International Journal of Technology Assessment in Health Care, **18:1** (2002), 67–80.

COST-MINIMIZATION ANALYSIS OF GENETIC TESTING VERSUS CLINICAL SCREENING OF AT-RISK RELATIVES FOR FAMILIAL ADENOMATOUS POLYPOSIS

Yamina Chikhaoui
Huguette Gélinas
Quebec Agency for Health Services and Technology Assessment

Lawrence Joseph
Montreal General Hospital

Jean-Marie Lance
Quebec Agency for Health Services and Technology Assessment

Abstract

Objective: Familial adenomatous polyposis (FAP) is a well-known hereditary colorectal cancer-predisposing syndrome. Genetic testing for colorectal cancer risk is now part of standard medical practice, but very little is known about the economic impact of this technology. The aim of this study was to assess, from a healthcare system perspective, the direct costs of two strategies for screening at-risk relatives of FAP patients: clinical screening versus genetic testing for FAP.
Methods: A systematic review of the literature was carried out. Additional information was gathered from experts in research and clinical laboratories and in hospital departments. A decision tree was constructed to compare per-person and per-family costs of the two strategies for screening at-risk relatives of FAP patients. Sensitivity analysis was performed to assess the stability of the model across the full range of plausible values for all key parameters.
Results: According to the decision analysis, with FAP screening starting at puberty, the average screening costs are $3,181 and $2,259 (Canadian dollars), respectively, for the clinical screening and the genetic testing strategies. Genetic screening is cost saving up to a first screening age of 36. Sensitivity analysis shows that the results of the baseline analysis hold across a variety of assumptions concerning the parameter values.
Conclusions: The genetic testing strategy is cost saving relative to the clinical screening alternative. Apart from its lower costs, it is associated with many other benefits. Accordingly, under predefined conditions, predictive genetic testing seems to be the optimal screening strategy for FAP.

Keywords: Familial adenomatous polyposis, Genetic testing, Clinical screening, At-risk relatives, Cost analysis

Familial adenomatous polyposis (FAP) (OMIM: 175,100) is a well-known hereditary form of colorectal cancer (CRC) (12). FAP accounts for approximately 1% of all CRC patients

Table 1. Description and Characteristics of FAP

Incidence	1/6,000–1/13,000
Proportion of all CRCs	0.5–1.0%
Gene	APC
Molecular mechanism	Tumor suppressor
Localization	5q21-22
Penetrance	Almost complete
Predictive genetic testing methods	PTT and other techniques (RPA, SSCP, DGGE)
Main feature	Polyps (hundreds to several thousand)
Clinical features	Weight loss and inanition
	Bowel obstruction or bloody diarrhea
	Ocular CHRPE
	Adenomatous polyps in the upper gastrointestinal tract
	Cutaneous and skeletal features (jaw cysts, sebaceous cysts and osteoma)
Extracolonic cancers	Duodenum, brain, thyroid, and others
Prophylactic surgery	Polypectomy, subtotal colectomy, or total colectomy with protectomy
Follow-up	Flexible sigmoidoscopy or colonoscopy

Abbreviations: APC = adenomatous polyposis coli; CHRPE = congenital hypertrophy of the retinal pigment epithelium; PTT = protein truncation test; RPA = ribonuclease protection assay; SSCP = single-strand conformation polymorphism; DGGE = denaturing gel gradient electrophoresis.

(15). FAP affects about 1 in 10,000 individuals and is nearly 100% penetrant (6;44). Thus, virtually every person who inherits the mutated gene will develop the disease, and when mutations are absent in relatives from mutation-positive families, the risk is returned to the usual rate in the nonmutated population. However, 20% to 25% of FAP cases result from *de novo* mutations and thus occur without a family history of the disease (6). FAP is an autosomal-dominant disease caused by mutations of the adenomatous polyposis coli (*APC*) gene located on chromosome *5q21-22* (7;31;34;38;41). The offspring of an affected individual have a 50% risk of inheriting the altered APC gene. FAP is characterized by numerous colorectal adenomatous polyps (Table 1). One or more polyps will progressively evolve to malignancy in untreated mutated gene carriers. Carcinoma may arise at any age from late childhood through the seventh decade, with a median age at clinical diagnosis of 40 years (12;51).

Recent findings in molecular genetics have led, for the first time in cancer syndromes, to predictive genetic testing of at-risk relatives of FAP patients (7;19;22;28;31;33;38;46;47). The large size of the APC gene and the number of known mutations—more than 300—are not conducive to DNA mutation analysis. However, about 90% of mutations cause premature truncation of the APC protein (26). A test based on this finding (52) detects approximately 80% of truncated APC proteins; thus, this test is positive in about 80% of individuals with FAP. The objective of screening for the presence of colorectal adenomatous polyps is to prevent CRC in asymptomatic at-risk relatives of FAP patients. Early recognition of FAP may allow for timely intervention and improved final outcome (9;10;11;23;54;55;57;64). Conventional clinical screening is intensive and consists of regular bowel examinations and repeated sigmoidoscopies or colonoscopies, beginning at age 10–12 years and continuing to age 50 (1;2;3;4;8;13;21;65).

The use of DNA-based testing for early identification of at-risk family members is recommended by the Agency for Health Care Policy and Research (AHCPR) and the American Academy of Family Physicians (AAFP) (64).

The purpose of this study was to compare, from a healthcare system perspective, the direct costs (per person and per family) of two strategies for screening at-risk relatives of FAP patients: conventional clinical screening and predictive genetic testing for FAP.

METHODS

A systematic review of the literature was carried out. The literature was searched using MEDLINE, CancerLit, Health-STAR, and Current Contents for references published from 1980 to December 2000. Keywords in various combinations were "familial adenomatous polyposis," "hereditary colorectal cancer," "adenomatous polyposis coli gene," "clinical screening," "genetic testing," "familial risk," "cost analysis," "colonoscopy," "mutated gene," and "at-risk relative." We manually identified additional studies through reference lists, review articles, and meeting summaries. Additional information was gathered from experts in research and clinical laboratories and in hospital departments. The target population of this study consisted of persons at-risk for FAP, defined as first-degree relatives (parents, siblings, and offspring) of the proband.

Clinical Screening Strategy

The first-degree relatives of a FAP patient have a 50% risk of inheriting the mutated gene and developing the disease. The asymptomatic at-risk relatives require long-term clinical screening on a regular basis. Since polyposis often starts before puberty, flexible sigmoidoscopy beginning at puberty is recommended as a screening procedure (59;64). When adenomatous polyps (a few or many) become evident, prophylactic surgery—polypectomy, subtotal, or total colectomy—is necessary to prevent CRC.

