Cancer Prevention Research

Health Benefits and Cost-Effectiveness of Primary Genetic Screening for Lynch Syndrome in the General Population

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Abstract

In current clinical practice, genetic testing to detect Lynch syndrome mutations ideally begins with diagnostic testing of an individual affected with cancer before offering predictive testing to at-risk relatives. An alternative strategy that warrants exploration involves screening unaffected individuals via demographic and family histories, and offering genetic testing to those individuals whose risks for carrying a mutation exceed a selected threshold. Whether this approach would improve health outcomes in a manner that is cost-effective relative to current standards of care has yet to be demonstrated. To do so, we developed a simulation framework that integrated models of colorectal and endometrial cancers with a 5-generation family history model to predict health and economic outcomes of 20 primary screening strategies (at a wide range of compliance levels) aimed at detecting individuals with mismatch repair gene mutations and their at-risk relatives. These strategies were characterized by (i) different screening ages for starting risk assessment and (ii) different risk thresholds above which to implement genetic testing. For each strategy, 100,000 simulated individuals, representative of the U.S. population, were followed from the age of 20, and the outcomes were compared with current practice. Findings indicated that risk assessment starting at ages 25, 30, or 35, followed by genetic testing of those with mutation risks exceeding 5%, reduced colorectal and endometrial cancer incidence in mutation carriers by approximately 12.4% and 8.8%, respectively. For a population of 100,000 individuals containing 392 mutation carriers, this strategy increased quality-adjusted life-years (QALY) by approximately 135 with an average cost-effectiveness ratio of $26,000 per QALY. The cost-effectiveness of screening for mismatch repair gene mutations is comparable to that of accepted cancer screening activities in the general population such as colorectal cancer screening, cervical cancer screening, and breast cancer screening. These results suggest that primary screening of individuals for mismatch repair gene mutations, starting with risk assessment between the ages of 25 and 35, followed by genetic testing of those whose risk exceeds 5%, is a strategy that could improve health outcomes in a cost-effective manner relative to current practice. *Cancer Prev Res; 4(1): 9–22. ©2010 AACR.*

Introduction

It is estimated that 2% to 4% of all diagnosed colorectal cancers (1) and 2% to 5% of all diagnosed endometrial cancers (2) are due to Lynch syndrome, an autosomal, dominantly inherited predisposition to cancer resulting from germline mutations in the genes that regulate DNA mismatch repair. As the most common heritable cause of colorectal cancer, mismatch repair mutations confer a lifetime colorectal cancer risk of 35% to 80%, and a lifetime endometrial cancer risk of 34% to 71% (1, 3). The syndrome is further characterized by synchronous or metachronous malignancies at sites including the ovaries, hepatobiliary tract, urinary tract, and others. It is highly penetrant, and the associated cancers have high rates of recurrence.

Despite a mutation carrier prevalence in the general U.S. population estimated to be in excess of 1 in 440 (4), the condition remains clinically underrecognized (5, 6). Studies have indicated, however, that when mismatch repair mutation carriers are identified, enhanced surveillance by colonoscopy, and prophylaxis by total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) mitigate the morbidity and mortality associated with the syndrome (7–9).

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Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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Genetic tests to detect mutations in genes that cause Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) are clinically available. In the broad context of genetically heritable cancers, genetic testing and counseling prior to manifestation of disease have been advocated when an individual has a personal or family history suggestive of a cancer susceptibility condition, and when an interpretable genetic test can aid in the diagnosis or management of the individual or at-risk family members (10). Genetic screening guided by risk assessment in unaffected women for the breast cancer susceptibility mutations *BRCA1/2*, for example, has been a successful implementation of this strategy (11–13). Although genetic testing in breast cancer is most informative when it begins with an affected family member, the imperfect access to information about these affected family members who may be unavailable, uninsured, or deceased leads to the common clinical scenario of testing unaffected women on the basis of their pretest probabilities of carrying a mutation. This practice is far less common for Lynch syndrome, even though the same limitations of family member availability apply. Current national consensus guidelines recommend that a molecular diagnostic work-up for Lynch syndrome begins at the time that individuals present with malignancies that are clinically suspicious (14–16), rather than prior to cancer diagnosis. Individuals who are at risk for Lynch syndrome on the basis of suspicious family histories are currently referred for genetics consultation, although recognition and uptake are low. Therefore, it is worthwhile to evaluate an alternative strategy involving primary screening for mismatch repair mutations by risk assessment in unaffected individuals—using, for example, published risk calculators (4, 17)—followed by genetic testing in those whose risk is high. This approach stands to identify individuals and families at risk for Lynch syndrome when prophylaxis, surveillance, and early detection might be most effective.

