

TO KNOW OR NOT TO KNOW;

The Psychological Implications of Presymptomatic DNA Testing for Autosomal Dominant Inheritable Late Onset Disorders

A.C.DUDOK DE WIT

**TO KNOW OR NOT TO KNOW;
The Psychological Implications of presymptomatic DNA testing for Autosomal
Dominant Inheritable Late Onset Disorders**

**HET WEL OF NIET WETEN;
De Psychologische Implicaties van Voorspellende DNA-diagnostiek voor later in
het Leven Optredende Erfelijke Aandoeningen**

Proefschrift

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Liedje

Het duurt altijd langer dan je denkt,
ook als je denkt
het zal wel langer duren dan ik denk
dan duurt het toch nog langer
dan je denkt.

Het is altijd veel duurder dan je denkt,
ook als je denkt
het zal wel duurder worden dan ik denk
dan wordt het toch nog duurder
dan je denkt.

Het kost meer moeite dan je denkt
ook als je denkt
het zal wel meer moeite kosten dan ik denk
dan kost het toch meer moeite
dan je denkt.

Het duurt veel korter dan je denkt
ook als je denkt
het zal wel korter duren dan ik denk
dan duurt het toch
nog korter dan je denkt.

(Judith Herzberg *Zoals*, 1992)

Ter ere van mijn Grootmoeder, en voor Bart

Het beschreven onderzoek werd uitgevoerd vanuit de afdeling Klinische Genetica van het Academisch Ziekenhuis te Leiden (AZL), de afdeling Klinische Genetica van het Academisch Ziekenhuis Dijkzigt (AZD) en de afdeling Medische Psychologie en Psychotherapie van de Erasmus Universiteit Rotterdam. Het project is financieel ondersteund door de Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Gebied Medische Wetenschappen (no 960-10/803).

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Druk: Anker Grafisch Bedrijf Kampen

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CHAPTER 1

INTRODUCTION AND AIM OF THE STUDY

1. What can be known?

1.1. General introduction

The individual in modern society is confronted with the impressive developments of genetic research [1, 2]. Previously unimagined genetic understanding is continuously revealed, resulting from, amongst others, the progressive characterisation of the human genome. This leads to the identification of genes involved in numerous hereditary diseases. Analyses of gene function will eventually enable dramatic breakthroughs in our understanding of etiology and pathophysiology. The individuals at-risk for a variety of hereditary diseases may obtain greater opportunities to learn about their personal genetic make-up, their reproductive alternatives and future health prospects [3].

To some it seems that science was never before able to give such precise risk estimates concerning the future health of an individual. This information changes an individual neither into a patient needing immediate treatment, nor declares him healthy and free of medically relevant conditions. Individuals and medical professionals are challenged to make beneficial use of the achievements of molecular genetics and the new options, such as predictive DNA testing and (sometimes) early interventions, as in the cancer syndromes. However, the ethics and the psychology of doing genetic research in families and confronting them with genetic risks, has scarcely been studied; but the current progress has already prompted controversies on employment, access to insurance and discrimination. The political debate on these issues has just started. A proposal of the life insurance companies in the Netherlands to exclude individuals with **any** relative affected by either Huntington's Disease (HD) or Myotonic Dystrophy (MD) has been subject to criticism by the Department of Health Care, but has not been withdrawn by the insurance world.

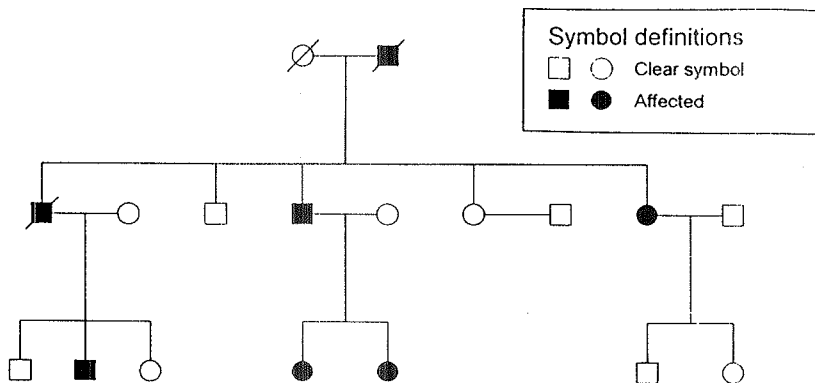
Informing the public on developments in genetics is a continuous process in the visual and written media, with their avid interest in health-related issues. The associated field of genetic engineering holds a promise for reducing the impact of some genetic diseases. For the individual, however, these developments often imply a confrontation with the personal risk for a future disease affecting oneself or a relative. Some families are acquainted with a disorder segregating for generations, such as Huntington's Disease. Other families only recently became confronted with the hereditary nature of, for example, a cancer syndrome. Predictive testing enables the identification of an individual who has inherited the gene causing the specific disorder in the family, before symptoms have appeared. The option of predictive testing, necessitates decisions on ***whether they want to know, or not***, with all its implications. For balanced decisions individuals need to consider medical implications such as possible treatment; psychological implications such as relief of uncertainty; and moral considerations such

as telling the children, planning a family and prenatal testing. The psychological evaluation of this new and far-reaching technique is the subject of this thesis.

1.2. Risk Assessment

Prior to predictive DNA testing, individuals at-risk could only obtain risk estimates as the basis for making decisions on family planning, preventive surgery, etc. Mendelian risks, based upon the mendelian modes of inheritance, were used for this purpose. One of the "mendelian" modes of inheritance is autosomal dominant, that is when a single faulty (mutated) gene, inherited from one parent leads to a disease, such as Huntington's Disease. The risk to offspring of a patient is 50%, regardless of gender (see fig. 1). The risk for transmission of the gene is independent of its expression; expression may be variable. Healthy individuals have no increased risk for affected offspring provided that the disorder is always fully penetrant, at least in adulthood. In practice, many disorders show variability in severity of symptoms and in age of onset of symptoms [4].

Fig. 1. A pedigree of a family with Huntington's Disease



Risk estimation becomes complicated when it is not known at what age one may safely assume to have "escaped" the disease (as in a disease with a late or variable age of onset) or when the faulty gene is present but symptoms do not appear (incomplete penetrance, which occurs in $\pm 10-15\%$ of BRCA1 carriers, causing Hereditary Breast and Ovarian Cancer; HBOC) [5]. Also the degree in which the disorders is expressed may differ between individuals (variation in expression) or is dependent on the sex of

the gene carrier (as for males with a gene for HBOC). Single "new" cases of a disorder in the family may represent new mutations occur (as known for Familial Adenomatous Polyposis; FAP) and that may complicate risk estimates for relatives.

In 1987 more precise risk assessment became available for individuals at-risk for HD [6]. Predictive testing became an option using linked DNA markers. Family studies were necessary to establish segregation of genetic markers for the disease locus in each family. Linkage studies were only possible in large families with sufficient cooperating affected/unaffected participating relatives.

Further developments in the 1990s allowed cloning of several disease genes (see below) allowing highly accurate predictive testing for the respective disorders, using direct analysis of the mutation involved. Predictive testing by mutation analysis provides results with almost complete certainty. Involvement of relatives is only required to establish the pathogenic (disease-causing mutation) in the family under study.

1.3. Predictive DNA testing

Huntington's Disease is the first autosomal dominant genetic disorder for which unaffected individuals at-risk could obtain a predictive DNA test [6]. Predictive testing is now also available for other autosomal dominant neurological late onset disorders such as autosomal dominant cerebellar ataxias (ADCA), SCA1 and SCA2 [7, 8], Neurofibromatosis [9], Myotonic Dystrophy (MD) [10, 11], Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type (HCHWA-D) [12] and familial Alzheimer disease [13-16]. It is expected in the future that, genetic factors involved in the occurrence of neuropsychiatric disorders, manic depressive psychosis and schizophrenia will be detected.

The hereditary cancer syndromes differ in the complexity of possible treatment and the amount of organs affected. Multiple Endocrine Neoplasia type 2A (MEN2A) [17], is an example of a cancer syndrome with a well-defined (prophylactic) treatment policy [18]. The Familial Dysplastic Nevus Syndrome (FNDS) [19-21], causing 5% of all melanoma's, is an example of a hereditary cancer syndrome for which control and early intervention is less easily made because as an increasing number of tumors may develop. HBOC [22-24], FAP [25, 26] and HNPCC [27-32], also give complex risks, for multiple organs and with far-reaching options (such as prophylactic mastectomy, ovariectomy or colectomy resp.) for early intervention. More rare types of hereditary cancer syndromes affecting multiple organs and giving limited options for early treatment are von Hippel Lindau disease, and the Li Fraumeni syndrome [33-36].

Predictive testing has become an option for relatives of patients diagnosed with one of the above-mentioned syndromes. In the near future it is expected that genes involved

in the development of other genetic cancers, such as the hereditary prostate carcinoma (HPC), will become defined.

Only autosomal dominant genetic disorders have been mentioned, but (predictive) DNA testing is relevant to all fields of medicine and for disorders of all modes of inheritance. This thesis, however, addresses individuals at-risk for autosomal dominant genetic disorders.

2. Autosomal dominant inherited disorders in this study; disease characteristics and detection methods

At the start of this study, November 1992, predictive testing was available for Huntington's disease (HD), Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type (HCHWA-D) and Familial Adenomatous Polyposis (FAP) in the departments of Clinical Genetics in Leiden and Rotterdam. Predictive testing for Hereditary Breast and Ovarian Cancer (HBOC) became available in 1994. In this section, disease characteristics and detection methods are described. For a more detailed description of the techniques used and the technical terms see Dracopoli (1994/1995) [37, 38].

2.1. Neurological disorders

2.1.1. Huntington's Disease (HD)

HD is an incurable neurodegenerative disorder with nearly complete lifetime penetrance, characterised by involuntary movements, changes in behaviour and personality, and cognitive impairment [39, 40]. The average age of onset is 40 (\pm 12) years with a range from 2 to 75 years [41, 42]. In the Dutch population it is estimated that 4000 individuals are at-risk for HD and about 520 individuals at-risk have taken the predictive test since 1987 in Leiden [43]. HD is caused by the expansion of a trinucleotide repeat (CAG repeat) in the IT15 or Huntington gene on chromosome 4p16.3. The CAG repeat is polymorphic in the normal population (6 to 35 CAG repeats) and stably inherited. In patients with HD, 36 to more than 100 repeats are found and this number of repeats can change upon transmission to the offspring. Intermediate alleles (about 29 to 36 repeats) have a small chance (<5%) of expanding into the affected range upon paternal transmission [44]. In the Netherlands predictive testing is performed by determining the number of CAG repeats in the DNA of the at-risk person [44-46]. Direct mutation testing started in September 1993 and a reliability of >99% is indicated. Before September 1993 predictive testing was performed using flanking markers giving a reliability of 95-99% depending on the informativity of the markers

Table 1. Autosomal dominant neurological disorders and cancer syndromes in the Netherlands, as included in the study.

	HD ¹⁾	HCHWA-D ²⁾	FAP ³⁾	HBOC (caused by the BRCA1 gene) ^{4),5)}
Age of onset	mean age of onset 40 ± 12 years, onset at 2 and 80 years has also been reported	40-65 years	from 12 years onwards	from 25 years onwards
Disease characteristics	involuntary movements, changes in behaviour and personality, and cognitive impairment	acute occurrence of headache, nausea and focal neurological deficits with or without loss of consciousness	development of numerous (at least 100) colorectal polypi and multiple extracolonic symptoms	breast and ovarian cancer for women, possible colonic cancer for both men and women, possible prostatic carcinoma for men
Duration of the illness	± 15 years (range 2-45 years)	variable ⁶⁾	variable ⁷⁾	variable ⁸⁾
Surveillance	-	-	colonoscopy, sigmoidoscopy, rectoscopy	breast examination, palpation, mammography, ultrasound screening, etc.
Treatment modalities	-	-	colectomy	(prophylactic) mastectomy and/or ovariectomy
Degree of penetrance	100% (lifetime)	100% (by age 60)	100% (by age 40)	95% (lifetime)
Predictive DNA testing linkage analyses since: mutation analyses since:	1987 1993	1991 1991	1989 1991	1991 1994
Frequency	± 4000 at-risk	± 400 at-risk	434 ⁹⁾ at-risk	-
Incidence	-	-	-	± 750 new patients each year
Uptake (till 1997)	± 520 at the Department of Clinical Genetics in Leiden	± 60 tested	295 ⁹⁾ tested	± 100 tested at the Department of Clinical Genetics in Rotterdam

¹⁾ [40,41,42], ²⁾ [49], ³⁾ [54], ⁴⁾ [5, 61, 62] ⁵⁾ HD = Huntington's Disease, HCHWA-D = Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type, FAP = Familial Adenomatous Polyposis and HBOC = Hereditary Breast and Ovarian Cancer. ⁶⁾ Two-third of the patients die as a consequence of their first stroke, in the remaining patients neurological deficits depending on the location of the lesions modify the clinical picture. ⁷⁾ Duration of the illness depends on the success of the treatment. ⁸⁾ Registered with the Dutch Foundation of Hereditary Tumors (STOET). It is estimated that there are still 5 or 6 families not registered and new cases do occur, due to new mutations.

used and of the family structure [47]. Family size and lack of cooperation could lead to uninformativity of a family [48]. In these cases it was not always possible to give a result.

2.1.2. Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type (HCHWA-D)

HCHWA-D is characterised by acute occurrence of headache, nausea and focal neurological deficits, with or without loss of consciousness, which usually occur between 45 and 60 years of age. Two-third of the patients die from their first stroke and the others will have focal neurological deficits depending on the location of the strokes [49]. The number of individuals at-risk for HCHWA-D in the Dutch population is estimated to be 400 [50]. Up to early 1997 about 60 individuals at-risk took the test since it became available in 1991 [51]. HCHWA-D, in these families is caused by one specific mutation (G.C. at position 1852; APP 693) in the amyloid precursor protein (APP) gene located on chromosome 21 (this is the β -amyloid subunit). DNA diagnosis is performed by a PCR reaction followed by SSCP analysis [12].

2.2. Cancer Syndromes

2.2.1. Familial Adenomatous Polyposis Coli (FAP)

FAP is characterised by the development of numerous (at least 100) colorectal polyps. Age at onset is variable, but polyps usually develop in teenage years and penetrance is almost complete at the age of 40 years [52]. Colorectal carcinoma develops inevitably unless prophylactic colectomy is performed [53]. Variant additional features may include polyps in the upper gastrointestinal tract, extraintestinal manifestations such as osteomas and epidermoid cysts, desmoid tumors, congenital hypertrophy of retinal pigment epithelium and other malignant changes, such as thyroid tumors [54]. Most Dutch families with FAP are registered at the Foundation of Hereditary Tumors (STOET). Up to early 1997, 295 individuals at-risk have been presymptomatically tested [54]. Another 434 individuals at 50% risk are registered [56]. Only 5 to 6 families with FAP are not registered with the Foundation of Hereditary Tumors.

FAP is caused by mutations in the APC gene on chromosome 5q21-22. Locus heterogeneity has been reported (about 5%) [57]. Prior to predictive testing, for each family either a mutation or linkage must be established. The index patient is studied for the presence of a mutation with the combination of PCR and DGGE or PTT [58, 59]. In about one-third of the families no mutation is found; linkage studies may be attempted when the family structure is appropriate (sufficient number of cooperative relatives). Using polymorphic intra- or extragenetic markers an informative situation may give a

reliability from 95-99%. In about 25% of the families an informative test is impossible as yet.

2.2.2. Hereditary Breast and Ovarian Cancer (HBOC)

About 5% of all breast cancer cases and about 25% of the breast cancer cases occurring before the age of 30 are estimated to be caused by genetic factors [60]. HBOC is caused by mutation in the BRCA1 gene in approximately 45% of families with early onset (< 50 years) hereditary breast cancer, and in at least 80% of families with combined early breast and ovarian cancer [61]. The gene is not fully penetrant. Women carrying BRCA-1 gene mutations have a 85% risk of developing breast cancer and a 63% risk of developing ovarian cancer before the age of 70. They have a 95% lifetime risk of developing at least one of these cancer types [5]. Male gene carriers have three-fold the population risk for prostatic carcinoma before the age of 70. Male and female gene-carriers have a four-fold population risk for colonic cancer before the age of 70 [62]. The factors that contribute to non penetrance in particular families or individuals are unknown.

The efficacy of intensive screening (self-examination and/or mammography) in this high risk group, and also of prophylactic surgery remain controversial [63-66]. A recent publication, however, states that prophylactic mastectomy in BRCA mutation carriers will decrease the risk of breast cancer from \pm 80% to nearly 0% and that prophylactic oophorectomy will decrease the risk of ovarian/peritoneal cancer from between 17-63% to 3-8% [67].

In the Netherlands, about 750 new patients each year develop breast cancer due to genetic factors. Between January 1994 and November 1996, approximately 100 individuals at-risk for HBOC have been tested in the Netherlands [68]. HBOC can be caused by the BRCA1 gene, BRCA2 gene or other not yet identified genes [24]. HBOC families in this study were all at-risk for mutations in the BRCA1 gene. Frameshift and nonsense mutations, which make up over 80% of all reported mutations in BRCA1 [69], are rapidly detected by PTT [70]. If no mutation has been found and the family structure is appropriate, linkage analysis is attempted using polymorphic intragenetic or flanking markers [71]. In an informative situation the reliability can range from 95-99%.

2.3. Differences and similarities between the disorders in this study

No treatment is available as yet for either of the neurological disorders in this study. Both diseases are associated with irreversible loss of functioning of the brain. A gene carrier will almost certainly develop the disease in adulthood, sooner or later. For HD the period before the disease manifests can be very long (unless there is paternal

transmission of the HD repeat). Moreover, once affected, the HD patient will suffer from a progressive disease during ± 14 years. In case of HCHWA-D the individual is prone to die suddenly of the first stroke.

There are surveillance and treatment options for the cancer syndromes. FAP causes bowel cancer and the possible treatment can have far-reaching effects on defecation, and may affect body image and sexuality. The treatment options in case of HBOC ((prophylactic) mastectomy and oophorectomy), have major consequences for the body image of a women and her sexual identity. A FAP gene carrier knows that he/she will develop the disease at a relatively young age; this means that when the individual is older and without symptoms the chance increases that he/she will prove to be a noncarrier. In case of HBOC, an individual can be a gene carrier without developing breast cancer but can also develop breast cancer without being a gene carrier.

3. What is known about the psychological implications of predictive testing?

3.1. Neurological disorders in this study

3.1.1. Huntington's Disease (HD)

Interest in testing of risk carriers

About 70% of the American and 56% of the European risk carriers for HD, indicated interest in the predictive test before it became available [72-84]. Identified gene carriers were expected to become at-risk for post-test psychiatric morbidity which led to active involvement of mental health professionals [85].

The actual uptake of the predictive DNA test for HD since its introduction in 1987 fell significantly behind the a priori expectation [86-89]. A qualitative study of interviews with ten individuals at 50% risk for HD, showed that the attitude towards testing was greatly determined by early life experiences with HD, age (the older, the more positive about testing) and the quality of the relation with the affected parent (the better the relation, the less positive about testing) [90].

Reasons for and against predictive testing

Reasons for taking the test were to end uncertainty, to obtain some control over the future (planning future life and family) and to inform offspring and relatives [91-95]. Participants believed that taking the test would produce more positive than negative outcomes [93].

Reasons for not taking the test were the concern about the increased risk for the children if they were found to be a gene carrier, the absence of an effective cure, the potential loss of health insurance, the financial costs of testing and the inability to "undo" the knowledge [96]. However, the main reason seemed to be the fear of inability to cope when receiving a high-risk result [92, 94, 97-100]. One interesting

finding was that those refraining from testing learned about their risk for HD in their adolescence while test participants did so in adulthood [99].

Psychological implications of predictive genetic testing

Early reports were based on small numbers and focused upon the possible catastrophic effects. Initial reactions ranged from joy and relief to disappointment, sadness and demoralization and feelings of depression; however, without need for hospitalisation of participants. It seemed that participants cope well, at least in the short term, when testing is performed in a clinical context with pre-test education and counselling, post-test psychological support and regular follow-up [101-103].

Later reports confirmed these observations [48, 84, 100, 104-115]. Identified gene carriers had no major psychopathology, they showed relief from prior psychological distress and a tendency to minimize the impact of the outcome on their future. On the other hand, noncarriers often experienced lack of relief, numbed emotions, survivor's guilt and difficulties developing a new life-perspective [108, 111, 116]. The feared catastrophic events as described by Kessler et al.[85] have only incidentally been observed [117-119]. Additionally, the individuals at-risk who have come for the test until now, are considered a selection who believe that they are better equipped to handle "bad news" and to dispose of considerable mental resources [100, 104, 107]. Those not taking the test had a significantly more pessimistic outlook about themselves and their future [99].

Mutation testing

With the introduction of direct mutation analysis, testing became available for individuals at-risk from smaller, so far, uninformative families and the test could easier be offered at multiple centres. Revised guidelines for predictive testing in HD were developed [120, 121]. Geneticists advised a cautionary approach towards the dilemmas of testing 25% risk carriers and prenatal exclusion testing [48, 122]. The direct mutation test became the method of choice for new applicants and those who had an uninformative result previously. Those tested by linkage rarely asked for re-testing by mutation analysis [123].

Adaptation to the test result; denial

Six months after testing Tibben et al. [111] observed denial and minimisation of the ultimate impact of an increased risk result. Most gene carriers (80%) rated their current life situation as good. However, the test did not bring the anticipated control over their future [106]. Codori et al. found that denial of the illness may be appropriate for as yet asymptomatic gene carriers, also because no intervention is possible. Moreover, the majority of tested high-risk persons significantly underestimated the risk shown for HD [106].

Adaptation to the test result; the course of distress

Wiggins et al. [113] and Tibben et al. [112, 114] focused on the course of distress; from pre-test, to immediately after the test and 6 to 36 months after testing. In the Dutch study, one week after the test result carriers were found to be more hopeless and noncarriers less hopeless than prior to testing [114]. These effects disappeared after 6 months and did not recur.

After one year Wiggins et al. [113] found that, carriers and noncarriers were less distressed than before, and carriers were also less depressed. They commented on the potential psychological benefits of testing, irrespective of its outcome. In the three years follow-up study of the Dutch group, it was found that partners of carriers showed the same course of distress as the carriers. Having children contributed to the distress experienced by partners of carriers. Partners of noncarriers were significantly less distressed than noncarriers after three years [114].

Adaptation to the test result; predicting post-test distress

Only three studies, so far, identified pre-test predictors of post-test distress [123-126]. Tibben et al. [124] found a relation between pre-test and post-test distress. Among carriers, pre-test distress was more often associated with post-test suffering from intrusive thoughts and feelings, than among noncarriers. Post-test avoidance of HD related situations was observed in those who only recently learned about HD, they were less satisfied with the available support and at the same time more optimistic about the future. In general, high post-test distress was equally found amongst both carriers and noncarriers of the HD gene [125].

Decruyneare et al. [126] reported that more ego strength in combination with the ability to use comforting ideas as a coping strategy were associated with less post-test anxiety. Post-test depression was found to be associated with pre-test depression, and more post-test ego strength was associated with more pre-test ego-strength, all independently of the carrier status. Codori et al. [127] report that factors leading to poor adjustment were being a gene carrier, being married, having no children, or being close to the estimated age of onset. What makes knowing to be a gene carrier distressing for some and not for others is still not clear.

Studies addressing the partner and the family

The implications of HD for the partners was studied by only a few research groups [84, 110, 111, 113, 128, 129]. For the partner, the mental deterioration and personality changes of the carrier are the feared aspects. Moreover, most dramatic is the threat that their children may later on develop the same disease [84].

Kessler [128], describes the disorganizing effect on the family of: 1) keeping HD a secret from the spouse, 2) illness of a parent in a young family, 3) the difference

between either a father or a mother becoming affected, and 4) the compromises asked from the non-affected spouse between, amongst others, the need for autonomy and the care taking. Especially difficult for the partner may be the sudden change in expectations about the future after predictive testing. A central therapeutic approach for psychologists working with these families is to help spouses to deal with feelings of guilt and disappointment on the sudden required role shift [129].

Following couples during predictive testing Quaid et al. [110] found that, at pre-test, partners were significantly more depressed than the individuals at-risk. Couples opting for testing (after pre-test counselling) were more positive about their relationship than the couples who withdrew. Up to 12 months after testing the "gene carrier couples" were found to be more distressed than the "noncarrier couples". Also in the Netherlands Tibben et al. stress the importance of early involvement of the partner in the counselling process [116]. At pre-test most partners (76%) gave planning for the future as the main reason for the test, and most couples denied that the identification of a gene carrier might have an effect on their mood, quality of life, or marriage [94]. Three years after testing, partners of noncarriers were found to be less distressed than partners of carriers [114].

The effects on other relatives have rarely been studied. Family coping strategies may include patient preselection in which relatives (un)consciously act together to designate a relative as a future patient, denial of symptoms, and even suicidal behaviour [129]. The profound impact of a genetic disease on the balance of the relationship with the partner or family has received some attention [108, 131-133]. Loyalties felt among several generations, feelings of guilt, debt and gratitude [134] play an important role in the reactions to a test result [131]. Central themes are questions such as: is the life given by our parents worth living when at-risk? Are the parents blamed when a proven gene carrier decides to refrain from having children? Are the loyalties ruptured when one proves to be a noncarrier?

3.1.2. Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type (HCHWA-D)

The experiences at the department of Clinical Genetics in Leiden have learned us that predictive testing for HCHWA-D gives similar reactions as in testing for HD. Awareness of early symptoms in HCHWA-D is focused upon headaches while in HD this is upon involuntary movements [135]. Individuals coming for testing felt more separated from their family [136]. The general attitude in the strictly religious region where HCHWA-D is found, is against testing.

3.2. Hereditary cancer syndromes in this study

3.2.1 Familial Adenomatous Polyposis Coli (FAP)

Psychological implications of predictive genetic testing

From the beginning onwards, analysis of the psychological implications of predictive testing for FAP was noted to be an essential component of the test [137]. However, the reports on the psychological implications of predictive testing for FAP are limited. Codori et al. reported that those who refrained from testing were men who also declined colonoscopy [138]. In Australia, a high uptake of predictive testing has significantly improved clinical management in patients and families. However, to monitor the long-term psychological effect of testing, a follow-up study is still needed [139]. Petersen et al. [140] also reported that family interactions and perceived identity were strongly influenced by FAP. Adults and children needed pre- and post-test counselling. Even well-prepared parents were found to be "shocked" and "devastated" when learning of their child's genetic status, particularly when the number of children (often parents want all children tested at once) or which specific children were found to be a gene carrier differed from their prior expectations [140].

In a qualitative study, several English patients at-risk for FAP presented FAP as "not a problem" and "non-threatening" [141]. The hospital appointments for essential bowel screening were a form of social family gathering. Intestinal screening itself was experienced as both necessary, and as reassuring. Even noncarriers wished to continue screening, which is contradictory to the experiences in the Netherlands [142].

3.2.2 Hereditary Breast and Ovarian Cancer (HBOC)

Women from families with multiple cases of breast and ovarian cancers have become identified in cancer registers. These women have high levels of distress and persistent, intrusive worries about developing breast cancer [143-147]. However, recommended breast cancer screening guidelines are not followed regularly. The guidelines include a mammography from age 25 onwards, or 5 years younger than the earliest expression of breast cancer in a women's first degree relative, monthly self-breast examination (SBE), and twice yearly examination of their breasts by a physician [148].

A psychoeducational intervention was found to significantly increase the adherence to screening and to lower feelings of distress [149]. Women with less formal education benefitted the most. However, women who tend to focus on and amplify health threats (e.g. having a monitoring coping style [150]) became more distressed by receiving additional information, independently of the kind of information [151].

The fears involved in being a member of a hereditary cancer family [133, 152-155] (see chapters 3 and 7) have been described in detail.

Interest in testing by risk carriers prior to the availability of the test

The uptake of the predictive DNA test among first degree relatives of familial breast cancer patients was expected to be high [156-160], especially among female relatives who are reported to anticipate a higher negative impact compared to males [161]. More recent work, however, indicated that only a subset of HBOC family members are likely to request predictive testing when available [162] (see also Discussion).

Reasons for predictive testing

The main reasons for wanting the test are to clarify the situation for their offspring, to be reassured, and to help research [163, 164].

Psychological implications of predictive genetic testing

In general, the psychological implications of breast and ovarian cancer and its treatment have been extensively studied; for a review see [165-167].

Early reports on small groups at-risk for HBOC and taking the predictive test, showed absence of emotional disturbance [168]. Others found feelings of guilt about passing on the gene in a family [169]. Young women resented their family history and even their own breasts [169]. Relief in noncarriers was of short-lived duration and soon replaced by doubts about the reliability the test, and concern about relatives recently identified as carriers. At one month after testing, noncarriers were less depressed, and had less complaints about their daily and sexual functioning, while identified gene carriers had unchanged levels of depression and impairment of their everyday activities [162]. Others report that, two weeks post-test, general distress remained unchanged in gene-carriers but test-related distress was significantly higher than in noncarriers. The highest levels of distress were found in carriers who had no prior cancer diagnosis or preventive surgery [170]. In a European study, Watson et al. [171] found that levels of psychological morbidity and cancer specific concerns were not unusually high in the first year after the test, except for those who did not expect to become identified as a gene carrier.

Men have been incompletely studied for the (expected) implications of predictive testing for the BRCA1 gene; this general neglect is also apparent in the Statement of the American Society of Human Genetics on genetic testing for HBOC [172].

Studies addressing the partner and the family

Family communication [155, 173] can influence genetic counselling and vice versa (see also chapter 3b). On the one hand, a person who wants to learn about his/her genetic risk needs to gather information from the family, necessary for the counsellor to assess the genetic risk. On the other hand, there may be a perceived obligation to pass on the information obtained by genetic counselling to the rest of the family. This perceived

obligation is often balanced with that of not causing alarm. It is stressed that genetic professionals should be aware of their role in this communication network.

3.3. Other autosomal dominant inheritable disorders

Some predictive testing programmes for other late onset disorders involve a psychological study; most, however, do not. Many of the reports and observations describe similar psychological reactions, although the practical implications of testing may differ widely. We address some of the further literature and personal experiences with predictive testing. To stay within the scope of this thesis we focused on autosomal dominant inheritable neurodegenerative disorders and cancer syndromes.

3.3.1. Neurological disorders

As in the HD studies [95] the expectations about predictive testing for Alzheimer's disease/cerebral haemorrhage (FAD-CH) and hereditary Pick disease (HPD), and the planned uptake were investigated. The majority of participants would take the test, but most did not feel ready yet (64% of the participants would request the test; two-third of the 64% did not feel ready yet). Another observation was that people at-risk for HPD were significantly more preoccupied with the occurrence of potential symptoms in themselves, compared with those at-risk for FAD-CH [174].

Myotonic Dystrophy is characterized by anticipation, the phenomenon of increasing severity and earlier onset with each generation, meaning that a child may be significantly more handicapped than the parent. So far predictive testing has been conducted without a psychological study. The experiences with predictive testing for MD at the department of Clinical Genetics in Nijmegen show that asymptomatic adults often opt for predictive testing because they are planning to have children, or to inform their existing children [175]. Prenatal testing has often been the subsequent option for gene carriers in the case of MD.

3.3.2 Cancer Syndromes

The multiple genetic cancer syndromes differ in age of onset, organs involved and possibilities for treatment. The experiences with the psychological implications of predictive testing for Multiple Endocrine Neoplasia 2A (medullary thyroid carcinoma, pheochromocytoma and parathyroid hyperplasia or adenoma) [176] have been well described [177]. The main reason for participation has been to reduce uncertainty. Identified gene carriers experienced feelings of anxiety, depression and relief; they focused on possible symptoms and identified themselves with other carriers and affected relatives. Most noncarriers felt relief, but also worry; some felt guilty and

isolated from their families. Fewer psychological complaints were reported 12 months after testing. Identified gene carriers preferred immediate preventive treatment to periodic screening [177]. A much higher uptake was observed amongst risk carriers for MEN2A in comparison to those at-risk for HD and, to a lesser extent, in families with HNPCC [178]. This might be due to the fact that predictive testing for MEN2A can be a part of the diagnostic work-up of relatives at-risk, and forms an important identification for thyroidectomy at an early age.

In case of HNPCC much effort is still needed to identify the specific mutation in each individual family, which may also be relevant to predict the clinical course of the disease. The psychological studies so far report that anxiety might be heightened by discussing numerical risks and the possibility of malignancy. However, participants were also relieved to discuss their risks and take responsibility for their screening [178]. Interest for testing among risk carriers is found to be high. The main reasons for wanting the test were to know if screening by colonoscopy ought to be continued, to clarify the situation for their offspring, but also to be reassured. Barriers to testing included concerns about insurance, test accuracy and how one's family would react emotionally. Most participants anticipated that they would become depressed and anxious if they were identified as gene carriers, while many would feel guilty and still worry if they proved to be noncarriers [180]. Risk carriers with less formal education and with lower levels of social support were found to be more anxious and depressed prior to testing [181].

Less is known about psychological implications of predictive testing for more complex cancer syndromes such as Von Hippel Lindau disease (VHL) and the Li Fraumeni Syndrome (LFS). Multiple organs can become affected, some with and some without clear treatment options. As in the HD studies only a minority of those at-risk for LFS opted for testing [182].

3.4. Summary

Several themes seem to be emerging from the literature so far:

- * Actual uptake of predictive testing has been lower than initially expected by risk carriers.
- * Reasons for testing were to end uncertainty, to obtain some control over the future, to inform offspring and other relatives; some also mentioned to help research. Several participants at-risk for the cancer syndromes opted for testing to be reassured.
- * Main reason against testing was the fear of inability to cope with a high-risk result.

* Reactions to testing have been more complex than expected, though major psychiatric problems post-test did not occur, as once expected. However, the long-term burden of predictive testing is **not** negligible, for neither the neurological diseases or the cancer syndromes.

* Gene carriers cope reasonably well by restricting themselves to live by the day, while the partners are much more worried about the future.

* Noncarriers have difficulties to develop a new life-perspective and often feel guilty. The numbed emotions and the lack of relief are hard to understand for themselves, their partners and others in their immediate social environment.

* A hereditary disease and predictive testing have an unsettling effect on the partner relationship and the family.

* Reaction to the test result is largely determined by the meaning given to it by the family (e.g. patient preselection, secrecy, denial, etc.) and also by the meaning given by the medical profession.

In general, the expectation has been that predictive testing would be less distressing for people at-risk for disorders with treatment options; however, this is certainly an underestimation of the situation, as has been shown in the literature.

4. Adaptation to the test result, the psychological theory

Reactions to stressors often include alternating phases of intrusive feelings and avoidance of certain ideas and situations associated with the specific traumatic event [183]. In the present study the stressor was the genetic disease with the ultimate stressful event of taking the test. The alternation of intrusion and avoidance, according to the individual's idiosyncratic pattern, may last until a period of working through occurs [184]. The stress response theory of Horowitz [185] and our own observations on individuals at-risk and their families, led to expect that post-test adjustment involves (re)experiencing untoward intrusive feelings and thoughts, and denial-avoidance of situations associated with the specific hereditary disease.

The Impact of Event Scale (IES) [185] (for more details see chapter 2) permits careful and systematic evaluation of the stress responses that follow traumatic events by assessing the amount of intrusive thoughts and feelings and avoidance over the previous week (see chapters 4, 5, 6, and 8). Zilberg et al. [186] recognized three stress response patterns; 1) a group frozen in avoidant states (high avoidance/low intrusion scores); 2) a group stuck in undercontrolled intrusion states (high intrusion/low avoidance scores); and 3) a group oscillating between intrusion and avoidance (resulting in similar ratings for intrusion and avoidance). According to Zilberg et al. [186] the first two patterns represent a blocked response pattern, the last an active response pattern

indicating working through. Schwarzwald et al. [184] recognized two groups in those reporting similar levels of intrusion and avoidance: those reporting high respectively low intrusion and avoidance. They assume that this reflects a single, general dimension of stress level, either high or low stress [182]. Participants facing the predictive test have to deal with the stress provoked by the test, and will show behaviour that may represent one of these patterns (see chapter 8).

5. Aims of the psychological follow-up study, what do we want to know?

Healthy people who are at-risk for a life-threatening disease carry a substantial stress burden because of the threat of the disease and the uncertainty about the risks. Testing for risk factors may help to reduce uncertainty but will also produce new stressors [187], as observed in studies on late onset neurological disorders or genetic cancer syndromes. Comparative studies on the implications of predictive testing for these different disorders were not performed before. The experiences with presymptomatic testing for HD became a leading paradigm in the analysis of predictive testing in other late onset disorders, such as cancer syndromes (e.g. HBOC, FAP, HNPCC) [125, 188]. All show: autosomal dominant inheritance, an onset of a variety of symptoms with increasing age, and a major impact on personal health, life expectancy and on the family relations. The cancer syndromes differ, however, from HD by absence of neuropsychiatric symptoms and the availability of far-reaching choices for treatment [189].

Within this field of rapid developments this comparative study addresses the following questions;

- 1) Are the concepts on the effects of predictive testing for HD equally valid in testing for other late onset disorders?
 - 1a) Do stress responses differ among those tested for dissimilar late onset disorders?
 - 1b) Can we identify factors contributing to (mal)adjustment after the test result?
 - 1c) Which interaction patterns can be observed in families that broaden our understanding of the impact of predictive testing on a family?
- 2) What are the contributions from a comparative psychological follow-up study of neurological disorders and cancer syndromes, to the improvement of guidelines for genetic counselling, psychological support and interventions?

6. Outline of this study

This thesis comprises nine chapters. In **chapter 1**, the disorders in this study are introduced and a review of the literature on the psychological implications of predictive testing for late onset disorders is presented. The methods and techniques used in the psychological study are described in **chapter 2**. **Chapter 3** describes the first family in the Netherlands opting for predictive testing for HBOC and illustrates the complexity of the problems provoked by the availability of a genetic test. Pre-test distress (conceptualized by intrusion and avoidance, as measured with the Impact of Event Scale) was assessed in individuals at-risk for HD, HCHWA-D, FAP or HBOC and their subsequent partners (**chapter 4**). The association between; a) experience with the disorder, b) motivation to be tested, and c) the expected impact of the test result, with the distress prior to testing was investigated. **Chapter 5** presents an analysis of the course of distress, assessed prior to the test and at one week and six months after testing for participants at-risk for HD, FAP or HBOC. In **chapter 6**, we analysed factors predicting distress six months after testing, such as the test outcome, the type of disorder, biographical data and baseline psychological characteristics. **Chapter 7** is a case description, illustrating the contradictions between the distress reported by participants of a predictive testing protocol and the distress observed by the researcher. Our clinical, and the experimental observations of Shedler et al. [190] indicated the limitations of questionnaire studies to fathom the real influence of events like predictive testing. In **chapter 8**, questionnaire results and the impression of distress obtained by interview are compared. **Chapter 9** presents the general conclusions and suggestions for further prospective research.

The **epilogue** is a more philosophical contemplation on whether "to know or not to know" is a meaningful question for those at-risk opting for predictive testing.

