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# Comprehension of cancer risk one and 12 months after predictive genetic testing for hereditary non-polyposis colorectal cancer

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EDITOR—The main purpose of offering predictive genetic testing for hereditary cancer is to reduce unnecessary worry among those with a low risk of cancer (mutation negative) and to recognise those with a high risk (mutation positive), so as to promote preventive measures.[1 2] Ideally, those shown to be at high risk would understand this, would learn to live with the knowledge, and, most importantly, would attend cancer surveillance programmes regularly. Those at low risk would feel relieved and no physically and emotionally uncomfortable surveillance would be needed. This result would be seriously hampered if those tested did not fully understand the meaning of the test results, which could lead to unnecessary worry or failure to adhere to surveillance. At present, most predictive tests are performed in carefully organised settings, which include comprehensive pre- and post-test counselling that would be expected to minimise the risk of misunderstanding the test result. However, commercial tests predicting cancer are already available,[3] and this has raised concerns about predictive testing with minimal counselling or even without personal contact with a health care professional.[1 4]

The impact of genetic counselling on risk perception and impact of risk perception on genetic testing intentions has been studied previously.[5] However, this is the first report on the comprehension of test results (perception of cancer risk) after predictive genetic testing for cancer, in this case hereditary non-polyposis colorectal cancer (HNPCC), which is the most common form of hereditary colon cancer. HNPCC is an autosomal dominant disease of adulthood with an 80-90% lifetime risk for colorectal cancer and a lesser risk of extracolonic cancers, the most common of which are endometrial and gastric cancer.[6] Hereditary colorectal cancer differs essentially from other hereditary cancers, of which hereditary breast cancer is a good example. Firstly, in HNPCC, the life long risk of developing colorectal cancer among mutation positive subjects is uniformly very high (80-90%),[7 8] while in breast cancer the corresponding risk varies between 40 and 80%.[9–11] Secondly, for HNPCC, in contrast to breast cancer, clinical surveillance among those at high risk has been shown to reduce mortality from colorectal cancer substantially.[12 13] Predictive genetic testing is now possible in all the families with HNPCC in which the predisposing germline mutation is known. Previous studies among first degree relatives of patients with colorectal cancer have suggested a great interest in possible testing and intention to learn the results.[14 15] Reports on the actual offering of predictive genetic tests to HNPCC families have shown that the acceptance rates have varied greatly (14-81%).[16–19] This study describes how the members of HNPCC families comprehended their predictive test results in terms of their risk of developing colorectal cancer and discusses what may have influenced this.

## Methods

During 1995-1997, we offered counselling about predictive genetic testing to adults at 50% risk in 36 HNPCC families in which mutations in the *MLH1* gene had previously

been characterised.[20 21] The counselling and testing procedure has been described in detail elsewhere.[17 22] Briefly, all known eligible (aged 18 or older and without a diagnosis of cancer) members of these HNPCC families were informed about the study by letter. Those who consented to participate in the study were invited to an individual pre-test counselling session, which followed a uniform scheme, comprising taking the family history and giving information about HNPCC, its mode of inheritance, the gene defect, the nature and the 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, including verified colorectal cancer in at least three relatives (one of whom was a first degree relative of the other two) in at least two successive generations, and at least one of the cases had been diagnosed before the age of 50 years.[23] Therefore, the risk of colorectal cancer was estimated to be very high, close to 100%. This was communicated to the counsellees at the pre-test session. Furthermore, the benefits and disadvantages of a predictive gene test were thoroughly discussed.

After a two week period for reflection, counsellees were contacted by telephone and asked if they wanted the test. Those who chose to take the test signed a consent form and donated a blood sample. Those who declined the test and remained at 50% risk were encouraged to adhere to the clinical surveillance, comprising colonoscopy every three years and gynaecological examinations yearly for females over 35 years old.

Those tested were invited, preferably with an accompanying person, to a post-test counselling session at which the test result and its implications were discussed. For those who had the mutation, the high risk of colorectal cancer (close to 100%) was reiterated and clinical surveillance was organised. Subjects who did not have the mutation were reminded of the general risk of cancer, to prevent any false reassurance. The result of the mutation analysis and, accordingly, surveillance recommendations were also given in written form.

