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Genetic Testing in Families With Hereditary Nonpolyposis Colon Cancer

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HEREDITARY NONPOLYPOSIS colorectal cancer (HNPCC) is the most common form of inherited colon cancer, accounting for about 9000 cases each year and affecting about 1 in 200 men and women.¹ It is characterized by an autosomal dominant mode of genetic transmission of susceptibility to colorectal cancer, a preponderance of early-onset colon cancers, a propensity toward proximal colon tumors, and frequent multiple primary tumors. Tumors integral to HNPCC include carcinoma of the endometrium, ovary, upper urologic tract, stomach, and small bowel. Molecular studies have identified 5 mismatch repair genes (*hMSH2*, *hMLH1*, *PMS1*, *PMS2*, and *hMSH6*) that are responsible for most HNPCC cases.²⁻⁵ Mutations in these genes confer a lifetime risk of colon cancer of approximately 80% to 85%.^{6,7}

Although long-term outcome data in carriers of HNPCC-predisposing mutations are not yet available, it is expected that cancer risk may be reduced by regular colonoscopic examination and removal of premalignant polyps.⁸

Context Genetic testing for hereditary nonpolyposis colon cancer (HNPCC) is available, but the rates of acceptance of testing or barriers to participation are not known.

Objective To investigate rates and predictors of utilization of genetic testing for HNPCC.

Design Cohort study conducted between July 1996 and July 1998.

Setting Hereditary nonpolyposis colon cancer family registry.

Participants Adult male and female members (n = 208) of 4 extended HNPCC families contacted for a baseline telephone interview.

Interventions Family education and individual genetic counseling.

Main Outcome Measure Participant acceptance of HNPCC test results.

Results Of the 208 family members, 90 (43%) received test results and 118 (57%) declined. Of 139 subjects (67%) who completed a baseline telephone interview, 84 (60%) received test results and 55 (40%) declined. Of the 84 subjects who received test results, 35 (42%) received information indicating that they had HNPCC-associated mutations and 49 (58%) that they did not. Test acceptors had higher education levels (odds ratio [OR], 3.74; 95% confidence interval [CI], 2.49-5.61) and were more likely to have participated in a previous genetic linkage study (OR, 4.30; 95% CI, 1.84-10.10). The presence of depression symptoms significantly reduced rates of HNPCC test use (OR, 0.34; 95% CI, 0.17-0.66). Although rates of test use were identical among men and women, the presence of depression symptoms resulted in a 4-fold decrease in test use among women (OR, 0.25; 95% CI, 0.08-0.80) and a smaller, non-significant reduction among men (OR, 0.49; 95% CI, 0.19-1.27).

Conclusions Despite having significantly elevated risks of developing colon cancer, a relatively small proportion of HNPCC family members are likely to use genetic testing. Barriers to test acceptance may include less formal education and the presence of depression symptoms, especially among women. Additional research is needed to generalize these findings to different clinical settings and racially diverse populations.

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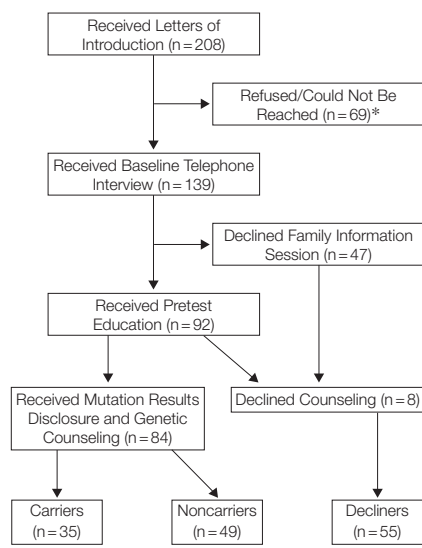
Based on data collected from participants from the Dutch HNPCC registry, Vasen and colleagues⁹ estimated that colonoscopy performed every 2 to 3 years could increase the life expectancy of mutation carriers by about 7 years. Despite these potential medical benefits, genetic testing and disclosure of mutation status may have psychological and social risks, including loss of privacy and genetic discrimination.

