. Others are: long term adaptation of partners of identified carriers, influences on family planning and effects on children.

Further follow-up on the coping of identified carriers with their inevitable fate once they become clinically symptomatic, including their reproductive decisions is essential. Non-carriers should be followed-up to establish how they manifest the relief of being free from HD.

Only when the following questions in this study are fully answered will we obtain a better insight into the implications of any presymptomatic testing programme.

1. Can we predict the long term reactions and coping behaviour of participants using such factors as the characteristics of coping in the first year after the test, general health, future expectancies and defensive behaviour? How will the foreknowledge affect carriers as they approach the impending onset of the disease?
2. If in some cases manifest choreatic movements are preceded by early affective and/or cognitive changes (Folstein, 1991), which subtle neuropsychological correlates in carriers will be the most useful indicators prior to full clinical manifestation? Do these correlates interfere with specific coping behaviour, or psychological and social adjustment?

3. Which consequences will presymptomatic testing eventually have in the access to jobs and (life) insurance? For example, if in The Netherlands, the Government made a temporary agreement with the life insurance companies about non-enforceable disclosure of genetic data in insurance coverage below a certain threshold (Dutch Health Council Report, 1990), then it remains to be seen whether or not this option will be maintained indefinitely.

4. What recommendations can be suggested for further genetic counselling and support? Genetic counselling of prospective candidates for presymptomatic testing and their partners might become optimized using findings from this study; psychosocial workers and clinical psychologists from these centres could develop protocols for this purpose.

5. What further insight can be obtained in those at-risk individuals who are knowledgeable about the test but who have not yet applied for it? What are the characteristics of non-applicants for a presymptomatic testing programme? The actual state of the art is, that only one contemporary study of non-applicants from the same cohort as the applicants (chapter 3b) is available and these studies have been shown to be much more relevant than other studies undertaken prior to the introduction of similar tests.

6. Which psychotherapeutic interventions are most likely to minimize adverse outcomes of being informed on one's genetic status? A most important outcome of these observational follow-up studies is the assessment of the need for professional psychological and/or psychotherapeutic long term support, after presymptomatic diagnosis. Even if the actual data on HD (with international follow-up of \pm one year) do not indicate a substantial need, the frequency of relationship disturbances and suicidal ideation among identified carriers of HD need careful follow-up to establish their long-term frequency and intervention requirements.

Little is known about how to apply the new developments so as to ensure that their use will provide the most benefit and least harm in the long term. Presymptomatic diagnosis will become available for an increasing number of hereditary disorders thus providing a variety of treatment prospects. However, these disorders may vary e.g. in the pre-testing of risk status of patients (general population or specific risk group for disorders with in the age of onset or in severity of symptoms (Friedmann 1990; Galjaard, 1990; Chapman, 1992; Terrenoire, 1992). In addition, those offering testing may vary in knowledgeability about all aspects of testing programmes (whether specifically trained in genetics or not) The need for public and professional education escalates. Physicians and other health care providers will be forced to struggle with complex psychological, social and ethical issues in the application of molecular genetic technology to clinical practice (Brandt et al., 1989;

Galjaard, 1990; Terrenoire, 1992).

The results from the HD studies will obviously influence the attitude of professionals as well as the public. The data will become essential for a future medical-ethical evaluation of presymptomatic testing. Other late onset disorders must be studied in a similar way, addressing aspects of: (partial) treatability (familial cancer syndromes, polycystic kidney disease), information on genes with substantial differences in transgenerational effects (fragile X-syndrome, myotonic dystrophy), or disorders with an all or none effect (familial cerebral haemorrhage).

To obtain a balanced image of the future, a growing and equal partnership of the psychosocial sciences, molecular biology and genetics should be established in conducting research in this area (Galjaard, 1990; Reiss et al., 1991).

Conclusions

It is apparent that both carriers and non-carriers may need more than one year to become fully aware of their new genetic status and to integrate it in daily life. This includes interpersonal relationships and anticipation of a future, either with or without the disease. This process might be referred to as grieving, i.e. losing a familiar and perhaps often safe identity (being at 50% risk) may induce (un-)conscious conflicts. That is understandable and normal and such a process of working through will take time. Some individuals may be able to accomplish this process, others may not.

In The Netherlands, the presymptomatic DNA-testing programme for HD is already a clinical service, centralized in Leiden. 'Are we ready for widespread community implementation of presymptomatic testing for HD?', pondered Hayden (1991). Terrenoire (1992) in her comprehensive literature review agrees with Hayden that it is too premature to recommend that genetic testing with DNA markers should become a routine in clinical medicine.

There is at present no evidence that shows any potential harm resulting from the new genetic knowledge. We only know that within a limited controlled counselling protocol, including psychological follow-up research, presymptomatic testing has not led to significant adverse effects for most tested individuals (Hayden, 1991; Chapman 1992; this study). We also know that many individuals have not yet fully appreciated the impact of the test result, probably due to psychological defences such as denial and minimization (this thesis). The research projects in different countries should obtain further insight in the medium- and long-term effects of DNA-test results.

Hence, in conclusion:

1. Both the genetic counselling protocol and the psychosocial research protocol for presymptomatic testing for HD have shown that they can serve as a model for the introduction of predictive programmes for other late onset genetic diseases.
2. More longitudinal follow-up research is needed to study the actual psychological and social consequences of testing.
3. DNA-testing for HD and other late onset diseases should not be introduced into the community without appropriate support in pre-test and post-test counselling.
4. Presymptomatic DNA-testing for late onset genetic disorders is only to be implemented after thorough experimental evaluation in a multidisciplinary setting until the medium- and long term effects of the programme are sufficiently evaluated.
5. Long term funding of research on the psychological and social consequences of presymptomatic testing should be safeguarded and is as equally vital as funding for DNA-research.
6. Educating and training sufficient genetic counsellors to meet the current demands of the increasing number of predictive testing, is essential.
7. Clinical genetic centres may facilitate the integration of genetics in the primary and secondary health care, both by continuous attention to postdoctoral medical teaching and training and by making integrative networks with clinical specialists in different medical fields.

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Summary

Summary

The dramatic progress in molecular genetics gives to individuals, who are at-risk for a variety of hereditary diseases, completely new options to learn with more accuracy about their personal genetic make-up and, subsequently, the reproductive alternatives and future health prospects.

Huntington's disease (HD) is a progressive, autosomal dominant inherited disorder, characterized by involuntary movements, behavioral and personality changes and dementia. The mean age at onset is 40 (\pm 12) years and the mean duration of the illness is \pm 16 years. No cure is available yet. Children of an affected parent have a 50% risk of inheriting the gene for HD. HD was the first late-onset disorder which could be detected in *risk-carriers*, preceding the manifestation of symptoms of the illness (presymptomatic DNA-testing). As such, HD was regarded as a paradigm for late onset disorders, such as polyposis coli, hereditary cerebral haemorrhage with amyloid-Dutch type, myotonic dystrophy, specific cases of Alzheimer's disease and cardiovascular disease. In Leiden, presymptomatic DNA-testing for HD was introduced in 1987 and a prospective psychological follow-up programme was added in 1989. The aim of the psychological study was to identify factors that are related to later psychological functioning and adjustment, allowing early identification of those at-risk for later adjustment problems, to facilitate intervention, additional follow-up and aftercare. Furthermore, the study served to tailor the genetic testing protocol and to develop strategies to manage untoward psychological responses to the DNA-test results.

Prior to the prospective follow-up study, the first 18 consecutively tested individuals (period 1987-1989) were followed-up one year after disclosure of the test results. Identified *carriers* apparently functioned well, using repression and avoidance as psychological defense strategies. Using the data from this research group, we reported on the unexpected reactions in *non-carriers* such as absence of relief, survivor guilt, numbed emotions and difficulties in creating a new life perspective and in *carrier-partners*, who displayed loyalty problems towards the carriers (**chapter 2**).

Between April 1, 1989 and April 1, 1991, a total of 114 at-risk individuals entered the presymptomatic DNA-testing programme. Criteria for enrolment in the psychological follow-up study were 1. ability to understand the questionnaires, 2. informed consent and 3. having received a DNA-test result. Seventy-three individuals at-risk and their partners, who received a DNA-test result (29 *carriers* and 44 *non-carriers*), were followed-up up to 6 months after disclosure. General characteristics are presented in **chapter 3a**. The methodology was a combination of psychological measurements and in-depth interviews with both the applicant and the partner at pre-test, one week and 6 months after

disclosure.

The main reasons for taking the test were family planning (60%), to reduce uncertainty (43%), or to obtain certainty (38%). Partners of applicants stated that planning for the future (76%) and family planning (55%) were the most important reasons. Obtaining certainty was expected to enable applicants to increase control over their future. Most applicants (>89%) and partners (>93%) denied that an unfavourable result would have adverse effects on either personal mood, quality of life, or marriage.

Prior to actual introduction of the test, attitudinal studies in the US and Canada showed a 70-50% willingness to participate among risk-carriers (having a risk of 50% for HD) and many of them expected depression and suicidal feelings. After introduction, the uptake of the test proved to be 10-20% in several countries.

In **chapter 3b**, we did a first study on 28 non-participants, during the actual availability of the test (1992). They anticipated more adverse effects after an unfavourable test result in comparison to applicants. Non-participants' reasons against the test included fear of an unfavourable result and inability to cope with that result. They did not expect to obtain more control over their future. These findings demonstrate that attitudinal research prior to introduction of this and possibly other tests may not give insight in the actual attitude of at-risk individuals at the time the test is available. This emphasizes the importance of psychological follow-up research from the moment a new technology is available.

