

Attitudes toward Colon Cancer Gene Testing: Factors Predicting Test Uptake¹

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Abstract

Objectives. Genetic discoveries in hereditary nonpolyposis colorectal cancer (HNPCC) have made possible genetic testing to determine susceptibility to this form of colorectal cancer (CRC). This study measured the uptake of genetic testing for HNPCC among first-degree relatives of CRC patients and conducted a preliminary analysis of the predictors of test uptake.

Materials and Methods. We compared 77 test acceptors and 181 decliners on demographic, medical history, and psychological characteristics, controlling for distance from the testing center. The psychological factors studied were risk perception for CRC, frequency of cancer thoughts, and perceived ability to cope with unfavorable genetic information.

Results. In the final regression model, after accounting for all variables, the significant predictors of test uptake were increased risk perception, greater perceived confidence in ability to cope with unfavorable genetic information, more frequent cancer thoughts, and having had at least one colonoscopy. The association between risk perception and uptake was dependent on frequency of cancer thoughts. Among those who thought about getting CRC more often, the probability of testing increased as perceived risk increased to ~50% likelihood of getting CRC and then leveled off. In contrast, among those who never or rarely thought about getting CRC, risk perception was unrelated to testing decision.

Conclusions. Our findings are consistent with the associations reported between psychological factors and other cancer screening behaviors.

Introduction

Genetic discoveries in HNPCC³ (1–5) have made possible genetic testing to determine susceptibility to this form of CRC.

HNPCC is an autosomal dominant cancer syndrome that is characterized by a 70–80% lifetime risk of early-onset CRC and an elevated risk for other cancers (6–8). It is estimated to account for 1–5% of all CRC (9–11). Mutations in five genes that function in the DNA mismatch repair system appear to account for ~60–70% of HNPCC mutations in families meeting ICG criteria (12–14), suggesting that other genes remain to be discovered. Through proper surveillance, persons who carry one of the predisposing mutations can reduce their risk of developing cancer when adenomatous or premalignant polyps are detected and removed (15, 16). Colonoscopy is the rational choice for HNPCC screening, due to a predominance of right-sided tumors (17). Because of limited data on tumorigenesis in CRC, there are no definitive guidelines on screening frequency (18, 19), and screening guidelines vary considerably, based on considerations related to age or family history (15, 20–23).

The ability of genetic testing to identify those at increased cancer risk can advance prevention and early detection only if it leads to improvements in current screening and surveillance rates. Adherence with most forms of CRC screening strategies is quite low, ranging from 25 to 67% (24–29). Explanatory models of health behavior and studies of endoscopic screening adherence (29–31) suggest that the knowledge that one is carrying a predisposing mutation could increase surveillance by increasing one's perceived susceptibility to CRC. If genetic testing increases perceived susceptibility, it could increase willingness to engage in appropriate screening and surveillance behaviors. Thus, it is of interest to identify factors associated with the decision to take a genetic test among persons who are at increased risk of developing CRC. This study was part of a longitudinal study evaluating the effect of genetic counseling and testing for HNPCC on psychological well-being and cancer prevention and early detection behaviors. Using preliminary data, we investigated the predictors of uptake of genetic testing for HNPCC.

Materials and Methods

Participants. The participants were adult FDRs of CRC patients ascertained through the Johns Hopkins University Colorectal Cancer Registry between June 1, 1995, and July 31, 1998. This registry began in 1973 and contains >2120 families with hereditary CRC syndromes or familial aggregation of colorectal carcinoma. Cancer diagnoses are confirmed with medical records.

Selection Criteria. In this study, eligible persons were at least 18 years old, had no personal history of CRC, and as detailed below, had at least one FDR with CRC. The ICG criteria (9) were used to identify potential HNPCC families: CRC in three or more relatives from at least two generations, with at least one

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³ The abbreviations used are: HNPCC, hereditary nonpolyposis colorectal cancer;

CRC, colorectal cancer; ICG, International Collaborative Group; FDR, first-degree relative; CI, confidence interval.

diagnosed before age 50. It has been noted that these criteria underidentify hereditary CRC in small families with poor documentation of medical history (8). A number of studies have found HNPCC mutations in affected persons from families not meeting ICG criteria, suggesting that genetic testing is warranted in cases in which there are multiple affected members and/or young age at onset (32, 33). Even in the absence of an obvious autosomal dominant inheritance pattern, having a single affected FDR increases risk for CRC by a factor of 1.64; having two or more affected relatives increases risk by a factor of 2.83 (34).