While genetic testing for HNPCC-associated mutations is becoming more widespread in clinical practice,¹⁰ there are no published studies of the rates of acceptance of such testing or the barriers to

testing in members of high-risk families. Surveys conducted prior to the availability of genetic testing indicated that 83% of respondents in the general population and 82% of first-degree relatives

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Figure. Flow of Study Procedure

Asterisk indicates that 6 individuals who did not participate in the baseline interview opted to receive test results.

of colon cancer patients were interested in receiving a genetic test.^{11,12} However, research on genetic testing for breast cancer susceptibility has shown that statements of interest in testing can greatly overestimate actual uptake rates.^{13,14}

To address this gap in our knowledge, we evaluated the utilization of genetic testing for HNPCC-associated mutations in members of extended families in which hereditary cancer had been linked to 1 of the HNPCC-associated genes. We also sought to identify factors that may motivate or deter participation in HNPCC testing programs. Of particular interest was the role of psychological distress, which has been shown to influence participation in other forms of genetic testing and cancer surveillance.^{15,16} In addition, because previous research has pointed to sex differences in the use and determinants of colorectal cancer screening,^{17,18} we also examined if the determinants of HNPCC test uptake differed for men and women. A better understanding of the factors that influence participation in HNPCC genetic testing would help guide the development of protocols for patient ascertainment and genetic counseling.

METHODS

Study Population

Eligible subjects included 208 at-risk adult male and female members of 4 extended HNPCC families in which a risk-conferring mutation had been identified in a proband. Because cancer cases in these families may be sporadic and not due to inherited HNPCC mutations (ie, phenocopies), both affected and unaffected family members were included in the study sample.

Procedures

All study procedures were approved by the institutional review boards at Creighton University School of Medicine, Omaha, Neb, and the Georgetown University Medical Center, Washington, DC. Eligible individuals were notified about the availability of genetic counseling and testing by an introductory letter that explained the study and invited them to participate in a family education session. Individuals who did not return the enclosed refusal card within 2 weeks were contacted by telephone to obtain oral consent for a baseline telephone survey (FIGURE). This 40-minute structured interview was conducted approximately 4 weeks prior to the education session by a professional telephone interviewer from the Georgetown University Medical Center using a computer-assisted telephone interviewing program. All persons were informed that completing the survey did not obligate them to participate in the education session or receive genetic testing.

A second letter containing specific information about the education session (ie, dates and locations) was mailed to all individuals (survey respondents and nonrespondents) about 2 weeks after the introductory letter. Education about HNPCC and genetic testing was provided during 1- to 2-hour semistructured group family information sessions (FISs). All FISs were conducted by an oncologist-geneticist in geographic areas convenient to most family members. The following topics were addressed after obtaining written informed consent: (1) inheritance of cancer sus-

ceptibility in HNPCC families; (2) background information on linkage analysis, gene identification, and the meaning of mutation test results; (3) potential benefits (eg, early detection), limitations (eg, imperfect prediction), and risks (eg, insurance discrimination, increases in psychological distress) of genetic testing; (4) potential impact of alternate testing decisions on personal relationships and goals; and (5) options for risk reduction and surveillance and their limitations. Specifically, participants were advised that regular colonoscopy screening could potentially increase the life expectancy of mutation carriers by identifying premalignant and/or early lesions.⁹ They were also informed that persons identified as noncarriers could be relieved of persistent worry and the need to undergo frequent surveillance. The potential benefits of other screening tests (endometrial aspiration biopsy) and risk-reduction options (subtotal colectomy and prophylactic total abdominal hysterectomy) were also discussed; however, the lack of efficacy data was acknowledged.

