ORIGINAL INVESTIGATION

Genetic Counseling and Testing in Families With Hereditary Nonpolyposis Colorectal Cancer

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Background: Genetic testing to refine cancer risk is available. However, little is known about factors affecting the uptake of testing for the most common hereditary colon cancer, hereditary nonpolyposis colorectal cancer. This study investigated attitudes, intentions, and uptake of genetic testing within newly identified families with hereditary nonpolyposis colorectal cancer.

Methods: Cohort study conducted at the National Institutes of Health between April 15, 1996, and November 20, 1999. Data were collected through questionnaires before semistructured education sessions, individual counseling sessions, and the offer of genetic testing.

Results: Of the 111 eligible first-degree relatives, 51% chose to participate in education and individual counseling sessions. Participation was associated with greater numbers of first-degree relatives with cancer; no association was found between participation and personal history of cancer. Before education and individual counseling sessions, 64% of participants had heard little about genetic testing for cancers; however, most (97%) stated intentions to pursue testing. Fifty-one percent identified learning about their children's risks as the most important reason to consider testing. Thirty-nine percent identified the potential effect on their health insurance as the most important reason to not undergo testing. Of the 111 eligible first-degree relatives, 51% chose to undergo genetic testing. Participants' intentions to pursue genetic testing were significantly affected by concerns regarding the ability to handle the emotional aspects of testing and the psychosocial effect on family members.

Conclusions: Genetic counseling and testing offers the potential to focus cancer screening resources in individuals truly at increased risk, thereby reducing mortality and morbidity. Fears of discrimination and concerns about psychological and psychosocial issues may present barriers to the use of current cancer prevention strategies, including genetic counseling and testing.

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HEREDITARY nonpolyposis colorectal cancer (also known as HNPCC and Lynch syndrome) is the most common hereditary form of colon cancer. It is estimated to account for between 1% and 5% of the individuals who develop colon cancer.[1] It has been estimated that the prevalence of HNPCC mutation carriers among the general population in Western countries is 1 in 740.[2] This means that in the United States approximately 380 000 individuals carry an HNPCC mutation and have a greater than 90% lifetime risk of developing one of the cancers associated with HNPCC.[3] Some evidence suggests that the risk of colon cancer may vary between men and women.[4] In addition to colon cancer, individuals with HNPCC are at increased risk (compared with the general population) for developing cancers of the uterus, small intestine, stomach, urinary tract, kidney, ovary, and other sites.[5-7] Lifetime estimates for developing a cancer associated with HNPCC approach 85% for colorectal cancer[8] and 40% to 60% for uterine cancer[9] (by age 70 years). Risks for cancer of the small intestine, stomach, urinary tract, kidney, ovary, and brain are also elevated but lower compared with the risks for colon and uterine cancer. Accurate and age-related risks for these cancers are not yet available.[10]

Before the identification of the gene mutations, the diagnosis of HNPCC was primarily made based on clinical criteria and family history.[11] At a time when the genetic cause of HNPCC was not known, the Amsterdam criteria were developed for research purposes in an attempt to clinically identify individuals and families likely to carry mutations.[12] The Amsterdam criteria are as follows:

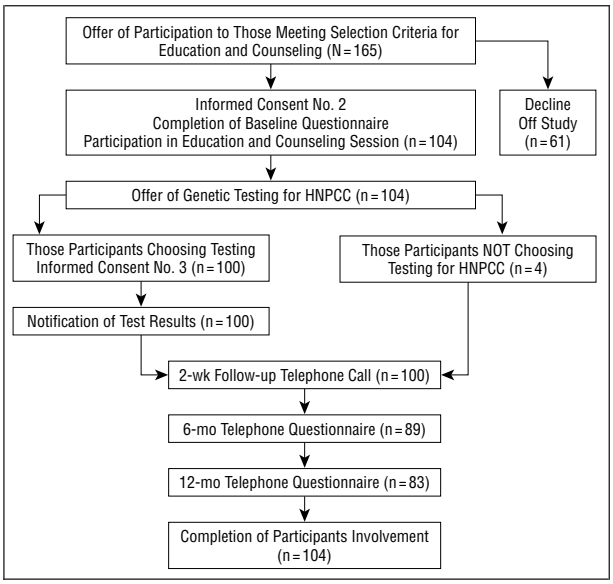
1. Histologically verified colorectal cancer in 3 or more relatives, 1 of whom is a first-degree relative of the other 2;
2. Colorectal cancer involving at least 2 successive generations; and
3. One or more colorectal cases diagnosed before the age of 50 years.
4. All of the above criteria must be met, and familial adenomatous polyposis must be ruled out as a cause for each colorectal cancer.

