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Predictive Genetic Testing and Counselling for
Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

A prospective follow-up study of
acceptance and psychosocial consequences

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Academic dissertation

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The road not taken

*Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveler, long I stood
And looked down one as far as I could
To where it bent in the undergrowth.*

*Then took the other, as just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for that the passing there
Had worn them really about the same.*

*And both that morning equally lay
In leaves no step had trodden black.
Oh, I kept the first for another day!
Yet knowing how way leads on to way,
I doubted if I should ever come back.*

*I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I --
I took the one less traveled by,
And that has made all the difference.*

Robert Frost, 1915

to Jussi, Oskar and Johannes

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1. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles referred to in the text by their Roman numerals:

- I Aktan-Collan K., Mecklin J-P., Järvinen H., Nyström-Lahti M., Peltomäki P., Söderling I., Uutela, A., de la Chapelle A., and Kääriäinen H. Predictive genetic testing for hereditary non-polyposis colorectal cancer: uptake and long-term satisfaction. *Int J Cancer*, **89**, 44-50, (2000).
- II Aktan-Collan K., Mecklin J-P., Peltomäki P., de la Chapelle A., Uutela A., and Kääriäinen H. Evaluation of a counselling protocol for predictive genetic testing for hereditary non-polyposis colorectal cancer. *J Med Genet*, **37**, 108-113, (2000).
- III Aktan-Collan K., Haukkala A., Mecklin J-P., Uutela A., and Kääriäinen H. Psychological consequences of predictive genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): a prospective follow-up study. *Int J Cancer*, **93**, 608-611, (2001).
- IV Aktan-Collan K., Haukkala A., Mecklin J-P., Uutela A., and Kääriäinen H. Comprehension of cancer risk 1 and 12 months after predictive genetic testing for hereditary colon cancer. *J Med Genet*, **38**, 787-792, (2001).
- V Aktan-Collan K., Haukkala A., and Kääriäinen H. Life and health insurance behaviour among individuals who have undergone predictive genetic testing programme for hereditary non-polyposis colorectal cancer (HNPCC). Submitted.

Some unpublished results will also be presented.

2. ABBREVIATIONS

ANOVA	analysis of variance
<i>BRCA1</i>	breast and ovarian cancer gene-1
<i>BRCA2</i>	breast and ovarian cancer gene-2
CI	confidence interval
FAP	familial adenomatous polyposis
HD	Huntington's disease
HNPCC	hereditary non-polyposis colorectal cancer
ICG-HNPCC	the international collaborative group on HNPCC
LFS	Li-Fraumeni syndrome
MEN	multiple endocrine neoplasia
<i>MLH1</i>	human mutation l-homologue 1
MMR	mismatch repair
<i>MSH2</i>	human mutation s-homologue 2
<i>MSH6</i>	human mutation s-homologue 6
OMIM	online Mendelian inheritance in man
OR	odds ratio
<i>PMS1</i>	human postmeiotic segregation increased-1
<i>PMS2</i>	human postmeiotic segregation increased-2
SD	standard deviation
SPSS	statistical package for the social sciences
STAI	state-trait anxiety inventory

3. ABSTRACT

Predictive genetic testing for hereditary cancer allows identification of those individuals with the mutation (mutation-positive), who should be subjected to cancer surveillance aiming at early detection of cancer, and those individuals without the mutation (mutation-negative), whose unnecessary worry may be alleviated and who need not undergo frequent surveillance. Nevertheless, there is a risk that the psychosocial burden of knowing that one is at high risk of developing cancer may outweigh the possible benefits.

During 1995-1996, predictive genetic testing and counselling were offered to members of 36 families with hereditary non-polyposis colorectal cancer, which is the most common form of hereditary colon cancer. Simultaneously, acceptance of counselling and the psychosocial impact of testing were assessed with prospective follow-up questionnaires. Assessments were also made before the first counselling, at the test disclosure session, and 1 and 12 months after testing. The counselling protocol included a first baseline educational session, a 2-week period for reflection and a test disclosure session.

Of the 446 eligible high-risk subjects, 90% (n=401) initially consented to the study, 85% (n=381) returned the baseline questionnaire, 80% (n=347) attended the first counselling session and 75% (n=334) accepted the test. According to a logistic regression analysis, men, those living alone and those without a previous history of colorectal cancer surveillance were more likely than the others not to participate in the questionnaire study and, consequently, not to take the test. Among those who participated in the study, employment was found to predict uptake of the test. Of those tested, 30% (n=99) were mutation-positive and 70% (n=234) mutation-negative. The 1- and 12- month follow-up questionnaires were filled in only by those accepting the test: 67% (n=299) and 61% (n=271) of all those initially eligible for the study. One year after testing, irrespective of the test result, the great majority was content with their decision to take the test, had confidence in the result and would have made the same decision again.

The pre-test counselling was considered fairly or very useful by 89% of the respondents and over 80% of the respondents considered a single post-test session sufficient. Fifty-two per cent might have used extra psychological support, had it been offered with the counselling. On

enquiry 1 year after receiving the test result, only 2% stated that the need for support was greatest at that time, while the majority (46%) reported that the need for support had been greatest at the moment of test disclosure.

Although, at every phase of the study, the mutation-positive individuals were more afraid of cancer than those who were mutation-negative, in both groups fear of cancer decreased significantly from baseline. The mutation-positive subjects were more anxious than their counterparts immediately after the test disclosure but, at the follow-ups, the differences had disappeared.

Although practically all the respondents recalled whether they had inherited the mutation, only 48% (n=40) of the mutation-positive subjects, compared with 92% (n=170) of the mutation-negative subjects, interpreted their likelihood of developing colorectal cancer correctly ($p < 0.0001$). At the 1-year follow-up, incorrect interpretation (underestimation of the risk) among the mutation-positive group had increased ($p < 0.05$). According to multiple regression analyses, the best predictor of understanding, irrespective of the test result, was the pre-test perception of risk. Among the mutation-negative subjects, heightened anxiety, measured immediately after the test disclosure, also predicted misunderstanding.

In this large-scale research setting, the uptake of the predictive test was high. No signs of overall harmful psychosocial effects of testing were detectable in the study; however, some individual reactions differed from the average. Furthermore, misunderstanding of the meaning of the test result was common among the mutation-positive subjects. The small number of those remaining worried by the high risk of cancer or despite an actual low risk should be taken into account, possibly by offering further counselling sessions, with emphasis on psychological support.

4. INTRODUCTION

Genetic testing has become a useful tool in diagnosing genetic disorders and predicting future genetic illnesses, and may reach new dimensions when genes predisposing to common diseases become known (Collins and McKusick, 2001). Characterisation of such genes may eventually lead to a deeper understanding of the diseases, resulting in better prevention and treatment. Even before that, finding such genes will make predictive testing possible, and possibly lead to more patients and relatives being tested. As increasing amounts of information about many diseases are easily accessed by the internet, concerns have been expressed about uncontrollable phenomena, such as commercial genetic testing without involvement of medical professionals (Harper, 1997a; Ponder, 1997; Nelkin, 1998). Distinguished committees on genetic testing and screening have stressed the importance of pilot studies and related investigations before genetic tests move to widespread or routine clinical use (Nuffield Council on Bioethics, 1993; Andrews et al., 1994). Professionals concerned with ethics have emphasised the importance of understanding the psychosocial impact of genetic testing and the ways in which testing may be supplied (Knoppers and Godard, 1998).

Recent advances in molecular genetics have made predictive genetic testing for hereditary cancer possible. Cancer is rarely hereditary (Fearon, 1997), but hereditary forms of cancer have been described in almost every type of cancer, hereditary colon cancer being one of the most common forms (Online Mendelian Inheritance in Man, OMIM). Predictive genetic testing for hereditary cancer may offer benefits to an individual or a family (Lynch et al., 1999). If the mutation is identified in the family, it is possible to offer testing that will end the uncertainty about the mutation status. Testing often tells that the individual does not have the suspected mutation and, thus, relieves unnecessary worry. Alternatively, the mutation is found and the information may lead to identification of treatable cancers at an early stage. The result may also clarify the cancer risks of other close family members. Besides the benefits, however, there are obvious adverse effects, including the risk of increased anxiety about one's health and uncertainty about whether to disclose the genetic information to other family members (Julian-Reynier et al., 1996; Julian-Reynier et al., 2000).

The previous literature on predictive genetic testing for late-onset disease mainly comprises experience of presymptomatic genetic testing for Huntington's disease (HD). These studies have clearly suggested that testing, and even the offering of a test, have deep psychological impacts on the individual (Codori and Brandt, 1994; Kessler, 1994). After comprehensive counselling, only a minority (10-15%) of the individuals at risk have consented to be tested (Hayden, 2001). However, among those tested, the number of catastrophic psychological events has been minimal (Almqvist et al., 1999). As HD is a condition with progressive dementia and no preventive treatment, these experiences cannot be simply applied to other types of disease.

Cancer in general has negative associations, such as death and fear (Evers-Kiebooms et al., 2000). It is important to investigate of the influence of predictive genetic testing on these connotations. Thus far, very few studies have provided results concerning the short and longer term psychological consequences of predictive genetic testing for cancer, based on hundreds of unaffected individuals and including individualised genetic counselling and a period for reflection, which are considered essential for autonomous decision making (Decruyenaere et al., 2000). Furthermore, no studies of predictive genetic testing for cancer have investigated the understanding of the test result, in terms of the post-test risk of cancer, which may be a crucial factor affecting cancer surveillance behaviour. This study was conducted to investigate these aspects of genetic testing and counselling with special reference to hereditary non-polyposis colorectal cancer (HNPCC).

5. REVIEW OF THE LITERATURE

5.1. GENETIC COUNSELLING AND PREDICTIVE GENETIC TESTING FOR LATE-ONSET AUTOSOMAL DOMINANT DISEASE

5.1.1. Genetic counselling

The process of genetic counselling can be defined as the provision of information about inherited conditions (Harper, 1998). In a broader perspective, it can be seen as a communication process, in which a trained person tries to help counsellee(s) (a) to understand the medical facts (diagnosis, prognosis, treatment), (b) to see how heredity is involved in the disorder and how it may affect their relatives, (c) to realise the possibilities of risk recurrence, (d) to choose the best possible way to act in terms of the counsellees' view of their risk, values, and goals, and (e) to adjust to the situation in the best possible way (Fraser, 1974).

Decision-making and personal adjustment are regarded as especially essential components of genetic counselling; however, the role of such counselling is not to persuade the counsellees to take certain medical decisions but to help them to make the best decisions for themselves (Clarke, 1997). Traditionally, genetic counselling has aimed to be non-directive (Shiloh, 1996), which can be defined as helping counsellees to arriving at the best decisions from a personal perspective but not guiding them towards any particular decision. The overall possibility of this method has been contested. A complementary term and approach, named shared decision-making, has been introduced for use in situations where non-directiveness is not possible, such as when the clinicians or counsellor would like the counsellee to transmit information about their genetic condition to their family members or when the person at risk could clearly benefit from medical surveillance (Elwyn et al., 2000). In the shared decision-making model, the wide system of values covered by the counsellees is respected and emphasised, but the importance of the opinion of the medical expert is not forgotten in the process.

5.1.2. Applications of genetic testing

Regarding genetic testing for late-onset autosomal dominant diseases, there are two main applications: diagnostic and predictive testing. Diagnostic testing means detection of the presence or absence of a genetic mutation in a patient with a disease, whereas predictive testing means detection of a mutation in a healthy individual with a high a priori risk. Diagnostic genetic tests can be considered, in many respects, similar to conventional medical testing, such as blood count, as both inform about the current condition. By contrast, predictive testing tells about the probability of developing a disease in the future, carrying a degree of uncertainty (Evans et al., 2001). Both the expressions predictive and presymptomatic are used in the literature concerning genetic testing of healthy individuals at risk. Some authorities have suggested a clear distinction between the concepts predictive and presymptomatic (Harper, 1997b). The term predictive is suggested be used in connection with a broader range of tests that reveal a low or high susceptibility to a disease but do not necessarily imply any degree of certainty, whereas the term presymptomatic should be used only for diseases with Mendelian inheritance that almost inevitably will develop, such as Huntington's disease (HD). However, the world-wide use of these terms in the publications concerning testing for HD and hereditary cancer has not been systematic.

In this thesis, the term predictive has been chosen to describe the nature of the testing for HNPCC and other cancers, because of incomplete penetrance of the genes governing their susceptibility, leaving a degree of uncertainty in the prognosis.

5.1.3. Ethical aspects of genetic testing

Genetic testing is problematic, in that it gives information that has implications not only for the person tested but also for the family members, sometimes leading to complex ethical questions (Knoppers and Godard, 1998). In the context of genetic testing, four ethical principles have often been emphasised: the principle of right to autonomy, the principle of justice, the principle of beneficence and the principle of non-maleficence (Beauchamp and Childress, 2001). These principles outline the importance of informed consent and also time to reflect on the decision about the test to enable autonomous decision-making and privacy issues in genetic testing (Nuffield Council on Bioethics, 1993; Wood-Harper and Harris, 1996). All this may best be assured by the prerequisite that predictive genetic testing for late-

onset disease should be offered only in conjunction with genetic counselling (International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea, 1994; Biesecker and Garber, 1995; Harper, 1997b). Several recommendations supporting this view have been given by different societies and by professionals of medicine, of ethics and of psychology (Nuffield Council on Bioethics, 1993; Statement of the American Society of Human Genetics on genetic testing for breast and ovarian cancer predisposition, 1994; Statement of the American Society of Clinical Oncology, 1996, Ponder, 1997; Schneider, 1997; Decruyenaere et al., 2000; Järvinen and Aarnio, 2000; Eng et al., 2001).