The order of the chapters does not reflect their chronology, but attempts an optimal organization of the subject matter. To enhance the readability of chapters 3b, 4, 5, 6, 7 and 8 (based on original publications), we omitted the introduction on the genetic disorders (which are described in full detail in chapter 1), and the methods and techniques (which are described in full detail in chapter 2). The literature review (chapter 1) was written in 1997 and includes more recent studies.

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CHAPTER 2

METHODS AND TECHNIQUES

1. Participants

Between September 1, 1993 and August 31, 1995, successively 129 individuals at-risk for HD (n=47), HCHWA-D (n=12), FAP (n=60) or HBOC (n=10) were asked to participate in the psychological study at the department of Clinical Genetics of the University Hospital Leiden. In the same period, 20 individuals at-risk for HBOC were also asked to participate in the psychological study at the department of Clinical Genetics of the University Hospital Dijkzigt, Rotterdam. Partners were invited to join the study. The predictive DNA test and the psychological follow-up study were offered to individuals aged 18 years and over at 50% risk. The inclusion criteria for the psychological study were an ability to give informed consent and adequate understanding of the questionnaires.

2. Procedures

Information about the availability of the DNA test was given by either general practitioner, neurologist, oncologist, clinical genetic service, relatives or one of the respective patient organizations. Families who did participate in the research phase for linkage study of the cancer syndromes were informed about the possibility of predictive testing by the department of Clinical Genetics in Leiden and Rotterdam, or by the Dutch Foundation for Hereditary Tumors (STOET). Information from the public media made a number of participants aware of the autosomal dominant inheritance of the disorders in their family.

The study protocol was adapted from the HD-protocol [1] (table 1). As in the study of Tibben et al. [2] interviews were used in the present study in order to gain a detailed picture of a participant's belief about, perceptions and accounts of predictive testing and the hereditary late onset disorder. This method allows the researcher to follow up particularly interesting avenues that emerge in the interview and the participant is able to give a fuller picture. This adds flexibility to the more conventional questionnaire method.

Two pre-test and two post-test sessions were held with the psychologist (ACDdW) (table 2). At the first session at the Department of Clinical Genetics the psychological study was introduced. Subsequently, the following psychological self-report inventories were handed out to the participants at-risk and the partners; an Attitude Questionnaire, the Symptom Checklist (SCL'90), the Impact of Event Scale (IES), the Beck Hopelessness Scale (BHS) and the Hospital Anxiety and Depression Scale (HAD) (for more details see section 4.3.). One month later at the second session at the department of Clinical Genetics blood samples were taken by the clinical geneticist when participants wanted actual testing. This session was followed by an

Table I. Predictive DNA testing at the department of Clinical Genetics, Leiden and Rotterdam.

session*	<u>PREPARATION FOR TEST</u>
1	exploration test demand and motivation <ul style="list-style-type: none"> - information about <u>the disorder</u>, inheritance, DNA test - <i>introduction to the psychological follow-up study</i> - <i>exploration of the family history, experiences with death and disease and the motivation to be tested</i> - <i>completion of questionnaires</i>
2	additional information about DNA testing and blood sampling <ul style="list-style-type: none"> - exploration of consequences of disclosure alternatives, discussion of possible treatment - blood sampling - <i>in-depth interview separately with the individual at-risk and the partner, discussing pros and cons of testing, etc.</i> - <i>completion of questionnaires</i>
3	DISCLOSURE OF TEST RESULT <ul style="list-style-type: none"> - handing out the test result, asking for consent to contact GP and specialist - <i>contact with psychologist</i>
	<u>FOLLOW-UP AFTER DISCLOSURE</u>
4	<i>within 24 hours telephone contact to discuss initial response to the test result</i>
5	after 1 week <ul style="list-style-type: none"> - <i>in-depth interview with the tested individual and the partner separately</i> - <i>completion of questionnaires</i>
6	after 6 months <ul style="list-style-type: none"> - <i>in-depth interview with the tested individual and the partner separately</i> - <i>completion of questionnaires</i>

* the clinical geneticist conducts sessions with the individual at-risk and the respective partner, followed by the appointment with the psychologist (*in italics*)

appointment with the psychologist for an interview (for more details see section 4.4.), separately for the participant and the partner. Although the interviews were semi-structured, a checklist served to ensure that the following areas were covered: the experience and coping with stressful events in general, and with the disorder in particular; the preparation for the test result; expectations about the test result; the possible consequences of either result; and the contact with the partner, parents, siblings and friends. The last three summarizing questions were recorded and transcribed. These transcripts resulted a coherence score by a panel of five psychologists (for more details see section 4.4.). At that appointment participants and partners were asked to fill out the Dutch adaptation of the Family adaptability and

Table 2. Instruments used for the psychological assessment in the study on the implications of predictive DNA testing.

	Introduction	Blood sampling	<i>Test result</i>		
	pre-test	pre-test 4 weeks later	8 weeks later	post-test 1 week after the test result	post-test 6 months after the test result
Interview ^{1,2}		X		X	X
Attitude Questionnaire ^{1,2}	X				
SCL90 (Symptom Checklist) ^{1,2}	X				
Impact of Events Scale ^{1,2}	X			X	X
Beck Hopelessness Scale ^{1,2}	X				
Hospital Anxiety and Depression Scale ^{1,2}	X				
Dutch adaptation of the Family Adaptability and Cohesion Evaluation Scales (FACES) ¹		X			
Social Support Questionnaire ¹		X			
Loneliness Scale ¹		X			

¹ predictor variables

² outcome variables

X = conducted or filled out at that moment of the study

cohesion evaluation scale (FACES), the Social support questionnaire (SSQ) and the loneliness scale (for more details see section 4.3.).

After 6 to 8 weeks the participants were invited to receive their test result. Follow-up interviews, similar to the interview after blood sampling, were conducted approximately 1 week and 6 months after the test result. Participants and partners were asked to fill out the IES, one week and six months after the test result. If a need for additional psychological support was expressed, the individual at-risk and his/her partner were referred to another psychologist of the team (AT, PGF, MWZ).

3. Uptake

At the first appointment at the department of Clinical Genetics 13 individuals at-risk (10 of them for FAP), opted for the DNA test but decided against the psychological study. Another six, who initially consented to participate, did not return their pre-test questionnaires. Nine participants did not want to be tested (yet). In total the data of 121 individuals at-risk and 80 partners, gathered at the first appointment, were analyzed; these data are presented in **chapter 4**.

The questionnaire results of 119 participants, gathered at the first appointment, and the interviews of 78 participants, gathered at the second appointment were analyzed; these data are presented in **chapter 8**. Two additional questionnaires (included in this part of the study compared to that part described in chapter 4) were not completed. Seventeen participants withdrew from the testing protocol on second thought, they did not want to be tested (yet). A total of 102 interviews were held; 17 of these could not be scored due to audiotaping failure and 7 participants, all at-risk for the cancer syndromes, chose not to have their interviews recorded.

Before receiving their test result another 10 individuals, all at-risk for the cancer syndromes, withdrew from the psychological follow-up study. Three participants at-risk for FAP did not receive a test result as neither mutation nor linkage analysis was possible, and were lost to follow-up [3]. All the individuals at-risk for HCHWA-D were excluded from the statistical analysis of the follow up data as too few participated; this group belongs to a small religious community which tends to refuse predictive testing.

A total of 91 individuals, at-risk for HD, FAP or HBOC did participate in the psychological follow-up study while receiving their test result. After the test result 33 participants withdrew from the follow-up appointments (see table 3). Finally, 58 individuals at-risk completed the follow-up period of 6 months and are included in the statistical analysis: see **chapters 5 and 6**.

Table 3. Reasons for not receiving follow-up data after the test result from participants formerly at-risk for either Huntington's Disease, Familial Adenomatous Polyposis or Hereditary Breast and Ovarian Cancer

	HD ¹⁾ (n = 12) ²⁾ 32% ³⁾	FAP (n = 13) 36%	HBOC (n = 8) 44%
not wanting follow-up appointments (n):	6	12	5
- postponing appointments	2	2	1
- found talking too difficult	4	2	2
- found talking not necessary		8	2
not returning the questionnaires (n)	6	1	3

¹⁾ HD = Huntington's Disease, FAP = Familial Adenomatous Polyposis and HBOC = Hereditary Breast and Ovarian Cancer. ²⁾ n = number of persons. ³⁾ percentage of individuals lost to follow-up as part of the total population receiving their test result while participating in the psychological follow-up study.

The participants who were lost to follow-up after they received their test result (n=33), could be identified as having a higher education than those continuing participation by means of a logistic regression analyses (Exp(B) = .36; $p < .03$) (Exp(B) = adjusted odds ratio). The other variables in the model (type of disorder, test result, number of children and gender) did not contribute significantly to identification of dropouts. In a second model, including psychological instead of biographical variables, again dropouts were identified as having a higher education (Exp(B) = .38; $p < .03$) whereas the other variables in the model (intrusion, avoidance, number of children, and gender) did not contribute to the identification.

4. Variables

4.1. Medical Characteristics

The DNA test result and the type of disorders were obtained from medical files.

4.2. Biographical Data

Gender, age, education, religion, marital status and number of children were obtained by questionnaire.

4.3. Questionnaires

An Attitude Questionnaire (AQ) (for more details see Appendix) was used, consisting of 15 questions covering three areas: i) experience with the disorder; ii) motivation for the test; and iii) expected impact of the test result. Seven questions were open-ended and 9 were multiple choice. Answer categories were compiled to accommodate the

common themes emerging from the responses to the open-end questions. An adjusted version of the questionnaire was given to the partners, which covered the partners' experiences with the disorder in the family of his/her spouse/partner at-risk. The questionnaire was modified from the Dutch HD study to accommodate both the neurodegenerative disorders and the cancer syndromes [1].

Psychological measures:

From the Symptom Checklist (SCL-90) [4, 5] (SCL-90) the subscales agoraphobia, obsessive compulsive behaviour, interpersonal sensitivity, hostility, sleeping problems and the residual items were used to assess the 'psychological complaints'. The subscales anxiety and depression were deleted to prevent overlap with the HAD. The subscale somatization was deleted to prevent over-reporting of symptoms of the specific familial disease. The resulting 'psychological complaints' scale consisted of 52 items (min = 52; max = 260). 'Psychological complaints' was highly correlated with the total SCL-90 score ($r = .96$; $p < .001$; one tailed). In the SCL-90, patients rate the degree of stress they have experienced in the preceding week for each of the 90 items on a five-point Likert scale (1 = not at all, 5 = extremely). Validity and reliability have been demonstrated in the Dutch population [6].

Stress responses were measured using the Impact of Event Scale (IES) [7-9]. The IES classifies the effects of stress into two major categories: intrusion and avoidance. Intrusion refers to intrusively experienced ideas, images, feelings or bad dreams. Avoidance refers to consciously recognized avoidance of certain ideas, feelings or situations. The IES is a reliable, self-reported scale that can be anchored to any specific life event. In this study the IES was anchored to the disease in the family, either HD, HCHWA-D, FAP or HBOC. Items read like: "I thought about *Huntington disease* when I didn't mean to" or "I avoided letting myself get upset when I thought about *hereditary breast and ovarian cancer* or was reminded of it". The IES permits assessment of individuals over time, comparison of the degree of stress between subgroups, and comparison of the impact of various life events. The IES consists of seven items that form the intrusion subscale (score range 0-35, with a higher score indicating more reported intrusion) and eight items of the avoidance subscale (score range 0-40, with a higher score indicating more reported avoidance). The items are scored by choosing one of four indicators of occurrence of the specified event (never = 0, seldom = 1, often = 3 and continuously = 5).

Pessimistic expectations concerning oneself and one's future were assessed with the Beck Hopelessness Scale (BHS) [10]. The scale consists of 20 true-false items of which 9 were keyed false and 11 were keyed true, each response was assigned a score of 0 or 1. The total "hopelessness score" was the sum of the scores on the individual items

(min 0; max 20; 0-3=normal, 4-8=mild, 9-14=moderate and ≥ 14 =severe hopelessness). Hopelessness is regarded as a possible predictor of depression and suicidal behaviour [10-12]. Reliability and validity have been demonstrated [10, 12].

Anxiety and depression were assessed with the Hospital Anxiety Depression Scale (HAD) [13]. It has 14 questions, of which half reflect anxiety and half depression. The answer options, indicate intensity of the given mood. The sum of the individual's scores gives an overall anxiety (min 0; max 21) and depression (min 0; max 21) score. A score of 8 to 10 on either subscale is an indication of borderline anxiety or depression, a score of 10 or higher on either subscale is an indication of clinical anxiety or depression. Validity and reliability have been proven [14].

Social interaction measures:

Family functioning was assessed by the Dutch adaption of the Family Adaptability and Cohesion Evaluation Scales (FACES) of Olson et al. [15-17], the Family Dimension Scales [18]. Subjects had to indicate whether items like 'At home we always ask each other for help; Every decision is made with the whole family; We are used to take care of our own matters at home' were 'never true' or 'always true' on a 4-point Likert scale. The scale has three subscales: cohesion (the commitment experienced towards other family members); adaptability (the flexibility of power and role structures within the family, as a reaction to external and internal stressors); and social desirability (the family representation). Each subscale is divided into four levels, these are curvilinear. Family scoring in the middle is considered as optimal, and on either extreme of each scale is considered as dysfunctional [19].

To assess the access to supportive allies of participants at-risk we used the 6-item Social Support Questionnaire (SSQ) developed by Sarason et al. [20]. Each item has 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?". Subjects can indicate no-one, up to a maximum of nine persons (min=0, max=54). The second part of each item measures the degree of *satisfaction* with the perceived support (SSQS). Subjects can indicate how satisfied they were on a 6-point Likert scale from 'very dissatisfied' to 'very satisfied'. All scores are added and divided by six (min=1, max=6).

Loneliness was measured by the Loneliness Scale by De Jong-Gierveld et al. [21]. The scale consists of 11 items; six are formulated negatively and five are formulated positively (min=0, max=11). The five category responses for every question are transformed in dichotomous responses (0, 1). The scale assesses a continuum from severe loneliness, to not being lonely.

4.4. Interview

All participants and partners were interviewed separately, after the blood sample was taken, one week and six months after testing, by a psychologist (ACDdW) unfamiliar with the scores of the previous interviews with the participants. Although the interviews were semi-structured, a checklist served to ensure that the following areas were covered; the experience and coping with stressful events in general, and with the disorder in particular, the preparation for the test result, expectations about the test result, the possible consequences of either result and the contact with the partner, parents, siblings and friends. Before the actual interview, participants were asked whether they were prepared to answer three summarizing questions at the end of the interview which would be audiotaped. The questions were: "What does *the genetic disorder* (HD or HCHWA-D or FAP or HBOC) mean to you?", "What does the predictive DNA test mean to you, which is going to confirm or exclude (and after testing: which confirmed/excluded) you from being a gene carrier?", and : "What does the predictive DNA test mean for your marriage/relationship (or, when there is no partner, for your relations with your next of kin)?"

Each interview was transcribed and corrected before analysis. Each transcript was judged by a panel of five psychologists. The system developed by Main and Goldwyn [22] for scoring "the coherence of transcript" was translated and adapted for the present study by RWT. An answer is considered coherent when it is: 1) truthful, providing evidence for what is said, 2) succinct and yet complete, 3) relevant or perspicacious, presenting what has to be said so that it is plainly understood, 4) clear and orderly [23]. A participant is then showing a readiness, a preparedness to discuss and evaluate memories, experiences and feelings about the hereditary disorder and the test, with a clear and consistent flow of ideas [24]. Such a transcript receives a high score (min = 1, max = 9). Lower scores represent lower levels of coherency, which may reflect either a dismissal or preoccupation with the subject.

If scores differed one point between judges, a mean score was computed. If judges differed 2 or more points, further discussion of the transcript followed until a consensus score could be assigned. (In 36% of the last 100 transcripts one judge differed more than 1 point from the others, in 20% two judges differed more than 1 point from the others, and in 10% three judges differed more than one point from the others).

Three answers, or parts of answers, of 50% risk carriers for HD are given as an example of more or less coherent answers. The following is considered to be a fairly coherent response (score 7): Interviewer: "What does HD mean to you?" *Participant: "Eh -- it is, could be seen as, how should I put it, it has enriched my life, I know a bit more about life: that it is not all honey and roses, it made that clear. You have to live*

with it all your life. It is also difficult because it comes with fear and tension piling up so high that you don't know where to go, you can't live your life as free and unconcerned as you would wish. That really puts me down. I really feel like I should continue, but how, what; the fear is so enormous that I find it very hard to live with it at the moment (etc.)."

The next two examples are considered to be less coherent (both score 3). Interviewer: "What does HD mean to you?" Participant: *"Most people have no idea about what it means, they think people are drunk, I witnessed that several times".*

Interviewer: "What does the predictive test mean for you and your partner? Does it have an influence on your relation? " Participant: *" No absolutely not, I just continue with what I have been doing always (8 sec silence). I'm a member of the board on the general meeting of the housing cooperation and I must go to the meeting tonight, I'm the secretary the treasurer of the department (name of town). It is a lot of work, I will just continue to do it. If the test proves that I have a chance than I know when to quit. If I notice that it, that it will start then I know I have to quit I'm also in the board of the staff association of the company I used to work ... (etc.)."*

The first quotation clearly shows the individual at-risk is able to consider the various aspects of being at-risk and to describe the associated feelings convincingly. The second participant reacts briefly and evasively by describing the behaviour observed in other people, without reflecting upon what HD means for him/her personally. The third participant does not answer the question either. A description of the implications of being a gene carrier for his sideline activities is given in great detail instead of a description of the implications of testing for his partner-relation. Furthermore the sentence *"if the test proves that I have a chance then I know when to quit"* is vague as well as incorrect. All participants have been counselled by a clinical geneticist, at this stage at least twice, at both sessions the genetics and characteristics of the specific genetic disorder are discussed in great detail. This participant is told and explained that the test provides certainty and not an estimation. When proven to be a gene-carrier one will develop HD sooner or later (testing is done by mutation analysis and the gene is fully penetrant). Moreover, the test does not provide any information about the onset of the disease.

5. Data Analysis

All data analyses were obtained using SPSS for Windows version, 6.1. To differentiate the categories of genetic disorders, with regard to biographical data, one-way analysis of variance for continuous data was applied. Chi square test was used for nominal data. The significance level was set at 0.05, two-sided. If the testing was statistically

significant, post hoc comparisons for continuous data among the genetic disorders were done according to Scheffé's S method and for nominal data Bonferroni's procedure was applied.

The distributions of the psychological tests appeared to be skewed to the right. Therefore, raw scores were square root transformed in order to get normal distributions, which are paramount for multivariate analyses of variance and for multiple regression variance.

5.1. Association between the experience with the disorder, the motivation to be tested, the expectations about the test result and pre-test distress (chapter 4)

In order to estimate the association between attitudinal characteristics (e.g. experience with the disease, motivation to be tested, and the expected impact of the test result) and the two subscales of the IES, intrusion and avoidance respectively, the standardized regression coefficient (B), as a measure of relative importance, was estimated. The level of statistical significance was set at 0.05, two-sided.

5.2. The course of distress (chapter 5)

For missing data at one week after the test result, the mean substitution procedure was applied [25]. To test the effect of the test result, multivariate analysis of variance (MANOVA) for repeated measurements was performed with the factors: test result (carrier/noncarrier), disease, gender, as dependent variables: two psychological variables (the two subscales of the IES, intrusion and avoidance) were assessed three times (prior to the test, 1 week after disclosure and 6 months after disclosure of the test results). The three timepoints were decomposed into the orthonormalized polynomial contrasts. Both linear and quadratic trends were tested. At least two measurement points are needed to detect a linear trend (one line between two points); to identify a quadratic trend at least three time points are needed (i.e. a curve through three points). First, we investigated whether there was multivariately a significant effect ($p < .05$, two-tailed) in DNA test outcome for gender, type of disorder and their interactions. Second, we performed a stepdown analysis in order to detect possible significant linear and quadratic trends. A p-value < 0.05 (two-tailed) was considered significant.

5.3. Predicting adaptation to the test result (chapter 6)

We present two different statistical models for the prediction of post-test intrusion and avoidance behaviour, because we have been looking for the best fitting prediction model for each. Every categorical predictor containing more than two categories were

transformed into a dummy variable. The number of dummy variables equaled the number of categories minus one.

Intrusion: In order to estimate the outcome variable intrusion, the method of multiple regression analysis was applied. The multiple correlation (MR) of the final model was used as a measure of a goodness of fit. Basically, this measure is the correlation between the actual and the predicted outcome variable. The squared value of MR (also called coefficient of determination) represents the variance explained by the regression model. The regression procedure was as follows: as a first step, all candidate predictor variables were entered into the regression model; next, step by step the candidate predictor variables were eliminated from the model if they were not significant at 0.05 level. For the sake of simple interpretation and comparison of the importance of the predictor variables in the final model, the standardized regression coefficients and the standard errors of these coefficients were presented. The significance of the final model was tested by F statistic, the significance level was fixed at 0.05.

Avoidance: The distribution of the score on the avoidance subscale could not be transformed to a normal distribution. We therefore choose a clinical relevant cut off point, which in daily practice could be considered more than "average". For this dichotomized outcome variable avoidance, the method of multiple logistic regression analysis was applied. The maximum likelihood was used to estimate the parameters of the model. In order to estimate the relative importance of the predictor variables, these variables were standardized with the exception of the dichotomized predictor variables. The logistic regression coefficient can be interpreted as the change in the log odds of the dichotomized outcome variable corresponding with a one-unit change in the predictor variable while the values of the other predictor variables in the model remain unchanged. The antilog B ($\exp(B)$) indicates the change in the odds corresponding with a one-unit change in the adjusted predictor variable. Model Chi-square, comparable to the usual F statistic for regression analysis, is used to estimate the significance of the model with the significance level set at 0.05.

To test the adequacy of both methods of regression analysis, the following assumptions were checked [25, 26]: normality (normal probability plot), homoscedasticity (plot of standardized deleted residuals against predicted values), linearity (plot of standardized deleted residuals against predicted values), influential observations (Cook's distance, leverage, SDBETA) and multicollinearity (variance inflation factor). It appeared that the final model met all these assumptions.

5.4. Psychological characteristics, a comparison between questionnaires and interview results (chapter 8)

To differentiate the four categories of genetic disorders with regard to anxiety, depression, hopelessness and psychological complaints, one-way analysis of variance for continuous data was applied. These data were adjusted for gender and age. Chi square test was used for nominal data. The significance level was set at 0.05, two-sided. If the statistical testing was significant, post hoc comparison between the four genetic disorders was done for continuous data according to Scheffé's S method; for nominal data Bonferoni's procedure was applied.

Intrusion and avoidance levels were dichotomized at the median score. Four reported distress patterns were compiled: i) high intrusion and avoidance, ii) high intrusion and low avoidance, iii) low intrusion and high avoidance, iv) low intrusion and avoidance. To differentiate the four stress response patterns with regard to anxiety, depression, hopelessness, psychological complaints and coherence, one-way analysis of variance for continuous data was applied. The significance level was set at 0.05 two-sided. If statistic testing was significant, post hoc comparison between the four genetic disorders was done for continuous data according to Scheffé's S method. No outliers were detected (Mahalanobis distance measure, Cook's distance measure and leverage).

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CHAPTER 3a

PERCEPTIONS OF A DUTCH FAMILY AT-RISK FOR HEREDITARY BREAST AND OVARIAN CANCER (HBOC) UTILISING PREDICTIVE DNA TESTING

PERCEPTIONS OF A DUTCH FAMILY AT-RISK FOR HEREDITARY BREAST AND OVARIAN CANCER (HBOC) UTILISING PREDICTIVE DNA TESTING

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Data from the International Linkage Consortium suggest that half of familial breast cancer cases and at least three quarters of the familial breast/ovarian cancer cases may be linked to the BRCA-1 gene on chromosome 17q [1]. We have started a collaborative predictive DNA testing programme for a Dutch family with BRCA-1 linked (multipoint lodscore of 1.5) hereditary breast and ovarian cancer (HBOC).

The predictive testing protocol developed for Huntington's disease [2] was adapted for the specific problems in HBOC. Newly identified gene carriers might experience anxiety about death and confusion, in view of the outlook and the mutilating nature of preventive surgery and its potential effects on psychosexuality. Moreover, the expected relief in non-gene carriers may become tempered by the concern about relatives who proved to be gene carriers [3]. In our programme, psychological effects of the test have been studied from the moment that predictive testing became available. Initially, 3 male and 5 female of 10 family members at 50% risk of HBOC requested genetic counselling about predictive testing, 7 of whom decided to undertake testing. 5 women have been identified as gene carriers, implying a 95% life-time risk of developing breast and/or ovarian cancer [4]. 1 woman proved not to be a gene carrier, leaving her with a population-based lifetime risk, and 1 man was identified as gene carrier.

Obviously, attention should be paid to the psychological reactions such as denial and minimisation in identified gene carriers, and survivor guilt in non-gene carriers [3], but we would emphasise some specific problems related to the impact of HBOC in a family. During the testing procedure, the original proband's condition -after previous treatment for bilateral breast cancer with metastases- worsened because of recurrence of metastases. This deterioration had a very unsettling effect on the whole family. A

woman who had first decided against the test wanted to undertake the test and asked for psychological support. Furthermore, individuals with an increased risk felt that the decision to undergo prophylactic mastectomy and ovariectomy became less difficult.

The recurrence of metastases in a relative may result in overidentification with the patient and increase death-anxiety in identified gene carriers and individuals at-risk; this may lead to the wish to accelerate the predictive testing procedure. It is important to anticipate this desire and at the same time to allow sufficient time for an informed decision to be made. The impact of the test result for the male gene carrier was not seen as an immediate threat, but it might become so when his daughter reaches adolescence.

There is no evidence that preventive options such as intensive screening or chemoprevention are of benefit in this high-risk group, and prophylactic surgery is still controversial [5]. The decision to have the predictive test is thus complicated by the choice of preventive strategy if one is identified as a gene carrier. Therefore it is important that all professional care providers express consistent views, to avoid confusion within families. That psychological support is available should be clearly stated besides the research appointments for questionnaires and interviews. Insight into the profound effect of threat within families is needed to offer the best pre-test and post-test support.

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CHAPTER 3b

BRCA1 IN THE FAMILY: A CASE DESCRIPTION OF THE PSYCHOLOGICAL IMPLICATIONS

BRCA1 IN THE FAMILY: A CASE DESCRIPTION OF THE PSYCHOLOGICAL IMPLICATIONS

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ABSTRACT

Our experience with the first family in the Netherlands for whom predictive DNA testing for Hereditary Breast and Ovarian Cancer (HBOC) became an option is described. This serves to illustrate the complex emotional impact on a family as a whole, and upon the members separately, of becoming aware that breast and ovarian cancer is hereditary, and the implications of undergoing predictive testing. All family members received genetic counselling and were offered pre- and post-test psychological follow-up.

We observed two important roles within the family. One member became the *messenger of the news* informing the relatives of the hereditary character of cancer in the family. Another was the *first utilizer* of the new options; namely, the predictive DNA test and preventive surgery. This first utilizer became the example to the rest of the family. Decisions made about preventive treatment (prophylactic ovariectomy and/or mastectomy) were based on the experiences within the family, whether one identified with an affected family member with breast or with ovarian cancer.

The actions and reactions perceived were illustrative of what kind of support provisions should be provided in addition to the genetic and oncological counselling for HBOC. Moreover HBOC should be considered both as an individual and a family problem and be treated as such in genetic counselling.

INTRODUCTION

In 1993, the International Breast Cancer Linkage Consortium reported that approximately 45% of families with a high incidence of early onset (age < 50 years) breast cancer, and at least 80% of families with increased incidence of combined early breast and ovarian cancer, are due to the BRCA1 gene on chromosome 17q [1]. This finding made predictive DNA testing by linkage analysis possible for some families. In October 1994, the identification of a strong candidate for BRCA1 allowed direct mutation analysis in individuals at-risk [2].

Women carrying the BRCA1 gene have an 85% risk of developing breast cancer and a 63% risk of developing ovarian cancer before the age of 70 [3]. Male gene carriers have an 8% risk of prostatic carcinoma before the age of 70 (threefold the population risk). Male and female gene carriers have a 6% risk of colonic cancer before the age of 70 (fourfold the population risk) [4]. The efficacy of chemoprevention or intensive screening (self-examination and/or mammography) in this high risk group, and also prophylactic surgery, are still controversial [5].

The uptake of the predictive DNA test among first degree relatives of familial breast cancer patients is expected to be high [6-9], especially among female relatives who are reported to anticipate a higher negative impact compared to males [10]. More recent work, however, indicates that only a subset of Hereditary Breast and Ovarian Cancer (HBOC) family members are likely to request predictive testing when available [11]. Until recently the psychological aspects of being at-risk, and actually undergoing predictive DNA testing for HBOC were rarely studied. Studies so far report that the main reasons for wanting the test are to help research and to clarify the situation for their offspring [12]. Women at-risk were found to have high levels of psychological distress, as well as persistent and intrusive worries about developing breast cancer [13-15]; a substantial proportion, however, does not follow recommended breast cancer screening guidelines. It has also been observed that young women at high risk expressed resentment about their family history and even of their own breasts [16]. Identified female gene carriers suffered from depression, confusion, persistent worries and sleep disturbances shortly after disclosure of the test results [17]. The relief felt by noncarriers was short lived and soon replaced by worries about possible erroneous results of the test and concerns about relatives who were identified as carriers. More recently it has been reported that, one month after testing, noncarriers showed reduction in depression, role and sexual impairment, while for proven gene carriers depression and role impairment stayed the same [11]. It also has been reported that individuals at-risk for HBOC have indicated that there is a need for consistent

information from all those professionals (e.g. oncologist, clinical geneticist, gynaecologist, etc.) that they are consulting [18].

So far, individuals at-risk and the implications of the test for them have been described. Little to no attention has been paid, however, to the implications of the test on the whole family. The one aspect, i.e. the individual and her/his reasons for testing, can not be understood without knowledge on the other, i.e. the family and an understanding of what testing for HBOC means for them. Family dynamics play a major role in how individuals at-risk cope with the threat of an autosomal dominant late-onset disease [19], and in the motivation for taking the test and their eventual adaptation to the test result [20]. Case descriptions are rare in the genetic field. The advantage of a case description is that the topic, i.e. the psychological implications of predictive DNA testing for the BRCA1 gene, is also made accessible to those with different theoretical orientation. A detailed description can guide the reader to a better understanding [21].

Empirical observations of families coming for the test revealed the crucial roles of either being *the messenger of the news*: the family member who starts the study investigating the genetic nature of HBOC in a family, or being *the first utilizer*: the first at-risk person in such a family who decides to take the predictive test, or to undergo preventive surgery. Noticing these highly vulnerable roles, we decided to describe this family from *their* perspective. The intense contrasting flows of emotions, tensions and anxieties are exemplified in the case history presented, and may help other professionals to identify and support relatives in families with hereditary late-onset disorders in similar situations.

MATERIALS AND METHODS

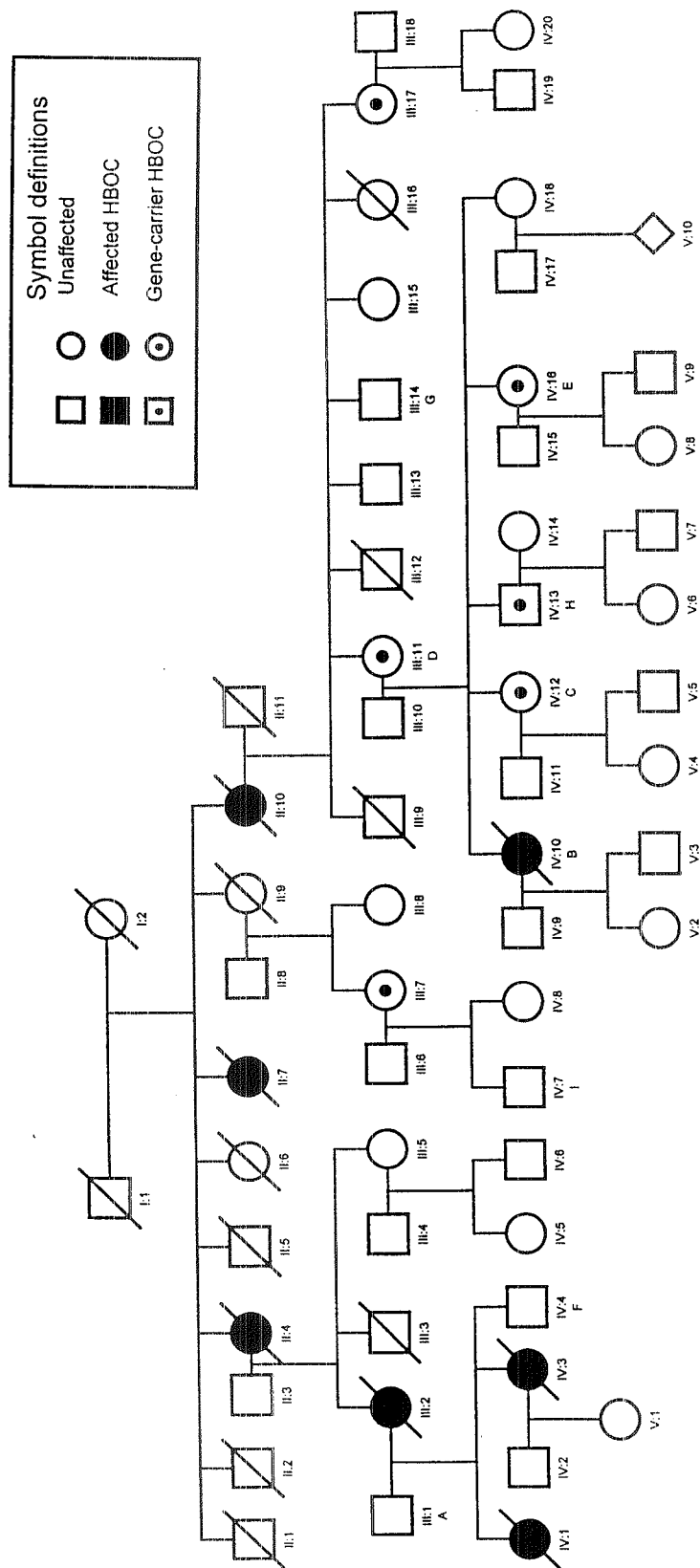
Linkage and mutation analysis.

In January 1994 presymptomatic DNA testing for HBOC, by linkage analysis, was offered at the Dept. of Clinical Genetics in Rotterdam, to a family (see fig.1.) of whom some members (III-1, III-10, III-11, III-12, III-13, III-15, IV-2, IV-3, IV-9, IV-10, IV-11, IV-13 and IV-15) had provided blood samples for previous genetic studies [1].

The family consisted of two branches, descending from two grandmaternal sisters (II-2 and II-8) who were both diagnosed with ovarian cancer. Breast cancer was diagnosed at the ages of 43, 35, 29 and 34 in one daughter (III-2) and three granddaughters (IV-1, IV-3 and IV-9), respectively, of these two women.

The likelihood ratio for linkage, expressed as the lod score, was calculated using the LINKAGE algorithm, under assumption of incomplete age dependent penetrance as

Fig. 1. Altered pedigree to keep anonymity.



described by Easton et al. [1]. A lod score of 1.31 was obtained using D17S250 and D17S479 in a three-point analysis [22]. Because this family by definition has hereditary breast-ovarian cancer (e.g. multiple breast and ovarian cancer cases among first degree relatives at a young age), the posterior probability that it is due to BRCA1, on the basis of this lod score and observed heterogeneity [1], was $> 98\%$. As this was considered sufficiently reliable, the family was offered the individual predictive DNA test, by linkage analysis. Those who responded (III-7, III-8, III-13, III-15, IV-8, IV-11, IV-13, IV-15 and IV-17) were re-sampled for diagnostic testing in order to confirm the research data, when having participated in the research phase.

When it became possible, the linkage results were confirmed by direct mutation analysis of BRCA1. A 1 bp insertion in codon 431 (exon11), leading to a frameshift and premature chain-termination during protein translation, was identified in all those individuals (II-2, II-5, II-8, III-2, III-7, III-11, III-15, IV-1, IV-3, IV-9, IV-11, IV-13 and IV-15) previously shown to carry the at-risk haplotype [23] (for more details see chapter 7).

Participants

The family members who participated in the research phase of the linkage study were informed by letter that predictive DNA testing was possible. They were invited to the Dept. of Clinical Genetics, to further discuss the implications of this test. All were offered psychological follow-up during this first session. To date, all family members with whom a contact was established (the entire third and fourth generation with exception of Mrs.III-4 and her children, see fig.1), accepted the invitation, but not all took the predictive test or wanted psychological follow-up. Eight females at 50% risk wanted to be tested (III-7, III-8, III-13, III-15, IV-8, IV-11, IV-15 and IV-17). One woman (IV-9), at that moment without symptoms, had been treated for breast cancer and wanted to know her own risk of ovarian cancer and the chances of passing the gene on to her children. Another woman (III-11) was expected to be an obligate gene carrier; both her mother (II-8) and daughter (IV-9) were affected.

One married-in spouse (III-1) whose wife and daughter died and whose other daughter was in the terminal phase of breast cancer, requested additional counselling. One male at 50% risk (IV-13) did take the predictive DNA test. Three others (III-12, IV-2, IV-7) came for information but did not opt for the test (yet) [24].

Methods The methods are described in full detail in chapter 2.

RESULTS

The messenger of the news: Mr. A (III-1)

Mr. A, in his late forties, was the first "messenger of the news". He lost his wife to ovarian cancer and a daughter, mother of a young girl, to breast cancer. Another daughter developed breast cancer with metastases, in spite of regular screening, and was in the terminal phase of the disease. When Mr. A suspected the hereditary nature of breast cancer in his wife's family, he wanted it studied particularly in view of the future of his three-year-old granddaughter. His attempts to contact his wife's relatives to tell them about the genetic nature of breast and ovarian cancer were not appreciated by most of them. It seemed to induce reactivation of the grief felt by the children (III-11, III-12, III-13 and III-15) at the early loss of their mother (II-8). As one of them, Mrs. (III-11), stated "it was in the past it and it will stay in the past"; she refused any further contact with him. Mr. A was resented for having started this myriad of information. However, partly due to Mrs. (IV-9)'s efforts to mobilize her branch of the family for the linkage study, Mr. A eventually succeeded in obtaining pedigree information on breast and ovarian cases in his wife's family resulting in the realization of the predictive DNA test, first by linkage, later by mutation analysis.

The other "messenger of the news" in this family and the "first utilizer" of the predictive DNA test: Mrs. B (IV-9)

Mrs. B was both a "messenger of the news" and the "first utilizer" of the predictive DNA test. Mrs. B had had bilateral breast conserving surgery because of breast cancer in her early thirties and feared metastases. Now, in her mid-thirties, she wanted to know more about her risk of ovarian cancer and the risk for her children. She identified herself with her terminally ill cousin and was afraid to die. Although she resented Mr. A (III-1) for causing emotional upheaval, she took up the information because of her own death anxiety. Within her own branch of the family, she tried to persuade her relatives to join the study on linkage analyses. She felt rather isolated during this period because her symptom-free mother (III-11) and two of her three sisters (IV-15 and IV-17) neither understood nor appreciated her actions to obtain all the information in order to realize the predictive DNA test for herself and her relatives.