Chapter 4 presents the results of the 6-month follow-up study on post-test attitudes and appreciation. In general, *carriers* have shown a rapid recovery within a week after hearing the outcome of the test, although they were disappointed about feeling of not being any longer in control of their situation and had greater difficulty in making plans for the future. Only 6% experienced that the test result had adversely affected the quality of their life and relationship. Although these reactions in the other 94% may seem unrealistic, they may be also adequate in the short term, indicating enormous resilience, ego-strength and well functioning psychological defences. It should be further studied whether these defences are adequate in the long term, e.g. when the clinical symptoms of the disease become manifest.

The ability of *carriers* to cope was difficult to reconcile with the significance of the outcome for their partners, who have indicated their need to discuss the implications of the result but did not dare to effectuate this, for fear of hurting the carrier's feelings. This may have adverse short and long term effects on the marital relationship.

One-third of the *non-carriers* positively valued the current influence of the test. Other *non-carriers* showed absence or lack of relief at least within the first six months after the

test. Most of them experienced emotional and/or social problems, including problems with affected relatives. However, they saw their previous ideas confirmed with regard to gaining control in the future, including having a family.

This is the first study that presented the experiences of the *partners* of applicants for the test (**chapter 2, 3a and 4**). Generally, *partners* found great relief in being able to talk about their feelings. *Carrier-partners* experienced a short period of intense sorrow and anger and saw their future more overshadowed by the illness. They often found it difficult to understand why carriers coped so well. *Partners* were able to face the possible effects of the disease and its far-reaching consequences and wished to share their feelings, although half of them missed the support of others, including relatives. *Carrier-partners* generally tend to be loyal to the denial or minimization in their spouses. Their needs for support must be appreciated, since they often do not express this, out of concern or loyalty to their partner.

Half of the *non-carrier-partners* stated that nothing had changed, compared to the pre-test situation, with the exception that they perceived more control over their own future. The other half found relief: the option of having children was now open for them.

Specific psychological characteristics could be identified in dealing with the pre-test distress (**chapter 5**). Females were more inclined to turn their threatening feelings against themselves and showed internal control beliefs. Males turned their unacceptable feelings against the outer world and passively allowed their health prospects to depend upon fate. Furthermore, it was found that those, expecting a favourable test result, showed more denial-avoidance, whereas pessimistic applicants suffered more from HD and reported more health complaints. Those who did not anticipate a specific outcome, could generally face the HD burden, but isolated their feelings about it.

The strength and uniqueness of this study, in comparison with others, is that we have built a prognostic model aimed at identifying individuals at risk for psychological maladjustment to their new genetic status, as reflected by the amount of suffering from HD, denial-avoidance behaviour and expectancies about the future (**chapter 6 and 7**). This was achieved by use of the statistical method of multiple regression analysis. The second important finding was that our observations were in accordance with the 'working through' model, reflected by the patterns of unwanted intrusive thoughts and denial-avoidance behaviour.

Chapter 6 examines the predictability of post-test distress, using the Impact of Event

Scale. The items of the IES were specifically coupled to HD. The best predictor for post-test distress in both *carriers* and *non-carriers* was the level of distress, one week after disclosure of the test results. In addition, if females had severely suffered from HD prior to the test, than they were at higher risk for post-test distress in comparison to male applicants. *Carriers* who had high pre-test distress were found to be more at-risk for post-test distress than *non-carriers*. Individuals who experienced low stress shortly after disclosure and were longer acquainted with HD in their family, reported low stress after 6 months.

The analysis of intrusive thoughts and denial-avoidance behaviour as aspects of 'working through' (chapter 7) shows:

1. the more that applicants suffered from intrusive feelings about HD and tried strongly to avoid HD-related situations, prior to the test, the greater the chance that they will probably experience this after the test if they subsequently proved to be a carrier. This was the only difference that could be found between *carriers* and *non-carriers*.
2. the more that both *carriers* and *non-carriers* tried to avoid HD-related situations prior to the test, and had suffered from HD and the less contented they were with available support, the greater the chance that they will show avoidance behaviour after the test.
3. the more *carriers* as well as *non-carriers* were pessimistic about their future when they applied for the test, the more they avoided situations that might confront them with HD and the more dissatisfied they were about their available support (pre-test), the greater the chance that they perceive their future with pessimism after disclosure (with a risk for depression and suicidal ideation).

The individual patterns of intrusion and denial-avoidance may provide useful indicators for additional support when necessary or when requested. Long term follow-up should provide more insight in how these coping processes develop and in which individuals this is likely to lead to inadequate psychological functioning.

Pre-test in-depth interviews with a sample of 20 applicants allowed a deeper insight in their (un)conscious defense processes (chapter 8). The pre-test defense style in highly anxious participants involved more immature defense mechanisms, such as denial in fantasy, acting out and turnings against self, in comparison with low anxiety participants. No differences could be found between prospective *carriers* and *non-carriers* prior to the test disclosure. However, highly anxious *carriers* showed increased avoidance behaviour and decline of hopelessness over time, which means an increased risk for maladaptive functioning. Highly anxious *non-carriers* reported slightly decreased feelings of hopelessness, reflecting difficulties in adopting a new life scenario.

In **chapter 9**, the practical implications of this study were discussed.

1. the genetic counselling may be improved by introducing concepts from the accrued experience gained by the presymptomatic counselling of HD and other late onset diseases. We encourage test applicants and their partners to discuss the test and its consequences with specifically chosen relatives or friends and asked them to indicate their preference for the most suitable moment and method of disclosure of the test results, to heighten their sense of control and responsibility.
2. the results of this study may help genetic counsellors, general practitioners and other health care providers to identify needs for support and signs of maladjustment in carriers, non-carriers and their partners.
3. the quality and acceptability of an entire presymptomatic testing procedure might be safeguarded and improved by a closer involvement of the applicant's general practitioner; this is seen as desirable by the applicants and a questionnaire study among Dutch general practitioners shows their willingness to assume this role.
4. clinical geneticists may familiarize themselves with the specific problems of applicants for presymptomatic testing. Clinical genetic centres, with a close relationship to academic institutes, have an unique task to perform research not only on the information transfer and decision processes, but also on the psychodynamic and social consequences of the implications of the "new" genetics.
5. the various observations indicate long term effects after a 6 month period. Hence long term observation is mandatory. The long term coping of *carriers*, their potential depression and suicidal ideation and the eventual adaptation of *non-carriers* to the new genetic status are only two fields of unsolved questions.

This study has showed that presymptomatic DNA-testing has fulfilled the expectations of the test candidates, given that testing is performed in a clinical context that includes profound pre-test counselling, psychological support and regular follow-up. No one in our study has regretted testing thus far. It should be further studied how *carriers*, their partners and their family can find a balance between fully using their current capacities to fulfil their life expectancies and slowly adjusting to their future burden. *Non-carriers* may apparently need more than one year to fully face the new genetic knowledge and feel the full relief. Both *carriers* and *non-carriers* go through a process that might be referred to as grieving: the process of working through these effects will take time.

Samenvatting

Door de spectaculaire ontwikkelingen in de moleculaire genetica kunnen diegenen die een hoog risico lopen met betrekking tot diverse erfelijke aandoeningen (risicodragers) met grotere nauwkeurigheid hun persoonlijk risico laten vaststellen, waardoor zij bijvoorbeeld beslissingen kunnen nemen ten aanzien van bijv. gezinsplanning en hun toekomstige gezondheid/ziekte-situatie.

De ziekte van Huntington (HD) is een progressieve, autosomaal dominant erfelijke ziekte, die gekenmerkt wordt door een toename van onwillekeurige bewegingen, gedrags- en persoonlijkheidsveranderingen, en dementie. De gemiddelde leeftijd waarop de ziekte begint is 40 (plus of min 12) jaar, en de gemiddelde ziekteduur is ± 16 jaar. Er is momenteel geen behandeling mogelijk. Kinderen van een aangedane ouder hebben 50% kans de ziekte te erven (risicodragers). HD is de eerste later in het leven beginnende erfelijke ziekte, die kan worden aangetoond bij risicodragers, vóórdat de kenmerkende symptomen zijn waar te nemen (zgn. presymptomatische DNA-diagnostiek). De presymptomatische diagnostiek van HD wordt als voorbeeld gezien voor zulk onderzoek bij andere erfelijke aandoeningen, zoals de polyposis coli, myotone dystrophie, erfelijke hersenbloedingen, bepaalde vormen van de ziekte van Alzheimer en familiale hart- en vaatziekten. Het Klinisch Genetisch Centrum Leiden is in 1987 met de presymptomatische DNA-diagnostiek begonnen, vanaf 1989 aangevuld met een psychologisch follow-up onderzoek. Het doel van dat onderzoek was het vastleggen van de psychologische gevolgen voor de onderzochten en het identificeren van factoren die bepalend zijn voor het toekomstig psychologisch functioneren en de aanpassing aan de nieuwe situatie. Daardoor zou het mogelijk worden om diegenen te identificeren die na een test kans hebben om later problemen te krijgen, zodat bijv. tijdig adequate hulp en nazorg kan worden geboden. Voorts zijn de gegevens nodig voor het verbeteren van het presymptomatische DNA-programma en de ontwikkeling van strategieën om op onverwachte, en/of ongewenste reacties adequaat te kunnen reageren.

Voorafgaand aan de prospectieve studie is, een jaar na de test-uitslag, een follow-up onderzoek gedaan bij de eerste 18 geteste personen (periode 1987-1989). Geïdentificeerde *gendragers* functioneerden ogenschijnlijk goed, waarbij psychologische afweermechanismen zoals verdringing van affect, en vermijding werden waargenomen. Onverwachte reacties bij *niet-dragers*, zoals overlevingsschuld, vervlakte emoties, en problemen met de opbouw van een nieuw levensperspectief, en bij *partners van gendragers* werden voor het eerst door ons gerapporteerd (hoofdstuk 2).