We selected potential subjects if an HNPCC mutation had been previously identified in the family (13 kindreds) or if the family met ICG criteria for HNPCC. Given that the ICG criteria underdiagnose HNPCC, we also selected potential subjects if there was at least one affected FDR diagnosed before age 50 or if there was an affected FDR diagnosed after age 50 along with additional family history of CRC. Given their risk status, all individuals invited to participate would be expected to have had at least one colonoscopy prior to our invitation. We invited all at-risk persons from a kindred, provided at least one at-risk person lived in the Baltimore area. This ascertainment strategy offered several advantages. (a) The subjects were recruited, not self-referred, giving us a denominator for calculating the acceptance rate. (b) People were invited regardless of their geographic location. By inviting entire families, all at-risk persons in a family learned of the study simultaneously, standardizing the way in which eligible persons learned about the study. (c) Previous research has shown that inviting persons to participate in cancer prevention services produces a more representative sample of the target population than does including only self-referred persons (35). One drawback to this ascertainment strategy was that, because we invited a large number of persons who lived great distances from the testing center, a high percentage of persons declined to participate. This was the case because participants were required to come to Johns Hopkins for counseling and testing.

Procedures. This project was approved by the Johns Hopkins Joint Committee on Clinical Investigation. Phase I consisted of baseline data collection and a genetic counseling session. Phase II involved additional counseling, genetic testing, and follow-up data collection. Participants gave separate informed consents for each phase.

Genetic testing for the study is conducted in a conditional, stepwise fashion. If a HNPCC mutation had been previously identified in the family, the at-risk person was offered testing for that mutation. If the family mutation was unknown and there was a living affected relative, the affected person was offered testing. If that result was positive, the at-risk person was offered testing for that mutation. If the family mutation was unknown and there was no living affected relative, the at-risk person was offered testing. Affected relatives received genetic counseling and gave informed consent to be tested and to have their results disclosed to the at-risk person after they received the results.

Invitation letters announced the discovery of CRC-causing mutations, the availability of free genetic counseling, and the option of free genetic testing through a research study. Also included in the one-page letter was information about the study selection criteria, purposes, procedures, instructions for completing the enclosed postcard, and our interest in inquiring about reasons for declining. Letter recipients accepted or declined the invitation to receive more information about the study by returning a postage-paid postcard and responding

“yes” or “no.” The study coordinator contacted all “yes” responders to explain the study and to schedule appointments for those interested in participating. The coordinator contacted the “no” responders to inquire about their reasons for declining and, with their consent, conducted a brief telephone interview. Persons not returning the postcard within 8 weeks were considered decliners and were contacted accordingly. Generally, project staff made up to four telephone calls to contact decliners. When leaving messages, we advised persons that they could call back collect. After leaving two messages, we considered nonresponders to be lost to follow-up.

Acceptors were defined as those who decided to participate in both phases of the study (Fig. 1). They visited Johns Hopkins Hospital in Baltimore, where they met with an investigator to discuss the study to give informed consent, to complete questionnaires, and to have two genetic counseling sessions, separated by at least 2 weeks. After both genetic counseling sessions, acceptors also provided 10-ml blood samples for genetic testing. As described above, when there was no known mutation and there was a living affected relative, the relative was tested first. Relatives had blood samples taken for testing only if the at-risk person intended to be tested if the result were positive. The decliners did not participate in either phase of the study. Acceptors received mileage reimbursement, up to a maximum of \$25.00.

The first genetic counseling session was conducted by a certified genetic counselor. The pretest counseling content included a discussion of the clinical and genetic characteristics of HNPCC, the genetic test, and the risks and benefits of testing, including the possibility of insurance and employment discrimination. The counselor also explained that the alternative to genetic testing was to begin or to continue regular surveillance. Participants received verbal and written screening guidelines. Briefly, the guidelines recommend colonoscopy every 3–5 years for persons with one FDR diagnosed after age 50 and additional family history of CRC, and colonoscopy every 1–3 years when there is at least one FDR diagnosed before age 50 with additional family history of CRC.

