

Cost-Effectiveness of Microsatellite Instability Screening as a Method for Detecting Hereditary Nonpolyposis Colorectal Cancer

Scott D. Ramsey, MD, PhD; Lauren Clarke, MS; Ruth Etzioni, PhD; Mitchell Higashi, MBA; Kristin Berry, MS; and Nicole Urban, ScD

Background: The National Cancer Institute has published consensus guidelines for universal screening for hereditary nonpolyposis colorectal cancer (HNPCC) in patients with newly diagnosed colorectal cancer.

Objective: To determine the cost-effectiveness of screening compared with standard care in eligible patients with colorectal cancer and their siblings and children.

Design: Cost-effectiveness analysis.

Data Sources: National colorectal cancer registry data, the Creighton International Hereditary Colorectal Cancer Registry, Medicare claims records, and published literature.

Target Population: Patients with newly diagnosed colorectal cancer and their siblings and children.

Time Horizon: Lifetime (varies depending on age at screening).

Perspective: Societal.

Interventions: Initial office-based screening to determine eligibility (based on personal and family cancer history), followed by tumor testing for microsatellite instability. Those with microsatellite instability were offered genetic testing for HNPCC. Siblings

and children of patients with cancer and the HNPCC mutation were offered genetic testing, and those who were found to carry the mutation received lifelong colorectal cancer screening.

Measurements: Life-years gained.

Results of Base-Case Analysis: When only the patients with cancer were considered, cost-effectiveness of screening was \$42 210 per life-year gained. When patients with cancer and their siblings and children were considered together, cost-effectiveness increased to \$7556 per life-year gained.

Results of Sensitivity Analysis: The model was most sensitive to the estimated survival gain from screening siblings and children, to the prevalence of HNPCC mutations among patients with newly diagnosed cancer, and to the discount rate. In probabilistic analysis, the 90% CI for the cost-effectiveness of screening patients with cancer plus their relatives was \$4874 to \$21 576 per life-year gained.

Conclusion: Screening patients with newly diagnosed colorectal cancer for HNPCC is cost-effective, especially if the benefits to their immediate relatives are considered.

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For author affiliations, current addresses, and contributions, see end of text.

Genetic testing for predisposition to many hereditary cancer syndromes is now feasible. One important hereditary cancer syndrome is hereditary nonpolyposis colorectal cancer (HNPCC), an autosomal dominant syndrome that is estimated to account for between 1% to 5% of all cases of colorectal cancer (1, 2). Persons with the syndrome have been found to carry germline mutations in one of six DNA nucleotide mismatch repair genes. Mutation carriers are at high risk for colorectal cancer at an early age (median age at diagnosis, 45 years) and have increased risk for several extracolonic neoplasms, such as endometrial, small-bowel, gastric, renal pelvis, ureter, and ovarian cancer (3, 4). A recent controlled study suggested that regular intensive screening with colonoscopy can significantly prolong the lives of HNPCC mutation carriers (5).

Detection of the HNPCC mutation is problematic because there are no overt symptoms or signs before onset of the associated malignancies. Because of the

complexity and expense of direct DNA analysis, population-wide genetic screening for HNPCC is not currently considered feasible (6). Several groups have proposed algorithms that focus testing efforts on persons who are at high risk for HNPCC. Most algorithms define high-risk persons as those with newly diagnosed colorectal cancer who meet certain clinical criteria and have one or more first-degree relatives with an HNPCC-associated malignancy (7–11). In patients who meet the criteria, tumors are tested for microsatellite instability. Microsatellite instability is a tumor phenotype that is characteristic of HNPCC but can also occur in up to 15% of cases of sporadic colon cancer (12, 13). Because this test is sensitive but less specific, patients who have microsatellite instability–positive tumors are then tested for the most common mutations associated with HNPCC, *MLH1* and *MSH2*. One of these algorithms, known as the Bethesda guidelines, is described in Table 1.

Because colon cancer is highly prevalent, widespread

Table 1. Algorithm for Identifying Potential Carriers of the Hereditary Nonpolyposis Colorectal Cancer Mutation among Those with New Colorectal Cancer*

<p>Test colorectal tumor for microsatellite instability if any of the following criteria are met:</p> <ul style="list-style-type: none"> Cancer in families that meet the Amsterdam criteria† Two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers‡ Colorectal cancer and a first-degree relative with colorectal cancer, HNPCC-related extracolonic cancer, or a colorectal adenoma, when one of the cancers is diagnosed at <45 years of age and the adenoma is diagnosed at <40 years of age Colorectal cancer or endometrial cancer diagnosed at <45 years of age Right-sided colorectal cancer with an undifferentiated pattern (solid or cribriform) on histopathologic examination diagnosed at <45 years of age§ Signet-ring cell-type colorectal cancer diagnosed at <45 years of age Adenomas diagnosed at <40 years of age

* Based on the Bethesda guidelines (8). HNPCC = hereditary nonpolyposis colorectal cancer.

† 1) At least three relatives with histologically verified colorectal cancer, where one family member is a first-degree relative of the other two; 2) at least two successive generations with colorectal cancer; 3) diagnosis of colorectal cancer before 50 years of age in one of the family members; and 4) diagnosis of familial adenomatous polyposis excluded.

‡ Endometrial, ovarian, gastric, hepatobiliary, or small-bowel cancer or transitional-cell carcinoma of the renal pelvis or ureter.

§ Solid or cribriform defined as poorly differentiated or undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small gland-like spaces.

|| Composed of >50% signet-ring cells.

application of the screening programs for HNPCC could have an important impact on the health care community and on society. During 1999, approximately 129 000 new cases of colorectal cancer were diagnosed in the United States (14). To carefully review the clinical and family histories of each patient with new colorectal cancer to determine whether they warrant microsatellite instability testing would require substantial time and resources. In addition, several thousand patients with new colorectal cancer would receive genetic counseling and genetic testing. For the estimated 1300 to 6500 persons with HNPCC who would be identified, clinical management would change. Finally, once a person is found to carry a mutation, it is likely (and perhaps desirable) that immediate family members will be notified. Given this potential cascade of effects, it is important to understand the economic and policy implications of implementing screening programs for HNPCC.

Using a decision model and available data, we estimated the cost-effectiveness of identifying HNPCC carriers among patients with newly diagnosed colorectal cancer. We compared this approach with the current practice of not screening for genetic susceptibility. Since patients with colorectal cancer and their close relatives

may be affected by the guidelines, we present our results two ways: considering costs and benefits only for probands (patients with colorectal cancer) and for probands and their siblings and children.