In de periode tussen 1 april 1989 en 1 april 1991, hebben 114 risicodragers zich voor de presymptomatische DNA-test aangemeld. De criteria om aan de psychologische follow-up

studie mee te kunnen doen waren 1. het kunnen begrijpen van de vragenlijsten, 2. toestemming, en 3. een DNA-test uitslag. Drieënzeventig risicodragers, aan wie een uitslag gegeven kon worden (resultaat: 29 *gendragers* en 44 *niet-gendragers*), werden gevolgd tot 6 maanden na de uitslag. Algemene kenmerken van deze groep zijn beschreven in **hoofdstuk 3a**. Het onderzoek bestond uit het beantwoorden van psychologische vragen en semi-gestructureerde diepte-interviews met risicodragers en hun partners, vóór de test, en 1 week en 6 maanden na de testuitslag.

De belangrijkste redenen om de test te ondergaan waren gezinsplanning (60%), en/of het verminderen van de onzekerheid (43%) òf het verkrijgen van meer zekerheid (37%). De partners vonden algemene toekomstplanning (76%), en gezinsplanning (55%) de belangrijkste redenen. Risicodragers verwachtten dat het verkrijgen van zekerheid of verminderen van onzekerheid hen in staat zou stellen om meer greep te krijgen op hun toekomst. De meeste risicodragers (> 89%) en hun partners (>93%) verwachtten dat een *ongunstige* uitslag geen negatieve invloed zou hebben op de stemming, kwaliteit van leven, of huwelijk/partner-relatie.

In **hoofdstuk 3b** tonen wij aan dat risicodragers (n=28), die zich *niet* voor de DNA-test aanmelden, meer negatieve effecten verwachten van een *ongunstige* uitslag, vergeleken met hen die de test wel ondergingen. Redenen de test niet te willen toepassen waren o.a. de angst voor een *ongunstige* uitslag, en het onvermogen deze te verwerken. Voorts dachten zij dat een test-uitslag hun niet méér greep op de toekomst zou kunnen geven. Voorafgaand aan de introductie van de presymptomatische test (1984-1986) had attitude onderzoek in de VS en Canada getoond dat 70-50% van ondervraagde risicodragers de test wilde ondergaan, en dat velen van hen verwachtten met depressie en suicidaal gedrag te reageren op een ongunstige uitslag. Sinds de test beschikbaar is, blijkt slechts 10-20% van de onderzochten zich voor de test aangemeld te hebben. Wij concluderen dat onderzoek naar de houding van risicodragers, vóór de feitelijke beschikbaarheid van deze en wellicht ook andere testen, blijkbaar niet het juiste inzicht geeft in de feitelijke houding op het moment dat de test wél beschikbaar is.

De attitude en de beleving, 6 maanden na de uitslag is besproken in **hoofdstuk 4**. Hoewel *gendragers* zich binnen een week na het vernemen van de uitslag hebben hersteld, waren zij toch teleurgesteld dat de uitslag hun niet die greep op de toekomst had gegeven die zij voordien hadden verwacht. Slechts 6% vond dat de test uitslag een negatieve invloed had op de kwaliteit van leven, hun huwelijk of partner-relatie. De overige 94% zou de betekenis van de test kunnen onderschatten - hetgeen adequaat kan zijn op de korte termijn - en aangeven dat zij een groot psychisch herstelvermogen, aanzienlijke ik-sterkte,

en goed functionerende afweermechanismen bezitten. Echter, vervolgonderzoek moet aantonen of deze reacties ook voldoen op de langere termijn, bijv. wanneer de eerste symptomen van de ziekte manifest worden.

De goede acceptatie van de *gendragers* waren tegengesteld aan de betekenis van de uitslag voor de *partners*, die behoefte hadden over de gevolgen van de test te kunnen praten. Zij deden dit echter niet uit vrees de gevoelens van de *gendragers* te kwetsen. Deze tegengestelde reacties in *gendragers* en *partners* kunnen ongewenste gevolgen hebben voor huwelijk of partner-relatie, op zowel korte als lange termijn.

Eén-derde van de *niet-dragers* vond dat de test-uitslag een positieve invloed had op hun leven. Overeenkomstig onze eerdere waarneming (hoofdstuk 2) bleek de meerderheid van de *niet-dragers* de betekenis van een goed uitslag nog niet ten volle te (kunnen) beseffen. Zij voelden de eerste 6 maanden na de uitslag algemeen weinig of geen opluchting. Velen van hen hadden emotionele en/of sociale problemen, met inbegrip van problemen met aangedane familieleden. Zoals van tevoren verwacht, hadden de meeste *niet-dragers* wel het gevoel meer greep op hun toekomst te hebben, inclusief gezinsplanning.

De ervaringen van *partners van risicodragers* werden niet eerder systematisch onderzocht (hoofdstuk 2, 3a, en 4). Algemeen waren *partners* opgelucht dat zij over hun gevoelens konden praten. *Partners van gendragers* maakten een korte periode van verdriet en woede mee, en zagen hun toekomst overschaduwd door de ziekte. Zij vonden het vaak moeilijk te begrijpen dat *gendragers* het ogenschijnlijk gemakkelijker hadden. *Partners van gendragers* konden de verstreckende gevolgen van de ziekte goed onder ogen zien en wilden hun gevoelens graag met anderen delen. De helft miste echter de steun van anderen, inclusief van familieleden. *Partners van gendragers* bleken algemeen loyaal te zijn aan de ontkenning of bagatellisering door *gendragers*. Er dient rekening gehouden te worden met hun behoefte aan steun omdat zij die vaak zelf niet aangeven uit vrees de gevoelens van de *gendrager* te kwetsen.

Voor de helft van de *partners van niet-gendragers* was er niets veranderd, vergeleken met de situatie vóór de uitslag, behalve dat zij het gevoel hadden hun eigen toekomst meer in eigen hand te hebben. De andere helft ervaaarde opluchting: zij hebben de mogelijkheid om aan een gezin te denken.

Omdat het krijgen van een uitslag van een presymptomatische test opgevat kan worden als een gebeurtenis vol stress, werd er onderzoek gedaan naar specifieke psychologische kenmerken die werden gevonden in het omgaan met de stress vóór de uitslag (hoofdstuk 5). Vrouwen neigden ertoe bedreigende gevoelens tegen zichzelf te richten, en hadden meer het gevoel dat zij zelf verantwoordelijk waren voor ziekte en gezondheid. Mannen

richtten daarentegen hun bedreigende gevoelens meer op de buitenwereld en vonden dat hun gezondheid vooral afhankelijk is van toeval. Zij, die een *gunstige* test uitslag verwachtten, vertoonden meer vermijdingsgedrag en ontkenning, terwijl degenen met een sombere verwachting méér gebukt gingen onder de dreigende ziekte en tevens meer gezondheidsklachten vertoonden. Zij, die géén specifieke uitkomst verwachtten, konden algemeen de dreiging wel onder ogen zien, maar hadden er geen of weinig gevoelens bij.

Het unieke van dit onderzoek, in vergelijking met andere studies naar effecten van presymptomatische diagnostiek, is, dat wij een prognostisch model hebben ontwikkeld om personen te identificeren die een verhoogde kans hebben op verwerkings- en aanpassingsproblemen, zoals weerspiegeld door de mate waarin iemand gebukt gaat onder de ziekte van Huntington, ontkenning en vermijdingsgedrag, en toekomstverwachting. Deze factoren werden geanalyseerd door middel van multiple regressie analyse (hoofdstuk 6 en 7).

Een tweede belangrijke waarneming is dat het *verwerkingsmodel* een goede verklaring geeft voor onze bevindingen; dat gaat uit van individuele patronen van alternerende cycli van ongewenste gevoelens/gedachten en ontkenning-vermijdingsgedrag.

In **hoofdstuk 6** is onderzocht in hoeverre post-test stress (na 6 maanden) bij geteste personen te voorspellen is. De Schokverwerkingslijst waarvan de vragen specifiek betrekking hadden op de ziekte van Huntington, bleek daartoe geschikt. De beste voorspeller voor post-test stress bij zowel *gendragers* als *niet-gendragers* bleek de mate van stress, één week na de uitslag. Voorts bleek dat, hoe meer vrouwen vóór de uitslag gebukt gingen onder HD, hoe groter de kans dat zij na de uitslag ook lijden onder HD. Tevens bleek dat hoe meer risicodragers vóór de test onder HD gebukt gingen, hoe meer zij na de uitslag lijden aan gevoelens en gedachten over HD indien zij *gendrager* blijken te zijn.

Personen, die een week na de uitslag, weinig stress ervaarden en die reeds lang bekend waren met HD, vertoonden ook na 6 maanden weinig stress .

De analyse van intrusie en ontkenning-vermijding als aspecten van verwerking (hoofdstuk 7) toont dat:

1. hoe meer men vóór de test gebukt ging onder ongewenste gevoelens en gedachten met betrekking tot HD, hoe meer men dat ook zal ervaren na de test, als de test toont dat men *gendrager* is. Dit bleek tevens het enige verschil dat gevonden werd tussen *gendragers* en *niet-gendragers*.
2. hoe meer zowel *gendragers* als *niet-gendragers* vóór de test getracht hebben HD te

vermijden in allerlei situaties, hoe meer zij gebukt gingen onder de last van HD, en hoe ontevredener zij waren over de beschikbare steun in de omgeving, hoe méér zij waarschijnlijk geneigd zijn HD-gebonden situaties na de uitslag te ontlopen.