Of the eligible subjects (n=446), 90% (n=401) consented to participate in the study and 85% (n=381) returned a baseline questionnaire I.[17] The educational counselling session was attended by 347 subjects, of whom 333 (96%, 75% of the total population) opted for a predictive genetic test. Seven subjects refused to fill in any further questionnaires. A follow up questionnaire was sent at one month to 326 subjects, of whom 299 (92%) replied. Another follow up questionnaire was sent at one year to these 299 subjects, of whom 271 (91%) filled in this final form. Thus, the study sample consisted of those 271 subjects who attended both counselling sessions, and completed the pre- and post-test questionnaires. Of the subjects, 68% attended the pre-test session conducted by a nurse specifically trained for pre-test counselling and 32% by a physician specialising in medical genetics (KA-C). Fifty seven percent had a post-test counselling session conducted by the physician (KA-C) and the rest were counselled by a gastroenterological surgeon (J-PM). Both pre- and post-test sessions were standardised as far as possible, in that all counsellors followed a similar structured protocol including similar, previously agreed, risk counselling.

Of the study subjects (n=271), 57% were women, 72% lived with a spouse or partner, 73% had children, 76% were employed, and 62% had an education higher than primary level.[22] The participants were aged 19-77 years (mean 43 years) and 68% had a previous history of clinical cancer surveillance because of their high risk status. Thirty one percent (n=84) were mutation positive. The differences between the groups defined by mutation status are presented in table 1. The subjects lost to follow up (n=62) who did not complete questionnaires after the post-test counselling session did not differ significantly from the study subjects in any of the variables described here.

The study is based on questionnaires, which were filled in three times during the procedure: before the first counselling session (baseline measurement) and one month and one year after the test disclosure session. Exceptionally, the anxiety scale was filled in at the test disclosure session soon after the test result had been communicated. Understanding of the test result was assessed in both follow up questionnaires by two questions. (1) "What was your test result?" (1 = I was found to have the mutation predisposing to colorectal cancer, 2 = I was found not to have the mutation). (2) "What does your risk of developing colorectal cancer look like after testing? In this connection, the risk refers to what the cancer risk would be without regular cancer surveillance aimed at prevention of cancer." (1 = the risk is high, close to 100%, 2 = the risk is approximately 50%, 3 = the risk is quite low, corresponding to that of the general population.) The alternatives chosen were based on the information given in the pre-and post-test counselling. Accordingly, the correct options were 3 for the mutation negative subjects and 1 for the mutation positive subjects. In the analysis, those who chose the correct option were labelled "understanding" the result and those

*Table 1 Associations of baseline demographic variables with groups defined by mutation status*

| | *Mutation negative (n=187)* | *Mutation positive (n=84)* | $\chi^2$ | *t test* |
|---|---|---|---|---|
| Mean age in years (SD) | 45.6 (12.9) | 37.8 (11.5) | | p<0.001 |
| Female | 110 (59%) | 45 (54%) | NS | |
| Having children | 145 (78%) | 54 (64%) | | |
| Married or cohabiting | 139 (74%) | 57 (68%) | NS | |
| Employed | 132 (71%) | 70 (84%) | p<0.05* | |
| Previous history of cancer surveillance | 126 (67%) | 58 (69%) | NS | |
| Education in years: mean (SD) | 11.05 (3.49) | 12.06 (3.22) | | p<0.05* |
| Pre-test risk perception: mean (SD) | 1.98 (0.51) | 2.11 (0.56) | | NS |

NS = non-significant.
*After adjustment for age, the difference disappeared.

choosing the incorrect option "misunderstanding" the result. Sociodemographic information obtained from the questionnaires included age, gender, having children (1 = yes, 2 = no), marital status (1 = married or cohabiting, 2 = single, divorced, or widowed), employment status (1 = employed, 2 = unemployed or retired), education in years, previous history of colorectal cancer surveillance (1 = colonoscopy/colonoscopies performed previously, 2 = no colonoscopy performed) pre-test risk perception (risk of having HNPCC: 1 = low, 2 = medium, 3 = high). General anxiety was measured by the state measure of the State-Trait Anxiety Inventory (STAI) which is a 20 item scale.[24] Response categories for the items range from 1 (not at all) to 4 (very much so). Scores range from 20 to 80, the higher scores indicating greater state anxiety. In this study, the measurements were performed at baseline and at the test disclosure session. In both measurements, Cronbach alpha was 0.9, indicating high internal consistency. Worry about the risk of developing colorectal cancer based on the test results was assessed at the one year follow up by a question with multiple choice answers. "Are you worried about your current risk of developing colorectal cancer?" (1 = not at all worried, 2 = worried to some extent, 3 = very worried, 4 = can't say).

