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Strategies to Identify the Lynch Syndrome Among Patients With Colorectal Cancer:

A Cost-Effectiveness Analysis

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Abstract

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Background—Testing has been advocated for all persons with newly diagnosed colorectal cancer to identify families with the Lynch syndrome, an autosomal dominant cancer-predisposition syndrome that is a paradigm for personalized medicine.

Objective—To estimate the effectiveness and cost-effectiveness of strategies to identify the Lynch syndrome, with attention to sex, age at screening, and differential effects for probands and relatives.

Design—Markov model that incorporated risk for colorectal, endometrial, and ovarian cancers.

Data Sources—Published literature.

Target Population—All persons with newly diagnosed colorectal cancer and their relatives.

Time Horizon—Lifetime.

Perspective—Third-party payer.

Intervention—Strategies based on clinical criteria, prediction algorithms, tumor testing, or up-front germline mutation testing, followed by tailored screening and risk-reducing surgery.

Outcome Measures—Life-years, cancer cases and deaths, costs, and incremental cost-effectiveness ratios.

Results of Base-Case Analysis—The benefit of all strategies accrued primarily to relatives with a mutation associated with the Lynch syndrome, particularly women, whose life expectancy could increase by approximately 4 years with hysterectomy and salpingo-oophorectomy and adherence to colorectal cancer screening recommendations. At current rates of germline testing, screening, and prophylactic surgery, the strategies reduced deaths from colorectal cancer by 7% to 42% and deaths from endometrial and ovarian cancer by 1% to 6%. Among tumor-testing strategies, immunohistochemistry followed by *BRAF* mutation testing was preferred, with an incremental cost-effectiveness ratio of $36 200 per life-year gained.

Results of Sensitivity Analysis—The number of relatives tested per proband was a critical determinant of both effectiveness and cost-effectiveness, with testing of 3 to 4 relatives required for most strategies to meet a threshold of $50 000 per life-year gained. Immunohistochemistry followed by *BRAF* mutation testing was preferred in 59% of iterations in probabilistic sensitivity analysis at a threshold of $100 000 per life-year gained. Screening for the Lynch syndrome with immunohistochemistry followed by *BRAF* mutation testing only up to age 70 years cost $44 000 per incremental life-year gained compared with screening only up to age 60 years, and screening without an upper age limit cost $88 700 per incremental life-year gained compared with screening only up to age 70 years.

Limitation—Other types of cancer, uncertain family pedigrees, and genetic variants of unknown significance were not considered.

Conclusion—Widespread colorectal tumor testing to identify families with the Lynch syndrome could yield substantial benefits at acceptable costs, particularly for women with a mutation associated with the Lynch syndrome who begin regular screening and have risk-reducing surgery. The cost-effectiveness of such testing depends on the participation rate among relatives at risk for the Lynch syndrome.

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The Lynch syndrome, an autosomal dominant cancer-predisposition syndrome that confers substantial risk for colorectal, endometrial, and other types of cancer, is a paradigm for personalized medicine based on genomic information (1–3). Germline testing (see Glossary) to identify mutations in DNA mismatch repair genes (see Glossary), which are the molecular basis of the Lynch syndrome, permits risk stratification in affected families (4 – 6). Intensive

surveillance and risk-reducing surgery substantially improve outcomes in persons with the Lynch syndrome (7–12), whereas those without their family's Lynch syndrome–associated mutation can have average-risk screening.

Although the Lynch syndrome accounts for only approximately 3% of all cases of colorectal cancer (13–18), screening persons with newly diagnosed colorectal cancer for the Lynch syndrome has been proposed as a means to identify affected families (19). Applying such a policy to the 143 000 new cases of colorectal cancer in the United States each year (20) could yield significant clinical benefit but also incur substantial costs. Previous decision analyses (21–26) suggest that screening persons with colorectal cancer for the Lynch syndrome could be cost-effective. However, these analyses did not consider risk for gynecologic cancer, sex differences, or various age limits for screening. We hypothesized that these factors could strongly influence the effectiveness and cost-effectiveness of strategies to diagnose the Lynch syndrome.

We used decision analytic modeling to explore the clinical and economic consequences of competing strategies for identifying families with the Lynch syndrome, beginning with persons with newly diagnosed colorectal cancer. Our analyses focused on families in aggregate, female or male probands (see Glossary) with cancer, and female or male relatives without cancer. Screening for the Lynch syndrome was considered either for all persons with newly diagnosed colorectal cancer, regardless of age, or only for those younger than a certain age. Our purpose was to identify key variables that merit further clinical research and to inform public policy.

Methods

Appendix 1 (available at www.annals.org) describes our decision analytic model and its data sources. Appendix 2 (available at www.annals.org) lists key concepts related to the Lynch syndrome.

Decision Analytic Model

Persons with newly diagnosed colorectal cancer entered a decision tree that modeled clinical or tumor-testing (see Glossary) strategies; up-front germline testing for mutations in DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) (5, 27); or a referent strategy of no active effort to diagnose the Lynch syndrome, which currently applies to most clinical settings. The population that entered the model included a small subpopulation of persons with the Lynch syndrome, which reflects the prevalence of the Lynch syndrome in the population modeled. A person with colorectal cancer and the Lynch syndrome was labeled a proband.

If a mutation was identified in a proband, relatives were offered single-site germline testing. The sequelae for female and male probands and relatives were modeled in separate Markov subtrees. The major clinical events were a first case of colorectal, endometrial, or ovarian cancer; metachronous colorectal cancer; screening and treatment complications; and death from cancer or other causes. We modeled varying levels of germline testing acceptance and adherence with preventive interventions and varying upper age limits for screening for the Lynch syndrome. A few families in our model had no identifiable mutation but were defined clinically as having the Lynch syndrome because of tumor features and a strong family pedigree that fulfilled the Amsterdam II criteria (28). In the base case, probands entered the model at a mean age of 48 years (15, 26, 29 –33) and relatives at a mean age of 25 years (34). Preventive interventions were offered until age 75 years. Our simulation estimated outcomes until death or age 100 years.

Screening Strategies for the Lynch Syndrome

Tumors associated with the Lynch syndrome usually exhibit microsatellite instability (MSI) (see Glossary), and the absence of a mismatch repair gene product can be demonstrated with immunohistochemistry (IHC) (see Glossary) (6, 35), which can guide germline testing (34). Any strategy for identifying the Lynch syndrome consists of up to 4 phases (Appendix 2): an initial screening; further selection for germline testing, with possible tumor testing by IHC to guide germline testing; germline testing; and site-specific germline testing in relatives at risk, including waves of testing for all relatives with a 50% risk for carrying a mutation (cascade testing).

The clinical criteria for the Lynch syndrome (see Glossary) used in the strategies in our model included the Amsterdam II criteria (36), which were developed to identify families with the classic Lynch syndrome; the revised Bethesda guidelines (37), which were developed to select tumors for testing; and mutation risk-prediction algorithms (MMRpro, PREMM[1,2,6], and MMRpredict; the strategy name implies application of the model with that name) (14, 38 – 40). When clinical criteria were met or clinical algorithm scores suggested a greater than 5% probability of carrying a mutation, phase 2 IHC was performed and then germline testing was offered (for example, "MMRpro/IHC") or germline testing was offered directly (for example, "MMRpro/germline"). Immunohistochemistry was selected as the phase 2 tumor-based test on the basis of clinical practice, which acknowledges its unique attributes as a sensitive and specific test that can also guide which genes to target.

The tumor-testing strategies included MSI testing, IHC, MSI testing and IHC combined, and the addition of *BRAF* mutation testing (see Glossary) to IHC to detect sporadic loss of *MLH1* function. When MSI or IHC results were abnormal, germline testing was offered.

When available, IHC results guided germline testing, with sequential testing of 1, 2, or more genes as required (34). In strategies without IHC, *MLH1* and *MSH2* were tested first and *MSH6* and *PMS2* were tested only if no mutation was found in the first 2 genes.

Clinical Management Programs

The intensive management program for persons with the Lynch syndrome included offering annual colonoscopy to probands after colorectal cancer diagnosis and to relatives with a germline mutation starting at age 25 years. For women, it also included annual gynecologic screening with transvaginal ultrasonography and endometrial sampling, starting at age 35 years, and prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) at age 40 years, after completion of childbearing (34). Colonoscopic surveillance in the Lynch syndrome was assumed to decrease colorectal cancer incidence by 58% and mortality by 76% in the base case (7, 12). Because of the lack of proven benefit for gynecologic screening, this screening was assumed to incur costs but yield no benefit, which represents a bias against screening for the Lynch syndrome. We assumed that TAH-BSO eliminated the risk for endometrial and ovarian cancers (8). This intensive program was also offered to relatives whose status was uncertain because they had declined site-specific germline testing but who had a 50% risk for carrying a mutation; to probands in whom the Lynch syndrome was diagnosed clinically on the basis of Amsterdam II criteria and tumor features, despite the lack of a detectable mutation; and to their first-degree relatives. Persons whose tumors showed abnormal IHC or MSI results but who had normal germline testing results and did not meet Amsterdam II criteria were not offered intensive management of the Lynch syndrome, because such cases most likely represent false-positive results on tumor tests for the Lynch syndrome rather than false-negative results on germline tests. Sensitivity

analyses were performed to address the consequences of screening for gastroduodenal cancer with upper endoscopy every 2 years without proven clinical benefit.

In our model, relatives proven to lack a mutation associated with the Lynch syndrome in their family were offered an average-risk colorectal cancer screening program of colonoscopy every 10 years starting at age 50 years (41). Colonoscopic screening was assumed to decrease colorectal cancer incidence and mortality by magnitudes suggested in the available literature and in previous decision analytic models (42– 45). This program was also offered to probands with the Lynch syndrome who were misdiagnosed as having average risk, all of their relatives, and relatives of probands who declined germline testing (whose status was therefore unknown).

Costs

Costs were derived from published sources and Medicare schedules (Appendix 1).

Model Outputs and Cost-Effectiveness Analyses

Our principal model outputs were life expectancy and costs in 2010 U.S. dollars, discounted by 3% annually (46). Health state utilities are not available for the risk categories we used in the model, such as living with the knowledge that one carries a mutation or choosing not to test and living with uncertainty. Therefore, we did not estimate quality-adjusted life-years. Secondary outputs included number of cancer cases by type; deaths by cause; and, for illustrative purposes, undiscounted life-years.

Analyses were performed from the perspective of a third-party payer by using TreeAge Pro (TreeAge Software, Williamstown, Massachusetts) and Microsoft Excel 2003 (Microsoft, Redmond, Washington), in accordance with published recommendations (47, 48). We compared the various strategies and estimated incremental cost-effectiveness ratios (ICERs), rounded to the nearest $100 (47, 48). Base-case analyses focused on families with a representative number of at-risk relatives, and the results reflect weighted averages for probands as well as mutation-carrying and noncarrier relatives. Because the base-case results represent a weighted average for female and male probands and relatives (in which probands and relatives entered the model at different ages), and these results depend on the number of relatives tested, we also present separate analyses that focus exclusively on female or male probands or relatives. In the base case, we assumed rates of acceptance of germline testing, adherence with screening recommendations, and risk-reduction operations that were consistent with the literature (Appendix Table 1, available at www.annals.org).