Subsequent molecular studies have identified several key genes that function in DNA mismatch repair and whose alteration leads to the increased risks for the cancers associated with HNPCC.[13-15] Six genes have been identified to date, *MLH1*, *MLH3*, *MSH2*, *MSH6*, *PMS1*, and *PMS2*. Current estimates suggest that *MLH1* and *MSH2* account for 80% to 90% of these cancers, while *MLH3*, *PMS1*, and *PMS2* are much less frequent.[16-19] More recent studies[20,21] suggest a growing role for *MSH6* in families with HNPCC, accounting for 5% to 10% of families in which *MSH2* and *MLH1* mutations have been excluded. It has been suggested that families with mutations in the *MSH6* gene have, in general, a later age of onset (51-52 years), a family history of cancer that does not often meet the Amsterdam criteria, and more frequently occurring endometrial cancer than in families with mutations in *MLH1* or *MSH2*.[22]

Understanding is growing about the factors affecting decision making regarding genetic testing and the psychosocial, medical, and behavioral effects of testing for mutations that predispose to cancer. Potential benefits to testing include informed decisions regarding cancer screening and reduced incidence of late-stage cancer following increased surveillance in at-risk individuals.[23] Despite the potential medical benefits, genetic testing also has the potential of adverse events, such as increased anxiety or depression, negative effect on family relationships, and loss of privacy and genetic discrimination.[24]

Since the advent of genetic testing, research has shown that an individual's intention to pursue testing significantly overestimates the actual uptake of testing when offered.[25,26] To date, 1 American study[27] and 1 Finnish study[28] have explored interest in genetic testing within families known to have HNPCC mutations. The American study found that a smaller proportion of family members with HNPCC (43% of family members eligible, 60% of those participating in the study) was likely to pursue genetic testing and receive results. Suggested barriers to test acceptance included higher formal education levels and the presence of depressive symptoms, especially in women. In the Finnish study, uptake of testing was higher, with 75% of eligible subjects choosing testing. Logistic regression analysis in the Finnish study identified employment status as the only significant factor predicting test acceptance; those employed were significantly more likely than others to choose genetic testing and receive the test results.

To further elucidate factors affecting decisions regarding genetic testing, we evaluated perceptions, intentions, attitudes, and uptake of genetic testing at baseline in individuals from families with newly identified HNPCC.



Flow diagram of study procedures. HNPCC indicates hereditary nonpolyposis colorectal cancer.

METHODS

STUDY POPULATION

The subjects were members of a cohort study conducted at the National Institutes of Health between April 15, 1996, and November 20, 1999. One hundred sixty-five adult men and women from 15 families identified with HNPCC mutations were considered eligible. Overall, 104 men and women chose to participate. Participants included individuals with HNPCC-associated cancers demonstrating microsatellite instability or a family history suggestive of HNPCC (index cases, n=47) and first-degree relatives at 50% risk of inheriting the family mutation (n=57).

PROCEDURES

The study was approved by the institutional review boards at the National Human Genome Research Institute and the National Naval Medical Center. A flow diagram of the study is depicted in the **Figure**. Probands were identified through cancer clinics at the National Cancer Institute and the National Naval Medical Center through the collection of family medical histories. Probands were also referred from unselected local and regional health care providers throughout the United States who became aware of the research protocol. Individuals with colon cancer identified through these means initially gave informed consent for the purpose of collecting a family medical history and to obtain tumor blocks for assessment of microsatellite instability.

GENETIC EDUCATION AND COUNSELING

Through telephone contact, those individuals meeting selection criteria were offered participation in the education and counseling portions of the study. Individuals whose families were previously known to have HNPCC mutations through other research or clinical efforts and are at 50% risk of inheriting the mutation were also eligible to participate. However, no participants were referred through these criteria or included in the data analyzed for this study.

An individual's decision to participate in the education and counseling portion of the study included the agreement to com-

plete a baseline questionnaire, receive genetic education and counseling pertaining to HNPCC, and participate in telephone interviews at 6 and 12 months after the intervention. All persons were reminded that participating in the education and counseling sessions did not obligate them to undergo genetic testing. Education and counseling sessions were conducted at the National Naval Medical Center, with partial reimbursement for the participant's travel expenses. Following consent to the education and counseling portion of the study, participants provided information pertaining to their demographics, knowledge, awareness, expectations, intentions, mood, attitudes, perceived risk, cancer worries, family relationships, spirituality, coping, and health beliefs through a baseline questionnaire. Participants were then provided with a standardized (scripted) genetic education session accompanied by slides. Depending on each participant's preference and consent, we provided an individual or a single-family education session. The sessions were presented by a board-certified genetic counselor (n=1; D.W.H.) or a cancer research nurse (n=2; J.J. or E.D.). Topics covered at the education sessions included (1) basic facts about the incidences of cancer and colon cancer; (2) risk factors for cancer; (3) inheritance of cancer susceptibility in families with HNPCC; (4) possible outcomes of genetic testing for HNPCC; (5) potential benefits, limitations, risks, and psychological or relational effects associated with genetic susceptibility testing; and (6) a review of cancer surveillance and screening guidelines recommended for families with HNPCC.[29] Information regarding surveillance and screening for uterine and ovarian cancer in women within these families was also provided, along with risk reduction options of prophylactic colectomy and hysterectomy. However, the lack of data about the efficacy of prophylactic surgery was noted. The potential benefit of early detection was discussed, including the potential of increasing life expectancy by the identification of premalignant or early lesions in mutation carriers.[22] All participants were given a pamphlet that reviewed the information provided during the education session.