All data analyses were done with the program SPSS for Windows version 9.0. We studied bivariate associations between groups defined by understanding the results and explanatory variables, including sociodemographic information, anxiety at baseline and at the test disclosure session, and associations between understanding the risk and perceived worry about it. Differences between categorical variables were assessed with $\chi^2$ (df) tests and McNemar tests (table 2), and differences between continuous variables with independent sample *t* tests. The variables showing statistical significance in bivariate analysis (p<0.05) were subjected to binary logistic regression analysis to predict misunderstanding of the cancer risk among mutation positive and mutation negative subjects. Among the mutation negative subjects, 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 subjects, those who claimed that their risk was low or 50% were compared with those who correctly stated their risk to be near 100%. All predictors were analysed as continuous variables and were entered simultaneously.

*Table 2 Perception of the post-test risk of developing colorectal cancer, assuming that no clinical surveillance existed at the one month or the one year follow up*

| | *One month follow up* | | *One year follow up* | |
|---|---|---|---|---|
| *Perception about the risk of colorectal cancer* | *Mutation negative group* | *Mutation positive group* | *Mutation negative group* | *Mutation positive group* |
| Great risk | — | **40 (48%)** | 2 (1%) | **29 (35%)*** |
| 50% risk | 14 (8%) | 41 (49%) | 16 (9%) | 46 (56%) |
| Low risk | **170 (92%)** | 3 (3%) | **167 (90%)** | 7 (9%) |
| Total | 184 (100%) | 84 (100%) | 185 (100%) | 82 (100%) |

Correct answers are printed in bold.
*McNemar test p<0.05 (mutation positive group: one month follow up *v* one year follow up).

*Table 3 Factors predicting understanding of the results at one month follow up according to a logistic regression analysis*

| *Variable* | *Mutation negative group (n=187) OR (95% CI)* | *Mutation positive group (n=84) OR (95% CI)* |
|---|---|---|
| Age | 0.99 (0.93–1.05) | 1.03 (0.98–1.08) |
| Education in years | 1.02 (0.83–1.25) | 0.85 (0.70–1.02) |
| Baseline anxiety | 0.98 (0.89–1.07) | 1.01 (0.94–1.08) |
| Anxiety immediately after test disclosure | 1.11 (1.01–1.22)* | 1.00 (0.94–1.07) |
| Pre-test risk perception | 5.00 (1.49–16.83)† | 0.30 (0.11–0.81)* |

*p<0.05.
†p<0.01.

## Results

Nearly all the respondents (268/268 at the one month follow up and 266/268 at the one 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% *v* 48%, $\chi^2$=68.17 (1), p<0.0001), and at the one year follow up, the difference was even greater (90% *v* 36%, $\chi^2$=86.19 (1), p<0.0001) (table 2). The answers were similar, irrespective of the counsellor at the pre-test or the test disclosure session. Regarding the mutation positive subjects, misunderstanding at the one month follow up was more common among the older (*t*=−2.09, p<0.05), the less educated (*t*=3.19 p<0.001), and those who had perceived the pre-test risk as lower than the others (*t*=3.17, p<0.01). Among mutation negative subjects, those few who misunderstood their risk had perceived their (pre-test) risk to be high (*t*=−3.0, p<0.01) and had high scores on anxiety immediately after the test disclosure session (*t*=−3.01, p<0.01 ) as compared with those who understood their risk. With regard to other demographic data, the groups did not differ.

According to the logistic regression model presented in table 3, the only predictor of misunderstanding the result was 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 one year follow up, we carried out 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 one 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 ($\chi^2$=59.75 (3), p<0.0001). Fig 1 illustrates an analysis that compares worry about the risk with a correct or incorrect