3. hoe meer zowel *gendragers* als *niet-gendragers* sombere toekomstverwachtingen hadden toen zij zich aanmeldden voor de test, en hoe meer zij ook trachtten HD te ontlopen, en hoe ontevredener zij waren met de beschikbare steun vóór de test uitslag, hoe meer kans zij hebben op pessimistische toekomstverwachtingen (met risico voor depressie en suïcidaal gedrag).

De individuele patronen van intrusie, en ontkenning-vermijdingsgedrag kunnen aanknopingspunten bieden voor aanvullende steun wanneer nodig of gewenst. Lange termijn onderzoek moet meer inzicht geven in hoe deze verwerkingsprocessen zich verder ontwikkelen, en bij welke personen dit leidt tot problemen en inadekwaat psychologisch functioneren.

Diepte-interviews die vóór de test werden gehouden met een groep van 20 risicodragers gaf meer inzicht in de processen die zij doormaken (**hoofdstuk 8**). De pre-test psychologische afweerstyl in zeer angstige risicodragers bevatte meer zogenaamde onrijpe afweermechanismen, zoals bezwering, ageren, en keren tegen zichzelf, in vergelijking met minder angstige personen. Er werden geen pre-test verschillen gevonden tussen toekomstige *gendragers* en *niet-gendragers*. Echter, na de test vertoonden zeer angstige *gendragers* een toename van vermijdingsgedrag en waren zij minder somber met betrekking tot hun toekomst, hetgeen tijdelijk adequaat kan zijn maar wat ook kan leiden tot een inadekwate aanpassing op langere termijn. Zeer angstige *niet-gendragers* toonden slechts een lichte afname van pessimistische gevoelens, hetgeen hun problemen weerspiegelt t.a.v. het verwerken van hun nieuwe genetische status en het moeten aanvaarden van een nieuw levensperspectief.

In **hoofdstuk 9** worden de praktische implicaties voor de patientenzorg van dit onderzoek besproken.

1. de praktische uitvoering van het presymptomatisch DNA-onderzoek kon worden verbeterd door de groeiende ervaring, die ook van wezenlijk belang lijkt voor presymptomatisch onderzoek bij andere erfelijke ziekten die op latere leeftijd ontstaan. Risicodragers en hun partners worden aangemoedigd de DNA-test en de mogelijke gevolgen te bespreken met specifiek gekozen vrienden en/of familieleden. Om het gevoel van controle en zelfverantwoordelijkheid te verhogen, wordt hen gevraagd hun voorkeur aan te geven hoe de uitslag gegeven dient te worden, en vooral zelf te bepalen welk moment het meest geschikt is om de uitslag te vernemen.

2. de resultaten van dit onderzoek kunnen klinisch genetici, huisartsen, en andere werkers in de gezondheidszorg helpen de behoefte aan steun en tekenen van inadekwate aanpassing te signaleren bij zowel *gendragers*, als *niet-gendragers* en *partners*.
3. de kwaliteit en aanvaardbaarheid van een presymptomatisch DNA-onderzoek kan worden gegarandeerd en verbeterd door een nauwere betrokkenheid van de huisarts van de risicodrager. De geteste risicodragers zelf achtten dat wenselijk en uit een enquête onder huisartsen bleek dat velen daartoe bereid waren.
4. klinisch genetici kunnen zich vertrouwd maken met de specifieke problemen van risicodragers die presymptomatisch DNA-onderzoek wensen te ondergaan. Klinisch-genetische centra, verbonden aan universiteiten, hebben de unieke taak om onderzoek te doen naar niet alleen de informatie-overdracht en besluitvormingsprocessen, maar ook de psychodynamische en sociale gevolgen van de implicaties van de "nieuwe" genetica.
5. de verschillende bevindingen tonen mogelijke lange termijn effecten (> 6 maanden) waardoor onderzoek op langere termijn noodzakelijk is. De langere termijn verwerking bij *gendragers*, hun risico's voor depressie en suïcidaal gedrag, en de uiteindelijke aanpassing van *niet-gendragers* aan hun nieuwe genetische status zijn slechts twee gebieden met nog open vragen.

Presymptomatisch DNA-onderzoek blijkt aan de verwachtingen van de geteste personen te hebben voldaan. Een klinische context lijkt nodig met de mogelijkheid om uitgebreide pre-test counselling, psychologische steun, en regelmatige vervolgesprekken aan te bieden. In de hier onderzochte groep had niemand er spijt van het DNA-onderzoek ondergaan te hebben. Nader onderzocht moet worden hoe *gendragers*, hun partners, en hun gezinnen een evenwicht kunnen vinden tussen hoe zij enerzijds hun huidige mogelijkheden kunnen gebruiken om hun levensverwachtingen te vervolmaken, en anderzijds hoe zij zich kunnen voorbereiden op een toekomstig lijden. *Niet-gendragers* hebben meer dan een half jaar nodig om werkelijk de volledige betekenis van de gunstige uitslag te beseffen en de bijhorende opluchting te voelen. Zowel *gen-dragers* als *niet-gendragers* maken een soort rouwproces door: het verwerken van deze gevoelens en gedachten kost tijd.

Appendices

APPENDICES

- Appendix A Request for Participation in Follow-Up Study
- Appendix B Biographical Data
- Appendix C Attitude Questionnaire (At-Risk, Pre-test)
- Appendix D Impact of Event Scale
- Appendix E Beck Hopelessness Scale
- Appendix F Social Support Questionnaire
- Appendix G Grading List Pre-Test In-Depth Interview

Geachte mevrouw/ mijnheer

U hebt zich aangemeld voor onderzoek, met behulp van DNA-probes, naar de ziekte Chorea van Huntington. Omdat dit onderzoek sinds kort mogelijk is, weten wij nog weinig van de beleving en verwerking die dit onderzoek ongetwijfeld met zich mee brengt. Om voor een goede opvang en begeleiding te kunnen zorgen moeten we goed inzicht hebben in de factoren die van invloed zijn op het omgaan met de uitslag van de test. Daartoe heeft een projectgroep in samenwerking met de afdeling Medische Psychologie en Psychotherapie van de Erasmus Universiteit in Rotterdam, de afdeling Klinische Genetica in Rotterdam, de afdeling Psychiatrie in Leiden, de afdeling Neurologie in Leiden en het Klinisch Genetisch Centrum in Leiden een onderzoek opgezet.

Ik verzoek u daarom vriendelijk om, gedurende de periode dat u de presymptomatische test voor de ziekte van Huntington ondergaat en enige tijd na de uitslag, mee te willen werken aan dit onderzoek. Met uw medewerking levert u een bijdrage aan de ontwikkeling van de opvang en begeleiding van hen die in de toekomst de voorspellende test ondergaan. Het onderzoek houdt in dat aan u en uw eventuele partner gevraagd wordt om met de onderzoeker drs.A.Tibben, psycholoog, op verschillende momenten een gesprek te hebben (totaal drie gesprekken). Tevens zal aan u en uw partner worden gevraagd om een aantal vragenlijsten in te vullen. Het onderzoek zal zoveel mogelijk aansluiten op uw bezoek aan het Klinisch Genetisch Centrum in Leiden.

De gegevens zullen vertrouwelijk en anoniem worden behandeld en alleen voor wetenschappelijke doeleinden worden gebruikt.

Deelname aan het onderzoek geschiedt geheel vrijwillig en het staat u altijd vrij om zich uit het onderzoek terug te trekken. Wanneer u niet deelneemt aan dit onderzoek dan zal dat van geen enkele invloed zijn op uw verdere behandeling en deelname aan de presymptomatische test.

Het onderzoek wordt uitgevoerd met medewerking en goedkeuring van prof.dr.J.J.P.van de Kamp, klinisch geneticus, prof.dr.F.Verhage, psycholoog, prof.dr.H.G.M.Rooymans, psychiater, prof.dr.M.F.Niermeijer, klinisch geneticus en dr.R.A.C.Roos, neuroloog.

U kunt uw bereidheid kenbaar maken in het eerstvolgende gesprek dat u met mij heeft.

Wanneer u bereid bent tot deelname aan het onderzoek, dan kunt u met drs. A.Tibben kennismaken op de dag dat u met mij een gesprek heeft. Hij zal u dan tevens verzoeken enkele vragenlijsten in te vullen. De invultijd wordt geschat op twee uur.

met vriendelijke groet,

hoogachtend, mede namens de projectgroep

M.Vegter-v.d.Vlis, neuroloog

Appendix B: Biographical Data

Biographical Data

Number	Date
1. Gender	<input type="checkbox"/> male <input type="checkbox"/> female
2. Age	_____ years
3. Do you live alone or with others?	
	<input type="checkbox"/> I live alone
	<input type="checkbox"/> with my parents
	<input type="checkbox"/> with spouse/partner
	<input type="checkbox"/> with others
4. What is your marital status?	
	<input type="checkbox"/> married
	<input type="checkbox"/> single
	<input type="checkbox"/> divorced
	<input type="checkbox"/> widow/widower
	<input type="checkbox"/> common-law
5. How many children do you have?	_____ child(ren)
6. Are you religious affiliated?	<input type="checkbox"/> yes <input type="checkbox"/> no
7. What schooling did you complete	
	<input type="checkbox"/> Elementary school
	<input type="checkbox"/> Lower vocational school
	<input type="checkbox"/> Secondary school
	<input type="checkbox"/> Secondary vocational school
	<input type="checkbox"/> Higher vocational school
	<input type="checkbox"/> University

ATTITUDE QUESTIONNAIRE

AT-RISK

This survey is designed to find out what some of your attitudes and opinions are about Huntington's disease, the presymptomatic DNA-test and the prenatal test (done on an unborn child during pregnancy). Furthermore you will find some questions related to the impact of the result on for instance employment and life insurance.