According to the diagram presented in Figure 1, APC mutation carriers and "no mutation detected" patients require CRC surveillance. This strategy relies on flexible sigmoidoscopy or colonoscopy. Usual clinical practice is to screen annually between the ages of 12 and 25 years, every other year between the ages of 25 and 35 years, and every third year between the ages of 36 and 50 years (1;2;4;37;54). At-risk relatives exit the model when adenomatous polyps are identified. Relatives who have not developed multiple adenomatous polyps on complete bowel examination by the age of 50 are assumed to be unaffected by FAP and exit the model. At-risk relatives who are diagnosed with multiple adenomatous polyps are assumed to be affected and are referred for FAP management (surgery).

Colonoscopy is preferred over flexible sigmoidoscopy because it is now generally believed that colonoscopy is the most sensitive and specific method to identify adenomatous polyps in the colon and rectum (25;30;35;48;54). Although this procedure is relatively more costly, it also has the advantage of allowing polypectomy. Morbidity and mortality related to colonoscopy are not very well documented, but are currently believed to be 0.03%–0.17% and 0.02%, respectively (32). With the current acquired expertise, however, colonoscopy is considered to be a safe procedure and is recommended for CRC high-risk persons (17;23;25;35;43). For this study, the morbidity and mortality rates of colonoscopy were considered as nil. It was also assumed that compliance with the clinical surveillance was the same for the two strategies considered.

Genetic Testing Strategy

Under this strategy, the proband is tested first to guide subsequent testing and screening decisions. Detection of an APC mutation in the proband confers a mutation-known status to the family, which allows testing of the at-risk relatives (49;51;58). At-risk relatives who have the APC mutation require clinical surveillance to detect the phenotypic onset of FAP. Once adenomatous polyps are detected, the person exits the model. At-risk relatives who are tested negative forgo any further screening and exit the model at the time of genetic test results. However, if an APC mutation is not detected in the proband, all the at-risk relatives of the FAP patient require clinical screening (Figures 1 and 2).

Since more than 90% of the mutations in FAP lead to a truncated protein, it has become routine to use the protein-truncated test (PTT) for detecting mutations. When a truncated

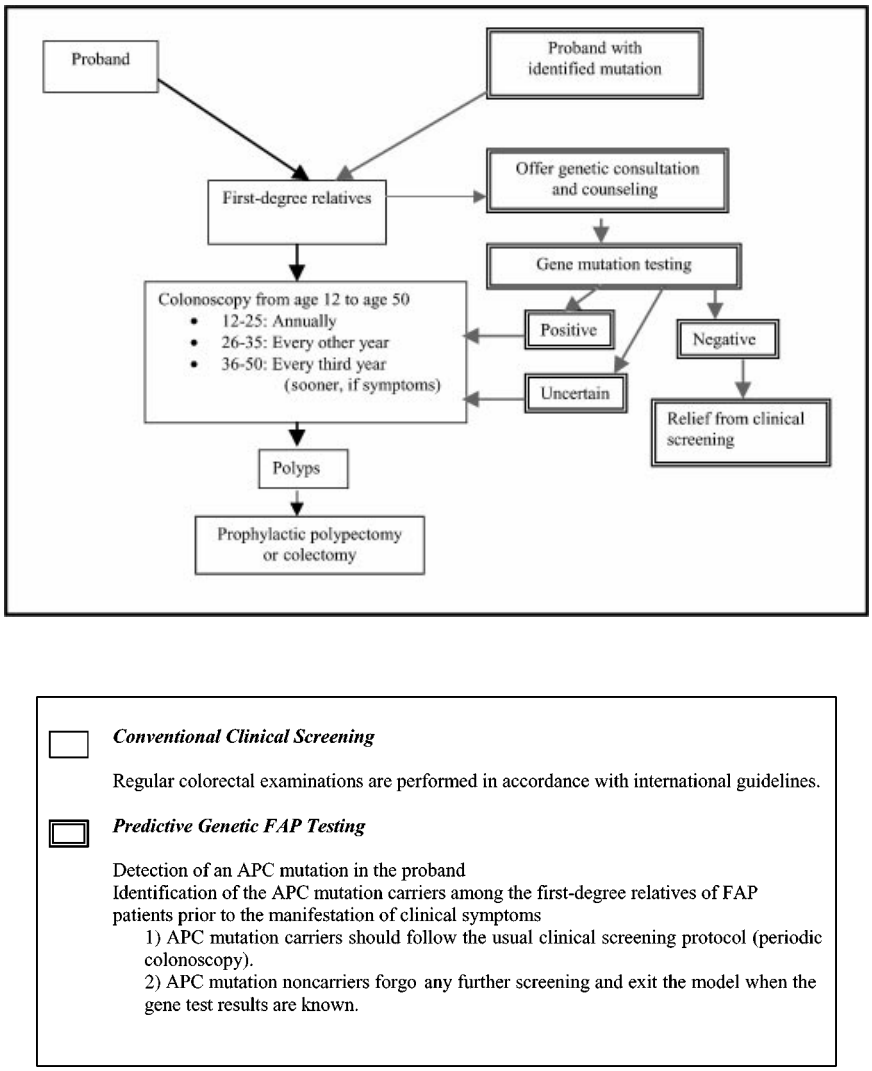


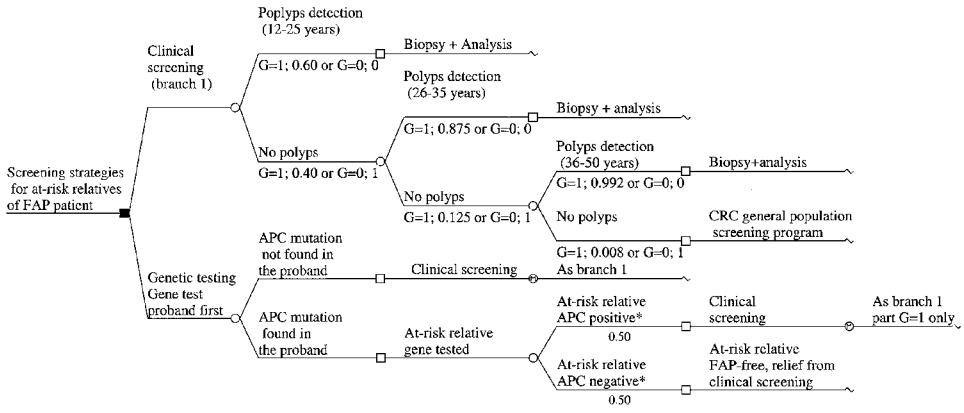
Figure 1. Screening strategies for at-risk relatives of FAP patient.

protein is found, it is possible to localize the mutation to a specific segment of the gene and then use DNA sequencing to precisely identify the mutation. This two-step procedure for FAP genetic testing has become a common practice because it is a simple and less expensive screening technique followed by a definitive test (14;52;58).