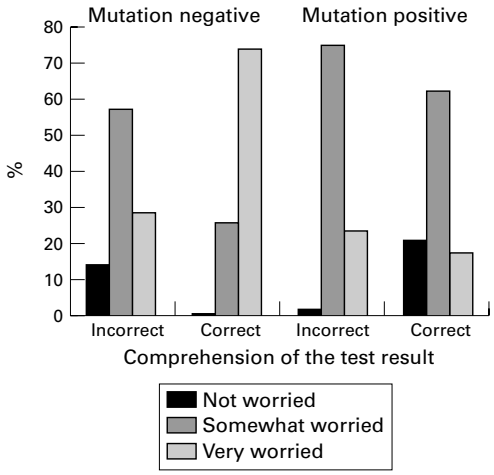


*Figure 1 The association between comprehending the test result (cancer risk) correctly and extent of worry about it one year after receiving the test result.*

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 (mean scores 2.03 *v* 1.78, $t$=2.04, p<0.05). By contrast, the mutation negative subjects who misunderstood the test result were more worried about the risk than their counterparts (mean scores 1.86 *v* 1.27, $t$=−4.37, p<0.001).

## Discussion

The purpose of predictive genetic testing, as stated in the introduction, was partly met in our study since nearly all the respondents recalled their test results correctly and most of those who were mutation negative correctly interpreted their test result. However, a majority of the mutation positive subjects underestimated their cancer risk as being only 50% or below, 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, simplifying the risk, either it will happen or it will not. The misunderstanding may also reflect protective coping mechanisms such as denial, for the misunderstanding was more common among those who actually had high risk. A similar phenomenon has been described in studies of testing of cystic fibrosis carriers.[25 26] According to multivariate analysis, the only significant predictor of this phenomenon was an initially low perception of the risk, which could reflect incorrect information or, again, protective coping mechanisms. Denial may be, on the one hand, an important coping mechanism which enables the mutation positive subjects to face the future. On the other hand, if it decreases adherence to clinical surveillance, it could have serious consequences.

Few data are available on cancer surveillance behaviour after genetic testing. Lerman *et al*[27] reported that many women (32%) with *BRCA1/2* mutation did not follow mammography surveillance recommendations one year after testing. However, the impact of risk perception was not studied and only young age (<40 years) predicted non-adherence, which may reflect the absence of data on the efficacy of mammography among younger women.

In previous studies, the amount of worry about cancer has been found to be associated with cancer screening behaviour in a complicated manner. Lerman *et al*[27] found, in a population based study, that women who were excessively worried about breast cancer were less likely to attend mammography.[28] Moderate worry, however, may serve as an important promoter of cancer screening behaviour.[29] Pre-test worry about cancer has been shown both to be positively associated with high perceived risk of developing cancer[30] and with intentions and uptake of genetic testing.[5] In our study, most of the mutation positive subjects were worried, at least to some extent, about their risk of developing colorectal cancer and misunderstanding the result was associated with less worry. There is a danger that misunderstanding connected with less worry may disturb adherence to surveillance. There is a pressing need of studies to clarify this issue.

Misunderstanding of the results was much less common (only 8-10%) among the mutation negative subjects. It was predicted by a higher estimate of the pre-test risk and high scores on anxiety immediately after hearing the test results. Consistently, these subjects were more worried about their risk than those who answered correctly. This could reflect the previously described adverse feelings about testing in the mutation negative subjects, such as trouble in finding a new life perspective, survivor guilt, or worry about the mutation positive family members.[31 32]

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.[5] This reflects the challenges faced by health care professionals with regard to the patients' understanding of their risk. Should those underestimating their risk be reinformed about the actual risk after testing? This might even be impossible in a normal clinical setting without post-test questionnaires. However, as risk perception seems to be a complex issue, further research about the impact of different post-test counselling approaches on comprehension of cancer risk is needed. In any case, it is necessary to ensure that clinical surveillance is readily available and that adherence to the surveillance is actively supported.

In contrast, if the health professionals were aware of some who overestimated their post-test risk and were worried about it, should the subjects concerned be offered further counselling? In the present study, the subjects involved 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, published reports suggest that improving risk comprehension may not be

successful among those with high levels of cancer related distress. Thus, it is possible that counselling with the emphasis on the psychological issues may be more beneficial than traditional risk counselling.[33]

Our study population consisted of those who had completed the whole testing procedure, including the questionnaires. Although those lost to follow up did not differ from the participants in any of the background variables used in this study, we know nothing about the post-test risk perception, worry, or anxiety of the dropouts. The risk perception based on the test result was assessed with one categorical variable. Alternatives of the question were based on information given during counselling (very high, close to 100%, for the mutation positive and very low for the mutation negative). Before the test, all the participants had been informed that they ran a 50% risk of cancer. The categorical alternatives make the distinction between correct and incorrect options easier to assess. Assessment using risk perception as a continuous variable (0-100 scale) would have been problematical because we had not provided exact numerical risk figures during counselling. Furthermore, it should be noted that possible findings of colon polyps or cancer after the test may have acted as potential confounding factors on risk perception.