I. Experience with HD and being at-risk

1. At what age did you first learn about Huntington's Disease (HD) being in the family?
2. At what occasion did you first learn about HD?
3. Which relatives with HD do you know or have you known (e.g. grandfather, grandmother, father, mother, aunt, uncle, brother, sister)?
4. Which symptoms did you consider most significant at your affected parent?
5. Which symptoms did you consider most significant at other affected relatives?
6. At what age did you first learn that you are at risk to develop Huntington's Disease?
7. Who first informed you of your at-risk status?

- ☐ parents
- ☐ grandparents
- ☐ brother/sister
- ☐ other family member
- ☐ general practitioner
- ☐ others, i.e. _____

8. From what source have you received most information about HD?

- ☐ from family
- ☐ from general practitioner
- ☐ HD patient organization
- ☐ newspaper
- ☐ radio/television
- ☐ others, i.e. _____

9. How does or did HD affect your life?

II. Reasons for taking the test

10. You have applied at the clinical genetics centre and you have decided to undergo presymptomatic testing for HD. We could imagine that, preceding your decision, you had different and varied reasons to take or not to take the test. Please state your main reasons for and against the test below.

reasons for taking the test

reasons against taking the test

Appendix C: Attitude Questionnaire

- 11.
- | | |
|--|-------------------------------|
| a. The decision to take the presymptomatic test must be made by the individual at-risk him/herself | agree / not agree / uncertain |
| b. The decision to take the presymptomatic test must be made together with the spouse/ partner | agree / not agree / uncertain |
| c. The decision to take the presymptomatic test must be made after discussion with a professional counsellor who is familiar with HD | agree / not agree / uncertain |
12. I believe that taking the presymptomatic test and being told that I will probably not get HD, I will respond as follows:
- | | |
|---|-------------------------------|
| a. the quality of my life will diminish | agree / not agree / uncertain |
| b. my problems will increase | agree / not agree / uncertain |
| c. the problems of my spouse or partner will increase | agree / not agree / uncertain |
| d. the problems of my children will increase | agree / not agree / uncertain |
| e. my marriage/relationship will be adversely affected | agree / not agree / uncertain |
| f. I will avoid my family | agree / not agree / uncertain |
| g. it will enable me to plan the future of my family better | agree / not agree / uncertain |
| h. it will enable me to plan my own future better | agree / not agree / uncertain |
| i. it will cause me to become depressed | agree / not agree / uncertain |
13. I believe that taking the presymptomatic test and being told that I will probably not get HD, I will respond as follows:
- | | |
|---|-------------------------------|
| a. it will enhance the quality of my life | agree / not agree / uncertain |
| b. it will decrease my problems | agree / not agree / uncertain |
| c. it will decrease the problems of my spouse/ partner | agree / not agree / uncertain |
| d. it will decrease the problems of my children | agree / not agree / uncertain |
| e. it will enhance my marriage/relationship | agree / not agree / uncertain |
| f. it will result in my avoiding relatives | agree / not agree / uncertain |
| g. it will enable me to plan the future of my family better | agree / not agree / uncertain |
| h. it will enable me to plan my own future better | agree / not agree / uncertain |
| i. it will cause my mood to improve | agree / not agree / uncertain |
14. From what source have you received most information about HD?
- [] parents
- [] brother/sister
- [] other relatives
- [] general practitioner
- [] medical specialist
- [] HD lay organization
- [] Clinical Genetics Centre
- [] newsletters/magazines
- [] news media
- [] others, _____

15. Before you had decided to undergo the presymptomatic test, did you talk about it with:
- | | |
|-------------------------|----------------------------|
| a. parents | yes / no / not appropriate |
| b. spouse/partner | yes / no / not appropriate |
| c. children | yes / no / not appropriate |
| d. brothers/sisters | yes / no / not appropriate |
| e. general practitioner | yes / no / not appropriate |
| f. others | yes / no / not appropriate |
16. If you were told that you will probably get HD in the future, would you tell:
- | | |
|---------------------|----------------------------|
| a. parents | yes / no / not appropriate |
| b. spouse/ partner | yes / no / not appropriate |
| c. parents-in-law | yes / no / not appropriate |
| d. children | yes / no / not appropriate |
| e. brothers/sisters | yes / no / not appropriate |
| f. others | yes / no / not appropriate |
17. If you were told that you will probably not get HD in the future, would you tell your
- | | |
|---------------------|----------------------------|
| a. parents | yes / no / not appropriate |
| b. spouse/ partner | yes / no / not appropriate |
| c. parents-in-law | yes / no / not appropriate |
| d. children | yes / no / not appropriate |
| e. brothers/sisters | yes / no / not appropriate |
| f. others | yes / no / not appropriate |
18. Some people, even though they know intellectually that their risk of having inherited the gene for HD is 50%, feel either that they likely have inherited the gene or that they have not. In your opinion, how likely is it that the test will show that you will or will not get HD?
- ☐ I am certain that I will not get HD
- ☐ I often think that I will not get HD
- ☐ I often think that I will get HD
- ☐ I am certain that I will get HD
- ☐ I am uncertain
- Please explain your answer
19. If the test shows that I will not get HD,
- ☐ I will certainly not doubt
- ☐ I probably will not doubt
- ☐ I am uncertain whether I will not doubt
- ☐ I probably will doubt
- ☐ I will certainly doubt
20. If the test shows that you will get HD,
- ☐ I will certainly not doubt
- ☐ I probably will not doubt
- ☐ I am uncertain whether I will not doubt
- ☐ I probably will doubt
- ☐ I will certainly doubt

Appendix C: Attitude Questionnaire

21. What will you do differently in your life if the test shows that you probably will not get HD?
22. What will you do differently in your life if the test shows that you probably will get HD?
23. If you were told that you probably will get HD in the future, would you like the opportunity to talk about this:
- | | |
|-----------------------------------|----------|
| a. in a support group | yes / no |
| b. with a professional counsellor | yes / no |
| c. with a social worker | yes / no |
| d. with a psychologist | yes / no |
| e. with a minister/priest | yes / no |
| f. others | yes / no |
24. Should minor children (under 18 years) be offered the presymptomatic test? (check one)
- yes / no / uncertain
- Please explain your answer
25. Have you met any problems with employment or getting a job since you know you are at-risk for HD?
- ☐ I have not had any problems
- ☐ I have had problems:
26. If the test shows you will probably get HD, do you expect this to be of any influence in employment or getting a job, in the next 12 months?
- ☐ I am certain this will have influence
- ☐ I think this will have influence
- ☐ I am uncertain
- ☐ I think this will not have influence
- ☐ I am certain this will not have influence
27. If the test shows you will probably get HD, do you expect this to be of any influence in employment or getting a job, after the next 12 months?
- ☐ I am certain this will have influence
- ☐ I think this will have influence
- ☐ I am uncertain
- ☐ I think this will not have influence
- ☐ I am certain this will not have influence
28. Have you met any problems with insurances since you know you are at-risk for HD?
- ☐ I have not had any problems
- ☐ I have had any problems:
- ☐ with life insurance
- ☐ with disability insurance
- ☐ increased premium because of being at-risk

V. The test can also be used as a prenatal test (done on an unborn child during pregnancy). This section will ask for your attitudes about prenatal testing. Please answer the questions even if you do not intend to have any (or any more) children yourself.

29. Do you want to have any/any more children yourself?

yes / no / uncertain

Please explain your answer

30. If you or your spouse/partner were pregnant would you use the presymptomatic test for prenatal diagnosis? (with chorionic villus sampling in the 10th week of pregnancy)

yes / no / uncertain

Please explain your answer

31. If you or your spouse/partner were pregnant: in which circumstances do you think abortion is acceptable:

I think abortion is acceptable if:

- | | |
|---|------------------------------|
| a. health of mother is in danger because of pregnancy | agree / no agree / uncertain |
| b. prenatal diagnosis shows a serious disease | agree / no agree / uncertain |
| c. prenatal diagnosis shows Down syndrome | agree / no agree / uncertain |
| d. prenatal diagnosis shows increased risk for HD | agree / no agree / uncertain |
| e. the baby is unwanted (for other than medical reasons) | agree / no agree / uncertain |
| f. abortion is not acceptable in all circumstances, mentioned above | agree / no agree / uncertain |

Appendix D: Impact of Event Scale

Impact of Event Scale

Below is a list of comments made by people after stressful life events. Please check each item, indicating how frequently these comments were true for you *during the past seven days*. If they did not occur during that time, please mark the "not at all" column.