When the family study showed to be informative for predictive testing by linkage analysis, she took the test, thus becoming the "first utilizer". She was strongly motivated to establish her risk for ovarian cancer as soon as possible. She considered prophylactic ovariectomy if found to be a gene carrier. She was, not unexpectedly, identified as a gene carrier; nevertheless, the confirmation of her fears still came as a shock. Following this result, she and her husband requested additional psychological

counselling on the timing and carrying out of ovariectomy. Being well informed, she feared premature menopausal symptoms, which in her case could not be prevented by hormonal substitution because that would bring an additional cancer risk for her remaining breast tissue. Eventually, when she underwent an ovariectomy in the Rotterdam cancer centre, by chance microscopic metastases of her breast cancer were found. Distant metastases manifested afterwards, without clear objective response to different systematic treatment modalities. She deeply regretted that bilateral total mastectomy had not been carried out instead of the breast conserving surgery and radiotherapy that she had received in the general hospital she visited in the past. She urged her family to take appropriate notice of what had happened to her.

The family reacted very strongly to the news of her recurrent metastases and progressively declining health, they paid less attention to the hereditary background of HBOC in the family and their own personal risks. For long, the family was focused upon Mrs. B and could hardly believe that she could not be cured. Within the year she died.

Her sisters (IV-11 and IV-15), brother (IV-13) and later also her youngest sister (IV-17) took the predictive DNA test. Her youngest sister, who became pregnant after a good result, told that she felt guilty towards Mrs. B and was afraid that her pregnancy would be held against her. She did not dare discuss her feelings about her pregnancy with Mrs. B.

"The first utilizer" of preventive surgery: Mrs. C (IV-11)

Mrs. C was the second family member, but the first symptom-free risk carrier (50% genetic risk) to take the predictive DNA test, and was also the "first utilizer" of preventive surgery. She wished to know her risk and the options for preventive measures if necessary. She proved, like her sister, to be a gene carrier. The worsened physical condition of her sister Mrs. B (IV-9) strengthened her pre-test opinion in favour of preventive surgery. After oncological counselling, she opted for prophylactic mastectomy first, and a prophylactic ovariectomy in a later stage, so hormone substitution to prevent premature menopausal symptoms would become an option.

Mrs. C did not want to share her worries and fears about the preventive surgery with her relatives, wishing to be a good and strong example for her own daughter (not yet a teenager) and the other female relatives. In this way she wished to show her daughter how to cope with the disease and anxieties, and to reassure her should she be found to be a gene carrier as well.

Mrs. C was supported by the positive attitude of her surgeon who emphasized the importance of personal decision-making on preventive surgery. He also introduced her to a woman who had undergone mastectomy with breast reconstruction with whom Mrs. C could share her fears and uncertainties about the impact of preventive surgery.

Her husband supported her in the decision for prophylactic surgery. The impact of HBOC upon the sexual relationship, however, could hardly be discussed.

Other identified gene carriers

Mrs. (IV-15), a sister of Mrs. B (IV-9) and Mrs. C (IV-11), also proved to be a gene carrier. She decided against prophylactic surgery, while benign breast tissue abnormalities had already been found shortly after the test. She did receive regular screening. During a screening session, taking place in the week her sister died, abnormalities in the ovaries were observed which appeared to be of a benign and temporary nature. At the cremation of her sister Mrs. B (IV-9), Mrs.(IV-15) decided to have a total mastectomy.

Three identified female gene carriers (III-7, III-11 and III-15) from the older generation chose to have a prophylactic ovariectomy, but no mastectomy. They viewed ovarian cancer as threatening because in their previous generation the women had died of ovarian cancer at the same age as they were now. Two of these women found the decision to undergo prophylactic ovariectomy somewhat easier since they were already postmenopausal and had completed families. One woman had difficulty losing the necessary amount of weight in order have a prophylactic ovariectomy. All three women regarded preventive breast removal a too intrusive option.

An obligate gene carrier: Mrs. D (III-11)

A symptom free woman/man with an affected mother and a child who develops symptoms can be seen as "sandwiched" between two generations with cancer. The proof by linkage or mutation analysis that breast and ovarian cancer is caused by the BRCA1 gene in such a family immediately implies that such a person is an obligate gene carrier, leaving the women 85% risk of developing breast cancer and a 63% risk of developing ovarian cancer before the age of 70 [3].

In this family Mrs. D was still free of symptoms while her mother (II-10) died from ovarian cancer, and her daughter Mrs. B (IV-9) had had bilateral breast cancer. Both of them proved to be gene carriers. Initially, Mrs. D strongly avoided any confrontation with information on HBOC. However, she was persuaded by her eldest daughter Mrs. B (IV-9) to have a blood sample taken in the research phase. When the family study showed to be conclusive for predictive testing by linkage analysis, Mrs. D was informed about the heredity of breast and ovarian cancer in her family and thus her own risk. The diagnosis had been confirmed in the laboratory, but no additional testing was offered to her. She expressed no intention to pay much attention to HBOC. Her husband was upset and expressed his fears concerning his eldest daughter Mrs. B (IV-9), with whom he was particularly close. At a later stage, he sought professional support for his wife, in contradiction to her own wishes, because he felt she could not handle the situation.

Later he understood that such an incentive should come from his wife herself. No appointment for psychological support was made till now.

Throughout the testing period and after the results Mrs. D stayed very close to her third daughter Mrs. (IV-15). Mrs. D described herself as being a very good example of the fact that being a female gene carrier is not that devastating, since she is still symptom-free in her mid-fifties. However, Mrs. D eventually decided to have a prophylactic ovariectomy and follows a breast control program in the Rotterdam cancer centre. She developed peritoneal ovarian cancer at a later stage and subsequently became terminally ill.

The male test candidate: Mr. E (IV-13).

Mr. E's first cited reason to take the predictive DNA test was to help research; he later reported that he wanted to know his test result for his daughter. He failed to attend the second appointment on two occasions. Mr. E was found to be a gene carrier. After the test result he talked at great length about HBOC and the impending death of his sister Mrs. B (IV-9). Six months later the impact of his test result was still overshadowed by his sister's illness.

DISCUSSION

The messenger of the news: Mr. A (III-1)

Mr. A was unable to express his grief on the previous and imminent losses. However, he expressed anxiety about the risk for HBOC in his granddaughter. The search for the genetics of HBOC in his family apparently served as a containment of the threat, and an attempt to obviate future disaster for his granddaughter. This has been described as "the crusade of the ultimate rescuer" and might serve as a psychological defense against anxiety and intense grief [25].

In this particular family, Mr. A had a very active role as "messenger of the news" in motivating his family members to participate in a linkage study. Now that testing is becoming more easily available there will be less necessity for this role. However, even when mutation analysis is possible the news still has to spread through the family and there will always be members who want to "rescue" their relatives [25].

The "messenger of the news" is often particularly vulnerable. He/she sees him/herself confronted by the task to inform relatives (both healthy and affected) and to ask them to participate in linkage and/or mutation analysis. This is initially on a research basis, but it will lead to routine family study which enables risk prediction for at-risk persons (risk carriers). Guilt feelings may be induced in the "messenger of the news" when seeing what this information has done to his/her family. Aggression and revulsion

could be directed against the "messenger of the news" by relatives invited to participate.

Ego strength and the coping capacities of "the one who dares to come for the information" are easily overestimated by the strength of the motivation of the messenger. Professionals involved must recognize this difficult role and acknowledge the emotional ramifications. It is important to take the pre-existing family relations into account: is there any contact and if so what kind of contact? The "messenger of the news" may be helped by discussing: - how to bring the news to the family, in personal contact, by phone, mail, the whole family together or separately - what kind of reactions can be expected - what type of information will be gained and will be provided by the program - is there someone in the family to share this role with, etc.? On the other hand the "messenger of the news" also might need to be coached, in order to help him/her to understand that there might be relatives who do not want to be "saved", or who have a different pace and need to take things slow. Additional counselling on the experienced emotions certainly needs to be offered.

Counsellors should be aware that there might be some inherent conflict in their relationship to the "messenger of the news": he/she may serve a useful purpose in alerting and encouraging participation, but the messenger's role is not a "sanctioned" one. Counsellors should be aware of their own feelings of helplessness [26-28] and be careful not to consider the test as the only option. Furthermore, counsellors should recognize that the messenger's view of the family is the view of only one individual and other avenues and perspectives on the family should be sought in order to obtain an "objective" view of the family ¹).

The other "messenger of the news" in this family and the "first utilizer" of the predictive DNA test: Mrs. B (IV-9).

It seemed that warding off the death anxiety was the driving force behind the information seeking behaviour of Mrs. B [29]. As "the first utilizer", she was the ultimate person who exemplifies the meaning of both the genetic risk (by her illness) and the predictive DNA test to the family. Mrs. B reported that she felt like a "guinea pig" during the initial phase of the study. Professionals involved and laymen did take an interest in her case, but she felt they were not interested in her as a person. She was tired of being always the first and strongest, and she longed for someone she could lean on. This prompted her request for additional professional support for herself and her husband.

¹) We thank the anonymous reviewers for this suggestion.

The "first utilizer" of preventive surgery: Mrs. C (IV-11).

Mrs. C was the first identified gene carrier in the family who chose preventive surgery. She said that she felt she had no choice after seeing her sister Mrs. B (IV-9) and her cousins (IV-1 and IV-3) die at such a young age. She felt very responsible to give a good example, and to diminish the fear in her relatives to take similar decisions. Therefore she did not dare to ask for support within the family. The associated responsibility concerning her relatives was a great burden for her. At the same time her family was mainly focused upon Mrs. B's (IV-9) terminal illness.

It is important to discuss in counselling what will be gained by prophylactic mastectomy and/or ovariectomy as well as what will be lost for a woman and her husband. We did notice, however, that expected changes in the sexual relation after preventive surgery were not easily discussed beforehand. After the operation the couple talked more freely about their sexual relationship, but only in positive terms. The adverse effects of prophylactic ovariectomy and total mastectomy on their sexual relationship were not discussed. We found it an important observation that this couple could not acknowledge the less positive aspects of the operations (e.g. prevention versus loss). Although this one observation is not enough to draw conclusions, it definitely indicates that further study is needed.

The "first utilizer" is often under pressure to provide benefits for herself as well as the family. The family has no experience with predictive DNA testing, therefore the "first utilizer" feels obliged to show how it all works. In counselling, the individual choice and the meaning of this for the other family members are of course linked, but should not be addressed as one subject; they should be discussed as different topics so as to enable the first utilizer to perceive the unexpected burdens resulting from functioning as an "example" in their family.

The obligate gene carrier: Mrs. D (III-11)

Having knowledge about the dominant inheritance pattern of HBOC might imply that a person "sandwiched" between an affected mother and child understands that she/he has to be a gene carrier. On the other hand, it is comprehensible that such a person maintains hope that it is "just coincidence", so the other children (and in case of a woman, she herself), are not at an increased risk for breast and ovarian cancer. In counselling an obligate gene carrier it is important to take both options - acknowledgment and denial - into account. This woman, Mrs. D, participated in the research phase of the linkage study, when linkage was found she was informed about her genetic status. She was not offered additional testing as it was assumed that she already understood that she had to be a gene carrier now that her mother and daughter had proven to be gene carriers. She had, however, been denying the possible

consequences of the found linkage to herself, and had been seeing her affected daughter as a sporadic case of breast cancer. We learned from this woman how important it is to start testing the oldest generation first (when wanting to be tested), and to offer all individuals in a HBOC family the same information and options in a testing protocol; this because it is never certain that even very "obvious" information is understood and taken in.

In this family, being without symptoms and nevertheless a gene carrier, Mrs. D could deny the impact of the test results in her family. She was, at that moment, living proof that one does not have to die young from breast and ovarian cancer when found to be a gene carrier. This might have enabled her to suppress feelings of guilt about passing the gene on to her children and their offspring.

The male test candidate: Mr. E

The main focus of attention and concern has been the women at-risk, both for most professionals involved [30] and for the men in the family [24] (for more details see chapter 7). By focusing on their female relatives and their risks (life and death) the impact of testing for the men at-risk is put into a perspective which minimalizes its relevance. It is important to keep in mind that men are also deeply affected when their female relatives (mothers, sisters and daughters) are at-risk, with all the potential consequences.

Advantages and disadvantages of a case description

We have described one family as a mere inspiration to all health-care workers working with families at-risk for HBOC and other late-onset disorders. Through this case description of an HBOC family we aim to enhance understanding of what testing means, not only for the individual but also for the entire family. One of the main advantages is, as already described in the introduction, that the impact of DNA testing, is made understandable to others with a different theoretical orientation [21]. Besides advantages there are also disadvantages to a case description. Only one family has been described which might reduce the generalizability of the findings. However, we recognized similar observations in work done with newly diagnosed families with Huntington's disease (unpublished data), and families at-risk for presenile dementia [31]. The latter publication, reported that the "messenger" was often the patient's spouse because the hereditary disease was generally first discussed with him/her; their informing the relatives often caused emotional upheaval and they were often resented for this. In addition, the family members participated both in the research phase of linkage analysis and in the actual testing protocol; this might introduce some bias by potential extensive attention from the researchers [32].

The observations described are restricted to the appointments with the psychologist at the department of Clinical Genetics, from the first contact until the last approximately nine months later (the time range of the psychological follow-up study they participated in). Events happening within the family within this period could be described. The impact of events taking place afterwards, such as the illnesses of Mrs (III-11), could not be described as no new contact was established. The author working at the Rotterdam cancer centre (JGMK) added the information.

Counselling

In order to maintain confidentiality when counselling family members simultaneously, strict organization is necessary. The counsellors (geneticist, psychologist, oncologist, administrative staff) involved should do their best to respect the privacy of the family members. During the first session the following could be addressed:

1. Attention is focused on the needs of the individual who has the appointment. Counsellors should be aware not to be seduced into discussing the implications of the genetic status of family members (such as whether a family member made the right decision etc.). However, the impact of the ongoing events in the family on the particular participants may be addressed.
2. Although part of a family, each member is, as far as possible, counselled as an individual case. The individual at-risk may have heard all kinds of information from family members or even no information at all. It is important that the knowledge of DNA and predictive testing is thoroughly checked and completed when needed.
3. Taking the test, or not, should be an enterprise of the person at-risk and the respective partner and not a family enterprise; however, the decision will be influenced by the events taking place in the family.
4. The individual taking the test is the only one to whom the test result will be disclosed; the test result can not be transmitted via another relative. (This not taking into consideration the discussion about those at 25% risk [33]). He/she is free to postpone the appointment until the last second, when necessary.
5. Concerning the test result, it is very important to discuss whether they want to be with relatives at the department of Clinical Genetics, or not. When various relatives want to receive their test result at the same time, multiple rooms should be reserved i.e. a separate room for each of them to receive their own test result. After everybody has received his/her own test result they can meet together if they so wish.

If someone does not want other family members to know that he/she is taking the test, an appointment is scheduled distinctly apart from that of other family members.

In conclusion practical issues, such as mentioned above, should be discussed with individuals at-risk planning to be tested in order to be able to safeguard their privacy. Contradictory as it may seem, to be fully able to treat all family members as individuals, the psychological impact of predictive testing on both the individual and family level should be addressed in genetic counselling. This in order to differentiate between, and to understand the motivation fed by both individual and family matters. A multidisciplinary team including a psychologist, is needed to offer counsellors supervision concerning the intertwinement of individual and family motives for predictive testing. If a need for additional psychological support is expressed, the individual at risk and his/her partner can be referred to the psychologist of the team.

Concluding remarks

In genetic counselling for predictive DNA testing it is very important to acknowledge that individuals show a variety of mechanisms to cope with threatening information and treatment options. Care-givers involved in predictive testing programs should be aware of these personal adaptation mechanisms.

The family unit ought to be preserved and guarded, and certainly not harmed. Participants of predictive testing need to know what the test can do to the family unit and existing relationships. It should be ensured that predictive testing will provide the most benefit and least harm for all individuals and families involved.

There are major challenges in genetic research to obtain consent, protect privacy and confidentiality, and safeguard divergent and conflicting intrafamilial and intergenerational interests; and all this whilst keeping the research on track [34]. Our experience emphasizes that a strong collaboration of all disciplines involved (molecular and clinical geneticist, oncologist, psychologist, medical ethicist, general practitioner) involved is a sine qua non for conducting genetic studies, in order to meet these challenges.

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CHAPTER 4

PSYCHOLOGICAL DISTRESS IN PARTICIPANTS OF PREDICTIVE DNA TESTING FOR AUTOSOMAL DOMINANT INHERITABLE LATE ONSET DISORDERS

PSYCHOLOGICAL DISTRESS IN APPLICANTS OF PREDICTIVE DNA TESTING FOR
AUTOSOMAL DOMINANT INHERITABLE LATE ONSET DISORDERS

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ABSTRACT

In a comparative study on effects of predictive DNA testing for late onset disorders, pre-test psychological distress was assessed in people at-risk for Huntington's disease (HD; n=41), cerebral haemorrhage (HCHWA-D; n=9), breast and ovarian cancer (HBOC; n=24) and polyposis coli (FAP; n=45). Partners, if available, also participated in the study. Distress was measured with the subscales Intrusion and Avoidance of the Impact of Event Scale.

Individuals at-risk for the neurodegenerative disorders reported more avoidance than those at-risk for the cancer syndromes. People at-risk for FAP and partners of those at-risk for HBOC reported less intrusion than the others at-risk, resp. the other partners. Subjects who were more distressed, reported more experiences with the disease in close relatives, the disease having a great impact on their lives, having considerations against predictive testing, expecting that being identified as a gene carrier would have

adverse effects and expecting great relief after being identified as a noncarrier. Test candidates who expected an increase of personal problems showed higher avoidance, whereas those who could better anticipate future life as a carrier had higher intrusion levels.

Generally, subjects with high distress are of more concern to the health-care professional than those with low distress levels. However, high distress may reflect worrying as a mental preparation for the test result, whereas low distress may indicate denial-avoidance behaviour and poor anticipation of the test outcome. In pre-test counselling sessions, this should be acknowledged and addressed.

INTRODUCTION

The rapid developments in molecular genetics has made predictive testing by linkage analysis and direct mutation analysis possible for a growing number of neurodegenerative disorders (for example Huntington's Disease (HD), Myotonic Dystrophy (MD), Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type (HCHWA-D), familial Alzheimer disease) [1-5], and cancer syndromes (for example Hereditary Breast and Ovarian Cancer (HBOC), Familial Adenomatous Polyposis (FAP), Hereditary Non-polyposis Colonic Cancer (HNPCC)) [6-10]. Informativeness and reliability of predictive testing is increasing and, as techniques become widely available, testing will be offered by an increasing number of institutes. Methods for familial genetic studies and counselling of individuals requesting testing will be essential in every program. More knowledge about the implications of predictive testing is also needed by society, in order to be able to decide upon the appropriate uses to which predictive testing may be put and about any controls that might be deemed necessary [11].

Predictive testing for HD has been suggested to be a useful paradigm for the study of other late onset disorders, such as cancer syndromes (for example HBOC, FAP, HNPCC) [12]. The similarities between HD and these hereditary cancer syndromes are autosomal dominant inheritance, the onset of a variety of symptoms with increasing age, and major impact on the family. The cancer syndromes differ, however, from HD by absence of neuropsychiatric symptoms and the availability of choices for treatment [13]. Study is needed as to what extent the experiences with presymptomatic testing for HD can be generalized to other dominant inheritable late onset disorders such as cancer syndromes.

Experience so far indicate that, as for HD [14-16] the uptake of the predictive DNA test for HBOC has been lower than expected [17]. Although a higher uptake of the test can be reported for the cancer syndromes in the Netherlands, so far 26% of those at-risk for FAP took the test till now (personal communication STOET) in the Netherlands, while in Rotterdam 33% of individuals at-risk for HBOC have been tested (personal communication LN Lodder, EJ Meijers-Heijboer). It is estimated that in the Netherlands about 15% of the individuals at-risk for HD [18] and about 10% of the individuals at-risk for HCHWA-D [19] have been presymptomatically tested. Those coming for the test are considered a selection who believe that they are better equipped to handle "bad news" and to dispose of considerable mental resources [20, 21]. Those not taking the test had a significantly more pessimistic outlook on themselves and their futures [22]. Reasons for being tested were to end uncertainty, to have some control over the future (planning future life and family) and to give information to offspring and relatives [23-27]. Those at-risk for the cancer syndromes reported the same reasons to want the test, with an additional mentioning of the preventive treatment options [28].

The consequences of predictive testing for the family has been shown in limited studies so far. Personal stories and case descriptions, however, have indicated that hereditary disease have a profound impact on the family [29-31]. Furthermore, partners of identified carriers felt burdened by the distressing prospect [32-35], and more so when they had children [36].

Clinical and empirical evidence has shown that potentially traumatic events may produce psychological symptomatology [37]. Alternating phases of experiencing intrusive feelings and avoidance of certain ideas and thoughts associated with the specific traumatic event are often seen in maladaptive reactions to such stressors [38]. The stress response theory of Horowitz [39] and our observations on individuals at-risk and their families, led the expectation that post-test adjustment involves (re)experiencing untoward intrusive feelings and thoughts, and denial-avoidance of situations associated with the specific hereditary disease. On the other hand, intrusive feelings may reflect worrying as psychological anticipation of a threatening event [40], which can be useful in preparation for the test outcome.

The present study aimed to gain insight into reported pre-test psychological distress in terms of preparation for the test result. The first question addressed was whether the pre-test psychological distress in participants of predictive testing for HD, HCHWA-D, FAP and HBOC, would differ, and the same was assessed for partners. The second question was whether the psychological distress experienced could be predicted by the experience with the disorder in the family, that is, with the affected parent/relatives. The third question was whether motivation to be tested predicted pre-test psychological

distress and, finally, whether the expected impact of the test result predicted pre-test psychological distress.

This study is a part of a longitudinal follow-up study on predictive testing focusing on: (1) the course of adjustment of individuals at-risk and their partners after the DNA test results; and (2) identification of psychological determinants of adjustment problems after test disclosure. The aim is to increase the understanding of the psychological ramifications of the predictive testing for late onset disorders, in order to further develop counselling and support strategies.

SUBJECTS AND METHODS

The genetic disorders are described in full detail in chapter 1, the participants, procedures, questionnaires and the statistical analysis are described in full detail in chapter 2. 121 subjects at-risk (HD $n=42$, HCHWA-D $n=10$, FAP $n=45$ and HBOC $n=24$) and 80 partners (HD $n=31$, HCHWA-D $n=8$, FAP $n=19$ and HBOC $n=22$) entered the study. The psychological questionnaires given at the introduction of the study included the Impact of Event Scale (IES), a questionnaire assessing stress response patterns, and the Attitude Questionnaire (AQ) (see appendix).

RESULTS

Descriptive

General characteristics of the study population are given in table 1.

We found that participants at-risk for FAP were younger than those at-risk for HD and HBOC, using Scheffé's S method to differentiate between the four groups. There was no significant difference between the groups of participants concerning the age they learned about the hereditary nature of the disorder in the family. The participants at-risk for FAP were younger when they learned about their own risk than those at-risk for HBOC. This is, however, over the age of 12 years when screening is first advised for participants at-risk for FAP. Participants at-risk for FAP are younger, more often single and without children.

Difference in psychological distress in the four groups at-risk, and partners.

Table 2 presents mean scores on the two subscales of the IES, intrusion and avoidance for participants at-risk for HD, HCHWA-D, FAP and HBOC, and their partners. The group differences are tested for significant difference.

Table 1. Pre-test characteristics of participants at-risk

	HD (n = 42)	HCHWA-D (n = 10)	FAP (n = 45)	HBOC ¹⁾ (n = 24)	statistic	d.f.	p
Male/Female at-risk	15/27	4/6	22/23	5/19			
Age (years), Mean (sd)	37.1 (10.9)	35.1 (16.4)	29.8 (11.5)	41.3 (11.6)	F = 5.68	3,116	.01
Age (years) learned about the disorder in the family, Mean (sd)	25.8 (14.9)	25.6 (4.2)	17.9 (11.6)	27.9 (15.2)	F = 1.12	3,115	.35
Age (years) learned about being at-risk, Mean (sd)	28.8 (15.2)	26.3 (4.9)	20.1 (19.6)	33.5 (12.6)	F = 3.79	3,115	.02
► <i>Marital status</i> n (%)							
married/common law	31 (74%)	8 (80%)	19 (43%)	22 (92%)	X ² = 19.89	3	.001
► <i>Children</i> n (%)							
child(ren)	21 (50%)	8 (80%)	16 (36%)	21 (87.5%)	X ² = 24.2	6	.15

¹⁾ HD = Huntington's Disease, HCHWA-D = Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type, FAP = Familial Adenomatous Polyposis and HBOC = Hereditary Breast and Ovarian Cancer. d.f., F, X², see text for details, n = number of persons.

Table 2. Intrusion and Avoidance in the four groups of at-risk participants, and their partners.

At-risk									
Variable	HD (n = 41)		HCHWA-D (n = 9)		FAP (n = 45)		HBOC ¹⁾ (n = 24)		p
	Mean	sd	Mean	sd	Mean	sd	Mean	sd	
Intrusion	9.3	1.3	7.3	1.1	4.0	1.6	6.3	1.3	<.001
Avoidance	8.1	1.1	7.6	.6	4.4	1.4	4.4	1.3	<.001
Partner									
Variable	HD (n = 32)		HCHWA-D (n = 7)		FAP (n = 18)		HBOC (n = 8)		p
	Mean	sd	Mean	sd	Mean	sd	Mean	sd	
Intrusion	4.8	.7	3.8	.4	3.3	.7	1.4	.6	<.001
Avoidance	4.6	.9	4.6	.5	3.3	.9	1.3	.7	<.001

¹⁾ HD = Huntington's Disease, HCHWA-D = Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type, FAP = Familial Adenomatous Polyposis and HBOC = Hereditary Breast and Ovarian Cancer. d.f., F, see text for details, n = number of persons.

Participants at-risk

A statistically significant difference ($p < .001$) was found between the four groups of participants for both subscales of the IES. Concerning *intrusion*; we found, using Scheffé's S method, that participants at-risk for HD reported more intrusion than the other three groups at-risk (HCHWA-D, HBOC and FAP). Subjects at-risk for FAP reported less intrusion than the other three groups at-risk (HD, HCHWA-D and HBOC). Concerning *avoidance*; we found that participants at-risk for the neurodegenerative disorders (HD and HCHWA-D) reported more avoidance than those at-risk for the cancer syndromes (FAP and HBOC).

Partners

A statistically significant difference ($p < .001$) was also found for the four groups of partners for both subscales of the IES. We found, using Scheffé's S method, that partners of participants at-risk for HD reported more intrusion than the other partners (HCHWA-D, HBOC and FAP). Partners of participants at-risk for HBOC reported less intrusion than the other partners (HD, HCHWA-D and FAP), and also less avoidance than the other partners (HD, HCHWA-D and FAP). The partners of participants at-risk for the neurodegenerative disorders (HD and HCHWA-d) reported more avoidance than those at-risk for the cancer syndromes (FAP and HBOC).

In order to establish whether the previous experience with the disease, were associated with psychological distress we conducted a regression analysis with intrusion and avoidance as the dependent variable for the participants at-risk and the partners, respectively, and the experiences with the disorder (section A of the AQ), age, and the specific disorder as potential predictor variables. The same regression analysis were conducted with respectively, the motives for and against testing (section B of the AQ), and the expectations about the impact of the test result (section C of the AQ) as potential predictor variables. Only the statistically significant results are presented in Table 3, 5 and 6.

Experience with the disorder as predictor of psychological distress (table 3)

Participants at-risk

It was found that intrusion was associated with key experiences with the disease and by emotional descriptions of the impact of the disease on the participant's life so far. Participants who reported disease specific key experiences such as: "seeing mum and dad cleaning the bed in the middle of the night" (FAP), "hearing people laughing at and scorning the affected parent for drunken-like behaviour", "seeing father tied in his

Table 3. Experience with the disorder as a predictor of psychological distress: intrusion and avoidance¹⁾.

Experience	At-risk			
	Intrusion		Avoidance	
	B ²⁾	p	B	p
Report of disease specific characteristics in affected parent	.19	.04	–	–
Report of disease specific characteristics in affected family members	.19	.05	–	–
Emotional report of the impact of the disorder on one's life till now (e.g. shame fear and anger)	.21	.02	.26	.005
Experience	Partner			
	Intrusion		Avoidance	
	B	p	B	p
Emotional report of the impact of the disorder on one's life till now (e.g. shame fear and anger)	.40	«.001	.27	.03

¹⁾ experience was assessed with section A of the Attitude Questionnaire, ²⁾ B = standardized regression coefficient

chair" (HD), "Mother in her hospital bed unable to use her arm" or "Mother having a fat belly and always in pain" (HBOC), and "parent rubbing his head all the time because of headaches" (HCHWA-D), had high levels of intrusion. Test candidates who described the impact of the disorder on their personal life in emotional terms (for example shame, fear, or anger) also had higher intrusion and avoidance levels. Neither age nor the type of disorder was associated with psychological distress.

Partners

Partners who described the impact of the disease on their own life in emotional terms (for example shame, fear, or anger) had higher scores on both intrusion and avoidance.

Motivation to be tested as predictor of psychological distress.

Commonly cited considerations for, and against testing are presented in Table 4.

Participants at-risk (table 5)

None of the motives to undergo testing were associated with psychological distress. However, participants who regarded the negative implications of knowing oneself to be a gene carrier as a possible reason against testing had high intrusion and avoidance levels.

Those who could not think of any considerations against uptake had low distress scores on both intrusion and avoidance. Neither age nor type of disorder was associated with psychological distress.

Table 4. The motivation to be tested.¹⁾

Considerations to take the test	Cited by ²⁾
the burden of being at-risk	62%
to know for the children	35%
for preventive treatment or check-up	16%
to plan the future	13%
regarding the wish to have children	11.5%
Considerations against testing	
expected adverse reactions of knowing to be a gene-carrier	34%
new uncertainties after knowing to be a gene-carrier	5%
no gain by knowing	5%
could think of no reason against testing	31%

¹⁾ motivation was assessed with section B of the Attitude Questionnaire, ²⁾ percentages of the total population.

Table 5. The motivation to be tested as predictor of psychological distress: intrusion and avoidance.¹⁾

Considerations not to take the test:	Intrusion		Avoidance	
	B ²⁾	p	B	p
Psychological burden of knowing to be at-risk	.30	α.001	.29	.002
No idea	-.18	.05	-.28	.05

¹⁾ motivation was assessed with section B of the Attitude Questionnaire, ²⁾ B = standardized regression coefficient

Partners

No statistically significant results were found.

Psychological Distress in Applicants of Predictive DNA testing

Table 6. The expected impact of test result as a predictor of psychological distress: intrusion and avoidance ¹⁾.

	At-risk			
	Intrusion		Avoidance	
future expectations:				
when proven to be a gene carrier:	B ²⁾	p	B	p
life becomes less worthwhile	.19	.04	.40	«.001
problems increase	—	—	.18	.05
try to avoid family	.17	.04	.22	.02
become depressive	.30	«.001	.26	.005
has not that much effect ³⁾	-.30	«.001	-.20	.04
anticipate the future ³⁾	.21	.03	—	—
when proven to be a <i>noncarrier</i> :				
life becomes more worthwhile	.28	.002	.31	«.001
problems decrease	.34	«.001	.28	.003
be able to better plan the future	.24	.02	.24	.02
mood improvement	.43	«.001	.37	«.001
experience relief ³⁾	.35	«.001	.22	.02
doubt the test result	.18	.05	—	—
	Partner			
	Intrusion		Avoidance	
when partner proves to be a gene carrier:	B ²⁾	p	B	p
problems increase	.28	.03	—	—
try to avoid family	.25	.03	—	—
doubt the test result	.22	.05	.24	.04
when partner proves to be a <i>noncarrier</i> :				
try to avoid family	.25	.03	—	—
nothing changes ³⁾	-.23	.05	-.31	.009
think everything over ³⁾	.35	.003	—	—

¹⁾ the expected impact was assessed with section C of the Attitude Questionnaire, ²⁾ standardized regression coefficient, ³⁾ answer to open-end question

Expected impact of the test result as predictor of psychological distress (table 6)

Participants at-risk

Those who reported that knowing oneself to be a gene carrier would not affect their personal life had the lowest scores on intrusion and avoidance. Test candidates who thought that knowing to be a gene carrier allowed them to better anticipate the future reported the most intrusion. Those who thought that confirmation of gene carriership would increase their problems reported more avoidance.

Participants who acknowledged that knowing not to be a gene carrier would affect their lives in a positive way, resulting in better mood and relief, and allowing them to plan the future better, reported more intrusion. However, high intrusion was also associated with the expectation that an exclusion of gene carriership may be doubted. Neither age nor the type of disorder was associated with psychological distress.

Partners

In the partner groups, high levels of psychological distress were associated with the strong belief that confirmation of gene carriership could be doubted. Partners with high intrusion were those who expected that problems may increase and that such result would lead to avoiding the relatives of the identified gene carrier.

Partners with high intrusion also expected that exclusion of gene carriership might lead to avoiding the non-carrier's relatives. Those who would re-evaluate their personal situation reported the highest intrusion. Partners who believed that an exclusion of gene carriership would have no influence on their life had the lowest intrusion and avoidance scores.

DISCUSSION

Interpretation of the reported psychological distress

To introduce the discussion of the findings, we describe the possible implications of high and low distress scores. The reported psychological distress is measured as intrusively experienced ideas, images, feelings or bad dreams (intrusion) and the consciously recognized avoidance of certain ideas, feelings or situations (avoidance). The resulting score implies more than that people with high scores are doing "badly" and people with low scores are doing "well". It was in fact the intolerable psychological burden of being at-risk that was the prime reason for uptake of the predictive test for HD, as mentioned previously [14, 23, 25, 26]. And these participants were considered to have considerable mental resources [20, 21]. Moreover, the well-being of HD carriers

had improved one year after testing [41]. High intrusion levels may reflect great suffering from being at-risk, but also worrying as a preparation for the test result [40]. A follow-up study on effects of predictive testing for HD [42] reported that high avoidance levels predicted post-test feelings of hopelessness, whereas high pre-test intrusion levels did not. Thus high pre-test intrusion scores could also be valued positively and be seen as indicative of an adjustment process.

It should be noted that low scores on "mental health scales" can reflect opposite conditions. Low scores usually indicate good psychological health; on the other hand distress may be present, but denied in order to "maintain an illusion of mental health" [43]. A participant at-risk (or a partner) may try to convince themselves that there is no reason to worry and report very low distress scores, while in fact they are emotionally affected by the predictive test.

Major findings

Difference in psychological distress in the four groups at-risk, and partners.

Interestingly, individuals at-risk for HD, reported the highest levels of distress (high intrusion and avoidance scores), while those at-risk for FAP reported the lowest levels of distress (low intrusion and avoidance scores). No treatment options are available for the first group, whereas there are (drastic) options for individuals at-risk for FAP. Also the long and very incapacitating course of HD will influence the pre-test distress. The perception of immediate risk may also differ among the various participants. Those at-risk for HD, HCHWA-D and HBOC are within the average age for disease occurrence in gene carriers; FAP participants are mostly older than the average age at onset [44-47]. This could explain why participants at-risk for FAP report significant less intrusion than the other three groups at-risk.

HD imposes a considerable burden on the partner [32], especially when the couple has children [36]. Partners of people at risk for HD reported significantly higher levels of distress than the other partners. Unexpectedly, we found that partners of participants at-risk for HBOC reported significant lower psychological distress as all the other partners. Six out of 8 partners, in the HBOC sample, are male. This led us to speculate whether these men were just undisturbed by the predictive test, or whether other psychological mechanisms were at work (e.g. defensive denial). Breast cancer is reported to have a significant impact on the woman's partner [48]. Further studies in a larger sample may learn how partners of women at-risk for HBOC cope with the impending threat of breast and ovary cancer and the treatment options for their wife.

Although in the present study a profound difference was found in reported psychological distress when comparing the four groups of disorders, there was no

indication that the type of disease, or age, predicted pre-test psychological distress in the additional analyses. We examined whether experience with the disorder, motivation to be tested, and the expected impact of the test result, could predict distress. To a certain extent they did, as discussed below. Other characteristics of the population (for example educational level, cultural identity, religious faith, thoughts and beliefs about their luck and destiny, other perceived dangers in life) were not analyzed, although these factors are obviously relevant in coping with personal risks and test results.

Experience with the disorder as predictor of psychological distress.

A clear recollection of symptoms observed by the participant in the affected parent/relatives predicted high levels of intrusion. Also, when participants at risk and partners described the impact of the disease on their life in emotional terms (such as anger, fear and shame) an association was found with high levels of both intrusion and avoidance. They tried to distract themselves from ideas, images and feelings they intrusively experience. This pattern may reflect problems in adjusting to the effects of the disease on their life and needs to be paid attention to.

Motivation to be tested as predictor of psychological distress.

As previously described for neurodegenerative disorders [14, 23, 25-27], we found that the main reasons for testing were: intolerable psychological burden of being at risk, giving information to offspring and relatives, and planning future life and family. Only 16% of all participants (while 57% were at-risk for the hereditary cancer syndromes) stated that preventive treatment or check-up was their reason for testing.

Interestingly, those who were worried about the possible adverse effects of knowing to be a gene carrier and who considered it as a possible reason not to take the test, reported the highest psychological distress (high intrusion and avoidance scores); yet they all took the test. This "worrying" can be considered as preparation to the test-result. The possible adverse effects of being a gene-carrier are considered and acknowledged [40]. It is important, however, to enable the participant to discuss his/her worries in order to demystify fears sometimes rooted in childhood experiences with the disease. Those who had no reasons against the test reported little or no psychological distress. Experience with HD test candidates have shown that some participants who had gone through lengthy considerations, are not willing to undergo all the ramifications of pre-test counselling [35]. They were determined to have the test and were anxious at that stage to re-experience previous ambivalence. The reluctance to consider reasons against testing may reflect a denial-avoidance behaviour to minimize the full impact [43]. The mechanisms of defensive denial which enables test

candidates to ward off anxieties should be respected as his/her way of dealing with threat; this should be handled carefully but with acknowledgement of the underlying fear.

Expected impact of the test result as predictor of psychological distress.

In general, the anticipation of adverse effects of becoming identified as a gene carrier was associated with high levels of intrusion and avoidance (all participants wanted to be tested). An expected increase of personal difficulties after confirmation of gene carriership was associated with high avoidance but not with intrusion. High pre-test avoidance was earlier found to be associated with a pessimistic post-test attitude [35]. The possible adverse effects of being a gene carrier are kept away instead of being worked through, this "lack of worrying" can be considered to lead to being less prepared [40].