When the mutation in a family is already identified from one or more affected members previously investigated, only one test—usually PTT—needs to be performed. A positive result is considered mutation-positive, while a negative finding is a mutation-negative result.

When the mutation in a family is not known, the PTT is useful only when it is positive. If no mutation is detected, the test is noninformative and must not be interpreted as a negative result because the PTT misses about 20% of APC mutations. Moreover, even by combining two or more techniques such as single-strand conformation polymorphism, heteroduplex analysis, or Monoallelic mutation analysis, it is not possible to achieve 100% sensitivity because the mutations may not be in the coding region of the gene or because FAP exhibits locus heterogeneity (29).

https://doi.org/10.1017/S0266462302108075 Published online by Cambridge University Press



□ Decision node representing the point in time at which one of the two strategies is chosen.

_ Chance node representing the point in time at which the patient moves to an outcome based on probability estimates of the outcomes.

_ Markov chains used to model the progression of patients from asymptomatic status (without polyps) to symptomatic status (with colorectal polyps) during colonoscopic examinations.

G=1: The relative inherited the same gene as the proband. The cumulative probability to detect polyps during this period is indicated. A beta (4.3, 1.15) distribution was used to represent the uncertainty in this probability value. This distribution has a mean of approximately 80% and a 95% interval of approximately 50% to 100%.

G=0: The relative did not inherit the mutated gene.

*: These probabilities that are age-dependent multiply the G=1 or G=0 branch. They were extended to ages intermediate to those for whom results are available by constructing a model with a piecewise constant hazard between these ages.

Probability	0.5	0.33	0.285	0.03
Age (years)	12	25	35	50

Figure 2. Decision model used in the cost-minimization analysis of genetic testing versus clinical screening of at-risk relatives for FAP.

Cost Estimates

This economic evaluation is a cost-minimization analysis because both of the strategies use the same clinical screening. The effectiveness of clinical screening, as measured by survival and lives saved, is well documented (5;36;43). The genetic component of the second strategy allows the targeting of high-risk relatives carrying the mutated gene. The cost analysis was performed from the Quebec healthcare system perspective according to the data obtained from experts in research and clinical laboratories, in hospital departments, and from *Régie d'Assurance Maladie du Quebec*, the payer organization (53).

The direct costs for genetic testing, including genetic counseling, were evaluated in the context of a newly developing molecular clinical laboratory performing these tests. Laboratory equipment and supplies, technologist labor time, data interpretation and reporting by the laboratory head, and counseling time, before and after the test, were included. Essential laboratory equipment such as a sequencer was valued using current replacement costs on an annualized basis, using a 5% discount rate and with an assumed working life of 5 years (40). Twenty percent of total testing costs was allocated to overhead.

The APC gene test cost was estimated at $500 for the proband and $250 for at-risk relatives from a mutation-known family.

https://doi.org/10.1017/S0266462302108075 Published online by Cambridge University Press

Table 2. Cost Estimates

Variable	Baseline value
Cost of a colonoscopy	
Equipment	16.75
Professional fees	209.25
Other personnel fees	24.13
Overheads (20%)	50.02
Total	300.15
Cost of colonic biopsies and histologic interpretation	
Polyp exeresis	70.00
Histologic examination	38.00
Laboratory fees	86.00
Overheads (20%)	38.80
Total	232.80
Genetic testing cost	
Proband	
Professional fees	105.00
Genetic counseling (pre and post-test)	125.90
Test (technologist labour and supplies)	185.10
Overheads (20%)	84.00
Total	500.00
Relative	250.00

These costs were estimated according to the data obtained from experts in research and clinical laboratories, in hospital departments, and from the payer organization, RAMQ (*Régie d'assurance maladie du Québec*).

Each component of the clinical management of FAP was evaluated, including the medical specialists' fees, the technicians' and nurses' salaries, and the procedure (colonoscopy, polypectomy) costs. A 5% annual discount rate was applied to the costs of each subsequent procedure following the baseline endoscopy. Recurrent inputs, medical and surgical supplies, and the use of the colonoscope were evaluated on an annualized basis, using a 5 year working life. Twenty percent of the total surveillance costs for each procedure was allocated to overhead, accounting for administrative and support services, utilities, and cost for use of the hospital space.

The costs for colonoscopic biopsies and histologic interpretation include the endoscopy units' fees for obtaining and handling the biopsy specimens as well as the histopathologic interpretation by the pathologist (Table 2) (45). The model assumes that colorectal biopsy specimens are obtained at the time of diagnosis.

Discounting is used to quantify the magnitude of time-related consumer preferences in paying for goods and services. In this analysis discounting is important because the model spans almost 40 years. A 5% annual discount rate was used, as is standard for cost-effectiveness analyses in health and medicine (16;63); we also used a 3% rate, according to the recommendations of the Washington group (42), in order to compare our study with others.

Baseline estimated costs are listed in Table 2.

Decision Analysis

A decision analysis was performed to determine the least costly management strategy under baseline assumptions. This analysis relied on the creation of a decision algorithm describing the management of the FAP patient and his or her relatives (Figure 2). Diagnostic test results and related management decisions, as well as costs for the screening strategies, were incorporated into the model. The baseline estimates and range of values used for sensitivity analysis in the decision model are listed in Table 3.