These issues have become increasingly important now that researchers have sequenced the whole genome during the Human Genome Project and there is an ongoing campaign to find ever-increasing numbers of genes and to understand their function and meaning. Along with the project, a committee was established for investigating the ethical, social and legal implications of genetic testing, and the themes especially addressed were confidentiality of data, informed consent, freedom from constraint and selection in insurance (Collins and McKusick, 2001).

The number of reports concerning **predictive genetic testing for children** is markedly smaller than of reports on testing of adults in hereditary cancer. The issue of autonomy and the right not to know are especially relevant when testing of children is considered (Wertz et al., 1994). Given that the disease will not develop for tens of years and that the psychosocial consequences of testing are not well known, it has been argued that testing should always be postponed until the children are able to decide for themselves about testing when they become (legally) adults. However, if the disease develops in childhood or in adolescence and there are methods for preventive treatment, such as in families with familial adenomatous polyposis (FAP) or with the syndromes of multiple endocrine neoplasia (MEN), testing has been considered to be motivated (Wells et al., 1994; Codori et al., 1996; Evans et al., 1997; Grosfeld et al., 2000a; Grosfeld et al., 2000b).

5.1.4. Predictive genetic testing for Huntington's disease (HD)

The concept of presymptomatic genetic testing for an autosomal dominant disease with late onset was first introduced for HD in 1986, based on linkage analysis (Harper, 1991). As HD is

a severe neuropsychological disease occurring in adults, with neither cure nor prevention, the psychological consequences of the testing, such as anxiety, depression, family conflicts, and ultimately suicides, were a public concern for HD at that time. Initially, the test would reveal a statistically increased risk of having inherited the disease-predisposing mutation that would finally lead to almost inevitable disease and death, and expose the children to a 50% risk. Alternatively, the result could be a decreased risk, which would with high probability, mean that there was no risk of the disease or risk to the children. The history of predictive genetic testing is well illustrated by the example of HD: at first the testing was uncertain, and, only in 1993, when direct detection of the mutation became possible, did the test result become more definite, in that, in practice, the mutation was either found or not found (International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea, 1994). To ensure that the meaning of the test and its consequences were understood, the testing was only offered after a number of genetic counselling sessions (2-4), which thoroughly covered information about the nature of the disease, its mode of inheritance, advantages and disadvantages, and at least two blood samples were taken and analysed to minimise any mistakes during the technical laboratory processes. Several post-test sessions, with emphasis on psychological support, succeeded the test disclosure session. A counselling procedure often used in counselling for HD is presented in Figure 1 (Harper, 1997c).

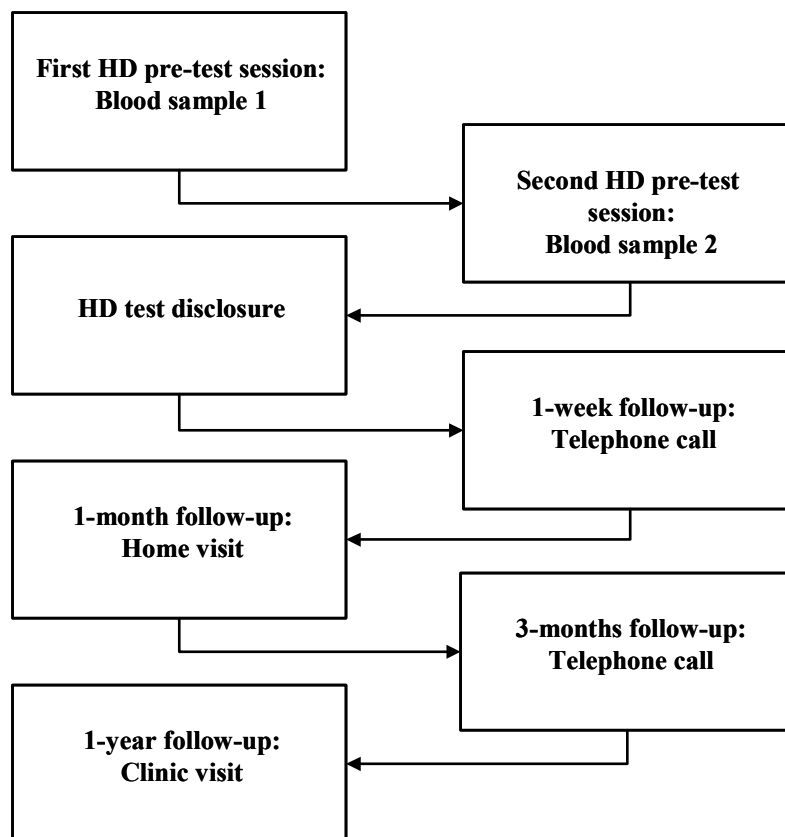
The uptake of the predictive genetic testing for HD has been reported to be low (10-15%) in different countries (Craufurd et al., 1989; Tibben et al., 1992; Quaid and Morris, 1993; Hayden, 2001). The lengthy counselling protocol has also been considered a relevant reason for refusing the counselling and the test (Kessler, 1994; Decruyenaere et al., 1997). Predictors of the test uptake have revealed that those undergoing the procedure are characterised by strong ego characteristics, perceived ability to cope with the test result and a high perceived pre-test risk (Decruyenaere et al., 1997; Decruyenaere et al., 1999).

The risk of post-test adverse psychological reactions has been suggested to be minimal (Wiggins et al., 1992) and, indeed, a recent world-wide multi-centre survey revealed that a gratifyingly low rate of catastrophic events (ultimately suicides) had occurred among those tested (Almqvist et al., 1999). Characteristic features found for those few (<1% of those tested world-wide) more likely to have faced a catastrophic event were previous psychiatric history, female sex and unemployment status. No differences in catastrophic events have been

detected between those tested by linkage analysis and by direct mutation analysis (Almqvist et al., 1999). Moreover, among those having the good test result, a number of adverse effects of testing have been described, such as "survivor guilt", difficulties in finding a new life perspective, and worry about relatives with the mutation (Huggins et al., 1992; Tibben et al., 1993).

Possible reasons for the rarity of the problems described after testing for HD have been speculated. Apparently, those few proceeding to take the test, are psychologically strong (Decruyenaere et al., 1997; Decruyenaere et al., 1999). However, some authors have suggested that, among those who are found to have the mutation, the impact of the test result is largely denied (Tibben et al., 1993; Tibben et al., 1997). Most of the studies investigating the psychological consequences of presymptomatic testing for HD (and concluding that it is overall beneficial) have comprised only a short follow-up (1 week-6 months), but the few studies with a longer term follow-up (3-15 years) have supported these results (Tibben et al., 1997; Hayden, 2001).

Figure 1. A frame of the counselling procedure used in Huntington's disease (HD)



5.1.5. Predictive genetic testing for hereditary cancer

Cancer is exceedingly common in Western countries. In Finland, one in four will get the disease (Finnish Cancer Registry, 2001). Although cancer is a disease caused by gene defects, it is hereditary only in 5-15% of cases (Fearon, 1997; Lynch and de la Chapelle, 1999). Although rare, hereditary forms have been described in almost every type of cancer (OMIM). In these cases, the gene defects have been transmitted from parents to children in the gametes, often leading to increased susceptibility to cancer. Typical features of inherited cancer syndromes are numerous family members diagnosed with cancer at an especially young age or affected individuals developing multiple primary cancers.

There are similarities between HD and many types of hereditary cancer in the mode of inheritance (autosomal dominant) and the age at diagnosis, which is usually in adulthood in both diseases. In contrast to HD, in hereditary cancer, of which colorectal cancer is as an example, methods for early detection and treatment are available (Benson et al., 2000; Järvinen et al., 2000; Renkonen-Sinisalo et al., 2000). However, it should be noted that in different cancers the possibilities of early detection and treatment are highly variable.

Predictive genetic testing for hereditary cancer allows identification of those with the mutation (mutation-positive), who should undergo cancer surveillance aiming at early detection (if available) and those without the mutation (mutation-negative), whose unnecessary worry can be alleviated and who need not undergo frequent surveillance (Ponder, 1997; Petersen and Codori, 1998).

Experience of studies on genetic testing for hereditary colorectal and breast cancer

The studies reviewed below focus on hereditary colorectal cancer (represented by HNPCC and FAP) and hereditary breast cancer being two of the most common forms of hereditary cancer syndrome.

Although there are many reports of anticipated responses to the (hypothetical) offer of testing (Struewing et al., 1995; Lerman et al., 1996a; Codori et al., 1999; Glanz et al., 1999; Petersen et al., 1999; Vernon et al., 1999), there are few published accounts of actual uptake of genetic tests for cancer, especially among healthy individuals.

Table 1 is a list of description of 21 studies concerning (predictive) genetic testing for either colorectal or breast cancer. The studies were made between 1993 and 2001. Of these studies, eight concerned HNPCC testing (one of which also involved FAP), one FAP, and 12 hereditary breast cancer. Twelve of the studies were performed in the US (Lynch et al., 1993a; Lerman et al., 1996b; Lynch et al., 1996; Croyle et al., 1997; Lynch et al., 1997; Vernon et al., 1997; Lerman et al., 1998; Loader et al., 1998; Gritz et al., 1999; Lerman et al., 1999; Johnson et al., 2000; Miron et al., 2000), four in the Netherlands (Menko et al., 1996; Lodder et al., 1999; Meijers-Heijboer et al., 2000; Lodder et al., 2001), three in the UK (Watson et al., 1995; Watson et al., 1996; Evans et al., 1997), one in New Zealand (van de Water et al., 1994), and one in Australia (Stanley et al., 2000). Concerning genetic testing procedures, 18 studies were based on direct mutation analysis and three on genetic linkage analysis. In 11 studies, the testing comprised both affected (patients with cancer) and unaffected subjects (diagnostic and predictive testing) and in three studies included entirely those affected with cancer (diagnostic testing). Six studies consisted exclusively of predictive genetic testing. Eight of the 21 studies were based on one or two families. The number of subjects varied from 32-682.

Concerning **counselling protocols**, 13 out of the 21 studies reported that they had provided genetic counselling before the test and all but one at the test disclosure. No studies reported randomisation concerning counselling. In seven of the studies, pre-test counselling was offered individually and in three of the studies the education counselling was held in group sessions including 20-40 family members. In some studies (5/21), counselling was provided after the mutation analysis had been performed, prior to test disclosure. In these studies, the family members had earlier provided blood samples for research purposes but had made no commitment to receive the results. If they wished to hear their result, this was possible immediately after the information counselling. A period for reflection was reported to have been included in the counselling protocol in two studies. **Test uptake** varied between 14 and 96%.

Psychological measures were used in eight studies, all of which consisted of baseline assessment and seven included a follow-up after the test disclosure (after 1 week to 12 months). Vernon et al. studied baseline characteristics of psychological distress among **colorectal cancer** patients who wanted the diagnostic test for HNPCC (Vernon et al., 1997).

Less formal education, fewer social contacts and less satisfaction with them predicted high scores of both anxiety and depression. Gritz et al. present preliminary 2-week follow-up data of 11 patients from the same study population who tested positive for HNPCC (Gritz et al., 1999). Those who were initially distressed continued to be distressed although mean anxiety and depression decreased. Lerman et al. assessed predictors of gene test uptake among affected and unaffected subjects in HNPCC families (Lerman et al., 1999). They found that the presence of depressive symptoms reduced the rates of uptake. By contrast, a high level of education and previous participation in a genetic linkage study predicted test uptake.

Watson et al. found that in healthy individuals at high risk for **hereditary breast cancer**, levels of psychological morbidity and concerns about cancer were not especially high 1 year after testing, except among those who had expected the opposite result (Watson et al., 1996). Croyle studied both affected and unaffected members of families that were mutation-positive for *BRCA1*. Although general distress remained unchanged among all the mutation-positive individuals, those who were unaffected although they had inherited the mutation had the highest degree of distress 2 weeks after the test disclosure (Croyle et al., 1997). Lerman and colleagues found a difference in post-test distress: those who were positive for the *BRCA1* mutation were more distressed than those who were mutation-negative (Lerman et al., 1998). However, this was explained by the decrease in distress among the mutation-negative individuals rather than by an increase in distress among the mutation-positive subjects. Lodder et al. studied the levels of pre-test distress among high-risk individuals in *BRCA1/BRCA2* families and found increased levels of distress in 25% of the subjects (Lodder et al., 1999). However, additional psychological support was received only by 7% of all subjects. In the same study sample, they later found that 20% of the mutation-positive and 11% of the mutation-negative women reported high post-test anxiety at 3-6 weeks follow-up (Lodder et al., 2001).