OFFER OF GENETIC TESTING

Following the education session, participants were provided a client-centered counseling session to consider the implications of genetic testing for HNPCC. All counseling sessions were undertaken individually to facilitate independent decisions regarding the option of genetic testing. The counseling sessions encouraged the participant to personally assess expectations of test results, review implications of test results on cancer risks, discuss plans regarding communication within the family, and identify motivating factors for or against testing. Following the counseling session, participants were presented with the options regarding genetic testing. Participants were offered the options of (1) taking additional time to further consider the option of testing, (2) not undergoing genetic testing at that time, or (3) undergoing phlebotomy for genetic testing. Those individuals who chose to be tested underwent an additional informed consent process focusing on the potential benefits, risks, limitations, and social and psychological issues pertaining to genetic testing. They then had a blood sample collected by an oncology nurse (J.J. or E.D.), which was sent for testing at a Clinical Laboratory Improvement Act–approved facility. The blood samples were labeled only with the participant's code number; no other identifying information was provided.

MUTATIONAL ANALYSIS

At the approved molecular diagnostics laboratories, blood samples provided by the initially affected individuals in each family (probands) had whole-gene sequencing of the 2 most common HNPCC-associated genes, *MSH2* and *MLH1*. The individual exons (16 of *MSH2* and 19 of *MLH1*) of these genes were amplified using polymerase chain reaction, followed by direct DNA sequencing. The mutations were identified by forward and reverse sequencing and were confirmed by the allele-specific oligodeoxy-nucleotide (probes) or restriction fragment length polymorphism (patterns) polymerase chain reaction method. Individuals opting for genetic testing within families with known HNPCC mutations had directed mutational analysis completed. Payment for the gene sequencing was provided through the research budget.

PROVISION OF GENETIC TEST RESULTS

When results became available, the participants were notified by telephone. Those interested in receiving results were offered an appointment for a return visit to receive and discuss the results in person. Participants were also given the option of deferring the receipt of their results. All participants were encouraged to bring a support person with them to the results session. The participant, his or her designated support person, a clinical oncologist (I.K.), a board-certified genetics counselor (D.W.H.), and an oncology nurse (J.J. or E.D.) attended the results sessions. Results were provided within a standardized format and included the following topics: (1) thoughts and concerns experienced since the decision to pursue genetic testing; (2) expectations about the test results; (3) the genetic test results; (4) risk estimates for the cancers associated with HNPCC; (5) a review of cancer surveillance and screening guidelines; (6) plans and approaches for sharing genetic test results with others (family, friends, and health care providers); and (7) supportive counseling. Results sessions typically lasted 1 hour, with no other data collection occurring during that visit. The oncology nurse telephoned each participant 2 weeks after the results session to address questions since the last contact and to provide support or referral as appropriate. A follow-up letter was provided that summarized the results session.

RECRUITMENT OF FAMILY MEMBERS

In those individuals in whom HNPCC mutations were identified, participation in the education and counseling session was offered to relatives at 50% risk of inheriting the mutation. In cases in which the first-degree relative was deceased, the offer to participate was extended to second-degree adult relatives. The contacting of relatives and an offer to participate in the study could be accomplished in 3 ways. The options included (1) personal contacting of relatives; (2) providing the relative with a letter informing them of the identification of an HNPCC mutation within the family, with or without identification of the relative; or (3) our contacting the relative via telephone following notice by the participating relative. In all cases, participants chose to personally contact eligible relatives to inform them of the study.

MEASURES

All demographic and predictor variables were assessed through the baseline questionnaire before the education and counseling sessions and the offer of genetic testing. A broad array of key independent and dependent variables was elicited. Selected variables relevant to this analysis are listed in this subsection. The questions assessing awareness of genetic testing, risk perception, intentions regarding genetic testing, and pros and cons of genetic testing were adapted from previous research[24,30-34] in individuals and families considering genetic testing for hereditary breast and ovarian cancer. In addition, all tools used in this study were included as part of a core set of instru-

Table 1. Study Participants (n = 104)*

Characteristic	Value
Median (range) age, y	43 (18-83)
Ethnicity	
White	87
African American	7
Hispanic	3
Asian American	2
Native American	1
Sex	
Female	57
Male	43
Annual household income, $	
≥50 000	52
<50 000	48
Religious preference	
Protestant	51
Catholic	31
Jewish	3
Other	7
None	9
Cancer history	
Personal history of cancer	62
No cancer history	38

*Data are given as percentage unless otherwise indicated. Some percentages do not sum to 100 because of rounding.

ments for a consortium of genetic testing projects funded by the National Institutes of Health (Cancer Genetics Studies Consortium of the Ethical, Legal and Social Implications Program of the National Human Genome Research Institute).