Table 3. Baseline Estimates and Range of Values Used in the Decision Model

Variable	Baseline estimates	Range tested
Risk of carrying APC mutation (%)	50	-
Sensitivity of colonoscopy (%)		
Detection of FAP polyps at age 15[a]	50	
Detection of FAP polyps at age 25	60	
Detection of FAP polyps at age 35	95	
Detection of FAP polyps at age 50	100	
Sensitivity of the genetic test in the proband(%)[b]	80	
Number of at-risk relatives in a family	1	3–12
Age of at-risk relative at initiation of screening	12	12–50
Cost of a colonoscopy (CAN $)	300.15	216.56–402.15
Cost of colonic biopsies and histological interpretation (CAN $)	232.80	145.20–268.80
Cost of genetic testing for APC mutation in proband (CAN $)	500.00	200.00–700.00
Cost of genetic testing of each relative (CAN $)	250.00	-
Frequency of colonoscopy screening[c]	1/2/3	1/1/1–2/3/5
Discount rate (%)	5	0–3

[a] A beta (4.3, 1.15) distribution was used to represent the uncertainty in this probability value. This distribution has a mean of approximately 80% and a 95% interval of approximately 50% to 100%.
[b] These probabilities were extended to ages intermediate to those for whom results are available by constructing a model with a piecewise constant hazard between these ages.
[c] The first number refers to age range of 12–25 years; the second to 26–35; the third to 36–50, and the value refers to the frequency of the colonoscopic examination during each period.

All analysis was carried out using customized functions of the Splus statistical programming language (version 5.0 for UNIX; MathSoft, Seattle, WA). A Markov model with age-dependent probabilities was used to evaluate the costs under both strategies. Using this model, the mean and the 95% range of costs were calculated for each arm of the decision tree by backfolding the tree, as per the usual steps dictated by decision analysis.

Costs for typical families were calculated using an assumed age structure for families of size 3 through 12. For the clinical screening arm, this was calculated as the simple sum of the costs for the individuals in each family. Total family costs for the genetic testing arm were calculated similarly, except that the initial genetic screening of the index case needs to be carried out only once per family, and the probability of knowing the mutation result from the index case screen remains fixed for all family members.

Sensitivity Analysis

The model's stability was examined while varying baseline assumptions over a range of probability and cost estimates. One-way sensitivity analyses were performed on variables that are within the control of those responsible for the screening program.

RESULTS

Decision Analysis

When FAP screening starts at puberty, the average screening costs are $3,181 ($533–4,104) and $2,259 ($750–4,664), respectively, for the conventional clinical screening and the genetic testing strategies.

Genetic screening is cost saving up to a starting age of 36 years (Figure 3). Since the probability of having undetected FAP decreases with age, the extent of cost savings is dependent on the initial age at which screening starts. At age 12, for example, the average cost of clinical screening is $3,180.95 (95% confidence interval [CI] for an individual:

https://doi.org/10.1017/S0266462302108075 Published online by Cambridge University Press

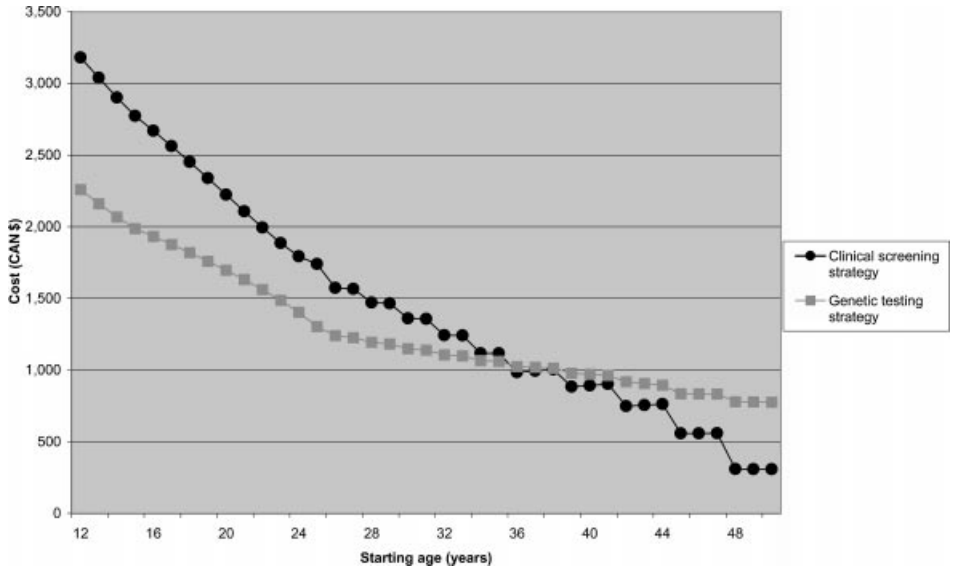


Figure 3. Average lifetime cost per at-risk relative according to age at first screening.

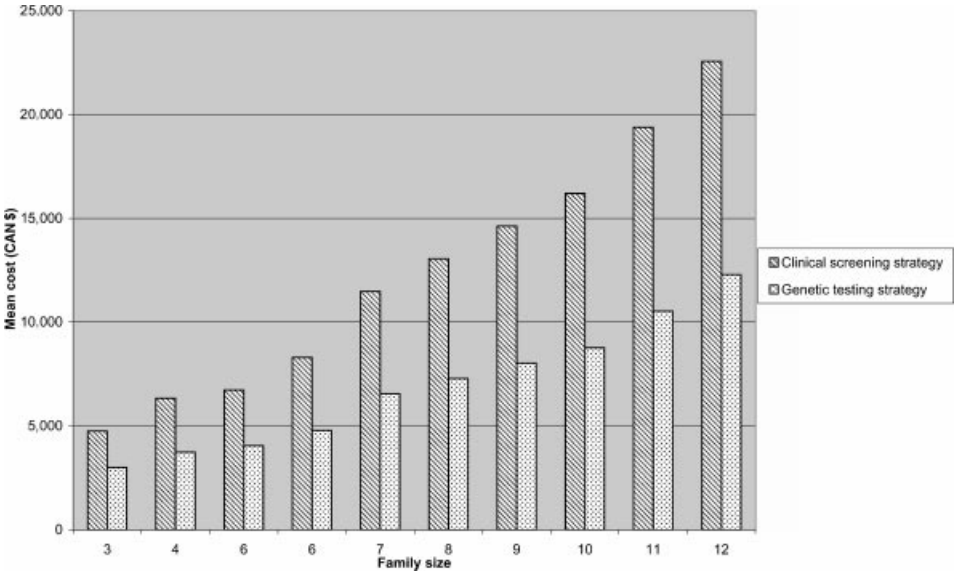


Figure 4. Average lifetime cost per at-risk family according to family size.

$532.95–4,103.90), while the average cost in the genetic screening arm is $2,259.23 (95% CI: $750.00–4,664.43). The average savings per person screened with initial screening at age 12 are thus $921.72. With an initial screening age of 20, however, this average savings reduces to $526.84, and by age 30 it is further reduced to $211.67. Finally, at age 36, clinical screening becomes the path of lesser cost, but by only $36. This advantage increases to $468.21 by age 50.