Preparation for the future was associated with high intrusion but not with avoidance, which supports our hypothesis that such behaviour reflects worrying [40]. Those who expected their life to become better/easier when proven to be a noncarrier reported high distress (high intrusion and avoidance scores). High expectations about exclusion of gene carriership, reflects the difficulties experienced in dealing with the threat of the disease. Such an expected outcome leads to vulnerability given that the test outcome is unsure. It also reflects an underestimation the possible adverse effects of exclusion of gene carriership, as was described in several studies on HD [29, 35, 36]. Partners who would doubt a diagnosis of gene carriership in the at risk individual reported high distress (high intrusion and avoidance scores). This is in accordance with the finding that partners of identified carriers felt burdened by the distressing prospect [32-36].

Areas for further study.

This is the first comparative study of predictive testing for hereditary neurodegenerative and cancer syndromes in two centres. The relatively small numbers in some groups is a limitation. The higher number of participants at-risk for FAP and HBOC opting against the psychological protocol reflect a possible specific attitude in this group. They were determined to take the test without further psychological assessment, since they experienced their choice as a purely medical decision. The HBOC group consisted of some individual subjects and the first three Dutch families that could be tested. This might introduce some bias by potential extensive attention from the researchers [13, 41]. Future analysis of test candidates with and without psychological evaluation and support, using besides self-report also observer-reports is indicated [43].

Furthermore, in future follow-up research on predictive testing for late onset genetic disorders, the IES as measure for psychological distress, may be standardized for specific groups with high personal risk to develop a specific disease.

Conclusions

Candidates at-risk for the four disorders differed from each other in the reported distress, as did the partners. The type of disorder, however, was not found to predict the reported distress. Aspects of the experiences with the disease, the motivation to be tested and the expected impact of the test result were associated with the reported distress. However other more socio-demographic characteristics (for example educational level, cultural identity, religious faith) were not taken into account while these may be associated with the reported distress and should therefore be taken into account in genetic counselling.

For clinical practice it is important to be aware that those responding to the subject (remembering affected relatives, preparing for the future), those who may seem preoccupied or even overly involved, might in fact be engaged in preparing themselves for the test result. Participants at-risk may be very upset when recounting the impact of the disease and their reasons to be tested, which may worry the health-care professional. However, professionals must be able to positively value these "state of minds" as they may be indicative of psychological strength and adequate preparation for the test result. Those who refrain from discussing the implications of the test (seeing no reason not to do the test, reporting little or no distress) may be unable to face all possible impacts and need to convince themselves that everything is under control. However, such apparent strength may lead to under-diagnosis of distress, while some may need specific attention. In short, people with high distress scores may be actively dealing with the problem, while people with low distress scores might (as yet) be unable to face the problems.

It is important to identify and respect the chosen strategy of coping with threat. Additional research is needed to gain more understanding of the relationship between the (un)reported psychological distress and the preparation for, and later adaptation to the test result. Only then will it be possible to decide upon the appropriate uses to which predictive testing may be put and about any controls that might be deemed necessary [11].

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CHAPTER 5

**THE COURSE OF THE DISTRESS EXPERIENCED BY PEOPLE AT 50%
RISK FOR AN AUTOSOMAL DOMINANT INHERITABLE DISORDER,
PARTICIPATING IN A PREDICTIVE TESTING PROGRAM**

THE COURSE OF THE DISTRESS EXPERIENCED BY PEOPLE AT 50% RISK FOR AN AUTOSOMAL DOMINANT INHERITABLE DISORDER, PARTICIPATING IN A PREDICTIVE TESTING PROGRAM

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ABSTRACT

The first comparative study on presymptomatic genetic testing for Huntington's Disease (HD) and cancer syndromes (Familial Adenomatous Polyposis (FAP) and Hereditary Breast and Ovarian Cancer (HBOC)) in two centres is reported. To compare the effects of predictive DNA testing, psychological distress was measured with the Impact of Event Scale, prior to testing (baseline), 1 week and 6 months after the test result, in individuals at 50% risk for either HD ($n=25$), FAP ($n=23$), or HBOC ($n=10$).

In general carriers of the disease genes showed unchanged levels of distress over the study period while noncarriers showed the expected decrease. Men reported less distress than women. One week after the test result a sharp increase in reported distress was observed in male noncarriers followed by a steady decline until 6 months later. The course of distress over time reported by carriers and noncarriers of the three disease genes was similar. However, those formerly at-risk for HD reported more distress than those at-risk for FAP and HBOC. Our clinical experience indicates that

individuals at-risk for FAP and HBOC are more inclined to ward off the emotions involved. Further qualitative studies should be undertaken to investigate this aspect.

INTRODUCTION

As the progress in genetic knowledge escalates, the numerous applications of human genome analysis, such as predictive DNA testing, are being implemented with increasing rapidity [1, 2]. Predictive testing first became possible in Huntington's disease [3]. The psychological implications have been studied by several groups [4-16]. Identified gene carriers did not have major psychopathology, but showed relief from prior psychological distress and a tendency to minimize the impact of the test result on their future. Noncarriers often experienced lack of relief, numbed emotions, survivor's guilt and difficulties developing a new life-perspective [6, 10].

Predictive testing is now available for autosomal dominant neurological late onset disorders such as Myotonic Dystrophy (MD), Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type (HCHWA-D) and familial Alzheimer disease [17-20] and for genetic cancer syndromes such as, Hereditary Breast and Ovarian Cancer (HBOC), Familial Adenomatous Polyposis (FAP), Hereditary Non-polyposis Colonic Cancer (HNPCC) and Multiple Endocrine Neoplasia type 2 (MEN-2) [21-26].

Reports on the effects of predictive testing for HNPCC, FAP, MEN-2 are still scarce [27-31]. Testing for HBOC was more extensively analyzed, and some reports indicate little emotional disturbance after disclosure [32] and relatively normal levels of psychological morbidity [33, 34]. Others report emotional upheaval in families confronted with the genetic nature of HBOC and the option of testing [35, 36].

Individuals at-risk for becoming affected by a late onset genetic disorder lived under potentially stressful conditions resulting in prolonged uncertainty, lack of control and, until recently, without means of escape [37]. The only option in life was to live with the distress provoked by the disease. Recently, a choice became available: there is the option of a test to learn about one's fate. Taking the predictive test is a way to end uncertainty but it is also an ultimate confrontation with the past, childhood fears, and the family history of disease and death. It may lead to a dreaded future determined by the disease, with deterioration of the neurodegenerative disorders and radical treatment in case of cancer. The test result may deeply influence the present and the future well-being of the person tested and their close relatives and relations. If one becomes identified as a gene carrier, this may lead to fear, anxiety and helplessness. If one is not

a gene carrier, relief may be expected. Many people prefer either outcome over continuing uncertainty [38-43].

Reactions to stressors, such as taking a predictive test, often include alternating phases of intrusive feelings and avoidance of certain ideas and situations associated with the specific traumatic event [44]. Also the experience of a potentially traumatic event may induce psychological symptomatology. The stress response theory of Horowitz [45] and our own observations on individuals at-risk and their families, led to expect that post-test adjustment involves (re)experiencing untoward intrusive feelings and thoughts, and denial-avoidance of situations associated with the specific hereditary disease.

Predictive testing for Huntington's Disease (HD) has been suggested to be a useful paradigm for other late onset disorders, including cancer syndromes [46]. The similarities between HD and these hereditary cancer syndromes are: autosomal dominant inheritance, the onset of various symptoms with increasing age, and major impact on the family. The cancer syndromes differ from HD by absence of neuropsychiatric symptoms and the availability of choices for treatment [35].

The present study examined whether experiences from predictive testing for HD can be generalized to predictive testing for other inheritable late onset disorders, including cancer syndromes. At pre-test, individuals at-risk for HD had significantly higher levels of intrusive thoughts and feelings than those at-risk for HCHWA-D, FAP and HBOC while risk carriers for FAP reported significantly lower levels of intrusive thoughts and feelings [42]. Risk carriers for HD/HCHWA-D showed significantly stronger avoidance of disease-related feelings or situations than those at-risk for FAP and HBOC [42].

In this article we first present the course of the psychological distress as indicated by intrusive feelings and thoughts and avoidant behaviour, measured prior to the test, and 1 week and 6 months after the test result. It was expected to find a reduction in distress for both carriers and noncarriers, as reported earlier [7, 13]. Second, we examined differences in the course of distress between carriers and noncarriers of three disorders (HD, HBOC and FAP). We hypothesized that the relief felt by noncarriers of a cancer gene (e.g. no longer facing invasive treatment) would result in a stronger decrease of distress immediately after the test compared with the noncarriers of the HD gene. We also hypothesized that the distress experienced by gene carriers of a cancer gene immediately after the test (e.g. having to face invasive treatment) would show a stronger increase compared with carriers of the HD gene. Third, we examined whether the course of distress would differ between men and women proving to be carriers and noncarriers. We expected women to report more distress than men, as women are less inclined to ward off distressing emotions [38, 47].

This study is a part of a longitudinal follow-up study on predictive testing focusing on: a) the adjustment of individuals at-risk and their partners after the DNA test results, and b) identification of psychological determinants of adjustment problems after the test result. Our aim is to contribute to the improvement of guidelines for genetic counselling, psychological support and interventions.

METHODS AND PARTICIPANTS

The genetic disorders are described in full detail in chapter 1, participants, procedures, questionnaires and the statistical analysis are described in full detail in chapter 2. The follow-up period of six months was completed by 58 individuals (HD $n=25$, FAP $n=23$ and HBOC $n=10$). The Impact of Event Scale (IES), a questionnaire assessing stress response patterns, was handed out prior to testing, one week and six months after the test result.

RESULTS

Descriptive Analyses

General characteristics of the study population are given in Table 1.

Participants at-risk for FAP were younger than those at-risk for HD and HBOC, using Scheffé's S method to differentiate between the three groups of participants. They were also more often single and without children.

After the test result and oncological counselling, one of the three women who were carriers of the BRCA1 gene (causing HBOC) opted for prophylactic mastectomy first, and a prophylactic ovariectomy in a later stage. Another women opted for a prophylactic ovariectomy and regular screening of her breasts. The third women needed more time to decide upon prophylactic surgery and opted for regular screening in the time being. Gene carriers of the polyposis gene continued or resumed screening.

Follow-up Assessments

The means and standard deviations on intrusive thoughts and feelings and avoidance of feelings or situations, measured at three time points (at baseline, and at 1 week, and 6 months after the test result) are given in Table 2.

Table 1. Pre-test biographical characteristics of 58 participants in the psychological follow-up study

	HD ¹⁾ (n = 25)	FAP (n = 23)	HBOC (n = 10)	statistic	d.f.	p
Male/Female at-risk	11/14	9/14	2/8	$\chi^2 = 1.77$	2	.41
Gene carrier/noncarrier	9/16	7/16	4/6	$\chi^2 = .22$	2	.87
Age (years), Mean (sd)	39.5 (11.5)	28.6 (9.1)	42.6 (6.3)	$F = 6.77$	3.57	$\alpha .001$
Married/common law	17 (74%)	8 (38%)	10 (100%)	$\chi^2 = 12.8$	3	.005
Child(ren) n (%)	13 (52%)	7 (30%)	9 (90%)	$\chi^2 = 21.5$	6	.044
Education n (%):						
1 low	7 (28%)	3 (14%)	5 (50%)	$\chi^2 = 5.9$	6	.43
2 middle	13 (52%)	15 (72%)	4 (40%)			
3 high	5 (20%)	3 (14%)	1 (10%)			

¹⁾ HD = Huntington's Disease, FAP = Familial Adenomatous Polyposis and HBOC = Hereditary Breast and Ovarian Cancer.

²⁾ 1 = elementary school and low vocational school, 2 = high school, secondary school, or secondary vocational school, and 3 = high vocational school, university or college.
d.f., F, χ^2 , see text for details.
n = number of persons.

Table 2. Means and standard deviations of intrusion and avoidance during presymptomatic testing for either Huntington's Disease, Familial Adenomatous Polyposis or Hereditary Breast and Ovarian Cancer

Variable	HD ¹⁾						FAP				HBOC			
	Carriers (n = 9)			Noncarriers (n = 16)			Carriers (n = 7)		Noncarriers (n = 16)		Carriers (n = 4)		Noncarriers (n = 6)	
	M	sd		M	sd		M	sd	M	sd	M	sd	M	sd
IES-I														
Baseline	8.3	6.7		8.5	5.8		1.4	2.2	5.7	6.4	4.5	2.7	7.5	5.4
1 week > disclosure	7.0	4.0		10.6	6.2		4.1	6.9	6.0	5.3	4.3	4.3	6.9	7.2
> 6 months	4.7	2.3		8.0	6.2		2.1	4.1	3.3	3.9	4.3	4.8	3.2	3.4
IES-Av														
Baseline	4.6	3.8		8.6	7.5		1.7	2.2	4.7	6.8	2.5	5.0	3.7	4.0
1 week > disclosure	8.4	7.6		9.0	5.7		3.2	3.6	5.6	5.4	2.3	2.2	2.1	2.1
> 6 months	4.1	4.5		6.1	5.4		1.3	2.2	3.2	4.7	1.8	2.4	3.3	5.9

IES = Impact of Event Scale; I = Intrusion; Av = Avoidance.

¹⁾HD = Huntington's Disease, FAP = Familial Adenomatous Polyposis and HBOC = Hereditary Breast and Ovarian Cancer

n = number of persons

Table 3. Multivariate testing on the course of intrusion and avoidance for carriers and noncarriers, men and women, three groups at-risk, at baseline, one week after disclosure and 6 months after disclosure of the result of presymptomatic DNA testing.

MANOVA					
	DNA test result by time			DNA test result by gender	
	<i>F(df)</i>	<i>p</i>	<i>F(df)</i>	<i>p</i>	DNA test result by type of disease by time
IES-I					
Multivariate ^a	<i>F</i> (2,44) = 2.34	.11	<i>F</i> (2,44) = 3.68	.03	<i>F</i> (4,90) = 1.15
Stepdown					<i>p</i> .34
linear trend	<i>F</i> (1,45) = 1.31	.26	<i>F</i> (1,45) = .23	.64	<i>F</i> (2,45) = .71
quadratic trend	<i>F</i> (1,44) = 3.30	.076	<i>F</i> (1,44) = 7.10	.01	<i>F</i> (2,44) = 1.57
					<i>p</i> .50
					<i>p</i> .22
IES-Av					
Multivariate	<i>F</i> (2,44) = 1.05	.34	<i>F</i> (2,44) = 1.62	.21	<i>F</i> (4,90) = .31
Stepdown					<i>p</i> .87
linear trend	<i>F</i> (1,45) = .94	.34	<i>F</i> (1,45) = 2.13	.15	<i>F</i> (2,45) = .13
quadratic trend	<i>F</i> (1,44) = 1.17	.29	<i>F</i> (1,44) = 1.09	.30	<i>F</i> (2,44) = .48
					<i>p</i> .88
					<i>p</i> .62

DNA = deoxyribonucleic acid; IES = Impact of Event Scale; I = Intrusion; Av = Avoidance.

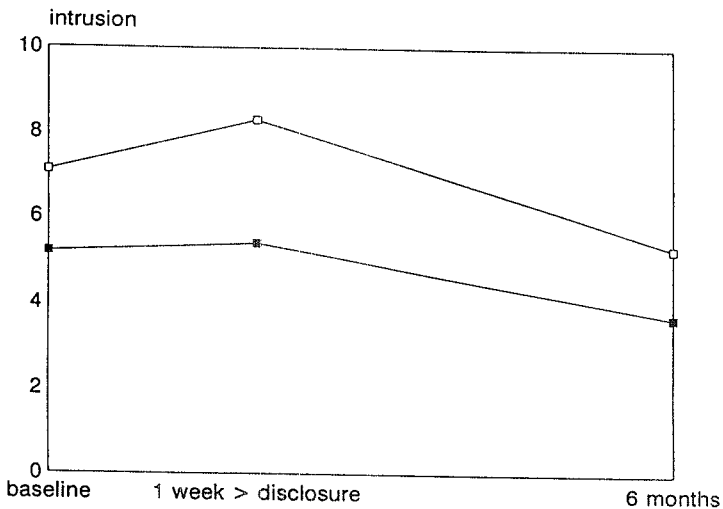
^a Pillai's multivariate test;

Distress compared between carriers and noncarriers.

To detect whether the course of reported distress would differ between carriers and noncarriers, a repeated measures MANOVA (Table 3) was conducted.

Intrusion A marginally significant trend, indicating a quadratic interaction effect of time modified by the test result was found. Noncarriers tended to show an increase in reported intrusion from baseline until 1 week after the test result, and a decrease until 6 months after the test result (Fig 1).

Fig.1. Course of intrusion over time for carriers (■) and noncarriers (□).



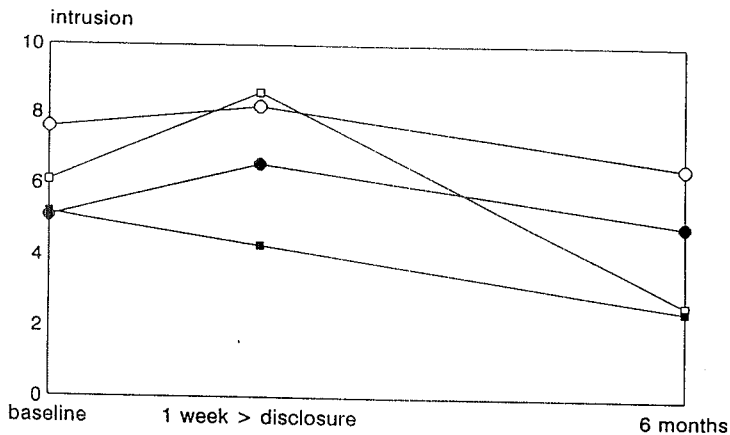
Avoidance No significant interaction effects were revealed for time modified by the test result (Table 3). Carriers and noncarriers did not differ over time in their course of reported avoidance of feelings and situations associated with the disorder.

Distress compared between male and female carriers and noncarriers.

Intrusion A multivariately significant effect of time modified by test result and gender was found. On average, women reported more intrusive thoughts and feelings than men. Also, a quadratic interaction effect of time modified by the test result and gender was found (Table 3). Male noncarriers showed a strong increase of intrusive thoughts and feelings from baseline to 1 week after the test result, and a steep decrease of intrusive thoughts and feelings until 6 months after the test result (Fig. 2).

Avoidance No significant interaction effects were found for time modified by the test result and gender (Table 5). Male and female carriers and noncarriers did not differ over time in their course of reported avoidance of feelings and situations associated with the disorder.

Fig.2 Course of intrusion over time for male carriers (■) and noncarriers (□), and female carriers (●) and noncarriers (○).



Distress compared between carriers and noncarriers of the three disorders.

Intrusion No significant interaction effects were found for time modified by the test result and the type of disorder (Table 3). Carriers and noncarriers of the three disease genes did not differ over time in their course of reported intrusive thoughts and feelings associated with the disorder.

Avoidance No significant interaction effects were found for time modified by the test result and the type of disorder (Table 3). Carriers and noncarriers of the three disease genes did not differ over time in their course of reported avoidance of feelings and situations associated with the disorder.

DISCUSSION

The course of distress

Distress in carriers and noncarriers.

In the present study, all gene carriers together showed neither an increase nor a real decrease in distress, whereas others have reported a post-test decrease in distress in carriers of the HD gene [6, 7, 11, 16, 48-50]. We now speculate on reasons why in the present study predictive testing did not bring a decrease in distress.

First, besides those individuals at-risk who were already, for a long time, familiar with the disease, we have seen participants who only recently learned about HD, HBOC or FAP in their family. They had not yet developed an "at-risk identity" as seen in HD [6, 10, 51], with long standing worries about the future. They often sought the test for reassurance, wanting to return to their previous life [52]. The test may also bring relief from uncertainty but, even more, a profound confrontation with the hereditary nature of the disease in the family resulting in distress instead of relief.

Second, those participating in predictive testing for HD so far, have been described to belong to a self selected group who believe they are able to cope with either test result, "as it would always be better than uncertainty". Those feeling less able to cope did not come for the test (yet) [12, 53]. As most reports now describe relatively favourable personal outcome after testing [6, 7, 11, 16, 48-50] individuals at-risk who initially refrained from testing may, on second thought, apply for it and become more distressed after testing.

Noncarriers showed a slight increase in distress shortly after the test result. As soon as the threat is gone they seem able to face the possible adverse results of testing which they did not dare to face before. Noncarriers show the expected decrease in distress, six months after the test, as was found in other studies on HD [6, 7, 11, 16, 48-50].

Overall, 6 months after testing no increase of stress was found either in carriers or in noncarriers. Similar observations were reported after predictive testing for HD [6, 7, 11, 16, 48-50], HBOC [32, 33] and FAP [28, 29].

Distress in male and female carriers and noncarriers.

Women reported more distress than men. Other reports state that men may have a greater tendency to deny their feelings [47] and might be less able to face their fear and acknowledge the implications of testing [38, 54]. Also, more women than men tend to come for predictive DNA testing which has been ascribed to their more intimate involvement with the process of childbearing [38, 55].

The course of distress differed between male carriers and noncarriers (Fig. 2). Male carriers showed no increase in distress, while male noncarriers were almost shocked by their test result. All previously unfelt emotions seem to break through after learning

they are not a carrier. They only seem able to face the possible adverse effects of testing after the threat is gone (as was also suggested for all the noncarriers). Six months after the test result the reported distress declines to the same level as in carriers.

Distress compared between carriers and noncarriers of the three disorders.

The course of distress was identical for carriers and noncarriers of the three disease genes. However, we previously found a lower level of distress, prior to the test, for the cancer syndromes as compared to the level in the neurodegenerative disorders [42]. We therefore performed an additional analysis of the course of distress in participants being tested for HD, HBOC or FAP (not divided into carriers and noncarriers). A univariate analysis of variance (ANOVA) was performed. A p-value <0.05 (two-tailed) was considered significant.

We found a main effect for the type of disorder and no interaction effects with time. A significant difference between the three groups of disorders was found for the reported intrusion ($F(2,51)=6.48, p=.003$) and avoidance ($F(2,51)=6.23 p=.004$). At all three time points (prior to testing, and at 1 week and 6 months after the test result) test participants for HD reported more distress than test participants for the cancer syndromes (see Fig. 3 and 4).

Fig.3 Course of intrusion over time for participants tested for either, Huntington's Disease (■), Familial Adenomatous Polyposis (▲), or Hereditary Breast and Ovarian Cancer (●).

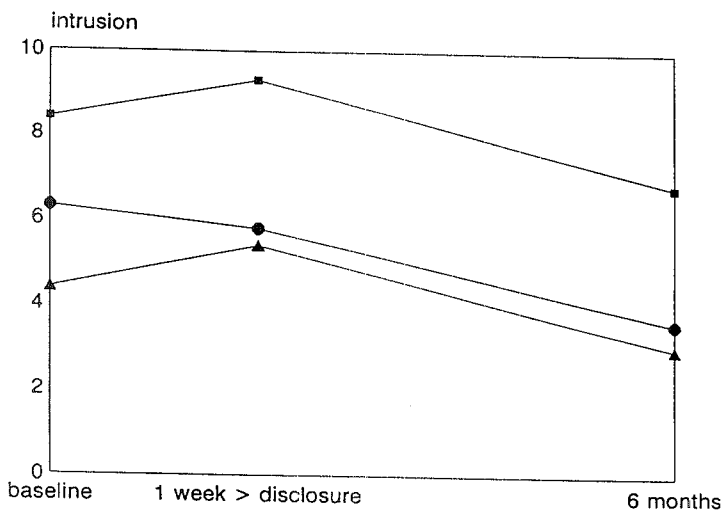
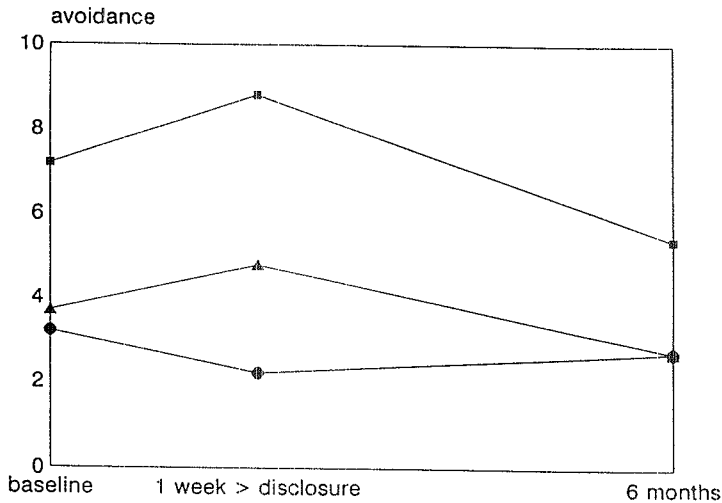


Fig.4 Course of avoidance over time for participants tested for either, Huntington's Disease (■), Familial Adenomatous Polyposis (▲), or Hereditary Breast and Ovarian Cancer (●).



Another Dutch group reported similar differences in stress reported in individuals at-risk for HD, HNPCC and MEN2A [56], with stress most often reported by those at-risk for HD and, to a lesser extent, in HNPCC families.

As the course of distress, in the present study is similar for the three types of disorders we might conclude that the experience with the predictive test for Huntington's Disease can indeed be a useful paradigm for the study of other dominant inheritable late onset disorders [46]. However, the differences in the amount of distress deserve further discussion (see below "Does the present study give us the full picture?").

Loss to follow-up

The loss to follow-up was 32 to 44% of the participants receiving their test result while still participating, at that time, in the psychological follow-up study. The loss to follow-up in HD is similar to that reported in other HD studies [7, 16]. The dropouts had a higher level of education than the remaining participants. One might speculate that the higher educated persons were in less need of the support provided by the follow-up appointments. Others may have left the psychological follow-up because they did not want to, or could not, discuss their emotions (rationalization, wanting to show a brave face).

Pre-test data are the main source of information to compare dropouts and participants. However, post-test reactions/emotions may also influence participation. The reasons for withdrawal from the psychological study (Table 3) may provide some clues about the participant's state of mind after the test result.

Table 3. Reasons for not receiving follow-up data after the test result from participants formerly at-risk for either Huntington's Disease, Familial Adenomatous Polyposis or Hereditary Breast and Ovarian Cancer

	HD ¹⁾ (n = 12) ²⁾ 32% ³⁾	FAP (n = 13) 36%	HBOC (n = 8) 44%
not wanting follow-up appointments (n):	6	12	5
- postponing appointments	2	2	1
- found talking too difficult	4	2	2
- found talking not necessary		8	2
not returning the questionnaires (n)	6	1	3

¹⁾ HD = Huntington's Disease, FAP = Familial Adenomatous Polyposis and HBOC = Hereditary Breast and Ovarian Cancer. ²⁾ n = number of persons. ³⁾ percentage of individuals lost to follow-up as part of the total population receiving their test result while participating in the psychological follow-up study.

Both carriers of the HD gene and noncarriers who withdrew mentioned that they found it difficult to talk about the test and its implications, or they came to the appointment but without filling in the questionnaires at home. Those failing to come feared re-experiencing the emotions provoked by the test result, prompted by driving up, entering the building and discussing things they were trying hard to put behind them.

The dropout rate for carriers and noncarriers of the cancer genes is higher than among those tested for HD, especially for HBOC. Carriers for HBOC missing at the follow-up appointments reported seeing multiple specialists for their check ups and information on prophylactic surgery. They first wanted to do things and delay discussing their emotions until "things have settled down". Noncarriers wanted to put "the whole thing" behind them.

Most of the test participants for FAP found talking about the test unnecessary. FAP patients may be less likely to think or worry about their illness compared with other medical conditions [57]. FAP test participants not coming for the appointments with the psychologist after testing, did not know what they should talk about, nor what could be gained by talking. They experienced their choice as a purely medical decision and valued the appointment with their clinician.

For all three disorders the dropouts are probably those not able to discuss their emotions about the test at that particular moment; therefore, the results of the present

study need to be interpreted carefully as the more extreme scores for distress might be missing.

Does the present study give us the full picture?

In general we found, as did others, that those at-risk for HD valued the appointments in which they could discuss their reasons to be tested [16, 38]. Most wanted to take their time before their final decision as they knew that the test result could never be undone. They were focused upon the qualitative aspects of life, how to enjoy it, how to make life worthwhile, what to sacrifice for it, e.g. upon the meaning of life, or upon existential problems.

Those at-risk for the cancer syndromes were less willing to discuss their emotions, their focus was much more upon immediate survival, they wanted to know whether they were going to have to fight cancer or not [36]. There was less room for contemplation on the emotional impact of testing. Also, the decision about screening or surgery, which has to be made, may imply a feeling of control, one's fate is not entirely surrendered to the disease. This helps to ward off the threat of cancer and the subsequent emotions.

We consider that the difference in the distress score is much more the result of a difference in handling the distress, (acknowledging versus warding off) than it is the result of being more or less distressed. Prior to testing we found that candidates at-risk for HD, HBOC and FAP, differed from each other in the reported distress. The type of disorder, however, was not found to predict the reported distress. Aspects of the experiences with the disease, the motivation to be tested, and the expected impact of the test result were associated with the reported distress [42]. Above all we reported that people with high distress scores may be actively dealing with the problem, while people with low distress scores might (as yet) be unable to face the problems [42]. Questionnaire results give no immediate answer as to who is "worse" and who is "better" off. Low scores can reflect opposite conditions [58]. Low scores on questionnaires usually indicate no complaints, while distress may be present, but denied in order to "maintain an illusion of not being distressed". Similarly, participants may try to convince themselves that they are doing well and report very low distress scores, while in fact they are emotionally affected by the predictive test. Additional research is needed to gain more understanding on the relationship between the (un)reported psychological distress and the adaptation to the test result.

Clinical implications

For clinical practice it is important to identify and respect the chosen strategy of coping with threat and to bear in mind that people with high distress scores may be actively dealing with the problem, while people with low distress scores might (as yet) be unable to face the problems. The lessons learned from the HD studies can be generalized to testing for cancer genes. The individual differences in reacting to, and

acting upon the test result are larger than the similarities in the three groups of disorders. It is important to focus upon the experience with the disorder, the reasons for, and expectations about testing (e.g. the personal circumstances of the participant) in order to supply appropriate support.

Areas for further study

Psychological follow-up studies can contribute to improvement of the counselling of individuals at risk, and further psychological support as required. The relatively small numbers in some groups of this first comparative study of predictive testing in two centres are a limitation, especially when looking at interaction effects between time, test result, type of disorder and gender.

Also, the HBOC group consisted of some individuals as well as first three Dutch families that could be tested. This might introduce some bias by potential extensive attention from the researchers [7].

For knowledge about the meaning of predictive testing for those confronted with the hereditary nature of a disorder in their family, additional studies should focus on those not wanting to be tested. We want to argue in favour of more case descriptions, i.e. descriptions of what we see happening to those wanting and not wanting to be tested. In the present study, our understanding of the possible implications of testing was gained from observation and by the interview, helping us to interpret the questionnaire results. As said before, additional research is needed to gain more understanding of the relationship between the (un)reported psychological distress and the adaptation to the test result. Also, describing the psychological implications of predictive DNA testing from observations can make them accessible to those with different theoretical orientation (e.g. medical specialists, nurses, social workers etc.) and may guide those involved reader to a better understanding for the benefit of the patient [59].

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CHAPTER 6

PREDICTING ADAPTATION TO PRESYMPTOMATIC DNA TESTING FOR LATE ONSET DISORDERS: WHO WILL EXPERIENCE DISTRESS?

PREDICTING ADAPTATION TO PRESYMPTOMATIC DNA TESTING FOR LATE ONSET DISORDERS: WHO WILL EXPERIENCE DISTRESS?

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Submitted

ABSTRACT

The first comparative study on predicting post-test distress (conceptualized by intrusion and avoidance, measured with the Impact of Event Scale) after presymptomatic genetic testing for Huntington's Disease (HD, n=25) and cancer syndromes (Familial Adenomatous Polyposis (FAP, n=23) and Hereditary Breast and Ovarian Cancer (HBOC, n=10)) is reported.

The *prima facie* simple notion that a "favourable" result of **not** being a gene carrier will result in relief, and that the "unfavourable" result of being a gene carrier will give distress, proved a misrepresentation of the complex reality. The test result was not associated with post-test distress. Participants who were depressed prior to the test were more distressed after testing, on the other hand we found that those who were anxious prior to the test were *less* distressed, i.e. did have less intrusive thoughts post-test. It is important to estimate depression and to pay adequate attention to depressive feelings to prevent possible adjustment problems after predictive testing. Other factors associated with a higher level of post-test intrusion were gender (i.e. being a woman),

having children and pre-test intrusion. Religion and being at-risk for HBOC were associated with less post-test intrusion. Participants who showed avoidance behaviour prior to the test and those who had many persons available for support showed more avoidance behaviour post-test. The impressions obtained by a semi-structured interview proved to be most relevant for the interpretation of the questionnaire results. Guidelines for clinical practice are presented in detail in the discussion.

INTRODUCTION

Predictive testing is now available for several autosomal dominant inheritable disorders with different disease characteristics (e.g. age of onset, (in)complete penetrance, (no) treatment options etc.) including Huntington's Disease (HD), Myotonic Dystrophy (MD), Hereditary Cerebral Hahages with Amyloidosis Dutch type (HCHWA-D), Familial Alzheimer Disease, Hereditary Breast and Ovarian Cancer (HBOC), Familial Adenomatous Polyposis (FAP), Hereditary Non-polyposis Colonic Cancer (HNPCC) and Multiple Endocrine Neoplasia type 2A (MEN-2A) [1-11].

The psychological implications of predictive testing for Huntington's Disease (HD) have been described in several studies [12-26]. Catastrophic events have, fortunately, only incidentally been observed as was confirmed by the Vancouver Group in a world-wide survey. A total of 107 centres from 20 countries provided data from 5781 individuals who received results since the advent of testing. Most catastrophic events occur within one year after the test result, 5 individuals committed suicide and 16 attempted such [12]. In general, however, carriers were reported to show relief from prior psychological distress and a tendency to minimize the impact of the test result on their future. A substantial number of noncarriers experienced no relief, numbed emotions, survivor's guilt and difficulties developing a new life-perspective [19, 23].

For the cancer syndromes predictive testing was generally found to be well received by both patients and families at risk for FAP; carriers for HBOC and noncarriers at post-test showed consistent reduction in distress and impairment [27-47].

In a previous report on the comparative study on predictive testing for HD, FAP and HBOC we found that the course of distress through time reported by the participants at risk is similar. However, participants tested for HD reported more distress than those tested for FAP or HBOC. Also women tend to report more distress than men [48].

The majority of these studies only described the psychological impact of predictive testing in general. For clinical practice, however, is it important to identify those participants who may need additional support to prevent maladjustment after testing.

Only three studies identified pre-test predictors of psychological adaptation after predictive testing for HD [17, 49-51].

Tibben et al. [49] found that distress prior to the test was associated with post-test distress. Distress among carriers was more often found to be associated with post-test intrusion than distress among noncarriers. Participants who were more avoidant of HD-related situations post-test, often only recently learned about HD, were less satisfied with the available support and at the same time more optimistic about the future. In general, high post-test distress was equally found amongst both carriers and noncarriers of the HD gene [50]. Decruyneare et al. [17] reported that less post-test anxiety was associated with more ego-strength in combination with the ability to use comforting ideas as a coping strategy. Post-test depression was found to be associated with pre-test depression, and more post-test ego-strength was associated with more ego-strength pre-test, all independent of the carrier status. Codori et al. [51], however, reported that those less well adjusted had proven to be gene carriers, were married, had no children, or were closer to their estimated age of onset.

The present report examined whether the associations between post-test distress and pre-test variables (e.g. distress, psychological and biographical variables) found in the HD studies so far, will be found again and whether they can be generalized to presymptomatic DNA testing for other late onset genetic disorders. We present predictors of distress, as measured with the two subscales (intrusion and avoidance) of the Impact of Event Scale, after presymptomatic testing for HD, FAP and HBOC. As potential predictors of post-test distress, the test result, the type of disorders, biographical data, social interaction measures, and psychological variables were taken into consideration.

This study is a part of a longitudinal follow-up study on predictive testing focusing on: a) the adjustment of individuals at-risk and their partners after the DNA test results, and b) identification of psychological determinants of adjustment problems after test disclosure. Our aim is to facilitate early detection of individuals at risk for maladjustment to a test result.

METHODS AND PARTICIPANTS

The genetic disorders are described in full detail in chapter 1. The participants, procedures, questionnaires and the statistical analysis are described in full detail in chapter 2. The follow-up period of six months was completed by 58 individuals (HD n=25, FAP n=23 and HBOC n=10). The self-report inventories given prior to the test

included the Impact of Event Scale (IES), the Beck Hopelessness Scale (BHS), the Hospital Anxiety and Depression Scale (HAD), the Symptom Checklist (SCL-90), the Social Support Questionnaire, the Loneliness Scale and the Family Dimension Scale (GDS) (see chapter 2). These were the predictor variables together with the medical characteristics (DNA test result and the type of disorder) and the biographical data (gender, age, religion, marital status and number of children). Six months after the test result the IES was again handed out to the participants. The two subscales of the IES, intrusion and avoidance were the outcome variables.

RESULTS

Post-test intrusive thoughts and feelings

Table 1 presents the variables that were associated with the level of intrusion, six months after the test result. Women tend to report more post-test intrusion than men. Parents reported more post-test intrusion than childless participants. Pre-test intrusive thoughts and feelings were associated with the similar feelings post-test.

Table 1. Prediction of intrusive thoughts and feelings, six months after predictive DNA testing.

	Intrusion ¹⁾		
	B ²⁾	SeB ³⁾	p
type of disorder			
at-risk for HBOC ⁴⁾	-.38	.11	.002
biographical variables			
gender	.35	.10	.002
having children	.34	.12	.01
religion	-.29	.11	.01
psychological variables			
depression ⁵⁾	.29	.12	.02
anxiety ⁵⁾	-.57	.15	<.001
intrusion at baseline ⁶⁾	.48	.14	.002

¹⁾ Multiple $R = .76$, $R^2 = .57$, $F = 7.44$, $p < .001$

²⁾ B = standardized regression coefficient

³⁾ SeB = standard error of the standardized regression coefficient

⁴⁾ HBOC = Hereditary Breast and Ovarian Cancer

⁵⁾ assessed with the Hospital Anxiety and Depression Scale

⁶⁾ assessed with the Impact of Event Scale

Pre-test depression was associated with more post-test intrusion, pre-test anxiety, on the other hand, was associated with less intrusion after the test. Risk carriers for HBOC report less post-test intrusion than those formerly at-risk for HD and FAP. Less post-test intrusion was reported by participants with a religion, compared to those without a religious conviction.

Post-test avoidance of feelings and situations related to the disorder.

Table 2 presents the variables that are associated with post-test avoidance behaviour. Women show more post-test avoidance of the disorder than men. Pre-test depression was associated with more post-test avoidance of the disorder. Participants having multiple supportive persons reported more avoidance than those having fewer supporters. Pre-test avoidance behaviour was associated with the same behaviour post-test.

Table 2. Prediction of avoidance of feelings and situations, six months after predictive DNA testing.

	Avoidance ¹⁾			
	B ²⁾	SeB ³⁾	Exp(B) ⁴⁾	p
biographical variables				
gender	1.04	.43	2.83	.02
psychological variables				
depression ⁵⁾	.99	.40	2.70	.02
number of supportive persons available ⁶⁾	.75	.39	2.12	.06
avoidance at baseline ⁷⁾	1.09	.43	2.98	.02

Note a logistics regression analysis was conducted upon the z-scores of the variables in the equation, for reasons of comparability of the beta's in Table I with those in Table II.