Sociodemographics

Sex, age, marital status, employment status, income level, religious background, health insurance status, number of relatives with cancer (and degree of relatedness), and personal history of cancer were assessed through the questionnaire.

Awareness of Genetic Testing

A series of 4 Likert-style questions assessing awareness of genetic testing, in general, and cancer genetic testing for hereditary forms of breast and colon cancers was used.[30] Participants were asked, "How much have you read or heard about genetic testing" for (1) inherited disease, (2) cancer, (3) breast cancer, and (4) colon cancer? Possible responses to each of the questions were (1) almost nothing, (2) relatively little, (3) a fair amount, or (4) a lot.

Risk Perception

Participants' perceptions of having an altered gene associated with HNPCC were evaluated through their response to a 4-item, Likert-style question adapted from previous research.[31] Participants were asked, "In your opinion, how likely is it that you have an altered HNPCC gene?" Possible responses to the question included (1) not at all likely, (2) somewhat likely, (3) very likely, or (4) definitely.

Intentions Toward Genetic Testing for HNPCC

Participants' intentions toward genetic testing for HNPCC were evaluated through their response to a single, Likert-style question adapted from previous research.[24,32,33] Participants were asked, "Which of the following statements best describes the way you are feeling right now?" Possible responses to this question included (1) I definitely do not want to be tested for HNPCC genes, (2) I probably do not want to be tested for HNPCC genes, (3) I probably want to be tested for HNPCC genes, or (4) I definitely want to be tested for HNPCC genes.

Pros and Cons of Genetic Testing

A series of 14 Likert-style items adapted from previous research[33,34] was used to assess perceptions of the benefits, limitations, and risks of genetic testing. Participants read a list of benefits (7 items) and limitations and risks (7 items) of gene testing for HNPCC and were asked to rate the level of importance (not at all important, somewhat important, or very important). The 2 scales have been validated in previous research by Lerman and colleagues[30,31,33] (Cronbach α coefficients, 0.73 [7 pro items] and 0.85 [7 con items]). In addition, the participants were asked to choose the single most important benefit and limitation or risk of genetic testing from the lists.

STATISTICAL ANALYSIS OF DATA

In general, data were analyzed via 2-dimensional contingency tables. When both variables represented unordered categories, the χ^2 test was used to assess the statistical significance of the association between 2 factors being evaluated. When any of the data in a table reflected ordered categories, a Cochrane-Armitage test for trend, Kruskal-Wallis test for categorical data, or Jonckheere-Terpstra test for trend was used, as appropriate, according to whether 1 or both factors were ordered and the number of categories. Continuously measured factors were compared between 2 groups using the Wilcoxon rank sum test. All categorical analyses were performed with an exact procedure; thus, the reported *P* values, which are all 2-tailed results, are correct, even for sparse 2-way tables. This analysis was done in an exploratory fashion, with many associations investigated that are not reported. In view of the large number of statistical tests performed, only $P<.01$ should be interpreted as possibly being statistically significant, while *P* values between .01 and .05 would indicate a strong trend.

RESULTS

CHARACTERISTICS OF STUDY SAMPLE

Table 1 gives the characteristics of participating individuals. Fifty-seven percent of the participants completing the baseline questionnaire were female and 43% were male. Eighty-seven percent of the study sample were white, 7% African American, 3% Hispanic, 2% Asian American, and 1% Native American. The median age of participants was 43 years (range, 18-83 years); 50% of participants were between 34 and 52. Fifty-one percent reported themselves to be Protestant, 31% Catholic, 3% Jewish, 7% following another religion (not listed), and 9% had no religious affiliation. Forty-eight percent had an annual family income less than $50 000. Sixty-two percent reported a medical history of cancer. Forty-five (96%) of 47 probands had colon cancer; the remaining 2 (4%) had HNPCC-associated cancers. Seventeen (30%) of 57 family members had experienced cancer before their participation in the study; 13 had experienced colon cancer and 7 had experienced multiple primary HNPCC cancers. Other cancers experienced by family members

included uterine (4 patients), ovarian (2 patients), cervical (2 patients), brain (1 patient), pituitary (1 patient), skin (2 patients), prostate (1 patient), and breast (1 patient).

BASELINE QUESTIONNAIRE

Of the 165 persons identified as eligible to participate, including index cases and first-degree relatives, 104 (63%) elected to participate. Because the identification of families in this study began with an affected individual (index case or proband) within a family suspected of having HNPCC mutations, we sorted probands from eligible family members. This identified 54 probands who were eligible to participate; 87% chose to participate, completed a baseline questionnaire, and received education and counseling. Of the 111 family members eligible to participate in the study, 51% chose to participate by completing the questionnaire and receiving education and counseling.

AWARENESS OF GENETIC TESTING

Sixty-five percent of participants had read or heard almost nothing or relatively little regarding genetic testing for cancer before their participation in this study. Likewise, 64% reported that they had read or heard almost nothing or relatively little regarding genetic testing for colon cancer.