Sensitivity Analyses

We performed 1-way sensitivity analyses and threshold analyses and examined varying levels of implementation of the strategies. Upper bounds for the potential benefit of the strategies were explored by assuming 100% acceptance of germline testing, screening, and risk-reducing operations. Institution of an upper age limit for screening for the Lynch syndrome was also explored, and ICERs that compare the more liberal with the more conservative age limits are presented.

We derived distributions of appropriate form (49) for input variables (Appendix Tables 1 and 2, available at www.annals.org) and performed probabilistic sensitivity analyses (Monte Carlo simulation). Stabilization of variances was observed in runs of 500 to 1000 iterations; results for 1000 iterations are presented. These analyses yielded predictions about the optimal strategy under conditions of uncertainty, as a function of willingness to pay, which took incremental comparisons between all strategies into account and considered simple and

extended dominance. Median estimates with 95% CIs and cost-effectiveness acceptability curves (with the referent strategy as a comparator) are also presented.

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Results

Base Case

All strategies reduced cancer incidence and deaths and yielded more life-years per person than the referent strategy (Table 1 and Figure 1). Accounting for incomplete acceptance of germline testing, screening, and prophylactic TAH-BSO, the various strategies reduced incidence of colorectal cancer by 5% to 29% and deaths by 7% to 42%, and incidence of endometrial and ovarian cancer and deaths by 1% to 6% (Table 1). Up-front germline testing in all probands was the most effective strategy. Because of their sensitivity for mutations in each mismatch repair gene, the tumor-testing strategies as a group were more effective than the clinical criteria strategies as a group.

The more effective strategies tended to be more costly (Table 1 and Figure 1). Assuming perfect implementation of all strategies, the tumor-testing strategies were more costly than the clinical criteria strategies, with an ICER of $117 000 per life-year gained for MSI plus IHC with *BRAF* testing compared with Bethesda/germline (Table 1). Up-front germline testing had an ICER of $293 000 per life-year gained.

Among the clinical criteria strategies, MMRpro/germline had an ICER of $41 400 per life-year gained and Bethesda/germline had an ICER of $50 200 per life-year gained. Among the tumor-testing strategies alone, IHC with *BRAF* testing had an ICER of $36 200 per life-year gained and MSI plus IHC with *BRAF* testing had an ICER of $108 000 per life-year gained.

Tumor-Testing Strategies Compared With Clinical Criteria Strategies

As the relative rate of implementation of clinical criteria strategies decreased compared with that of tumor-testing strategies, the tumor-testing strategies became progressively more cost-effective. The ICER of IHC with *BRAF* testing compared with MMRpro/germline was $49 400 per life-year gained when the clinical criteria under MMRpro/germline were not applied to 15% of persons with colorectal cancer who would otherwise have tumor testing.

Differential Effect on Probands and Relatives and the Effect of Sex

Testing showed greater potential benefits for women than for men. Table 2 illustrates the results for MMRpro/ germline, which had an acceptable ICER among the clinical criteria strategies, and IHC with *BRAF* testing, which emerged as the preferred strategy in probabilistic sensitivity analysis. The preferred strategies did not differ by sex.

The clinical benefit of all strategies accrued primarily to relatives with a mutation associated with the Lynch syndrome (Table 2); in particular, the mean life expectancy of female relatives could be increased by up to 1.4 discounted life-years (4.5 undiscounted life-years) if they agreed to germline testing, screening, and TAH-BSO, depending on the strategy, with the most benefit achieved by up-front germline testing. The greater potential benefit for women was attributed to prevention of gynecologic cancer by TAH-BSO and to women having a longer life expectancy than men.

Every strategy had a substantially higher ICER when subsequent management tailored to risk was implemented only for a proband than when it was implemented only for a relative (Table 2). The higher costs for women were attributed to the costs of gynecologic cancer screening and treatment and prophylactic TAH-BSO.

Acceptance of Germline Testing and Preventive Interventions

The clinical benefit of all strategies increased as acceptance of germline testing and preventive interventions increased (Table 2 and Appendix Table 3, available at www.annals.org). In an optimal scenario that assumed universal acceptance of germline testing, screening, and prophylactic TAH-BSO at age 40 years after completion of childbearing, the strategies reduced colorectal cancer incidence by 8% to 47%, death from colorectal cancer by 12% to 68%, endometrial cancer incidence and death by 13% to 71%, and ovarian cancer incidence and death by 12% to 64%. The cost-effectiveness of the strategies improved as the rate of prophylactic TAH-BSO increased (Table 2).

Number and Age of Relatives Tested

The number of relatives tested per proband was a critical variable. All strategies became progressively more cost-effective as more relatives were tested. When 3 relatives were tested, all clinical criteria strategies, IHC, and IHC with *BRAF* testing cost less than $50 000 per life-year gained and the remaining tumor-testing strategies cost less than $60 000 per life-year gained compared with the referent strategy. When 4 relatives were tested, all clinical criteria and tumor-testing strategies cost less than $50 000 per life-year gained compared with the referent strategy.

The preferred strategy in probabilistic sensitivity analysis, IHC with *BRAF* testing, met a cost-effectiveness threshold of $100 000 per life-year gained compared with the referent strategy when 1 relative per proband was tested and a threshold of $50 000 per life-year gained when 3 relatives were tested (Figure 2). When no relatives were tested, the cost of IHC with *BRAF* testing was approximately $140 000 per life-year gained (Figure 2).

As the mean age of tested relatives increased, screening for the Lynch syndrome became progressively less cost-effective. Immunohistochemistry with *BRAF* testing met a cost-effectiveness threshold of $50 000 per life-year gained compared with the referent strategy at a mean age of 55 years but not 60 years (Appendix Table 3).

Upper Age Limit to Screen for the Lynch Syndrome

Instituting an upper age limit for screening for the Lynch syndrome decreased the size of the screened population while increasing the proportion of screened patients with the Lynch syndrome, but at the expense of excluding some older persons with the Lynch syndrome. This tradeoff resulted in increasing ICERs for higher compared with lower age limits (Table 3). For example, instituting an upper age limit of 50 years meant screening only 11% of all persons with newly diagnosed colorectal cancer, among whom the prevalence of the Lynch syndrome increased to 16%, and including 57% of all persons with the Lynch syndrome who presented with colorectal cancer (Table 3).

Applying IHC with *BRAF* testing only to persons aged 50 years or younger who presented with colorectal cancer cost $27 900 per life-year gained compared with the referent strategy. Immunohistochemistry with *BRAF* testing had an ICER of $33 800 per life-year gained with an upper age limit of 60 years versus 50 years, $44 200 per life-year gained with an upper age limit of 70 years versus 60 years, and $88 700 per life-year gained with no age limit versus an upper age limit of 70 years (Table 3).

Additional 1-Way Sensitivity Analyses

As the prevalence of the Lynch syndrome decreased, the cost-effectiveness of all strategies worsened, but not dramatically. For instance, IHC with *BRAF* testing had an ICER of $55 700 per life-year gained compared with the referent strategy if the Lynch syndrome was assumed to account for 1% of colorectal cancer cases. Up-front germline testing achieved an ICER of $49 900 per life-year gained when the cost of germline testing decreased to $150 per gene tested and $99 700 per life-year gained when the cost of germline testing was $400 per gene tested.

Varying individual model inputs in extensive 1-way sensitivity analyses (Appendix Table 3) affected the ICERs between strategies but did not change the global conclusions suggested by our base-case results. Including the economic costs of screening for gastroduodenal cancer without assuming any clinical benefit did not affect the conclusions (Appendix Table 3).

Monte Carlo Simulation

At a threshold of $50 000 per life-year gained, IHC with *BRAF* testing was the optimal strategy in 53% of iterations, MMRpro/germline in 15% of iterations, no testing in 7% of iterations, and other strategies in fewer than 5% of iterations each. At a threshold of $100 000 per life-year gained, IHC with *BRAF* testing was the optimal strategy in 59% of iterations and MSI plus IHC with *BRAF* testing in 26% of iterations.

Compared with that in the referent strategy, a large proportion of the estimated cost-effectiveness ratios of most strategies were within traditional ranges of willingness to pay for a life-year gained (Figure 3 and Appendix Table 4, available at www.annals.org). The median cost per life-year gained by IHC with *BRAF* testing compared with the referent strategy was $39 500 (95% CI, $18 900 to $77 000).

Discussion

Our results suggest that the systematic application of strategies to diagnose the Lynch syndrome among patients with newly diagnosed colorectal cancer could provide substantial clinical benefits at acceptable costs. Such strategies are predicted to provide greater benefits to younger relatives without cancer than to older probands who present with colorectal cancer and greater benefits to women than men. The ultimate benefit and cost-effectiveness of any strategy are predicted to be highly dependent on the number of relatives per proband who have germline testing and take advantage of opportunities for cancer risk reduction.

The number of relatives tested per proband emerged as a key determinant of the cost-effectiveness of all strategies in our model. The reported rates of acceptance of germline testing by relatives at risk for the Lynch syndrome vary widely, ranging from 19% to 75% (50). Predictors of testing include family dynamics, personal beliefs, socioeconomic and educational factors, and comorbid conditions (51–53). Active involvement by dedicated professionals may increase testing rates (54, 55), but optimal strategies for the diffusion and application of genomic information in families need to be designed. Whether physicians have a duty to warn relatives at risk is a question with clinical, ethical, and legal dimensions (56 –58). Our analysis identifies the testing of at-risk relatives as an important focus for future research and public policy initiatives.

Although strategies based on clinical criteria performed relatively well in our model when universally applied, even low rates of failure to apply the clinical criteria made tumor-testing strategies the preferred alternatives. Testing all tumors in pathology laboratories may be more feasible than ensuring widespread application of clinical criteria (32). Some medical

centers have already adopted laboratory-based strategies (59, 60). These approaches do not require clinicians to risk-stratify patients or order specific tumor tests; however, they require clinicians to act on the basis of the results. Whereas discussions about genetic risk and genetic counseling are best handled in specialized clinics, the growing role of genetics in clinical medicine will require primary care clinicians to have ever-greater knowledge of its relevant principles and clinical applications.

Immunohistochemistry with *BRAF* testing, in which IHC tumor staining for mismatch repair gene products is followed by *BRAF* mutation testing of the tumor when *MLH1* staining is absent, emerged as a preferred strategy in our model. This strategy focuses germline testing on the specific genes that probably harbor a mutation and can identify many cases of sporadic colorectal cancer with *MLH1* promoter methylation, making germline testing more efficient. The slight gains in effectiveness by other tumor-testing strategies were achieved at high costs per life-year gained. However, the tradeoff between strategies depended on the specific combinations of test performance characteristics and costs assigned to each test. In settings in which IHC cannot be performed with high sensitivity and specificity (61), substituting or adding MSI testing may represent an effective and cost-effective alternative (62).