## Conclusions

This study provides the first data on comprehending 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 the danger that misunderstanding the test result may affect adherence to surveillance. We therefore suggest that predictive genetic testing for HNPCC should be offered in conjunction with a well organised cancer surveillance programme to promote participation independently of risk perception. The small number of those remaining worried despite an actual low risk should be taken into account, possibly by offering further counselling sessions with emphasis on psychological support.

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- Comprehension of predictive genetic test results and factors influencing it were measured with a questionnaire survey one and 12 months after disclosure in 271 subjects tested for HNPCC.
- Nearly all respondents recalled correctly whether or not they had inherited the mutation predisposing to HNPCC.
- A majority of the mutation positive subjects incorrectly interpreted (underestimated) their test result in terms of cancer risk at both follow ups.
- A great majority of the mutation negative subjects interpreted their likelihood of developing cancer correctly.
- Perceived pre-test risk seemed to be the best predictor of misunderstanding, irrespective of the test result.
- As misunderstanding the test result may complicate adherence to cancer surveillance, offering predictive testing in conjunction with a well organised cancer programme might be beneficial.

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# Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region

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EDITOR—Prader-Willi syndrome (PWS) is a genetically determined disorder in which the absence of expression of one or more maternally imprinted gene(s) in the chromosomal region 15q11-13 results in a characteristic facial appearance, learning disabilities (mental retardation), and severe overeating behaviour owing to an abnormal satiety response to food intake, together with a range of other behaviours. Initially, as reported by Prader *et al*,[1] PWS was conceived as a syndrome of obesity, short growth, cryptorchidism, and mental retardation following hypotonia in the neonatal period. As more and more people with PWS were reported and research into the syndrome began, behavioural characteristics and other clinical features were added, culminating in the consensus diagnostic criteria.[2] Concurrently, the genetics of the disorder were receiving attention. First was the discovery that for many there was a visible chromosomal deletion in the proximal part of the long arm of chromosome 15 (15q11-13). Reports of an apparently similar deletion being associated with a phenotypically very different syndrome (Angelman syndrome, AS),[3] and the observation that PWS was the result of a deletion on the chromosome 15 of paternal origin, and AS the chromosome 15 of maternal origin, led to the recognition that gender specific imprinting of genes at that locus accounted for two diverse syndromes being associated with apparently similar chromosomal deletions.[4] Maternal chromosome 15 disomies, mutations of an imprinting centre, and chromosomal translocations accounted for non-deletion cases of PWS.[5]

In published reports on Prader-Willi syndrome (PWS), prevalence has been variously quoted as "about 1 in 25 000 live births",[6] "between one in 25 000 and one in 10 000 live born children",[7] "[estimates] vary 6-fold from 1 in 5000 to 10 000; 1 in 10 000; 1 in 15 000; 1 in 25 000; to 1 in 10 000 to 30 000".[8] Only two estimates appear to be based on epidemiological data, those of Akefeldt *et al*[7] and Burd *et al*.[8] In the latter North Dakota study, the authors surveyed paediatricians, neurologists, and clinical geneticists and also contacted the state's comprehensive evaluation centre, the state hospital, the state institution for the "mentally retarded", and group homes for the developmentally disabled, including one for people with PWS. In most communities, at least four of these sources of information were consulted. Each was sent a one page questionnaire pictorially illustrating the signs of PWS to aid identification. The response rate was 99%. These procedures yielded eight males, eight females, and one person whose gender was not given, with an age range from 9 to 30 years. At that time the population of North Dakota for that age range was 263 444, giving a prevalence rate of 1:16 062, equivalent to 1:38 395 in the entire population. No figures were given for the number of cases with a genetic diagnosis.

In the study of Akefeldt *et al*,[7] the authors estimated the prevalence of PWS in the age range 0 to 25 years in the rural Swedish county of Skaraborg, by surveying paediatricians, neuropaediatricians, child psychiatrists, school health visitors, general practitioners, and doctors working in the fields of general medicine, rehabilitation, and mental disabilities. The