Genetic screening is cost saving regardless of the family size (Figure 4). The cost savings increase with family size. However, since genetic screening is age-dependent, the screening of young families will result in larger cost savings than screening of older families.

https://doi.org/10.1017/S0266462302108075 Published online by Cambridge University Press

For a pedigree of six at-risk relatives, which is considered a typical family size in Quebec, the genetic testing strategy yields a cost saving of $3,511.

Sensitivity Analysis

The mean cost differentials observed are in favor of the genetic screening strategy up to a starting age of 36 (Figures 5–9). The results of the baseline analysis hold across a variety of assumptions concerning the parameter values.

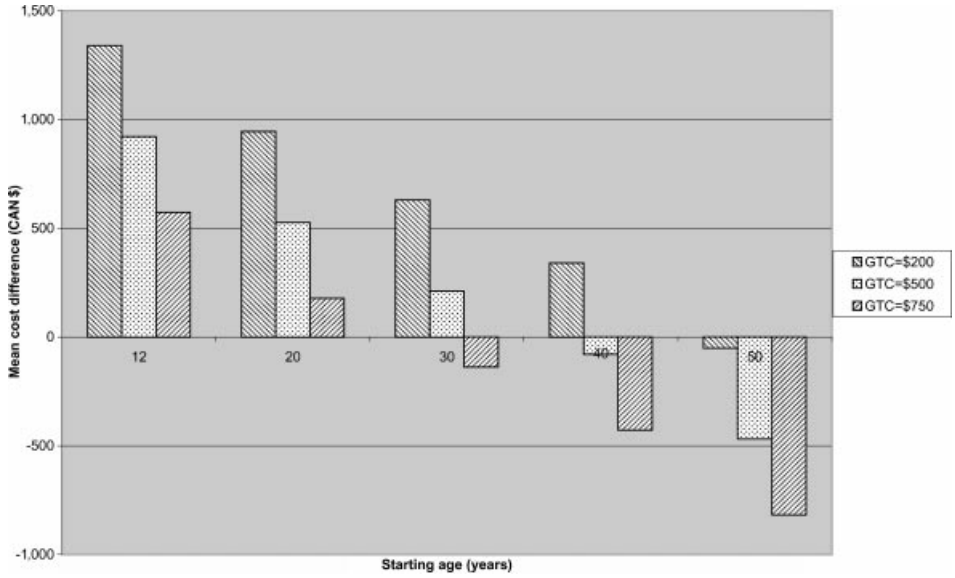


Figure 5. Sensitivity analysis: Mean cost differential between the two screening strategies according to the genetic test cost (GTC).

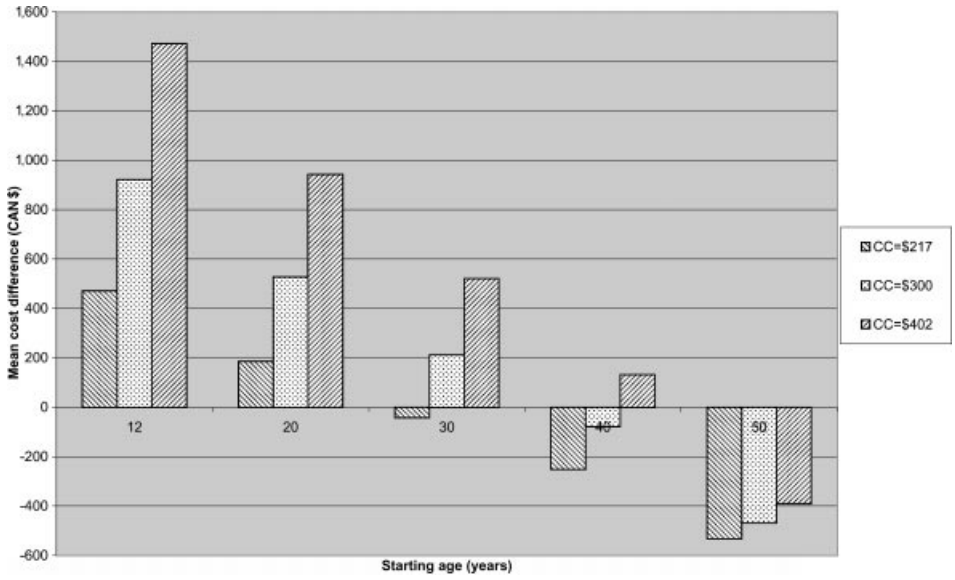


Figure 6. Sensitivity analysis: Mean cost differential between the two screening strategies according to the colonoscopy cost (CC).

https://doi.org/10.1017/S0266462302108075 Published online by Cambridge University Press

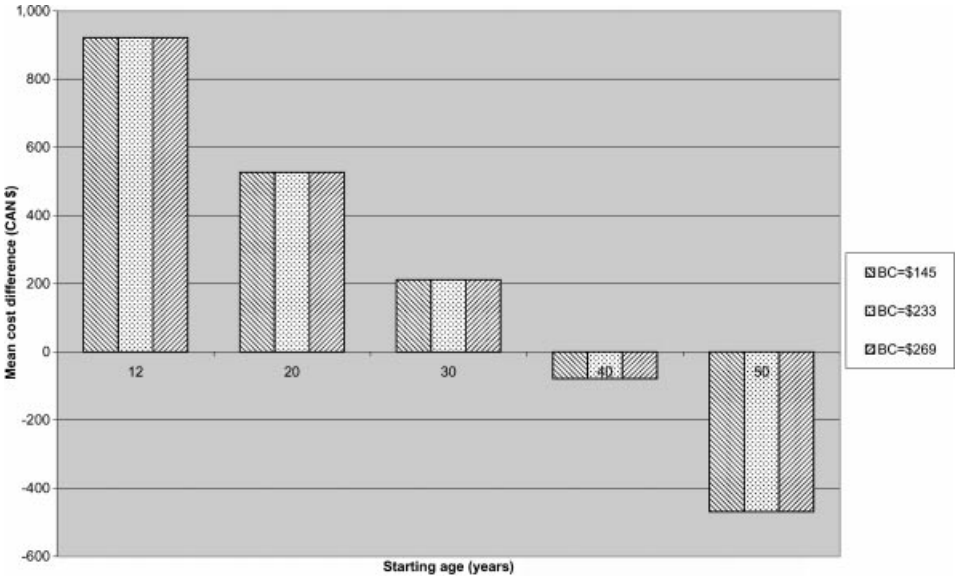


Figure 7. Sensitivity analysis: Mean cost differential between the two screening strategies according to the biopsy cost (BC).