Our exploration of an upper age limit for screening for the Lynch syndrome illustrates how to achieve a smaller screening population that includes a larger proportion of persons with the Lynch syndrome but at the expense of not capturing some older persons with the Lynch syndrome. On the basis of our results, screening for the Lynch syndrome up to age 70 years seems reasonable, and screening all persons with colorectal cancer (regardless of age) may also be acceptable, depending on society's willingness to pay. However, we did not directly address the demands for resources and the total budget effects of various age limits. These questions merit further research.

Our results are consistent with those of previous decision analyses (23) that suggest that screening for the Lynch syndrome could be cost-effective and that tumor-testing strategies based on IHC may be preferred. To our knowledge, our study is the first to address the critical issues of risk for gynecologic cancer, detailed exploration of the consequences for relatives compared with probands, sex differences, and upper age limits for screening. We explored strategies that target persons with cancer, rather than population-based screening of young adults (63), because such strategies are currently more viable.

Future developments could influence the strategy of choice. As more families with the Lynch syndrome are identified, the cost-effectiveness of testing in unselected cases of colorectal cancer may diminish, but testing will probably remain cost-effective until most families with the Lynch syndrome have been identified. With substantial decreases in the cost of germline testing, up-front germline testing could become the preferred strategy. Given the fast pace of advances in DNA sequencing, the technical and up-front financial barriers to widespread germline testing for the Lynch syndrome and other diseases may soon be minor compared with the logistical and, in some cases, ethical and legal challenges.

The Lynch syndrome serves as a paradigm for personalized medicine. Our analysis illustrates some general principles. First, we found that the cost-effectiveness of screening for the Lynch syndrome depended on testing a minimum number of at-risk relatives per proband. For scenarios in which the potential benefits of germline testing do not extend predictably beyond probands, which may be the case for multigene testing, the benefits to probands may need to be substantially higher or the testing costs substantially lower than those in our simulation for germline testing to be cost-effective. Second, if disease-related risks are substantially lower than those we modeled, or if the ability to alter the disease

course is poor, then the costs of testing may be unacceptably high compared with the benefits. Finally, applying upper age limits for screening may help optimize the balance among benefit, cost, and resource availability.

The strengths of our analysis include the consideration of multiple clinical and tumor-based strategies, incorporation of gynecologic cancer risk, prediction of global effects for families as well as differential effects for probands versus relatives and women versus men, acknowledgment of the comparatively favorable prognosis of colorectal cancer associated with the Lynch syndrome, consideration of an upper age limit for screening, and exploration of uncertainty by using probabilistic sensitivity analyses.

Our study has limitations. First, we did not model the risk for gastric, urologic, or other types of cancer because the benefits of screening for those types of cancer are uncertain. If such screening incurred substantial costs without clear benefit, the cost-effectiveness of searching for the Lynch syndrome would diminish. Second, we did not explicitly model testing of second-degree relatives who, on the sole basis of information about the proband, had a 25% risk for carrying a mutation; however, we assumed that cascade testing would clarify which of these persons actually had a 50% risk. Third, we did not incorporate health state utilities, because no data were available to inform the health states in which persons spend most of their life, characterized by the degree of knowledge of risk and acceptance of risk-reducing programs. Patient preferences among these health states could affect our results. Fourth, we did not include promoter methylation testing in addition to or as a substitute for *BRAF* mutation testing. Fifth, we did not apply value-of-information analysis to select variables for future research. Finally, our model does not consider adoption, uncertain paternity, lack of knowledge of family history, or the consequences of genetic variants of unknown significance.

In conclusion, widespread colorectal tumor testing to identify families with the Lynch syndrome could yield substantial clinical benefits at acceptable costs. Arguments have been advanced both in favor and against widespread tumor testing to identify probands with the Lynch syndrome (64, 65). Because risk-reducing interventions can have a profound effect on persons who carry mutations associated with the Lynch syndrome, colorectal tumor testing should be viewed as a clinically viable and economically acceptable approach to identify families with the Lynch syndrome. For this approach to be cost-effective, it is imperative to overcome barriers to germline testing and risk-reduction interventions among relatives at risk.

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Glossary

BRAF*mutation testing*	Testing for the V600E mutation in the *BRAF* gene. Presence of the mutation in tumors with absent *MLH1* protein suggests sporadic cancer
Clinical criteria for the Lynch syndrome	Criteria based on family history and pathologic features that help to identify the Lynch syndrome. Includes the Amsterdam II criteria and revised Bethesda Guidelines
Germline testing	Testing of a blood sample to identify mutations by means of sequencing, deletion or duplication analysis, or

	rearrangement analysis. For the Lynch syndrome, germline testing may identify a mutation in a mismatch repair gene
Immunohistochemistry	Uses monoclonal antibodies against proteins to determine protein expression in tissue samples. For the Lynch syndrome, this shows the presence or absence of the protein products of mismatch repair genes
Microsatellite instability	A change of any length in a microsatellite (a DNA region with repeated patterns of base pairs) in a tumor compared with normal tissue, identified by using molecular testing. The presence of instability indicates impairment in the DNA replication and repair system, which may be caused by mutations in mismatch repair genes
Mismatch repair genes	*MLH1* (mutL homolog 1), *MSH2* (mutS homolog 2), *MSH6* (mutS homolog 6), or *PMS2* (postmeiotic segregation increased 2). Mutations in these genes result in impairment of the DNA replication and repair system. These mutations are the molecular cause of the Lynch syndrome
Prediction models	Models that use family history and pathologic features to calculate a probability that a person with colorectal cancer has the Lynch syndrome. Such models include MMRpredict, MMRpro, and PREMM(1,2,6)
Proband	The first person with colorectal cancer and the Lynch syndrome discovered in a family, whose identification allows for subsequent identification and testing of family members
Tumor testing	Testing strategies to examine mismatch repair protein deficiency. Strategies include immunohistochemistry with or without selective *BRAF* testing and testing for microsatellite instability

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Appendix 1: General Model Description

Persons with newly diagnosed colorectal cancer entered a decision tree that modeled the application of clinical criteria or predictive clinical algorithms; tumor testing; up-front germline testing for mutations in DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), which constitute the molecular basis of the Lynch syndrome (5, 27, 66); or a referent strategy of no active effort to diagnose the Lynch syndrome, which currently applies to most clinical settings (Appendix Figure).

With all strategies, if a mutation was identified in a person with colorectal cancer, relatives with a 50% risk for carrying that mutation (such as first-degree relatives) were offered single-site germline testing. Thus, all persons with colorectal cancer due to the Lynch syndrome (probands) and their relatives were assigned to categories that reflected certainty or uncertainty regarding whether they carried a mutation associated with the Lynch syndrome and whether the Lynch syndrome had been clinically diagnosed despite the lack of a detectable mutation. The accuracy of the categorization was determined by the sensitivity and specificity of the strategy and the level of acceptance of germline testing. For the prediction algorithms, the sensitivities reflected detection of *MLH1*, *MSH2*, and *MSH6* mutations.

Each of the categories for female and male probands and female and male relatives led to separate Markov subtrees with 1-year cycles that reflected the natural history of each scenario, with or without risk-reduction interventions. The major clinical events were the development of an initial or metachronous case of colorectal cancer, the development of endometrial or ovarian cancer, treatment of these cases of cancer, complications from treatments or preventive interventions, death from cancer, death related to preventive interventions, or death from other causes. The model was calibrated to reflect the age-specific and overall lifetime risk for these types of cancer in persons with or without the Lynch syndrome, as reflected by data from the SEER (Surveillance, Epidemiology, and End Results) program and published literature (Appendix Table 1) (67– 88). Additional validation of the natural history of persons with the Lynch syndrome against independent sources was not possible, because all available data were used for calibration. However, the age- and cancer-specific risks illustrated in Appendix Table 1 lend confidence that our model calibration was appropriate. We accounted for the more favorable prognosis of colorectal cancer associated with the Lynch syndrome versus sporadic cancer (89). On the

basis of published literature that reported stage at diagnosis, as well as our previous models, persons with cancer detected by screening or surveillance had a more favorable prognosis than those whose cancer was diagnosed after symptomatic presentation.

We modeled varying levels of germline testing acceptance and adherence with preventive interventions. The development of other types of cancer associated with the Lynch syndrome, such as gastric or urinary tract cancer, was not explicitly modeled because of the lack of evidence to support preventive interventions for these types. Some families with the Lynch syndrome have no mutation that can be found with current methods (28), for which our model also accounted.

In the base case, probands entered the model at age 48 years, the mean age of onset of colorectal cancer in the Lynch syndrome (15, 26, 29 –33), and relatives entered the model at age 25 years, the age at which colorectal cancer surveillance is first recommended in the Lynch syndrome (34). Preventive interventions were offered until age 75 years. The Markov processes continued until age 100 years or death.

Base-case values and ranges for variables in the model were derived first from the recent meta-analysis and systematic review performed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative (50). We also conducted supplementary literature searches for inputs that were not included in the EGAPP review (Appendix Tables 1 and 2) (90 –94). Searches of PubMed were conducted in December 2009 for English-language literature published between April 2006 and December 2009 by using the search strategy (“colorectal neoplasms, hereditary nonpolyposis”[MeSH Terms] OR (“colorectal” [All Fields] AND “neoplasms”[All Fields] AND “hereditary”[All Fields] AND “nonpolyposis”[All Fields]) OR “hereditary nonpolyposis colorectal neoplasms”[All Fields] OR (“lynch”[tiab] OR “lynch syndrome”[All Fields]). We reviewed the titles and abstracts of articles that resulted from this search for information about testing validity, colorectal cancer risk, extra-colonic cancer risk, adherence to screening and prevention services, acceptance of germline testing, risk for dying of cancer related to the Lynch syndrome, and cost data. Inputs derived from meta-analyses or systematic reviews were chosen when available. Cancer risk estimates were calculated on the basis of data from the SEER program (86). We repeated our searches in March 2011 and found no major articles that provided data to challenge the assumptions in our analyses.

Costs were derived from published sources and Medicare professional and facility fee schedules (90, 91) and updated to 2010 U.S. dollars by using the medical component of the Consumer Price Index (95). Costs reflected all direct expenses associated with cancer care, screening for the Lynch syndrome, germline testing, preventive interventions, complications, and genetic counseling.

Appendix 2: Key Concepts

The existence of the entity now called the Lynch syndrome was first suggested by the observation of clusters of cancer cases, notably cases of colorectal cancer, diagnosed at a young age in certain families. Remarkable scientific progress has led to the identification of 4 DNA mismatch repair genes; mutations in these genes explain most cases of the Lynch syndrome. Colorectal tumors of patients with the Lynch syndrome often display characteristic features, including MSI and abnormal IHC results for mismatch repair genes.

Because the Lynch syndrome has associated clinical features, tumor characteristics, and germline mutations, various approaches can be considered for identifying persons with the syndrome. Strategies can be constructed that include 1 or more clinical criteria or risk-

prediction algorithms, specific tumor tests, or germline testing. The search for persons with the Lynch syndrome can be considered to have 4 phases (Appendix Figure 1).

First, some form of screening can be performed to include a greater proportion of persons with the Lynch syndrome in the population that will be further evaluated and may ultimately receive germline testing. One component of this screening may be to include only persons with newly diagnosed colorectal cancer. This already-selected group may be further screened by applying clinical criteria or risk-prediction algorithms, performing tumor testing, or instituting age criteria for screening. The cumulative initial screening could be complex if multiple criteria or tests are applied. The selected persons may proceed either to the second phase or directly to the third phase.