An appropriate implementation of primary screening for mismatch repair mutations in individuals without a history of cancer would involve two steps: (i) assessment of an individual's risk of carrying a mutation based on personal demographics and family history, and (ii) genetic testing for individuals whose risks exceed a certain threshold.

The objective of the present study was to identify (i) whether primary screening for Lynch syndrome leads to improved health outcomes, (ii) whether such a strategy is cost-effective, (iii) an appropriate age to initiate screening by risk assessment, and (iv) an optimal risk threshold at which to implement genetic testing.

Materials and Methods

The model

The Archimedes Model is a large-scale simulation model that has been described in the literature (18, 19). The core of the Archimedes Model is a set of algebraic and differential equations that represent physiology, diseases, and health care systems. Currently, the Archimedes Model includes diabetes, congestive heart failure, coronary artery disease, stroke, hypertension, obesity, and cancers of the breast, lung, colon, and endometrium. The cancer models were developed in collaboration with the American Cancer Society and make use of large-scale databases, including Surveillance Epidemiology and End Results (SEER; 20) and the Clinical Outcomes Research Initiative (CORI; 21). The Archimedes Model has been validated against studies such as the Cancer Prevention Study II Nutrition Cohort, and the Veterans Affairs Cooperative Study Group on colorectal cancer screening (22). Details are available in the Appendix in the Supplementary Data, and similar methods of validating the model have been published in the literature (23).

Lynch syndrome in the model includes the natural histories of colorectal and endometrial cancer associated with mismatch repair gene mutations, and captures the interactions of individuals and their first-degree relatives with the health care system via screening, diagnosis, surveillance, and treatment. For colorectal cancer, data were synthesized from clinical trials, colonoscopy studies, retrospective analyses, population surveys, and national databases (Table 1 and the Appendix in the Supplementary Data), capturing (i) early onset, (ii) accelerated adenoma–carcinoma sequence, (iii) higher probability of colorectal tumor location in the proximal colon, and (iv) high risk of metachronous malignancy for individuals with Lynch syndrome relative to individuals with sporadic colorectal cancer. For endometrial cancer, incidence was derived from a meta-analysis of the literature, and survival was found to be similar to that for sporadic endometrial cancer (Table 1 and the Appendix in the Supplementary Data).

The model also includes the following tests, interventions, and treatments:

(i) *Mutation testing*: genetic sequencing and rearrangement including 1-, 3-, and 4-gene panels; single-site testing (in relatives of known carriers); and immunohistochemistry (IHC) and microsatellite instability (MSI) tumor testing (the latter not used to guide genetic testing),
(ii) *Cancer surveillance/screening*: colonoscopy, endometrial biopsy, and transvaginal ultrasound,
(iii) *Prophylactic procedures*: TAHBSO, polypectomy,
(iv) *Cancer treatment*: total and segmental colectomy, TAHBSO, aggregated pharmacologic and radiation therapy.

Population generation

Using data from the literature and publicly available data sets (Table 1 and the Appendix in the Supplementary Data), we created a virtual population of 100,000 individuals representative of the U.S. population. We constructed natural history models of sporadic and Lynch syndrome-associated colorectal and endometrial cancers, and generated subpopulations of noncarriers and carriers of mutations of *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes (1).