After the education session, an oncology nurse collected blood samples from participants who wished to receive testing after obtaining written informed consent for testing. It should be noted that some individuals (n = 38) had provided blood samples as part of an earlier study to determine linkage of cancer in these families to 1 of the HNPCC-associated genes. However, because mutation analysis was not performed in the prior study, none of these individuals received genetic test results prior to the current study (participation in the previous genetics study was controlled for in the statistical analyses). Samples from an initial affected proband were screened for HNPCC-associated mutations (*MLH1*, *MSH2*, *PMS1*, and *PMS2*). Once a mutation was identified in a proband, samples from other family members were tested for the same mutation.

When genetic test results became available, participants were notified by mail. Participants who wished to receive results contacted Creighton Uni-

versity to arrange to receive genetic counseling and test result disclosure. They also had the option to defer their decision. Genetic counseling was provided using a standardized format in which the following topics were addressed: (1) expectations about the test result, (2) the genetic test result and cancer risk estimates, (3) plans for discussing genetic test results with relatives, and (4) supportive counseling. Participants could request test results at any point after providing written informed consent and receiving pretest education and genetic counseling.

Predictor and Outcome Variables

All predictor variables were assessed during the baseline telephone interview prior to the FIS and offer of genetic test results. Sex, age, marital status, education level, employment status, and income level were assessed. Personal history of cancer (affected or unaffected) and participation in the previous genetics study were determined from registry records. Colonoscopy screening in the past year was assessed during the baseline interview. The Center for Epidemiological Studies Depression Scale was used to measure psychological distress. This instrument assesses the frequency of depression symptoms and had good internal consistency in this sample (Cronbach $\alpha = .86$). The Center for Epidemiological Studies Depression Scale has been used in previous research on the impact of *BRCA1/BRCA2* testing.¹³ Scores on this instrument range from 0 to 60; individuals whose score was 16 or higher were classified as having clinically significant depression symptoms.¹⁹ The intrusion subscale of the Impact of Events Scale²⁰ was used to measure cancer-related distress. This subscale had good internal consistency in this sample (Cronbach $\alpha = .82$). Scores on the Impact of Events Scale have been shown to predict utilization of *BRCA1/BRCA2* testing.¹⁵

Individuals who received test results at any point during the course of the study were classified as acceptors

and those who did not receive test results were classified as decliners.

RESULTS

Baseline Telephone Interview

As shown in the Figure, of the 208 eligible subjects, 139 (67%) completed the baseline telephone interview and 69 (33%) did not. Those who completed the baseline telephone interview did not differ significantly in sex, age, or cancer history (as determined from registry data). The vast majority of subjects who did not complete the baseline telephone interview (63/69) also declined genetic counseling and testing.

Characteristics of Study Sample

Fifty-five percent of the study sample (persons completing the baseline interview, $n = 139$) were women and 45% were men. Most of the participants were married (71%), had a high school education (74%), and had an income level of less than \$50 000 (74%). The average age of participants was 47 years (SD, 14.0 years). With the exception of 1 person reporting Native American ethnicity, all participants were white. In terms of clinical variables, 19% had a personal history of cancer and, of these, 14 were affected with colon cancer and 12 were affected with other forms of cancer (skin, $n = 4$; endometrial, $n = 2$; uterine, $n = 2$; breast, $n = 1$; bile duct, $n = 1$; bladder, $n = 1$; melanoma, $n = 1$). Eighteen percent of participants (23% of women and 13% of men; $P = .14$) reported clinically significant depression symptoms at baseline (compared with population rates of about 21%).¹⁹ Thirty percent of participants had participated in the previous genetics study.

Descriptive Data on Uptake of HNPCC Testing

Rates of participation in the FISs and receipt of test results are shown in the Figure. In the total sample of 208 eligible participants (including interview nonresponders), 90 participants (43%) received test results and 118 (57%) declined. Among the 139 who completed the baseline telephone interview, 92 participated in an FIS and

47 did not. Among those who participated in an FIS and provided a blood sample, 84 received their HNPCC test results and 8 declined (3 participants provided a blood sample after the FIS but subsequently decided not to be tested). Thus, among the 139 interview participants, 84 (60%) received their HNPCC mutation test results and 55 (40%) declined. Of those tested, 35 (42%) received information indicating that they had HNPCC-associated mutations and 49 (58%) that they did not. The following analyses are based on the sample of interview participants.