Second, the efficiency of germline testing can be enhanced by methods that narrow down the suspect mismatch repair genes in a particular person by inspecting tumor IHC results. If tumor IHC is itself the first screening test, then the first and second phases are the same.

Third, comprehensive testing of the relevant mismatch repair genes can be pursued, which involves full DNA sequencing; testing for deletions or insertions; and, in specific cases, testing for alterations in gene transcription regulatory regions.

Finally, when a specific mutation is detected in a person (for example, a man with early-onset colon cancer), site-specific DNA testing for this particular mutation can be offered to the person's first-degree relatives (for example, the man's brother and sister). If any of these relatives are found to carry the family's Lynch syndrome–associated mutation (for example, the brother), then their additional first-degree relatives can be offered germline testing (for example, the brother's daughter [the niece of the man with early-onset colon cancer]). This is referred to as *cascade testing*.

The Lynch Syndrome

The Lynch syndrome (sometimes referred to as hereditary nonpolyposis colorectal cancer [HNPCC]) is a hereditary cancer-predisposition syndrome with elevated risks for colorectal, endometrial, ovarian, and other types of cancer. It is caused by a germline mismatch repair gene mutation that is inherited in an autosomal dominant manner (96, 97). Mutations in these genes result in mismatch repair protein deficiency, which affects the repair of DNA mismatches that occur during DNA replication. The propagation of such defects can result in abnormal cell growth.

Mutations in the following mismatch repair genes are known to cause the Lynch syndrome: *MLH1* (mutL homolog 1), located on the short (p) arm of chromosome 3 at position 21.3; *MSH2* (mutS homolog 2), located on the short (p) arm of chromosome 2 at position 21; *MSH6* (mutS homolog 6), located on the short (p) arm of chromosome 2 at position 16; and *PMS2* (postmeiotic segregation increased 2), located on the short (p) arm of chromosome 7 at position 22.2 (98).

Clinical Criteria and Prediction Models

Clinical criteria and prediction models may be used to target tumor or germline testing to identify persons with the Lynch syndrome. Clinical criteria include the Amsterdam II criteria, which are specific but not sensitive, and the revised Bethesda Guidelines (developed to select patients for tumor testing for MSI), which are more sensitive but less specific. Researchers have also developed several prediction models to estimate pretest gene mutation probability on the basis of several variables. The clinical criteria and the variables included in prediction models are described here.

Amsterdam II Criteria

The Amsterdam II criteria (36) require that at least 3 relatives, 1 of whom should be a first-degree relative of the other 2, have an HNPCC-associated cancer (colorectal cancer or endometrial, small bowel, ureter, or renal pelvic cancer); at least 2 successive generations should be affected; the cancer should be diagnosed in at least 1 of the relatives before age 50 years; familial adenomatous polyposis should be excluded in any patients with colorectal cancer; and tumors should be verified by pathologic examination.

Revised Bethesda Guidelines

According to the Bethesda Guidelines (37), tumors should be tested for MSI in the following situations: colorectal cancer diagnosed in a patient who is younger than 50 years; presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age; colorectal cancer with the high level of MSI histology diagnosed in a patient who is younger than 60 years; colorectal cancer diagnosed in 1 or more first-degree relatives with an HNPCC-related tumor, with 1 such case being diagnosed in a person younger than 50 years; or colorectal cancer diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

MMRpredict

In the MMRpredict model (14), variables investigated as possible predictors of mismatch repair gene defects for the first stage include patient age at onset, sex, differentiation of the tumor (well, poor, or moderate), histology (standard mucinous), location of the tumor (right or left side), and other synchronous or metachronous tumors (no or yes). For first- and second-degree relatives, variables include colorectal cancer (no, yes and diagnosed at age <50 years, or yes and diagnosed at age ≥50 years) and number of relatives with colorectal cancer, endometrial cancer (no, yes and diagnosed at age <50 years, or yes and diagnosed at age ≥50 years) and number of relatives with endometrial cancer, gastric cancer (no, yes and diagnosed at age <50 years, or yes and diagnosed at age ≥50 years) and number of relatives with gastric cancer, kidney cancer (no, yes and diagnosed at age <50 years, or yes and diagnosed at age ≥50 years) and number of relatives with kidney cancer, and any other cancer (no, yes and diagnosed at age <50 years, or yes and diagnosed at age ≥50 years) and number of relatives with any other cancer.

MMRpro

The MMRpro model (99) has the following inputs for each counselee and each first- or second-degree relative: exact relation to the counselee, colorectal cancer status (affected or unaffected) and age at diagnosis (in years) if affected, endometrial cancer status and age at diagnosis if affected, and current age or age at last follow-up if unaffected; result of MSI testing (instability present or not present) or IHC staining (loss of expression or present), if tumor is available; and result of previous germline testing of *MLH1*, *MSH2*, or *MSH6* (positive or not found). Any input can be left unspecified if not available, with the exception of relation to the counselee.

PREMM(1,2,6)

In the PREMM(1,2,6) model (14, 39, 96, 97), the variables related to the proband are presence and age at diagnosis of colorectal cancer and number of cases (0, 1, 2, or more) of colorectal, endometrial, or other Lynch syndrome–related cancer (including cancer of the stomach, small intestine, pancreas, bile ducts, ovaries, urinary tract [kidney or ureter], brain [glioblastoma multiforme], or sebaceous glands). The variables related to the proband's family members are number of relatives with colorectal, endometrial, or other Lynch syndrome–related cancer; minimum age at diagnosis for each case of cancer in the family;

presence of a relative with more than 1 Lynch syndrome–associated cancer; and degree of relationship to the proband (limited to first- or second-degree relative).

Tumor Testing

Any of the tumor-testing strategies described here may be used to examine mismatch repair protein deficiency.

IHC

Immunohistochemistry uses monoclonal antibodies against the MMR proteins to determine mismatch repair protein expression in tissue samples. Because the mismatch repair proteins form complexes (*MLH1–PMS2* heterodimer and *MSH2–MSH6* heterodimer), losing expression in 1 mismatch repair protein sometimes results in loss of expression in the partner protein (100). By showing loss of expression of specific proteins, IHC can guide germline testing. For example, IHC that shows loss of expression of *MSH2* and *MSH6* but not *MLH1* and *PMS2* would suggest germline testing of only the *MSH2* gene first and then of the *MSH6* gene if no mutations are found in *MSH2* (101).

BRAF Testing

Sporadic loss of MLH1 protein expression may result from hypermethylation in the *MLH1* gene promoter. To help distinguish between colorectal cancer associated with the Lynch syndrome and sporadic cancer, *BRAF* (V600E) mutation testing may be used. This mutation is frequently present in sporadic colorectal cancer with *MLH1* hypermethylation. Therefore, tumors that show loss of MLH1 protein but neither *BRAF* V600E mutations nor hypermethylation are suspected of being associated with the Lynch syndrome (62).

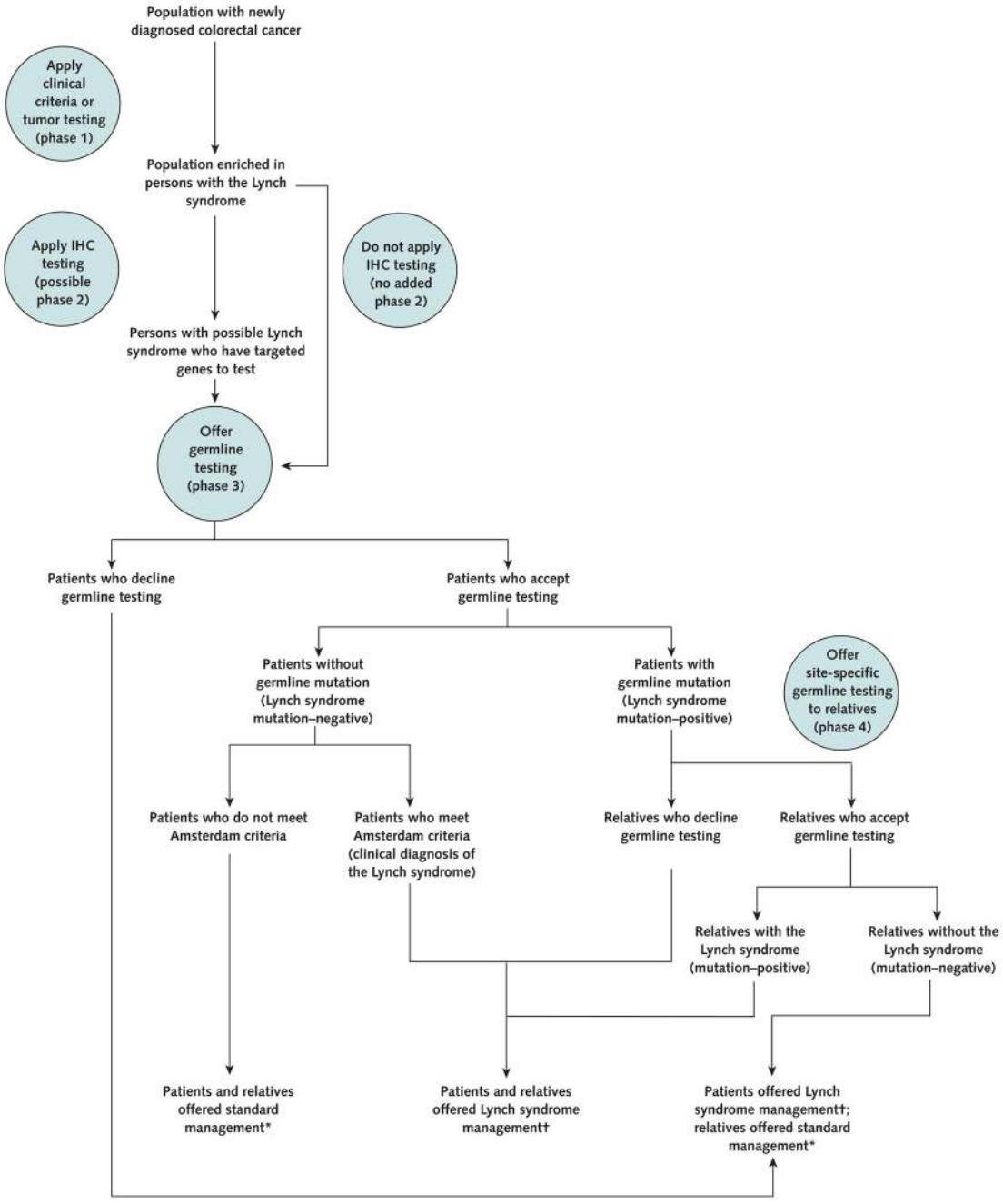
Testing for MSI

Molecular testing of tumor samples for MSI indicates impairment in the DNA replication and repair system, which may have resulted from mismatch repair protein deficiency (62, 102). Microsatellites are segments of DNA with repeated base pair patterns, such as TA repeated 20 times. In the presence of mismatch repair deficiency, daughter cells may harbor different repeat lengths at this microsatellite, such as 18 or 24 repeats. The National Cancer Institute recommends testing specific markers (such as *D2S123*, *D5S346*, *D17S250*, *BAT25*, and *BAT26*) to determine the presence of MSI, or “a change of any length due to either insertion or deletion of repeating units, in a microsatellite within a tumor when compared to normal tissue” (103). Instability is considered high-level when found in more than 30% of the markers and low-level when found in fewer than 30% of the markers. Microsatellites are considered stable in the absence of microsatellite alterations.