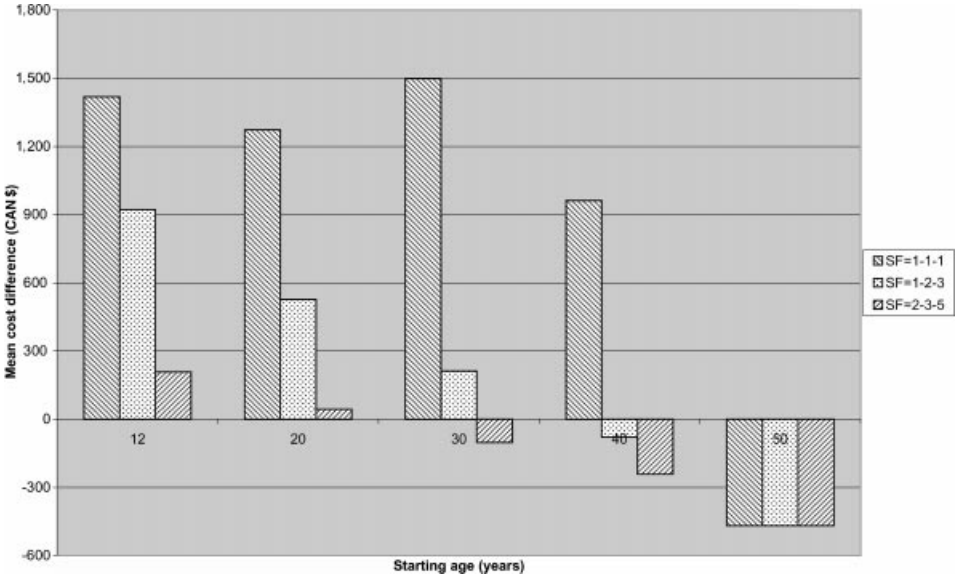


Figure 8. Sensitivity analysis: Mean cost differential between the two screening strategies according to the surveillance frequency (SF).

DISCUSSION

In this cost-minimization study, it was implicitly assumed that the two screening strategies were equally effective in detecting adenomatous polyps, and thus in preventing colorectal cancer mortality.

Similar to the results obtained by other investigators (3;21), our results suggest that the genetic strategy can reduce the cost of the follow-up of at-risk relatives of FAP patients. However, our results show that genetic screening is cost-saving only up to age 36. Beyond

https://doi.org/10.1017/S0266462302108075 Published online by Cambridge University Press

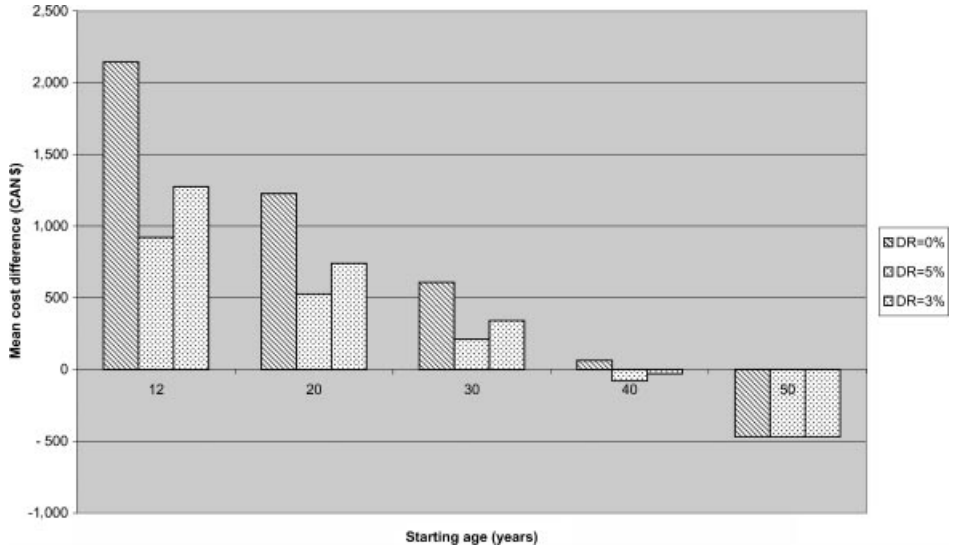


Figure 9. Sensitivity analysis: Mean cost differential between the two screening strategies according to the discount rate (DR).

this age, the direction of the savings is reversed. These savings are achieved by identifying at-risk individuals who are not carrying the APC gene mutation detected in the proband. These persons are freed from unnecessary repeated colonoscopic examinations between the ages of 12 and 50 years. When a mutation is detected in a FAP patient, his or her first-degree at-risk relatives (parents, siblings, and offspring) may have a wide range of ages. We simulated this by varying the age at which an at-risk relative begins screening to determine the least costly FAP screening strategy. The cost savings due to genetic testing decrease as the starting age of the at-risk relative increases until 36 years. At this age, genetic screening becomes more expensive than clinical screening (Figure 3). However, genetic screening is cost saving regardless of the family size (Figure 4), across all the typical family structures tested.

Our model shows that cost savings are age-dependent, since the probability of having the mutation and being symptom-free at age 12 is approximately 50%; this probability decreases with age, conditional on not yet being detected at a future age.

Variations in the costs of the genetic test, the colonoscopy, the biopsy, the surveillance frequency, and the discount rate parameters used to examine the robustness of the model did not change the model's results. All of the mean cost differentials were in favor of the genetic screening strategy up to age 36 (Figures 5–9).

APC mutation carriers also require surveillance for extracolonic neoplasms and other clinical manifestations, such as congenital hypertrophy of the retinal pigment epithelium. The related costs are saved for the mutation noncarriers. Furthermore, the cost-minimization analysis was performed from the perspective of a healthcare system, and thus all personal and indirect costs, such as loss of productivity of patients and accompanying persons during each clinic visit for the colonoscopy, were not included. All of these costs would be saved for noncarriers under the genetic testing strategy.

As a precancerous syndrome, FAP constitutes a model for cancer prevention (20;56;60). Prophylactic surgery in affected individuals eliminates the risk of colon or colorectal cancer, depending on the type of surgery performed. Subsequent screening of the rectum and for other extracolonic manifestations associated with FAP is part of the follow-up of FAP patients. Clinical screening ensures that at-risk relatives of FAP patients benefit from early diagnosis and treatment. Genetic testing allows targeting the follow-up to only the

https://doi.org/10.1017/S0266462302108075 Published online by Cambridge University Press

mutated-gene carriers identified as high-risk and frees the mutation noncarriers from unnecessary clinical screening.