¹⁾ χ^2 20.68; df = 4; $p < .001$

²⁾ B = logistic regression coefficient

³⁾ SeB = standard error of the logistic regression coefficient

⁴⁾ Exp(B) = antilog B

⁵⁾ assessed with the Hospital Anxiety and Depression Scale

⁶⁾ assessed with the Social Support Questionnaire

⁷⁾ assessed with the Impact of Event Scale

DISCUSSION

Predicting distress after presymptomatic DNA testing:

Medical characteristics

The test result As observed in two of the Huntington's disease studies, post-test distress is not related to the test result itself [17, 50]. The prima facie simple notion

that a "favourable" result of **not** being a gene carrier will result in relief, and that the "unfavourable" result of being a gene carrier will give distress, proved a misrepresentation of the complex reality. However, the test result (proven to be a gene carrier) has also been reported to associated with post-test distress [49, 51]. But as stated by Codori et al. [51]: these findings may raise more questions than they can answer. Once the knowledge of being a gene carrier is there, it is not yet clear which critical factors contribute to the post-test distress in some and not in others. Further research is needed to clarify this.

Type of disorder: HBOC The participants at-risk for HBOC had reduced post-test intrusive thoughts and feelings, independent of their post-test genetic status. Previous description of this group suggested that they might be a self-selected and highly motivated group, being the first to undergo the test [52]. Similar assumptions were made about the first participants in the presymptomatic HD studies [14]. Also these first families received extensive attention from the clinical researchers during all the years of linkage studies, which might have introduced a bias [26, 44].

However, low post-test distress in identified HBOC carriers and noncarriers was unexpected and contradicted our clinical observations where we found that predictive testing provoked emotional reactions in different family members up to six months after testing [31]. This observation may be explained as follows:

- 1) Actual predictive testing, first by linkage and then by mutation analysis, was introduced cautiously. After informing individuals about the option of informative testing a waiting period of 4 weeks elapsed before blood sampling, for the actual presymptomatic DNA test was done. Most participants stressed their impatience, during the interview. They had been waiting for a result for "so long" (the research phase for linkage). This long-standing anticipation apparently had a positive effect on their subjective capability to cope with any test outcome. The implications of an informative test result might have been on their minds for a long time; on the other hand, the end of waiting for an informative test, in itself might have generated relief. Additionally, after wishing and striving for a test result, adverse effects are likely to be neglected, as the burden of participation had otherwise not been worthwhile [53].

- 2) The psychological study was often experienced as psychological assessment (e.g. assessing their ability to handle the test outcome) with implications for further testing. One could speculate that reporting little distress may be interpreted as wanting to prove that testing ought to be continued. Similarly, in the first family to be tested for HBOC in the Netherlands, "the example", the first person to be presymptomatically tested felt a responsibility to reduce the fear in relatives and consequently did not report her own

fears [31]. Those to be tested in the future will be less tempted to under-report fears , because they will no longer be pioneers.

3) Shedler et al. [54] indicated that low scores on "mental health scales" may reflect opposite conditions. Low scores usually indicate no complaints; but they may also result from denial so as to "maintain an illusion of not being distressed". This is also shown in a comparative study on questionnaires and interview results, assessing the experienced distress before predictive testing for late onset disorders [52].

4) The options for preventive treatment in HBOC, although drastic, may offer some feeling of control in identified gene carriers and give a feeling of self determination. However, the options as such may also provoke distress.

Biographical variables

Women As expected, women tend to report more post-test intrusive thoughts and feelings, and avoidance behaviour about the disorder than men [48]. Other studies confirm that men may have a greater tendency to deny their feelings [55] and might be less able to face their fear and the implications of testing [30, 56]. Overall, more women come for predictive DNA testing which is also explained by their role of caretaker and their involvement with childbearing [50, 56, 57]. After becoming identified as a gene carrier their worries will concern: "who will take care of the children and keep the family united?" [25]. Female noncarriers often take on worrisome tasks caring for affected relatives [19] Tibben, 1997 personal communications.

However, Codori et al. [51], in their Huntington study found no difference between men and women and contributed this to the fact that participants asked for the information they received. Further research is needed to clarify the factors that contribute to the difference in distress between men and women.

Children Participants with children experienced more intrusive thoughts and feelings after the test, independent of the outcome. Giving information to offspring was often a motive to be tested [56, 58-62] and having children is experienced as an additional stressor during testing [25, 63, 64].

In the semi-structured interview with the psychologist (ACDdW) participants expressed their concern about becoming ill in the future. Above all, however, it was found almost unbearable that they might have transmitted the disorder to their children. Both carriers and noncarriers were still dealing with these emotions six months after testing.

Codori et al. [51] report that childless participants were found to be less well adjusted after testing. The percentage of parents in the present study and in Codori's study is similar (50% and 48% respectively). In our Huntington population (n=25) no

correlation was found between post-test intrusion and having children, which confirms the results of Tibben et al. [25]. An explanation for the difference between the two studies might be that in the study of Codori et al. individuals at-risk were determined to refrain from having children after they proved to be gene carriers. The existential gap of not leaving something of yourself to this world while at the same time knowing that life might be short, is distressing. In the present study, especially participants at-risk for cancer considered an unfavourable result no reason to refrain from having children. The subsequent worry about their offspring is then experienced as distressing.

Religion Being religious was associated with less intrusive thoughts and feelings at six months post-test. This support may be twofold. First, church attendance and clerical attention may function as a source of support [65]. Secondly, faith may give guidance in questions on the meaning and essence of life, such as "why (not) me?" [65-68].

Social interaction measures

Social support Those with more persons for support, prior to testing, showed more avoidance post-test. The avoidance subscale of the IES consists of items such as: "I avoided letting myself get upset when I thought about *the disorder* or was reminded of it; I stayed away from things or situations that might remind me of *the disorder*; I tried not to talk about *the disorder*". One way to illustrate this behaviour is looking for company as a form of distraction. On the other hand, more persons for support may also indicate that a participant has to tell his/her story more often, and subsequently finding him/herself to be occupied by the disorder often. The attention can be experienced as over-attention stimulating avoidance behaviour.

Psychological variables

Intrusive thoughts and feelings Pre-test intrusive thoughts and feelings were associated with similar feelings post-test. Tibben et al. [49] found this for carriers of the HD gene, and for noncarriers they found less intrusive thoughts and a sustained emotional numbness. In the present study, many noncarriers were informed that depressed emotional feelings were a normal post-test reaction [19, 69]. Patient organization brochures have also addressed this point. Noncarriers, learned how the doom of the disease might have prevented them from dealing with the emotions of contacts with affected relatives, both pre-test and after testing. We speculate that such information set in motion the working through of the scenario of a "favourable" test result. This might explain the differences between the results of the present study and those reported by Tibben et al.

Avoidance of feelings or situations Similar to Tibben et al. [49], we found that the avoidance behaviour prior to the test among carriers and noncarriers was associated with post-test avoidance behaviour. The problems related to the disorder seem to continue independently of the test result. Noncarriers may have experienced a shift of focus, first facing the threat of being a gene carrier and post-test the care for affected relatives, unresolved memories concerning the disorder, and feelings of guilt [19, 69]. Additionally, carriers may experience that the relief of knowing, becomes overshadowed by the fear of developing the disease.

Depression Depression prior to testing was associated with high distress (e.g. intrusion and avoidance) post-test, which is similar to the findings of Decruyenaere et al. for HD [17]. Pre-test depression seems to interfere with preparation for the possible test result. Lack of preparation may result in post-test avoidance of ideas, images and feelings they intrusively experience. This pattern may reflect problems in adjusting to the effects of the disorder on their life and needs attention.

Anxiety High anxiety prior to the test predicts less intrusion. High anxiety at pre-test may represent "work of worrying" [70], helping the participant to work through their anxiety and grief, and to cope effectively with the subsequent crisis [98]. On the other hand, less intrusion can also be interpreted as the result of the need to undo the impact of testing. As the test result can not be undone, personal disintegration can sometimes only be prevented by undoing the psychological impact of the test.

Interaction effects

We did not find that interaction effects (e.g. type of disorder by gender, or test result by psychological variable) contributed to a better fitting model for predicting post-test distress.

Who will experience distress? Guidelines for clinical practice.

The findings of the present study support earlier observations on predicting distress after presymptomatic testing for HD [17, 49-51]. Because most observations can be explained in more than one way (e.g. a low score might indicate absence or denial of distress) we make the following suggestions for everyday practice:

1. Participants tested for HBOC were less distressed post-test. The psychological dynamics leading individual to present him/herself as not distressed need attention. Either one is indeed not distressed, or one can only cope by denial and minimisation. During a face to face contact one may be able to assess whether a participant is able to face the implications of testing. When a participant needs all his/her psychological strength to diminish the threat of testing (e.g. by denial and minimisation), this way

of coping should be respected. It is helpful not to force, but to tell that the fears can be discussed at a later stage in time.

2. Women tend to become more distressed (intrusive thoughts and feelings and avoidance behaviour) post-test than men. Besides the general tendency of women to report more emotions, this is often linked to their roles in caretaking and childbearing. Adequate attention is needed when a woman wants to have (more) children. Feelings about existing children and their risk for the genetic disorder also need attention. Also, care for the family of origin and the affected relatives should be addressed.

3. Having children gives additional stress to testing. Time is needed to discuss the possible implications of testing for the children. "Are the parents going to tell the test result to the children?, When should this be done, How could this be done? What do the children know already, do they want to know? If the children want to know, but the parent does not, should the parent continue testing?", etc.

4. Helping the participant to see whether they have additional sources for support, is useful, such as religion, which can provide an anchor when the purpose of life may become less clear.

5. Having several persons for support and involved with the well-being of the participant led to post-test avoidance behaviour. It is helpful to assess, with the individual, whether friends and relatives are experienced as really supportive or rather curiosity/sensation seeking? It can help the participant to discuss, prior to testing, which relatives/others will be allowed to know about the test and the result. People differ in what they need at such a moment; and thinking about it prior to the test, however, may help them to create the support needed.

6. Intrusion prior to the test was associated with post-test intrusion. Participants with such intrusive thoughts and feelings, may be helped by assessing whether they are preoccupied with the subject as a measure of preparation, or whether they are becoming overwhelmed. The first option is a realistic way of preparation and eventual adaptation. Becoming overwhelmed, however, indicates a need for additional support to enable them to cope with the impending events.

7. Also, avoidance behaviour prior to the test was associated with post-test avoidance behaviour. This can be explained in several ways. A participant may seek distraction after a period of active involvement with the disorder, or because of inability to face the implications of testing. In the latter situation additional support seems indicated.

8. Depressed participants tend to become more distressed post-test, as reflected by avoidance of the intrusive thoughts and feelings about the disorder. Counsellors

should be able to recognize depression. During pre-test counselling of a depressed participant, the option of delaying the test may be discussed when it seems to be burdensome at that time. For others the test may function as the start for the working through of emotions blocked by previous continuing indecisiveness about the test and one's future. The best strategy can only be individualised, and enough time should be taken to find this out.

9. Anxious participants suffer less from intrusive thoughts and feelings after the test. Pre-test is easy to understand. The different implications of either test result will usually be associated with a certain level of anxiety, and this may help post-test adaptation. Some participants, however, may be too anxious to allow their emotions to be felt. This may prevent them from thinking about the implications of either test result, which may result in inadequate adaptation in the long term. Counsellors should be trained to recognize the over-anxious in order to offer them additional support.

Recommendations for further research

This first comparative study on predictive testing for hereditary neurodegenerative and cancer syndromes is limited by the relatively small study populations, which makes generalization difficult. However, the amount of individuals formerly at-risk for HD lost to follow-up, 32%, is similar to that reported in previous HD studies [10, 25]. Up to 44% was lost to follow-up among those formerly at-risk for a cancer gene. Dropouts were generally higher educated than those continuing to participate [48]. Participants with a higher education might have less need of the support provided by the follow-up appointments (they had already prepared themselves thoroughly).

In the case of predictive testing for HD, counselling within a multidisciplinary setting with follow-up appointments is strongly recommended [71]. For BRCA1 testing a similar approach is advised in case of evaluating the behavioural and psychosocial effects [72]. We would like to stress the importance of a thorough evaluation, both by interview and other psychometric techniques, to obtain a full understanding of the psychological implications of predictive DNA testing for the growing number of disorders. One should also focus on the long-term effects, as recent studies indicate that adaptation to a test result may take longer than three years [25].

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CHAPTER 7

MALES AT-RISK FOR THE BRCA1-GENE, THE PSYCHOLOGICAL IMPACT

MALES AT-RISK FOR THE BRCA1-GENE, THE PSYCHOLOGICAL IMPACT

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ABSTRACT

In recent literature the psychological impact of predictive DNA testing for Hereditary Breast and Ovarian Cancer (HBOC) for male individuals at-risk has not been considered. We have observed that confrontation with the hereditary nature of breast/ovarian cancer does have a psychological impact on males at-risk. From the first Dutch family for whom predictive DNA testing for HBOC became an option, four males started the testing protocol with the inclusion of pre-test genetic and psychological counselling and psychological follow-up. They all postponed appointments and only one took the test. During counselling of the men, the main focus of attention was on the impact of the past and future (possible) deaths and serious illnesses of female relatives. They tended to deny or minimise the emotional impact of the occurrence of HBOC in their personal life and their future. They avoided discussion about their emotions and focused upon the medical implications of the disorder for their female relatives. It is important to understand the underlying conflicts which lead to warding off the test in males at risk, in order to offer adequate genetic counselling and to enable the males to better cope with the hereditary disorder in the family.

INTRODUCTION

In 1993, the International Breast Cancer Linkage Consortium reported that approximately 45% of families with early onset (<50 years) and high breast cancer incidence, and at least 80% of families with increased incidence of combined early breast and ovarian cancer are due to the BRCA1 gene on chromosome 17q [1]. This finding made predictive DNA testing by linkage analysis possible for a few specific

families. From October 1994, the identification of a strong candidate for BRCA1, allowed direct mutation analysis in individuals at-risk [2].

Women carrying the BRCA-1 gene have a 85% risk of developing breast cancer and a 63% risk of developing ovarian cancer before the age of 70 [3]. Male gene-carriers have an 8% risk of prostatic carcinoma before the age of 70 (three-fold the population risk). Male and female gene-carriers have a 6% risk of colonic cancer before the age of 70 (four-fold the population risk). The relative risks of colon and prostate cancer do not appear to be any higher at young ages [4]. The efficacy of chemoprevention or intensive screening (self-examination and/or mammography) in this high-risk group, and also prophylactic surgery are still controversial [5].

The uptake of the predictive DNA test among first degree relatives of familial breast cancer patients is expected to be high [6, 7] especially among female relatives who, in the study of Struewing et al. [8], reported to anticipate a higher negative impact compared to males. In further publications [9-13] about the use of the predictive DNA test for HBOC, the main focus was on women. In the statement of the American Society of Human Genetics on genetic testing for the HBOC predisposition it is documented that: "Predictive testing should always be provided on a voluntary basis and should be conducted only in women who have been fully informed in an effective manner and who consent to testing" [14]. The position of the males at-risk for HBOC has received little to no attention.

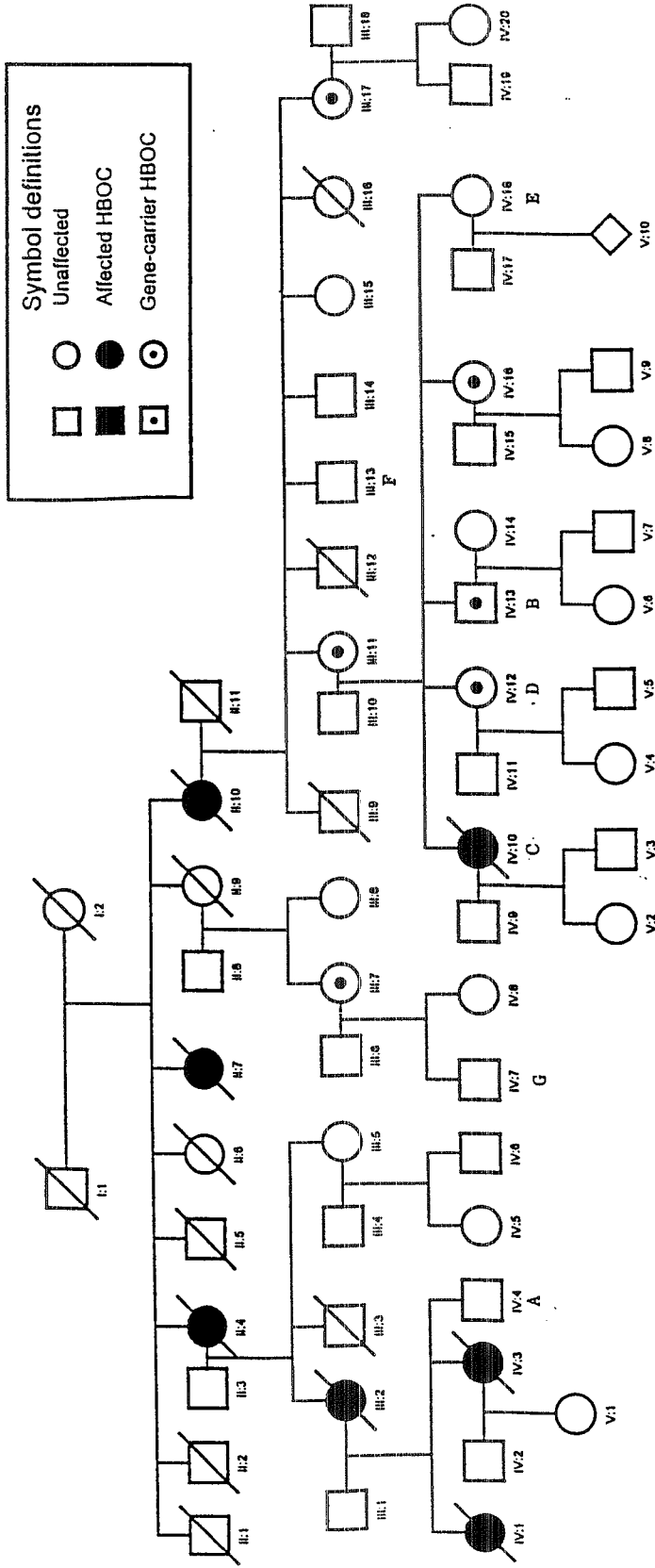
In this article we describe our experiences with male test candidates at-risk for the BRCA-1 gene.

PARTICIPANTS AND METHODS

Molecular genetics and the participants, as presented in Fig. 1 are described in full detail in chapter 3b (participants and methods). The protocol for genetic counselling and the psychological follow-up study are described in full detail in chapter 2.

Four males at 50% risk are presented in this case description. The four males had one or more appointments at the department of Clinical Genetics. Only one (IV-13) underwent predictive testing, another (IV-7) is still in the pre-test counselling process.

Fig. 1. Altered pedigree to keep anonymity



CASE DESCRIPTIONS: MALES AT-RISK FOR THE BRCA-1 GENE

All four men coming to the department of clinical genetics expressed feelings of concern and sorrow regarding their female relatives, but were reluctant to discuss feelings regarding their own risk.

Mr.A (IV:4), aged 20, wished to be further informed about the predictive test. During the first session he spoke about the loss of both his mother (III:2) when he was 12, one of his sisters (IV:1) when he was 18, to HBOC and his other terminally ill sister (IV:3), who was expected to die in the near future. He described the whole situation as "shit", and became very emotional when talking about his mother and sisters. He expressed that he could not talk about this with anybody and had a hard time concentrating on his daily activities. Although he did not want to be tested at that particular moment, he would come back if he wished to start a family.

The next appointment with the psychologist was postponed because his sister had died and the cremation was to take place. Two weeks later at the next appointment, he said: "I do not need to talk to a stranger anymore, in the past 8 years I succeeded in coping with a loss, so I will be able to handle it now as well". He wished to close the book on cancer since everybody at-risk, he knew, had died. At the same time he said that there was nobody to share his feelings with. He felt there was a generation gap between himself and his father and his second wife. Although he had close contact with his stepbrother, he could not really talk about the death of his sisters and mother with him. He did not want to make use of further psychological support.

Mr.B (IV:13), age 36, wanted to take the predictive DNA test to help research. He said that he felt close to his eldest sister Mrs.C (IV:10) who had a bilateral breast-conserving surgery because of breast cancer in her early thirties. She had feared for her own health, and persuaded her siblings and parents to participate in the linkage study, which subsequently made the predictive test an option for the whole family. Mr.B reported that he wanted to know his test result for his children, particularly for his daughter.

Mr.B postponed the next appointment twice. When he visited again he spoke about his concern and worries regarding his two sisters Mrs.C (IV:10) and Mrs.D (IV:12), who both were identified as gene-carriers. He could not understand why his eldest sister Mrs.C was so involved in finding even more information about HBOC. His youngest sister Mrs.E (IV:18) did not want to be informed about the predictive test. His wife described the awkward situation of the family not being able to talk about breast and ovarian cancer and the predictive test whenever Mrs.E was around.

Mr.B was found to be a gene carrier. Just before his test result Mrs.C underwent an ovariectomy, and microscopic metastases of her breast cancer were found. Distant metastases manifested afterwards, without clear objective response to different systematic treatment modalities. As a result Mrs.E decided that she could no longer ignore the facts and decided that she wanted to take the predictive DNA test.

A week after his test result Mr.B talked at great length about HBOC and the coming death of his sister. When comparing himself to his sisters he felt he had no right to complain, his test result had not altered his personal life perspective. He was afraid though, what would happen in the future with his daughter, as she was now at 50% risk to be a gene-carrier.

He and his wife worried about his youngest sister and whether she would be able to cope being a gene-carrier. They both reported that talking to friends about HBOC was difficult because they did not really understand the issue.

Six months after his test result, Mr.B said that he felt helpless seeing his sister Mrs.C dying. He could not really comment on what the test result had meant to him personally. The main focus of his attention was on what was happening to his sisters.

Mr.F (III:13), aged 45, commented upon the situation in his sister's (III:11) family at his first session. He was very concerned about his nieces (IV:10, IV:12, IV:16 and IV:18) and felt that the tension and anxiety were becoming too high. He was not really concerned about his own personal risk to be a gene-carrier. Even if he would have passed the BRCA-1 gene on to both his two sons (23 and 18 years old) it was no big concern to him as they could not develop breast and ovarian cancer. Actually, he felt that testing was more relevant for them in case they wished to have children. His partner, not the mother of his sons, did not want to get involved in the testing procedure. The second appointment, in which the blood sample was to be drawn, was cancelled twice by him. It was agreed that he would take the initiative to make a new appointment if he wished to continue the testing procedure. Until now no appointment has been made.

Mr.G (IV:7), aged 27, and his sister (IV:8), aged 23, came after their mother (III:7) was identified as a gene-carrier. Although Mr.G was single he wished to know the possible risk for his prospective children. He said that he feared that his mother would not have the necessary operations because she was too afraid of the surgery involving prophylactic ovariectomy. He was moved to tears when talking about his worries regarding both his mother and sister. He and his sister decided to wait another six months before taking the test so that his sister could finish her studies first. Additional psychological counselling was offered to him but no use has been made of it yet.

DISCUSSION

It is understandable that women are the main focus of attention when discussing HBOC, because women at-risk may develop cancer and can take precautions when identified as gene carriers [14]. For men, the risks of cancer are relatively low and do not apply at a young age [4]. Our observations however have shown that the profound psychological impact of the occurrence of HBOC in the family and the option of predictive testing upon the males at-risk for the BRCA-1 gene should not be underestimated.

Using the stress-response theory of Horowitz [15] we have observed that the males at-risk suffered from intrusive feelings and thoughts regarding unresolved grief about past and future losses, and guilt about passing on a potentially lethal gene to their future offspring. They tended to deny or minimise the emotional impact of the occurrence of HBOC in their personal life and their future. They avoided discussion of their emotions and focused upon the medical implications of the disorder for their female relatives. Moreover, they prolonged the testing procedure by cancelling appointments and postponing or withdrawing from testing which was also reported by Streuwing et al. [8]. The latter authors concluded that males at-risk are less concerned about their risks and the need of predictive testing. However, our observations obviously lead to contrary conclusions.

The over-attention for female relatives and the withdrawal from testing, reflect an attitude or defense style in males that apparently reduces the psychological distress. Minimisation and denial-avoidance can be adequate in the short term, they do not need to be considered as maladaptive or inadequate. However, in the long term they can lead to difficulties in coping with the problems evoked by the hereditary disorder in the family. In addition, long term denial-avoidance behaviour and minimisation is associated with health problems [16-18]. Denial and minimising behaviour may hamper males in discussing the heredity issues with relatives and, in particular, with their (future) offspring. Furthermore, it may prevent males to ask for professional support when needed.

The family must be considered as the patient when conducting linkage and mutation analysis research and subsequent predictive DNA testing programs [19]. Consequently, genetic counselling for predictive testing requires a family approach. Often, a family has been overshadowed by multiple cases of early onset cancers in females over more than two generations. Family members are aware that there is 'something' in the family. The system coping strategies need to be reconsidered and adapted when genetic research and subsequent predictive testing is offered [20]. Participation or not in genetic

research and predictive testing may result in a shift of mutual bonds and roles. Subsequently, identification of carriers and noncarriers can lead to far-reaching changes in communication and interaction patterns. The internal conflicts in males may be reinforced or induced by these family dynamics. Therefore, the psychological reactions of males in families with HBOC must also be understood from a family system theory point of view [21, 22].

At first sight, males may seem neither interested nor concerned about predictive testing. The denial-avoidance behaviour and minimisation in the males at-risk may lead to an underestimation and consequently underdiagnosis of the psychological distress. This behaviour can cover underlying conflicts that are fed by fear, guilt or unresolved grief and loyalty conflicts. When health care givers recognize these psychological phenomena, they can offer the males and their partners to further discuss these issues. Also, appreciation of these psychological issues may help the males to face and accept their emotions and behaviour. This might enable them to better cope with the hereditary disorder in the family.

The defense styles we discussed are the most emerging and perhaps less difficult to observe from a variety of psychological defense mechanisms or coping strategies that cover a large spectrum of human behaviour. However, health care givers who are less familiar with psychological theory and observations, may be able to recognize denial-avoidance and minimization.

We suggest that the training program of clinical geneticists and genetic counsellors includes education in the basics of family system theory in order to recognize and explore family coping strategies (denial-avoidance versus approach of a specific hereditary disease; characteristic roles within the family; inter-generational interactions etc.).

Psychodynamic and family system mechanisms deserve close attention in both health care and psychological follow-up research. Clinical descriptive case studies are needed to enhance our understanding of predictive DNA testing for late onset disorders.

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CHAPTER 8

**DISTRESS IN INDIVIDUALS FACING PREDICTIVE DNA TESTING FOR
AUTOSOMAL DOMINANT INHERITABLE LATE ONSET DISORDERS;
COMPARING QUESTIONNAIRE RESULTS WITH IN-DEPTH INTERVIEWS**

DISTRESS IN INDIVIDUALS FACING PREDICTIVE DNA TESTING FOR AUTOSOMAL DOMINANT INHERITABLE LATE ONSET DISORDERS; COMPARING QUESTIONNAIRE RESULTS WITH IN-DEPTH INTERVIEWS.

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ABSTRACT

In 50% risk carriers for Huntington Disease (HD (n=41)), Hereditary Cerebral Haemorrhage with Amyloidosis Dutch type (HCHWA-D (n=9)), Familial Adenomatous Polyposis Coli (FAP (n=45)) and Hereditary Breast and Ovarian Cancer (HBOC (n=24)), pre-test intrusion and avoidance (Impact of Event Scale), anxiety and depression (Hospital Anxiety and Depression Scale), feelings of hopelessness (Beck Hopelessness Scale) and psychological complaints (Symptom Checklist), were assessed. The manner of discussing the genetic disorder, the test and its implications during a semi-structured interview (reflecting upon one's emotions without getting carried away or dismissing/minimizing the subject) was judged in terms of coherence. Participants at-risk for neurodegenerative disorders had higher anxiety and depression scores and more psychological complaints than those at-risk for cancer syndromes. Those reporting high intrusion/high avoidance had higher anxiety and depression scores and more

psychological complaints than those reporting low intrusion/low avoidance. The scoring of the interview however, showed that participants reporting high intrusion/high avoidance were more reflective about their emotions without getting carried away or dismissing the subject (e.g. more coherent) than those reporting low intrusion/low avoidance. This suggests that participants with higher stress scores may be actively dealing with the emotional implications of the test, whereas people with low stress scores may (as yet) be unable to face these implications. It is important to identify the strategy of coping with threat in order to provide suitable counselling and necessary guidance. Long term follow-up however, is needed to learn the consequences of a denying coping strategy for those participating in a genetic testing program.

INTRODUCTION

Individuals at-risk for inheriting a late onset genetic disorder live under potential stressful conditions resulting in uncertainty, lack of control and, until recently, prolonged confinement in a situation with no means of escape [1]. Predictive testing by linkage analysis and direct mutation analysis is now available for a growing number of both neurodegenerative disorders and cancer syndromes [2-13]. Predictive testing, however, brings its own stress: it is a confrontation with the past, the family history of disease and death, and with a future that may become determined by the disease (with deterioration in the neurodegenerative disorders and radical treatment in case of cancer).

Stress responses

The stress response theory of Horowitz involves alternating phases of intrusive thoughts and feelings and avoidance of feelings or situations related to the stressful event [14], in this study the genetic disorder. Intrusion and avoidance may alternate according to the individual's idiosyncratic pattern until a period of working through occurs [15]. The Impact of Event Scale (IES) [14] permits careful and systematic evaluation of the stress responses that follow traumatic events by assessing the amount of intrusive thoughts and feelings and avoidance over the past week. Zilberg et al. [16] recognized three stress response patterns: 1) a group frozen in avoidant states (high avoidance/low intrusion scores); 2) a group stuck in undercontrolled intrusion states (high intrusion/low avoidance scores) and 3) a group oscillating between intrusion and avoidance (resulting in similar ratings for intrusion and avoidance). According to Zilberg et al. [16] the first two patterns represent a blocked response pattern, the last an active response pattern indicating working through. Schwarzwald et

al. [15] recognized two groups in those reporting similar levels of intrusion and avoidance, namely those reporting high intrusion and avoidance and those reporting low intrusion and avoidance. They assume that this reflects a single, general dimension of stress level, either high or low stress [15]. Participants facing the predictive test have to deal with the stress provoked by the test, and will show behaviour that may represent one of these patterns, either low intrusion/low avoidance, high intrusion/high avoidance or a blocked stress pattern, either high intrusion/low avoidance or low intrusion/high avoidance.

Predictive testing for Huntington disease compared to predictive testing for other late onset disorders

Experience with predictive testing has been gathered in studies on the psychological implications of predictive testing for Huntington's Disease (HD). These experiences have been suggested to be a useful paradigm for the study of other late onset disorders, such as cancer syndromes (e.g. Hereditary Breast and Ovarian Cancer (HBOC), Familial Adenomatous Polyposis (FAP), Hereditary non-Polypoid Colorectal Cancer (HNPCC), Multiple Endocrine Neoplasia type 2 (MEN-2)) [17]. The similarities between HD and these hereditary cancer syndromes are: autosomal dominant inheritance, the onset of a variety of symptoms with increasing age, and major impact on the family. The cancer syndromes, however, differ from HD by absence of neuropsychiatric symptoms and the availability of choices for treatment [18]. It needs to be studied whether the experiences with presymptomatic testing for HD can be generalized to other dominant inheritable late onset disorders such as cancer syndromes.

Generally, the studies examining the psychological effects of DNA testing for HD, showed no severe adverse reactions in carriers but did show relief from prior psychological distress and a tendency to minimize the impact of the test result on their future [19-33]. On the other hand, noncarriers often experienced lack of relief, numbed emotions, survivor's guilt and difficulties developing a new life-perspective [26, 30, 34]. Only recently have the effects of predictive testing for cancer syndromes (HNPCC, FAP, MEN-2A) been studied [35-40]. Most reports are about HBOC. On the one hand little emotional disturbance after disclosure [41] and relatively normal levels of psychological morbidity are reported [42, 43]. On the other hand, clinical impressions indicate that the test may provoke emotional upheaval in families confronted with the possibility of testing [18, 44, 45]. Predictive testing might prove beneficial for some high-risk individuals who receive their result within a setting including counselling. It is also expected, however, that only a subset of HBOC family members are likely to request BRCA1 testing [46].

In a comparative study [47], it was demonstrated for the first time that individuals at-risk for HD had significantly higher levels of intrusion than those at-risk for HCHWA-D, FAP and HBOC whereas participants at-risk for FAP reported significantly lower levels of intrusion than the other groups. With regard to avoidance, we found that those at-risk for the neurodegenerative disorders (HD and HCHWA-D) reported significantly higher levels than those at-risk for the hereditary cancer syndromes (FAP and HBOC).

Potential bias of questionnaire results

Results from studies based on scales measuring psychological health may be biased, because low scores can reflect opposite conditions. Shedler et al. [48] describe in their study on mental health (measured with questionnaires, clinical interviews and physiological measures) that low scores can indicate that people deny health problems, trying to "maintain an illusion of mental health" [48]. In the same vein, people with low stress scores may be denying stress in order to "maintain an illusion of not being stressed". Low stress scores may thus also reflect opposite conditions.

High scores are normally the result of being stressed. However, high scores may also reflect the person's psychological anticipation to the threatening event (work of worrying) [49]. This "work of worrying" could also be useful in preparation for the genetic test result.

It is often concluded that participants of predictive testing programs are doing well because their questionnaire results (measuring stress, well being etc.) are low. However, case descriptions show that this is not always the case [26, 44, 45, 50]. In order to provide adequate support it is important not to take the information about the experienced stress at face value. High levels of intrusion and avoidance may imply working through, but can also imply uncontrolled mood swings. Low levels of intrusion and avoidance may imply that the event is not stressful, but it may also mean denial of stress. Especially those who deny their stress need careful looking after, because although denial may be adaptive at the short term [20, 51] it is not known yet what the long term consequences will be.

Questions in the present study

The present study first analyzes differences in the reported levels of anxiety, depression, hopelessness and psychological complaints between the four groups at-risk (HD, HCHWA-D, HBOC and FAP) when they applied for testing. Secondly, to get an understanding of the possible meaning of different stress response patterns, psychological variables of individuals showing four different stress response patterns (concerning high and low levels of intrusion and avoidance) were assessed. The third question addressed the comparison of self-reported stress response patterns with the independent judgement of interview texts concerning the reactions to the disease and

the test. We hypothesized that some of those with low stress scores would reflect less upon their emotions by dismissing/minimizing the subject, which would represent a denying attitude.

This study is part of a longitudinal follow-up study on predictive testing focusing on: a) the adjustment of individuals at-risk and their partners after the DNA test results, and b) identification of psychological determinants of adjustment problems after test disclosure. Our aim is to provide guidelines for genetic counselling, psychological support and interventions.

METHODS AND PARTICIPANTS

The genetic disorders are described in full detail in chapter 1, the participants, procedures, questionnaires and the statistical analysis are described in full detail in chapter 2. A shortened version of the methods is presented. The psychological questionnaires given at the introduction of the study included the Symptom Checklist (SCL'90), the Impact of Event Scale (IES), the Beck Hopelessness Scale (BHS) and the Hospital Anxiety and Depression Scale (HAD). At the second session at the department of Clinical Genetics blood samples were taken by the clinical geneticist when participants wanted actual testing. This session was followed by an interview with the psychologist, separately for the participant and the partner. Seventeen interviews could not be analyzed due to audiotaping failure. Seven participants, all at-risk for the cancer syndromes, did not want to have their interviews recorded. Finally, 119 questionnaires and 78 interviews could be used for analysis.

Each interview was transcribed and corrected before analysis. Each transcript was judged by a panel of five psychologists. The system developed by Main and Goldwyn [52] for scoring "the coherence of transcript" was translated and adapted for the present study by the last author (RWT). An answer is considered coherent when it is: 1) truthful, providing evidence for what is said, 2) succinct and yet complete, 3) relevant or perspicacious, presenting what has to be said so that it is plainly understood, 4) clear and orderly [53]. A participant is then showing a readiness to discuss and evaluate memories, experiences and feelings about the hereditary disorder and the test, with a clear and consistent flow of ideas [54]. Such a transcript receives a high score (min = 1, max = 9). Lower scores represent lower levels of coherency.

Three answers, or parts of answers, of 50% risk carriers for HD are given as an example of more or less coherent answers. The following is considered to be a fairly coherent response (score 7): Interviewer: "What does HD mean to you?" *Participant:*

"Eh -- it is, could be seen as, how should I put it, it has enriched my life, I know a bit more about life: that it is not all honey and roses, it made that clear. You have to live with it all your life. It is also difficult because it comes with fear and tension piling up so high that you don't know where to go, you can't live your life as free and unconcerned as you would wish. That really puts me down. I really feel like I should continue, but how, what; the fear is so enormous that I find it very hard to live with it at the moment (etc.)".

The next two examples are considered to be less coherent (both score 3). Interviewer: "What does HD mean to you?" Participant: *"Most people have no idea about what it means, they think people are drunk, I witnessed that several times".*

Interviewer: "What does the predictive test mean for you and your partner? Does it have an influence on your relation?" Participant: *" No absolutely not, I just continue with what I have been doing always (8 sec silence). I'm a member of the board on the general meeting of the housing cooperation and I must go to the meeting tonight, I'm the secr eh the treasurer of the department (name of town). It is a lot of work, I will just continue to do it. If the test proves that I have a chance than I know when to quit. If I notice that it, that it will start then I know I have to quit I'm also in the board of the staff association of the company I used to work ... (etc.)"*

The first quotation clearly shows the individual at-risk to be able to consider the various aspects of being at-risk and to describe the associated feelings convincingly. The second participant reacts briefly and evasively by describing the behaviour observed in other people, without reflecting upon what HD means for him/her personally. The third participant does not answer the question either. A description of the implications of being a gene carrier for his sideline activities is given in great detail instead of a description of the implications of testing for his partner-relation. Furthermore the sentence *"if the test proves that I have a chance then I know when to quit"* is vague as well as incorrect. All participants have been counselled by a clinical geneticist, at this stage at least twice, at both session the genetics and characteristics of specific genetic disorder are discussed in great detail. This participant is told and explained that the test provides certainty and not an estimation. When proven to be a gene carrier one will develop HD sooner or later (testing is done by mutation analysis and the gene is fully penetrant). Moreover the test does not provide any information about the onset of the disease.