Germline Testing

Loss of mismatch repair protein expression may result from inherited mutations in the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*). Germline testing of a blood sample can identify mutations through sequencing, deletion or duplication analysis, or rearrangement analysis. When a specific mutation is identified in a proband, subsequent germline testing can focus on identifying the same mutation in that single site among relatives.

Appendix Figure



Model schematic of the strategies to identify persons with the Lynch syndrome and the management options based on risk stratification

IHC = immunohistochemistry.

* Includes offering colonoscopy every 10 y starting at age 50 y for persons at average risk, with more frequent surveillance after adenoma detection and earlier and more frequent screening on the basis of family history.

† Includes offering annual colonoscopy starting at age 25 y, annual gynecologic screening with transvaginal ultrasonography and endometrial sampling starting at age 35 y, and prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy at age 40 y.

Appendix Table 1

Base-Case Values and Ranges for Variables in the Model

Variable	Base-Case Value	Range in Sensitivity Analyses	Distributions for Monte Carlo Simulations	References
Proband and relative characteristics				
Probability that proband is female	0.5	0 to 1	Not varied	
Age of proband, *y*	48	44 to 50	Normal; mean, 48 (SD, 2)	15, 26, 29–33
Age of relative, *y*	25	25 to 70	Normal; mean, 25 (SD, 2.5)	34
Female relatives, *n*	4	2 to 6	Normal; mean, 4 (SD, 1)	50, 67
Male relatives, *n*	4	2 to 6	Normal; mean, 4 (SD, 1)	50, 67
Disease and gene prevalence				
Prevalence of the Lynch syndrome	0.03	0.01 to 0.05	□ □= 8.73, □= 282.27	50
Prevalence of *MLH1* mutation among persons with the Lynch syndrome who have an identifiable mutation	0.32	Not varied	Not varied	50
Prevalence of *MSH2* mutation among persons with the Lynch syndrome who have an identifiable mutation	0.39	Not varied	Not varied	50
Prevalence of *MSH6* mutation among persons with the Lynch syndrome who have an identifiable mutation	0.14	Not varied	Not varied	50
Prevalence of *PMS2* mutation among persons with the Lynch syndrome who have an identifiable mutation	0.15	Not varied	Not varied	50
Prevalence of no known germline mutations among persons with the Lynch syndrome	0.15	0.05 to 0.25	□ □= 5.31, □= 30.10	Expert opinion
Probability of germline mutation in a relative	0.5	0 to 1	Not varied	Assumed
Clinical criteria				
Amsterdam II criteria				
Sensitivity	0.22	0.13 to 0.67	□ □= 4, □= 14	15, 17, 40

Variable	Base-Case Value	Range in Sensitivity Analyses	Distributions for Monte Carlo Simulations	References
Specificity	0.98	0.97 to 1	□ □= 3218, □= 60	14, 17, 38, 40
MMRpredict model *				
Sensitivity	0.69	0.68 to 0.75	□ □= 32, □= 14	14, 38
Specificity	0.9	0.86 to 0.94	□ □= 1861, □= 193	14, 38
Revised Bethesda Guidelines				
Sensitivity	0.82	0.78 to 0.91	□ □= 28, □= 6	15, 16
Specificity	0.77	0.75 to 0.79	□ □= 945, □= 277	16
MMRpro model *				
Sensitivity	0.89	0.6 to 1	□ □= 3.87, □= 0.48	40
Specificity	0.85	0.6 to 1	□ □= 4.82, □= 0.85	40
PREMM(1,2,6) model *				
Sensitivity	0.9	0.6 to 1	□ □= 3.60, □= 0.40	39
Specificity	0.67	0.6 to 1	□ □= 6.58, □= 3.24	39
Tumor testing				
IHC				
Sensitivity	0.83	0.75 to 0.89	□ □= 94.77, □= 9.41	50
Specificity	0.89	0.68 to 0.95	□ □= 18.21, □= 2.30	50
MSI				
Sensitivity	0.85	0.75 to 0.93	□ □= 59.15, □= 10.44	50
Specificity	0.9	0.87 to 0.93	□ □= 353.47, □= 38.40	50
Mean germline genes tested after IHC, *n*	1.4	1 to 3	Not varied	Expert opinion
Proportion of false-positive IHC results correctly identified as sporadic *MLH1* by *BRAF* testing	0.4	0.1 to 0.7	Not varied	50
Acceptance and adherence probabilities				
Proband accepts germline test	0.9	0.88 to 0.94	□ □= 155, □= 18	68, 69
Relative accepts germline test	0.52	0.34 to 0.69	□ □= 17.96, □= 16.58	50
Probands and relatives with the Lynch syndrome	0.8	0.67 to 0.87	□ □= 526.758, □= 130.242	11, 12, 50, 70–72

Variable	Base-Case Value	Range in Sensitivity Analyses	Distributions for Monte Carlo Simulations	References
adhere to Lynch syndrome screening recommendations				
Probands with family history suggestive of the Lynch syndrome adhere to Lynch syndrome screening recommendations	0.58	0.38 to 0.78	□ □= 18, □= 13	70 and expert opinion
Probands and relatives who seem to be at average risk adhere to average screening recommendations	0.63	0.53 to 0.73	□ □= 58.74, □= 34.50	73
Probands with Lynch-like tumors adhere to Lynch syndrome screening recommendations	0.7	0.5 to 0.9	□ □= 3.68, □= 1.58	Expert opinion
At-risk relatives untested for the Lynch syndrome adhere to Lynch syndrome screening recommendations	0.5	0.4 to 0.6	□ □= 12.50, □= 12.50	Expert opinion
Screening				
Age to start screening average-risk relative for colorectal cancer, *y*	50	40 to 60	Normal; mean, 50 (SD, 2.5)	41
Fraction of colonoscopies with lesion removal	0.4	0.2 to 0.6	□ □= 4.27, □= 6.40	Expert opinion
Colonoscopy complications				
Bleeding	0.0016	0.0011 to 0.0021	□ □= 28.40, □= 17720.93	74, 75
Perforation	0.00085	0.00033 to 0.00330	□ □= 0.32, □= 377.14	74–78
Death	0.000064	0.00005 to 0.00014	□ □= 2.56, □= 39994.88	74, 76, 78
Age to stop screening for colorectal or gynecologic cancer, *y*	75	Not varied	Not varied	41
Risk-reducing surgery and complications				
Subtotal colectomy				
Accepted by proband with the Lynch syndrome	0.01	0.00 to 0.04	□ □= 3, □= 271	11, 50
Accepted by relative with the Lynch syndrome at diagnosis of colorectal cancer	0.03	0.00 to 0.04	□ □= 7, □= 235	11
Death rate	0.01	0.004 to 0.020	□ □= 3.96, □= 392.04	79–82
TAH-BSO				

Variable	Base-Case Value	Range in Sensitivity Analyses	Distributions for Monte Carlo Simulations	References
Accepted by proband with the Lynch syndrome	0.19	0.10 to 0.30	□ □ = 61, □ = 254	8
Accepted by relative with the Lynch syndrome	0.18	0.03 to 0.25	□ □ = 138, □ = 642	8, 11, 71, 83–85
Death rate	0.0003	0.0002 to 0.0004	□ □ = 2, □ = 6681	50
Probability of developing colorectal cancer				
With average risk				
Women	Age-specific and calibrated (e.g., 2.5% by age 70 y)	Varied within =20% of base-case value	Multiplied by factor with normal distribution; mean, 1 (SD, 0.1)	86
Men	Age-specific and calibrated (e.g., 3% by age 70 y)	Varied within ±20% of base-case value	Multiplied by factor with normal distribution; mean, 1 (SD, 0.1)	86
With the Lynch syndrome				
Women	Age-specific and calibrated (e.g., 46% by age 70 y)	Varied within ±20% of base-case value	Multiplied by factor with normal distribution; mean, 1 (SD, 0.1)	3, 86
Men	Age-specific and calibrated (e.g., 54% by age 70 y)	Varied within ±20% of base-case value	Multiplied by factor with normal distribution; mean, 1 (SD, 0.1)	3, 86
Relative risk for colorectal cancer (compared with no screening)				
With average risk				
Adheres to average-risk screening recommendations	0.3	0.2 to 0.6	Log-normal; □ = −1.20, □ = 0.28	42–45
Adheres to Lynch syndrome screening recommendations	0.2	0.1 to 0.3	Log-normal; □ = −1.61, □ = 0.50	Expert opinion
With the Lynch syndrome				
Adheres to Lynch syndrome screening recommendations	0.42	0.22 to 0.82	Log-normal; □ = −0.87, □ = 0.34	7, 12
Adheres to average-risk screening recommendations	0.9	0.8 to 1.0	Log-normal; □ = −0.11, □ = 0.09	Expert opinion
Probability of probands and relatives with the Lynch syndrome dying of colorectal cancer, by year after cancer diagnosis				
1	0.12872	0.10298 to 0.15446	Not varied	86, 87
2	0.06153	0.04922 to 0.07384	Not varied	86, 87

Variable	Base-Case Value	Range in Sensitivity Analyses	Distributions for Monte Carlo Simulations	References
3	0.04563	0.03650 to 0.05476	Not varied	86, 87
4	0.03301	0.02641 to 0.03961	Not varied	86, 87
5	0.02813	0.02251 to 0.03376	Not varied	86, 87
Probability of dying of sporadic colorectal cancer, by year after cancer diagnosis				
1	0.16875	0.13500 to 0.20250	Not varied	86
2	0.08900	0.07120 to 0.10680	Not varied	86
3	0.06539	0.05231 to 0.07847	Not varied	86
4	0.04585	0.03668 to 0.05502	Not varied	86
5	0.03742	0.02994 to 0.04490	Not varied	86
Relative risk for dying of colorectal cancer after diagnosis (compared with no screening)				
With average risk				
Adheres to average-risk screening recommendations	0.7	0.55 to 0.85	Log-normal, $\mu = -0.36$, $\sigma = 0.15$	42–45, 86
Adheres to Lynch syndrome screening recommendations	0.7	0.55 to 0.85	Log-normal, $\mu = -0.36$, $\sigma = 0.15$	42–45, 86
With the Lynch syndrome				
Adheres to Lynch syndrome screening recommendations	0.56	0.45 to 0.65	Log-normal, $\mu = -0.58$, $\sigma = 0.14$	7, 12
Adheres to average-risk screening recommendations	1	0.9 to 1.0	Log-normal, $\mu = -0.11$, $\sigma = 0.09$	Expert opinion
Probability of woman developing ovarian cancer				
With average risk	Age-specific and calibrated (e.g., 0.8% by age 70 y)	Varied within ±20% of base-case value	Multiplied by factor with normal distribution; mean, 1 (SD, 0.1)	86
With the Lynch syndrome	Age-specific and calibrated (e.g., 7.4% by age 70 y)	Varied within ±20% of base-case value	Multiplied by factor with normal distribution; mean, 1 (SD, 0.1)	50, 86
Probability of dying of ovarian cancer, by year after cancer diagnosis				
1	0.247	0.19760 to 0.29640	Not varied	86