Table 1. Studies on (predictive) genetic testing for hereditary colorectal and breast cancer

Reference	Test for subjects	Study subjects	Family n	Subjects n	Counseling before testing	Reported time for reflection	Test disclosure counseling	Test uptake	Psychological measures	BL	Follow-up assessment
(van de Water et al., 1994)	HNPCC	A, UA	1	75	-	-	+	80%	-	-	-
(Lynch et al., 1996)	HNPCC	A, UA	1	50	+F	-	+	NR	-	-	-
(Menko et al., 1996)	HNPCC	A, UA	2	NR	+I	-	+I	NR	-	-	-
(Evans et al., 1997)	FAP	UA	74	140	+I	-	NR	85%	-	-	-
(Vernon et al., 1997)	HNPCC	A	NR	267	-	-	+I	80%	STAI, CES-D	+	-
(Gritz et al., 1999)	HNPCC	A	NR	269	-	-	+I	NR	Social support STAI, CES-D, IES, MBSS,	+	2 weeks (n=11)
(Stanley et al., 2000)	HNPCC	UA	1	48	+I	-	+I	81%	-	-	-
(Lerman et al., 1999)	HNPCC	A, UA	4	208	+F	-	+I	43%	CES-D, IES	+	-
(Johnson et al., 2000)	FAP, HNPCC	A, UA	NR	91, 57	+	-	-NR	85%, 14%	-	-	-
(Lynch et al., 1993a)*	BRCA	A, UA	1	176	+F	-	+I	32%	Opinions	+	3-6 weeks
(Watson et al., 1995)*	BRCA	UA	2	32	NR	-	-	41%	NR	NR	NR
(Watson et al., 1996)*	BRCA	UA	2	32	+I	+	+(1 month)	41%	GHQ12, STAI, CAHS, IES	+	1-2 weeks, 3+12 months
(Lerman et al., 1996b)	BRCA	A, UA	13	279	-	-	+I	43%	CES-D, Functional health	+	1 month
(Lynch et al., 1997)	BRCA	A, UA	14	388	-	-	+I	47%	Opinions	+	-
(Croyle et al., 1997)	BRCA	A, UA	1	213	+I	-	-	28%	STAI, IES	+	1-2 weeks
(Lerman et al., 1998)	BRCA	A, UA	33	327	-	-	+I	57%	IES, CES-D	+	1 and 6 months
(Loader et al., 1998)	BRCA	A, UA		140	+I	+	+I	70%	-	-	-
(Lodder et al., 1999)	BRCA	UA	33	118	+I	-	+I	72%	IES, HAD, Personality traits	+	-
(Miron et al., 2000)	BRCA	A	NR	221	+	NR	+	96%	-	-	-
(Meijers-Heijboer et al., 2000)	BRCA	UA	53	682	+I	+	+I	38%	-	-	-
(Lodder et al., 2001)	BRCA	UA	33	118	+I	-	+I	72%	IES, HAD	+	3-6 weeks

* only linkage-analysis performed

A= affected, BL=baseline assessment, BRCA= breast cancer, CAHS= Cancer Anxiety and Helplessness Scale, CES-D= Center for Epidemiological Studies-Depression, F= families together, FAP= familial adenomatous polyposis, GHQ= General Health Questionnaire 12, HAD= Hospital Anxiety and Depression, HNPCC =hereditary non-polyposis colorectal cancer, I= individualised, IES= Impact of Event Scale, MBSS= Miller Behavioral Style Scale, NR= not reported, STAI =State and Trait Anxiety Inventory, UA= unaffected

Other cancers

Some studies of small populations have compared the effects of predictive genetic testing for neurodegenerative disease and cancer, and their preliminary results suggest that those at risk for cancer are less distressed than those at risk for untreatable disease (Dudokdewit et al., 1997; Dudokdewit et al., 1998a; Dudokdewit et al., 1998b; Dudokdewit et al., 1998c). Studies concerning the genetic testing of cancer syndromes such as MEN, Li-Fraumeni syndrome (LFS) and von Hippel-Lindau disease have also been published and in some of them (LFS), it seems that the uptake might be as low than in HD. In some of these studies, the test was also offered to children (Wells et al., 1994; Evans et al., 1997; Grosfeld et al., 2000a).

5.1.6. Insurance and genetic testing

”Among the various social implications of new developments in genetics, fear of discrimination in the field of insurance has given more concerns than almost any other issue” (Harper, 1997d). During recent years, issues concerning the impact of genetic tests on insurance policies have been widely discussed by geneticists and insurance companies and also by the public in general, and the following concerns have repeatedly been raised (Rothstein, 1995; Morgan, 1996; Harper, 1997d; Ponder, 1997; Reilly, 1998; Volpe, 1998; Wiesing, 1999): Are those who are revealed to be at high genetic risk of contracting a disease entitled to the same types of insurance as others? And from the opposite standpoint, are insurance companies entitled to discriminate against individuals because of their genetic make-up?

Finland has a public health care and social security system. Thus, the market for private life or health insurance is small. Life insurance serves mainly as an extra guarantee of the financial survival of close family members in case of death. Finnish citizens do not need a life insurance in order to buy a house, for instance, as the house itself serves as a mortgage for the loan, and the health care system is based mainly on a public tax-funded organisation. The system has been created to maintain equal opportunities among the citizens, irrespective of their economic or social status, to achieve social security and have access to health care services. Despite this, 20% of the total Finnish population and 30% of those employed were covered by life insurance policies in 1999 (Statistics Finland, 1999; The insurance companies 1999, 2001). In Sweden, where a similar social security and health care system is in force, the corresponding percentage of life insurance has been reported to be almost twofold (Rosen,

1999) and in the UK manyfold, because of its importance in house purchase (Wilkie, 1998). There are no official statistics concerning private health insurance in Finland, perhaps on account of its minor role in the health care system. The reason for taking a health insurance is primarily not to ensure the possibility of health care, which is offered by the public system anyway, but to obtain easier access and more convenient services than are available in the public sector (including the possibility to choose the physician).

Concerns over genetic discrimination in Finland, especially regarding insurance issues, have been expressed both by health care professionals and by the public (Jallinoja et al., 1998; The Ministry of Social Affairs and Health, 1998). Thus far, there is no legislation concerning insurance and genetic testing. Finnish insurance companies have undertaken not to query the family history or the results of genetic tests at the moment of underwriting. However, no time limits have been given for this moratorium.

5.2. HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)

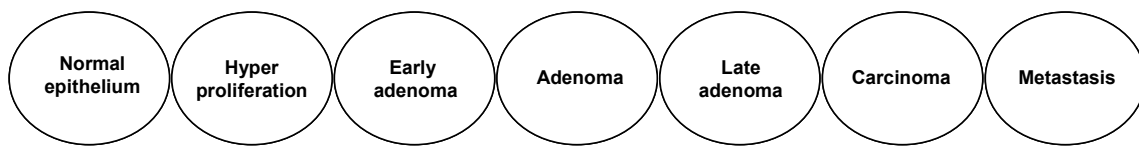
5.2.1. Characteristics of HNPCC

HNPCC, also named Lynch syndrome, was first described by Warthin in 1913 (Warthin, 1913) and more recently characterised by Lynch (Lynch and Krush, 1971). In Finland, clinical studies in families with HNPCC were started by Peltokallio some 40 years ago and continued by Mecklin and Järvinen who laid the groundwork for this project (Peltokallio and Peltokallio, 1966; Mecklin, 1987). Many of the families concerned originate from two small geographical areas, in Eastern and South-Eastern Finland. For many of the families, genealogical and genetic studies have traced their descent from two common ancestors some 500 years ago (Nyström-Lahti et al., 1994; Moisio et al., 1996).

In 1993, clues about the genetic basis of HNPCC were found when the susceptibility genes were mapped to chromosome 3 (Aaltonen et al., 1993; Peltomäki et al., 1993). Soon after that, several genes and mutations were cloned and characterised (Fishel et al., 1993; Leach et al., 1993; Nicolaides et al., 1994; Palombo et al., 1996). Some clues about the nature of the genes were discovered: mutations in five mismatch repair (MMR) genes *MLH1*, *MSH2*, *PMS1*, *PMS2*, *MSH6* seemed to account for a great portion of familial colorectal cancer (Kinzler and Vogelstein, 1996; Peltomäki and de la Chapelle, 1997).

If an MMR gene, such as *MLH1*, is inactivated, this gives rise to MMR deficiency, which in turn, induces secondary mutations in others genes (Peltomäki, 2001). As a result of accumulated mutations in oncogenes and tumour suppressor genes, cells may show adenomatous growth, which may eventually develop into cancer (see Figure 2) (Kinzler and Vogelstein, 1996).

Figure 2. The tumour development model in colorectal cancer. Modified from Kinzler and Vogelstein (1996).



Colorectal cancer in Finland has an incidence of over 2000 cancer diagnoses per year (Finnish Cancer Registry, 2000). Most of the cases of colorectal cancer are sporadic. Although HNPCC is the most common form of hereditary colon cancer, according to a recent large study, it seems to account for only about 2-3% of the total colorectal cancer burden (Aaltonen et al., 1998).

In HNPCC (OMIM 120435, 120436 and 114500), the mode of inheritance is autosomal dominant (Lynch et al., 1993b; Lynch and de la Chapelle, 1999). The name includes "non-polyposis"; however, a few adenomatous polyps are often detected as benign or pre-malignant pre-stages of cancer. Diagnostic criteria (see Table 2) for HNPCC were first proposed by the International Collaborative Group (ICG) on HNPCC in 1990 and later revised to include various extracolonic cancers (Vasen et al., 1991; Vasen et al., 1999). Colorectal cancer is diagnosed on average at the age of 45, is often multiple and, in the majority of patients, is located proximally in the colon (Lynch et al., 1993b; Lynch and de la Chapelle, 1999).

Table 2. International Collaborative Group on HNPCC (ICG-HNPCC): Diagnostic criteria

Classic criteria (Amsterdam I, (Vasen et al., 1991))
<ul style="list-style-type: none"> • at least three relatives should be affected with colorectal cancer • one of those affected should be a first-degree relative of the other two affected individuals • at least two successive generations should include affected family members • at least one of the colorectal cancer cases should be diagnosed before the age of 50 years • FAP should be excluded • all the preceding criteria should be included
Revised criteria (Amsterdam II, (Vasen et al., 1999))
<ul style="list-style-type: none"> • At least three relatives should be affected with an HNPCC-related cancer, including colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis • one of those affected should be a first-degree relative of the other two affected individuals • at least two successive generations should include affected family members • at least one of the colorectal cancer cases should be diagnosed before the age of 50 years • FAP should be excluded • all the preceding criteria should be included
adapted from (Vasen, 2000)

5.2.2. Risk of different cancers in HNPCC

Earlier studies suggested that the risk of colorectal cancer in at-risk individuals was exceedingly high, 85-90% (Lynch and de la Chapelle, 1999). More recent studies, based on the risk to mutation-positive individuals, have indicated that the risk of colorectal cancer is actually lower, 70-80% (Vasen et al., 1996; Aarnio et al., 1999a). Individuals who have inherited the faulty MMR gene have an additional risk for various extracolonic cancers such as cancer of the endometrium, stomach, ovary, small bowel, brain, and hepatobiliary and urinary tracts (Watson and Lynch, 1993; Aarnio et al., 1995; Vasen et al., 1996; Dunlop et al., 1997; Aarnio et al., 1999a). The risk of endometrial cancer is markedly higher than that of the other extracolonic cancers, among the women in some families even exceeding that of colorectal cancer (Vasen et al., 1994; Watson et al., 1994; Aarnio et al., 1995; Aarnio et al., 1999a). The overall prognosis for patients with HNPCC has been suggested to be better than for those with non-hereditary colorectal cancer (Sankila et al., 1996; Watson et al., 1998).

5.2.3. Early detection and prevention of HNPCC

Cancer surveillance programmes for the mutation-positive family members have been recommended with the purpose of early detection, prevention and treatment of cancer. Because of the accelerated carcinogenesis, the life-long examinations should start at the age of 20-25 years and be repeated at two-three year intervals (Vasen, 2000). Long-term follow-up studies have shown that regular surveillance (at three-year intervals) reduces both morbidity and mortality from colorectal cancer not only among the high-risk members of HNPCC families (Järvinen et al., 1995), but also among the mutation-positive individuals (Järvinen et al., 2000). The studies showed that the time interval concerned was effective enough in terms of prevention of deaths. However, a large number of interval cancers have been detected (Vasen et al., 1995; Renkonen-Sinisalo et al., 2000) and, therefore, internationally the guidelines for follow-up screening have recommended two rather than three years from the age of 20-25 (Järvinen and Aarnio, 2000; Vasen, 2000). The benefits of surveillance are further supported by a cost-effective analysis of colorectal surveillance among those positive for HNPCC mutations, indicating that colorectal cancer surveillance increases life expectancy by approximately seven years and the costs of surveillance remain lower than the costs without a surveillance strategy (Vasen et al., 1998).

Thus far, the benefits of surveillance of other HNPCC-related cancers are unknown (Burke et al., 1997; Vasen, 2000). However, preliminary guidelines have been given to the mutation-positive individuals. Gynaecological examinations (endometrial suction biopsy) and transvaginal ultrasound examinations (for **endometrial cancer**), gastroduodenoscopies (for **gastric cancer**, if it runs in the family), and abdominal ultrasound examinations, and urine cytology (for **urinary tract cancer**, if it runs in the family) are recommended from the age of 30-35 years to be repeated annually or biennially. In some families, the surveillance may be started even earlier (from 20-25 years), in case relatives are affected at an exceptionally young age by certain types of cancer (Brown et al., 2001). On the other hand, it has been suggested that, as it is impossible to prevent all cases of cancer in HNPCC, one should concentrate on the surveillance methods that are directed to types of cancer with highest risk and are beneficial such as colorectal cancer polypectomies and perhaps endometrial cancer to ensure the compliance of the mutation-positive individuals (Järvinen and Aarnio, 2000).

For the mutation-positive individuals, **prophylactic surgery** (e.g. colectomy or hemicolectomy) offers an option for cancer prevention instead of life-long endoscopic surveillance (Church, 1996; Lynch and de la Chapelle, 1999). This issue however, is complex and requires thorough counselling to make sure that the optimal form of prevention is chosen (Syngal et al., 1998). The benefits of surgical removal of high-risk organs include reducing the high-risk tissue, thus decreasing the risk significantly and minimising surveillance, which involves personal inconvenience and a risk of colon perforation. However, despite a low rate of mortality, complications after surgery include a higher rate of morbidity (frequent bowel movements). Nevertheless, there may valid reasons for performing prophylactic procedures: these include severe phobia of colonoscopies, large adenomatous polyps, "difficult colon" or when the performance of 20-30 colonoscopies life-long is impossible for other reasons (Aarnio, 1999b).