Table 1. Pre-test characteristics of participants in the predictive testing program

	HD ¹⁾ (n = 42)	HCHWA-D (n = 10)	FAP (n = 45)	HBOC (n = 24)	statistic	d.f.	p
Male/Female at-risk	15/27	4/6	22/23	5/19			
Age (years) Mean (sd)	37.1 (10.9)	35.1 (16.4)	29.8 (11.5)	41.3 (11.6)	F = 5.68	3, 116	.01
Married/Common law n (%) ²⁾	31 (74%)	8 (80%)	19 (43%)	22 (92%)	$\chi^2 = 19.89$	3	.001
Children n (%) ²⁾	21 (50%)	8 (80%)	16 (36%)	21 (87.5%)	$\chi^2 = 24.21$	6	.001
Education level n (%) ^{2,3)}							
1	10 (24%)	5 (50%)	9 (20%)	9 (37%)	$\chi^2 = 9.52$	6	.15
2	22 (52%)	2 (20%)	31 (69%)	10 (42%)			
3	10 (24%)	3 (30%)	5 (11%)	5 (21%)			

¹⁾ HD = Huntington's Disease, HCHWA-D = Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type, FAP = Familial Adenomatous Polyposis and HBOC = Hereditary Breast and Ovarian Cancer. ²⁾ n = number of persons, (%) = percentage of all individuals who are at-risk for respectively HD, HCHWA-D, FAP or HBOC who are married, have children or have level 1 to 3 of education. ³⁾ 1 = elementary school and low vocational school, 2 = high school, secondary school, or secondary vocational school, and 3 = high vocational school, university or college. d.f., F, χ^2 , see text for details.

Table 2. Mean anxiety, depression, hopelessness and psychological complaints scores in four groups of participants in the predictive testing program.

Variable	HD ¹⁾ (n = 41)		HCHWA-D (n = 9)		FAP (n = 45)		HBOC (n = 24)		F	d.f.	p
	Mean	sd	Mean	sd	Mean	sd	Mean	sd			
Anxiety	6.5	.7	6.9	.4	5.3	.9	5.0	.7	30.25	3, 115	<.001
Depression	3.5	.2	3.2	.2	2.4	.3	1.8	.2	291.21	3, 115	<.001
Hopelessness	6.6	.2	7.9	.2	5.5	.2	3.6	.2	1750.31	3, 115	<.001
Neuroticism	72.3	1.6	72.8	.9	72.1	1.7	59.4	1.6	414.29	3, 115	<.001

Note Anxiety and depression are assessed with the Hospital Anxiety and Depression Scale, Hopelessness is assessed with the Beck Hopelessness Scale and Psychological Complaints with the Symptom Check List⁹⁰. d.f., F, see text for details, n = number of persons.

RESULTS

Comparison of participants at-risk for HD, HCHWA-D, FAP and HBOC.

Descriptive

General characteristics of the study population are given in Table 1.

Participants at-risk for FAP are younger than those at-risk for HD and HBOC, more often single and without children.

Anxiety, depression, hopelessness and psychological complaints.

Table 2 presents the mean anxiety, depression, hopelessness and psychological complaints scores, adjusted for gender and age, of participants at-risk for HD, HCHWA-D, FAP and HBOC. The four groups are not classified as anxious, nor depressed, as the mean scores do not rise above 7 [55]. Risk carriers for HD, HCHWA-D show mild signs of hopelessness (4-8), while risk carriers for HBOC show normal signs of hopelessness (< 4) [56-58]. Participants at-risk for HD, HCHWA-D and FAP fall in the normal range of the composed 'psychological complaints' score while those at-risk for HBOC score below normal compared to a normal Dutch population [59].

The four groups of disorders differ statistically significantly ($p < .001$) for anxiety, depression, hopelessness and psychological complaints, using one-way ANOVA. Those at-risk for the neurodegenerative disorders (HD and HCHWA-D) report significantly higher levels of anxiety, depression and hopelessness, than those at-risk for the cancer syndromes (HBOC and FAP). Those at-risk for HD report significantly higher levels of depression than those at-risk for HCHWA-D, while those at-risk for HCHWA-D report significant higher levels of hopelessness than those at-risk for HD. Those at-risk for HBOC report significantly lower levels of both depression and hopelessness than those at-risk for FAP. Participants at-risk for HBOC seem to have significantly less psychological complaints than those at-risk for HD, HCHWA-D and FAP.

Figure 1 presents transformed scores, for reasons of comparability, for anxiety, depression hopelessness and psychological complaints, of participants at-risk for HD, HCHWA-D, FAP and HBOC.

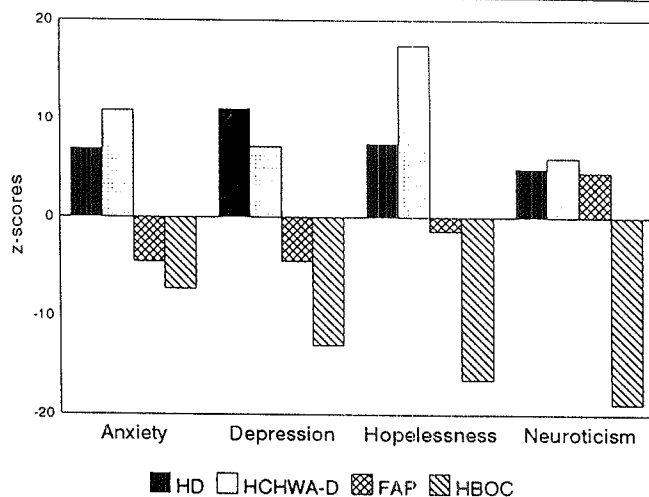
Four patterns of reported stress

Descriptive

The four patterns in which stress can be reported on the IES are: I) high intrusion/high avoidance, II) high intrusion/low avoidance, III) low intrusion/high avoidance, and IV) low intrusion/low avoidance. Intrusion and avoidance were dichotomized at the median.

The general characteristics of four groups, classified according to these patterns are given in Table 3.

Fig.1. Mean scores for Anxiety, Depression, Hopelessness and Psychological Complaints.



Note adjusted for gender and age

The distribution of these stress response patterns indicates that either high intrusion/high avoidance (group I) or low intrusion/low avoidance (group IV) are the main stress response patterns. The four groups differed significantly with regard to the type of disorder; 62% and 50% of the participants at-risk for HD and HBOC were found in group I (high intrusion/high avoidance). Twenty-seven percent of the participants at-risk for FAP were found in group I (high intrusion/high avoidance) while 50% was found in group IV (low intrusion/low avoidance). Participants at-risk for HCHWA-D were found either in group I (high intrusion/high avoidance) (44%) or group III (low intrusion/high avoidance) (33%).

Anxiety, depression, hopelessness and psychological complaints.

Table 4 (Section a) presents the mean scores on the two subscales of the HAD (anxiety and depression) and of the BHS (hopelessness) and psychological complaints (SCL'90) of the participants distinguished by stress response patterns according to the IES. The mean scores on the HAD indicate that those in group I (high intrusion/high avoidance)

Table 3. Different patterns of reported stress; pre-test characteristics of participants in predictive testing program.

	I I + / A + ¹ (n = 54)	II I + / A - (n = 8)	III I - / A + (n = 14)	IV I - / A - (n = 43)	statistic	d.f.	p
Male/Female at-risk	16/38	2/6	10/4	18/25			
Age (years Mean (sd	36.7 (10.5)	35.1 (5.4)	29.8 (6.9)	39.0 (14.6)	F = 5.68	3, 114	.09
At-risk for n (%) ²							
HD ³	26 (62%)	3 (7%)	3 (7%)	10 (24%)	X ² = 19.14	9	.03
HCHWA-D ⁴	4 (44%)	1 (11%)	3 (33%)	1 (1%)			
FAP ⁵	12 (27%)	2 (4.5%)	7 (16%)	23 (52%)			
HBOC ⁶	12 (50%)	2 (8%)	1 (4%)	9 (38%)			
Married/Common law n (%) ⁷	16 (34%)	2 (33%)	8 (62%)	12 (30%)	X ² = 4.41	3	.23
Children n (%) ⁷	30 (56%)	5 (63%)	4 (29%)	25 (58%)	X ² = 4.22	3	.24
Education level n (%) ^{7,8}							
1	13 (14%)	1 (13%)	1 (8%)	11 (27%)	X ² = 7.31	6	.30
2	28 (52%)	3 (38%)	10 (77%)	23 (56%)			
3	13 (24%)	4 (50%)	2 (15%)	7 (17%)			

¹ I + A + = high intrusion and high avoidance scores, I + A = high intrusion and low avoidance scores, I - A + = low intrusion and high avoidance scores, I - A = low intrusion and low avoidance scores on the Impact of Event Scale. ² n = number of persons, (%) = percentage of all individuals at-risk for resp. HD, HCHWA-D, FAP and HBOC, who have stress pattern I, II, III or IV. ³ HD = Huntington's Disease. ⁴ HCHWA-D = Hereditary Cerebral Haemorrhages with Amyloidosis Dutch type. ⁵ FAP = Familial Adenomatous Polyposis. ⁶ HBOC = Hereditary Breast and Ovarian Cancer. ⁷ n = number of persons, (%) = percentage of all individuals having respectively stress pattern I, II, III, IV who are married, have children or have level 1 to 3 of education. ⁸ 1 = elementary school and lower vocational school, 2 = high school, secondary school, or secondary vocational school, and 3 = higher vocational school, university or college. d.f., F, X², see text for details.

Table 4. Different patterns of reported stress, Section a: anxiety, depression, hopelessness and psychological complaints and section b: coherence established by the interview.

Section a: Questionnaires									
Variable	I I+/A+ ¹ (n = 54)		II I+ /A- (n = 8)		III I-/A+ (n = 14)		IV I-/A- (n = 43)		statistic
	Mean	sd	Mean	sd	Mean	sd	Mean	sd	
Anxiety	8.2	4.1	4.9	2.5	5.3	4.2	3.1	2.8	17.75 3,124 <.001
Depression	4.0	3.7	.6	.9	2.9	3.7	1.6	1.8	7.70 3,124 <.001
Hopelessness	6.2	3.7	6.3	3.5	5.9	4.4	5.4	.6	.30 3,125 .82
Psychological Complaints	75.5	20.4	59.2	8.9	77.6	23.8	62.5	15.7	5.94 3,123 <.001

Section b: Interview									
Variable	I I+/A+ (n = 35)		II I+ /A- (n = 5)		III I-/A+ (n = 10)		IV I-/A- (n = 28)		statistic
	Mean	sd	Mean	sd	Mean	sd	Mean	sd	
Coherence	4.8	1.6	4.8	1.9	4.6	1.5	3.8	.9	3.09 3,79 <.04

Note: Anxiety and depression are assessed with the Hospital Anxiety and Depression Scale, Hopelessness is assessed with the Beck Hopelessness Scale, Psychological Complaints with the Symptom Check List' 90 and coherence is a score of the interview text assessed according to the classification system developed by Main and Goldwyn (in press translated and adapted by the last author (RWT for this study, d.f., F, see text for details, n = number of persons.¹ I+/A+ = high intrusion and high avoidance scores, I+/A- = high intrusion and low avoidance scores, I-/A+ = low intrusion and high avoidance scores, I-/A- = low intrusion and low avoidance scores on the Impact of Event Scale.

are borderline anxious (8-10), but not depressed (<8) [55]. All four groups show signs of moderate hopelessness [56-58]. Participants in group I (high intrusion/avoidance) and group III (low intrusion/high avoidance) fall in the normal range of the composed psychological complaints score while those in group II (high intrusion/low avoidance) and in group IV (low intrusion/avoidance) score below normal compared to a normal Dutch population [59].

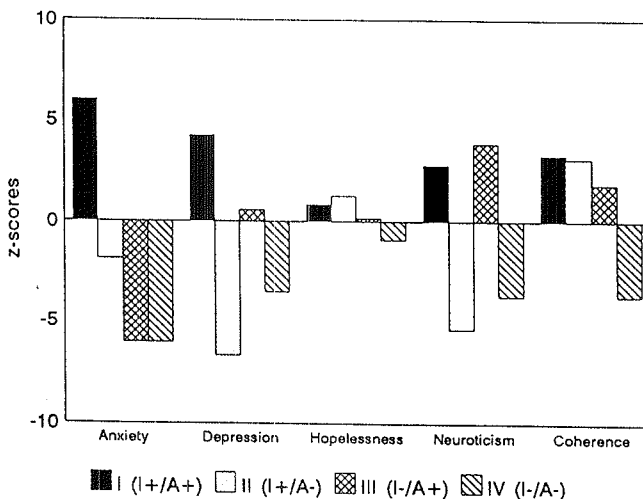
Anxiety, depression and psychological complaints differ significantly ($p < .001$) between the four groups, using one-way ANOVA. Using Scheffé's S method, we detected which groups did differ. Participants at-risk in group I (high intrusion/high avoidance), report significantly higher levels of anxiety, depression and more psychological complaints than those in group IV (low intrusion/low avoidance). Participants at-risk in group I (high intrusion/high avoidance) also report significantly higher levels of depression than those in group II (high intrusion/low avoidance).

Coherence score of the interview text

Descriptive

The reported stress response patterns, anxiety, depression, hopelessness, psychological complaints, gender distribution and age are not significantly different between participants with ($n = 78$) and without ($n = 41$) a coherence score of the interview text.

Fig. 2. Four stress response patterns; questionnaire and interview results



Note I = high intrusion/high avoidance, II = high intrusion/ low avoidance, III = low intrusion/ high avoidance, IV = low intrusion/low avoidance.

Coherence

Table 4 (Section b) presents the mean scores for coherence of the interview in participants from the various stress response patterns. The interview scores differ significantly ($p < .04$) among the four groups, using one-way ANOVA. Using Scheffé's S method, participants at-risk in group I (high intrusion/high avoidance) were found to have significantly higher coherence scores for their interviews than those in group IV (low intrusion/low avoidance).

Figure 2 presents transformed, for reasons of comparability, scores for anxiety, depression, hopelessness, psychological complaints and coherence for participants divided by stress response patterns according to the IES.

DISCUSSION

General Results:

Comparison of participants at-risk for HD, HCHWA-D, FAP and HBOC.

Individuals at-risk for the neurodegenerative disorders are more anxious, depressed and hopeless when they applied for the predictive test than those at-risk for the hereditary cancers. This might be a reflection of a future of HD with its incapacitating and long course [60] or, the sudden death due to a stroke, as in most of the gene-carriers for HCHWA-D [61]. The prospect of such a sudden disease as HCHWA-D apparently leads to feelings of hopelessness, while the long course of HD leads to more depressive feelings; moreover therapy is unavailable for both disorders. For the cancer syndromes preventive surgery may, to varying extent, prolong their life span, and at least offer gene carriers an option to fight against the disease. This may explain the lower anxiety, depression and hopelessness scores.

The perception of the immediate risk may be different among the various participants. Those at-risk for HD, HCHWA-D and HBOC have an average age equal to average age of onset of the disease in gene carriers; FAP participants are mostly older than the average age at onset [61-64]. HBOC participants, however, were less depressed and hopeless than those at-risk for FAP. Half of the HBOC participants report high intrusion and high avoidance and at the same time relatively low depression, hopelessness and have less psychological complaints compared to those at-risk for the other disorders. Whether this reflects a self selection of participants at-risk or whether this represents a firm belief in the treatment options needs to be studied. It could be argued that these first groups, having been involved in the research studies on hereditary breast and ovarian cancer, would experience considerable relief with the test

becoming available, as we experienced in our first family [44]. This effect does not apply to the other disorders for which testing was already available for a longer period (Table 1, chapter 2).

Four patterns of reported stress.

This study is a first attempt to correlate stress response patterns (in terms of reported intrusion and avoidance) [14-16] with being at-risk for different diseases and with other personality items. How these patterns are associated with future pathological post-test reactions and adjustment disorders needs to be studied [32].

Generally, stress response patterns were either high intrusion/high avoidance (45 %), representing an active response pattern indicating working through, or low intrusion/low avoidance (36%) indicating little stress. The resulting 19 percent showed a blocked stress response patterns [16]; 12 percent high avoidance/low intrusion scores (frozen in avoidant states) and 7 percent high intrusion/low avoidance scores (stuck in undercontrolled intrusion states).

High intrusion/high avoidance was reported by the majority of the participants at-risk for HD (62%), 50 percent of those at-risk for HBOC, 44 percent of those at-risk for HCHWA-D and a 27 percent of those at-risk for FAP. On the one hand these participants experienced intrusive thoughts and feelings about the disorder. On the other hand they tried to distract themselves from feelings and situations related to the disorder. This pattern is more often accompanied by anxiety, depressive feelings and psychological complaints than in the low intrusion/low avoidance stress pattern (group IV).

Fifty-two percent of the participants at-risk for FAP, 38 percent of those at-risk for HBOC, a 24 percent of those at-risk for HD and 10 percent of those at-risk for HCHWA-D reported low intrusion/low avoidance (group IV). They have little or no psychological complaints. It could be argued that group IV is less distressed than the participants in group I.

Participants in group II (n=8) report high intrusion and low avoidance which has been described as "undercontrolled intrusive state" [16]. These participants appear not to be distracting themselves from the impending life event, but have intrusive thoughts and feelings. However, this smaller group was less depressed than those in group I (high intrusion/high avoidance). Maybe this group did not need to distract themselves from the intrusive thoughts and feelings, which could thus be thought of as "work of worrying" [49]. Further research is needed to study the (mal)adaptive characteristics of this stress pattern for participants of genetic testing programs.

Participants in group III ($n = 14$) had low intrusion and high avoidance scores (frozen in avoidant states) [16]. Two-thirds of the group were men (in the other three groups men were in the minority: Table 3). In literature on predictive testing for HD it has been suggested that men are less able to face their fear and to acknowledge the implications of testing. Moreover, they may have a greater capacity to deny their feelings [65, 66]. Participants in this group were also more often married/living together, compared with participants in the other three groups. Those with a family seem to have more difficulties in facing the impact of the hereditary disease on their own and subsequently on their children's life [32, 50, 67].

Coherence of the interview text, four patterns of reported stress and anxiety, depression and hopelessness.

Clinical observations tell us that families with hereditary disorders are affected emotionally by the developments in molecular genetics [26, 44, 45, 50, 66]. Questionnaire results, however, indicate that participants are doing reasonably well (e.g. low distress scores). This contradiction stimulated us to compare questionnaire results with the coherence score of the interview text. Based on the findings in the Adult Attachment Interviews (AAI) studies we considered the coherence score in the present study as a measure of the defensiveness of the individual [52, 54, 68, 69]. Participants who were able to discuss the topics, reflecting upon their emotions, feelings and ideas without getting carried away or dismissing/minimizing the subject, received relatively high scores for coherence, whereas the others received relatively low coherence scores.

We found, that the participants who reported high intrusion/high avoidance (group I) were significantly more coherent in describing the implications of the predictive test during the interview than those who reported low intrusion/low avoidance (group IV). On average, the group reporting less stress on the questionnaires was less coherent. This finding leads us to speculate that those less coherent in their interview, but at the same time reporting little stress, used defensive denial [48] "to maintain an illusion of not being stressed".

In the AAI studies a low coherence score is associated either with dismissal of attachment related issues (the discourse appears to be aimed at minimizing the importance of attachment-related experiences, the responses are superficially collaborative, but internal contradictions render them apparently untruthful [54]) or with preoccupation with attachment (e.g. the interview indicates an excessive, confused, and either angry or passive preoccupation, with attachment figures or attachment-related events, as shown in violations of manner, relevance and quality [53, 54]). It has

been found that those who are "dismissing" of attachment have developed strategies for minimizing stress [52, 69], whereas those who are "preoccupied" with attachment do not minimize stress, but exaggerate or maximize stress [52]. Dismissing subjects report less general distress than others, but were observed to be more distressed [68]. The question is, whether such a division between a dismissing (denial) and a preoccupied (lack of denial) could be observed in our study group, we therefore added an exploratory analysis. In the present sample of participants with a relatively low coherence score ($n=38$) we were able to differentiate those with a "dismissing" strategy ($n=23$) from those with a "preoccupied" strategy ($n=15$), with regard to intrusion, avoidance, anxiety, depression, and psychological complaints (Main-Whitney nonparametric test for two independent samples). The significance level was set at 0.05, one-sided. Marginally significant differences between those with a "dismissing" strategy and those with a "preoccupied" strategy for intrusion ($p<.08$), avoidance ($p<.06$), depression ($p<.08$) and hopelessness ($p<.06$) were found. Those with a "dismissing" strategy tend to report less intrusion and avoidance than those with a "preoccupied" strategy.

The findings in the present study are concordant with research conducted in the area of attachment just mentioned [52, 54, 68, 69]. The findings seem to point towards an interesting avenue for further research. In our view it is very well possible that the standard interpretation of questionnaire results measuring distress may conceal a subgroup of individuals who deny their distress. This is in concordance with the results from the study done by Shedler et al. [48]. It needs to be further investigated though, if, in relation to preparing oneself for the possible test result of predictive DNA testing, "defensive denial" may lead to a failure of doing "work of worrying" [49]. This might prevent the participant to start working through their anxiety and grief, and to make plans that might enable him/her to cope more effectively with the subsequent crisis.

Conclusions

Concerning the impending event, getting to know whether one is a gene carrier or not, a person may very well be anxious, he/she may show his/her stress while this represents finding a way to deal with the provoked tension. Some however, may need to feel in control and cannot allow themselves to feel the anxiety and worries. So far it has been "good clinical practice" to treat those, who need to minimize the implications of the event, carefully in order not to heighten their fears and to support them when necessary. This study stresses the importance of precise follow up as it is not known yet, what the long term effects may be of using denial a coping style for participants of a genetic testing program.

Areas for further study

The relatively small numbers in some groups of this first comparative study of predictive testing in two centres, represent a limitation, especially because not all participants could/wanted to take part in the interview. The higher number of participants at-risk for FAP and HBOC opting against the psychological protocol reflect a possible specific attitude in this group. They were determined to take the test without further psychological assessment, since they experienced their choice as a purely medical decision. The HBOC group consisted of some individuals together with the first three Dutch families that could be tested. This might introduce some bias by potential extensive attention from the researchers [18, 33].

Furthermore, in future follow-up research on predictive testing for late onset genetic disorders, the IES as measure for psychological stress may be standardized for specific groups with high personal risk to develop a specific disease.

To interpret questionnaire results, a judgment of psychological defenses is necessary. In further studies on psychological implications of presymptomatic DNA testing attention should be paid to this. The promising experiences with the classification system developed by Main and Goldwyn [52] shows that this might be a very fruitful instrument to obtain a such a judgment in a standardized way [68, 70, 71]. However, to gain insight into the implications of denial behaviour upon the adaptation to a genetic test result a sensitive independent measure of mal-adaptation ought to be included, for example the Health Sickness Rating Scale (HSRS) [72, 73], an observer-rating scale of psychological functioning with elaborately defined scale points.

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CHAPTER 9

DISCUSSION AND CONCLUSIONS

1. Introduction

Nowadays, people are confronted with new options for decisions about their future. Individuals may now ask themselves: "Do I want to know or not, whether I will develop the same disease as others in my family?" The developments in genetics, on their way to understanding and later possibly curing genetic diseases, already offer the possibility of predictive genetic testing. Knowing their family history, healthy individuals struggle with the fear of "I might become ill" and question "Do I want to know or not?". This idea becomes even more concrete when the experiences with disease and death in affected relatives are more profound [1].

In Huntington's disease, the affected parent may have psychiatric symptoms and child abuse is not uncommon. In the cancer syndromes, the painful disease and death of multiple relatives can be devastating. To cope with the associated insecurities, families develop their own strategies such as denial or information seeking. To get a feeling of control some families preselect the next patient [2]. In patient preselection the next "patient" role is assigned to an, as yet, healthy relative and the other relatives behave in the full belief of this assignment. The possibility of genetic studies may greatly disturb the family homeostasis, i.e. the balance achieved to deal with the threat of the disease. All relatives have to face the fact that certainty can be within reach and that testing may lead to knowledge in the near future.

Psychological aspects of genetic diagnosis of late onset disease have been addressed by many groups since the development of presymptomatic testing [3] and both the EEC and HUGO (Human Genome Project) have started ethical/legal/social implications committees to optimize the benefits of this new knowledge for human welfare [4]. The Ethical, Legal and Social Implications (ELSI) committee of HUGO provides policy options and programs capable of addressing the various implications of the new genetics [5]. Confidentiality of data, informed consent, freedom of constraint, and selection in insurance are themes addressed.

The desire for knowledge is shared by researchers, health-care providers, health professionals, and the public [6]. Motivation for testing may differ widely depending on the individual's viewpoint and that of society. Medical treatment options, obtaining certainty, the moral dilemmas to balance the wish for offspring with the risk of passing on a disease, are individual motives. Health- and life insurance companies and employers may see testing as a method for selection. More generally, the mere availability of the test may induce its utilisation ("technological imperative").

Enthusiasm for predictive testing by those at-risk, though, has been less than previously expected by risk carriers when testing was not yet feasible [7-11]. As described in detail in chapter 1, a test result for HD may lead to both beneficial and

burdensome consequences for those who took the test [12-26]. The knowledge obtained by predictive testing seems to provide certainty but also leaves many questions unanswered.

We performed a comparative psychological follow-up study to investigate whether, and to what extent, the experiences with HD can serve as a useful paradigm for studies on predictive DNA testing for other late onset disorders, as has already been suggested [27, 28]. We addressed the implications for both the individual and the family (see Table 1).

In the following sections all questions, and the answers found in this study, will be discussed and our findings will be compared with those of other studies. Subsequently, the areas needing further attention will be addressed. This is followed by the implications for further research, and the main conclusions.

Table 1. Questions addressed in the present comparative study (p 26 of the introduction)

- 1) Are the concepts on the effects of predictive testing for HD equally valid in testing for other late onset disorders?
 - a) Do stress responses differ among those tested for dissimilar late onset disorders?
 - b) Can we identify factors contributing to (mal)adjustment after the test result?
 - c) Which interaction patterns can be observed in families that broaden our understanding of the impact of predictive testing on a family?
- 2) What are the contributions from a comparative psychological follow-up study of neurological disorders and cancer syndromes, to the improvement of guidelines for genetic counselling, psychological support and interventions?

2. The questions of the present study

2.1.1. Are the concepts on the effects of predictive testing for HD equally valid in testing for other late onset disorders?

To answer this we address stress response patterns, the prediction of mal-adaptation and family interaction.

2.1.1a Do stress responses differ among those tested for dissimilar late onset disorders?

Prior to testing

Stress responses were compared in four patient groups at-risk and their partners: namely for HD, HCHWA-D, FAP and HBOC. At pre-test, distress (intrusion, avoidance,

anxiety, depression and psychological complaints) differed among the four groups, both for risk carriers and the partners (chapters 4 and 8). Participants at-risk (and their partners) for the neurodegenerative disorders tended to be more distressed than those at-risk for the cancer syndromes. Individual levels of distress were, however, determined by the person's experiences with the disease and its impact on his/her life, irrespective of the type of disorder. Profound memories of affected relatives and intense impact of the disorder on personal life were important distressing factors.

The course of distress

The course of the stress responses, i.e. the increase and decrease of stress (chapter 5) was similar for those at-risk for HD, FAP or HBOC, from pre-test to six months post-test. Participants at risk for HD reported more intrusion and avoidance from pre-test up to six months post-test as compared to those tested for FAP or HBOC.

Over all, distress levels did not *increase* for all gene carriers and noncarriers. This is concordant with the literature on HD [14, 18, 24, 25, 29-31], HBOC [11, 32] and FAP [33, 34]. However, in contrast to earlier studies on HD [14, 18, 24, 25, 29-31] gene carriers showed no *decrease* in distress. This may be explained by group differences, such as more participants in the present study who recently learned about their risk, and more who earlier refrained from testing (see chapter 5).

Conclusion

Stress responses over time are similar for those tested for different late onset disorders. Some participants, however, report more stress than others. On an individual level, we found this to be associated with the previous personal experiences with the disease and its impact on one's life, irrespective of the type of disorder. The *psychological* implications of predictive testing may be estimated largely from the coping of those especially distressed.

2.1.1b. Can we identify factors contributing to (mal)adjustment after the test result?

Focusing on (mal)adjustment or on distress?

When predictive testing was first possible for HD, maladjustments such as suicide, psychiatric admission, etc. were feared in identified gene carriers [35]. In early studies on predictive testing, maladjustment received much attention [29, 30, 36]. The feared catastrophic post-test events in HD have only been incidentally observed, as confirmed by the Vancouver Group in a recent world-wide survey. A total of 107 centres from 20 countries provided data on 5781 tested individuals. Most catastrophic events occurred within one year after the test result, 5 individuals committed suicide and 16 attempted suicide [26]. In general, suicide is more frequent in families affected by HD than in the general US population [37]. It is questionable whether the catastrophic events are a

direct consequence of the test, or whether this population is in general more prone to suicide. However, to designate predictive testing for HD as a "success story" [38] is an underestimation of the complicated psychological process that the majority of tested individuals, their partners, and their relatives have to go through, as was emphasized by workers from the first hour [39-41].

In general no elevated levels of distress, compared to a "normal" population, have been found in people at-risk for the cancer syndromes. In the present study, at six months post-test, carriers and noncarriers for HD, FAP or HBOC had no increased levels of distress (chapter 5). However, more subtle distress symptoms that can compromise quality of life might be present. Moreover, to better identify the psychological implications of predictive testing, studies could shift their focus from "catastrophic maladaptive reactions" to the dynamics of stress responses in participating and nonparticipating groups.

Identification of factors contributing to (di)stress after the test

The old notion that a "favourable" result of **not** being a gene carrier will result in relief, and that the "unfavourable" result of being a gene carrier will give distress, is a misrepresentation of the complex reality (chapter 6). The test outcome was not directly associated with post-test distress, but rather with psychological and biographical disease-related factors. Pre-test depression was strongly associated with post-test distress. However, pre-test anxiety is associated with *less* post-test distress, i.e. less intrusive thoughts. Post-test intrusion is also associated with gender (i.e. being a woman) and having children. Pre-test avoidance behaviour and having multiple persons available for support is associated with more avoidance behaviour post-test.

In the present study, many noncarriers were informed that their depressive emotional feelings were a normal post-test reaction [18, 42] and also that the "doom" of the disease might have interfered with handling emotions in pre- and post-test contacts with affected relatives. Such information may have set in motion the working through of a "favourable" test result. This might explain the more frequent reporting of depressed feelings and distress in noncarriers in the present study as compared to the study of Tibben et al. [43].

Being at-risk for Hereditary Breast and Ovarian Cancer predicting less post-test stress

That individuals at-risk for HBOC report less post-test stress than the other groups at-risk, contradicts our clinical observations and therefore merits further attention. Chapter 6 discusses various explanations, ranging from circumstantial to more psychological factors. Here we discuss some of the impressions obtained during the study.

The need to "be strong", in order to face all the (medical) implications of testing was strongest in those testing for HBOC. For identified gene carriers, post-test health related

decisions differ between HD, FAP, or HBOC. Those at-risk for HD, when proven to be a gene carrier, may only learn to live with the knowledge and its implications for themselves, their partner and their family. Carriers of the APC gene (causing FAP) may continue regular screening and opt in due time for surgery to prevent colonic carcinoma, which has a proven effectiveness. Women carrying the BRCA1 mutations need to make decisions about far-reaching surgery (prophylactic mastectomy and/or ovariectomy), which is highly burdensome because of the mutilating nature and uncertainty about definite improved survival. To decide for preventive surgery may help to give a feeling of control, but generally the focus has only been on what can be gained. This can be considered another reason why BRCA1 gene carriers report little distress: otherwise they become flooded by emotions and are unable to make important decisions.

Identified noncarriers of the BRCA1 gene, in the present study, were confronted with unresolved feelings of grief and loss, because multiple relatives had been affected and died. Although not having to face prophylactic surgery may generate relief, feelings of guilt, worries about other relatives, and sorrow about the past experiences with the disease were profoundly present (chapters 3a, 3b and 7).

Moreover, participants in the early stages of familial cancer screening who *also* enrolled themselves in the psychological follow-up study might have a specific combination of psychological resources, by being able to experience the stresses and demands of presymptomatic testing, and having the ability to express these experiences. Being able to do this, demands a rather stringent personal "containment" policy that can match the multitude of pre-test and post-test distresses.

Conclusions

Predicting post-test stress gives insight into relevant factors but also raises questions. Studies conflict about the distressing effect of being identified as a gene carrier or not. Greater uniformity in standards utilised is needed to obtain comparable results. The psychological factors contributing to post-test distress became better elucidated in the present study, but the dynamics of coping with distress needs further analysis, as does the need to identify participants especially vulnerable to post-test distress.

2.1.1c. Interaction patterns in families confronted with predictive testing

In a family with HBOC we described two key roles for relatives: *the messenger* (the bringer of the news) and *the first utiliser* of the test (the example for the family). The observation can be equally relevant for families becoming informed about other late onset genetic disorders. Similar patterns were observed in newly diagnosed families with Huntington's disease [44] and presenile dementia [41].

Different roles

In a family (chapter 3b) we observed the role of *messenger of the news*. The "messenger" informed the relatives about the hereditary character of cancer in the family. The fear provoked by this message was vented on the messenger. Ego strength and the coping capacities needed by "the one who dares to ask and to bring the information" were easily overestimated both by the messenger, the relatives and the medical profession. This left the messenger without the necessary support.

Green et al. [45] studied 46 women at-risk for HBOC, and their balancing between the obligations of passing on information and that of preventing alarm. Family communication in both obtaining, and giving information, was found to be impeded by adoption, divorce, remarriage, family rifts and large age gaps between siblings [45]. It is important to help the "messenger" with his/her difficult role, to acknowledge the emotional ramifications and offer additional support when needed.

Moreover, informing relatives is especially problematic in families unfamiliar with the genetic nature of a disease and/or with loose family ties, and may pose dilemmas concerning privacy and confidentiality [46]. Often the index patient (the one with the first appointment at the department of Clinical Genetics), or *messenger*, informs the relatives about the possibility of predictive testing [45, 47]. As also found in the fragile X syndrome, the pattern of loose-tied relations between relatives, the communication styles and family conflicts contribute to poor transmission of the information [48]. In the case of the fragile X syndrome McConkie-Russel et al. [49] gave some useful guidelines to facilitate the disclosure of information, such as informing different branches of the family by different relatives. If the genetic counsellor takes the initiative to inform relatives at risk, more individuals would be able to consider genetic counselling and DNA testing. However, this approach bypasses the principle of medical confidentiality which might be solved by the genetic counsellor obtaining permission to contact the relatives [48]. Whether such a strategy could help the *messengers of the news* in families with autosomal dominant late onset disorders with their difficult responsibility towards their relatives needs further investigation.

Another role was the *first utilizer* of the new options: the predictive DNA test and preventive surgery. The individual is under pressure to prove the benefits for himself/herself as well as relatives. Being a "good" example may reduce the fear in relatives. This implied responsibility towards relatives can be a great burden. In counselling, the choice for the benefits of the individual needs separate attention from the meaning of the choice for relatives. This to enable the first utilizer to perceive the unexpected burdens of the role of being an example in the family.

The counsellor may inadvertently become included in the specific coping style of the

family, an may feel responsible for family members and act accordingly. The challenge is to find a balance between sensitive understanding on the one hand and over-involvement (leading to entanglement) on the other. The relation with the *messenger of the news* may also be two-sided: on the one hand the counsellor may serve a useful purpose in alerting and encouraging participation; on the other hand, care is needed in how far a messenger is to be stimulated in this role. The recognition of feelings of helplessness in themselves, by the counsellors and the acceptance of the restraints of testing may well help in providing participants the freedom of choice needed in such complicated matters [50-52].

Focus of attention

HBOC is a disease primarily affecting women, therefore, they are the focus of attention for most professionals involved [53] and to the men in the family (chapter 7). However, men can be gene carriers, with a small associated risk for other cancers. They might be deeply affected by the at-risk status of mothers, sisters and daughters. The options and implications of testing males at-risk, as was experienced in our group, deserve similar attention as testing females.

Conclusions

Family dynamics play a major role in the way individuals at-risk cope with the threat of an autosomal dominant late onset disease [2], in the motivation for taking the test and their adaptation to its outcome [42]. The implications of testing for the whole family will have its effect on the individual. All genetic counselling of an individual, however, will have effects on relatives of the proband, whether these effects were intended or not. Informing families about the genetics of a disease, requires awareness of the roles taken up subsequently by different relatives and their influence on the counselling process.

2.1.2. General conclusions on the validity of the concepts on presymptomatic testing for HD in testing for other late onset disorders

The present study allows to conclude that the psychological reactions (see Table 2) to predictive testing follow similar mechanisms for participants at-risk for different genetic disorders. The psychological dynamics may be similar but the implications of testing differ for the participants at-risk for the specific disorders.

This general validity will show different utilities of coping strategies in the various diseases. For example, denial may help a carrier of the HD gene to live and even enjoy life from day to day, but denial can be maladaptive for women carrying the BRCA1 gene as it may keep her from regular screening or surgery.

Table 2. The concepts on predictive testing as developed during studies on Huntington's disease (page 24-25 of the introduction).

- 1) Actual uptake of predictive testing has been lower than initially expected by risk carriers.
 - 2) Reasons for testing were to end uncertainty, to obtain some control over the future, and to inform offspring and other relatives.
 - 3) Main reason against testing was the fear of inability to cope with a high-risk result.
 - 4) Reactions to testing have been more complex than expected; however, test-related psychiatric morbidity feared as once expected by health-care professionals, has not been profound.
 - 5) Gene carriers cope reasonably well by restricting themselves to live by the day, while the partners are much more worried about the future.
 - 6) Noncarriers have difficulties to develop a new life perspective and often feel guilty. The numbed emotions and the lack of relief are difficult to understand for themselves, their partners and others in their immediate social environment.
 - 7) Predictive testing may have an unsettling effect on the partner relationship and the family.
 - 8) Reaction to the test result is largely determined by the individual's experience with the disease, the meaning assigned to it by the family (e.g. patient preselection, secrecy, denial, etc.) and also by the meaning given by the medical profession.
-

2.2. What lessons provide the comparative psychological follow-up study of neurological disorders and cancer syndromes, for the improvement of genetic counselling, presymptomatic testing and psychological support?

The psychological concepts on predictive testing as developed during studies on HD are valid in testing for other late onset disorders, including the necessity to pay attention to the perception of the participant and his/her family of the test and its implications for them. Our observations in a family and in the study predicting distress resulted in the following practical guidelines for clinical genetics (see Tables 3 and 4).

Interpretation of questionnaire results: "looking bad" or "work of worrying"

Another important theme of this thesis is the interpretation of questionnaire results. High scores on questionnaires measuring distress are generally considered as the result of being distressed and inadequate functioning. However, high scores may also reflect the person's psychological anticipation to the threatening event (work of worrying) [54] when knowing that the event (the test outcome) is going to occur. "Work of worrying" might be useful in preparation for the genetic test result. Or it may reflect a reaction to the event. A certain caution in the interpretation of "doing bad" when having higher scores is warranted, as the distress may also reflect the working through process which can be considered beneficial and adaptive instead of maladaptive.

Table 3 Presymptomatic testing of multiple relatives and maintaining confidentiality (chapter 3b).