We also created a family history model to construct 5-generation family pedigrees (including first- and second-degree relatives) of each individual using methods similar

Table 1. Key parameters, assumptions, modeling approaches, and sources (full list may be found in the Appendix in the Supplementary Data)

Model parameter	Assumptions and approaches	List of sources
Colorectal Cancer Natural History in Lynch Syndrome		
Adenoma incidence, location, and growth	-Adenoma development was assumed to follow a nonhomogenous Poisson distribution. -Adenoma growth was described by a log-linear growth equation. -Anatomical distribution of adenomas in mutation carriers was derived from an author-conducted meta-analysis.	Mecklin et al. (41), Liljegren et al. (42), Lindgren et al. (43), Rijcken et al. (44), de Jong et al. (45), Pino et al. (46)
Cancer risk/malignant transformation	-Cancer risk as a function of age and gender in mutation carriers was derived from an author-conducted meta-analysis. -The malignant transformation rate of adenomas was a function of age, gender, and adenoma location.	Hendriks et al. (47), Buttin et al. (48), Dunlop et al. (49), Quehenberger et al. (50), Hampel et al. (40), Wagner et al. (51), Senter et al. (52), Barrow et al. (53), Stoffel et al. (54)
Cancer location	-Cancer location was based on an author-conducted meta-analysis.	Mecklin et al. (41), Lindgren et al. (43), Aaltonen et al. (55), de Vos tot Nederveen Cappel et al. (37)
Survival	-Difference in colorectal cancer survival between noncarriers and carriers was characterized by a hazard ratio derived from an author-conducted meta-analysis.	SEER (20), Gryfe et al. (56), Barnetson et al. (57), Watson et al. (58), Sankila et al. (59), Aarnio et al. (60), Barrow et al. (53)
Cancer recurrence	-Second primary colorectal cancers occurred as they arose from new adenomas after treatment of primary cancer.	Lin et al. (61), Mecklin and Jarvinen (62), Rodriguez-Bigas et al. (63)
Endometrial Cancer Natural History in Lynch Syndrome		
Endometrial cancer incidence	-Risk of developing endometrial cancer in mutation carriers was based on an author-conducted meta-analysis.	Hampel et al. (64), Senter et al. (52), Buttin et al. (48), Hendriks et al. (47), Stoffel et al. (54), Dunlop et al. (49), Quehenberger et al. (50), Aarnio et al. (65), Jenkins et al. (66), Schmeler et al. (67)
Survival	-Survival was assumed to be the same for sporadic and Lynch syndrome-associated endometrial cancer and was derived from the SEER database.	SEER (20), Boks et al. (68)
Prevalence		
Lynch syndrome prevalence among all colorectal cancer diagnoses (used to estimate mutation prevalence)	-On the basis of a conservative estimate of 2.2% from Hampel et al. (40) and on author estimates of rates of Lynch syndrome in families with no defined mutation, this value was set to 3.0%, in concordance with Table 13 in Palomaki (1).	Hampel et al. (40), Palomaki et al. (1)

Table 1. (Continued)

Model parameter	Assumptions and approaches	List of sources
Mutation type	- The distribution of different mutation types was taken to be: 32% *MLH1*, 39% *MSH2*, 14% *MSH6,* and 15% *PMS2*.	Palomaki et al. (1)
Tests and Procedures	**Values**	
Genetic test analytic sensitivity[a]	*MLH1*: 90%, *MSH2*: 90%, *MSH6*: 90%, *PMS2*: 62%	Palomaki et al. (1), Senter et al. (52)
Genetic test analytic specificity	*MLH1*: 99.97%, *MSH2*: 99.97%, *MSH6*: 99.97%, *PMS2*: 99.97%	Palomaki et al. (1)
Immunohistochemistry analytic sensitivity, specificity	83%, 88.8%	Palomaki et al. (1)
Colonoscopy: sensitivity, specificity of adenoma detection	Adenoma size 0–5 mm: sensitivity 75%, specificity 95% 6–10 mm: sensitivity 85%, specificity 95% >10 mm: sensitivity 95%, specificity 95%	Rex et al. (69)
Colonoscopy: segments screened	95% reach ascending colon, 70% reach cecum	Rex et al. (69)
Endometrial cancer surveillance	Endometrial aspirate biopsy: sensitivity 91%, specificity 98%	Dijkhuizen et al. (70), Dove-Edwin et al. (71)
Compliances and Practice Patterns		
Compliance to annual colonoscopy screening for known unaffected mutation carriers	81%	Palomaki et al. (1)
Compliance to annual endometrial biopsy for known unaffected mutation carriers	57%	Stoffel et al. (72), Wagner et al. (73), Collins et al. (74)
Compliance to genetic testing of first-degree relatives of mutation-positive probands	60% for siblings 70% for children 60% for parents (Only one parent of a proband was tested. If negative, then the other parent was considered an obligate carrier.)	Ramsey et al. (75)
Percent of individuals with malignancy who are seen by a physician who considers Lynch syndrome and the clinical criteria for testing for Lynch syndrome	17%	Grover et al. (6)
Surgical Mortalities		
Mortality associated with colonoscopy (occurring within thirty days after the procedure)	0.008%	Palomaki et al. (1)
Mortality associated with total colectomy with ileorectal anastomosis (occurring within thirty days after the procedure)	0.9%	Palomaki et al. (1)
Mortality associated with TAHBSO (occurring within thirty days after the procedure)	0.02%	Palomaki et al. (1)