In performing a cross tabulation of their awareness of genetic testing with other demographic variables, a statistically significant association was identified between participants' awareness of genetic testing and their household income. Specifically, those at higher household income levels were more aware of genetic testing for cancer ($P=.001$) and colon cancer ($P=.009$) than those at lower household income levels (**Table 2**).

No significant associations were found between participants' awareness of genetic testing and age, sex, intentions regarding genetic testing, personal cancer history, or number of first-degree relatives with cancer.

PERCEIVED RISK OF BEING A CARRIER FOR AN HNPCC MUTATION

Before education, counseling, and the offer of genetic testing, 72% of the participants thought that it was very likely (62%) or definite (10%) that they carried an HNPCC mutation. Twenty-five percent believed it was somewhat likely that they carried an HNPCC mutation, and 3% thought it was not at all likely. This study identified that participants' feelings about their chances of getting colon cancer are significantly associated with their beliefs about the likelihood that they carry a mutation ($P<.001$) (Table 2). In other words, those believing that they have a greater chance of getting colon cancer are also more likely to believe that they carry a mutation. Furthermore, participants' beliefs about whether they carry a mutation in a gene associated with HNPCC have a statistically significant association with their intention to pursue genetic testing ($P=.001$); those believing that they carry a mutation have greater intention to pursue genetic testing. Cancer status (having had cancer vs no personal history of cancer) demonstrated a positive association ($P=.005$) with their beliefs about carrying an HNPCC mutation, with 50 (79%) of 63 of those who had cancer believing that they definitely (n=10) or very likely (n=40) carry a mutation, in contrast to 25 (61%) of 41 of those without cancer who definitely (n=0) or very likely (n=25) believed that way. In other words, those individuals who had already experienced cancer were significantly more likely to have a perceived risk of carrying an HNPCC mutation than individuals without cancer.

INTENTIONS TOWARD GENETIC TESTING

Ninety-seven percent of participants stated before education and counseling that they probably (28%) or definitely (69%) wanted genetic testing, while 3% probably or definitely did not want testing. The intention to pursue genetic testing was found to have a positive association with participants' beliefs that cancer may be explained by family heredity ($P=.006$) (Table 2). Furthermore, participants' concern about the psychosocial effect of genetic testing on the family demonstrated a negative association with their intention to pursue testing ($P=.001$). In addition, participants' concerns about their ability to handle the emotional aspects of genetic test results demonstrated a negative association with their intentions to pursue testing ($P<.001$). There was no association found between the participants' age, sex, or cancer status in regard to their intentions toward genetic testing.

REASONS FOR PURSUING GENETIC TESTING FOR HNPCC

One half of those responding believed that the most important reason for undergoing genetic testing was to learn about their children's risk; the second most important reason (17%) was to guide cancer screening; and third in importance (13%) was to confirm their belief that they carry a mutation.

With respect to the importance of genetic testing for reproductive decision making, a statistically significant difference was detected between those younger than the median age of 43 years vs older (dichotomized age, $P=.002$). Younger participants placed increased importance on using genetic testing for reproductive decision making, with 24 (51%) of 47 participants younger than the median age reporting genetic testing as very important (n=6) or somewhat important (n=18), in contrast to 11 (22%) of 51 participants older than the median age of 43 years who thought that it was very important (n=1) or somewhat important (n=10). This association was confirmed through the analysis of age as a continuous variable ($P=.001$). Furthermore, we identified a trend for male participants to place greater importance than female participants ($P=.02$) on using genetic testing "to make decisions about having (more) children." Twenty-two (50%) of 44 men believed that genetic testing was very important (n=4) or somewhat important (n=18) for reproductive decision making, in contrast to 13 (24%) of 54 women who thought that it was very important (n=3) or somewhat important (n=10).

Table 2. Selected Associations*

Annual Household Income, $	Awareness of Genetic Testing for Cancer: Almost Nothing	Relatively Little	A Fair Amount	A Lot	Total	*P* Value
<20 000	3	5	1	0	**9**	.001
20 000-35 000	5	14	3	0	**22**	
>35 000-50 000	5	10	4	0	**19**	
>50 000-75 000	8	6	9	4	**27**	
>75 000	1	11	12	1	**25**	
Total	**22**	**46**	**29**	**5**	**102**	

Annual Household Income, $	Awareness of Genetic Testing for Colon Cancer: Almost Nothing	Relatively Little	A Fair Amount	A Lot	Total	*P* Value
<20 000	4	4	0	1	**9**	.009
20 000-35 000	6	8	7	1	**22**	
>35 000-50 000	3	13	3	0	**19**	
>50 000-75 000	6	10	9	2	**27**	
>75 000	2	10	10	3	**25**	
Total	**21**	**45**	**29**	**7**	**102**	