6. AIMS OF THE STUDY

The characterisation of genes predisposing to HNPCC made it possible to offer predictive testing to the healthy members of HNPCC families in which the mutation was known. In Finland, the situation was unique as two mutations seemed to cover a significant number of the HNPCC families. Predictive genetic testing for HNPCC was offered to identify those with the susceptibility mutation, who need surveillance, and those with the normal gene, who would not need to undergo surveillance. Little was known about the psychosocial impact of predictive genetic testing for cancer. The overall aim of this study was to investigate whether predictive genetic testing for HNPCC and the counselling preceding it are also acceptable in terms of psychological well-being.

The specific aims of the study were:

1. to investigate the acceptance of the predictive genetic test for HNPCC, and the factors predicting it,
2. to develop a counselling protocol for predictive testing for hereditary cancer, and evaluate its acceptability,
3. to investigate the need for and the utilisation of psychological support during the testing procedure,
4. to analyse the psychosocial consequences of predictive genetic testing for HNPCC.

7. SUBJECTS AND METHODS

7.1. STUDY SETTING

From 1983, the Finnish research HNPCC registry had collected data relating to HNPCC families all over Finland. In 1994, there were 90 verified or suspected HNPCC families in the registry. In 1995, it was possible to offer predictive testing to the healthy members of HNPCC families in which the mutation was known (Nyström-Lahti et al., 1995). The situation was unique as two mutations, both located in the *MLHI* gene, seemed to cover a significant number of the Finnish HNPCC families which greatly helped the laboratory process in that two tests were designed for detection of the mutations: simple diagnostic tests based on agarose gel electrophoresis or allele-specific oligonucleotide hybridisation were available (Nyström-Lahti et al., 1995). During the pre-test counselling part of the study in 1995-1996, altogether 36 HNPCC kindreds with three different previously characterised mutations in the *MLHI* gene were included in this study (Nyström-Lahti et al., 1995; Nyström-Lahti et al., 1996; Holmberg et al., 1998). The data concerning the mutations and the fulfilment of the clinical criteria of the study are presented in Table 3.

Table 3. Clinical and genetic data on the study kindreds

	<i>Study families (n=36)</i>
Fulfilling Amsterdam Criteria I:	32/36
Mutation in the <i>MLHI</i> gene in chromosome 3*:	
-at splice acceptor of exon 6	5/36
-at splice donor of exon 12	1/36
-genomic deletion of exon 16	30/36

*(Nyström-Lahti et al., 1995; Nyström-Lahti et al., 1996; Holmberg et al., 1998)

7.2. COLLECTION OF SUBJECTS

All eligible members at 50% risk of having inherited the predisposing gene in these 36 kindreds of whom the Finnish HNPCC research group held the addresses and a verbal consent to approach them for research purposes were approached with a letter that included a consent form (see Figure 4). The letter was sent by Docent Jukka-Pekka Mecklin, of the Department of Surgery, the Central Hospital of Jyväskylä, and Professor Albert de la Chapelle, of the Department of Medical Genetics, University of Helsinki, who had had contact with the index persons and their relatives in the families from previous surveillance and mutation search

studies. Subjects were considered eligible if they were aged 18 or older, without a cancer diagnosis, and without any cognitive disorder that precluded informed consent. Those who refused to participate or did not return the consent form after two rounds of reminders were not contacted further. Pre-test questionnaires were sent to those consenting.

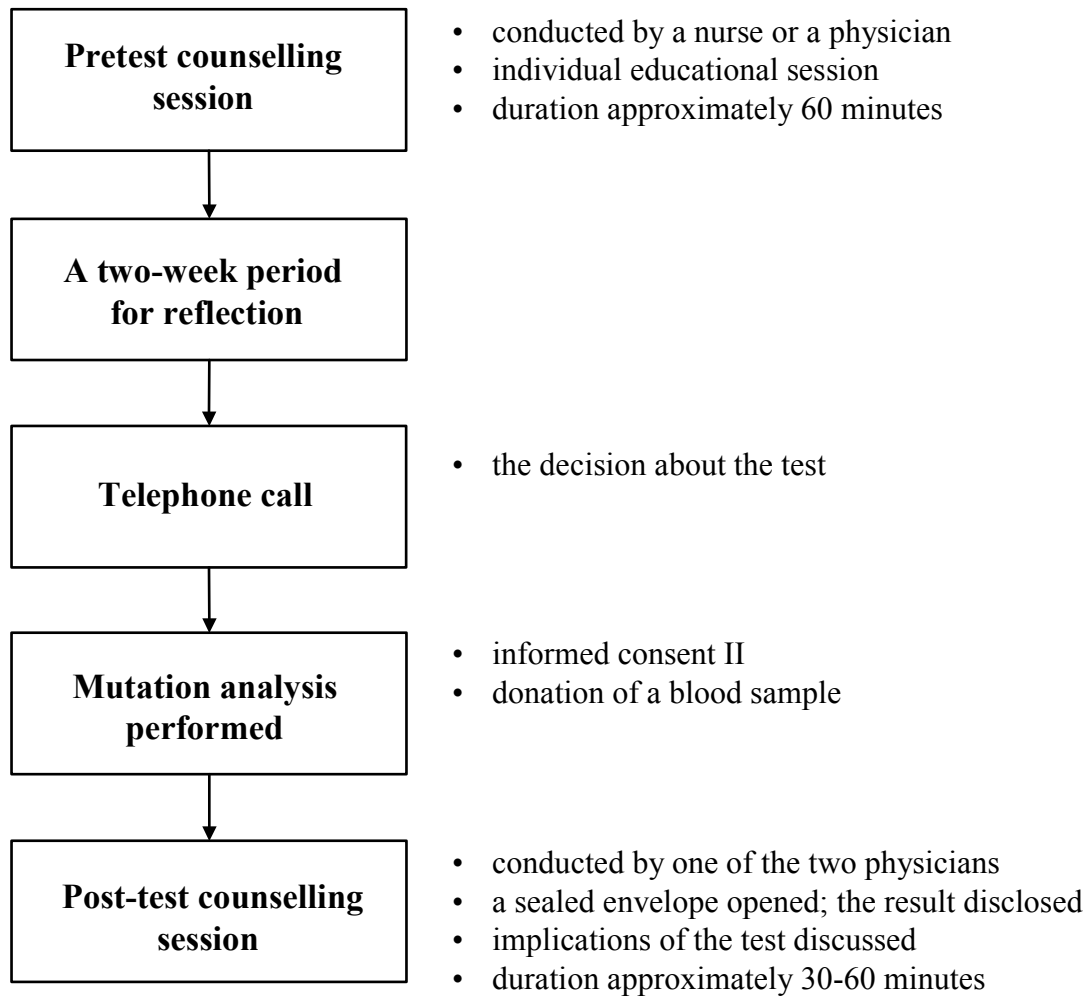
Counselling and testing protocol

Flow charts of the counselling protocol and of the testing procedure are presented in Figures 3 and 4, respectively. The counselling protocol was modified from that designed for HD but for practical reasons and because of nature of disease, it was decided to include only a single pre- and post-test session, and further sessions only if needed or requested. The counsellors were a physician (the author) (pre- and post-test counselling), a nurse (only pre-test counselling) and a gastroenterological surgeon (only post-test counselling). In addition, see also study II.

Pre-test counselling

Those who returned the questionnaire were invited to a face-to-face counselling session at or near the places of residence of the subjects. The interactive semi-structured counselling was similar for all participants, and included information about HNPCC, its mode of inheritance, the gene defect, the nature and risk of colon cancer, the risk of other cancers and the methods available for early detection of tumours. Early in 1995, when we started the counselling, no data on the risk of developing colorectal cancer were available for mutation-positive HNPCC family members. However, most (32/36) of the families were high-risk families fulfilling the Amsterdam criteria. Therefore, the risk of colorectal cancer for mutation-positive individuals was estimated to be very high, close to 100%. This was communicated to the counselees at the pre-test session. The benefits and disadvantages of a predictive gene test were discussed, including psychological reactions and possible difficulties about employment and insurance.

Figure 3. The counselling protocol planned for the study



Period for reflection

The counselees were asked to consider their decision during a 2-week period for reflection. The purpose of this period was to allow the counselees make an independent decision without any feeling of pressure from the medical professionals. After that, the counselees were telephoned and asked if they wanted the test. Those choosing to be tested signed a consent form and donated a blood sample. Those who declined the test were encouraged to attend a clinical surveillance programme comprising colonoscopy and gynaecological examinations for females every 3 years.

Post-test counselling session

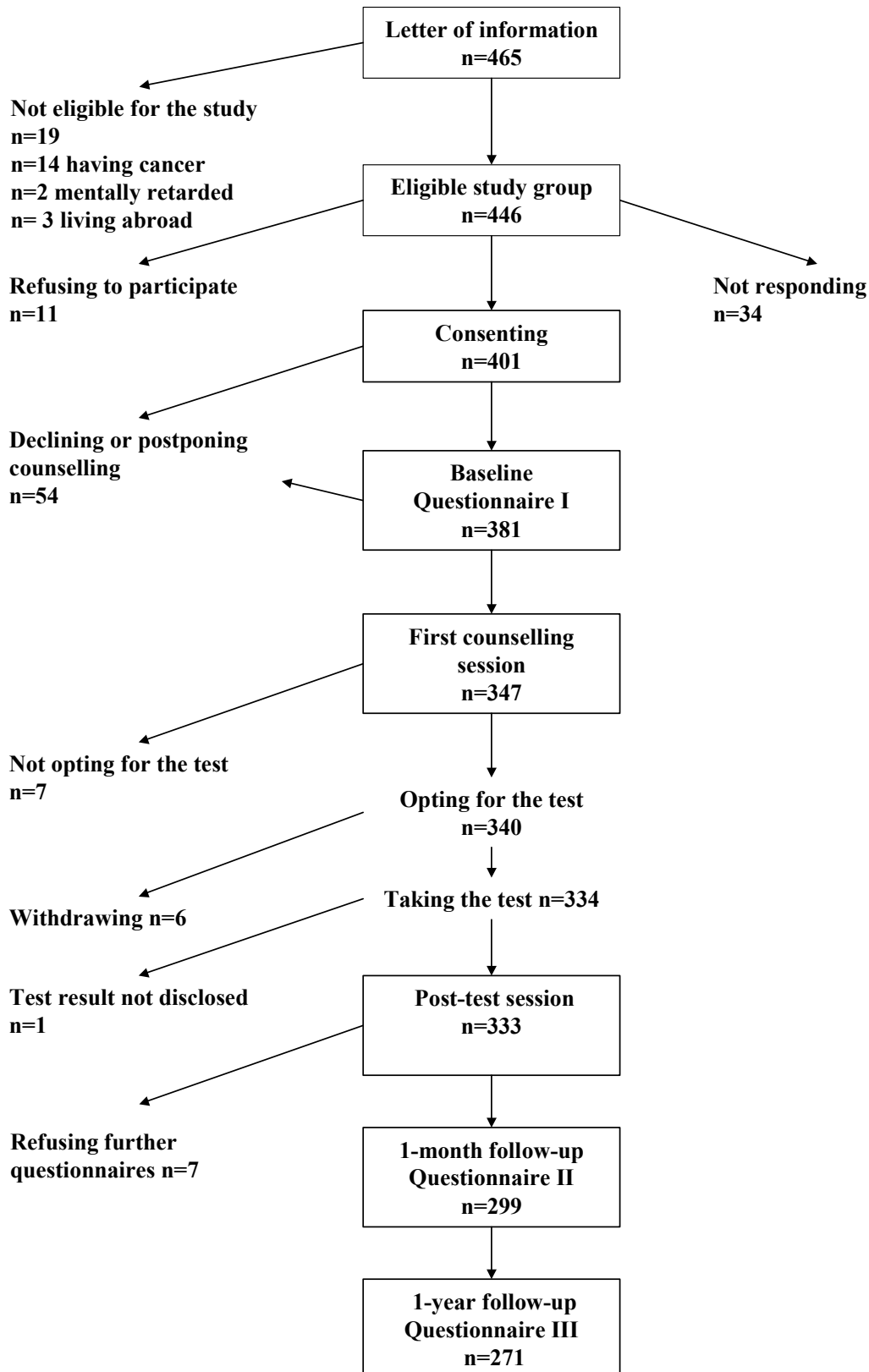
Those tested were invited, preferably with an accompanying person, to an individual post-test counselling session at which the test result and its implications were discussed. Individuals

having the mutation were reminded of the high risk of cancer (close to 100%) and informed about the clinical surveillance, and possible future preventive programmes. Subsequently, surveillance was organised for them. Subjects who did not have the mutation were reminded of the general cancer risk, to prevent any false reassurance. The result and its interpretation were also given to the subject in written form.

A flow chart with the participation rates is presented in Figure 4. The letter of information was initially sent to all known high-risk members of the 36 families. Nineteen individuals were excluded from the study because of previous diagnosis of cancer (n=14), cognitive disorder (n=2) or inability to attend counselling from abroad (n=3).

According to the pedigree, 435 of the 446 eligible study subjects had a 50% risk and 11 had a 25% risk, as the parent in question was deceased (n=10) or had refused to participate (n=1). Of the 334 who were tested, one did not want to hear the result and seven refused to fill in further questionnaires. Thirty per cent chose to have an accompanying person during the post-test session. Questionnaire II was sent to 326 subjects, and returned by 299. Questionnaire III was sent to these 299 subjects, and was completed by 271.