The existence of several other factors that may affect the choice of the best screening strategy requires further investigation. It will be important to pay attention to misuse of the gene test as reported by Giardiello et al., (29), and to the impact of predictive genetic testing on quality of life and patient preferences for knowing or not knowing their genetic status (18;24;27;39). There is also the possibility that gene test results could influence patient compliance to clinical screening.

A policy decision concerning the use of this technology should take into account its drawbacks, such as noninformative results, psychological distress, social and genetic discrimination, and confidentiality problems (61;62), as well as its potential benefits. These benefits include prognostic information for making timely informed choices, better compliance with medical recommendations for the carriers, early detection and prophylactic surgery, relief of anxiety for noncarriers, and release from unnecessary long-term and intensive follow-up for noncarriers and their children (3;21;50;54;56).

CONCLUSION

The genetic testing strategy is cost saving relative to the conventional clinical screening alternative, especially if the starting age of screening is young and the family size is large. Apart from its lower costs, genetic testing is associated with many other benefits. It reduces diagnostic uncertainty and—for at-risk relatives who have not inherited the mutated gene—relieves anxiety and reduces the need for costly screening procedures. Accordingly, predictive genetic testing appears to be the optimal screening strategy for FAP under predefined conditions.

REFERENCES

1. American Cancer Society. Detection and treatment: Advisory Group on Colorectal Cancer. *Cancer J Clin.* 1997;47:154-160.
2. American Gastroenterology Association. American Gastroenterology Association issues guidelines for colorectal cancer screening. *Am Fam Physician.* 1997;55:2860-2865.
3. Bapat B, Berk T, Mitri A, et al. Cost comparison of predictive genetic testing versus conventional clinical screening for familial adenomatous polyposis. *Gut.* 1999;44:698-703.
4. Bertario L, Arrigoni A, Aste H, et al. Recommendations for clinical management of familial adenomatous polyposis. *Tumori.* 1997;83:800-805.
5. Bertario L, Russo A, Sala P, et al. Survival of patients with hereditary colorectal cancer: Comparison of HNPCC and colorectal cancer in FAP patients with sporadic colorectal cancer. *Int J Cancer.* 1999;80:183-187.
6. Bisgaard ML, Fenger K, Bulow S, et al. Familial adenomatous polyposis (FAP): Frequency, penetrance, and mutation rate. *Hum Mutat.* 1994;3:121-125.
7. Bodmer WF, Bailey CJ, Bodmer J, et al. Localization of the gene of familial adenomatous polyposis on chromosome 5. *Nature.* 1987;328:614-616.
8. Bulow S, Burn J, Neale K, et al. The establishment of a polyposis register. *Int J Colorectal Dis.* 1993;8:34-38.
9. Burt RW. Screening of patients with a positive family history of colorectal cancer. *Gastrointest Endosc Clin N Am.* 1997;7:65-79.
10. Burt RW, Bishop DT, Lynch HT, et al. Risk and surveillance of individuals with heritable factors for colorectal cancer. WHO Collaborating Centre for the Prevention of Colorectal Cancer. *Bull World Health Organ.* 1990;68:655-665.
11. Burt RW, Petersen GM. Familial colorectal cancer, diagnosis and management. In Young GP, Rozen P, Levin B (eds). *Prevention and early detection of colorectal cancer*. Philadelphia: Saunders; 1996:171-194.
12. Bussey HJR. Family studies, histopathology, differential diagnosis, and results of treatment. In *Familial adenomatous polyposis.* Baltimore: Johns Hopkins University Press; 1975:9-17.

13. Byers T, Levin B, Rothenberger D, Dodd GD, Smith RA. American Cancer Society guidelines for screening and surveillance for early detection of colorectal polyps and cancer: Update 1997. *CA Cancer J Clin.* 1997;47:154-160.
14. Cama A, Guanti G, Mareni C, et al. Recommendations for the molecular diagnosis of familial adenomatous polyposis. *Tumori.* 1997;83:795-799.
15. Campbell WJ, Spence RA, Parks TG. Familial adenomatous polyposis. *Br J Surg.* 1994;81:1722-1733.
16. Canadian Coordinating Office for Health Technology Assessment. *Guidelines for economic evaluation of pharmaceuticals*. 2nd ed. Ottawa: CCOHTA; 1997.
17. Canadian Task Force on the Periodic Health Examination. Periodic health examination, 1994 update 2: Screening strategies for colorectal cancer. *Can Med Assoc J.* 1999;150:1961-1970.
18. Codori AM, Petersen GM, Miglioretti DL, et al. Attitudes toward colon cancer gene testing: factors predicting test uptake. *Cancer Epidemiol Biomarkers Prev.* 1999;8:345-351.
19. Cottrell S, Bicknell D, Kaklamanis L, Bodmer WF. Molecular analysis of APC mutations in familial adenomatous polyposis and sporadic colon carcinomas. *Lancet.* 1992;340:626-630.
20. Coughlin SS, Miller DS. Public health perspectives on testing for colorectal cancer susceptibility genes. *Am J Prev Med.* 1999;16:99-104.
21. Cromwell DM, Moore RD, Brensinger JD, et al. Cost analysis of alternative approaches to colorectal screening in familial adenomatous polyposis. *Gastroenterology.* 1998;114:893-901.
22. Dunlop MG. The case for surveillance of high-risk families. *Eur J Gastroenterol Hepatol.* 1998;10: 229-233.
23. Early DS. Colorectal cancer screening: An overview of available methods and current recommendations. *Southern Med J.* 1999;92:258-265.
24. Eisinger F. Ethics and oncogenetics: How to resolve the contradictions? *Bull Cancer.* 1998;85:246-250.
25. Elwood JM, Ali G, Schlup MM, et al. Flexible sigmoidoscopy or colonoscopy for colorectal screening: A randomized trial of performance and acceptability. *Cancer Detect Prev.* 1995;19:337-347.
26. Foulkes WD, Narod SA. Screening for cancer in high-risk families. *Cancer Treat Res.* 1996;86:165-182.
27. Flanders T, Foulkes WD. Cancers of the digestive system. In Foulkes WD, Hodgson SV, eds. *Inherited susceptibility to cancer: Clinical, predictive, and ethical perspectives*. New York: Cambridge University Press; 1998:153-200.
28. Giardiello, FM. Genetic testing in hereditary colorectal cancer (clinical conference). *JAMA.* 1997;278:1278-1281.
29. Giardiello FM, Brensinger JD, Petersen GM, et al. The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. *N Engl J Med.* 1997;336:823-827.
30. Giardiello FM, Offerhaus JG. Phenotype and cancer risk of various polyposis syndromes. *Eur J Cancer.* 1995;31:1085-1087.
31. Groden J, Thliveris A, Samowitz W, et al. Identification and characterization of the familial adenomatous polyposis coli gene. *Cell.* 1991;66:589-600.
32. Habr-Gama A, Waye JD. Complications and hazards of gastrointestinal endoscopy. *World J Surg.* 1989;13:193-201.
33. Heinimann K, Müllhaupt B, Weber W, et al. Phenotypic differences in familial adenomatous polyposis based on APC gene mutation status. *Gut.* 1998;43:675-679.
34. Herrera L, Kakati S, Gibas L, Pietrzak E, Sandberg AA. Gardner syndrome in a man with an interstitial deletion of 5q. *Am J Med Gen.* 1986;25:473-476.
35. Hunt LM, Rooney PS, Hardcastle JD, Armitage NC. Endoscopic screening of relatives of patients with colorectal cancer. *Gut.* 1998;42:71-75.
36. Jednak MA, Nostrant TT. Screening for colorectal cancer. *Prim Care,* 1998;25:293-308.
37. King JE, Dozois RR, Lindor NM, Ahlquist DA. Care of patients and their families with familial adenomatous polyposis. *Mayo Clin Proc.* 2000;75:57-67.
38. Kinzler KW, Nilbert MC, Vogelstein B, et al. Identification of a gene located at chromosome 5q21 that is mutated in colorectal cancers. *Science.* 1991;251:1366-1370.
39. Kodish E, Wiesner GL, Mehlman M, Murray T. Genetic testing for cancer risk, how to reconcile the conflicts. *JAMA.* 1998;279:179-181.