1. Attention is focused on the needs of the individual who has the appointment. Counsellors should be aware not to be seduced into discussing the implications of the genetic status of family members (such as whether a family member made the right decision, etc.). However, the impact of the ongoing events in the family on the particular participants may be addressed.
2. Although part of a family, each member is, as far as possible, counselled as an individual case. The individual at-risk may have heard all kinds of information from family members, or even no information at all. It is important that the knowledge of DNA and predictive testing is thoroughly checked and completed when needed.
3. Taking the test, or not, should be an enterprise of the person at-risk and the respective partner and not a family enterprise; however, the decision will be influenced by the events taking place in the family.
4. The individual taking the test is the only one to whom the test result will be disclosed; the test result can not be transmitted via another relative¹¹. He or she is free to postpone the appointment until the last second, when necessary.
5. Concerning the test result, it is very important to discuss whether they want to be with relatives at the department of Clinical Genetics, or not. When various relatives want to receive their test result at the same time, multiple rooms should be available i.e. a separate room for each of them to receive their own test result. After everybody has received his/her own test result they can meet together if they so wish.
If someone does not want other family members to know that he/she is taking the test, an appointment is scheduled distinctly apart from that of other family members.

¹¹ This not taking into consideration the discussion about those at 25% risk [55].

Table 4. Predicting post-test distress, suggestions for everyday practice (chapter 6).

1. Participants tested for HBOC were less distressed post-test. The psychological dynamics leading individual to present him/herself as not distressed need attention. Either one is indeed not distressed, or one can only cope by denial and minimisation. During a face to face contact one may be able to assess whether a participant is able to face the implications of testing. When a participant needs all his/her psychological strength to diminish the threat of testing (e.g. by denial and minimisation), this way of coping should be respected. It is helpful not to force, but to tell that the fears can be discussed at a later stage in time.
2. Women tend to become more distressed (intrusive thoughts and feelings and avoidance behaviour) post-test than men. Besides the general tendency of women to report more emotions, this is often linked to their roles in caretaking and childbearing. Adequate attention is needed when a woman wants to have (more) children. Feelings about existing children and and their risk for the genetic disorder also need attention. Also, care for the family of origin and the affected relatives should be addressed.

3. Having children gives additional stress to testing. Time is needed to discuss the possible implications of testing for the children. "Are the parents going to tell the test result to the children?, When should this be done, How could this be done? What do the children know already, do they want to know? If the children want to know, but the parent does not, should the parent continue testing?", etc.

4. Helping the participant to see whether they have additional sources for support, is useful, such as religion, which can provide an anchor when the purpose of life may become be less clear.

5. Having several persons for support and involved with the well-being of the participant led to post-test avoidance behaviour. It is helpfull to assess, with the individual, whether friends and relatives are experienced as really supportive or rather curiosity/sensation seeking? It can help the participant to discuss, prior to testing, which relatives/others will be allowed to know about the test and the result. People differ in what they need at such a moment; and thinking about it prior to the test, however, may help them to create the support needed.

6. Intrusion prior to the test was associated with post-test intrusion. Participants with such intrusive thoughts and feelings, may be helped by assessing whether they are preoccupied with the subject as a measure of preparation, or whether they are becoming overwhelmed. The first option is a realistic way of preparation and eventual adaptation. Becoming overwhelmed, however, indicates a need for additional support to enable them to cope with the impending events.

7. Also, avoidance behaviour prior to the test was associated with post-test avoidance behaviour. This can be explained in several ways. A participant may seek distraction after a period of active involvement with the disorder, or because of inability to face the implications of testing. In the latter situation additional support seems indicated.

8. Depressed participants tend to become more distressed post-test, as reflected by avoidance of the intrusive thoughts and feelings about the disorder. Counsellors should be able to recognize depression. During pre-test counselling of a depressed participant, the option of delaying the test may be discussed when it seems to burdensome at that time. For others the test may function as the start for the working through of emotions blocked by previous continuing indecisiveness about the test and one's future. The best strategy can only be individualised, and enough time should be taken to find this out.

9. Anxious participants suffer less from intrusive thoughts and feelings after the test. Pre-test anxiety is easy to understand. The different implications of either test result will usually be associated with a certain level of anxiety, and this may help post-test adaptation. Some participants, however, may be too anxious to allow their emotions to be felt. This may prevent them from thinking about the implications of either test result, which may result in inadequate adaptation in the long term. Counsellors should be trained to recognize the over-anxious in order to offer them additional support.

Interpretation of questionnaire results: "looking good" or "defensive denial"

Shedler et al. [56] distinguished, between those who "look good" on mental health scales, the psychologically healthy subgroup and the psychologically distressed subgroup who maintained "an illusion of mental health" through defensive denial of psychological distress.

In chapter 8 we compared questionnaire results with a measure of defensiveness established during an interview. Defensiveness was scored by the coherence of the interview text, representing the ability to freely discuss the test and its implications, without getting carried away or dismissing/minimising the subject, irrespective of potential negative or positive emotions provoked by the test (for a full description see chapters 2 and 8).

Those who told us on the questionnaires that they were *not* distressed, performed *less* well in discussing the predictive test without getting carried away or dismissing/minimising the subject (lower distress, lower coherence). Those who did tell us on the questionnaires that they were distressed were better able to talk about the test and its implications, without getting carried away or dismissing/minimising the subject (higher distress, higher coherence).

We also studied the association of less coherent behaviour (interview) and the outcome of questionnaires. The group with low coherence scores was subdivided into a group who dismissed and minimised the implications of testing (a dismissing attitude), and those who got carried away when describing the test (a preoccupied attitude). People who during the interview were *unable* to give a description of the test and its implications (dismissing attitude), tend to, on questionnaires, give the impression that they are *not* distressed. Participants who got carried away during the interview (preoccupied attitude), did give a distressed impression on the questionnaires. This is in line with the reports that those with a "dismissing attitude" tend to minimise distress, or those with a "preoccupied attitude" tend to maximize distress [57-60].

The participants with a dismissing attitude might indeed be denying their distress in order to "maintain an illusion of not being distressed" which is concordant with the results of Shedler et al. [56]. The effects of denial on long-term adaptation need further study. On the short term, denial is viewed as an adaptive coping strategy for those at-risk for HD as they are not yet ill, and they can not take any health-related actions [14, 22]. For those disorders with treatment options, denial is regarded to be less adaptive [61]. It is expected that long-term adaptation may be less favourable, especially when the full effect of any prophylactic surgery becomes noted. To get a full picture of the implications of predictive testing we need to learn from those who are at-risk but do not participate in genetic testing or in the psychological follow-up.

Conclusions

The main contributions of this comparative study to the improvement of guidelines for genetic counselling, psychological support and interventions are: a) sufficient attention should be paid to the impact of previous experiences with the specific disorder on participants of genetic testing (chapter 4); b) sufficient attention should be paid to the impact of predictive testing on a family and their way of coping with the threat of the disease (chapters 3a, 3b and 7); and c) the need for enhanced understanding and interpretation of high and low distress on questionnaires (chapter 8).

Conclusions a) and b) have been discussed in section 2 of this chapter: "Questions of the present study". Concerning the interpretation of distress, we conclude that counsellors should be able to identify and respect the chosen strategy of coping with threat and should remember that participants with higher distress scores may be actively dealing with the problem, while people with low distress scores might (as yet) be unable to face the problems. So far, it has been "good clinical practice" to treat those who need to minimize the implications of the event carefully in order not to heighten their fears and to support them when necessary. As long as we do not know the consequences of denial on the long-term adaptation to a test result, we think that this "good clinical practice" ought to be continued.

3. Areas of further attention

3.1. Within the scope of this study

3.1.1. Participants

At different stages during this study the participants either refused to cooperate further or withdrew from the psychological follow-up study. The exact numbers of participants at the different stages of the study (before testing, one week or six months after testing) are given in chapter 2. We describe here some qualitative findings on those not wanting to participate in the psychological follow-up study while opting for predictive testing.

The number of individuals who were asked to participate in the psychological follow-up study and who did not want to, was twice as high among those at-risk for FAP, than among those at-risk for HD or HBOC. The psychological study was introduced as a scientific investigation necessary for measuring the need for support and to enhance understanding on the psychological implications of predictive testing. Many participants, however, considered the offered contact with a psychologist as additional support which they felt as unnecessary.

The impression was obtained that persons at-risk for FAP experienced the clinical genetic centre as just a stop on their way to the surgeon. They are often familiar with

bowel screening and are referred by their gastroenterologist or surgeon, to know if screening needs to be continued. The genetic test is considered less invasive than a colonoscopy, and gives apparent full certainty about the need for further screening, surgery, etc.

Clinical geneticists are more often involved with families at-risk for HBOC. Most families will, at some stage, have been referred for family studies (including family history, analysis of medical records, review of histology, linkage and mutation analysis). In other families, the department of Clinical Oncology, or other related institutions, participated in the family work-up. Some participants did want to make use of the opportunity to discuss their emotions provoked by all the research and additional uncertainty and participated in the psychological follow-up study, others only wanted the genetic test and did not want to focus on the additional emotions.

For most people at risk for HD the clinical genetic centre became the place where, since 1987, risk differentiation became possible. Test participants often found it comforting to discuss the choices and emotions with someone familiar with the psychological implications of testing. Furthermore, testing was often considered as a method to increase control over one's life.

The motives for withdrawal from the psychological follow-up study have been described in chapter 5. In all three disorders the dropouts are probably those unable to discuss their emotions at that particular moment, so the more extreme scores for distress might be missing. The resulting groups are relatively small which makes generalization difficult. However, the results presented, in combination with the qualitative data, do provoke intriguing hypotheses for further research.

One of the questions which can be raised is, what are the motives of those who do not opt for predictive testing while familiar with its possibility. It will be difficult to obtain a representative study population because of the large dropout to be expected in such a study. Risk carriers tested for HD so far, are considered a self-selection believing themselves to be able to handle "bad news" and having considerable mental resources [12, 13, 15]. Those not taking the test had a significantly more pessimistic outlook on themselves and their futures [62]. The disease may be perceived as a topic which is too threatening to address. It will be a great challenge for the future to find a way to establish contact with those not wanting predictive testing and to assess the distress they are under provoked by the disorder and the availability of the test.

3.1.2. Partners

Partners, too, need further attention. In contrast to other studies, they were included from the onset of the present study, as reported in chapter 4. We describe here some

qualitative findings on the implications of testing for the partners.

Prior to testing, it was found that the distress experienced by the partners is determined by experience with the disorder so far (chapter 4). During testing most attention is focused on the person at-risk. The partner often wants to be strong for the person at-risk who is going through such a "rough time". This conflict of wanting to be strong and, on the other hand, having fears about the future is difficult for all partners but may be especially difficult for the partners of the women at-risk for HBOC. Prophylactic surgery has far-reaching consequences for the intimate relationship. Some couples find it difficult to discuss this, others stressed a need for additional support. Further research is needed to study the long-term implications of prophylactic surgery on the partner relation.

When an individual is proven to be a gene carrier the partner may grieve about a lost future, may want to anticipate this future, while the gene carrier tries to live from day to day and tries to keep the illness far away. When the result has been "favourable" it is often difficult for the partner to understand the numbed emotions. Most couples were relieved when the different implications of the test result for the two of them were discussed. Further research on the dynamics of post-test adaptation of couple is clearly indicated.

3.1.3. Comparing interviews with questionnaires

From the beginning of the present study in 1992, we tried to compare questionnaire results with clinical judgement from interviews. In 1993, Shedler et al. [56] compared self-report questionnaires, clinical judgement and physiological measures of distress. We compared questionnaires with the coherence score obtained from interviews, as a measure of defense. In the future an additional objective measure of distress as used by Shedler et al. (56) should be included. We hypothesize that those who minimise or dismiss the subject of the test in the interview actually do the same on the questionnaires. They seem not up to discussing the test and its implications, wanting to finish the topic as soon as possible and avoid acknowledging any distressing aspects of the disorder on the questionnaires. This was labelled denial; however, that which is denied should also be measured. This interesting avenue merits following up, however, with a psychiatric evaluation in order to determine whether those using defensive denial are actually distressed or not.

3.1.4. Case study

Kessler [63] stimulated HD research groups to publish case reports detailed enough to offer a basis for conclusions, also by those with differing theoretical orientations.

Objections against case reports may be their lack of generalizability. However, accurate observations of similar phenomena in single cases of different diseases, as we did in newly diagnosed families with Huntington's disease [44] and families at-risk for presenile dementia [64], remain important.

3.1.5. Research and clinical practice

A potential conflict of interest could occur when a researcher is involved in clinical practice. The families at risk for HBOC in the present study have participated both in the research phase of linkage analysis and in the actual testing protocol. This might introduce some bias by potential extensive attention from the researchers [25, 65]. More important is to clearly inform families about the options of participation in actual testing, especially if part of the family participated earlier in research for linkage. Some participants of the research phase of linkage studies were overwhelmed by the possibilities provided by the research results. Others expected immediate information about their individual risks.

3.1.6. Focus of the study

Did the study focus on that which is important for the participants? For the non-treatable disorders testing gives no options for treatment. In case of the cancer syndromes the screening and/or preventive options are a direct consequence of the test. The psychological implications of the screening and/or preventive options need further study to gain a full understanding of predictive testing for cancer syndromes.

So far, the participants in predictive testing showed unexpected resilience. Gene carriers seem to cope rather well using denial as a coping strategy [14, 22]. This is considered an adequate coping strategy, at least in the short term. The long-term effects (5 to 10 years after testing) and the dynamics involved should be observed in order to be able to judge whether predictive testing does have far-reaching emotional implications or whether, in general, individuals are resilient enough to cope with this knowledge about their own future, the future of their potential offspring and their kinship.

3.2. Beyond the scope of this study

Although beyond the scope of the present study, we wanted to address the following subjects to broaden the view on the implications of predictive testing as a psychosocial issue.

3.2.1. Prenatal testing

The choice for couples at-risk for HD for offspring is often very problematic. Also because of the late onset of symptoms, the strength of the wish for offspring, and the problem to differentiate the fate of the future child from the fate of HD in themselves or a parent. Although some find selective abortion difficult to justify, it is considered as a matter of personal choice [66]. The uptake of prenatal testing is lower than expected from the previous surveys, only 18% of eligible couples requested it in Canada [67].

In a similar line, prenatal testing for HBOC will probably be asked by only a minority of parents [68]. Psychological follow-up after prenatal testing has not been described in relation to other late onset disorders.

3.2.2. Children and predictive testing

Until 1994 committees examining the ethics of genetic testing [69, 70] have stated that "children should generally be tested only for genetic disorders for which there exists an effective curative or preventive treatment that must be instituted early in life to achieve maximum benefit". In an overview of screening for cancer susceptibility in children, it was stressed that in view of the flood of novel cancer-predisposing genes, evaluation of the psychological impact of predictive testing on children becomes more important [71]. In 1995 the American Society of Human Genetics and the American College of Medical Genetics indicated that the interest of the child *and* of their parents and families should be carefully weighed [72]. Counsellors will be required to engage individual families in comprehensive discussion of the medical, psychosocial and reproductive issues and to provide them with specific information and recommendations about genetic testing. Also paediatric nurses who take care of children with cancer need to become familiar with this new genetic testing, the treatment opportunities, and the ways that may maximise benefit and minimise potential harm to children and their families [73]. The debate as to whether predictive testing should be available for children remains unfinished [74-77].

Prior to starting widespread predictive testing of children, research is needed on the impact of testing, or of not testing, on the child and the family. Health-care delivery models need to be developed including child and adult psychologists or psychiatrists for counselling of the parents and the children. Long-term follow-up is needed on the consequences of counselling and on informing the children, if necessary, at a later appropriate age. Above all, continuing systematic investigation on the clinical effects of cancer-predisposing genes in childhood and the optimal time for prevention and intervention is essential [78, 79].

An interesting recent case description of two sisters, 2 and 4 years old, whose

parents requested their testing for FAP is relevant [80]. The parents felt it as their responsibility to decide about testing, whereas the health professionals should be restricted to giving information. From the pre-test interview up to 15 months later, the parents showed a stable attitude, a normal mood, no regrets about testing, and reported no changes in behaviour towards their children (one carrier and one noncarrier) [80]. This single case study will prompt others to follow, and will prompt long term and systematic studies.

In the future, teaching on genetic aspects of diseases in secondary schools (such as developed in the Netherlands by the Dutch Patient Organisation; VSOP) may help adolescents to understand these issues [81].

3.2.3. The attitude and knowledgeability of medical professionals towards predictive testing, those utilizing the test and the support needed by them.

Predictive testing is finding its place in every medical specialisation. The medical follow-up and counselling of people who receive a genetic test result is a task for both general practitioners and for medical specialists in genetics, oncology, neurology, etc. Although general practitioners and medical specialists are generally willing to play an important role in presymptomatic testing [51, 52, 82, 83], they may underestimate the difficulties in communicating genetic information and the psychosocial effects. A questionnaire study among HD families indicated how the majority saw their general practitioner as the first contact for support and follow-up, whereas the majority of GPs held themselves responsible for that task, even without the appropriate knowledge [52]. A recent American study revealed that patients who underwent genetic tests for FAP often received inadequate counselling and were given incorrectly interpreted results [84]. They stress that physicians should be prepared to offer or refer for genetic counselling if they order genetic tests.

The genetic counselling style of primary physicians is, according to some data, more directive than of genetic professionals. However, a growing involvement in genetics may change the attitudes of primary care physicians [85]. Another study of this same group indicates that knowledge of genetics and genetic testing is increasing among non-genetic health-care workers, but outspoken deficiencies remain [83].

In a postal questionnaire study (1996), Dutch clinicians were asked about experience and attitudes on presymptomatic DNA testing. The total response rate within 6 weeks was 40% and included 153 general practitioners (38% of the GPs addressed), 93 oncologists/surgeons (47%), 79 neurologists (32%), and 47 clinical geneticists (67%). These samples proved to be representative for the general populations of general practitioners, oncologists and neurologists with respect to age

and gender. Clinicians consider DNA testing to be useful but a number of conflicting points appeared: a) there is a positive attitude of clinicians and willingness towards informing, performing testing, and giving follow-up support in their own practice. However, the majority also indicates a self-perceived lack of knowledge and expertise in communicating results of DNA testing; b) most clinicians will inform about predictive testing, but the availability of therapeutic options is an important condition for most of them; c) personal and/or medical-ethical dilemmas are perceived by a majority of clinicians, reflecting the clinicians' struggle with the developing potential of DNA technology.

When any new medical technology is made available to health-care providers, there is often an initial excitement followed by a general increase in uptake, until the most appropriate indication for the new "tool" is determined. Genetic testing is likely to follow a similar learning curve. As with other new technologies, genetic testing will likely result in significant morbidity (and even mortality) simply because we have not discovered all of the medical and psychological implications of disclosure of genetic status [86]. This is not to imply that we should not proceed but, instead, that we proceed with the appropriate level of caution, foresight and willingness to learn from the experiences so far.

4. Summary

4.1. Further research

Areas for further research could include, amongst others, the *psychological implications of doing genetic research*. HD is a disease with which most families were familiar; for the cancer syndromes this is not the case. Especially in families at-risk for HBOC, whole branches may be unaware of the possible hereditary nature of this disease (especially when men have been transferring the gene). It is important to investigate what the implications are of getting to know that a particular disease in the family could be, or is, hereditary. As such, *the motivation of non-participants* ought to be investigated as well. *Long-term follow-up* is needed (5 to 10 years): we know that participants in a predictive testing program seem to cope reasonably well irrespective of their test result; however, we do not know what the implications of testing are on the long term. How do participants react to changes in their situation when confronted with (preventive) surgery, when confronted with a newly diagnosed affected relative, when the next generation is applying for the test, and when they need to inform the children, etc.

An important viewpoint from which further study could be undertaken is *the family perspective*, with additional attention for *the partner and family*

communication. A useful tool to portray possible problems are **case descriptions** of the clinical implications of genetics for individuals, families and health-care workers.

The attitude towards and the knowledge on genetics among health-care providers in general should be assessed. There were knowledge or skills seem to be lacking training should be offered so that the families at-risk may derive optimal benefit from the developments in genetics.

4.1. Conclusions

- 1) In general, when comparing groups, it was found that the groups at-risk for the neurodegenerative disorders report more distress than those at-risk for the cancer syndromes.
- 2) The individual differences in psychological distress between participants at-risk for a particular disorder are larger than the similarities. Experienced distress, on an individual level, was found to be determined by the experiences with the disease and the impact of the disorder on one's life until now.
- 3) Stress responses over time, develop similarly for those tested for different late onset disorders.
- 4) In order to understand what predictive testing will mean for an individual, the implications for the whole family should be considered as well.
- 5) All genetic counselling will have (un)intended effects on relatives of the proband. In informing families about the hereditary nature of a disorder, different relatives may take up different roles (such as *the messenger* or *the first utiliser*; chapter 3b) and this subsequently influences the counsellor and thus the counselling.
- 6) Participants with higher distress scores may be actively dealing with the problem, while people with low distress scores might (as yet) be unable to face the problems.

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EPILOGUE

**TO KNOW OR NOT TO KNOW?
IS THIS PERCEIVED AS A MEANINGFUL QUESTION
BY THOSE AT-RISK?**

In the course of addressing the initial scientific questions, other, more philosophical aspects of the study surfaced, including the still unexplored issue embedded in the title of this thesis: "To know or not to know? Is this perceived as a meaningful question by those at-risk?" The focus so far has been on the implications of predictive testing from the moment that participants enrolled in a predictive testing program until six months after the test result. It has been shown that getting the test result provokes similar distress reactions in persons tested for dissimilar disorders; however, actually knowing has different implications depending on the type of disorder.

The introduction began with the statement that individuals, nowadays, can **ask** themselves: **do I want to know or not?** Taking into consideration the observations made during the course of the study, I started to wonder if participants do perceive a freedom to decide whether they want to know if they will develop the particular disease, or not. Factors which may influence decision-making include, amongst others, moral dilemmas such as: the wish to have children versus transmitting the gene to the next generation; medical factors such as treatment or surveillance; socio-economic factors such as the attitude of relatives, friends or society towards testing; the attitude of the healthcare providers involved, and access to (or exclusion from) various types of insurance or employment. These factors influence the so-called free and autonomous choice. External pressures as well as personal motives (ambivalence, emotions, personal values, etc.) may lead to only one distinct option.

In the case of disorders without treatment options (in this study the neurodegenerative disorders HD and HCHWA-D) one can postulate that to know or not to know is perceived as a question. However, the individuals at-risk may feel differently. When life is becoming impossible because everything revolves around the question "Will I develop the disease or not?", to know or not to know is no longer a **meaningful** question, one feels the compelling need to know. Many participants opting for the test, say that they have no other choice, which reflects the compelling aspect of going through a test. Other individuals at-risk, however, may decide not to opt for certainty as they feel they still have a choice: living with the uncertainty is still more bearable than the prospect of knowing, and undergoing the test is not yet seen as the only option.

"To know or not to know" was not considered as a meaningful question (therefore not a real option) by many individuals at-risk for the disorders with a treatment option (in this study the cancer syndromes HBOC and FAP). Having seen, for example, a sister

dying, knowing that one has the opportunity to obtain knowledge about one's chances to develop cancer and thus undertake precautions, makes the option **not** to know out of the question. Moreover, medical specialists and relatives emphasize the inevitability of the choice and persuade individuals at-risk to take the test. However, also within this cohort of individuals, some preferred not to know because they could handle the uncertainty better than the certainty.

The main difference between people at-risk for disorders with and without treatment options seems to be, on the one hand, the obligation to life itself (to stay alive) for those at-risk with treatment options; and, on the other hand, the need to solve the anxiety about the future, the urge to find an answer to the questions: who am I and who am I going to be? for those at-risk for the disorders without treatment options. Psychological reactions to the test result, however, are often similar, as all participants are emotional human beings for whom testing may reactivate grief or early experiences with the disease, and all are witnessing or have seen family members suffering from the disorder. To do justice to the long process of doubt, deliberation and decision-making and to the experienced emotions concerning the disease by people at-risk who opt for predictive testing, it is important to acknowledge the fact that testing can be the only option. A free and autonomous choice seems to be far from reality, particularly when reality has been determined by their experiences with the disease and the distress or even the death of family members.

SUMMARY

As the progress in knowledge from human genome analysis escalates, numerous applications, such as predictive DNA testing, are being implemented with increasing rapidity. Individuals and medical professionals now have the option to make beneficial use of predictive DNA testing and (sometimes) early interventions, as in the cancer syndromes.

Huntington's disease (HD), a neurodegenerative disorder characterised by involuntary movements, behavioural and personality changes and dementia, was the first autosomal dominant inheritable late-onset disorder which from 1987 could be detected in risk carriers, prior to the onset of the illness (predictive DNA testing) in the Netherlands. Dominant inheritance means that any child of an affected parent has a 50% risk of inheriting the gene causing the disease. Predictive testing is now also available for, amongst others, Familial Adenomatous Polyposis (a type of colon cancer; FAP), Hereditary Cerebral Haemorrhage with Amyloidosis Dutch type (HCHWA-D), Myotonic Dystrophy, specific cases of Alzheimer's disease and Hereditary Breast and Ovarian Cancer (HBOC).

In the present study, the first comparative study on the psychological implications of predictive DNA testing we have investigated HD, HCHWA-D, FAP and HBOC.

Previous studies on the psychological implications of predictive testing (**chapter 1**) resulted in the following leading observations:

- 1) the actual uptake of predictive testing has been lower than initially expected by risk carriers;
- 2) the reasons for testing were to relieve uncertainty, to obtain some control over the future, to inform offspring and other relatives (sometimes also to help research or to become reassured);
- 3) the main reason against testing is the fear of being unable to cope with a high-risk result;
- 4) reactions after testing were more complex than expected; however, the anticipated major psychiatric problems post-test did not occur;
- 5) gene carriers cope reasonably well by restricting themselves to live by the day, while their partners are much more worried about the future;
- 6) noncarriers experience difficulties in developing a new life-perspective and often feel guilty. Their numbed emotions and the absence of relief are difficult to understand for themselves, their partners and others in their social environment;
- 7) a genetic disease and the options and problems around predictive testing may have an unsettling effect on partner and family relationships; and
- 8) reaction to the test result is also largely determined by the meaning assigned to

the test by the family (e.g. patient preselection, secrecy, denial, etc.) and by the medical profession.

The experiences with presymptomatic testing for HD became a leading paradigm in the analysis of predictive testing in other late-onset disorders, such as cancer syndromes. All show: autosomal dominant inheritance, an onset of a variety of symptoms with increasing age, and a major impact on personal health, life expectancy and on the family relations. The cancer syndromes differ, however, from HD by absence of neuropsychiatric symptoms and the availability of far-reaching choices for treatment in the present study in FAP and HBOC.

It generally was assumed that predictive testing would be less distressing for people at-risk for disorders with treatment options; however, this is an underestimation of the distress as reported in the recent literature.

This all prompted the question whether the concepts on the effects of predictive testing for HD are equally valid in testing for other late-onset disorders. The answer may help to understand the psychological ramifications of the predictive testing for late-onset disorders and to develop counselling and support strategies.

In **chapter 2** the methodological background of the first comparative study on predictive testing for two neurodegenerative disorders and two cancer syndromes by one group of investigators, is reported. Between September 1993 and August 1995, a total of 121 at-risk individuals and 80 partners entered the predictive testing programme and the psychological follow-up study (HD; n=42, HCHWA-D; n=10, FAP; n=45, HBOC; n=24), in two collaborating university hospital settings. The psychological follow-up study contained two appointments prior to testing and two after testing (at one week and six months).

Anxiety, depression, hopelessness, psychological complaints, and the attitude towards testing were assessed at the first appointment. The Hospital Anxiety and Depression Scale (HAD), the Beck Hopelessness Scale (BHS), the Symptom Checklist (SCL'90), and the Attitude Questionnaire (AQ, see Appendix) were used. At the second session the Warning Intimacy Questionnaire (WIQ), the Social Support Questionnaire (SSQ), a Dutch adaptation of the Family Adaptability and Cohesion Evaluation Scales (FACES) and the Loneliness Scale were handed out to those at-risk and their partners. During the second, third and last appointment distress experienced because of the hereditary disorder, was assessed by questionnaire (the Impact of Event Scale (IES)) and a semi-structured interview was held with the person at-risk and the partner separately. Three questions were recorded and transcribed. Each transcript was judged by a panel of five psychologist following the system developed by Main and Goldwyn

for scoring "the coherence of transcript". A transcript was considered coherent when the participant shows a readiness, a preparedness to discuss and evaluate memories, experiences and feelings about the hereditary disorder and the test with a clear and consistent flow of ideas.

All participants were 18 years old and over, and were at 50% risk. The inclusion criteria for the psychological study were an ability to give informed consent and adequate understanding of the questionnaires. Finally, 58 individuals at-risk for either HD, FAP or HBOC completed the follow-up period of 6 months after receiving their test result. All the individuals at-risk for HCHWA-D were excluded from the statistical analysis as too few participated; this group belongs to a small religious community which tends to refuse predictive testing and its discussion.

In the explorative phase of the investigation the implications of predictive testing in a family at-risk for HBOC were studied. The detection of linkage, quickly followed by the detection of the mutation gave a sudden urgency to the genetic aspects of HBOC. The complex emotional impact on this family and its individual members separately of becoming actually aware of the genetic nature of breast and ovarian cancer and the implications of undergoing predictive testing is presented in **chapter 3**.

Two important roles were seen in the family. One member became the *messenger of the news* informing the relatives of the hereditary character of cancer in the family. Another was the *first utilizer* of the new options: predictive DNA testing and preventive surgery. This first utilizer became the example for the rest of the family. Decisions about preventive treatment (prophylactic ovariectomy and/or mastectomy) were related to the experiences within the family, and feelings of identification with an affected family relative.

The urgency of actions and reactions perceived and the emotions and burdens of the messenger role illustrate the range of information and support needed in addition to the genetic and oncological counselling for HBOC to both the individual and the family.

In the comparative study on predictive testing for neurodegenerative disorders and cancer syndromes, the pretest distress experiences of the participants and their partners was analyzed and is presented in **chapter 4**. Distress was measured with the two subscales of the Impact of Event Scale (IES); intrusive thoughts and feelings, and avoidance behaviour. Individuals at-risk for the neurodegenerative disorders showed more avoidance behaviour towards disease-related events than those at-risk for the cancer syndromes. People at-risk for FAP and partners of those at-risk for HBOC suffered less from intrusive thoughts and feelings than the others at-risk, and

respectively the other partners.

The impact of the disease on one's life and the experience with affected relatives was found to be an important determinant for pretest distress, and this was not disease specific. Most distress was reported by those who also had considerations against testing; those expecting adverse effects of their identification as a gene carrier; and those expecting great relief of being identified as a noncarrier. We hypothesize that high distress may reflect "work of worrying" as a mental preparation for the test result, whereas low distress may indicate denial-avoidance behaviour and poor anticipation of the test outcome. Participants might be helped by addressing these feelings during preparation before testing.

In **chapter 5** we compared the course of distress during testing, from pretest to one week and 6 months after testing. In general, all carriers of the disease genes (either causing HD, FAP or HBOC) were as distressed prior to testing as they were after testing. Noncarriers became less distressed. Men reported less distress than women. However, male noncarriers experienced increasing distress immediately after testing. Six months later they were less distressed than when they started testing.

The course of distress reported by carriers and noncarriers of the three disease genes was similar. However, those tested for HD reported more distress than those tested for FAP and HBOC throughout the pre- and post-test period. Clinical experience suggests that individuals at-risk for FAP and HBOC are more inclined to ward off the emotions involved. However, this aspect needs further investigation.

In chapter 5 we compared the course of distress experienced from pretest to 6 months post-test of different groups. In **chapter 6** we studied whether baseline characteristics, either biographical, psychological or medical, might be associated with the distress experienced six months after testing. To achieve efficient prediction, we constructed a model including those variables contributing significantly to increased levels of either intrusion or avoidance. The test result, as such, is not included in the model as it was not associated with post-test distress. Participants who were depressed prior to the test were more distressed after testing; on the other hand those who were anxious pretest were *less* distressed, i.e. they had less intrusive thoughts post-test. It is clearly important to estimate depression and to pay adequate attention to depressive feelings to prevent possible adjustment problems after predictive testing.

Other factors associated with a higher level of post-test intrusion were gender (i.e. being a woman), having children and pre-test intrusion. Religion and being at-risk for HBOC were associated with less post-test intrusion. Participants who showed

Summary

avoidance behaviour prior to the test and those who had many persons available for support showed more avoidance behaviour post-test. The impressions obtained by a semi-structured interview proved to be most relevant for the interpretation of the questionnaire results. For example, depression can be an indication to postpone testing, on the other hand, depression may be an indication to proceed with testing when the depressive feelings are due to the continuing uncertainty.

In the comparative study questionnaire responses were analyzed and the impressions obtained in the interviews were used to interpret the results. Sometimes they seemed contradictory. The case report presented in **chapter 7** is an example of how participants may report little distress while they are clearly under stress due to diagnosis of HBOC in the family and due to the possibility of predictive testing.

Four males, from the first Dutch family for whom predictive DNA testing for HBOC became an option, started the testing protocol. They all postponed appointments and only one took the test. During counselling of the men, the main focus of attention was on the impact of the past and future (possible) deaths and serious illnesses of female relatives. They tended to deny or minimise the emotional impact of the occurrence of HBOC in their personal life and their future. They avoided discussion about their emotions and focused upon the medical implications of the disorder for their female relatives. It is important to understand these underlying conflicts which lead to warding off the emotions provoked by the test and the disorder, in males at risk. When discussed in genetic counselling these considerations may enable the males to better cope with the hereditary disorder in the family.

In **chapter 8** the pretest psychological questionnaire results of the four groups of risk carriers (including HCHWA-D again) were compared first. Participants at-risk for neurodegenerative disorders were more anxious and depressed, and had more psychological complaints than those at-risk for cancer syndromes.

In the literature on the stress response theory of Horowitz and the IES the description of several stress response patterns were found. Secondly the psychological profile coming together with the stress response patterns were investigated. The participants were divided in four groups and their scores on the psychological questionnaires were compared:

- 1) Group 1, High intrusion and High avoidance;
- 2) Group 2, High intrusion and Low avoidance;
- 3) Group 3, Low intrusion and High avoidance;
- 4) Group 4, Low intrusion and Low avoidance.

Participants in the first group were more anxious and depressed, and had more psychological complaints than those in the fourth group.

The coherence score of the interview text was included in the third analysis in order to compare questionnaire results with interview results. The coherence score represents the ability to freely discuss the test and its implications, without getting carried away or dismissing/minimising the subject, irrespective of potential negative or positive emotions provoked by the test. It can be understood as a measure of the defensiveness during the interview.

The coherence score of the interview showed that participants reporting high intrusion and high avoidance (group 1) were more reflective about their emotions without getting carried away or dismissing the subject (e.g. more coherent) than those reporting low intrusion and low avoidance (group 4). This suggests that participants with higher pretest stress scores may be actively dealing with the emotional implications of the test, whereas people with low stress scores may (as yet) be unable to face these implications.

It is important to identify the strategy of coping with threat in order to provide individualised counselling and necessary guidance. Long-term follow-up, however, is needed to establish the sequelae of a denying coping strategy by participants in a genetic testing programme.

In **chapter 9**, the major findings of the present study are discussed. Because of the comparative nature of this study we have been able to demonstrate these findings so clearly:

- 1) In general, when comparing groups, the groups at-risk for the neurodegenerative disorders report more distress than those at-risk for the cancer syndromes.
- 2) The individual differences in psychological distress between participants at-risk for a particular disorder are larger than the similarities. Distress experienced by an individual is, to a major degree, influenced by the experiences with the disease and the impact of the disorder on one's life until now.
- 3) Stress responses over time, develop qualitatively similar for those tested for different late-onset disorders.
- 4) When trying to understand the meaning of predictive testing for an individual, the implications for the whole family should be considered as well.
- 5) Genetic counselling will have (un)intended effects on relatives of the proband. When informing families about the hereditary nature of a disorder, different relatives may take up different roles (such as *the messenger* or *the first utiliser*) and this subsequently influences the counsellor and thus the counselling. Participants in a

testing programme may be helped by anticipating specific problems associated with these various roles.

6) Participants with higher distress scores may be actively dealing with the problem, while people with low distress scores might (as yet) be unable to face the problems.

Future work may learn how to differentiate counselling in those situations.

All this clearly indicates how universal the adaption mechanisms are as they have been described for the first risk-carriers, tested for HD; the present study deepens and broadens these impressions.

Many new questions are raised by these results (**chapter 9**). The first studies on the psychological sequela of predictive testing are primarily based on findings in test participants who also agree with psychological follow-up interviews/questionnaires. Validation of these findings, as well as an analysis of problems which hinder or limit acceptance of testing requires study of non-participants in genetic testing and non-participants of psychological follow-up. Such studies are needed to establish the real need for counselling and support strategies, and to learn about social or psychological blockades to the access of genetic testing.

Long-term follow-up is needed (5 to 10 years). Short-term coping seems reasonably good; however, preliminary data indicate the great psychological burden and strength needed on the long term. Another essential viewpoint for further study is the family perspective, with special attention to the partner and family communication. Among the useful tools to portray possible problems are case descriptions of the clinical implications of genetics for individuals, families and health-care workers.

The psychological implications of genetic studies in a family need further analysis. Most genetic family studies do not investigate the implications for the family of becoming informed that a particular disease is genetic. A family invited to participate in a research protocol for gene identification might be left on its own to deal with the personal, psychological and family dynamics of the "new knowledge".

SAMENVATTING

De laatste jaren is de kennis omtrent erfelijkheid in het algemeen, en in het bijzonder de erfelijkheid van bepaalde ziektebeelden bij de mens, enorm snel toegenomen. Deze ontwikkeling heeft onder andere geleid tot nieuwe mogelijkheden van onderzoek, zoals voorspellende DNA-diagnostiek. Voorspellende DNA-diagnostiek houdt in dat men in staat is de genetische oorzaak van een bepaalde ziekte bij iemand die deze ziekte in de familie heeft, op te sporen voordat de symptomen van de desbetreffende ziekte zich ontwikkeld hebben. Zowel artsen als de rest van de maatschappij worden voor de uitdaging geplaatst om van deze nieuwe techniek op een nuttige en constructieve wijze gebruik te maken.

De eerste ziekte waarvoor voorspellende DNA-diagnostiek in Nederland mogelijk werd was in 1987 de ziekte van Huntington (HD). HD is een autosomaal dominant overerfbare aandoening, gekarakteriseerd door een voortschrijdende achteruitgang van het zenuwstelsel (een neurodegeneratieve aandoening), wat leidt tot onwillekeurige bewegingen, gedrags- en persoonlijkheidsveranderingen en dementie. Dominant overerfbaar betekent dat elk kind van een aangedane ouder 50% kans heeft het ziekte veroorzakende gen geërfd te hebben. Andere dominant overerfbare aandoeningen waarvoor voorspellend testen inmiddels mogelijk is, zijn, o.a., Familiaire Adenomateuze Polyposis Coli (een vorm van darmkanker; FAP), een erfelijke vorm van hersenbloedingen (Hereditary Cerebral Haemorrhage with Amyloidosis Dutch type; HCHWA-D), een voortschrijdende spierziekte (Myotone Dystrofie; MD), sommige vormen van de ziekte van Alzheimer (dementie) en erfelijke borst- en ovariumkanker (HBOC).