Table 1. (Continued)

Model parameter	Assumptions and approaches	List of sources
Costs		
Multiple-gene testing for MLH1, MSH2, MSH6, and PMS2	$3,495	Calculated from a 2009 author survey of U.S. commercial genetic test providers[b]
Multiple-gene testing for MLH1, MSH2, MSH6	$2,618	Averaged from a 2009 author survey of U.S. commercial genetic test providers[b]
Single-gene testing for MLH1	$860	
Single-gene testing for MSH2	$771	
Single-gene testing for MSH6	$933	
Single-gene testing for PMS2	$884	
Single-site testing	$298	
Immunohistochemistry	$281	2009 Medicare reimbursement rate
Biopsy/polypectomy	$160	2007 Centers for Medicare & Medicaid Services (CMS) reimbursement projected to 2009
Colonoscopy	$532	2007 CMS reimbursement projected to 2009
Total colectomy for mutation carriers with advanced adenomas (costs for colorectal surgery for those with carcinoma are accounted for in the cost of colorectal cancer treatment)	$22,800	2009 Medicare reimbursement rate
Transvaginal ultrasound	$110	Kwon et al. (76)
Endometrial biopsy	$201	Kwon et al. (76)
Gynecology visit	$154	Kwon et al. (76)
Prophylactic TAHBSO	$20,445	Kwon et al. (76)
Treatment of endometrial cancer	$24,291	Kwon et al. (76)
Treatment of colorectal cancer by stages and phases		1998–2003 Medicare reimbursement rate (77)
Stage I, Initial/Continuing/Terminal	$27,221 / $2,166 / $48,791	
Stage II, Initial/Continuing/Terminal	$37,563 / $2,024 / $48,662	
Stage III, Initial/Continuing/Terminal	$45,804 / $2,883 / $51,276	
Stage IV, Initial/Continuing/Terminal	$59,812 / $8,945 / $68,809	
Health Utility Parameters		
Colorectal cancer Stage I	0.74	Ness et al. (78)
Colorectal cancer Stage II	0.67	Ness et al. (78)
Colorectal cancer Stage III	0.50	Ness et al. (78)
Colorectal cancer Stage IV	0.25	Ness et al. (78)
Endometrial cancer	0.83	Kwon et al. (76)
Total colectomy with ileorectal anastomosis or proctocolectomy and ileal pouch-anal anastomosis for individuals with advanced adenoma (Surgical disutility for those with colorectal cancer is accounted for in disutility due to colorectal cancer diagnosis)	0.84	van Duijvendijk et al. (79), SF-36 scores converted to health utility indices using the methods by Ara et al. (80)
TAHBSO	0.86	Kwon et al. (76)
Mismatch repair (MMR) mutation detected in an unaffected (tumor-naïve) individual	1.0 Decrease in quality of life due to detection of MMR mutation in unaffected carriers was found to be transient, returning to baseline at 6–12 months posttest result disclosure.	Gritz et al. (81)

[a]Analytic sensitivity of genetic tests was set by the authors to a level conservatively below subjective values cited in the literature (see text).
[b]List prices were used for genetic tests, as in Mvundura et al. (82).