Variable	Base-Case Value	Range in Sensitivity Analyses	Distributions for Monte Carlo Simulations	References
2	0.14741	0.11793 to 0.17689	Not varied	86
3	0.13084	0.10467 to 0.15701	Not varied	86
4	0.10573	0.08459 to 0.12688	Not varied	86
5	0.08016	0.06413 to 0.09619	Not varied	86
Probability of woman developing endometrial cancer				
With average risk	Age-specific and calibrated (e.g., 1.7% by age 70 y)	Varied within ±20% of base-case value	Multiplied by factor with normal distribution; mean, 1 (SD, 0.1)	86
With the Lynch syndrome	Age-specific and calibrated (e.g., 37% by age 70 y)	Varied within ±20% of base-case value	Multiplied by factor with normal distribution; mean, 1 (SD, 0.1)	50, 86
Probability of dying of endometrial cancer, by year after cancer diagnosis				
1	0.077	0.06160 to 0.09240	Not varied	86
2	0.04659	0.03727 to 0.05590	Not varied	86
3	0.02841	0.02273 to 0.03409	Not varied	86
4	0.01871	0.01497 to 0.02246	Not varied	86
5	0.01192	0.00954 to 0.01430	Not varied	86
Probability of dying of all other causes				
Women	Age-specific	Not varied	Not varied	88
Men	Age-specific	Not varied	Not varied	88

IHC = immunohistochemistry; MSI = microsatellite instability; TAH-BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.

*This prediction model has reported sensitivity for *MLH1*, *MSH2*, and *MSH6* mutations.

Appendix Table 2

Base-Case Costs and Ranges for Variables in the Model*

Variable	Base-Case Cost, $	Range in Sensitivity Analyses, $	Distributions for Monte Carlo Simulations		References
			□	□	
Cost of administering clinical criteria†	50	40–60	11.11	0.22	90
Cost of tumor testing					
BRAF testing	110	88–132	13.44	0.12	50

Variable	Base-Case Cost, $	Range in Sensitivity Analyses, $	Distributions for Monte Carlo Simulations		References
			[illegible]	[illegible]	
IHC	280	224–336	31.36	0.112	50
MSI	490	392–588	15.37	0.031	50
Cost of genetic testing and genetic counseling					
Germline test for 1 gene	880	600–1200	19.36	0.022	50
Single-site mutation testing	460	200–475	9.40	0.020	50
Approaching relative to offer genetic testing	110	88–132	13.44	0.122	50
Initial genetic counseling visit	185	148–222	38.03	0.206	50
Follow-up genetic counseling visit	105	84–126	12.25	0.117	50
Cost of screening and complications					
Colonoscopy	645	516–774	41.60	0.06	91
Colonoscopy complications					
Bleeding	6218	4974–7462	17.18	0.003	90, 91
Perforation	10 304	8243–12 365	26.54	0.003	90, 91
Polypectomy and pathology	235	188–282	22.09	0.094	91
Endometrial biopsy	224	179–269	13.94	0.062	91
Transvaginal ultrasonography	110	88–132	13.44	0.012	91
Cost of risk-reducing surgeries					
TAH-BSO	16 348	13 078–19 618	42.76	0.003	92
Subtotal colectomy	14 059	11 247–16 871	31.62	0.002	90, 91
Cost of colorectal cancer care in patients who do not have the Lynch syndrome					
Without screening					
Initial	43 471	34 777–52 165	18.90	0.0004	93
Year 1	3496	2797–4195	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 2	3184	2547–3821	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93

Variable	Base-Case Cost, $	Range in Sensitivity Analyses, $	Distributions for Monte Carlo Simulations		References
			[illegible]	[illegible]	
Year 3	3002	2402–3602	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 4	2904	2323–3485	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 5	2845	2276–3414	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
In year of death	52 440	41 952–62 928	27.50	0.0005	93
With screening					
Initial	38 711	30 969–46 453	14.99	0.0004	93
Year 1	2978	2382–3574	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 2	2801	2241–3361	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 3	2701	2161–3241	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 4	2647	2118–3176	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 5	2615	2092–3138	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
In year of death	50 930	40 744–61 116	25.94	0.0005	93
Cost of colorectal cancer care in patients with the Lynch syndrome					
Without screening					
Initial	38 568	30 854–46 282	14.87	0.0004	93
Year 1	3060	2448–3672	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 2	2839	2271–3407	Not varied in	Not varied in	93

Variable	Base-Case Cost, $	Range in Sensitivity Analyses, $	Distributions for Monte Carlo Simulations		References
			[illegible]	[illegible]	
			sensitivity analyses	sensitivity analyses	
Year 3	2715	2172–3258	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 4	2649	2119–3179	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 5	2610	2088–3132	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
In year of death	51 978	41 582–62 374	27.02	0.0005	93
With screening					
Initial	33 711	26 969–40 453	11.36	0.0003	93
Year 1	2457	1966–2948	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 2	2447	1958–2936	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 3	2439	1951–2927	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 4	2433	1946–2920	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
Year 5	2428	1942–2914	Not varied in sensitivity analyses	Not varied in sensitivity analyses	93
In year of death	49 210	39 368–59 052	24.22	0.0005	93
Cost of cancer care					
Endometrial cancer	31 027	24 822–37 232	15.04	0.0005	92
Ovarian cancer	32 379	25 903–38 855	10.48	0.0003	94

IHC = immunohistochemistry; MSI = microsatellite instability; TAH-BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.

*All costs are in 2010 U.S. dollars.

†Amsterdam II criteria, revised Bethesda Guidelines, or prediction models (MMRpredict, MMRpro, and PREMM[1,2,6]).

Appendix Table 3

One-Way Sensitivity Analyses for IHC With *BRAF* Testing Versus the Referent Strategy*

Variable	Base-Case Value	Value in Sensitivity Analysis	Discounted Incremental Life-Years per Person	Discounted Cost per Life-Year Gained, $
Discount rate	0.03	0	0.64434	19 500
		0.05	0.12597	54 000
Proband and relative characteristics				
Probability that proband is female	0.5	0	0.21525	36 100
		1	0.23448	36 300
Age of proband, *y*	48	44	0.22858	35 900
		50	0.22300	36 400
Age of relative, *y*	25	50	0.15345	42 300
		55	0.13058	48 000
		60	0.10892	55 500
		70	0.07219	77 300
Female relatives, *n*	4	2	0.22110	37 800
		6	0.22737	35 200
Male relatives, *n*	4	2	0.21853	42 000
		6	0.22908	32 500
Disease and gene prevalence				
Probability of germline mutation in a relative of a person with the Lynch syndrome	0.5	0	0.02295	344 000
		1	0.42678	19 600
Prevalence of the Lynch syndrome	0.03	0.01	0.22487	55 700
		0.05	0.22487	32 300
Prevalence of no known germline mutations among persons with the Lynch syndrome	0.15	0.05	0.22951	35 000
		0.25	0.22023	37 500
Tumor-testing strategies				
Sensitivity of IHC	0.83	0.75	0.20319	37 200
		0.89	0.24112	35 500
Specificity of IHC	0.89	0.68	0.22487	39 300
		0.95	0.22487	35 300
Germline genes in IHC, *n*	1.4	1	0.22487	36 000
		3	0.22487	37 100
Proportion of false-positive IHC results correctly identified as sporadic *MLH1* by *BRAF* testing	0.4	0.1	0.22487	36 900
		0.7	0.22487	35 500

Variable	Base-Case Value	Value in Sensitivity Analysis	Discounted Incremental Life-Years per Person	Discounted Cost per Life-Year Gained, $
Acceptance and adherence probabilities				
Proband accepts germline test	0.9	0.88	0.22043	36 400
		0.94	0.23375	35 800
Relative accepts germline test	0.52	0.34	0.20252	46 200
		0.69	0.24501	29 900
Probands and relatives with the Lynch syndrome adhere to Lynch syndrome screening recommendations	0.8	0.67	0.20249	38 200
		0.87	0.23692	35 300
Probands with family history suggestive of the Lynch syndrome adhere to Lynch syndrome screening recommendations	0.58	0.38	0.21868	36 200
		0.78	0.23105	36 200
Probands and relatives who seem to be at average risk adhere to average screening recommendations	0.63	0.53	0.22684	36 100
		0.73	0.22290	36 300
Probands with Lynch-like tumors adhere to Lynch syndrome screening recommendations	0.7	0.5	0.22408	36 200
		0.9	0.22565	36 200
At-risk relatives untested for the Lynch syndrome adhere to Lynch syndrome screening recommendations	0.5	0.4	0.20909	36 400
		0.6	0.24064	36 000
Screening and complications				
Age to start screening average-risk relative for colorectal cancer, *y*	50	40	0.22528	36 300
		60	0.22396	36 200
Fraction of colonoscopies with lesion removal	0.4	0.2	0.22487	34 400
		0.6	0.22487	38 000
Colonoscopy complications				
Bleeding	0.0016	0.0011	0.22487	36 100
		0.0021	0.22487	36 300
Perforation	0.00085	0.00033	0.22487	36 000
		0.0033	0.22487	37 100
Death	0.00006	0.00005	0.22714	35 800
		0.00014	0.21255	38 200
Risk-reducing surgery and complications				
Subtotal colectomy				
Accepted by proband with the Lynch syndrome	0.01	0	0.22495	36 200
		0.04	0.22463	36 200

Variable	Base-Case Value	Value in Sensitivity Analysis	Discounted Incremental Life-Years per Person	Discounted Cost per Life-Year Gained, $
Accepted by relative with the Lynch syndrome at diagnosis of colorectal cancer	0.03	0	0.22492	36 200
		0.04	0.22485	36 200
Death rate	0.01	0.004	0.22506	36 200
		0.02	0.22455	36 200
TAH-BSO				
Accepted by proband with the Lynch syndrome	0.19	0.1	0.22172	36 500
		0.3	0.22871	35 800
Accepted by relative with the Lynch syndrome	0.18	0.03	0.21791	37 100
		0.25	0.22811	35 800
Death rate	0.0003	0.0002	0.22492	36 200
		0.0004	0.22482	36 200
Probability of developing colorectal cancer				
With average risk (woman or man)	Age-specific and calibrated	−20%	0.22481	36 200
		+20%	0.22493	36 200
With the Lynch syndrome (woman or man)	Age-specific and calibrated	−20%	0.18641	45 800
		+20%	0.26111	29 800
Relative risk for colorectal cancer				
With average risk				
Adheres to average-risk screening recommendations	0.3	0.2	0.22446	36 300
		0.6	0.22609	35 900
Adheres to Lynch syndrome screening recommendations	0.2	0.1	0.22527	36 100
		0.3	0.22446	36 300
With the Lynch syndrome				
Adheres to Lynch syndrome screening recommendations	0.42	0.22	0.26291	28 400
		0.82	0.15481	60 500
Adheres to average-risk screening recommendations	0.9	0.8	0.21613	38 300
		1.0	0.23345	34 200
Probability of probands, relatives, and relatives with the Lynch syndrome dying of colorectal cancer	Year-specific and calibrated	−20%	0.18682	44 300
		+20%	0.26012	30 800
Relative risk for dying of colorectal cancer				
With average risk				
Adheres to average-risk screening recommendations	0.7	0.55	0.22459	36 200
		0.85	0.22513	36 100