- | | |
|--|---|
| 1. I thought about Huntington's Disease (HD) when I didn't meant to | Not at all / Rarely / Sometimes / Often |
| 2. I avoided letting myself get upset when I thought about HD or was reminded of it | Not at all / Rarely / Sometimes / Often |
| 3. I tried to remove HD from my memory | Not at all / Rarely / Sometimes / Often |
| 4. I had difficulty falling or staying asleep because of images or thoughts related to HD | Not at all / Rarely / Sometimes / Often |
| 5. I had waves of strong feelings about HD | Not at all / Rarely / Sometimes / Often |
| 6. I had dreams about HD | Not at all / Rarely / Sometimes / Often |
| 7. I stayed away from things or situations that might remind me of HD | Not at all / Rarely / Sometimes / Often |
| 8. I felt so unrealistic about it, as if nothing had happened | Not at all / Rarely / Sometimes / Often |
| 9. I tried not to talk about HD | Not at all / Rarely / Sometimes / Often |
| 10. Images about HD popped into my mind | Not at all / Rarely / Sometimes / Often |
| 11. Things I saw or heard suddenly reminded me of HD | Not at all / Rarely / Sometimes / Often |
| 12. I knew that I still have a lot of feelings about HD, but I didn't want to think about it | Not at all / Rarely / Sometimes / Often |
| 13. I tried not to think about HD | Not at all / Rarely / Sometimes / Often |
| 14. Any reminder of HD brought back feelings about HD | Not at all / Rarely / Sometimes / Often |
| 15. My feelings about HD were kind of numb | Not at all / Rarely / Sometimes / Often |

Beck Hopelessness Scale (BHS)

This questionnaire consists of a list of twenty statements. Please read the statements carefully one by one. If the statement describes your attitude for the past week, including today, circle **TRUE**, if it is false for you, circle **FALSE**. Please be sure to read and answer each sentence.

- | | |
|--|--------------|
| 1. I look forward to the future with hope and enthusiasm | true / false |
| 2. I might as well give up because there's nothing I can do about making things better for myself | true / false |
| 3. When things are going badly, I am helped by knowing that they can't stay that way forever | true / false |
| 4. I can't imagine what my life would be like in ten years | true / false |
| 5. I have enough time to accomplish the things I most want to do | true / false |
| 6. In the future I expect to succeed in what concerns me most | true / false |
| 7. My future seems dark to me | true / false |
| 8. I happen to be particularly lucky and I expect to get more of the good things in life than the average person | true / false |
| 9. I just don't get the breaks, and there's no reason to believe I will in the future | true / false |
| 10. My past experience have prepared me well for my future | true / false |
| 11. All I can see ahead of me is unpleasantness rather than pleasantness | true / false |
| 12. I don't expect to get what I really want | true / false |
| 13. When I look in the future I expect I will be happier than I am now | true / false |
| 14. Things just won't work out the way I want them to | true / false |
| 15. I have great faith in the future | true / false |
| 16. I never get what I want so it's foolish to want anything | true / false |
| 17. It is very unlikely that I will get any real satisfaction in the future | true / false |
| 18. The future seems vague and uncertain to me | true / false |
| 19. I can look forward to more good times than bad times | true / false |
| 20. There's no use in really trying to get something I want because I probably won't get it | true / false |

Appendix F: Social Support Questionnaire

SSQR

The following questions ask about people in your environment who provide you with help or support. Each question has two parts. For the first part, list all the people you know, excluding yourself, whom you can count on for help or support in the manner described. Give the persons' initials, their relationship to you (see example). Do not list more than one person next to each of the numbers beneath the question. For the second part, circle how satisfied you are with the overall support you have. If you have had no support for a question, check the words "No one", but still rate your level of satisfaction. Don not list more than nine persons per question. Please answer all the questions as best you can. All your responses will be kept confidential.

Example

A.1 Who do you know whom you can trust with information that could get you in trouble?

1.	A	K	brother	4.	O	B	colleague	7.		
2.	J	J	friend	5.	S	K	father	8.		
3.	P	S	sister	6.	L	M	spouse	9.		

No one ☐ (check if you have no support for this question)

A.2 How satisfied?

very satisfied	fairly satisfied	a little satisfied	a little dissatisfied	fairly dissatisfied	very dissatisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix F: Social Support Questionnaire

1.1. Whom can you really count on to be dependable when you need help?

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No one

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 (check if you have no support for this question)

1.2 How satisfied?

very satisfied	fairly satisfied	a little satisfied	a little dissatisfied	fairly dissatisfied	very dissatisfied						
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2.1. Whom can you really count on to help you feel more relaxed when you are under pressure or tense?

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No one

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 (check if you have no support for this question)

2.2 How satisfied?

very satisfied	fairly satisfied	a little satisfied	a little dissatisfied	fairly dissatisfied	very dissatisfied						
<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td></tr></table>		<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td></tr></table>		<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td></tr></table>		<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td></tr></table>		<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td></tr></table>		<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td></tr></table>	

Appendix F: Social Support Questionnaire

3.1. Who accepts you totally, including both your worst and your best points?

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No one

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 (check if you have no support for this question)

3.2 How satisfied?

very satisfied	fairly satisfied	a little satisfied	a little dissatisfied	fairly dissatisfied	very dissatisfied						
<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>	

4.1. Whom can you really count on to care about you, regardless of what is happening to you?

1.	<table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							_____	4.	<table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							_____	7.	<table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							_____
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No one

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 (check if you have no support for this question)

4.2 How satisfied?

very satisfied	fairly satisfied	a little satisfied	a little dissatisfied	fairly dissatisfied	very dissatisfied						
<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>		<table border="1"><tr><td></td></tr></table>	

Appendix F: Social Support Questionnaire

5.1. Whom can you really count on to help you feel better when you are feeling generally down-in-the-dumps?

1. <table border="1" style="display: inline-table; width: 60px; height: 40px; border-collapse: collapse;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> _____							4. <table border="1" style="display: inline-table; width: 60px; height: 40px; border-collapse: collapse;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> _____							7. <table border="1" style="display: inline-table; width: 60px; height: 40px; border-collapse: collapse;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> _____						
2. _____	5. _____	8. _____																		
3. _____	6. _____	9. _____																		

No one

 (check if you have no support for this question)

5.2 How satisfied?

very satisfied	fairly satisfied	a little satisfied	a little dissatisfied	fairly dissatisfied	very dissatisfied
<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>

6.1. Whom can you count on to console you when you are very upset?

1. <table border="1" style="display: inline-table; width: 60px; height: 40px; border-collapse: collapse;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> _____							4. <table border="1" style="display: inline-table; width: 60px; height: 40px; border-collapse: collapse;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> _____							7. <table border="1" style="display: inline-table; width: 60px; height: 40px; border-collapse: collapse;"><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr><tr><td style="width: 30px; height: 20px;"></td><td style="width: 30px; height: 20px;"></td></tr></table> _____						
2. _____	5. _____	8. _____																		
3. _____	6. _____	9. _____																		

No one

 (check if you have no support for this question)

6.2 How satisfied?

very satisfied	fairly satisfied	a little satisfied	a little dissatisfied	fairly dissatisfied	very dissatisfied
<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>	<table border="1" style="width: 40px; height: 25px; border-collapse: collapse;"></table>

Psychological Implications of Presymptomatic DNA-Testing for Huntington's Disease

Questionnaire on the Working Through Process of Individuals At-Risk

Pre-Test Defence Mechanisms, Working Through and Ego-Strength

(A.Tibben)

Dept. Medical Psychology & Psychotherapy
Erasmus University Rotterdam

Clinical Genetics Centre
University Hospital Leiden

Prinses Beatrix Fonds Project
project 88-2801/89-2984

General Data

Date

Respondent No.

Genetic Status

Gender

Age

Marital Status

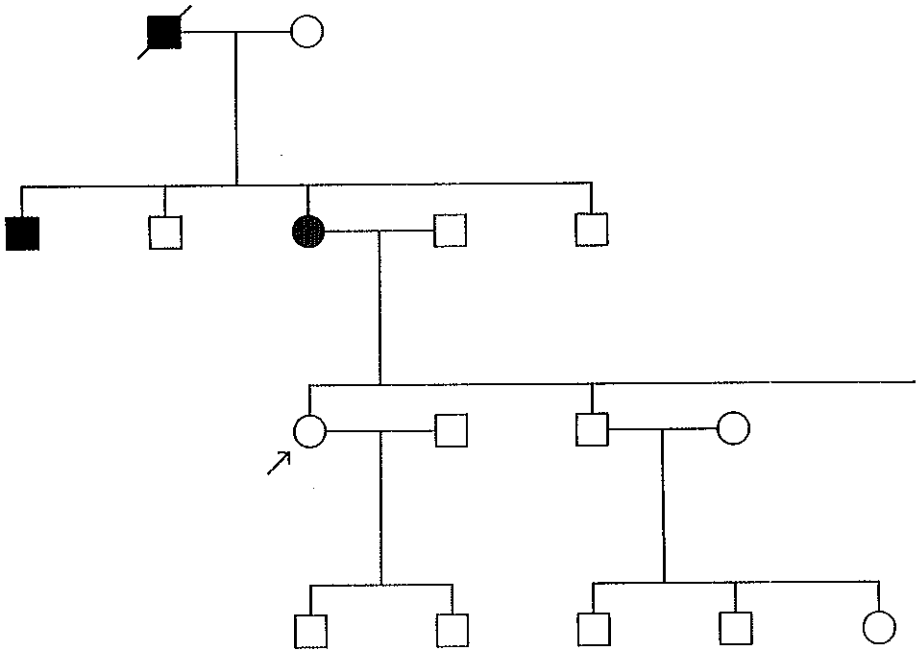
Education

Children

Judge

Interview

Pedigree (interviewee is indicated by an arrow):



Appendix G: Grading-list In-Depth Interview

1. Please describe some significant, concrete examples which you recognize as being defence mechanisms of the interviewee (to a maximum of 5)

1.1.

1.2.

1.3.

1.4.

1.5.

- 1.6. To what extent is interviewee feeling weighed down by fear?

not at all

to a high degree

- 1.7. To what extent is interviewee coping adequately with fear?

not at all

to a high degree

- 1.8. Do you think interviewee will be able to cope with the stress connected with a (possible) presymptomatic test for Huntington's disease?

not at all

to a high degree

Appendix G: Grading-list In-Depth Interview

2. Below you will find specific defence mechanisms and you are asked to assess whether interviewee is displaying any of these.