Risk Perception Regarding Colon Cancer	Beliefs About Likelihood of Carrying Mutation: Not at All Likely	Somewhat Likely	Very Likely	Definitely	Total	*P* Value
Much less	0	4	5	2	**11**	<.001
A little less	1	2	4	0	**7**	
About the same	0	9	7	1	**17**	
A little more	1	10	19	0	**30**	
Much more	0	1	30	7	**38**	
Total	**2**	**26**	**65**	**10**	**103**	

Intent to Pursue Genetic Testing	Beliefs About Likelihood of Carrying Mutation: Not at All Likely	Somewhat Likely	Very Likely	Definitely	Total	*P* Value
Definitely do not	0	1	0	0	**1**	.001
Probably do not	1	1	0	0	**2**	
Probably want	0	13	14	2	**29**	
Definitely want	2	11	51	8	**72**	
Total	**3**	**26**	**65**	**10**	**104**	

Intent to Pursue Genetic Testing	Cancer Is Explained by Family Heredity: Strongly Disagree	Somewhat Disagree	Somewhat Agree	Strongly Agree	Total	*P* Value
Definitely do not	0	0	1	0	**1**	.006
Probably do not	1	0	1	0	**2**	
Probably want	1	2	17	9	**29**	
Definitely want	0	1	34	37	**72**	
Total	**2**	**3**	**53**	**46**	**104**	

Intent to Pursue Genetic Testing	Effect of Genetic Testing on Family: Not at All Important	Somewhat Important	Very Important	Total	*P* Value
Definitely do not	0	0	0	**0**	.001
Probably do not	0	0	1	**1**	
Probably want	1	6	14	**21**	
Definitely want	9	32	15	**56**	
Total	**10**	**38**	**30**	**78**	

(*continued*)

Table 2. Selected Associations* (cont)

Intent to Pursue Genetic Testing	Ability to Handle It Emotionally: Not at All Important	Somewhat Important	Very Important	Total	*P* Value
Definitely do not	0	0	1	**1**	
Probably do not	0	1	1	**2**	
Probably want	2	15	10	**27**	<.001†
Definitely want	23	36	10	**69**	
Total	**25**	**52**	**22**	**99**	

*Data are given as number of subjects. Comparisons are by Jonckheere-Terpstra test unless otherwise indicated.
†Wilcoxon rank sum.

REASONS FOR NOT PURSUING GENETIC TESTING

The greatest concerns about genetic testing included worries about losing health insurance (39%), concerns about how it might affect the family (27%), and concerns about handling the results emotionally (10%).

A statistically significant difference ($P=.006$) was detected between those younger than the median age of 43 years (dichotomized age) compared with those participants older than 43 years with respect to concerns about handling the emotional aspects of genetic testing. Forty-two (86%) of 49 who were younger than the median age believed that their ability to handle the emotional effect of genetic testing was very important (n=15) or somewhat important (n=27), in contrast to 32 (64%) of 50 who were older than the median age who thought that the emotional effect of genetic testing on them was very important (n=7) or somewhat important (n=25) regarding their decision to pursue testing. Younger participants have greater reported concerns about their ability to handle the emotional effect of testing than older participants. Male participants tended to identify "I am concerned about the effect it (genetic testing) would have on my family" as an important issue more often than female participants ($P=.03$). Thirty-eight (97%) of 39 men reported that the effect on family members was very important (n=18) or somewhat important (n=20), in contrast to 30 (77%) of 39 women who believed that it was very important (n=12) or somewhat important (n=18).

TESTING DECISIONS

Table 3 gives the participation rates and uptake of genetic testing. Following education, counseling, and informed consent, 81% (44/54) of eligible probands eventually chose to undergo genetic testing for HNPCC. Nearly 51% (56/111) of eligible first-degree relatives chose to pursue genetic testing.

A significant proportion of those consenting to participate in the study chose to pursue genetic testing (Table 3), with 94% (44/47) of probands choosing to participate in the study eventually choosing to pursue genetic testing. Likewise, 98% (56/57) of family members, once consenting to participate in the study, chose to pursue genetic testing. Among the family members tested, 59% (33/56) received information indicating that they had HNPCC-associated mutations, and 41% (23/56) learned that they did not carry the family mutation.

Table 3. Participation Rates and Uptake of Genetic Testing*

	Probands	Family Members
Participation		
Eligible	54	111
Choosing to participate	47	57
Participating, %	87	51
Uptake of genetic testing		
Choosing genetic testing	44	56
Declining testing	3	1
Eligible choosing testing, %	81	51
Participants choosing testing, %	94	98

*Data are given as number of subjects unless otherwise indicated.

COMMENT

In interpreting the results of this study, the limitations should be considered. First, participation in the study was voluntary and required considerable commitment on the part of participants, including travel to and from the study site and often an overnight stay. To enlist a broad group of participants and to remove cost as a factor affecting participation and testing, most of the travel costs were covered for those choosing to participate. However, because of the time commitment and travel away from home and family, we believe that our study attracted those individuals who had previous intentions toward pursuing genetic testing and, therefore, may not represent a general sample of family members at 50% risk of inheriting mutations.