Figure 4. A flow chart of the testing procedure



7.3. SUBJECTS IN STUDIES I-V

The numbers and background information of the study populations analysed in the study 1 and studies II-V are presented in Table 4. Study I described the number of those tested and their sociodemographic backgrounds but as there was a drop-out in those responding to the questionnaires, the results that include the 1-year follow-up are based on the those individuals who returned all the questionnaires (n=271) (part of study I and studies II-IV completely).

Table 4. Characteristics of the study participants, in studies I-V

<i>Variable</i>	<i>Study I</i>	<i>Studies II-V</i>
number	446	271
mean age (SD), range in years	43 (14), 19-79	43 (13), 19-77
female	51%	57%
married or cohabiting	66%	72%
previous history of colonoscopies	55%	68%
more than primary education *	-	62%
employed*	-	75%
have children*	-	73%

* these data in study I were available only from the 381 participants who filled in the baseline questionnaire

7.4. MEASURES

The study was based on questionnaires, which were filled in three times during the procedure (Figure 4). Exceptionally, the anxiety scale was filled in four times (see Table 5). The questionnaires consisted of questions about sociodemographic factors, previous participation in colorectal cancer surveillance, satisfaction with the decision to take the test, and reasons for and against the test, satisfaction with the counselling protocol, need for psychological support, general anxiety, fear of cancer and death, views about the future, risk comprehension, and insurance behaviour (Table 5) which were used for studies I-V. Additionally, the questionnaires included general questions about life events, social support and perceived health which will be analysed in future studies.

Table 5. Groups of questions in the baseline and follow-up questionnaires (detailed in Appendix)

<i>Questions used in questionnaires (see in Appendix)</i>	<i>Baseline</i>	<i>1-month follow-up</i>	<i>1-year follow-up</i>
1. Sociodemographic factors (1-5)	X	X	X
2. Surveillance background (6)	X		
3. Pre-test risk perception (7)	X		
4. Reasons for decision-making about the test (8-9)		X	
5. Satisfaction with decision making (10-12)		X	X
6. Opinion of counselling (13-15)		X	X
7. Need for and utilisation of psychological support (16-18)			X
8. Views about life in general now and in the future (19-20)	X	X	X
9. Fear of cancer and death (21-23)	X	X	X
10. General anxiety STAI (24-43)*	X	X	X
11. Comprehension of cancer risk (44-45)		X	X
12. Worry about cancer risk (46)			X
13. Insurance issues (47-48)			X

* General anxiety was also measured at the test disclosure

The questions used in studies I-V are numbered (1-48) and are presented in detail in the Appendix section: in **I**, the findings were measured with questions 1-12, consisting of sociodemographic variables; other background variables included previous participation in cancer surveillance and pre-test risk perception, reasons for and against taking the test and satisfaction with the decision about testing. For data analysis purposes, the questions were combined into the categories presented in the methods section in study I.

In **II**, the outcome variables (opinions of counselling and the need for and the utilisation of psychological support) were analysed with questions 13-18 and their association with the background variables (1-7) was studied. For purposes of data analysis, the questions were combined into the categories presented in the methods section in study II.

In **III**, fear of cancer and death, view about the future and satisfaction with life and general anxiety were assessed (questions 19-43) at baseline, and at follow-ups:

General anxiety (24-43) was measured by the state measure of the State-Trait Anxiety Inventory (STAI) which is a 20-item scale (Spielberger et al., 1970). Response categories for

the items ranged from 1 (not at all) to 4 (very much so). Scores ranged from 20 to 80, the higher scores indicating greater anxiety. In III, the measurements were performed at baseline, at the test disclosure session and at post-test follow-ups. In the measurements, Cronbach alpha was 0.9, indicating high internal consistency (Heikkilä, 1998).

STAI is a validated scale and has been used widely (Vernon et al., 1997; Gritz et al., 1999). In Finland, Dr. Aro has used the scale in studies on the psychosocial aspects of women 50-59 years of age attending routine mammogram screenings (Aro, 1996). However, the values for the average Finnish population are not yet known (Antti Uutela, National Public Health Institute, personal communication).

Fear of cancer and death (21-23) were measured in terms of items derived from the Illness Attitude Scale, originally developed by Kellner and translated and culturally adapted by Aro (Aro, 1996). In our study, the dimensions of fear of cancer, fear of death and fear of dying soon were investigated, as they were considered important to the present study populations. These variables were analysed as continuous variables.

Satisfaction with life and attitude to the future (19-20) have been used previously in studies performed on Finnish populations (Puska et al., 1995).

In **IV**, comprehension of the cancer risk and worry about it (see appendix questions 44-46) were assessed. Accordingly, the correct option for the mutation-negative subjects was the third option and for the mutation-positive subjects the first. On analysis, those who chose the correct option were labelled as "understanding" the result and those choosing the incorrect option as "misunderstanding" the result. Worry about the risk of developing colorectal cancer based on the test result was assessed at the 1-year follow-up. Anxiety at baseline and at test disclosure (24-43), pre-test risk perception (7) and background factors (1-6) were analysed as predictors of risk comprehension at follow-ups. In the anxiety measurements, Cronbach alpha was ≥ 0.9 , indicating high internal consistency.

In **V**, the life insurance and health insurance issues were analysed (questions 47-48). For data analysis purposes, the questions were combined into the categories presented in the methods and results section in study V.

7.5. STATISTICAL ANALYSES

Chi-square and McNemar tests were used to determine whether there were differences for the categorical variables (see Table 6). The significance of the differences between the continuous variables was measured with t tests. For the analyses, the p values were two-tailed and a p value of less than 0.05 was considered to indicate statistical significance.

Table 6. Statistical methods used in the studies

<i>Statistical Methods</i> *	<i>Used in studies</i>
χ^2 test	I-V
McNemar test	II, IV
t test	I-V
Repeated measures ANOVA	I, III
Logistic regression analysis	I, IV

* SPSS programme, versions 7.0-9.0 for Windows, were used for the data analysis (*SPSS Base 8.0. User's guide.*, 1998).

Logistic regression analyses were performed to determine the relative impact of background variables on participation in the study (I), uptake of the test (I), and comprehension of the cancer risk (IV). In III, among the mutation-negative participants, those who incorrectly claimed that their risk was 50% or 100% were compared with those who correctly reported that their risk was low. Among the mutation-positive, those who claimed that their risk was low or 50% were compared with those who correctly stated their risk to be nearly 100%. In every case, all the explanatory variables were entered simultaneously.

Repeated measures analyses of variance were performed to compare changes in satisfaction with the test decision making (I), general anxiety (IV), fear of cancer and of death (IV), and satisfaction with life (IV) between and within the two groups during the course of the study. Two-tailed p values less than 0.05 were considered to indicate statistically significant differences.

The study plan including both the genetic counselling and testing protocol and the questionnaires had been approved by the Ethical Committee of the Department of Medical Genetics in University of Helsinki.

8. RESULTS

8.1. ACCEPTANCE OF TESTING AND FACTORS PREDICTING IT (I)

Of the 446 eligible study subjects, 90% (n=401) consented to take part in the study. The test was taken by 75% (334/446) of those who were eligible for testing, by 83% (334/401) of those preliminarily consenting to participate in the study, by 88% (334/381) of those returning the filled-in questionnaire, and finally, by 96% (334/347) of those who attended counselling. Of those tested, 30% were mutation-positive and 70% mutation-negative. This result was expected, as the mutation-positive family members diagnosed to have cancer were not included in the predictive genetic testing study.

Those subjects (n=65) who did not respond to the invitation to the study or who actively refused to participate in it were mostly men, living alone, and those who had not previously participated in the clinical surveillance (Table 7). In a logistic regression analysis including all explanatory variables, the most significant determinant of participation was found to be previous participation in clinical surveillance (see study I, Table I). Of those participating in the (questionnaire) study, acceptors differed from decliners in having a spouse or a partner, in being more often employed, and in having a higher education (Table 7). In a logistic regression analysis, the only significant factor proved to be the employment status; those who were not employed were more likely to decline the test (see study I, Table II).

Table 7. Comparison of those participating and not participating in the study

Variables	<i>All eligible study subjects</i>		<i>Participants</i>	
	Participants (n=381)	Non-participants (n=65)	Acceptors n=334	Decliners n=47
Age: mean (SD) years	42.9 (13.9)	43.5 (14.4)	42.5 (13.2)	46.2 (17.8)
Male	45% (173)	68% (44)*	45% (150)	49% (23)
Married or cohabiting	70% (266)	40% (26)***	72% (239)	57% (27)*
previous history of cancer surveillance	63% (240)	9% (6)***	64% (213)	57% (27)
has children	-	-	73% (242)	64% (30)
more than primary education	-	-	64% (213)	43%*(20)
employed	-	-	74% (246)	51% (24)**
pre-test risk perception high	-	-	14% (47)	11% (5)

*p<0.05; **p<0.01, ***p<0.001.

- indicates that data were not available

Reasons for taking the test

The reasons most frequently cited for and against taking the test in questionnaire II are listed in study I Table IV. These were not queried among those not consenting to the study, as the majority refused any further contact or did not respond at all. The reasons among those initially consenting, but not attending counselling, were discussed on the phone, and typical answers were "reluctance to fill in questionnaires or attend counselling sessions" and "feeling too overwhelmed at the time".

Satisfaction with the decision

No difference in satisfaction with the decision about the test between the groups defined by mutation status was found at the 1-month follow-up (Table 8). The mutation-negative individuals were less confident about the result at both follow-ups ($p < 0.001$ and $p < 0.05$) than those with the mutation. At the 1-year follow-up, the subjects who had not inherited the mutation were slightly more satisfied with their decision to take the test ($p < 0.05$). A slight, but statistically insignificant drop in levels of satisfaction with their decision was observed for both groups at the 1-year follow-up. Using repeated measures ANOVA, testing for the difference in the results between the groups during the follow-up gave a non-significant result ($p = 0.068$). At both follow-ups, the mutation-negative individuals were less confident about the result ($p < 0.001$ and $p < 0.05$) than those with the mutation. No change in confidence occurred within the groups during the follow-up, and the repeated measures ANOVA revealed no difference either. The question about whether they would have taken the test in the light of their present knowledge revealed no differences between or within the groups.

Table 8. Issues reported by those tested in studies I, II, IV and V. The results are presented in full in the studies.

ISSUE	<i>1-month follow-up</i>		<i>1-year follow-up</i>	
	Mutation-negative n=187	Mutation- positive n=84	Mutation- negative n=187	Mutation- positive n=84
% (n) reported that they...				
TESTING (I)				
were extremely satisfied with the test decision	97% (180)	91% (76)	96% (178)	86% (71)
would definitely have retaken the test again	95% (177)	94% (79)	95% (177)	93% (77)
trusted the result completely	89% (163)	98% (82)	86% (162)	95% (80)
COUNSELLING (II)				
found pre-test counselling very or fairly useful	-	-	89% (166)	88% (74)
considered a single post-test session sufficient	90% (166)	86% (71)	87% (160)	82% (68)
COUNSELLING AND SUPPORT (II)				
felt the need of psychological support at greatest				
in the pre-test period	-	-	39% (60)	10%*(7)
at the moment of test disclosure	-	-	47% (74)	47% (35)
after the test disclosure session	-	-	14% (22)	43%*(32)
might have used psychological support had it been provided by the team	-	-	52% (93)	58% (49)
actually used professional psychological help	-	-	0	2% (2)
PSYCHOLOGICAL AND SOCIAL ISSUES (IV,V)				
comprehended their cancer risk correctly after testing	93% (170)	48% (40)	90% (167)	36% (30)
were worried about the risk	-	-	38% (69)	80% (66)
had life insurance before the first counselling	-	-	28% (51)	36% (30)
had health insurance before the first counselling	-	-	11% (19)	36%*(17)
took a life insurance after genetic counselling before testing	-	-	3% (5)	4% (3)
took a health insurance after genetic counselling before testing	-	-	2% (4)	0
took a life insurance after genetic testing	-	-	2% (4)	4% (3)
took a health insurance after genetic testing	-	-	<1% (1)	0
planning to take a life insurance	-	-	3% (6)	2% (2)
planning to take a health insurance	-	-	<1% (1)	4% (3)

* p< 0.0001

- indicates that the question was not asked at 1-month follow-up

8.2. ACCEPTANCE OF COUNSELLING, AND NEED AND UTILISATION OF PSYCHOLOGICAL SUPPORT DURING THE PROCEDURE (II)

None of the respondents suggested major changes in the counselling. Ten percent (n=26) of the counselees proposed minor changes, most commonly asking for more written material concerning the methods of clinical surveillance and prevention. Those who had a university education suggested changes in the counselling more often than the others ($p<0.01$).

Gender and education were significantly associated with the perceived usefulness of the counselling. Women ($p<0.05$) and those with a lower level of education ($p<0.05$) more often considered the counselling useful than the others. Having children was positively associated with the opinion that an additional post-test session would have been desirable ($p<0.01$).

The mutation-positive wanted support in the post-test period more often than mutation negative ($p<0.0001$, see Table 8). There were also differences between men and women: the need for support at the decision-making phase was experienced more often by men than by women (20% vs. 7%, $p<0.01$), whereas women emphasised the need of support at the test result disclosure session phase (52% vs. 35%, $p<0.05$). Altogether 52% of the respondents indicated that they might have utilised professional psychological support in addition to counselling if it had been provided (Table 8). Such psychological support would have been utilised by women with children more often than by the others ($p<0.01$). However, only two subjects (both mutation-positive) reported that they had utilised psychological support provided by professionals.