You put a cross in column I when a particular defence mechanism is manifest.

	Defense	Conscious Representation	Column I
2.1	Repression	"in the past the tensions at home in connection with Huntington's disease must have been considerable, but I do not remember anything about them."	<input type="checkbox"/>
2.2	Denial	someone with obvious symptoms: 'it may be years before I get the first symptoms'	<input type="checkbox"/>
2.3	Ego-Restriction	'I never dared to fall in love for at some time or other you would have had to tell that you are at risk of being a carrier'.	<input type="checkbox"/>
2.4	Reaction Formation	'Hearing that I would get the illness we asked our sick father to come and live with us in order to look after him'.	<input type="checkbox"/>
2.5	Affect Isolation	'I do appreciate my parents' unwillingness to give blood for DNA testing'.	<input type="checkbox"/>
2.6	Rationalisation	'Somehow you are obliged to take the test as it is the only way by which the illness can be stopped'.	<input type="checkbox"/>
2.7	Projection	'If it becomes evident that I shall get Huntington's disease, my wife will not be able to cope'.	<input type="checkbox"/>

Appendix G: Grading-list In-Depth Interview

3. In what manner is interviewee preparing him/herself for the presymptomatic test result? You should base your answers only on what interviewee him/herself has actually expressed in words and behaviour?

Please, explain your answer as concretely as possible

4. Have you noticed anything specific which could have a favourable effect on the interviewee's working through process of the presymptomatic test result?

Please, explain your answer as concretely as possible

5. Have you noticed anything specific which could have an unfavourable effect on the interviewee's working through process of the presymptomatic test result?

Please, explain your answer as concretely as possible

6. Do you expect interviewee to get problems in case of an unfavourable⁷⁾ test result?

yes / no

Please, explain your answer as concretely as possible

7. Do you expect interviewee to get problems in case of a favourable⁷⁾ test result?

yes / no

Please, explain your answer as concretely as possible

⁷⁾ Note: By a *favourable* test result is meant: the presymptomatic DNA-test shows that the applicant is not a carrier of the Huntington gene and therefore will definitely not get the disease; by an *unfavourable* test result is meant: the test shows that the applicant is a carrier of the Huntington gene and therefore will get the disease at some time in the future.

8. Which of the following symptoms have you unmistakably found the interviewee to have? (i.e. not by interpretation). (please tick only if clearly present)

anger	<input type="checkbox"/>	helplessness	<input type="checkbox"/>
listlessness	<input type="checkbox"/>	powerlessness	<input type="checkbox"/>
resignation	<input type="checkbox"/>	uncertainty	<input type="checkbox"/>
tiredness	<input type="checkbox"/>	grief	<input type="checkbox"/>
fear	<input type="checkbox"/>	shame	<input type="checkbox"/>
irritability	<input type="checkbox"/>	loneliness	<input type="checkbox"/>
depression	<input type="checkbox"/>	apathy	<input type="checkbox"/>
despair	<input type="checkbox"/>	self-reproach	<input type="checkbox"/>
guilt feelings	<input type="checkbox"/>	indifference	<input type="checkbox"/>
hopelessness	<input type="checkbox"/>	nervousness	<input type="checkbox"/>
tension	<input type="checkbox"/>	other:	<input type="checkbox"/>

Circle '?' only if you are absolutely unable to choose one of the other two answers.

- | | |
|--|--------------|
| 9. Interviewee is able to distinguish fantasy from reality | yes / no / ? |
| 10. Interviewee has an insight into his/her own role in problematic situations | yes / no / ? |
| 11. Interviewee dares to confide personal matters to other people | yes / no / ? |
| 12. Interviewee does not shy away from self-confrontation? | yes / no / ? |
| 13. Interviewee is of the opinion that his/her problems are related to his/her own inner life | yes / no / ? |
| 14. Interviewee is prepared to be dependent on other people | yes / no / ? |
| 15. Interviewee's behaviour towards counsellor is one of contempt and denigration | yes / no / ? |
| 16. Interviewee recognizes that he/she has a responsibility for solving i.e. alleviating his/her own problems | yes / no / ? |
| 17. Interviewee has established at least one stable interrelationship | yes / no / ? |
| 18. Interviewee is able to think in psychological terms | yes / no / ? |
| 19. Interviewee relates his/her problems to his/her past history | yes / no / ? |
| 20. Interviewee experiences his/her problems as something happening to him/her as fate | yes / no / ? |
| 21. Interviewee has a different perception and interpretation of his/her situation after receiving new, additional information | yes / no / ? |
| 22. Interviewee is mentally prepared for the test result | yes / no / ? |
| 23. Interviewee has done a lot of thinking about his/her life history | yes / no / ? |

Appendix G: Grading-list In-Depth Interview

Circle '?' only if you are absolutely unable to choose one of the other two answers.

24.	Interviewee's tolerance of fear is	high/low/average/?
25.	Interviewee's tolerance of frustration is	high/low/average/?
26.	Interviewee's tolerance of uncertainty is	high/low/average/?
27.	Interviewee finds it difficult to talk about important decisions	yes / no / ?
28.	Interviewee is emotionally mature	yes / no / ?
29.	Interviewee made a life of his/her own at the various stages of life	yes / no / ?
30.	Interviewee is capable of fitting in new information into the existing situation	yes / no / ?
31.	Interviewee is interested in other people's feelings and thoughts about him/herself	yes / no / ?
32.	Interviewee experiences him/herself or his surroundings as unreal	yes / no / ?
33.	Interviewee is capable of establishing lasting emotional relationships	yes / no / ?
34.	The way interviewee talks about his/her feelings is contrary to reality	yes / no / ?
35.	Interviewee denies feelings of fear	yes / no / ?
36.	Interviewee is of the opinion that his/her own problems are mainly caused by his/her environment	yes / no / ?
37.	Interviewee is capable of self-reflection	yes / no / ?
38.	Interviewee succeeds in adapting him/herself adequately to new circumstances	yes / no / ?
39.	Interviewee is able to talk objectively about his/her situation and at the same time experience it as frightening/threatening	yes / no / ?
40.	Interviewee is able to deal easily with his/ her flow of thoughts	yes / no / ?
41.	Interviewee understands his/her situation and is able to assess it well	yes / no / ?
42.	Interviewee is capable of establishing lasting deep relationships	yes / no / ?
43.	Interviewee is capable of verbalizing his/her feelings adequately	yes / no / ?
44.	Interviewee clings to traumatic past events	yes / no / ?
45.	Interviewee has coped adequately with the most important problematic situation/experience	yes / no / ?

(items 9 - 45 are taken from H.J.Duivenvoorden: Motivation for Psychotherapy: an empirical exploration; Thesis, Erasmus University Rotterdam 1982

Dankwoord

Velen zijn bij de totstandkoming van dit proefschrift betrokken geweest. Een allen ben ik zeer erkentelijk. Ik wil de volgende personen in het bijzonder noemen.

Prof.dr.Frans Verhage, mijn eerste promotor: "Het schrijven van een proefschrift vormt je voor je verdere leven". Hij heeft me geleerd ook op de moeilijkste momenten de volle verantwoordelijkheid te nemen voor mijn doen en laten waardoor het uiteindelijk 'mijn' project werd en bleef. Hij heeft deze promotie tot een levensles gemaakt.

Met Prof.dr.Jacques J.P.van de Kamp, mijn tweede promotor, heb ik de toepassing van menige tussentijdse bevinding besproken. Hij heeft me het volste vertrouwen gegeven in het onderzoek. Ik ben hem dankbaar voor zijn open houding ten aanzien van de in het onderzoek verworven psychologische kennis en inzichten.

Prof.dr.Martinus F.Niermeijer heeft me als geen ander terzijde gestaan bij het schrijven van artikelen, (vervolg) subsidie-aanvragen en het voorbereiden van voordrachten. Door zijn indrukwekkende commentaren bij manuscripten en onze lange discussies heb ik de smaak te pakken gekregen van het klinisch-wetenschappelijke werk. Van hem heb ik geleerd een wetenschapper 'buiten de grenzen' te worden. Zijn uitgebreide kennis, overzicht en betrokkenheid bij de patienten in het onderzoek heb ik zeer gewaardeerd. Hij liet mij keer op keer zien hoe belangrijk het is om de vaak ingewikkelde psychologische bevindingen toegankelijk te maken voor leken-professionals.

Met Riet Vegter, neuroloog en genetisch counsellor, heb ik de afgelopen 4 jaar lief en leed gedeeld. Steeds weer die DNA-uitslagen met steeds weer onverwachte, aangrijpende reacties was soms een forse aanslag op ons incasseringvermogen. Zonder haar was het presymptomatisch DNA-onderzoek in Nederland niet wat het nu is. Haar jarenlange inzet voor het Huntington archief, haar encyclopedische kennis van vele Huntington-families en haar zorgvuldige genetische counselling zijn van onschatbare waarde voor het gehele Huntington programma. Het psychologische wetenschappelijke onderzoek kon alleen maar uitgevoerd worden dank onze goede samenwerking.

Door Dr.Petra G.Frets, psychologe, ben ik 'binnengehaald' in het onderzoeksproject. Zij ging mij voor in de klinische genetica. Haar ben ik zeer erkentelijk voor de steun, aanwijzingen, discussies en introductie in de boeiende, snel veranderende wereld van de klinische genetica.

Dr.Raymund A.C.Roos, neuroloog, heeft door zijn grote kennis van de ziekte van Huntington en betrokkenheid bij de genetische aspecten van deze ziekte een zeer inspirerende invloed op mij gehad. Zijn kritisch meelezen en -schrijven was leerzaam.