At the disclosure of the genetic test result, the screening guidelines were reviewed, and a follow-up letter detailing these recommendations was sent within a week. Those with HNPCC mutations were advised to have an annual colonoscopy; those with negative results were advised to follow the CRC screening guidelines for the general population (23). Persons who received inconclusive results (that is, a negative result in the absence of a previously identified mutation in the family) were advised to follow the guidelines appropriate to their family history (36).

Data Collection and Variables of Interest. We gathered data from decliners with a 10-min telephone interview. Acceptors completed self-administered questionnaires. Methodological studies have shown that data collected using self-administered and telephone surveys yield comparable answers to nonthreatening questions, such as those used here (37). The outcome variable was the decision to accept or decline the offer to take a genetic test for HNPCC. The predictor variables were the same for each group. From the acceptors and from the decliners who consented to the brief interview, we obtained information on demographic and psychological characteristics and medical history. The demographic information included sex, age, race, education, and marital status. Psychological characteristics included risk perception, cancer thoughts, and perceived ability to cope with a positive gene test. Medical history variables included number of FDRs with CRC and past CRC screening

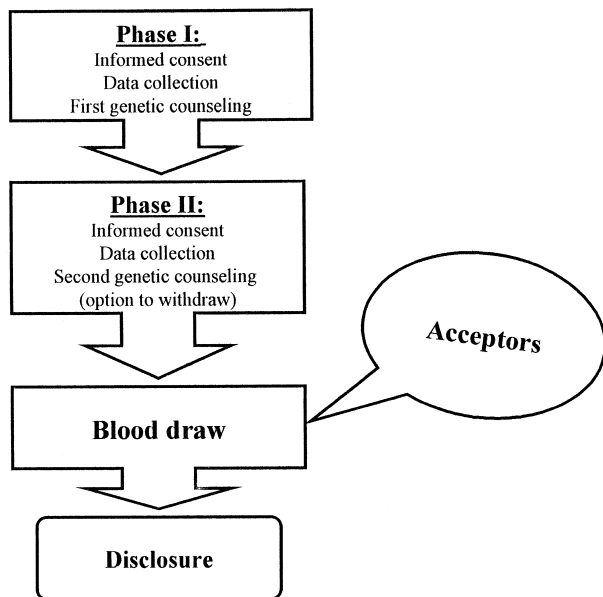


Fig. 1. Study procedures. Acceptors participated in Phases I and II and proceeded to blood draw.

behavior (had at least one colonoscopy *versus* no previous colonoscopy). Distance from Johns Hopkins Hospital was controlled for in the analysis.

Risk perception was evaluated on a scale from 0 (definitely will not get colon cancer) to 100 (definitely will get colon cancer). Decliners gave a number between 0 and 100; acceptors used a visual analogue scale. Visual analogue scales and numerical rating scales for measuring psychological constructs have been shown to be highly correlated (38–40). Subjects rated the frequency of their cancer thoughts over the previous month on a Likert-type scale from 1 (not at all/rarely) to 4 (a lot). This measure is part of the standard test battery developed by the Cancer Genetic Studies Consortium of the National Human Genome Research Institute. It has been shown to differentiate persons at high and low risk for breast cancer and has been associated with breast cancer screening behavior (41, 42). Subjects rated their perceived ability to cope with knowledge of having a colon cancer mutation on a scale from 0 to 100% (*i.e.*, 100% = certain I can cope). This item has been shown to distinguish those who choose to be tested from those who decide not to be tested for Huntington's disease (43). Subjects were categorized into those whose coping certainty was $\geq 90\%$ or $< 90\%$. Distance was calculated in miles from Baltimore using Rand McNally TripMaker (44).

Data Analysis. All analyses were performed using SAS Version 6.12 (45). The data consist of observations on 258 people in 95 families, with 1–12 persons per family. Possible correlations of responses between members of the same family were accounted for in all analysis using appropriate methods (46). Comparisons of continuous variables were made by fitting mixed models, including a random effect for family clustering of effects. Categorical variables were compared using the Mantel-Haenszel χ^2 test, adjusting for family. Logistic regression models were fitted using generalized estimating equations, with an exchangeable correlation structure for observations within a family.