METHODS

Overview

Our hypothetical cohort included all 129 400 patients with newly diagnosed colorectal cancer in the United States in 1999. Two separate cost-effectiveness evaluations were performed: one that considered costs and outcomes for probands only, and a second that included costs and outcomes for probands and their siblings and children. The first cost-effectiveness analysis considered probands at the time of diagnosis, when the initial decision between current management (standard treatment and post-treatment surveillance) and a management strategy that included microsatellite instability screening was made. For the latter strategy, we followed the recommendations of the National Cancer Institute, which are known as the Bethesda guidelines (8). The primary measure of effectiveness was life-years gained.

The second cost-effectiveness analysis extended the decision algorithm beyond the Bethesda guidelines to include contacting the siblings and children of patients found to carry the HNPCC mutation. These relatives were offered genetic testing, and those that had HNPCC mutations were offered intensive lifelong screening for colorectal cancer. Data used to inform both analyses were drawn from several sources. In cases where data elements needed to inform the decision pathways were not available, we made conservative assumptions (that is, assumptions less favorable to the screening program) about their values.

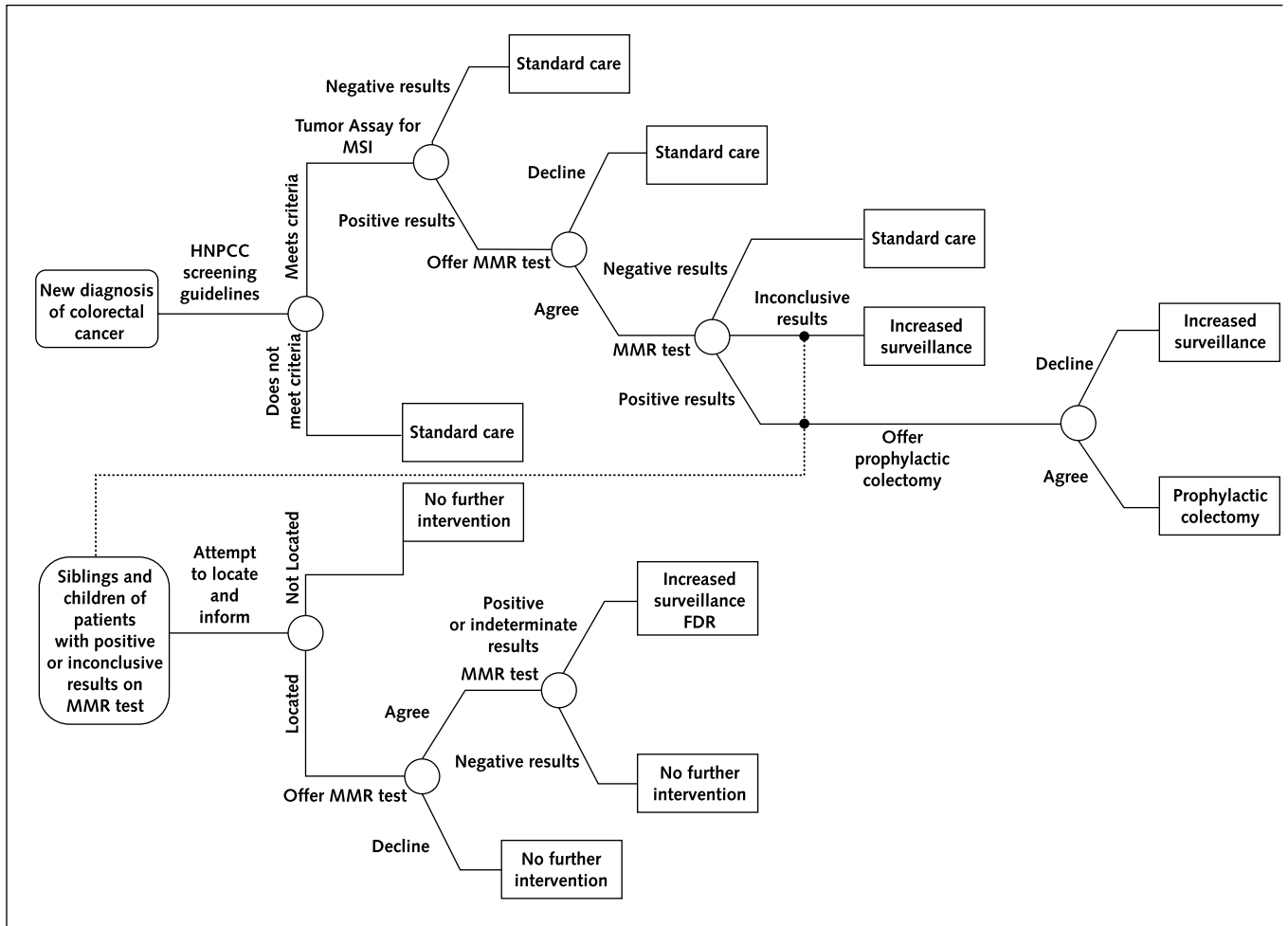
We created the decision model for the analysis using Microsoft Excel (Microsoft Corp., Redmond, Washington); subsequent sensitivity analyses were performed by use of @Risk, version 3.5.2 (Palisade Corp., Newfield, New York).

Management Pathway

Patients with Colorectal Cancer

When a patient received a diagnosis of colorectal cancer (Figure 1), the clinician determined whether his or her personal and family cancer history indicated eligibility for further testing (Table 1). Tumors from patients who met screening criteria were tested for micro-

Figure 1. Decision tree for microsatellite instability test and hereditary nonpolyposis colorectal cancer (HNPCC) mutation testing of patients with newly diagnosed colon cancer and their siblings and children.



The top half of the tree represents the decision pathway for those with newly diagnosed colorectal cancer (Bethesda guidelines); the lower half represents the pathway for screening of siblings and children of mutation carriers. Outcome states at the end of each branch (not shown) are either colorectal cancer followed by death or no colorectal cancer followed by death. Increased surveillance is defined as colonoscopy every 3 years; standard care is defined as standard post-colorectal cancer care (15). MMR = mismatch repair mutation; MSI = microsatellite instability.

satellite instability. Microsatellite instability-positive patients were then offered germline mismatch repair testing, preceded by genetic counseling from certified genetics counselors.

If results of the mismatch repair test were definitively negative, the patient returned to standard care and surveillance. Carriers of the HNPCC mutation were offered subtotal colectomy (16). Mutation carriers who declined subtotal colectomy (25% in the base case) received lifelong surveillance with regular colonoscopy, as recommended by the Cancer Genetics Studies Consortium (triannual examination in the base case) (16).

Those with indeterminate mismatch repair evaluations received lifelong surveillance with triannual colonoscopy. Although it is recommended that mutation carriers also undergo surveillance for extracolonic cancer (particularly cancer of the endometrium and ovary), data supporting these interventions are lacking; therefore, we did not consider the costs or benefits of these tests in this model.