Second, genetic education, counseling, and testing were offered free of charge to participants. This fact, in combination with participants' often stated perception that information and test results obtained within this study were less accessible to health insurers than if they pursued testing privately, seemingly lessened their concerns regarding insurance-related risks. These 2 issues may have resulted in certain selection biases, and we suspect that uptake rates of genetic testing within this study may overestimate those encountered in a clinical fee-for-service arena.

Third, because these were newly identified families and not part of an existing registry, the offer of par-

Table 4. Selected Characteristics of First-Degree Relatives*

Characteristic	Participants (n = 57)	Nonparticipants (n = 54)
Median (range), y	39 (18-83)	40 (18-78)
Sex		
Female	30 (53)	34 (63)
Male	27 (47)	21 (39)
Cancer status		
History of cancer	17 (30)	17 (31)
No history of cancer	40 (70)	38 (70)
No. of relatives with cancer		
First-degree	134	91†
Median (range)	2 (0-8)	1 (0-6)
Second degree	146	144
Median (range)	2 (0-7)	2 (0-9)
Total first- and second-degree	**280**	**235**

*Data are given as number (percentage) unless otherwise indicated.
†Significant at $P = .007$.

ticipation within families was dependent on participants' willingness to share information with other family members. Although this may mimic the diffusion of new information within families with newly identified disease-susceptible mutations, it does not provide an all-inclusive view of individuals who otherwise have reservations or concerns about genetic counseling and testing. Although we were aware of the number of eligible family members through the analysis of the medical family histories, we cannot be certain that all eligible family members were contacted and offered information about the study. Therefore, our comments provide insight primarily on those agreeing to participate in education and counseling sessions. Despite the noted limitations, we were able to analyze a few characteristics of first-degree relatives who did not participate, including sex, cancer status, and number of relatives experiencing cancer (**Table 4**). An association was identified between the number of first-degree relatives who had experienced cancer and participation in the study ($P = .007$), with participants having a median of 2 first-degree relatives who had experienced cancer, compared with a median of 1 first-degree relative with a history of cancer for nonparticipants. The number of second-degree relatives who had experienced cancer did not demonstrate an association. No significant association was identified between participating and nonparticipating first-degree relatives based on sex ($P = .34$), age ($P = .37$), or cancer status ($P = 1.0$).

Despite the suggested limitations, we observed an uptake of genetic testing by 51% of first-degree relatives of known mutation carriers. The uptake of genetic testing by family members was slightly higher in this study than that reported in a previous US study[27] (43%) investigating the uptake of genetic testing in families with documented mutations in genes associated with HNPCC. However, the difference in the uptake of testing between this study and the previous study does not represent a statistically significant difference ($P = .24$), with 56 (50%) of 111 undergoing genetic testing in this study and 90 (43%) of 208 undergoing genetic testing in the other study. In considering the Finnish study,[28] which also investigated the uptake of genetic testing in families with known HNPCC mutations, we noted a significant difference in the uptake compared with our experience ($P < .001$), 51% uptake of testing in this study vs 75% (334/446) undergoing testing in the Finnish study. The difference between the uptake of testing in the United States and Finland was suggested to be primarily because of the basic differences between health care systems, with the US health care system relying on private insurance.[28] This is supported by noting that concerns about insurance as a reason to not undergo genetic testing were almost absent (<2%) among participants in the Finnish study. The authors of the Finnish study suggested that Finnish citizens have a greater level of trust in their health care providers and system, which they predict increases the uptake of genetic testing.

The general lack of awareness of the availability of genetic testing for colon cancer by participants before their enrollment in the study suggests that continued efforts are necessary to inform the general public and families suspected of having hereditary forms of colon cancer. Research efforts are needed to identify the most effective approaches to educate and disseminate information to the general public and to families at increased risk.[35] Furthermore, the significant difference identified through this study between the awareness of genetic testing by individuals of lower vs higher socioeconomic means suggests that concerted efforts should focus on research to determine effective methods and strategies for providing information to individuals with limited economic resources.

Our findings demonstrate that participants who believe that they have a greater chance of getting colon cancer are more likely to believe that they carry a mutation. In addition, those participants who believe that they carry a mutation have greater intention to pursue genetic testing. Based on this line of evidence, it may be conversely hypothesized that some individuals who do not choose to participate in genetic counseling have a lower perceived risk of getting cancer, which lessens interest (intentions) toward genetic counseling and testing, despite their a priori 50% risk of carrying an HNPCC mutation. Previous research[28] suggests that nonparticipants appear to decline genetic testing and cancer surveillance. However, it is possible that a proportion of those not participating are appropriately following cancer-screening guidelines but not choosing to pursue genetic testing. To understand factors that affect perceived risk and the potential effect on compliance with cancer-screening recommendations for persons at risk in families with HNPCC mutations, additional research would be informative in developing education, counseling, and screening programs for cancer genetics programs.