In het huidige onderzoek worden voor het eerst de psychologische gevolgen van voorspellend onderzoek voor verschillende aandoeningen met elkaar vergeleken, namelijk HD, HCHWA-D, FAP en HBOC. Het beschreven onderzoek werd uitgevoerd in een samenwerkingsverband met de afdelingen Klinische Genetica van het Academisch Ziekenhuis Dijkzigt en het Academisch Ziekenhuis Leiden, de afdeling Medische Psychologie en Psychotherapie van de Erasmus Universiteit Rotterdam en de Daniël den Hoed Kliniek, Rotterdam.

Eerder onderzoek naar de psychologische gevolgen van voorspellende DNA-diagnostiek bij onder andere de ziekte van Huntington heeft het volgende aangetoond (hoofdstuk 1):

- 1) tot nu toe hebben minder mensen zich laten testen dan vóórdat de test een optie werd, verwacht was;
- 2) de voornaamste redenen om aan de test mee te doen zijn, een einde maken aan de onzekerheid, controle verkrijgen over de toekomst en het kunnen informeren van

kinderen en andere familieleden;

3) de angst dat men niet om zou kunnen gaan met een ongunstige uitslag was de voornaamste reden om niet aan de test mee te doen;

4) de reacties op de testuitslag zijn complexer dan verwacht, echter, psychiatrische problemen na een ongunstige testuitslag hebben zich nauwelijks voorgedaan (terwijl de artsen en verdere begeleiders daar wel bang voor waren);

5) bewezen gendragers blijken redelijk goed met hun uitslag om te kunnen gaan, zij richten zich met name op het leven van dag tot dag, terwijl hun partners zich zorgen maken over de toekomst;

6) degene die géén gendrager bleken te zijn, hebben moeite om hun leven inhoud te geven en voelen zich vaak schuldig. De gevoelsvervlakking, zoals een gebrek aan opluchting, is vaak moeilijk te begrijpen, voor henzelf, maar óók voor hun partners en anderen in hun directe omgeving;

7) een erfelijke aandoening en voorspellend testen kunnen de relatie met de partner en/of familieleden ontwrichten;

8) de reacties op de uitslag van de test worden mede bepaald door de betekenis die de familie daaraan toekent. Zo wordt in een aantal families met een erfelijke ziekte soms onbewust, soms openlijk besproken wie de volgende patiënt zal zijn, nog voordat er verschijnselen waargenomen zijn of dat er een testuitslag bekend is. Ook kan geheimhouding of ontkenning optreden. De medische beroepsgroep kan eveneens de betekenis die aan de uitslag gegeven wordt sterk beïnvloeden.

De ervaringen met voorspellend testen voor HD zijn een belangrijke leidraad geworden voor het testen voor andere dominant overerfbare aandoeningen, zoals voor HCHWA-D, en verschillende erfelijke kankersyndromen zoals HBOC en FAP. Deze aandoeningen hebben met elkaar gemeen dat er een verscheidenheid aan symptomen op latere leeftijd optreden die als (zeer) beperkend worden ervaren en levensbedreigend kunnen zijn. Verder hebben deze erfelijke aandoeningen een verregaande invloed op de onderlinge familierelaties.

De aandoeningen verschillen echter van elkaar in het feit dat er voor de neurodegeneratieve aandoeningen geen behandelingsopties zijn, terwijl er wel, zeer ingrijpende, behandelingsopties zijn voor de erfelijke kankersyndromen. Verder kunnen er bij de neurodegeneratieve aandoeningen duidelijke persoonlijkheidsveranderingen optreden terwijl dit bij de erfelijke kankersyndromen, over het algemeen, niet het geval is. De verwachting was dat voorspellende DNA-diagnostiek voor behandelbare aandoeningen minder ingrijpend zou zijn dan voor onbehandelbare aandoeningen. Uit het onderzoek tot dusver blijkt echter, dat dit een onderschatting is van de ervaren

spanning door risicodragers die zich laten testen voor een behandelbare aandoening.

Deze ervaringen leidden tot de vraag: "Zijn de ervaringsmodellen, ontwikkeld bij het vervolgonderzoek naar de aanpassing aan, en de verwerking van een DNA-testuitslag voor HD, eveneens van toepassing op testen voor andere later in het leven optredende erfelijke aandoeningen?"

Beantwoording van deze vraag zal de psychologische gevolgen van voorspellend testen meer begrijpelijk maken zodat mensen die een test laten doen, en hun families, beter begeleid kunnen worden.

In **hoofdstuk 2** wordt de methodologisch achtergrond van de vergelijkende studie beschreven. In deze studie worden de aanpassing aan en de verwerking van een DNA-uitslag voor de ziekte van Huntington, erfelijke hersenbloedingen (HCHWA-D), erfelijke darmkanker (FAP) en erfelijke borst- en ovariumkanker (HBOC) met elkaar vergeleken. Gedurende twee jaar (vanaf september 1993 tot en met augustus 1995) werkten 121 risicodragers en 80 partners mee aan het psychologische vervolgonderzoek. (HD; n=45, HCHWA-D; n=10, FAP; n=45, HBOC; n=24). Voor de testuitslag hadden risicodragers en hun partners twee afspraken met de klinische geneticus en aansluitend een afspraak met de psycholoog. De eerste afspraak met de klinisch geneticus was om geïnformeerd te worden over de test en de tweede voor de bloedafname. De motivatie voor de test en de verwachtingen omtrent de uitslag werden uitgebreid besproken met de psycholoog. Na acht weken volgde de uitslag. Daarna werden nog twee vervolgspraken met de psycholoog gemaakt, een week, en zes maanden na de uitslag.

Angst, depressie, hulpeloosheid, psychologische klachten en de houding ten opzichte van de voorspellende test werden op de eerste afspraak gemeten. Hiervoor werden de Hospital Anxiety and Depression Scale (HAD), de Beck Hopelessness Scale (BHS), de Symptom Checklist (SCL'90) en de Attitude Questionnaire afgenomen. Na het 2^e meetmoment werd met de Social Support Questionnaire (SSQ), de Gezins Dimensie Schalen (GDS) en de Eenzaamheidslijst de ervaren steun gemeten. Tijdens meetmoment 2, 3 en 4 werd met de Impact of Event Scale (IES) de spanningen met betrekking tot de erfelijke aandoening gemeten. Met de risicodrager en de partner afzonderlijk werden semi-gestructureerde interviews gehouden. De interviews werden gedeeltelijk op band opgenomen en uitgeschreven. De teksten werden door een team van psychologen beoordeeld op de coherentie van de tekst (een samenhangend, geloofwaardig en invoelbaar relaas) volgens de richtlijnen van het, door Main en Goldwyn ontwikkelde, Adult Attachment Interview.

Alle deelnemers waren 18 jaar of ouder, hadden een risico van 50% om gendrager te zijn, waren in staat de vragenlijsten te begrijpen, en hadden hun toestemming gegeven om de gegevens voor wetenschappelijk onderzoek te gebruiken. Uiteindelijk hebben 58 risicodragers voor HD, FAP of HBOC aan het volledige onderzoek deel genomen. Van de risicodragers voor HCHWA-D zijn alleen de gegevens van vóór de testuitslag vermeld omdat de meerderheid zich direct na de testuitslag uit het vervolgonderzoek terug trok. Zij waren allen afkomstig uit een gemeenschap met een sterk kerkelijke traditie die afwijzend tegenover de voorspellende test staat.

In de voorbereidende fase van de huidige studie is de invloed van de diagnose HBOC en van de voorspellende test op een familie bestudeerd. De beschreven familie werd in korte tijd zeer bewust van de erfelijkheid van kanker in hun familie omdat eerst de plaats van het ziektegen gevonden werd, en daarna al snel de specifieke ziekte veroorzakende verandering in het gen. **Hoofdstuk 3** toont de complexe, emotionele reacties op de diagnose "erfelijk" en op de keuzes die men moet maken omtrent de test.

Binnen de betrokken familie werden twee belangrijke rollen waargenomen. Eén familielid werd *de boodschapper van het nieuws*. Deze taak werd in een later stadium overgenomen door een ander familielid. Zij hadden de taak de overige familieleden te informeren over het erfelijke karakter van borst- en ovariumkanker en hen te motiveren voor het wetenschappelijke onderzoek naar de plaats van het ziektegen. De tweede rol was *het voorbeeld*, de eerste in de familie die besloot de test te ondergaan. Zij voelde zich verantwoordelijk om het goede voorbeeld te geven. Beslissingen omtrent het vroegtijdig verwijderen van borsten en eierstokken (profylactische chirurgie) werden met name bepaald door de ervaringen met de ziekte binnen de familie en het zich verwant of vergelijkbaar voelen met aangedane familieleden.

Voorspellend onderzoek voor erfelijke borst- en ovariumkanker is zowel een individueel als een familieprobleem. Het bespreken van de psychologische gevolgen van de rol die men op zich neemt, of toebedeeld krijgt, en daarmee het onderkennen van mogelijke problemen, zal testaanvragers en hun familieleden kunnen helpen in het omgaan met de erfelijkheid van de aandoening.

Voordat zij zich lieten testen is de ervaren spanning, door zowel testaanvragers als hun partners vergeleken voor de verschillende groepen aandoeningen (beschreven in **hoofdstuk 4**). Eveneens is onderzocht welke factoren, zoals de houding ten opzichte van de test, type aandoening en biografische variabelen, de spanning mede bepaalden. De psychologische spanning is gemeten met behulp van de IES. Deze test meet twee factoren; het gebukt gaan onder steeds terugkerende gedachten en gevoelens omtrent

de ziekte, en het ontwijken van dergelijke gedachten en gevoelens. De houding ten opzichte van de voorspellende test werd bestudeerd aan de hand van de ervaring met de aandoening in de familie, de redenen die men had om zich te laten testen, en de verwachtingen omtrent de invloed van de uitslag op het verdere leven.

Risicodragers voor de neurodegeneratieve aandoeningen (met voortschrijdende uitval van het zenuwstelsel) rapporteerden meer ontwijking van situaties en gevoelens die met de aandoening verbonden waren, dan risicodragers voor de kankersyndromen (FAP en HBOC). De risicodragers die het minst last hadden van steeds wederkerende gevoelens en gedachten betreffende aandoening waren risicodragers voor FAP. De partners van de risicodragers voor HBOC waren de partners die het minst last hadden van steeds wederkerende gevoelens en gedachten betreffende de aandoening.

De psychologische spanning bleek samen te hangen met de ervaring met de aandoening en de invloed van de aandoening op iemands leven tot nu toe. Degene die de meeste spanning rapporteerden waren: a) degene die zich wel lieten testen maar ook redenen konden bedenken om zich niet te laten testen; b) degene die bang waren dat een ongunstige uitslag ook nadelige gevolgen zou kunnen hebben; en c) en degene die verwachtten opgelucht te zijn als zij géén gendrager bleken te zijn.

Degene die de nadelen van de test in overweging namen bleken de meeste spanning te rapporteren. De mentale voorbereiding op de uitslag en op de eventuele gevolgen leidt blijkbaar tot een hogere spanning. Daarnaast kan een lage spanning het resultaat zijn van pogingen van iemand om de nadelige gevolgen van de test niet onder ogen te hoeven zien omdat hij/zij daar te angstig voor is. Tijdens de gesprekken voorafgaande aan de voorspellende test is het belangrijk om aandacht te besteden aan mogelijk vermijdingsgedrag enerzijds, en het met veel spanning gepaard gaande voorbereidingsgedrag anderzijds.

In **hoofdstuk 5** wordt het beloop van de spanning, gemeten vóór de test, een week, en zes maanden na de testuitslag, vergeleken voor degene die zich lieten testen voor HD, FAP of HBOC. In het algemeen bleek dat alle geïdentificeerde gendragers (voor HD, FAP en HBOC) net zo gespannen waren voor als na de test. Degene die géén gendrager bleken te zijn waren een half jaar na de testuitslag minder gespannen dan daarvoor. Mannen rapporteerden minder spanning dan vrouwen. Mannelijke niet-gendragers bleken zeer gespannen te zijn direct na de uitslag. Dit spanningsniveau was zes maanden na de testuitslag echter gedaald tot onder het niveau van voor de uitslag.

Het beloop van de gerapporteerde spanning was voor de drie aandoeningen gelijk. Echter, deelnemers die zich hadden laten testen voor HD, rapporteerden op elk moment meer spanning dan degene die zich hadden laten testen voor een kankersyndroom.

De opgedane klinische ervaring leidde tot de interpretatie dat deelnemers uit de FAP- en HBOC-groep hun emoties ontkenden. Deze veronderstelling dient verder onderzocht te worden.

In hoofdstuk 5 werd het beloop van de spanning tussen verschillende groepen vergeleken. In **hoofdstuk 6** werd onderzocht welke kenmerken gemeten vóór de test samenhangen met de spanning ná de test. Om efficiënt te kunnen voorspellen is naar een model gezocht wat inzichtelijk maakt welke factoren daadwerkelijk samenhangen met een toename van steeds terugkerende gedachten en gevoelens betreffende de ziekte of het ontwijken van zulke gedachten en gevoelens. Gekeken is naar biografische, psychologische en medische factoren. De testuitslag hing niet samen met de ervaren spanning zes maanden later. Deelnemers die depressief waren vóór de test, waren *meer gespannen* ná de test, echter degene die angstig waren vóór de test waren *minder gespannen* ná de test (hadden minder last van terugkerende gevoelens en gedachten). Het is belangrijk om passende aandacht te besteden aan depressieve gevoelens van deelnemers om eventuele aanpassingsproblemen na de uitslag te voorkomen.

Andere kenmerken die samenhangen met een toename van terugkerende gevoelens en gedachten zijn: geslacht (vrouw zijn), het hebben van kinderen en steeds terugkerende gevoelens en gedachten voor de test. Mensen die actief bezig zijn met hun geloof of risicodragers zijn voor HBOC, hadden daarentegen weer minder last van terugkerende gevoelens en gedachten na de test. Deelnemers die ontwijkend gedrag vertoonden vóór de test, of die veel mensen hadden die hun konden steunen, bleken situaties en gevoelens betreffende de aandoening meer te ontwijken na de testuitslag.

De indrukken opgedaan tijdens de interviews bleken bijzonder relevant voor de interpretatie van de bevindingen. Bijvoorbeeld: depressie kan een aanwijzing zijn om de test uit te stellen, maar kan ook het resultaat zijn van de voortdurende onzekerheid die slechts door het ondergaan van de test kan worden opgeheven.

In deze vergelijkende studie zijn de resultaten, die verkregen zijn na het analyseren van de vragenlijsten, geïnterpreteerd met behulp van de ervaringen opgedaan tijdens de interviews. Soms leken de scores op de vragenlijsten en de indrukken verkregen tijdens het interview tegenovergesteld aan elkaar.

De deelnemers die in **hoofdstuk 7** worden besproken zijn een voorbeeld van deelnemers die weinig spanning rapporteerden, maar echter duidelijk gebukt gingen onder de spanning die voortkomt uit de diagnose HBOC in de familie en de mogelijkheid van de voorspellende test.

Vier mannen, behorende tot de eerste familie in Nederland waarvoor voorspellend testen voor HBOC mogelijk werd, kwamen naar de afdeling Klinische Genetica voor aanvullende informatie. Alle vier stelden zij hun afspraken uit en maar één heeft zich daadwerkelijk laten testen. De belangrijkste gespreksonderwerpen bleken te zijn: de ervaringen met de ziekte tot dusver, de mogelijke ziekte van dochters en het toekomstige overlijden van anderen vrouwelijke familieleden. De mannen leken de invloed van de aandoening op hun persoonlijke leven onbeduidend te vinden in vergelijking tot wat het betekent voor hun vrouwelijke familieleden. Zij ontweken de emotionele betekenis om "overdrager" te kunnen zijn en richtten zich op de medische implicaties van de ziekte voor hun moeders, zusters, tantes, nichtjes, maar niet voor hun dochters.

Om passende steun en begeleiding te kunnen bieden is het van belang om dergelijke onderliggende conflicten te kunnen begrijpen die bij deze mannen leiden tot het afhouden van de emoties die door de test en de aandoening worden los gemaakt.

Hoofdstuk 8 behandelt drie vragen en richt zich op de ervaren spanning vóór de testuitslag. Als eerste zijn de scores op de psychologische vragenlijsten van de vier groepen risicodragers (weer inclusief HCHWA-D) met elkaar vergeleken. Risicodragers voor de neurodegeneratieve aandoeningen waren angstiger, meer depressief en hadden meer psychologische klachten dan degene die risicodragers waren voor de kankersyndromen.

Als tweede vraag is onderzocht welk samenstelsel van psychologische kenmerken horen bij welke reactiepatronen op de spanning. De deelnemers zijn daartoe verdeeld in vier groepen met verschillende stress-reactiepatronen zoals beschreven in onderzoek naar de stresstheorie van Horowitz:

- 1) groep 1: veel last van steeds terugkerende gevoelens en een duidelijk ontwijkingsgedrag;
- 2) groep 2: veel last van steeds terugkerende gevoelens en nauwelijks ontwijkingsgedrag;
- 3) groep 3: nauwelijks last van steeds terugkerende gevoelens en duidelijk ontwijkingsgedrag;
- 4) groep 4: nauwelijks last van steeds terugkerende gevoelens en nauwelijks ontwijkingsgedrag.

Deelnemers in de eerste groep waren angstiger, meer depressief, en hadden meer psychologische klachten dan degenen in de vierde groep.

In het derde deel van dit hoofdstuk werd de manier waarop de test besproken werd vergeleken met de scores op de spanningsvragenlijst (IES). De uitgeschreven interviews

hadden voor dit doel een coherentie-score gekregen. De coherentie-score geeft weer in hoeverre iemand in staat is om de test en de gevolgen op een betrokken en overtuigende wijze te bespreken zonder zichzelf te verliezen in bijzaken en zonder het onderwerp af te doen als niet belangrijk of onbespreekbaar. De coherentie-score kan opgevat worden als een weergave van de afweer zoals getoond in het interview.

Deelnemers die aangaven veel last te hebben van steeds terugkerende gevoelens en gedachten en deze ook trachten te vermijden (groep 1) waren *beter* in staat hun emoties betreffende de test en de aandoening te bespreken (coherenter) dan degene die minder last hadden van steeds terugkerende gevoelens en geen vermijdingsgedrag vertoonden (groep 4). Deze waarneming suggereert dat deelnemers met hogere spanningsscores op een actieve wijze bezig zijn met de emotionele gevolgen van de test, terwijl mensen met lage spanningsscores zich (nog) niet met deze gevolgen bezig (kunnen) houden.

Voor een passende begeleiding is het van belang om zicht te krijgen op het gegeven of iemand zich juist aan het voorbereiden is of overspoeld wordt door emoties, of dat iemand heel ontspannen de test tegemoet kan zien of juist de spanning onderdrukt omdat hij/zij te angstig is om de mogelijke gevolgen nu al onder ogen te zien. Onderzoek naar de lange termijn effecten zullen echter aan moeten tonen in hoeverre het weg houden van gevoelens omtrent de test, ongewenste effecten heeft op de aanpassing aan een test resultaat.

In **hoofdstuk 9** worden de belangrijkste resultaten van het onderzoek besproken. Voor het eerst zijn deze bevindingen zó duidelijk aangetoond, dankzij de vergelijkende aard van de studie. De resultaten zijn:

- 1) in het algemeen rapporteren risicodragers voor de neurodegeneratieve aandoeningen meer spanning dan de risicodragers voor de kankersyndromen (wanneer de groepen met elkaar vergeleken worden);
- 2) op individueel niveau echter blijkt de ervaren spanning vooral samen te hangen met de ervaringen met de aandoening en de invloed van de ziekte op iemands leven;
- 3) het verloop van de spanning (vóór, een week na en zes maanden na de uitslag), is gelijk voor risicodragers voor verschillende aandoeningen;
- 4) om te kunnen begrijpen wat de betekenis van de voorspellende test is voor het individu, dient de invloed op de hele familie in ogenschouw te worden genomen;
- 5) een erfelijkheids-adviesgesprek heeft door de daarin gegeven informatie óók verstreckende gevolgen voor de familieleden van degene die wordt geïnformeerd; iedereen zal verschillend op zowel het nieuws als op elkaar reageren. Dit heeft ook zijn weerslag op de arts-patiënt interactie. Rollen die familieleden op zich

kunnen/moeten nemen zijn bijvoorbeeld de *boodschapper* en de *eerste gebruiker*. Deelnemers kunnen geholpen worden door de verschillende problemen, die gekoppeld zijn aan deze rollen, te bespreken. De informerende artsen kunnen belangrijke hulp geven door hier op in te gaan; en

6) hoge spanningsscores kunnen wijzen op een actief voorbereiden op de mogelijke problemen terwijl lage scores kunnen wijzen op een onvermogen om de gevolgen onder ogen te zien. Deze aanwijzingen kunnen artsen gebruiken om de begeleiding aan de verschillende individuen aan te passen.

Met dit alles is duidelijk geworden hoe universeel de aanpassingsmechanismen zijn die ook zijn beschreven voor de eerste risicodragers die werden getest voor HD. Het huidige onderzoek geeft een aanzienlijke verdieping en verbreding van dit beeld.

Toekomst-perspectief. Dit onderzoek heeft nieuwe vragen opgeworpen. De studies naar de psychologische gevolgen van voorspellende DNA-diagnostiek hebben zich tot nu toe gericht op degene die zich laten testen en eveneens deelnemen aan een psychologisch vervolgonderzoek. Het is nog niet duidelijk of deze bevindingen ook gelden voor degene die niet willen weten of zij gendrager zijn of niet, of degene die zich wel laten testen maar niet deelnemen aan psychologisch onderzoek. Om te weten of de resultaten algemeen geldend zijn dienen eveneens van deze groepen de motieven en de ervaren spanning bestudeerd te worden. Zulke studies zijn ook nodig om de daadwerkelijke behoefte aan counseling en ondersteuning te bepalen en om zicht te krijgen op de sociale en psychologische blokkades tegen voorspellend DNA-onderzoek bij verschillende aandoeningen.

Onderzoek naar de lange termijn effecten van voorspellend onderzoek is meer dan ooit noodzakelijk. Vooral nu bekend is dat het "redelijk goed" gaat met gendragers en dat niet-gendragers moeite kunnen hebben met hun aanpassing aan een nieuw leven. Voorlopige gegevens tonen echter aan dat men sterk moet zijn om met de zware psychologische last van "het weten" te kunnen leven. Een ander belangrijk uitgangspunt voor verder onderzoek is het veranderend familieperspectief met speciale aandacht voor de partnerrelatie en de communicatie binnen de familie.

APPENDIX

This survey is designed to find out what some of your attitudes and opinions are about *the hereditary disorder*, 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 *the hereditary disorder* and being at-risk
1. At what age did you first learn about *the hereditary disorder* being in the family?

2. At what occasion did you first learn about *the hereditary disorder*?

3. Which relatives with *the hereditary disorder* 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 *the hereditary disorder*?

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 *the hereditary disorder*?
- ☐ from family
 - ☐ from general practitioner
 - ☐ from the department of Clinical Genetics
 - ☐ *the hereditary disorder* lay organization
 - ☐ newspaper
 - ☐ radio/television
 - ☐ others, i.e. _____

9. How does or did *the hereditary disorder* affect your life?
- _____

II. Reasons for taking the test

10. You have applied at the department of clinical genetics and you have decided to undergo presymptomatic testing for *the hereditary disorder*. 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 for not taking the test:

In this part we ask to rate whether or not you agree with the statements listed below (check the answer which is most appropriate).

- 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 *the hereditary disorder*

agree / not agree / uncertain

III.

12. I believe that taking the presymptomatic test and being told that I will probably get *the hereditary disorder*, 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 *the hereditary disorder*, 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 avoiding my 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 *the hereditary disorder*?
- ☐ parents
 - ☐ brother/sister
 - ☐ other relatives
 - ☐ general practitioner
 - ☐ medical specialist
 - ☐ *the hereditary disorder* lay organization
 - ☐ department of Clinical Genetics
 - ☐ 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
 - g. I will tell nobody _____
16. If you were told that you will probably get *the hereditary disorder* 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 *the hereditary disorder* 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 *the hereditary disorder* 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 *the hereditary disorder*?

- ☐ I am certain that I will not get *the hereditary disorder*
☐ I often think that I will not get *the hereditary disorder*
☐ I often think that I will get *the hereditary disorder*
☐ I am certain that I will get *the hereditary disorder*
☐ I am uncertain

Please explain your answer

19. If the test shows that I will not get *the hereditary disorder*,
- ☐ 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 *the hereditary disorder*,
- ☐ 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

21. What will you do differently in your life if the test shows that you probably will not get *the hereditary disorder*?
-

22. What will you do differently in your life if the test shows that you probably will get *the hereditary disorder*?

23. If you were told that you probably will get *the hereditary disorder* in the future, would you like the opportunity to talk about this:
- a. in a support group yes / no
 - b. with a professional counselor yes / no
 - c. with a social worker yes / no
 - d. with a psychologist yes / no
 - e. with a minister/priest yes / no

- f. others

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 *the hereditary disorder*?
☐ I have not had any problems
☐ I have had problems:

26. If the test shows you will probably get *the hereditary disorder*, 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 *the hereditary disorder*, 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 *the hereditary disorder*?
- ☐ I have not had any problems
 - ☐ I have had any problems:
 - ☐ with life insurance
 - ☐ with disability insurance
 - ☐ increased premium because of being at-risk
 - ☐ other insurances

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 (please check your answer):

1 = agree

2 = no agree

3 = uncertain

a. health of mother is in danger because of the pregnancy	1	2	3
b. prenatal diagnosis shows a serious disease	1	2	3
c. prenatal diagnosis shows Down syndrome	1	2	3
d. prenatal diagnosis shows an increased risk for <i>the hereditary disorder</i>	1	2	3
e. the baby is unwanted (for other than medical reasons)	1	2	3
f. abortion is not acceptable in all cricumstances, mentioned above	1	2	3

Allereerst wil ik de testaanvragers en hun partners bedanken, die aan dit onderzoek hebben meegewerkt. Dankzij hun bereidheid om hun motieven en gevoelens toe te lichten heb ik inzicht verkregen in de invloed die een voorspellende test op iemand en zijn/haar directe omgeving kan hebben.

Verder wil ik alle medewerkers van de afdelingen Klinische Genetica in Leiden en Rotterdam bedanken. Enkele wil ik met name noemen. Om te beginnen de medewerkers van het "tijdelijke" gebouw 33 in Leiden. Ik heb met veel plezier met heel wat artsen samen gewerkt en mij bijzonder thuis gevoeld op deze afdeling. Het secretariaat onder leiding van Ank wil ik bedanken voor het werk dat zij hebben verzet, Prof. van de Kamp voor zijn interesse en de gele rozen toen het echte schrijfwerk moest beginnen, Arie voor de "FAP-samenwerking", Riet en Anneke voor de "HD-samenwerking", alle arts-assistenten uit de periode '92 tot en met '95 voor de "FAP- en HD-samenwerking", Simone voor de "HCHWA-D-samenwerking" en Jan voor de "HBOC-samenwerking". Iedereen wil ik bedanken voor het mee leven, zowel onderzoeksmatig als privé.

Van de Westzeedijk wil ik met name Hanne bedanken voor de "HBOC-samenwerking", Marijke die alle afspraken wist te coördineren en Marlies omdat zij altijd, als ik ergens een beetje vaag naar vroeg, toch weer met de desbetreffende referentie aan kwam zetten. Andere medewerkers zoals Dick, Anja en Bert wil ik bedanken voor hun interesse en het uitwisselen van ervaringen. Degene die echter heel belangrijk is geweest en wiens enthousiasme en inzet onmisbaar zijn geweest, is prof. Niermeijer. Ik bewaar bijzonder goede herinneringen aan het bespreken van menig artikel.

Ook wil ik alle mensen op "het lab" bedanken die enerzijds het testen mogelijk maakten en anderzijds altijd bereid waren het een en ander uit te leggen, op te schrijven, of op te zoeken. Hierbij denk ik met name aan Bert Bakker, Moniek Losekoot en Peter Devilee.

Furthermore I would like to thank prof. Ponder for his invitation and introduction to, amongst others Maggie Ponder, Josephine Green, Ros Eeles, Doug Easton and Maggie Watson. It was a great experience to go back to Cambridge for work, but most of all, it was a great opportunity to speak to so many enthusiastic colleagues. An international workshop on HBOC has been growing ever since.

Tot zover de "genetica" en nu de afdeling Medische Psychologie. Ik heb de afgelopen vier jaar met veel plezier op de afdeling gewerkt en veel van iedereen geleerd. Het Geïnteresseerde Enthousiaste Onderzoekers overleg, oftewel GEO-overleg kan hierbij niet onvermeld blijven, met onder andere Annette, Alec, Irma, Karina, Adriaan en Annelien. De informele structuur met inmiddels ook Erna, Josien, Litanja en Rianne, lijkt

de formele structuur toch beduidend langer te overleven. Van de "senioren" wil ik prof. Trijsburg bedanken voor de introductie bij Mary Main. Wim, het volgen van de AAI workshop was uniek, de locatie, het weer en natuurlijk de theorie. Verder wil ik je bedanken voor de vele interviewbesprekingen waardoor het toch mogelijk werd om de klinische indruk te vertalen in meetbare termen. Prof. Passchier wil ik bedanken voor zijn streven om dit proefschrift en de verschillende artikelen voor ook degenen die wat minder met de gehele materie bekend zijn, leesbaar te houden. Jan het was bijzonder prettig dat ik altijd wel even bij je binnen kon lopen. En natuurlijk Hugo, het spreekt vanzelf dat ik je wil bedanken voor je ideeën, je steun en je uitleg betreffende de statistische analyses. Meer nog wil ik je bedanken voor onze gesprekken, over het uitpluizen van wat nou echt de onderzoeksvraag is, wat ik wilde weten en over het onderzoek op zich. Ook jij hebt er toe bij gedragen dat de onderzochte personen nooit te veel op de achtergrond verdwenen.

Dan rest van alle mensen met wie ik gewerkt heb nog een uitzonderlijke categorie, de kamergenoten. Ik begin met terugwerkende kracht en eerst met Leiden. Sarina en Yvonne, natuurlijk is de nieuwbouw een vooruitgang maar alles heeft zijn keerzijde; iedereen heeft nu een eigen kamer. Het was heel prettig om even stoom af te kunnen blazen op onze kamer en na te kunnen praten over wat alle gesprekken ook bij ons losmaakte. Moniek, bij jou kon ik heel wat af kijken en kon ik terecht voor overleg als ik even niet meer wist hoe ik een gesprek zou voeren. Dan in Rotterdam, Annelien je bent mijn paranimf, niemand weet beter hoe ik aan dit proefschrift heb gewerkt. Het oeverloos tegen je aan kunnen praten terwijl je, je er niet aan stoorde was heel prettig. Daarvoor deelde we onze kamer ook met Erna: even sigaretje roken, even bijpraten, even ervaringen uitwisselen.

Ik begon echter met Aad en Petra op de kamer. Petra ik wil jou bedanken voor de samenwerking op HBOC gebied en je interesse gedurende het hele onderzoek. Aad, zonder jou was er geen eens een onderzoek geweest. Ik wil je bedanken voor het feit dat je me de gelegenheid hebt gegeven om het echt mijn onderzoek te maken, je vertrouwen en voor het feit dat ik wist dat ik altijd bij je terecht kon voor overleg. Je enthousiasme voor het onderzoek waarbij de praktijk, en de mensen centraal staan heb je zeker over weten te brengen.

Geen "genetica" en geen "medische psychologie", maar wel heel belangrijk, Laraine Visser ik wil jou bedanken voor het echt engels maken van mijn artikelen, de precisie van je werk, maar vooral voor je snelheid en je enthousiasme.

Naast werk was er gelukkig ook privé. De steun en trots van mijn vader en mijn moeder, mijn schoonouders, en mijn broers, zus en schoonfamilie (Willem en Mary-

Jean, Bram en Agnes, Frédérique en Dirk en Els en Peter plus alle kinderen) en vele vrienden is onmisbaar gebleken. Al was het maar om te bespreken waar we nou eigenlijk allemaal mee bezig zijn (niet waar Anne Griet, Jeannette, Cécille en Pauline) of om te fitness/kletsen (Sandra). Menig gelukkige gebeurtenis in onze omgeving, en soms ook moeilijkere gebeurtenissen, relativeerden de druk van het onderzoek en het schrijven van een proefschrift. Ira, mijn andere paranimf, je kent het onderwerp en je kent mij. Het is een bijzondere combinatie waardoor je me menig maal een hart (een fles Spumante) onder de riem hebt weten te steken. Bart één van die gelukkige gebeurtenissen was ons huwelijk, niet alleen toen, maar aldoor heb je me geholpen te genieten van ons leven samen, proefschrift of geen proefschrift. Jouw humor en relativeringsvermogen, "anders publiceer je toch in de Libelle, begint ook met een L", en je liefde maakte dat ik op momenten dat ik wat minder vertrouwen had, toch gewoon de draad weer op pikte. Ik heb jouw steun heel erg nodig gehad en je was er voor me, dank je.

Anne Christine Dudok de Wit werd geboren op 23 augustus 1966 in Utrecht.

Opleidingen/Werkzaamheden

- | | |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1979-1985 | 1 ^e Vrijzinnig Christelijk Lyceum te Den Haag; ongedeelde VWO (b-pakket). |
| 1985-1986 | Anglia Polytechnic University te Cambridge UK; Proficiency examen en Business Course. |
| 1987-1992 | Vrije Universiteit Amsterdam; Doctoraal Psychologie (afstudeerrichting klinische psychologie, differentiatie therapie).
Academisch Ziekenhuis Vrije Universiteit afdeling Medische Psychologie, sectie volwassenen; therapie- en onderzoekstage. Een retrospectief onderzoek naar de ervaren steun en begeleiding ten tijde van een In Vitro Fertilisatie behandeling. |
| 1992-1997 | Afdeling Klinische Genetica, Academisch Ziekenhuis Leiden, afdeling Klinische Genetica, Academisch Ziekenhuis Dijkzigt en de afdeling Medische Psychologie en Psychotherapie Erasmus Universiteit Rotterdam; Promotieonderzoek: de psychologische implicaties van voorspellend DNA-onderzoek bij later in het leven optredende erfelijke aandoeningen. Een kwalitatief, patiënt gebonden onderzoek. |
| 1997 | Afdeling Medische Psychologie en Psychotherapie, Erasmus Universiteit Rotterdam en afdeling Klinische Genetica, Academisch Ziekenhuis Leiden: een vervolgonderzoek naar de psychologische effecten op de langere termijn van voorspellende DNA-diagnostiek voor de ziekte van Huntington.
Vanaf september aan de RINO Noord-Holland te Amsterdam (Stichting Regionale Instelling Nascholing en Opleiding): de opleiding tot psychotherapeute (gedrags- en systeemtherapie). |

Stellingen

behorend bij het proefschrift

"The Psychological Implications of Presymptomatic DNA Testing for
Autosomal Dominant Inheritable Late Onset Disorders"

van A.C. Dudok de Wit

I

De psychologische reacties op voorspellend testen voor de ziekte van Huntington blijken een bruikbaar model voor testen voor andere later in het leven optredende erfelijke aandoeningen. (dit proefschrift)

II

De psychologische spanning die iemand voorafgaande aan een voorspellend genetisch onderzoek ondervindt, wordt vooral bepaald door de ervaring met de desbetreffende erfelijke ziekte binnen diens familie, en de mate waarin deze ziekte het leven van de betrokkene tot nu toe beïnvloed heeft. (dit proefschrift)

III

Wanneer een verhoogde psychische spanning voor, tijdens of na afloop van een voorspellend genetisch onderzoek blijkt, is dit een aanwijzing dat betrokkene actief bezig is de gevolgen van de testuitslag te verwerken. Een lage spanningsscore kan erop duiden dat verwerking (nog) niet is opgetreden. (dit proefschrift)

IV

De beleving en interpretatie van het gesprek waarin een adviesvrager informatie krijgt over de (mogelijke) erfelijkheid van een aandoening in diens familie, wordt mede beïnvloed door de vragen en angsten van niet aanwezige familieleden. (dit proefschrift)

V

Mensen die voor voorspellend genetisch onderzoek komen, hebben veelal reeds een afwegingsproces doorgemaakt waarbij zij voor zichzelf uiteindelijk één keuze hadden. De klinisch geneticus moet bij voorkeur in het eerste contact proberen dat afwegingsproces te volgen en niet te beoordelen of veroordelen. (dit proefschrift)

VI

De ontwikkeling in de afgelopen decennia van voorspellend genetisch testen wordt niet zelden als een succesverhaal bestempeld; een dergelijke uitspraak betekent echter een onderschatting van het gecompliceerde aanpassingsproces van geteste personen, hun partners en familieleden. (G.Evers-Kiebooms et al., M.Mlynik-Szmid, A.Tibben et al. Lancet 1997 vol 346 pag 808-9).

VII

De waarneming van Prof. Galjaard dat 'alle mensen ongelijk zijn', wordt ook door de bevindingen van dit proefschrift gesteund. (Prof.dr.H. Galjaard, *Alle mensen zijn ongelijk*, 1996, Balans, Amsterdam)

VIII

De invloed die doktoren (kunnen) hebben op het denken van patiënten over de consequenties van (erfelijke) ziekten is al te lang niet onderzocht door medisch psychologen.

IX

De motivatie tot therapeutische trials dient, naast de beoogde verlenging van de levensverwachting, ook gericht te zijn op de kwaliteit van leven van de patiënt en van diens naasten, alsmede op de kosten van de behandeling voor de gemeenschap. De te behandelen patiënten en hun naasten zouden ook daarover geïnformeerd moeten worden.

X

Ongewenste kinderloosheid vormt een grote leegte voor een paar met kinderwens. Om het leven op een andere wijze inhoud te geven is een zekere acceptatie noodzakelijk. De vanzelfsprekendheid van de steeds voortschrijdende mogelijkheden binnen de voortplantingstechniek legt ten eerste een verplichting bij het paar om te "bewijzen" wat zij over hebben voor een kind, en ten tweede stelt dit het moment van acceptatie van hun kinderloosheid steeds verder uit.

XI

Een mens zou, volgens de gehechtheidstheorie van Bowlby, het gelukkigst zijn wanneer het leven bestaat uit het exploreren van het onbekende met als continue basis een stabiele hechting. (J.Bowlby, *A secure base. Clinical applications of attachment theory*, 1988, Routledge London)

XII

Het kruid dat Hermes aan Odysseus gaf om hem tegen de toverdrank van Circè te beschermen, en dat door de goden 'molu' werd genoemd, is op grond van de beschrijving van de plant *zwarte wortel, witte bloem en moeilijk uit te graven*, en de werking als tegengif, waarschijnlijk identiek aan de Alruin (*Mandragora officinalis*), een mediterrane plant die tot de familie van de nachtschades behoort. (Homerus, *Odyssee*, boek X, vers 302-6)

XIII

Het schrijven van een proefschrift toont overeenkomst met de beklimming van een bergtop (zoals de 'Pain de Sucre' in de Franse Alpen). Wanneer je maar stug doorzet en je op iedere volgende stap concentreert, is de klus op een bepaald moment geklaard en de top bereikt. Echter in beide gevallen is een goede gids onontbeerlijk.