Siblings and Children of Mutation Carriers

The second cost-effectiveness analysis expanded the scope of the decision model to include costs and out-

comes for siblings and children of patients who are found to be mutation carriers (Figure 1). Standard procedures for contacting and counseling family members have not been established and may be affected by state and federal laws protecting the privacy of the physician–patient relationship, as well as laws regarding the duty of physicians to inform those who may be at risk but are not under their direct care (17–20). Although siblings and children may not always be contacted by genetic counselors, we assigned a time cost that was based on counselors' hourly wages. The probability of locating relatives was determined according to whether the relatives were siblings or children. Relatives were offered genetic counseling and mismatch repair gene testing. Siblings and children who agreed to testing and had positive or indeterminate results were placed in lifelong colonoscopic surveillance every 3 years beginning at 25 years of age or their current age, whichever was greater (16, 21).

Colorectal Cancer Stage and Age Distribution at Diagnosis

The distribution of ages and stages of patients with sporadic colorectal cancer at diagnosis was based on data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry (22). The age and stage distribution at diagnosis for HNPCC carriers was based on data provided by the Creighton International Hereditary Colorectal Cancer Registry (Watson P. Personal communication).

Performance Characteristics of Screening Tests for Hereditary Nonpolyposis Colorectal Cancer

It has been estimated that after initial office screening of patients with new colorectal cancer, approximately 15% to 20% would be eligible for further testing (7). Between 86% and 92% of benign and malignant tumors in patients with the HNPCC mutation exhibit the microsatellite instability phenotype (23). The sensitivity and specificity of microsatellite instability testing vary, however, because the test exhibits a relationship similar to that of a receiver-operating characteristic curve; sensitivity may be exchanged for specificity depending on the combination of microsatellite markers used to identify replication errors in the tumor DNA. It is currently recommended that a minimum of four markers be used and that instability be defined as alter-

ations in at least two of the four. In our base case, characteristics of the microsatellite instability test set sensitivity at 91% and specificity at 93% (24–26).

Although individual mismatch repair mutations are highly specific for HNPCC, the sensitivity of all known mutations for HNPCC is less clear. Most reports suggest that the *hMSH2* and *hMLH1* mutations account for most cases of HNPCC. In our base case, we assigned a sensitivity and specificity of 87% and 99.5%, respectively, to *hMSH2* and *hMLH1* assays. The likelihood of inconclusive test results was included in these calculations (21).

Survival under Standard Care, Increased Surveillance, and Colectomy

Survival for patients with colorectal cancer but no HNPCC mutation was based on the SEER registry (22). For case-patients diagnosed after 1982 in the SEER database, a Weibull model was used to convert survival rates to expected years of life (the primary outcome for the cost-effectiveness model). The Weibull distribution is a flexible two-parameter distribution commonly used to model survival (27).

Survival for HNPCC carriers was also based on the SEER registry. Age-adjusted survival may be higher for HNPCC carriers who develop colorectal cancer than for patients with sporadic colorectal cancer (1, 28–30). In our base-case analysis, we assumed that life expectancy was one third higher for patients with HNPCC mutations and early-stage cancer than for those with sporadic cancer; we assumed that life expectancy for HNPCC carriers decreased with more advanced stages at diagnosis. These assumptions, which reduce the benefits of screening, are more conservative than assigning equal survival to both groups.

Current guidelines recommend that HNPCC carriers with colonic tumors should undergo subtotal colectomy (16). To estimate the survival advantage for subtotal colectomy compared with standard therapy, we performed an observational matched case–control study using data from the SEER registry. Case-patients were identified as patients with a first diagnosis of colon cancer before 50 years of age and a second diagnosis of colon cancer at least 12 months after the first diagnosis. Controls had a single diagnosis of colon cancer that occurred before 50 years of age. Controls were matched

to case-patients according to age and stage at diagnosis and surviving to a second diagnosis. Details are available in a companion paper (Ramsey SD, Berry K, Etzioni R, Newcomb P. Estimated survival benefit from therapeutic subtotal colectomy for those at risk for hereditary nonpolyposis colorectal cancer. Submitted for publication).

Our survival estimates incorporated the mortality risks associated with endoscopic surveillance of mutation carriers and, for those with newly diagnosed cancer, the excess perioperative mortality rate for total colectomy compared with partial resection when tumors are resectable (21, 31–39).

Adherence to Testing and Treatment

Although a high proportion of patients with affected relatives express interest in obtaining genetic testing for colon cancer susceptibility (40, 41), fewer seem to actually take the test when it is offered, possibly because of fear of insurance or employment discrimination, or family issues (42, 43). On the basis of available information, the base case assumed that 65% of siblings of mismatch repair mutation carriers consented to counseling and that 65% of those who were determined eligible agreed to mismatch repair testing after counseling. For the children of mutation carriers, we assumed that 70% agreed to counseling and that 70% of those who were eligible obtained testing after counseling. The base case assumed that 75% of HNPCC mutation carriers who had localized disease and knew their gene status would elect to have colectomy as part of their initial treatment.

Costs of Testing and Treatment

The costs of microsatellite instability testing, genetic counseling, genetic testing, colorectal cancer treatment and surveillance under usual care, and prophylactic colectomy for HNPCC mutation carriers were based on several sources. Costs of microsatellite instability assays and genetic testing were based on a national survey of reimbursements to laboratories, which was undertaken for this study. Genetic counseling costs were based on a recent survey of reimbursements for services by the National Society of Genetic Counselors (44). Costs of colorectal cancer treatment and prophylactic colectomy were based on data from the SEER–Medicare database (45).

Expected costs over each lifetime were derived by using the Kaplan–Meier sample average estimator technique (46).

Data on Siblings and Children of Carriers

Siblings and children of mutation carriers must be identified and screened to determine their carrier status. Those with mutations must undergo regular colonoscopic screening (16). We used census tract data to determine the average number of siblings and children for each mutation carrier and their age at the time of genetic testing (47, 48). The life survival benefit of surveillance for mutation carriers was based on a recent randomized study by Järvinen and colleagues (5). The screening continued until death or until colon cancer was detected, at which time the patient had colectomy (16, 21). The costs and risks of colonoscopy were based on published studies (31–33). We prorated the benefit according to the age of the relative when the proband received a diagnosis of colon cancer. Survival for those who were not found to have mutations was based on U.S. Census life tables (49).

Discounting Future Costs

All costs are presented in 1999 U.S. dollars. As has been recommended for cost-effectiveness studies, future costs and benefits were discounted at 3% per year in the base case (50).

Sensitivity Analysis

We performed one-way sensitivity analysis on all variables in the model and then arranged them in order based on those that had the greatest impact on overall cost-effectiveness. Ranges for each variable were based on 95% CIs, if available from the source data, or on expert opinion if no range data were available. We also performed a multiway probabilistic sensitivity analysis of the database by creating probability density functions for each variable, then randomly drawing 1000 observations from those distributions and rerunning the analysis. In cases where the distributions were unknown, we created triangular distributions with mean values equal to the base-case value for the model. The extremes at either end of the ranges were used in the one-way analysis. Cost-effectiveness outcome points were then mapped onto a cost-effectiveness plane, and 95% CIs were tabulated.