Variable	Base-Case Value	Value in Sensitivity Analysis	Discounted Incremental Life-Years per Person	Discounted Cost per Life-Year Gained, *$*
Adheres to Lynch syndrome screening recommendations	0.7	0.55	0.22503	36 100
		0.85	0.22471	36 200
With the Lynch syndrome				
Adheres to Lynch syndrome screening recommendations	0.56	0.45	0.24063	33 700
		0.65	0.21227	38 400
Adheres to average-risk screening recommendations	1.0	0.9	0.21598	37 800
		1.0	0.22487	36 200
Probability of woman developing ovarian cancer				
With average risk	Age-specific and calibrated	−20%	0.22482	36 200
		+20%	0.22491	36 200
With the Lynch syndrome	Age-specific and calibrated	−20%	0.22460	36 300
		+20%	0.22513	36 100
Probability of dying of ovarian cancer, by year after diagnosis				
1/2/3/4/5	0.247/0.14741/0.1[illegible]	[illegible]	[illegible]	36 300
	0.29640/0.17689/0.15701/ 0.12682/0.11291			36 100
Probability of woman developing endometrial cancer				
With average risk	Age-specific and calibrated	−20%	0.22484	36 200
		+20%	0.22489	36 200
With the Lynch syndrome	Age-specific and calibrated	−20%	0.22507	36 300
		+20%	0.22466	36 100
Probability of dying of endometrial cancer, by year after diagnosis				
1/2/3/4/5	0.077/0.04659/0.02[illegible]	[illegible]	[illegible]	36 300
	0.09240/0.05590/0.03409/ 0.02246/0.01568			36 000
Relative risk for death from cancer in a woman with the Lynch syndrome who adheres to Lynch syndrome screening recommendations				
Ovarian cancer	1.0	0.9	0.22799	35 700
Endometrial cancer	1.0	0.9	0.23205	35 100
Probability of dying of all other causes				
Women or men	Age-specific and calibrated	−20%	0.23688	34 800
		+20%	0.21474	37 500
Cost of tumor testing, *$*				
BRAF testing/IHC/MSI	110/280/490	88/224/392	0.22487	34 500

Variable	Base-Case Value	Value in Sensitivity Analysis	Discounted Incremental Life-Years per Person	Discounted Cost per Life-Year Gained, $
		132/336/588	0.22487	37 800
Cost of genetic testing and genetic counseling, $				
Germline test for 1 gene/single-site mutation testing	880/460	600/200	0.22487	35 200
		1200/475	0.22487	37 000
Relatives/initial/follow-up	110/185/105	88/148/84	0.22487	36 100
		132/222/126	0.22487	36 300
Cost of screening and complications, $				
Colonoscopy/polypectomy/bleeding/perforation	645/235/6218/10 304	516/188/4974/8243	0.22487	30 500
		774/282/7462/12 365	0.22487	41 900
Endometrial biopsy/transvaginal ultrasonography	224/110	179/88	0.22487	35 100
		269/132	0.22487	37 300
Colonoscopy/upper endoscopy with biopsy (applied only with every other colonoscopy)	645/0	645/362	0.22487	43 500
Cost of risk-reducing surgeries, $				
TAH-BSO	16 348	13 078	0.22487	35 800
		19 618	0.22487	36 600
Subtotal colectomy	14 059	11 247	0.22487	36 200
		16 871	0.22487	36 200
Cost of cancer treatment, $				
Colorectal cancer in year 1				
Patients who do not have the Lynch syndrome, without screening/with screening; patients with the Lynch syndrome, without screening/with screening	43 471/38 711; 38 568/33 711	34 777/30 969; 30 854/26 969	0.22487	37 500
		52 165/46 453; 46 282/40 453	0.22487	34 900
Colorectal cancer in year of death				
Patients who do not have the Lynch syndrome, without screening/with screening; patients with the Lynch syndrome, without screening/with screening	52 440/50 930; 51 978/49 210	41 952/40 744; 41 582/39 368	0.22487	36 800
		62 928/61 116; 62 374/59 052	0.22487	35 600
Endometrial cancer	31 027	24 822	0.22487	36 300
		37 232	0.22487	36 100
Ovarian cancer	32 379	25 903	0.22487	36 200
		38 855	0.22487	36 200

IHC = immunohistochemistry; MSI = microsatellite instability; TAH-BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.

*The referent strategy reflects no active effort to diagnose the Lynch syndrome.

Appendix Table 4

Probabilistic Sensitivity Analyses With 1000 Iterations*

Strategy	Median Discounted Incremental Life-Years per Person (95% CI) vs. Referent Strategy	Median Discounted Cost per Life-Year Gained (95% CI) vs. Referent Strategy, $
Amsterdam/IHC	0.021 (0.003–0.066)	38 200 (18 000–84 100)
Bethesda/IHC	0.088 (0.018–0.189)	33 300 (16 200–64 000)
PREMM/IHC	0.081 (0.015–0.182)	35 800 (17 200–71 600)
MMRpredict/IHC	0.063 (0.013–0.138)	32 600 (15 900–62 400)
MMRpro/IHC	0.081 (0.015–0.175)	32 500 (15 700–63 700)
Amsterdam/germline	0.026 (0.004–0.081)	37 900 (18 300–83 100)
Bethesda/germline	0.107 (0.022–0.233)	36 300 (17 800–69 400)
PREMM/germline	0.098 (0.018–0.220)	39 900 (19 500–85 100)
MMRpredict/germline	0.077 (0.015–0.169)	34 200 (16 700–65 000)
MMRpro/germline	0.098 (0.018–0.214)	34 500 (16 400–68 800)
IHC	0.219 (0.135–0.310)	40 500 (19 200–78 900)
IHC with *BRAF* testing	0.219 (0.135–0.308)	39 500 (18 900–77 000)
MSI	0.226 (0.142–0.319)	47 500 (22 900–98 600)
MSI plus IHC	0.259 (0.164–0.362)	53 200 (26 000–110 900)
MSI plus IHC with *BRAF* testing	0.259 (0.164–0.362)	52 300 (25 800–108 000)
Up-front germline testing	0.293 (0.186–0.410)	81 100 (37 800–201 000)

IHC = immunohistochemistry; MSI = microsatellite instability.

*Assumes distribution for application rate of clinical criteria strategies, with a median of 0.5 and range of 0 –1.

Context

The Lynch syndrome is the most common genetic cause of colorectal cancer.

Contribution

This analysis suggests that it is cost-effective to test everyone with colorectal cancer for mutations associated with the Lynch syndrome and then screen healthy first-degree relatives of persons with cancer who screen positive for the Lynch syndrome.

Caution

Some mutations, relatives, and types of cancer were excluded from the analysis.

Implication

Testing everyone with colorectal cancer for the Lynch syndrome to identify relatives who should be screened seems cost-effective. Testing and counseling should probably occur in specialty clinics, but because patients whose relatives have had colorectal cancer may ask whether they can undergo testing, nonspecialty clinicians should understand the concepts and processes involved.

—*The Editors*

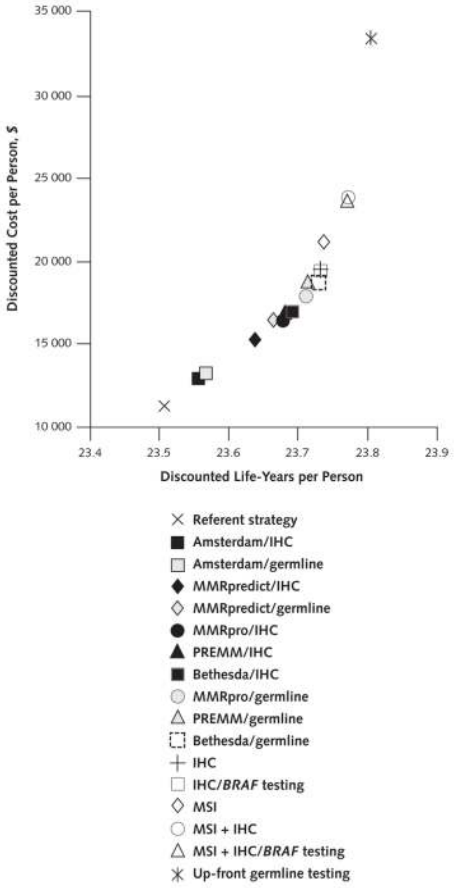


Figure 1. Discounted life-years and costs per person for all strategies in the base case

When comparing 2 strategies, the one toward the right of the graph is more effective and the one toward the top of the graph is more costly. Tumor-testing strategies were more effective and more costly than clinical criteria strategies. The slope between 2 strategies represents the incremental cost-effectiveness ratio, with steeper slopes reflecting higher costs per life-year gained. The referent strategy reflects no active effort to diagnose the Lynch syndrome. IHC = immunohistochemistry; MSI = microsatellite instability.

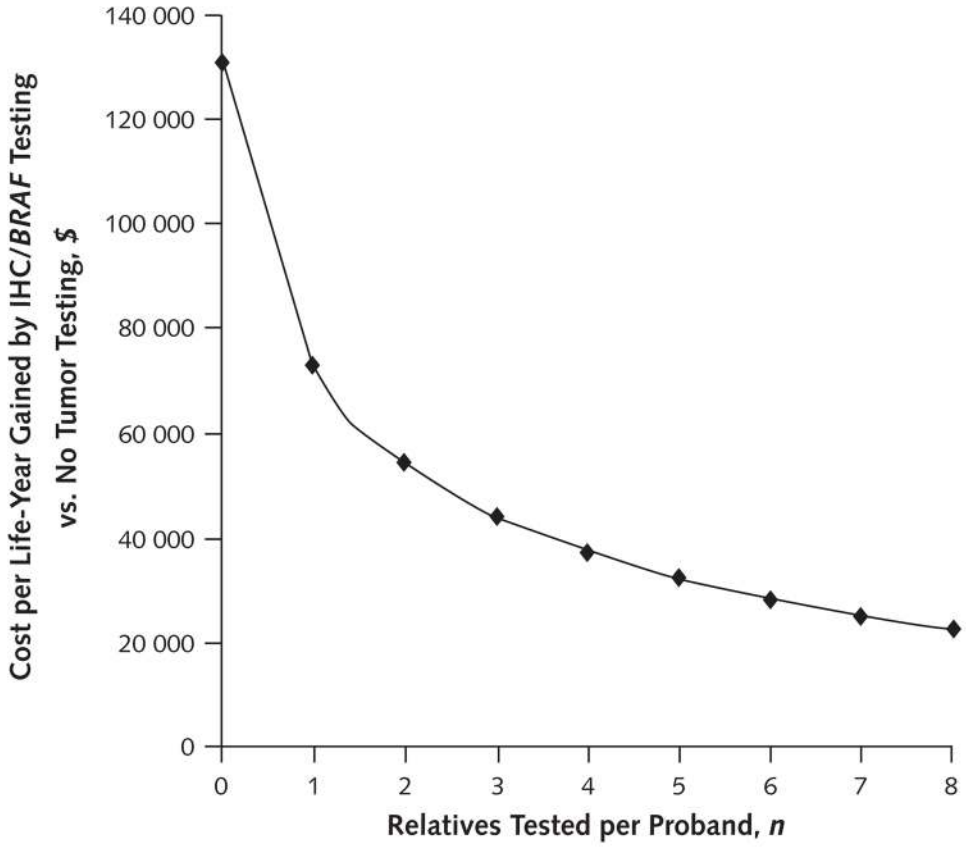


Figure 2. Sensitivity analysis of number of relatives tested per proband

Among tumor-testing strategies, IHC with *BRAF* testing had an incremental cost-effectiveness ratio <$50 000 per life-year gained when 3 relatives but not when 2 relatives were tested per proband. IHC = immunohistochemistry.