Prof.dr.Harry G.M.Rooijmans, psychiater, lid van de begeleidingscommissie van het Huntington-project en lid van de project-groep, heeft mij waardevolle adviezen gegeven over de inhoud van de manuscripten.

Prof.dr.G.J.B.van Ommen, anthropogeneticus, heeft zich altijd bijzonder geïnteresseerd in wat het voor de mens betekent hetgeen in het laboratorium 'uitgevonden' wordt.

Dr.Hugo J.Duivenvoorden, psycho-methodoloog en statisticus, heeft mij op een welhaast therapeutische wijze het onderzoek leren uitvoeren en analyseren. Zijn grote kracht is geweest dat statistiek en methodologie mij niet van de patient verwijderden, maar eerder

dichter bij hem/haar brachten. Dick Stronks heeft een belangrijke bijdrage geleverd aan de zorgvuldige invoering en analyse van de onderzoeksgegevens.

Alle gegevens van het onderzoek zijn door de ogen en handen van Alike van de Sijden-van de Beek gegaan. Zeer nauwgezet en consciëntieus heeft zij de gegevens verwerkt. De organisatie was bij haar in goede handen. Zij was ook zeer betrokken bij de mensen die het DNA-onderzoek ondergingen en heeft door haar verwondering een belangrijke bijdrage geleverd aan onze gesprekken over de bevindingen in het onderzoek.

Mijn grote dank gaat uit naar Dr.Benno Bonke, Dr.Ruud Erdman, Dr.Jan Out, Annelies Plekker, Irene Sallaerts-Boonekamp, Kathy Trijsburg-Peeters, Ruud van Tuyll, Dr.Monica Uniken Venema-van Uden en Herma Versluis-Bieman. Zij hebben jaren lang de interviews beoordeeld. Hun bijdrage leverde belangrijke inzichten op in de psychologie van de onderzochte personen.

Met Prof.dr.Wim Trijsburg, Prof.dr.Frank Verhulst en Prof.dr.Frans Verhage heb ik zeer leerzame en plezierige Panel-bijeenkomsten doorgebracht. Deze sessies waren werkelijke ontdekkingsstochten in de psychologie van risicodragers die presymptomatisch DNA-onderzoek ondergingen.

Dr.Geoff C.Beverstock heeft als 'native speaker' zeer kritisch de manuscripten gelezen, van commentaar voorzien en er mooi Engels van gemaakt (Dr.John M.Opitz: excellent job!).

Met mijn vrienden Joop de Kler en Till Erkens heb ik menigmaal mijn bevindingen en gedachten kunnen toetsen en aanscherpen. Joop's omslagontwerp laat zien dat hij een therapeutische kunstenaar is die met liefde zijn werk doet en dat hij mijn werk heeft begrepen.

Alle medewerkers van zowel het Klinisch Genetisch Centrum als de afdeling Medische Psychologie & Psychotherapie zijn altijd zeer geïnteresseerd geweest in de voortgang en bevindingen van het onderzoek en hebben mij door hun reacties in het spoor gehouden. Alle risicodragers en hun partners, die het presymptomatisch DNA-onderzoek ondergingen, ben ik dank verschuldigd voor hun vertrouwen en bereidwillige medewerking aan het psychologische onderzoek.

Prof.dr.H.Galjaard heeft in een vroeg stadium van het onderzoek al gezien dat de bevindingen van dit onderzoek van grote waarde zijn, met het oog op de grote veranderingen die de medische technologie met zich mee brengt voor de mens. Hem ben ik erkentelijk dat ik mijn werk in de patientenzorg en het wetenschappelijk psychologisch onderzoek in de klinische genetika kan voortzetten binnen zijn afdeling.

Tot slot met wie het allemaal begon: Uta. Zij heeft me gesteund wanneer ik het vroeg, me gelaten wanneer ik dat duidelijk maakte, maar me er ook uitgehaald als het te gek werd. Is promoveren een toetssteen voor de relatie? Wij hebben het samen in ieder geval ruimschoots gehaald, wij hebben er veel van geleerd en genoten en wij gaan met genoegen verder.

Curriculum vitae

Arend Tibben was born on March 24, 1952 in Dedemsvaart, The Netherlands. He passed secondary school in 1969 at the "Menso Alting Lyceum" in Hoozevee. He studied at the Free University Amsterdam and obtained his doctoral degree in clinical psychology in 1976. From 1977 until 1989 he worked in the Psychogeriatric Centre for Nursing and Day Hospital Treatment and Outpatient Psychiatric Clinic "Overduin", Katwijk aan Zee. He was involved in the development of a categorical ward for patients with Huntington disease, including a Day Hospital and Outpatient Treatment.

In 1978 he started his training in psychotherapy. In 1982 he was registered as Gestalt-psychotherapist, in 1984 as Rogerian Psychotherapist and in 1983 as Group Psychotherapist. In 1987 he was officially registered as a psychotherapist by the Chief Medical Officer. Since 1983 he has a private practice as a psychotherapist.

From January, 1989 until December, 1992, he conducted a follow-up study on the psychological effects of presymptomatic DNA-testing for Huntington's disease in collaboration with the Clinical Genetics Centre and the Departments of Neurology and Psychiatry, Academic Hospital Leiden and the Departments of Medical Psychology and Psychotherapy and Clinical Genetics, Erasmus University and Dijkzigt University Hospital, Rotterdam. Since January 1992 he is working at the department of Clinical Genetics, Dijkzigt University Hospital and Erasmus University, Rotterdam (Prof.Dr.H.Galjaard, Prof.Dr.M.F.Niermeijer).

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Stellingen behorende bij het proefschrift van A.Tibben:

"What is Knowledge but Grieving? On Psychological Effects of Presymptomatic DNA-Testing for Huntington's Disease."

1. De observatie in de eerste maanden na presymptomatisch DNA-onderzoek dat dragers van het gen voor de ziekte van Huntington de uitslag goed lijken te verwerken, betekent niet dat zij geen aandacht van hun hulpverleners behoeven. Met name het syndroom van de 'négation à deux' (tweezijdige ontkenning van hulpvrager en hulpverlener) dreigt te ontstaan. *(dit proefschrift)*
2. De emotie, verbonden met de grote zekerheid geen ernstige, erfelijke, invaliderende ziekte zoals de ziekte van Huntington te krijgen, vraagt een langdurige verwerking, analoog aan die bij andere ingrijpende veranderingen van centrale levensverwachtingen. *(dit proefschrift)*
3. Naarmate adviesvragers voor de DNA-test vóór de uitslag een pessimistischer toekomstperspectief hadden en méér geneigd waren situaties te ontlopen die hen met de ziekte van Huntington zouden confronteren, is de kans groter dat zij deze kenmerken 6 maanden ná de uitslag vertonen. Een gunstige of ongunstige test uitslag blijkt daarop niet van invloed. *(dit proefschrift)*
4. Ongeacht de aard van de DNA-test uitslag (gunstig of ongunstig) wordt het vertrouwen in de toekomst in belangrijke mate bepaald door de tevredenheid met de steun die men in de naaste omgeving ervaart. *(dit proefschrift)*
5. Zowel een ongunstige als gunstige uitslag van een presymptomatische test, zoals voor de ziekte van Huntington, kan voor de relatie-partners een zodanige schok zijn, dat daardoor de oorspronkelijke basis van hun relatie kan worden aangetast. *(dit proefschrift)*
6. Een ingrijpende verandering in de veronderstelde genetische identiteit bij een risicodrager voor de ziekte van Huntington is dikwijls een indicatie voor een inzichtgevende vorm van psychotherapie. Daartoe dienen aanwijzingen te worden gevonden in een gerichte evaluatie vooraf en tijdens de verwerkingsfase van de uitslag van presymptomatisch DNA-onderzoek. *(dit proefschrift)*
7. Niet bewuste motieven spelen een belangrijke rol in de beslissing tot presymptomatisch DNA-onderzoek. Daarom verdient het aanbeveling dat de klinisch geneticus kennis heeft van de psychodynamische persoonstheorie.

8. In confrontaties met grensverleggende medische situaties, die nieuwe dimensies aan het menselijk bestaan geven, is voor optimaal medisch informeren en adviseren kennis van de eigen psychodynamiek, met name van eigen emoties, bij de arts onontbeerlijk.
9. De adaptieve waarde van ontkenning als een vroeg, maar op de lange termijn beperkt, aanpassingsmechanisme wordt in de gezondheidszorg vaak ten onrechte ontkend. De hulpverlener dient geduld op te brengen waardoor in verloop van tijd de ontkenning kan worden opgegeven voor een meer aangepaste wijze van verwerken.
10. Hoewel de psychologische implicaties van erfelijke aandoeningen dikwijls niet erfelijk zijn, kunnen zij wel in opeenvolgende generaties worden overgedragen.
11. Arbeidsongeschikte mensen die langdurig, ook tot na het werking treden van de nieuwe wet op de WAO, hun formele arbeidsongeschiktheid weten uit te stellen, zouden voor deze inzet beloond moeten worden met de status van een 'oud WAO-geval'.
12. In specifieke zorgvormen in de psychogeriatric, zoals voor de ziekte van Alzheimer en de ziekte van Huntington, is aandacht noodzakelijk voor partners en nabije familieleden van de patiënt ten aanzien van verwerkings- en rouwproblematiek.
13. De D-mineur toonzetting van de bas-aria 'Komm, süßes Kreuz' uit de Matthäus Passion van J.S.Bach is een perfecte verklanking van de soms tegenstrijdige tempi en emoties die tijdens het schrijven van een proefschrift optreden.