Table 2. Projected Outcomes and Costs Resulting from Screening and Microsatellite Instability Testing of Persons with Newly Diagnosed Colorectal Cancer*

Outcome	Proband	First-Degree Relatives†
Colorectal cancer cases diagnosed in the first year of the program, <i>n</i>	129 400	
Tumors tested for replication error phenotype, <i>n</i>	20 833	‡
False-positive results on MSI tests, <i>n</i>	1332	‡
False-negative results on MSI tests, <i>n</i>	163	‡
Patients offered MMR mutation counseling and testing, <i>n</i>	2980	933
False-positive results on MMR assays, <i>n</i>	4	1
False-negative results on MMR assays, <i>n</i>	74	23
HNPCC carriers identified, <i>n</i>	860	291
Life-years gained (undiscounted)	1082	9102
Cost per carrier detected, \$	12 815	1047
Added cost per life-year gained (3% discount, costs and benefits), \$	42 210	7556§

* HNPCC = hereditary nonpolyposis colorectal cancer; MMR = mismatch repair mutation; MSI = microsatellite instability.

† Includes siblings and children of proband only. Parents of the proband are excluded.

‡ Replication error testing is not performed in first-degree relatives with mutations when colorectal cancer is detected.

§ Incremental cost-effectiveness of screening and treating both probands and first-degree relatives.

Role of the Funding Source

The National Cancer Institute funded the study; however, the authors had complete independence in design, conduct, and reporting.

RESULTS

Outcomes for Patients with Colon Cancer (Probands)

According to our base-case estimates, the personal and family history of patients who received a new diagnosis of colorectal cancer in 1999 identified 20 833 persons eligible for microsatellite instability tumor testing (Table 2). After microsatellite instability analysis, 2980 probands were appropriate for mismatch repair gene testing. After mismatch repair testing, 864 probands were offered prophylactic colectomies. Testing and performing prophylactic colectomies on eligible mutation carriers with malignancies added 1082 years of life (undiscounted) to this group, at an average cost of \$12 815 per carrier detected. After we discounted future costs and life-years, the incremental cost-effectiveness for microsatellite instability screening of patients with newly diagnosed colorectal cancer who met criteria was \$42 210 per life-year gained compared with current practice.

Outcomes for Siblings and Children of Patients with Colorectal Cancer

Expanding the model to include costs and benefits for siblings and children increased the number of mutation carriers identified and greatly improved the cost-

effectiveness of the program. Under base-case variables, 1944 surviving siblings and children of the probands were eligible for mismatch repair gene counseling and testing. When we accounted for the likelihood of contacting these relatives and their expected rate of adherence to testing, 291 siblings and children were identified as mutation carriers. Regular surveillance of these persons, followed by subtotal colectomy for those found to have malignancies, added 9102 undiscounted life-years to this cohort. The cost per relative included the costs of locating and contacting them; however, these costs were less expensive than those for probands because the genetic test requires sequencing of only one primer (approximately \$150) in relatives of carriers in whom the location of the mutation is known. Overall, screening of siblings and children represented a cost savings for this cohort because the savings from early intervention (screening and colectomy for those found to have malignancies) exceeded the costs of testing.

Outcomes for Patients with Colorectal Cancer and Their Siblings and Children

When probands and their siblings and children were included in the model, screening yielded 2009 discounted life-years gained at an additional (discounted) cost of \$15 181 504. The incremental (discounted) cost-effectiveness, therefore, was \$7557 per life-year gained for microsatellite instability screening compared with current practice.

Sensitivity Analysis

Figure 2 and the Appendix Table show the 15 variables that had the greatest impact on the outcome of the one-way sensitivity analysis. The three most influential variables were the relative mortality risk associated with increased surveillance in HNPCC-positive siblings and children, the overall prevalence of HNPCC mutation carriers among patients with new diagnoses of colorectal cancer, and the discount rate for future costs and benefits. On the basis of 95% CIs from published data (5), the cost-effectiveness of screening was \$5873 per life-year gained (best-case scenario) and \$41 581 per life-year gained (worst-case scenario) for relatives who were identified and began regular screening. At a plausible low-prevalence estimate of 0.5% for HNPCC, the cost-effectiveness of screening was \$20 411 per life-year

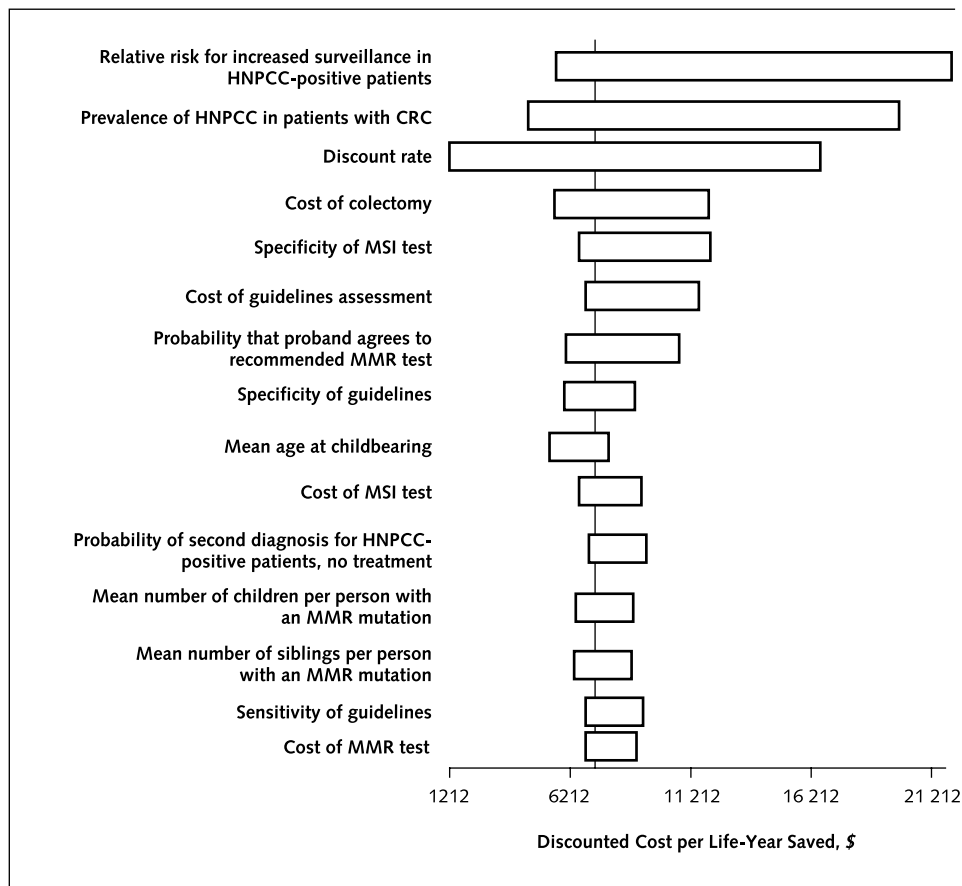
gained. At a high-prevalence estimate of 6%, the cost-effectiveness was \$4697 per life-year gained.