40. Krahn M, Gafni A. Discounting in the economic evaluation of health care interventions. *Med Care.* 1993;31:403-418.
41. Leppert M, Dobbs M, Scambler P, et al. The gene for familial polyposis coli maps to the long arm of chromosome 5. *Science.* 1987;238:1411-1413.
42. Lipscomb J, Weinstein MC, Torrance GW. Time preference. In Gold MR, Seigel JE, Russell LB, Weinstein MC, eds. *Cost-effectiveness in health and medicine*. New York: Oxford University Press; 1996:214-246.
43. Love RR, Morrissey JF. Colonoscopy in asymptomatic individuals with a family history of colorectal cancer. *Arch Intern Med.* 1984;144:2209-2221.
44. Lynch HT, Fusaro RM, Lynch JF. Cancer genetics in the new era of molecular biology. *Ann N Y Acad Sci.* 1997;833:1-28.
45. Ministère de la Santé et des Services sociaux (MSSS). *Laboratoires de biologie médicale—Mesure de production, Édition 1997–1998*. Québec: Gouvernement du Québec, Équipe ministérielle de soutien des laboratoires; 1997.
46. Miyoshi Y, Nagase H, Ando H, et al. Somatic mutations of the APC gene in colorectal tumors, mutation cluster region in the APC gene. *Hum Mol Genet.* 1992;1:229-233.
47. Nishisho I, Nakamura Y, Miyoshi Y, et al. Mutations of chromosome 5q21 genes in FAP and colorectal cancer. *Science.* 1991;253:665-669.
48. Norfleet RG. Screening for upper gastrointestinal neoplasms in patients with familial adenomatous polyposis and Gardner's syndrome. *Gastroenterology.* 1992;14:95-96.
49. Olschwang S, Laurent-Puig P. Strategy of screening for patients at high risk of colorectal neoplasm. *Gastroenterol Clin Biol.* 1998;22:S40-S43.
50. Petersen GM, Boyd PA. Gene tests and counselling for colorectal cancer risk: Lessons from familial polyposis. *J Natl Cancer Inst Monogr.* 1995;17:67-71.
51. Petersen GM, Slack J, Nakamura Y. Screening guidelines and premorbid diagnosis of familial adenomatous polyposis using linkage. *Gastroenterology.* 1991;100:1658-1664.
52. Powell SM, Petersen GM, Krush AJ, et al. Molecular diagnosis of familial adenomatous polyposis. *N Engl J Med.* 1993;329:1982-1987.
53. RAMQ-Régie d'assurance-maladie du Québec. *Manuel des médecins spécialistes*. Direction des services à la clientèle professionnelle. Mise à jour 52. Août 1998.
54. Read TE, Kodner IJ. Colorectal cancer: Risk factors and recommendations for early detection. *Am Fam Phys.* 1999;59:3083-3092.
55. Rhodes M, Bradburn DM. Overview of screening and management of familial adenomatous polyposis. *Gut.* 1992;33:125-131.
56. Stern H, Lagarde A. Genetics of hereditary colon cancer: A model for prevention. *Can J Surg.* 1998;41:345-350.
57. Thomson JPS. Leeds Castle Polyposis Group Meeting. *Dis Colon Rectum.* 1988;31:613-616.
58. van der Luijt R, Khan PM, Vasen H, et al. Rapid detection of translation-terminating mutations at the adenomatous polyposis coli (APC) gene by direct protein truncation test. *Genomics.* 1994;20:1-4.
59. Vasen HF. When should endoscopic screening in familial adenomatous polyposis be started? *Gastroenterology.* 2000;118:808-809.
60. Vasen HF, van der Luijt RB, Tops C, Slors JF. Molecular genetic tests as a guide to surgical management of familial adenomatous polyposis. *Lancet.* 1996;348:433-435.
61. Vernon SW, Gritz ER, Peterson SK, et al. Correlates of psychologic distress in colorectal cancer patients undergoing genetic testing for hereditary colon cancer. *Health Psychol.* 1997;16:73-86.
62. Watson EK, Mayall ES, Lamb J, Chapple J, Williamson R. Psychological and social consequences of community carrier screening program for cystic fibrosis. *Lancet.* 1992;340:217-220.
63. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel of Cost-effectiveness in Health and Medicine. *JAMA.* 1996;276:1253-1258.
64. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: Clinical guidelines and rationale [errata published in *Gastroenterology.* 1997;112:1060, and 1998;114:625]. *Gastroenterology.* 1997;112:594-642.
65. Winawer SJ, Zauber AG, Gerdes H, et al. Risk of colorectal cancer in the families of patients with adenomatous polyps. *N Engl J Med.* 1996;334:82-87.