The data from this study indicate that younger participants are concerned about their ability to handle the emotional outcomes of genetic testing, fear the potential effect on family members, and place increased importance on genetic testing for reproductive decision-making purposes. Concerns about the effect on self or family that were reported in the questionnaire were generally not vocalized within the informed consent session. This may suggest uneasiness on the part of participants to express these concerns. These findings support

the inclusion of discussions between the health care providers and patients, particularly younger persons, regarding the potential effect of genetic testing on themselves, their family, relationships, and reproductive decision making. Health care professionals may assist younger individuals and couples by acknowledging the complex personal and social challenges such information presents and by encouraging referral to genetics professionals for additional counseling to facilitate informed (factual and psychological) decisions pertaining to these issues. Depression has been identified as a barrier to individuals' pursuing genetic counseling services.[27] Therefore, discussions with individuals in families suspected of having inherited forms of cancer should include this as a potential factor complicating informed decision making. Some individuals may be offered genetic counseling and the option of testing at a time that is difficult practically or emotionally. Therefore, periodic discussions about cancer risks and adherence to recommended cancer-screening guidelines may benefit the individual at increased risk of cancer and aid the health care practitioner in providing optimal care.

In considering participants' reasons to not pursue genetic testing, the most common concern was regarding the potential negative effect on their insurability. This concern was expressed through the baseline questionnaire (allowing quantitative analysis) and verbally by consenting participants. Before participation, the issue of potential risks to insurability was routinely and straightforwardly addressed in each informed consent session. Acknowledgment of the potential was accompanied by a brief discussion of the status of state and federal laws attempting to protect individuals from genetic discrimination. We acknowledged that such discrimination could have significant medical and financial consequences; however, we further noted that few cases of genetic discrimination had been reported to date. This concern may have been mitigated by the facts that this protocol (1) holds a Certificate of Confidentiality through the National Cancer Institute, (2) does not require participants' reimbursement for testing (through insurance or personal funds), and (3) uses numeric codes to anonymize samples sent to the Clinical Laboratory Improvement Act–approved facility that performed the testing. We acknowledged that these safeguards could not guarantee confidentiality but would reduce the chances of information getting back to insurers or employers. Nevertheless, most participants at the time of informed consent focused the discussion about potential risks of participating and genetic testing on the potential of insurance companies' obtaining information that could place themselves or their family members at risk for discrimination. The concern about genetic testing and its potential effect on insurability is foremost in participants' minds. Given such a high degree of concern among participants about the issues related to insurability, we hypothesize that this may also be a significant factor affecting participation among relatives who chose not to participate in the study. This hypothesis is supported by recent data[36] from individuals who declined genetic counseling services for hereditary breast and ovarian cancer after referral. In that study, 41% identified their concern about health insurability for themselves and other family members as the most significant factor affecting their decision not to pursue genetic counseling services. The concern regarding discrimination may be extended, hypothetically, to individuals' efforts to obtain cancer screening, thereby increasing the number of individuals ultimately experiencing greater medical and psychological burden associated with the diagnosis of more advanced cancers.

A recent article[37] suggests that evidence for widespread discrimination by insurance companies is lacking and, therefore, may not warrant the level of concern expressed. However, until the public is reassured by legislation or additional evidence that discrimination is not occurring, the public's concern may override the uptake and use of information and testing to guide cancer screening. National and individual state legislation protecting individuals from genetic discrimination by health insurers may reassure patients and their families that they will not be harmed in seeking genetic counseling and testing services. Likewise, increased coverage of genetics services by third-party payers may improve patient access to services.

CONCLUSIONS

Our results suggest that the uptake of genetic testing for HNPCC among members of high-risk families may be lower than what was originally anticipated and more closely approaches those levels reported in a previous US study.[27] Nearly half of the individuals at 50% risk of inheriting an HNPCC mutation chose not to participate in the study. A clear understanding as to why such choices were made is unknown. Significant concerns are the potential that these individuals (1) do not perceive themselves at increased risk of cancer and therefore may not pursue cancer screening; (2) fear the potential consequences of genetic testing, eg, discrimination by insurers and employers, stigmatization, and the effect on themselves or family members; (3) are not aware of the availability of genetic testing; (4) experience financial or time constraints that limit their ability to pursue genetic counseling services; (5) perceive no benefit from genetic counseling services; or (6) are experiencing depression at a level that interferes with their potential to seek counseling and testing to clarify their risks and facilitate appropriate cancer screening.

These findings support the inclusion of psychological and psychosocial issues related to genetic testing as part of the informed consent process between health care providers and individuals considering genetic testing for HNPCC.

Future research is needed to identify more efficient means of reaching, educating, and counseling the general public, at-risk populations, and health care providers about medical genetics, genetic counseling, and testing. In particular, this research is relevant to understanding the extent to which lack of information, fear of insurance discrimination, and psychological or other barriers negatively affect cancer-screening behavior. However, until meaningful national legislative safeguards are established to address the concerns regarding insurance discrimination, we fear that a significant portion of persons will continue to live at increased risk, without the

benefit of information, counseling, and appropriate cancer screening to reduce the morbidity and mortality associated with cancer.

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