The n-way probabilistic sensitivity analysis, based on 1000 replications of the analysis with values drawn from distributions for the 15 most sensitive variables in the one-way analysis, demonstrated a 90% CI of \$4874 to \$21 576 per life-year gained.

DISCUSSION

Genetic testing for many types of hereditary colon cancer is now feasible, and international guidelines have been established for identifying and testing persons at risk. Our analysis suggests that microsatellite instability screening of patients with newly diagnosed colon cancer and an appropriate personal and family cancer history is

Figure 2. Results of one-way sensitivity analyses of input variables for the cost-effectiveness model.



Analysis concerns patients with cancer and their family members. CRC = colorectal cancer; HNPCC = hereditary nonpolyposis colorectal cancer; MMR = mismatch repair mutation; MSI = microsatellite instability.

cost-effective. Moreover, the cost-effectiveness of screening increases greatly if siblings and children of mutation carriers can also be identified and screened. The cost-effectiveness of screening seems to hold under worst-case assumptions of mutation prevalence, survival benefits of regular colonoscopy for mutation carriers, and adherence to diagnostic and therapeutic recommendations.

Patients at risk for hereditary colon cancer are not screened routinely in the United States. There are many potential barriers to implementing screening policies such as the Bethesda guidelines. Patients or private and public health insurance plans would have to bear the direct costs of testing and screening. Currently, many plans do not cover the costs of genetic screening, particularly for at-risk relatives without cancer (51). Since surveillance of mutation carriers also falls outside standard cancer screening procedures, it is possible that these interventions would also not be covered. It is not clear whether patients and family members would be willing to pay the full costs of testing and surveillance.

Another important potential barrier is legal restrictions regarding the release of confidential patient information to third parties. Even if it becomes clearly permissible to contact relatives, physicians may be unable or unwilling to contact family members of mutation carriers, many of whom could be estranged from the proband or living in distant cities. These issues and others must be considered and possibly studied before public policy on genetic screening for hereditary colon cancer is implemented.

Cost-effectiveness analysis holds promise as a way of synthesizing decisions and information about testing, treatment, and outcomes surrounding genetic testing for cancer susceptibility syndromes. Our study suggests that compelling clinical and economic rationales support initiation of microsatellite instability screening programs for patients with newly diagnosed colorectal cancer and appropriate risk profiles. If such screening is to become part of standard practice, clinicians would need to learn the Bethesda algorithm (Table 1) and apply it to patients with newly diagnosed colorectal cancer. It is also likely that more pathology laboratories would need to acquire the capacity to perform microsatellite instability testing, including study of DNA extracted from paraffin-embedded formalin-fixed tumor samples. If implemented nationwide, office screening of patients with newly diagnosed colorectal cancer, combined with micro-

satellite instability testing of those who meet Bethesda criteria and mismatch repair testing of microsatellite instability–positive patients, would cost approximately \$11 000 000 in the first year. Colectomies for mutation carriers would cost nearly \$20 000 000. Given that the additional costs to a single health system would be relatively low, we feel that it may be reasonable for clinicians to adopt the Bethesda guidelines and for health plans to cover the relatively modest genetic counseling and testing. Locating siblings and children of mutation carriers and performing mismatch repair tests would be less costly (approximately \$5 700 000), and annual colonoscopy costs would be less than \$300 000 in the first year of screening relatives with the mismatch repair mutation. Despite these comparatively low costs, however, we believe that the legal, health insurance, and health system barriers to contacting and screening relatives must be addressed before such a program can be implemented.

Our sensitivity analysis highlights the components that tend to have more influence on the overall cost-effectiveness of microsatellite instability screening for HNPCC. The model reaffirms the findings of an earlier economic analysis of such screening: The prevalence of HNPCC mutation carriers among all patients with new colorectal cancer is among the most important factors influencing cost-effectiveness (52). The prevalence of HNPCC is well described in only a few European populations. Further study is needed to understand the prevalence of HNPCC in other groups, such as Hispanic and African-American persons, before widespread screening is undertaken in a heterogeneous population like that of the United States. In addition, the accuracy of the microsatellite instability test is also important to overall cost-effectiveness. Recent efforts to standardize microsatellite instability screening are important because they help ensure that the screening is cost-effective wherever it is applied (24–26). While the discount rate for future costs and benefits may not be seen as a true model variable, we included it to highlight the fact that costs and benefits related to genetic screening for familial cancer syndromes are separated by a considerable amount of time. Finally, variations in some of the inputs in the model had much less effect on the cost-effectiveness of screening than anticipated. In particular, decreasing the cost of germline testing had a relatively small impact (Figure 2). When cost-effectiveness of such

Appendix Table. List of Variables Informing the Decision Model of Microsatellite Instability Testing for Hereditary Colorectal Cancer*