Results

Sample Characteristics and Bivariate Associations. Between June 1, 1995, and July 31, 1998, 505 FDRs of CRC patients from 118 kindreds were invited to participate. Fig. 2 summarizes the status of each person invited to participate. Table 1 shows data on 77 acceptors and 181 decliners, who made up the sample used for all analyses.

Decliner Characteristics. Comparisons of three groups of decliners [decliners who were interviewed, decliners who refused interview, and remaining decliners (those pending interview plus those not reached)] showed that a higher percentage of those pending interview and not reached were male; however, this was not statistically significant (60, 57, and 37% female, respectively; $P = 0.072$). Decliners who were interviewed and decliners who were pending interview or were not reached were younger than those who refused the interview (median ages of 50 and 46 years, compared to 65 years, respectively; t test from mixed model, $t = -3.85$, degrees of freedom = 164, $P = 0.013$; and $t = -2.52$, degrees of freedom = 164, $P < 0.001$).

Demographic Factors. Most of the subjects were married, Caucasian, and had some college education, reflecting the composition of the registry. The decliners were older, lived farther from Johns Hopkins Hospital, and were slightly less educated than the acceptors (Table 1).

Psychological Factors. As shown in Table 1, the acceptors had higher risk perception, thought more often about getting CRC, and were more confident that they could cope with knowing that they had a an HNPCC mutation.

Medical History Factors. There was no significant difference between acceptors and decliners on the strength of family history of CRC. Equal proportions of acceptors and decliners had two or more affected FDRs. Acceptors were more likely to have had at least one colonoscopy.

Logistic Regression. The final multivariate model is presented in Table 2. After controlling for traveling distance from Johns Hopkins Hospital and all other variables in the model, we found that significant predictors of acceptance were perceived ability to cope with a positive gene test result, risk perception, frequency of thoughts about CRC (not at all or rarely *versus* sometimes or more), and CRC screening history.

Persons who stated that they were at least 90% confident in their ability to cope with a positive test result had 4-fold greater odds of accepting testing than persons who were $< 90\%$ confident (95% CI = 1.5–10.3).

The probability of accepting genetic testing increased as perceived risk increased; however, the rate of increase slowed with increasing perceived risk and eventually leveled off. Those who thought about getting CRC at least sometimes (*i.e.*, sometimes, often, or a lot) were more likely to be tested than those who stated that they rarely or never thought about CRC. In addition, there was a borderline significant interaction between perceived risk and the frequency of thoughts about getting CRC. The relationship between risk perception and uptake was different for different levels of cancer thoughts. Among persons with more frequent cancer thoughts, there were significant linear and quadratic associations between perceived risk and the log-odds of being tested. As shown in Fig. 3, those with risk perception of 25% had 16-fold greater odds of not being tested than those with risk perception of 50% (95% CI = 12–23); however, the log-odds of being tested among persons with risk perception of 50% were no different from that