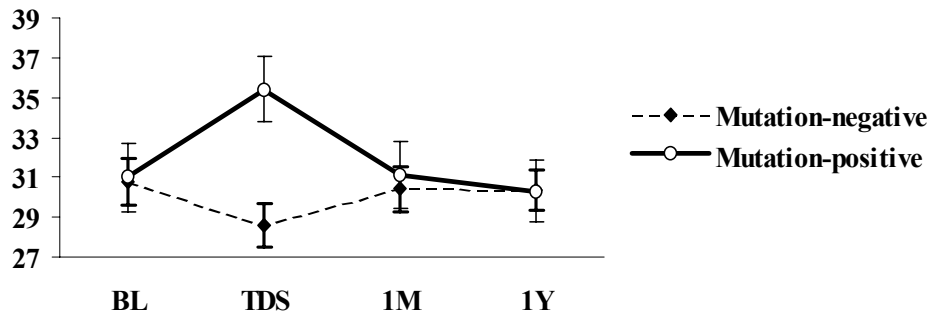
8.3. PSYCHOSOCIAL CONSEQUENCES OF TESTING (III-V)

General Anxiety (III)

Figure 5 illustrates the course of anxiety during the study. At the test disclosure session, the mutation-positive subjects who had just received the result had significantly higher scores and the mutation-negative subjects lower scores for anxiety than in the baseline measurement ($p<0.0001$), the difference between the two groups being significant ($p<0.001$). In the later measurements, the mean anxiety scores were similar to the baseline scores in both groups.

Figure 5. Illustration of the course of age-adjusted mean scores and 95% CI of anxiety during the testing procedure

**STAI
scores**



BL=baseline
TDS= test disclosure session
1M= 1-month follow-up
1Y= 1-year follow-up

Table 9 presents the results of changes in the psychological outcome variables. After 1 year, the fear of cancer had decreased from baseline in both groups. The mutation-positive subjects were slightly, though significantly, more afraid of cancer at every measurement. No significant time or time/mutation status interactions were found on fear of death, fear of dying soon, attitude to the future or satisfaction with life.

Table 9. Mean (SD) scores for pre-and post-test psychological variables (appendix questions 20-44) in the groups defined by mutation status (III)

<i>Variable</i>	<i>BL</i>	<i>TDS</i>	<i>1M</i>	<i>1Y</i>	<i>Change in time*</i>	<i>Time X mutation status interaction*†</i>
Anxiety					ns	p<0.0001
Mutation-negative (n=187)	30.9 (7.7)	28.7 (6.5)	30.4 (7.5)	30.3 (7.0)		
Mutation-positive (n=84)	31.6 (8.0)	35.4 (9.1)	31.5 (7.9)	30.0 (6.7)		
Fear of cancer					p=0.03	p=0.001
Mutation-negative	0.8 (0.9)		0.5 (0.8)	0.5 (0.7)		
Mutation-positive	1.1 (1.0)		1.2 (1.0)	0.9 (1.0)		
Fear of death					ns	ns
Mutation-negative	0.9 (0.9)		0.7 (0.8)	0.8 (0.9)		
Mutation-positive	0.8 (0.9)		0.8 (1.0)	0.7 (0.9)		
Fear of dying soon					ns	ns
Mutation-negative	0.3 (0.6)		0.3 (0.6)	0.3 (0.4)		
Mutation-positive	0.4 (0.8)		0.4 (0.7)	0.4 (0.7)		
Attitude to the future					ns	ns
Mutation-negative	3.6 (0.7)		4.0 (0.6)	3.7 (0.6)		
Mutation-positive	3.7 (0.7)		4.0 (0.7)	3.7 (0.7)		
Satisfaction with life					ns	ns
Mutation-negative	4.0 (0.8)		4.0 (0.6)	4.0 (0.7)		
Mutation-positive	4.2 (0.6)		4.0 (0.7)	4.2 (0.6)		

*adjusted for age

† indicates that change with time is different between the groups defined by mutation status

ns=non-significant

BL= baseline, TDS= test disclosure session, 1M= 1-month follow-up, 1Y= 1-year follow-up

Comprehension of cancer risk (IV)

Practically all the respondents (268/ 268 at the 1-month follow-up and 266/268 at the 1-year follow-up) correctly recalled whether or not they had inherited the mutation predisposing to cancer. However, the mutation-negative subjects understood their post-test risk of developing colorectal cancer significantly more often than those who were mutation-positive (92% vs. 48%, p<0.0001), and at the 1-year follow-up, the difference was even greater (90% vs. 36%, p<0.0001) (see Table 2 in study IV). The answers were similar, irrespective of the counsellor at the pre-test or the test disclosure session. Regarding the mutation-positive individuals, misunderstanding was more common among the older (p<0.05), the less educated (p<0.001) and those who had perceived the pre-test risk as lower than the others (p<0.01) at the 1-month

follow-up. Among the mutation-negative subjects, those few who misunderstood their risk had perceived their (pre-test) risk to be high ($p<0.01$) and had high scores on anxiety immediately after the test disclosure session ($p<0.01$) as compared with those who understood their risk. With regard to the other demographic data, the groups did not differ.

According to the logistic regression model (presented in Table 3 in study IV), the only predictor of misunderstanding the result was the initially lower pre-test risk perception among the mutation-positive group. Among the mutation-negative group, those who perceived their pre-test risk to be higher and were anxious immediately after the test disclosure were more likely to have misunderstood the result. Because misunderstanding had increased among the mutation-positive group at the 1-year follow-up, we carried out a similar regression analysis: the significant predictor for misunderstanding continued to be a lower pre-test perception of the risk [OR=0.27 (0.10-0.74)].

At the 1-year follow-up of the mutation-positive subjects ($n=83$), 8% reported that they were very worried about their risk of developing colorectal cancer, 69% that they were worried to some extent, 2% could not say whether they were worried or not, and 21% stated that they were not at all worried. The corresponding percentages for the mutation-negative subjects ($n=182$) were 2%, 25%, 11%, and 62%, respectively ($p<0.0001$). Figure 1 illustrates an analysis that compares worry about the risk with a correct or incorrect understanding of the test results. In the illustration, worry was analysed as a continuous variable (0=not worried; 1=worried to some extent; 2=very worried; the option can't say ($n=22$) was excluded). The mutation-positive subjects who understood the result were significantly more worried about the risk of developing colorectal cancer than those with the mutation who did not understand the result correctly ($p<0.05$). By contrast, the mutation-negative subjects who misunderstood the test result were more worried about the risk than their counterparts ($p<0.001$).

Insurance behaviour as an example of social implications (V)

Fewer than 2% of those tested had negative arguments against testing that concerned insurance or employment issues. One year after testing, the reported responses regarding life insurance and health insurance behaviour between the mutation-positive and mutation-negative subjects are presented in Table 8. In the comparisons, the difference between the mutation-positive and mutation-negative individuals concerning life insurance was not

significant ($p=0.17$), whereas, concerning health insurance, the mutation-positive individuals possessed health insurance more often than those who were mutation-negative ($p<0.05$).

Three per cent indicated that they had purchased life insurance, and 2% correspondingly health insurance before they were tested. Of the mutation-negative individuals, 2% and 1% reported that they had purchased life and health insurance, respectively, after they had learned their test results. Four per cent of the mutation-positive group stated that they had taken a life insurance after testing but no-one in the group reported having taken health insurance after testing. Planning to purchase a life or health insurance in the future was reported by 3% and 2% of the study subjects, respectively. The numbers in these categories were so few that no further analysis was possible. Compared with the mutation-positive group, there were more respondents in the mutation-negative group who reported that after testing they had never planned the purchase of a life or a health insurance. Those who had never planned the purchase of either life insurance ($p=0.12$) or health insurance ($p<0.05$) did not differ in their mutation status.

9. DISCUSSION

9.1. SUBJECTS AND STUDY PROTOCOL

Study setting and collection of subjects

The study material was in many respects unique. Many of the subjects were familiar with the cancer burden in the family and had been attending a regular cancer surveillance for years. The 446 individuals who were originally contacted came from 36 families which had been ascertained during a long period and covered all the known Finnish high-risk individuals from different parts of the country in families in which the mutations had been discovered. Genealogical tracing of family histories showed that most of the families (35 of the 36 in this study) were descended from two ancestors in the 16th and 18th centuries, respectively, and all but one of the families carried one or other of the two founder mutations (Nyström-Lahti et al., 1995). Therefore, predictive genetic testing was possible in many families, and testing could be offered to a large number of subjects, which increased the power of the study.

The individuals were approached in an identical manner with a short letter offering more information about the available predictive genetic testing. This approach is not comparable with a clinical setting in which the high-risk individuals themselves request counselling.

Those with a diagnosis of cancer and those who could not fill in the consent form (because of a cognitive disorder) were excluded from the questionnaire study. Those with the diagnosis of cancer are not considered to be similar to those at high risk in terms of psychology (Croyle et al., 1997). We were also asked for predictive genetic testing by the parents or guardian of two males with Down's syndrome belonging to two of these families. The grounds for testing were to know whether these individuals needed surveillance to prevent cancer, which in their case would mean investigations performed under anaesthesia. The tests were performed, however, these individuals are not included in the study. As HNPCC develops in adulthood, we decided not to offer testing to children or adolescents. The age limit was set at 18 years, as that is the age at which individuals legally become adults in Finland.

Of the 446 subjects considered eligible for the study, 347 (80%) finally came to the first counselling session. Thus, there were 99 subjects who either did not respond, refused to

consent to the study, or declined counselling, even after returning the baseline questionnaire. Of those attending the counselling session, only a small number refused testing.

We obtained very little information about those (n=65) who did not fill in the baseline questionnaire (non-participants), who comprised those who actively refused to participate, those who did not respond, and those who consented but did not return the questionnaires. This has been a problem in most studies on genetic testing for cancer and, thus, knowledge of those refusing the counselling and testing is scanty. Lerman and colleagues reported that, 1 and 6 months after offering the testing those who had been distressed and declined the test were more depressed than those who had accepted the test (Lerman et al., 1998).

We required completion of questionnaires, which would not have been required in a clinical setting. This may have reduced the participation. On the other hand, in the research setting, participation and testing were provided without charge and as near as possible to the subjects' residences, which may have increased the willingness to participate.

This study is based on the responses of the study subjects who consented to be tested, attended counselling, were tested and returned all three rounds of questionnaires. As noted recently by Broadstock et al., selective drop-out may, with time, cause a response bias (Broadstock et al., 2000). It is possible that those tested who failed to return the follow-up questionnaires (n=62) differed from the others in some respects that might have affected our results. However, we know from our baseline data that these dropouts did not differ from the study subjects in any measurements.

Counselling and testing procedure

Counselling and testing were performed in a carefully chosen research setting, which may have increased the sense of security of those participating in the programme. Counselling was given to each family member during an individual session and a period for reflection was allowed for making as autonomous a decision as possible, in this respect differing from some other studies in which counselling was organised for groups (Lerman et al., 1996b; Lerman et al., 1999). The test results were given during a counselling session that included plenty of time. The time required for the present protocol was, however, reasonable; the two

counselling sessions (1½ -2 hours) and telephone calls (10-30 minutes) took at most 2½ hours per counsellee. The counselling sessions were conducted by three different counsellors (a nurse, a physician specialising in medical genetics and a gastroenterological surgeon). The analyses showed no statistically significant differences between the counsellors regarding any of the outcome variables.

The model of genetic counselling has traditionally been non-directive. This has been especially important in the genetic counselling regarding decisions about reproduction after a genetic disease has been diagnosed or suspected in the family. The genetic counselling preceding predictive genetic testing for hereditary colon cancer can be seen to be different. The potential test result not only gives information but also tells whether or not cancer surveillance is needed. Given these aspects, our aim was to be as non-directive as possible in the pre-test counselling setting. By contrast, the counselling at the test disclosure session neared the shared decision making model (Elwyn et al., 2000), especially among those who had a mutation-positive test result, as they were strongly encouraged to participate in the regular cancer surveillance. It should be noted that two out of three already had a previous history of cancer surveillance.

We did not use any other counselling protocol as a randomised control, since, at the time when the project was started, we thought that every counsellee should receive counselling that would meet high standards in terms of the ethical principles of genetic testing. The subjects in this study were only familiar with the present protocol and could not compare it with, for instance, the more comprehensive counselling used in HD.

Questionnaires and measures

One of the aims of the study was to analyse the psychosocial consequences of testing by using newly developed or already available questionnaires. The design used was a prospective follow-up study. Although there have previously been studies resembling the present study of predictive genetic testing for cancer (see Table 3), some aspects of the present study were totally new. The follow-up time has rarely been so long as in this study. Furthermore, to our knowledge, comprehension of the cancer risk after predictive genetic testing and fear of

cancer have not been measured previously and anxiety immediately after receiving the result has been measured only once before (Watson et al., 1996).

The response rate in the study was high representing a substantial proportion of those tested. After two rounds of reminders, 90% (n=401) consented to the study. The baseline questionnaire was sent to all of them and the response rate was 90% (n=385). The anxiety scale at test disclosure was filled in by 98% (326/333) subjects. The response rates for the 1- and 12-month follow-up questionnaires were 92% (299/326) and 91% (271/299), respectively. Altogether 62 subjects did not to return the questionnaires after testing. It is possible that those completing the questionnaires represented slightly more educated and employed proportion of the Finnish population (see Table1 in study II) which may have affected the study compliance. On the other hand, response rates to health surveys in Finland are traditionally high (50-90%) (Jyrinki, 1974).