Variable	Range Used for Sensitivity Analysis			References	Cost per Life-Year Saved According to One-Way Sensitivity Analysis, \$		Rank†
	Low	High	Range		At Low Value	At High Value	
Disease							
Proband							
Prevalence of HNPCC in patients with colorectal cancer, %	2	0.5	6	1, 2	20 411	4697	1
Probability of second diagnosis for HNPCC-positive patients, no treatment	0.95	0.7	1	3, 4, 7	9549	7158	11
Mean time to second diagnosis in absence of intervention, y	5	4	6	3, 4, 7	7329	7777	35
Life expectancy under standard care for HNPCC-negative patients	‡	‡	‡	22	‡	‡	
Life expectancy under standard care for HNPCC-positive patients	‡	‡	‡	1, 22, 28–30	‡	‡	
Life expectancy under increased surveillance for HNPCC-negative patients	‡	‡	‡	22	‡	‡	
Life expectancy under increased surveillance for HNPCC-positive patients	‡	‡	‡	1, 22, 28–30	‡	‡	
Life expectancy after colectomy for HNPCC-negative patients	‡	‡	‡	22	‡	‡	
Life expectancy after colectomy for HNPCC-positive patients	‡	‡	‡	1, 22, 28–30	‡	‡	
Siblings and children							
Probability of first diagnosis in HNPCC-positive patients	0.8	0.7	1	59	7794	7081	28
Mean time until first diagnosis in HNPCC-positive patients, y	2	1	4		7532	7602	44
Relative mortality risk for increased surveillance in HNPCC-positive patients, %	34.8	12.2	99.9	5	5873	41 581	1
Operation and acceptance of tests							
Proband							
Probability of agreeing to guidelines assessment	1	0.5	1	§	7556	7556	55
Sensitivity of guidelines, %	70	50	80	8	9254	7026	14
Specificity of guidelines, %	85	75	95	8	8979	6133	8
Probability of accepting MSI test	1	0.75	1	42, 43	8260	7556	29
Sensitivity of MSI test, %	91	75	95	24–26	8485	7373	21
Specificity of MSI test, %	93	6	98	24–26	12 258	6843	5
Probability of accepting MMR test	0.6	0.3	1	42, 43	10 911	6215	7
Sensitivity of MMR test, %	92.5	87	95	21	8358	7230	19
Proportion of non-negative MMR test results that are inconclusive, %	6	2	10	21	7249	7889	30
Specificity of MMR test, %	99.7	98	100	21	7249	7889	30
Proportion of nonpositive MMR test results that are inconclusive, %	20	50	0	21	7726	7527	40
Probability of adhering to colectomy	0.75	0.5	1	16	7588	7535	45
Probability of death caused by colectomy	0	0	0	31, 32, 35	7556	7556	61
Siblings and children							
Probability that sibling complies with counseling	0.6	0.5	0.85	42, 43	8167	6328	17
Probability that sibling complies with MMR test	0.6	0.5	0.85	42, 43	8169	6324	16
Probability that child complies with counseling	0.7	0.65	0.8	42, 43	7810	7093	27
Probability that child complies with MMR test	0.7	0.65	0.8	42, 43	7813	7088	26
Probability that siblings and children are HNPCC positive given that the proband is HNPCC positive	0.5	0.5	0.5		7556	7556	63
Probability that siblings and children are HNPCC positive given that the proband is HNPCC negative	0.02	0.01	0.04		7557	7554	50
Contact information for siblings and children							
Mean siblings per MMR carrier, <i>n</i>	0.75	0.5	1	47, 48	8850	6560	13
Probability of locating sibling	0.65	0.5	0.75	§	8425	7059	18
Mean children per MMR carrier, <i>n</i>	1.5	1	2	47, 48	8840	6562	12
Probability of locating child	0.75	0.65	0.9	§	8044	6922	20
Mean age at childbearing, <i>y</i>	30	25	35	47, 48	5549	8092	9
Costs, \$							
Discount rate	0.03	0	0.05	50	1347	16 922	3
Cost of guidelines assessment	33	25	100	60	7057	11 887	6
Cost of MSI test	120	40	285		6727	9267	10

Continued on following page

Appendix Table—Continued

Variable	Range Used for Sensitivity Analysis			References	Cost per Life-Year Saved According to One-Way Sensitivity Analysis, \$		Rank†
	Low	High	Range		At Low Value	At High Value	
Cost of MMR test	2030	1378	3600		6976	8954	15
Cost of MMR counseling	365	300	1000	44	7499	8122	32
Cost of colectomy	30 673	25 000	45 000	60	5727	12 178	4
Cost to locate sibling	150	100	200	§	7540	7573	47
Cost to locate child	50	25	100	§	7540	7589	46
Cost of counseling siblings and children	100	75	125	44	7545	7568	48
Cost of MMR test for siblings and children	78	65	100		7552	7563	49
Yearly cost of standard care per HNPCC-negative person	100	50	150	§	7558	7555	52
Yearly cost of standard care per HNPCC-positive person	100	50	150	§	7954	7159	24
Yearly cost of increased surveillance per HNPCC-negative person	325	250	400	60	7556	7557	53
Yearly cost of increased surveillance per HNPCC-positive person	400	325	450	60	7379	7674	38
Yearly cost after colectomy per HNPCC-positive person	33	25	100	§	7510	7942	36
Mean attributable cost for second diagnosis, stage 1	27 794	22 235	33 353	45, 46	7858	7225	33
Mean attributable cost for second diagnosis, stage 2	28 872	23 098	34 647	45, 46	7869	7243	31
Mean attributable cost for second diagnosis, stage 3	33 658	26 927	40 390	45, 46	7921	7192	25
Mean attributable cost for second diagnosis, stage 4	49 352	39 482	59 223	45, 46	8091	7021	22
Mean attributable cost for first diagnosis, stage 1	25 516	20 413	30 620	45, 46	7638	7475	42
Mean attributable cost for first diagnosis, stage 2	28 166	22 533	33 800	45, 46	7720	7393	37
Mean attributable cost for first diagnosis, stage 3	31 907	25 526	38 289	45, 46	7646	7467	41
Mean attributable cost for first diagnosis, stage 4	45 393	36 314	54 471	45, 46	7602	7511	43

* Analysis concerns patients with cancer and their family members. Increased surveillance = colonoscopy every 3 years following cancer treatment; increased surveillance for siblings and children = colonoscopy every 3 years; mean attributable cost = mean attributable cost due to colorectal cancer; standard care = standard post-colorectal cancer care (60). HNPCC = hereditary nonpolyposis colorectal cancer; MMR = mismatch repair mutation; MSI = microsatellite instability.

† Rank of each variable's influence on cost-effectiveness estimates across the range used for the sensitivity analysis.

‡ Values vary on the basis of the patient's age and stage at the start of the intervention.

§ Expert opinion.

|| Facility survey.

screening programs is determined, anticipated reductions in cost may be less of an issue than, for example, patient acceptance.

Our analysis has several important limitations. First, as with many studies in which primary data are unavailable, some of the input variables are based on expert opinion. Fortunately, none of these variables seem to have a substantial effect on the overall cost-effectiveness of screening. Second, our analysis considers only direct medical costs associated with screening. Indirect costs, such as losses if patients experience job discrimination as a result of screening, may be important and should be evaluated in future studies. In addition, costs that may be associated with starting a screening program (for example, the cost of training physicians to identify potential mutation carriers using the Bethesda guidelines) are not included here. We also do not address the ways in which screening, having a colectomy, or living with colon cancer affect quality of life. Patients who learn that they carry a mutation that markedly increases their risk for a disease may develop negative psychological status

or decreased quality of life (53–56). The potential for decreased quality of life related to genetic testing must be weighed against the improvement in quality of life that would be realized by preventing colorectal cancer in this cohort. Finally, we do not address screening HNPCC carriers for other types of cancer that are common in patients with this syndrome. Endometrial cancer, in particular, is common in female HNPCC carriers; the lifetime risk is estimated to be up to 60% (57, 58). Annual screening for endometrial cancer by using endometrial aspirate or transvaginal ultrasonography has been widely advocated (57). Screening for endometrial cancer is less costly and probably carries less risk than colonoscopic screening for colorectal cancer. The added survival benefits of screening for endometrial cancer may further improve the cost-effectiveness of identifying mutation carriers in this population.

From Fred Hutchinson Cancer Research Center and University of Washington, Seattle, Washington.