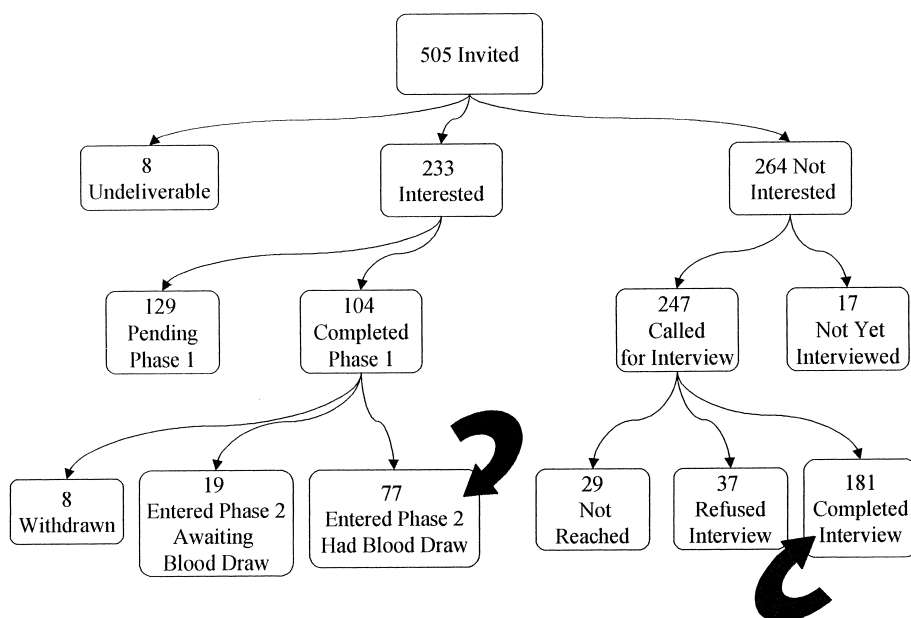


Fig. 2. Status of persons invited to participate in the study. **Bold arrows**, groups used for data analysis.

Table 1 Demographic, medical history, and psychological characteristics of acceptors and decliners of an offer to have genetic testing for HNPCC

	Acceptors (n = 77)	Decliners (n = 181)
Sex (% female)	55%	59%
Age, yr		
Median (IQR) ^a	44 (23)	50 (22) ^b
Range	19–70	22–83
Race (% Caucasian)	96%	100% ^c
Years of education, median (IQR)	16 (4)	15 (6) ^c
Marital status (% married)	71%	75%
Distance from Johns Hopkins Hospital, miles		
Median (IQR)	53 (163)	428 (702) ^d
Range	3–2867	3–2874
Risk perception, mean (SD) (0–100)	58 (19)	45 (26) ^e
Relative risk perception		
Less or about the same	8%	32% ^e
Higher	92%	68%
Cancer thoughts		
Rarely/never	37%	54% ^{c,f}
Sometimes	49%	35%
Often/a lot	14%	11%
Coping certainty		
≥90%	83%	52% ^e
<90%	17%	48%
FDRs		
One	66%	65%
Two	30%	19%
Three or more	4%	16%
Colorectal screening (% had colonoscopy)	82%	55% ^c

^a IQR, interquartile range.

^b $P < 0.01$.

^c $P < 0.05$.

^d $P < 0.0001$.

^e $P < 0.001$.

^f Rarely/never vs. sometimes/often/a lot.

of persons with perceived risk of 75% (odds ratio = 1.6, 95% CI = 0.19–13.1). This trend is much less pronounced for those who never or rarely think about getting colon cancer (Fig. 3). Given infrequent cancer thoughts, there was no

significant linear effect of perceived risk and a borderline significant quadratic effect.

Finally, having had at least one colonoscopy in the past was associated with a 2.2-fold increase in odds of accepting genetic testing (95% CI = 1.1–4.8).

Discussion

Our findings are generally consistent with the associations reported between psychological factors and cancer screening behaviors (47–53). In a meta-analysis, McCaul *et al.* (54) found a positive association between perceived susceptibility and mammography screening. Although there are fewer studies of CRC screening, Vernon (29) reported that all three studies examining the association between perceived susceptibility and sigmoidoscopy found a positive association; the data were less consistent for fecal occult blood testing. Our finding of a conditional effect of perceived susceptibility on genetic testing uptake is of interest and indicates that risk perception may be a motivating factor only in the context of thoughts about CRC. The existing studies of attitudes toward cancer genetic testing (55–62) along with the present study and others that have examined actual test-taking behavior (63–65) seem to indicate that at-risk persons may be motivated to take a genetic test for the same reasons that they would engage in other cancer prevention and control behaviors. Given the preliminary and descriptive nature of our data, these results should be viewed as hypothesis-generating observations until they are confirmed by other investigators.