A large set of questions evaluating different aspects of the mutation test were used in the study. However, it is relevant to ask whether the measures were appropriate for the study. Perhaps, with the measures used, the study could not detect potentially harmful effects that might have been found with other measures. However, as noted by Broadstock et al. in a recent review on the psychological consequences of (predictive) genetic testing, no studies using quantitative measures have been able to show any harmful effects of predictive genetic testing among those tested (Broadstock et al., 2000). This leads to an important question: Should there be other approaches, such as qualitative studies to investigating the issues?

Although we used several quantitative approaches, no qualitative analysis was performed. This approach might have deepened our understanding of the present findings, which are based on mean values. Mean values may mask individual reactions (Broadstock et al., 2000) and individual reactions may vary greatly (Chapman and Burn, 1999). Therefore, further studies using qualitative approaches might be warranted.

9.2. ACCEPTANCE OF TESTING AND FACTORS PREDICTING IT

The uptake of the test was 75% and 96% among all eligible individuals at-risk and among those who attended counselling, respectively. According to a logistic regression analysis, men,

those living alone and those without a previous history of colorectal cancer surveillance were more likely than the others not to participate in the questionnaire study and, thus, not to take the test. Among those who participated in the study, employment was found to predict uptake of the test. As most of the sociodemographic characteristics did not seem to be predictors for the test uptake, there must be other factors influencing the decision-making about the test such as psychological states, including depression, coping, levels of optimism, and thinking about cancer, which have been shown to be important determinants of participation in genetic testing (Codori et al., 1999; Lerman et al., 1999; Biesecker et al., 2000).

Our figures for uptake of the predictive genetic test for HNPCC greatly exceeded those reported recently from the United States (Lerman et al., 1999; Johnson et al., 2000). One reason for these differences may have been the differences in the study setting. Although, in the Lerman study, the method of approaching the study subjects was fairly similar to ours, the methods of counselling differed substantially (Lerman et al., 1999). Our subjects were counselled individually and allowed to have a period for reflection. This procedure was employed to enable autonomous, confidential decisions, which are far more difficult to obtain in information sessions with family groups. However, we assume that an even more likely reason for the discrepancy in the acceptance rates may relate to the fundamental differences between the health care and social security systems in the United States and in a European welfare state such as Finland. Lerman and colleagues found that test uptake was associated with higher education, often related to a better economic situation, which may be an important factor in an insurance-based health care system (Lerman et al., 1999). In contrast, our results suggest that in Europe, where, thus far, private health insurance plays a minor role, a predictive genetic test for a treatable disease may be more readily accepted. This is further supported by our finding that concern about possible difficulties in obtaining insurance was seldom (<2%) offered as a reason against the test (study I table IV).

In general, the Finnish population is accustomed to accepting the services offered by the public health care system, reflecting a high confidence in it. This has led to high rates of participation: 90% of women in the age group 50-59 attend breast cancer screenings, and 71-80% of women in the age groups 30-60 undergo screening for cervical cancer (Finnish Cancer Organisations, 1997). The same confidence seems to apply to genetic testing: a majority of the Finnish population generally approve of gene tests (Jallinoja and Aro, 2000) and 60% of a

sample of the general population were ready to undergo a hypothetical predictive genetic test for hereditary cancer (Hietala et al., 1995). However, the uptake of testing for HD in Finland has not been higher than elsewhere (Maarit Peippo, The Family Federation of Finland, personal communication).

Reasons for and against testing

The main reasons given for taking the test were reducing uncertainty, clarifying the risk for children and planning for the future (study I). Similar results have been obtained in previous studies (Lerman et al., 1996a; Lerman et al., 1996b; Dudokdewit et al., 1997). Although, clarifying the risk for children was the second most common reported reason for being tested, given by 69% of the respondents, having children was not significantly associated with the test uptake in our study, whereas parenthood has been previously reported to be a strong predictor of willingness to undergo testing for hereditary breast cancer (Meijers-Heijboer et al., 2000).

Those tested saw more positive than negative aspects of taking the test. This accords with recent reports on decision-making about genetic testing (Vernon et al., 1999). Furthermore, in conformity with the previous literature (Vernon et al., 1997), advice from a physician seemed to be an important factor in preventive health behaviour; of our subjects, 46% stated that one of the reasons for taking the test was its recommendation by a doctor. By contrast, it is noteworthy that only 30% stated that they took the test to know if they needed to prevent the disease. This reason was perhaps considered self-evident and was therefore not mentioned.

Family planning was barely mentioned. Thus, reproductive decisions did not seem to play a major role in predictive genetic testing for HNPCC. Consistently, prenatal genetic testing for HNPCC has not been performed, thus far, in the district covered by Helsinki University Central Hospital (Lauri Aaltonen, University of Helsinki, personal communication).

Satisfaction with the decision

The mutation-negative subjects were slightly more satisfied with their decision to take the test than those who had inherited the mutation (Table III in study I). However, they did not have such full confidence in their result as their mutation-positive counterparts, which may be related to loss of a sense of security when regular clinical surveillance was discontinued.

9.3. ACCEPTANCE OF COUNSELLING AND NEED FOR AND UTILISATION OF PSYCHOLOGICAL SUPPORT DURING THE PROCEDURE (II)

The majority of our participants considered the counselling sessions useful and did not suggest any improvements in them. The less educated the counselees were, the more satisfied they were with the counselling. Only a handful of the counselees would have been glad of another opportunity to discuss the post-test information with the physician who conveyed the result; the great majority considered one post-test session sufficient and the desire for additional counselling was not associated with utilisation of the mental health services. These findings indicate that offering a single post-test session is adequate, provided that a further session is an option.

Previous information on acceptance of counselling before and after genetic testing for cancer is scanty. A report on pre-test education for hereditary breast cancer has indicated that a counselling-based approach increases the awareness of the negative aspects of predictive testing (Lerman et al., 1997). This approach, however, does not decrease interest in the testing, as compared with a merely educational approach without counselling. This seems to support the statement that, in the course of predictive testing, counselling is essential to avoid decisions being taken too lightly (Statement of the American Society of Clinical Oncology, 1996).

The need for support was perceived to have been greatest at the time of the decision-making, when waiting for the results and, especially, at the moment of receiving the test results. On inquiry 1 year after receiving the test result, only 2% stated that the need for support was at its greatest at that time. Had our counselling team routinely provided psychological support, it might have been used by 52% of the study subjects at some stage of the procedure. On the other hand, only 1% had themselves sought professional psychological help. The need for support was apparently relative.

In the present study, all counselling was performed individually during two separate sessions. In previous studies, the amount of individualised counselling and number of sessions has varied (Table 3). In our study, only a minority stated that they would have welcomed additional counselling. On the other hand, half of the respondents might have used support from the counselling team if it had been available. In a recent study, based on small numbers,

it was shown that those who had tested positive for *BRCA1/BRCA2* mutation would have been glad of additional genetic (educational) counselling but rarely needed support counselling, at least in group sessions (Di Prospero et al., 2001). Perhaps this reflects the differences in the nature of the disease and its surveillance. For instance, for HNPCC in Finland the surgeons and internist often provide the patients with updates of medical information and research findings. Therefore, perhaps counselling in terms of clinical facts may not be felt necessary. Randomised studies are needed to evaluate the need for individualised counselling as well as whether we are providing too much or too little counselling.

Only little is known about the periods or moments when those tested for hereditary cancer have felt the need of support to be at its greatest. Some information is available concerning HD. Tibben et al. reported that carriers of the HD mutation experienced the pre-test period as the most stressful time in the testing procedure (Tibben et al., 1993). Somewhat similar results were obtained in our study, as this period was considered difficult, especially by men and by the mutation-negative individuals. The latter can be explained by the retrospective nature of this question. Understandably, the mutation-negative individuals felt more distressed before hearing the result than afterwards when they looked back at the matter after a year. By contrast, women, mutation-positive and younger subjects experienced the greatest need for support immediately after, and for some time after hearing the result. From these observations, it can be concluded that ample time should be allowed for the test disclosure session and that counselees should be encouraged to bring an accompanying person to this session.

9.4. PSYCHOSOCIAL CONSEQUENCES OF TESTING (III-V)

At every phase (including the baseline), the mutation-positive subjects were more afraid of cancer than those who were mutation-negative. In both groups, however, the fear of cancer decreased with time. In the mutation-negative subjects, this decrease was to be expected, while in the mutation-positive subjects it may reflect a sense of security caused by the organised cancer surveillance scheme. A significant proportion of the subjects (68%) had already been under cancer surveillance based on their high-risk status (study I). The fact that they had been in permanent contact with their HNPCC physician, who was readily available, may have reduced the fear of cancer and the distress. Furthermore, among these individuals, one of the most important reasons for taking the predictive test for HNPCC was given as

reduction of uncertainty (study I), and perhaps the testing really increased certainty and simultaneously relieved their fear of cancer. A relevant question is, of course, what amount of fear is necessary to induce adherence to the cancer surveillance programme but is nevertheless consistent with emotional well-being. Thus far, no data are available on whether fear of cancer affects surveillance behaviour among those who are mutation-positive, and this topic deserves further study.

Other fears, irrespective of the test result, had not changed significantly from the baseline values at the follow-ups. In addition, those tested seemed to view their future as promising and were as satisfied with their lives as before the testing. Consistently, 1 year after disclosure of the results the study subjects reported high levels of satisfaction with the decision to take the test (study I).

Although general anxiety remained unchanged between the baseline and the 1-year follow-up, there was a striking difference in anxiety scores between the groups defined by mutation status at the test disclosure. Surprisingly little attention has been paid to this topic in previous studies. Thus far, only one study has reported to have similarly assessed the anxiety at test disclosure; however, no detailed analysis of the results was given (Watson et al., 1996). Thus, this appears to be the first study that reported anxiety levels immediately after the test disclosure among groups defined by mutation status and, as expected, the mutation-positive individuals showed increased levels of anxiety, whereas the mutation-negative subjects showed decreased anxiety. Those receiving the bad result also afterwards felt that the greatest need of psychological support was at the moment of the test disclosure (study II). It can be concluded that all possible efforts should be undertaken to support the counselees at the moment of receiving the test results.

Comprehension of cancer risk

In the present study, pre-test risk perception was not significantly associated with the test uptake by our study participants. These results are at variance with previous studies (Lerman et al., 1996b; Jacobsen et al., 1997; Codori et al., 1999; Glanz et al., 1999). It should be remembered that in the present study the analysis was based on data obtained from those who

had filled in questionnaires, and that from those who did not, no information about risk perception was available.

This is the first study on how those tested comprehended their risk figure. Although practically all the subjects remembered correctly whether or not they had inherited the mutation, understanding of the test result seemed to be complex. At post-test follow-ups, the majority of the mutation-positive individuals underestimated their cancer risk as being only 50% or less, instead of the correct very high risk of which they had been informed in the counselling. One explanation may be the difficulty of expressing a high but not inevitable risk in percentages and, therefore, of simplifying the risk - either it will happen or it will not. The misunderstanding may also reflect protective coping mechanisms such as denial, for misunderstandings were more common among those who actually had a high risk. According to multivariate analysis, the only significant predictor of this phenomenon was an initial perception of a low risk, which could reflect incorrect information or, again, a protective coping mechanism. Denial may be, on the other hand, an important coping mechanism that enables the mutation-positive subjects to face the future. However, if it decreases adherence to clinical surveillance, its consequences may be serious.

Among the mutation-negative subjects, misunderstanding of the results was much less common (only 8-10%). In this group, misunderstanding was predicted by a higher estimate of the pre-test risk and high scores for anxiety immediately after hearing the test results. Consistently, these individuals were more worried about their risk than those who understood correctly. This may have reflected the previously described "adverse feelings" about testing in the mutation-negative individuals, such as troubles in finding a new life perspective, survivor guilt, or worry about the mutation-positive family members (Lynch et al., 1999).

A recent review of risk communication in genetic testing for cancer suggests that perceptions of personal risks of cancer are resistant to standard pre-test education and counselling (Croyle and Lerman, 1999). Another review on genetic risk and behavioural change indicated that informing individuals about their genetic risk of developing a common disease will be helpful, provided that they can be persuaded to adopt healthy lifestyles that reduce the risk (Marteau and Lerman, 2001). However, changing health behaviour is dependent on two essential factors; motivation to change and belief in one's own ability to change. Changing behaviour is

difficult, but the change is most likely to occur among motivated individuals who participate in effective interventions.

This reflects the challenges faced by health care professionals with regard to the patients' understanding of their risk and consequent health behaviour. Should those underestimating their risk be informed on a second occasion about the actual risk? This might even be impossible in normal clinical settings without post-test questionnaires. However, as risk perception seems to be a complex issue, further research is needed about the impact of different post-test counselling approaches on comprehension of the cancer risk. In any case, it is necessary to provide opportunities for readily available clinical surveillance and to encourage those at high risk to adhere to effective surveillance.

Cancer surveillance

Experience of participation in cancer surveillance among those tested for cancer susceptibility is still in a very preliminary stage. It has been reported that adherence to population-based colorectal cancer screening is not self-evident (Vernon, 1997) and several social and psychological factors, including perceived susceptibility to cancer, have been suggested to influence the response to cancer surveillance (Vernon, 1997).

Few data are available on the actual willingness to undergo cancer surveillance after genetic testing (Watson et al., 1996; Lerman et al., 2000; Meijers-Heijboer et al., 2000). Lerman et al. reported that 1 year after testing many women (32%) with the *BRCA1/2* mutation had not followed recommendations to undergo mammography. However, the impact of risk perception was not studied and only young age (<40 years) predicted non-adherence, which may reflect the fact that there are actually very few data about the efficacy of mammography among younger women. This is further supported by the results of a large-scale Dutch study, in which women positive for the *BRCA1/2* mutation more often chose prophylactic surgical procedures than clinical surveillance (Meijers-Heijboer et al., 2000).