Bivariate Analysis of Uptake of HNPCC Testing

χ^2 Tests of association and t tests were performed to identify predictors of uptake of HNPCC testing. As shown in TABLE 1, uptake was associated with a higher level of education, being married, participation in the previous genetics study, and the absence of depression symptoms. Men and women had identical rates of test uptake (60% for both). Acceptors and decliners of HNPCC testing did not differ significantly in terms of baseline cancer-related distress scores on the Impact of Events Scale (6.68 [SD, 6.70] vs 7.16 [SD, 6.40], respectively; $t = .42$; $P = .67$).

Multivariate Analysis of HNPCC Test Uptake

Logistic regression analysis with generalized estimating equations²¹ was used to identify independent predictors of test result uptake while controlling for possible intrafamily correlations in the outcome. All predictor variables with bivariate associations with test utilization ($P < .10$) were considered in the model (ie, education, provision of prior blood sample, marital status, and depression symptoms). Variables with significant independent associations with uptake were retained in the model. As shown in TABLE 2, education level, prior study participation, and depression symptoms had significant effects on uptake of testing. Participants who had a college education or greater and those who participated in the previous ge-

netics study were about 4 times more likely to receive test results. Depression symptoms were associated with a significant reduction in overall uptake.

A second model was generated to test for possible interacting effects of sex and other predictor variables on uptake. This model was identical to that described herein, except that terms for sex and the sex-by-predictor interactions were also included. Although the addition of the sex-by-depression interaction term did not significantly improve the model fit (likelihood ratio χ^2 , 1.33; $P = .25$), there was an indication of stronger effects of depression symptoms on women than on men. Among women, the presence of depression symptoms reduced uptake by almost 4-fold (odds ratio [OR], 0.25; 95% confidence interval [CI], 0.08-0.80). Among men, depression led to a smaller

reduction in uptake (OR, 0.49; 95% CI, 0.19-1.27). There were no other suggestions of modifying effects of sex on other predictor variables.

COMMENT

To our knowledge, the present study is the first to document rates of HNPCC genetic test utilization. Despite the fact that all study participants were members of families with clinical and molecular HNPCC documentation and had significantly elevated risks of cancer, only 43% elected to participate in the counseling and testing program. These rates are comparable with those reported in initial studies of genetic testing for hereditary breast cancer¹³ but are significantly lower than expected based on previous surveys of interest in genetic testing for colon cancer susceptibility.^{11,12}

The results of this analysis also shed light on potential barriers to genetic testing in this population. Among women who reported clinically significant depression symptoms on a baseline telephone interview, rates of test acceptance were reduced about 4-fold. Although previous evidence suggests that cancer-related distress may lead to increases in use of genetic testing for breast cancer susceptibility,¹⁵ other studies have shown reduced adherence to colorectal cancer surveillance among distressed individuals.²² Individuals with depression also tend to delay preventive medical care.²³ With regard to the present study, depression may engen-

der feelings of hopelessness or fatalism and, hence, diminish motivation to seek genetic information. The finding that the association between depression and HNPCC test uptake was stronger in women is consistent with the general notion that women are more attentive to psychological stressors,²⁴⁻²⁷ especially those that may affect family relationships.^{28,29} It should be noted, however, that although depression symptoms were predictive of test uptake in the current sample, the prevalence of such symptoms was not significantly different than in the general population.¹⁹