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Requests for Single Reprints: Scott D. Ramsey, MD, PhD, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North (MP-900), Box 19024, Seattle, WA 98109; e-mail, sramsey@fhcrc.org.

Current Author Addresses: Drs. Ramsey, Etzioni, and Urban, Ms. Clarke, and Ms. Berry: Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North (MP-900), Box 19024, Seattle, WA 98109. Mr. Higashi: School of Pharmacy, Box 357630, University of Washington, Seattle, WA 98195.

Author Contributions: Conception and design: S.D. Ramsey, L. Clarke, R. Etzioni, N. Urban.

Analysis and interpretation of the data: S.D. Ramsey, L. Clarke, K. Berry, N. Urban.

Drafting of the article: S.D. Ramsey.

Critical revision of the article for important intellectual content: S.D. Ramsey, L. Clarke, K. Berry, N. Urban.

Final approval of the article: S.D. Ramsey, N. Urban.

Provision of study materials or patients: S.D. Ramsey.

Statistical expertise: S.D. Ramsey, K. Berry.

Obtaining of funding: S.D. Ramsey, N. Urban.

Administrative, technical, or logistic support: S.D. Ramsey.

Collection and assembly of data: S.D. Ramsey, M. Higashi.

References

- Aaltonen LA, Sankila R, Mecklin JP, Järvinen H, Pukkala E, Peltomäki P, et al. A novel approach to estimate the proportion of hereditary nonpolyposis colorectal cancer of total colorectal cancer burden. *Cancer Detect Prev*. 1994;18:57-63. [PMID: 8162607]
- Houlston RS, Collins A, Slack J, Morton NE. Dominant genes for colorectal cancer are not rare. *Ann Hum Genet*. 1992;56(Pt 2):99-103. [PMID: 1503398]
- Ponz de Leon M. Descriptive epidemiology of hereditary non-polyposis colorectal cancer. *Tumori*. 1996;82:102-6. [PMID: 8644370]
- Lynch HT, Smyrk TC. Hereditary colorectal cancer. *Semin Oncol*. 1999;26:478-84. [PMID: 10528895]
- Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomäki P, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 2000;118:829-34. [PMID: 10784581]
- Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adopted on February 20, 1996. *J Clin Oncol*. 1996;14:1730-6. [PMID: 8622094]
- Vasen HF, Mecklin JP, Watson P, Utsunomiya J, Bertario L, Lynch P, et al. Surveillance in hereditary nonpolyposis colorectal cancer: an international cooperative study of 165 families. The International Collaborative Group on HNPCC. *Dis Colon Rectum*. 1993;36:1-4. [PMID: 8416772]
- Rodriguez-Bigas MA, Boland CR, Hamilton SR, Henson DE, Jass JR, Khan PM, et al. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. *J Natl Cancer Inst*. 1997;89:1758-62. [PMID: 9392616]
- Nakahara M, Yokozaki H, Yasui W, Dohi K, Tahara E. Identification of concurrent germ-line mutations in hMSH2 and/or hMLH1 in Japanese hereditary nonpolyposis colorectal cancer kindreds. *Cancer Epidemiol Biomarkers Prev*. 1997;6:1057-64. [PMID: 9419403]
- Wijnen JT, Vasen HF, Khan PM, Zwiderman AH, van der Klift H, Mulder A, et al. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. *N Engl J Med*. 1998;339:511-8. [PMID: 9709044]
- Salovaara R, Loukola A, Kristo P, Kääriäinen H, Ahtola H, Eskelinen M, et al. Population-based molecular detection of hereditary nonpolyposis colorectal cancer. *J Clin Oncol*. 2000;18:2193-200. [PMID: 10829038]
- Peltomäki P. The genetics of hereditary non-polyposis colorectal cancer and non-polyposis colon cancer. *Adv Exp Med Biol*. 1999;470:95-8. [PMID: 10709678]
- Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res*. 1998;58:5248-57. [PMID: 9823339]
- Cancer Facts and Figures 1999. American Cancer Society. Atlanta: American Cancer Society; 1999.
- Benson AB 3rd, Desch CE, Flynn PJ, Krause C, Loprinzi CL, Minsky BD, et al. 2000 update of American Society of Clinical Oncology colorectal cancer surveillance guidelines. *J Clin Oncol*. 2000;18:3586-8. [PMID: 11032600]
- Burke W, Petersen G, Lynch P, Botkin J, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. *Cancer Genetics Studies Consortium*. *JAMA*. 1997;277:915-9. [PMID: 9062331]
- Olick RS. Disclosing genetic information to family members. Do old paradigms fit the new medicine? *N J Med*. 2000;97:43-6. [PMID: 10647249]
- Marta MR. Genetic testing: do healthcare professionals have a duty to tell a patient's family members that they may be at risk? *J Healthc Risk Manag*. 1999;19:26-38. [PMID: 10538434]
- Suter SM. Whose genes are these anyway?: familial conflicts over access to genetic information. *Mich Law Rev*. 1993;91:1854-908. [PMID: 10129309]
- Deftos LJ. Genomic torts: the law of the future—the duty of physicians to disclose the presence of a genetic disease to the relatives of their patients with the disease. *Spec Law Dig Health Care Law*. 1998;9:41. [PMID: 10185166]
- Syngal S, Fox EA, Li C, Dovidio M, Eng C, Kolodner RD, et al. Interpretation of genetic test results for hereditary nonpolyposis colorectal cancer: implications for clinical predisposition testing. *JAMA*. 1999;282:247-53. [PMID: 10422993]
- Surveillance, Epidemiology, and End Results (SEER) Program Public-Use CD-ROM (1973-1997). National Cancer Institute, Division of Cancer Control and Population Sciences, Cancer Surveillance Research Program, Cancer Statistics Branch. Released April 2000.
- Aaltonen LA, Peltomäki P, Mecklin JP, Järvinen H, Jass JR, Green JS, et al. Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients. *Cancer Res*. 1994;54:1645-8. [PMID: 8137274]
- Bubb VJ, Curtis LJ, Cunningham C, Dunlop MG, Carothers AD, Morris RG, et al. Microsatellite instability and the role of hMSH2 in sporadic colorectal cancer. *Oncogene*. 1996;12:2641-9. [PMID: 8700523]
- Lothe RA, Peltomäki P, Meling GI, Aaltonen LA, Nyström-Lahti M, Pylkkänen L, et al. Genomic instability in colorectal cancer: relationship to