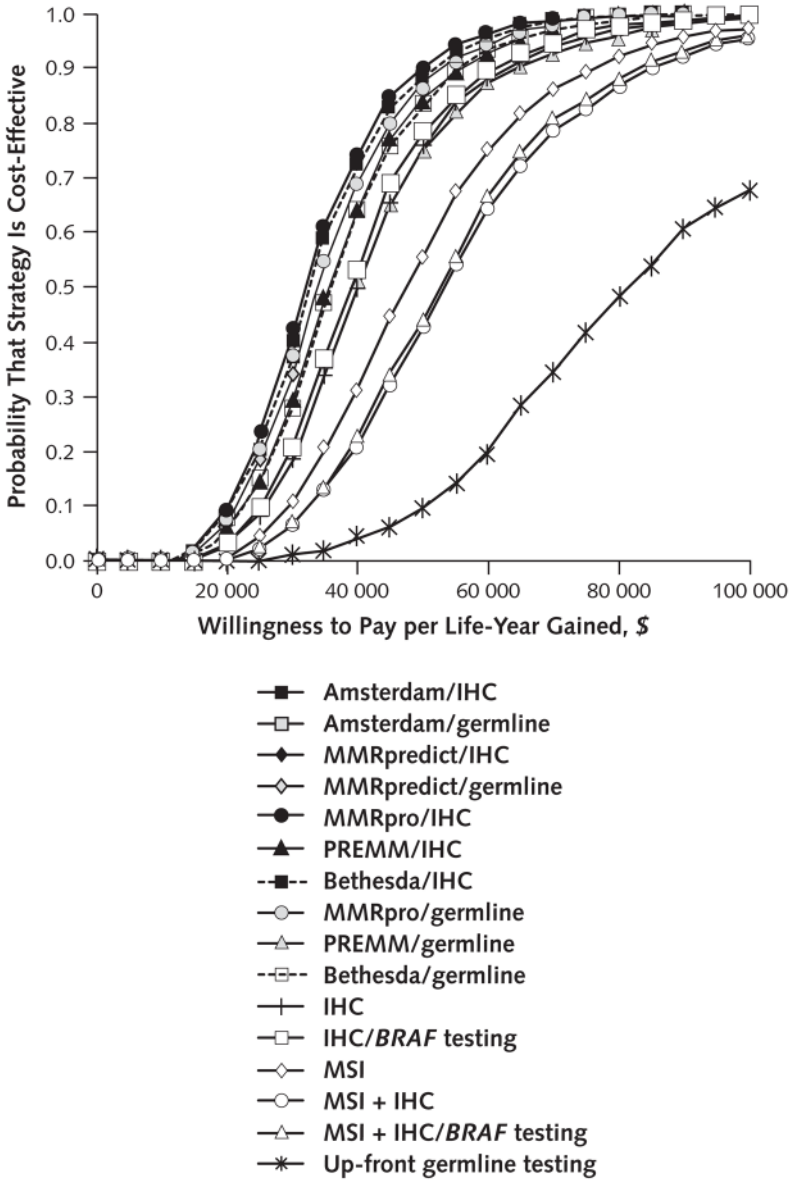


Figure 3. Cost-effectiveness acceptability curves for all strategies, constructed from probabilistic sensitivity analyses

For any given strategy, a higher willingness to pay per life-year gained meant a higher probability that the strategy was considered cost-effective. All strategies are compared with the referent strategy. IHC = immunohistochemistry; MSI = microsatellite instability.

Table 1

Base-Case Results *

Strategy	Discounted Life-Years per Person	Discounted Cost per Person, $	Colorectal Cancer Cases (Deaths) per 100 000 Persons, *n* (*n*)	Endometrial Cancer Cases (Deaths) per 100 000 Persons, *n* (*n*)	Ovarian Cancer Cases (Deaths) per 100 000 Persons, *n* (*n*)	Discounted Incremental Cost per Life-Year Gained, $†	Discounted Incremental Cost per Life-Year Gained, Excluding Clinical Criteria Strategies, $†
Referent strategy	23.5071	11 242	27 953 (7421)	10 266 (1720)	1909 (1004)	–	–
Clinical criteria strategies							
Amsterdam/IHC	23.5565	12 933	26 589 (6906)	10 167 (1703)	1891 (994)	–	–
Amsterdam/germline	23.5667	13 282	26 310 (6801)	10 147 (1700)	1887 (992)	–	–
MMRpredict/IHC	23.6390	15 319	24 317 (6048)	10 004 (1676)	1860 (978)	–	–
MMRpredict/germline	23.6660	16 375	23 572 (5767)	9950 (1667)	1851 (973)	–	–
MMRpro/IHC	23.6772	16 455	23 263 (5650)	9928 (1663)	1847 (971)	30 600	–
PREMM/IHC	23.6791	16 920	23 210 (5630)	9924 (1662)	1846 (971)	–	–
Bethesda/IHC	23.6915	17 021	22 869 (5502)	9899 (1658)	1841 (968)	39 600	–
MMRpro/germline	23.7120	17 873	22 302 (5288)	9858 (1652)	1834 (964)	41 400	–
PREMM/germline	23.7143	18 829	22 239 (5264)	9854 (1651)	1833 (964)	–	–
Bethesda/germline	23.7292	18 737	21 828 (5108)	9824 (1646)	1828 (961)	50 200	–
Tumor-testing strategies							
IHC	23.7319	19 551	21 753 (5080)	9819 (1645)	1827 (961)	–	–
IHC with *BRAF* testing	23.7319	19 381	21 753 (5080)	9819 (1645)	1827 (961)	–	36 200
MSI	23.7374	21 155	21 604 (5024)	9808 (1643)	1825 (960)	–	–
MSI plus IHC	23.7711	23 833	20 674 (4673)	9741 (1632)	1812 (953)	–	–

Ann Intern Med. Author manuscript; available in PMC 2013 October 09.

Strategy	Discounted Life-Years per Person	Discounted Cost per Person, $	Colorectal Cancer Cases (Deaths) per 100 000 Persons, *n* (*n*)	Endometrial Cancer Cases (Deaths) per 100 000 Persons, *n* (*n*)	Ovarian Cancer Cases (Deaths) per 100 000 Persons, *n* (*n*)	Discounted Incremental Cost per Life-Year Gained, $†	Discounted Incremental Cost per Life-Year Gained, Excluding Clinical Criteria Strategies, $†
MSI plus IHC with *BRAF* testing	23.7711	23 642	20 674 (4673)	9741 (1632)	1812 (953)	117 000	108 000
Up-front germline testing	23.8047	33 492	19 736 (4320)	9694 (1624)	1803 (948)	293 000	293 000

IHC = immunohistochemistry; MSI = microsatellite instability.

*Strategies are shown in order of increasing effectiveness. Total cohort size of 100 000 persons with a ratio of 8 relatives per proband, a germline testing acceptance rate of 0.52 by relatives, and the assumption that clinical criteria are determined for all probands. Cancer cases and deaths include those in probands and those in relatives with and without mutations associated with the Lynch syndrome. Results account for incomplete acceptance of germline testing, screening, and prophylactic surgery. For the clinical algorithm strategies that include IHC, IHC was reserved for those whose predicted probability of carrying a mutation was >5%.

†Strategies that were dominated by simple or extended dominance are excluded.

Table 2

Differential Benefit for Probands and Mutation-Carrying Relatives, by Sex, With Selected Strategies and Varying Rates of Germline Testing Acceptance and Adherence With Preventive Interventions

Scenario and Patient	MMRpro/Germline vs. Referent Strategy*			IHC With *BRAF* Testing vs. Referent Strategy*		
	Discounted Incremental Life-Years per Person	Undiscounted Incremental Life-Years per Person	Discounted Cost per Life-Year Gained, $	Discounted Incremental Life-Years per Person	Undiscounted Incremental Life-Years per Person	Discounted Cost per Life-Year Gained, $
Base case						
Female proband	0.174	0.365	83 300	0.191	0.401	106 600
Male proband	0.084	0.171	131 900	0.092	0.187	180 400
Female mutation-carrying relative	0.442	1.37	16 800	0.485	1.51	16 800
Male mutation-carrying relative	0.461	1.31	7400	0.506	1.44	7400
Universal acceptance of germline testing and perfect screening adherence						
Female proband	0.226	0.473	76 300	0.248	0.519	92 800
Male proband	0.108	0.219	117 900	0.118	0.240	152 500
Female mutation-carrying relative	0.768	2.39	16 900	0.843	2.62	16 900
Male mutation-carrying relative	0.801	2.28	7600	0.880	2.50	7600
Universal acceptance of germline testing, perfect screening adherence, and prophylactic TAH-BSO at age 40 y in all probands and relatives with the Lynch syndrome						
Female proband	0.576	1.20	37 100	0.632	1.32	43 600
Female mutation-carrying relative	1.06	3.46	13 300	1.16	3.79	13 300

IHC = immunohistochemistry; TAH-BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.

* The referent strategy reflects no active effort to diagnose the Lynch syndrome.

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Table 3

Effect of Instituting an Upper Age Limit to Screen for the Lynch Syndrome Among Persons With Newly Diagnosed Colorectal Cancer

Upper Age to Screen for the Lynch Syndrome	Persons With Newly Diagnosed Colorectal Cancer Who Are Eligible for Screening, %*	Prevalence of the Lynch Syndrome Among Persons Who Are Eligible for Screening, %*	Persons With the Lynch Syndrome Included Among Persons Eligible for Screening, %*	Prevalence of the Lynch Syndrome Among Persons Not Eligible for Screening, %*	Discounted Incremental Cost per Life-Year Gained With the IHC With *BRAF* Testing Strategy, $
50 y	11	16	57	1.5	27 900
60 y	27	9	78	0.9	33 800
70 y	49	6	91	0.5	44 200
None	100	3	100	–	88 700

IHC = immunohistochemistry.

* Derived from data in references 15 and 20. We assumed a prevalence of the Lynch syndrome of 3% among all persons with newly diagnosed colorectal cancer.