Significantly lower levels of uptake of HNPCC testing were also observed among persons who did not have a college education, suggesting that lack of formal education may pose a barrier to participation. Individuals with lower family incomes (<\$50 000) had reduced but not significantly different rates of test uptake than those with higher incomes. Persons of lower socioeconomic status may believe that testing would be less beneficial because they would not have access to recommended prevention and surveillance measures if they were to receive positive test results. Lower levels of utilization of colorectal cancer screening among persons of lower socioeconomic status have been documented in previous studies.³⁰⁻³² Alternatively, lack of formal education may have limited the ability of some individuals to comprehend the information about genetic testing that was included in the introductory letter and consent forms. This is supported by previous research in which education level was positively associated with comprehension of individualized cancer risk information.³³

It is an ongoing challenge for health care professionals to convey complex information about medical decisions so that it is easily accessible to persons of different socioeconomic and cultural backgrounds. Conveying such information to persons who are emotionally distressed is also challenging because the opportunity for genetic testing may generate personal and social concerns about risk and vulnerability. Findings re-

Table 1. Bivariate Analysis of Predictors of Uptake of Genetic Testing

	Uptake, %	P for χ^2 Test
Sex		
Male	60	.98
Female	60	
Age, y		
≥ 40	64	.25
<40	54	
Marital status		
Married	66	.05
Unmarried	48	
Education		
College degree or higher	78	.01
Less than college degree	54	
Income, \$		
$\geq 50\ 000$	73	.14
<50 000	58	
Previous genetics study		
Yes	71	.04
No	52	
Cancer status		
Affected	70	.24
Unaffected	58	
Colonoscopy in past year		
Yes	45	.30
No	61	
Depression symptoms		
Present	44	.05
Absent	65	

Table 2. Logistic Regression Model of Uptake of Genetic Testing*

Variables	Odds Ratio (95% Confidence Interval)	P Value
Education		
College degree or higher	3.74 (2.49-5.61)	<.001
Less than college degree	1.0 (Referent)	
Prior genetics study		
Yes	4.30 (1.84-10.10)	<.001
No	1.0 (Referent)	
Depression		
Present	0.34 (0.17-0.66)	.001
Absent	1.0 (Referent)	

*Model controlled for all variables listed plus provision of prior blood sample.

ported here amplify the importance of developing ways to make information about genetic testing comprehensible and relevant to the broad spectrum of individuals who are at increased risk.

In considering these findings, a few study limitations should be noted. First, study participants were members of a family HNPCC registry. As such, some of them received written educational materials and provided a blood sample for linkage analysis several years prior to this study. However, because of the investigational nature of those studies, test results were not provided (or expected by participants) and DNA testing was not performed prior to the current study. However, the results of our regression analysis suggest that prior participation in these studies may have stimulated interest in clinical genetic testing for HNPCC. Another factor related to the family-based registry is that it enabled us to conduct education sessions in family groupings. This process could have influenced testing decisions because family members may have been more likely to share their reactions and decisions with each other. A second consideration is that genetic testing and counseling were offered to participants free of charge. Thus, the utilization rates observed in the present study may overestimate those for newly ascertained high-risk individuals. Third, the models predicting utilization were based on the 69% of the study sample who participated in our baseline interviews. Although this subsample did not differ significantly from the total pool of eligible subjects in terms of age, sex, or cancer history, there may be other participation biases operating. A final consideration is that our study population was ethnically homogeneous. Thus, the current study should be replicated in more racially diverse populations and different clinical settings.

Despite these potential limitations, our results suggest that rates of utilization of genetic testing for HNPCC within high-risk families may be lower than originally anticipated. These findings also point to ways to make testing more accessible to those who might benefit. Since depression appears to be

a barrier to testing, physicians or genetic counselors may consider screening for such problems during initial patient visits and referring those individuals for psychosocial counseling. A previous study of newly diagnosed colorectal cancer patients considering genetic testing found that depression was more common in patients with less education who had inadequate social support.³⁴ By discussing testing decisions with family members, such patients may be able to enhance levels of practical and emotional support, thereby alleviating depression symptoms and facilitating informed decisions about genetic testing. Furthermore, written and verbal information about cancer genetics and testing must be made more accessible to persons with less education, as well as those from different cultural backgrounds.

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