- clinicopathological variables and family history. *Cancer Res.* 1993;53:5849-52. [PMID: 8261392]
26. González-García I, Moreno V, Navarro M, Martí-Ragué J, Marcuello E, Benasco C, et al. Standardized approach for microsatellite instability detection in colorectal carcinomas. *J Natl Cancer Inst.* 2000;92:544-9. [PMID: 10749909]
27. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data.* New York: J Wiley; 1980.
28. Myrholm T, Bisgaard ML, Bernstein I, Svendsen LB, Søndergaard JO, Bülow S. Hereditary non-polyposis colorectal cancer: clinical features and survival. Results from the Danish HNPCC register. *Scand J Gastroenterol.* 1997;32:572-6. [PMID: 9200290]
29. Gryfe R, Kim H, Hsieh ET, Aronson MD, Holowaty EJ, Bull SB, et al. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. *N Engl J Med.* 2000;342:69-77. [PMID: 10631274]
30. Percepe A, Benatti P, Roncucci L, Sassatelli R, Fante R, Ganazzi D, et al. Survival analysis in families affected by hereditary non-polyposis colorectal cancer. *Int J Cancer.* 1997;71:373-6. [PMID: 9139871]
31. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med.* 2000;343:162-8. [PMID: 10900274]
32. Jentschura D, Raute M, Winter J, Henkel T, Kraus M, Manegold BC. Complications in endoscopy of the lower gastrointestinal tract. Therapy and prognosis. *Surg Endosc.* 1994;8:672-6. [PMID: 8059305]
33. Lo AY, Beaton HL. Selective management of colonoscopic perforations. *J Am Coll Surg.* 1994;179:333-7. [PMID: 8069431]
34. Stevenson G. Description of diagnostic techniques. In: *Colon Cancer: Diagnosis in an Era of Cost Containment. Proceedings of a Professional Conference Sponsored by the ACR Commission on Education and Committee on Colon Imaging.* Reston, VA: American College of Radiology; 1989.
35. Macrae FA, Tan KG, Williams CB. Towards safer colonoscopy: a report on the complications of 5000 diagnostic or therapeutic colonoscopies. *Gut.* 1983;24:376-83. [PMID: 6601604]
36. Rouffet F, Hay JM, Vacher B, Fingerhut A, Elhadad A, Flamant Y, et al. Curative resection for left colonic carcinoma: hemicolectomy vs. segmental colectomy. A prospective, controlled, multicenter trial. *French Association for Surgical Research. Dis Colon Rectum.* 1994;37:651-9. [PMID: 8026230]
37. Stelzner M, Fonkalsrud EW. The endorectal ileal pullthrough procedure in patients with ulcerative colitis and familial polyposis with carcinoma. *Surg Gynecol Obstet.* 1989;169:187-94. [PMID: 2549648]
38. Coran AG. A personal experience with 100 consecutive total colectomies and straight ileoanal endorectal pull-throughs for benign disease of the colon and rectum in children and adults. *Ann Surg.* 1990;212:242-7. [PMID: 2396880]
39. Pedersen T, Eliassen K, Henriksen E. A prospective study of mortality associated with anaesthesia and surgery: risk indicators of mortality in hospital. *Acta Anaesthesiol Scand.* 1990;34:176-82. [PMID: 2343717]
40. Croyle RT, Lerman C. Interest in genetic testing for colon cancer susceptibility: cognitive and emotional correlates. *Prev Med.* 1993;22:284-92. [PMID: 8483865]
41. Kinney AY, Choi YA, DeVellis B, Kobetz E, Millikan RC, Sandler RS. Interest in genetic testing among first-degree relatives of colorectal cancer patients. *Am J Prev Med.* 2000;18:249-52. [PMID: 10722992]
42. Kolata G. Genetic testing falls short of public embrace. *The New York Times.* 27 March 1998.
43. Lerman C, Hughes C, Trock BJ, Myers RE, Main D, Bonney A, et al. Genetic testing in families with hereditary nonpolyposis colon cancer. *JAMA.* 1999;281:1618-22. [PMID: 10235155]
44. Bernhardt BA, Peshkin BN, Kemel Y. Billing and record-keeping for familial cancer risk counseling: a national survey. *J Genet Counsel.* 1998;7:317-330.
45. Potosky AL, Riley GF, Lubitz JD, Mentnech RM, Kessler LG. Potential for cancer related health services research using a linked Medicare-tumor registry database. *Med Care.* 1993;31:732-48. [PMID: 8336512]
46. Etzioni R, Urban N, Baker M. Estimating the costs attributable to a disease with application to ovarian cancer. *J Clin Epidemiol.* 1996;49:95-103. [PMID: 8598518]
47. Fertility of American Women: June 1995 (Update). Available at www.census.gov/prod/3/97pubs/p20-499.pdf. Accessed 1 June 2000.
48. Statistical Abstract of the United States. U.S. Census Bureau. Available at www.census.gov/prod/www/statistical-abstract-us.html. Accessed 1 June 2000.
49. Statistical Abstract of the United States, 1999. U.S. Census Bureau. Washington, DC: U.S. Government Printing Office; 2000.
50. Gold MR, Siegal JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine.* New York: Oxford Univ Pr; 1996:214-46.
51. Genetic Tests and Health Insurance: Results of a Survey. U.S. Congress, Office of Technology Assessment. Washington, DC: U.S. Government Printing Office; 1992.
52. Brown ML, Kessler LG. The use of gene tests to detect hereditary predisposition to cancer: economic considerations. *J Natl Cancer Inst.* 1995;87:1131-6. [PMID: 7674317]
53. Lynch HT, Watson P, Shaw TG, Lynch JF, Harty AE, Franklin BA, et al. Clinical impact of molecular genetic diagnosis, genetic counseling, and management of hereditary cancer. Part I: Studies of cancer in families. *Cancer.* 1999;86:2449-56. [PMID: 10630170]
54. Biesecker BB, Boehnke M, Calzone K, Markel DS, Garber JE, Collins FS, et al. Genetic counseling for families with inherited susceptibility to breast and ovarian cancer. *JAMA.* 1993;269:1970-4. [PMID: 8352830]
55. Lerman C, Croyle R. Psychological issues in genetic testing for breast cancer susceptibility. *Arch Intern Med.* 1994;154:609-16. [PMID: 8129493]
56. Freyer G, Dazard A, Schlumberger M, Conte-Devolx B, Ligneau B, Trillet-Lenoir V, et al. Psychosocial impact of genetic testing in familial medullary-thyroid carcinoma: a multicentric pilot-evaluation. *Ann Oncol.* 1999;10:87-95. [PMID: 10076727]
57. Aarnio M, Mecklin JP, Aaltonen LA, Nyström-Lahti M, Järvinen HJ. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. *Int J Cancer.* 1995;64:430-3. [PMID: 8550246]
58. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer.* 1999;81:214-8. [PMID: 10188721]
59. Boland CR. Hereditary nonpolyposis colorectal cancer. In: Vogelstein B, Kinzler KW, eds. *The Genetic Basis of Human Cancer.* New York: McGraw-Hill; 1998.
60. Medicare provider analysis and review (MEDPAR) of short-stay hospitals. Health Care Financing Administration. Available at www.hcfa.gov/stats/medpar/medpar.htm. Accessed January 2001.