In our study, persons who chose not to have a gene test also tended to choose not to have colonoscopies. Thus, our preliminary data suggest that the decliners avoid medical tests that could provide them with unfavorable health information. Consistent with this, and as shown in studies of persons at risk for Huntington's disease (66–71), test decliners had lower perceived ability to cope with knowledge of having a mutation. Lower perceived coping ability, therefore, may be a psychological barrier to CRC prevention and early detection behaviors. Our data indicate that those who choose not to take a genetic test for CRC will be similarly unlikely to undertake

Table 2 Predictors of the decision to accept genetic testing for HNPCC

	Estimate (SE)	Odds ratio ^a	95% CI	P
Intercept	2.97 (0.68)			
Log (distance)	-0.76 (0.12)	0.47	0.37-0.59	<0.001
Coping				
≥90% confident	1.38 (0.48)	4.00	1.53-10.3	0.005
Reference group: <90% confident				
Colorectal screening				
Never had a colonoscopy	-0.81 (0.37)	0.45	0.21-0.93	0.030
Reference group: had a colonoscopy				
Cancer thoughts				
Rarely/never				
Reference group: sometimes/often/a lot	-0.83 (0.49)	0.44	0.17-1.13	0.088
Risk perception (linear)	0.65 (0.28)	1.92	1.11-3.35	0.021
Risk perception (quadratic)	-0.19 (0.06)	0.83	0.73-0.94	0.004
Cancer thoughts *risk perception (linear)	-0.62 (0.33)	0.54	0.28-1.03	0.061
Cancer thoughts *risk perception (quadratic)	0.10 (0.08)	1.11	0.95-1.29	0.180

^aOdds ratios are adjusted for all other variables in the model.

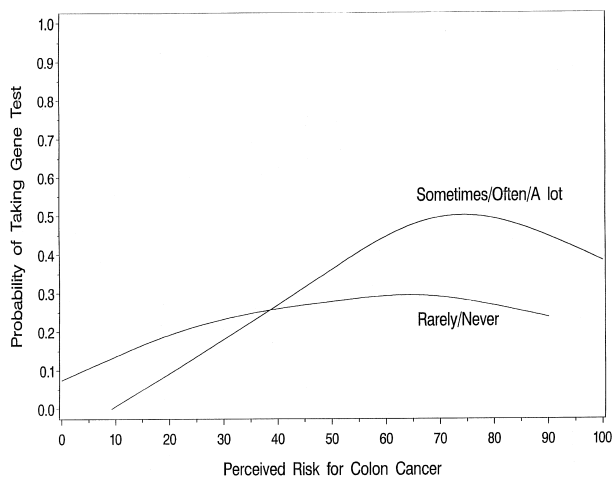


Fig. 3. Probability of being tested by perceived risk for CRC and frequency of cancer thoughts.

CRC surveillance. To overcome this barrier, some at-risk persons may need more psychological support and counseling to increase perceived ability to handle unfavorable medical information. It is important to note that 18% of those who were tested had never had a colonoscopy. Assuming that the genetic counseling prompts appropriate screening behavior in these persons, it could aid cancer prevention and early detection efforts in persons who might otherwise have avoided screening.

The testing uptake rate was lower than expected based on attitudinal studies (55–62). One reason is that we conducted the genetic counseling in person. Persons who might otherwise have chosen testing may not have done so because of the requirement to travel long distances to the testing center. The uptake rate was 58% among those for whom the traveling distance was within 50 miles.

A limitation of our study is that the subject pool was drawn from kindreds enrolled by an index case into a CRC family registry, a circumstance that selects for participants who have greater concern about CRC. On the other hand, we did not rely on self-referrals to ascertain subjects. We invited all eligible persons in a family, many of whom had never participated in

research studies. Previous research has shown that inviting persons to participate in cancer prevention services produces a more representative sample of the target population than samples limited to self-referred persons (35). Thus, a strength of this study is that we were able to describe the characteristics of the population from which the sample was drawn.

One factor operating against the study's generalizability to clinical populations is that the participants received free confidential genetic testing that did not generate a medical record. Clinical testing settings will not provide this protection or offer free testing, and these factors may influence test uptake as well as the characteristics of those willing to assume this risk.

Summary and Implications. This study measured the uptake of genetic testing for HNPCC among FDRs of CRC patients. Preliminary data from our study showed that people who believe they will get CRC, think about getting it, believe that they can cope with "bad news," and already engage in cancer prevention behaviors are more likely to be tested. Although at-risk people can be screened without ever having genetic testing, our data suggest that people tend to do both or neither. The implication is that genetic testing will advance cancer prevention only if it prompts surveillance in mutation carriers who previously avoided being screened. Whether genetic information changes screening behaviors is a major focus of our ongoing study.

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