In previous studies, the amount of worry about cancer has been found to be associated in a complicated manner with cancer screening behaviour (Lerman et al., 1991; Lerman et al., 1993). In our study, most of the mutation-positive individuals were worried, at least to some

extent, about their risk of developing colorectal cancer, and misunderstanding of the result was associated with less worry, a situation that may lessen adherence to surveillance.

In contrast, if the health professionals are aware of some who overestimated their post-test risk and are worried about it, should the individuals concerned be offered further counselling? In the present study, such individuals were very few in number, which suggests that further counselling could be performed without placing too great a strain on the health care system. However, the literature suggests that, among those with high levels of cancer-related distress, improving risk comprehension may not be successful (Croyle and Lerman, 1999). Thus, it is possible that counselling with emphasis on the psychological issues might be more beneficial than traditional risk counselling.

Social implications

It is possible that, in the Finnish population, genetic tests may not be experienced as socially threatening, possibly because of confidence in the health care and social security system. The present study supports this assumption: the result of the predictive genetic test for HNPCC did not seem to have a notable effect on attitudes to life and health insurance.

None of those declining the test expressed concern about losing insurance and fewer than 2% of those taking the test for HNPCC stated that they had considered problems of insurance and employment as an argument against taking the predictive genetic test. It has been reported from elsewhere that such concerns have more often been encountered when offering a predictive genetic test for breast cancer, irrespective of the type of health care system. In a US setting, Lerman et al. reported that those who did not have a health insurance were more likely to decline a genetic test for breast cancer (Lerman et al., 1996b). A Canadian study revealed, that despite the public health care system, almost one third of the study subjects were concerned about insurance discrimination issues when considering whether to undergo testing for hereditary breast cancer (Phillips et al., 2000).

In the present study, the mutation-positive subjects more often reported that they already possessed health insurance before they were invited to counselling than those who were mutation-negative. Before counselling and testing, however, they were undoubtedly unaware

of their mutation status. Thus, possible explanations may be that this was due to chance or that there were other differences between the groups defined by mutation status, such as age. It should be noted that our data in this study are based on self-reports and that the possibility of false reporting cannot be excluded, especially as the questionnaires were not anonymous. However, checking the data from insurance companies would have been impossible in terms of confidentiality.

Finnish insurance companies have agreed that neither the family history nor the results of genetic tests are queried at the moment of underwriting. However, this moratorium has been left indefinite. In this study, 4% of the mutation-positive group reported that they had purchased a life insurance policy after testing, but no-one in the group reported purchasing a health insurance policy. Parallel findings have been reported by Zick et al., who studied the insurance behaviour in mutation-positive American women 1 year after testing for *BRCA1* mutations (Zick et al., 2000). These findings, representing two essentially different health care systems, suggest that the information on high-risk status for a rare monogenic disease does not have a dramatic effect on the purchase of insurance. In addition, the number of families with these rare diseases is small in relation to the numbers of those insured.

Nevertheless, if there are to be tests for common, multifactorial diseases, tests that are able to predict future illness, and if such tests are widely used, this may impose constraints on insurers. From the European perspective, a solution to avoiding both the consequences of discrimination against clients and the possible constraints on insurers has been suggested to be that society should be responsible for creating and maintaining universal systems of health care (Harper, 1997d; European Society of Human Genetics Public and Professional Policy Committee, 2001).

10. CONCLUSIONS AND FUTURE PROSPECTS

The possibility of early detection and treatment of colorectal tumours makes predictive testing for HNPCC beneficial. The test was welcomed by the majority of individuals at risk of HNPCC and few reported having regretted the decision to take it. Thus, it can be suggested that all members of families with HNPCC should be actively informed about the predictive test by their physicians. The challenging task is to convey the initial offer in such a manner that individuals of different socioeconomic backgrounds become interested. However, as a minority are unwilling to be tested, or even counselled, and their decisions should be respected, participation should not be taken for granted. Research is needed on the barriers to participation in the test, and on the impact of such testing conducted outside the context of research protocols.

Our results support the view that, for the purpose of genetic counselling and predictive testing for HNPCC, the reduced form of the counselling protocol is suitable. A protocol that includes one comprehensive educational pre-test counselling session and a test disclosure session, supplemented with the option of professional psychological support seems to be sufficient for both the educational and the supportive needs of counselees at the psychologically critical phases. Only a minority expressed a need for a post-test follow-up session, which suggests that, in this disorder, resources can be directed to the beneficial surveillance programmes rather than to extensive psychological support. Further studies are needed to resolve the issue more thoroughly.

This study also provides the first data on comprehension of the predictive genetic test results in cancer, which suggest that the majority of the mutation-positive subjects tend to underestimate their risk. Whether post-test risk perception affects behaviour in terms of compliance with cancer surveillance is still unknown. There is a danger that misunderstanding the test result may affect adherence to surveillance, and this topic deserves further study. Before that, predictive genetic testing should be offered in conjunction with a well organised cancer surveillance programme.

The present study suggests that making the decision was psychologically demanding and, apparently, an even more stressful occasion was the moment at which the test result was

disclosed. With time, coping with the test result was found to be easier. This may be because of the existing beneficial surveillance and early treatment of cancer, which increases the sense of security among the mutation-positive subjects and, for the same reason, decreases the feelings of survivor guilt among those receiving the good news.

No signs of overall harmful emotional effects of testing were detectable in the study. Immediately after the test disclosure, the mutation-positive subjects had significantly higher anxiety scores than those who were mutation-negative, but the differences disappeared during the follow-up. However, the individual trends shown by anxiety among our study subjects were diverse and unique. These should be taken into consideration in terms of individualised counselling supplemented with the option of ongoing emotional support. At the 1-year follow-up, the testing had significantly decreased the fear of cancer from baseline values in both groups defined by mutation status. Thus, in this follow-up testing seemed to have relieved the fear of cancer and to have caused no overall harmful consequences. However, the emotional impact of testing should be studied after a longer interval to confirm these findings. Furthermore, studies investigating the impact of fear of cancer on surveillance behaviour among those who are mutation-positive are needed to evaluate the ultimate interpretation of these results.

The mutation-positive subjects did not differ from the others in life insurance or health insurance behaviour during and after the predictive genetic testing programme. However, they were significantly more often already covered by a health insurance than their mutation-negative counterparts before they were invited to the pre-test counselling.

HNPCC appears to be a disease in which mutation testing is well accepted. In the past, attitudes toward predictive genetic testing have been overshadowed by HD, which may have created fears of negative consequences. Apparently HNPCC, like many other forms of hereditary cancer, differs from HD, since preventive and therapeutic interventions are possible and general attitudes towards genetic testing appear to be more positive. However, it is quite evident that the period before testing and the actual moment of telling the result create significant amount of stress. It may be best to cope with this by providing adequate support and counselling. The results of our study suggested that there may be some subgroups which

may need more attention than others. One of the main goals in the future should be to identify these subgroups and measures that should be undertaken to give adequate support.

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13. APPENDIX

Background information

(1) What is your current marital status? (I-V)

1. married or cohabiting
2. single
3. divorced
4. widowed

(2) Do you have children? Please, indicate how many. If you have no children, indicate 0. (I-V)

__ children,

(3) How many years have you gone to school and studied on a full-time basis? The primary education is included. (I-V)

__ years

(4) If you have any of the forms of education mentioned below, please circle the option/options (I-II)

1. vocational education: _____
2. upper secondary education: _____
3. university degree: _____

(5) What is your current employment status? (I-V)

1. unemployed
2. laid off
3. partially employed, unwillingly
4. employed, but threatened by unemployment
5. normally employed, student or at home
6. retired

(6) Have you attended colorectal cancer surveillance examinations? (I- V)

1. never
2. yes, occasionally
3. yes, regularly

(7) How great do you estimate your own risk of developing hereditary cancer occurring in your family to be? (I, IV)

1. the risk is small
2. the risk is moderate
3. the risk is great

Decision making and satisfaction with it

(8) What affected your decision to be tested? (I)

	not at all	somewhat	a good deal	very much
1. Planning for the future	1	2	3	4
2. Marital decisions	1	2	3	4
3. Reproductive decisions	1	2	3	4
4. Clarifying the risk for children	1	2	3	4
5. Employment decisions	1	2	3	4
6. Reducing uncertainty	1	2	3	4
7. A doctor recommended it	1	2	3	4
8. Other reasons, what	1	2	3	4

(9) Try to remember the situation when you made your decision about the test. What kind of points related to decision making did you have in mind? Some of the points may have favoured the test and others may have been against it. You can also mention alternatives presented in the preceding question. (I)

The following points favoured the test:

The following points were against the test

(10) Are you satisfied with your decision to take the test? (I)

1. Extremely satisfied
2. Fairly satisfied
3. Uncertain
4. Rather dissatisfied
5. Extremely dissatisfied

(11) Do you trust the test result? (I)

1. Trust completely
2. Trust hesitantly
3. Uncertain
4. I am rather distrustful
5. I am extremely distrustful

(12) Now that you know the result, would you have taken the test in the first place? (I)

1. Would definitely have taken the test
2. Would probably have taken the test
3. Uncertain
4. Would probably not have taken the test
5. Would definitely not have taken the test

Opinions of the counselling

(13) What is your general opinion about the counselling protocol? (II)

1. Counselling sessions were easily comprehensible and I have no improvements to suggest
2. Counselling sessions were easily comprehensible but I would like to suggest the following minor changes concerning the counselling sessions, ...
3. I would like to suggest major changes concerning the counselling sessions, such as...

(14) Did you consider the pre-test counselling session useful? (II)

1. Very useful
2. Fairly useful
3. Slightly useful
4. Not at all useful
5. Can't say

(15) Did you consider one post-test counselling session sufficient? (II)

1. Yes, it was sufficient
2. No, I would have liked another
3. Can't say

The need for psychological support experienced during the testing procedure

(16) Would you have welcomed psychological support provided by the counselling team? (II)

1. Definitely
2. Most likely
3. Perhaps
4. Most unlikely
5. Definitely not

(17) At what moment did you experience the greatest need for psychological support? (II)

1. The decision making phase
2. Waiting for the result
3. The test disclosure session
4. Soon after the test disclosure
5. One month after the test disclosure
6. One year after the test disclosure

(18) Did you seek psychological help or use the mental health services after hearing the genetic test result? (II)

1. Yes
2. No

Satisfaction with life and view about the future

(19) Are you satisfied with your life in general at the moment? (III)

1. Extremely satisfied
2. Rather satisfied
3. Neither satisfied nor unsatisfied
4. Rather unsatisfied
5. Extremely unsatisfied

(20) What does your future look like? (III)

1. Extremely promising
2. Fairly promising
3. Can't say
4. Rather unpromising
5. Extremely unpromising

Fear of death and disease

(21) Does the thought of death scare you? (III)

1. No
2. Rarely
3. Sometimes

4. Often
5. Most of the time

(22) Are you afraid that you may die soon? (III)

1. No
2. Rarely
3. Sometimes
4. Often
5. Most of the time

(23) Are you afraid that you may have cancer? (III)

1. No
2. Rarely
3. Sometimes
4. Often
5. Most of the time

General anxiety (State-Trait Anxiety Inventory: state measure) (III-IV)

How do you feel now?

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate alternative to indicate how you feel right now, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any of the statement but give the answer that seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
24. I feel calm	1	2	3	4
25. I feel secure	1	2	3	4
26. I am tense	1	2	3	4
27. I am regretful	1	2	3	4
28. I feel at ease	1	2	3	4
29. I feel upset	1	2	3	4
30. I am presently worrying about possible misfortune	1	2	3	4
31. I feel rested	1	2	3	4
32. I feel anxious	1	2	3	4
33. I feel comfortable	1	2	3	4
34. I feel self-confident	1	2	3	4
35. I feel nervous	1	2	3	4
36. I am jittery	1	2	3	4
37. I feel "highly strung"	1	2	3	4
38. I am relaxed	1	2	3	4
39. I feel content	1	2	3	4
40. I am worried	1	2	3	4
41. I feel over-excited and rattled	1	2	3	4
42. I feel joyful	1	2	3	4
43. I feel pleasant	1	2	3	4

Comprehension of the test result and worry about it

(44) What was your test result? (IV)

1. I was found to have the mutation predisposing to colorectal cancer
2. I was found not to have the mutation

(45) How does your risk of developing colorectal cancer appear after testing? In this connection, the risk refers to what the cancer risk would be without regular cancer surveillance aimed at prevention of cancer. (IV)

1. The risk is high, close to 100%
2. The risk is approximately 50%
3. The risk is rather low, corresponding to that of the general population.

(46) Are you worried about your current risk of developing colorectal cancer?" (IV)

1. Not at all worried
2. Worried to some extent
3. Very worried
4. Can't say

Insurance

(47) Do you have a life insurance and if you do, when did you purchase it? (V)

1. I already had a life insurance before I was invited to the genetic counselling
2. I purchased a life insurance before undergoing the testing
3. I don't have a life insurance
4. I am planning the purchase of a life insurance
5. I purchased a life insurance after being tested
6. I have never planned the purchase of a life insurance

(48) Do you have a health insurance and if you do, when did you purchase it? (V)

1. I already had a health insurance before I was invited to the genetic counselling
2. I purchased a health insurance before undergoing the testing
3. I don't have a health insurance
4. I am planning the purchase of a health insurance
5. I purchased a health insurance after being tested
6. I have never planned the purchase of a health insurance