to those published elsewhere (24). These methods are described in detail in Section 6 of the Appendix. Briefly, pedigree structures representative of U.S. families were generated, and mutations and cancers were distributed among these pedigrees at appropriate prevalence and incidence rates. Although colorectal cancer and endometrial cancer were the only Lynch syndrome cancers tracked in probands, incidence of all Lynch syndrome-associated cancers (25) was accounted for in family pedigrees to calculate individuals' risks for carrying a mutation using the $PREMM_{126}$ risk prediction model (26), a recent update of the $PREMM_{12}$ model (ref. 17; Available at: www.dfci.org/premm). To address the sparsity of appropriate family history data for unaffected mutation carriers without encountering prevalence bias by drawing this information from Lynch syndrome registries, we conducted Monte Carlo simulations of families with Lynch syndrome to create surrogate family history parameters required as inputs by the $PREMM_{126}$ model, adapting established techniques (24). The family history model of cancer was then validated against data on family histories of colorectal cancer in the general population (27) and against data in a Lynch syndrome registry (28).

Cost-effectiveness

The model took into account direct medical costs associated with tests and interventions. These costs were primarily based on Medicare reimbursement rates (Table 1). All costs were adjusted to 2009 values using the medical care component of the Bureau of Labor Statistics Consumer Price Index (29).

Parameters for calculating quality-adjusted life-years (QALY) are shown in Table 1 and the Appendix. A societal perspective was used, with costs, benefits, and life-years discounted 3%, and with adherence to other recommendations of the Panel on Cost-Effectiveness in Health and Medicine (30). We defined the average cost-effectiveness ratio as cost per QALY saved of a given screening strategy relative to current practice, and the incremental cost-effectiveness ratio as cost per QALY saved of a given strategy relative to the nearest strategy on the efficient frontier (Fig. 1A). We considered a strategy to be "cost-effective" if the cost per QALY was below the often-quoted benchmark of $50,000 per QALY (31), although others have argued for higher thresholds (32).

Study design

We conducted a virtual clinical trial in which 100,000 simulated individuals, representative of the general U.S. population, were tracked from the age of 20, and were exposed to each of 20 primary screening strategies (experimental arms). These strategies (Tables 2 and 3), involved risk assessment at different ages (20, 25, 30, 35, or 40) using $PREMM_{126}$, followed by 4-gene mutation testing of those individuals whose risks for carrying a mutation exceeded a given threshold (0%, 2.5%, 5.0%, or 10%). A threshold of 0% was considered equivalent to universal screening in which all individuals received genetic testing without pre-
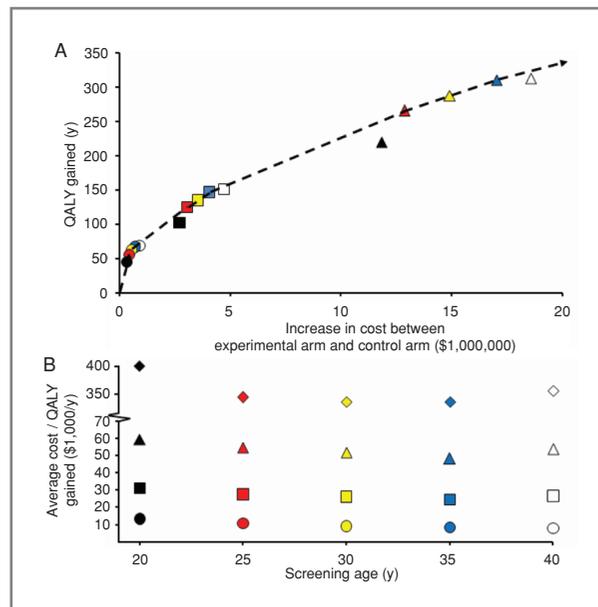

Figure 1. Cost-effectiveness of primary screening strategies for mismatch repair mutations in a simulated population of 100,000 individuals, representative of the general U.S. population. Risk thresholds representing the probability of carrying a mismatch repair gene mutation above which to initiate genetic testing: ◇ 0.0%, △ 2.5%, □ 5.0%, o 10%. Symbol color denoting screening initiation age: black = age 20, red = age 25, yellow = age 30, blue = age 35, white = age 40. A, Increase in QALY versus increase in cost for 15 screening strategies for Lynch syndrome compared with current practice. Dashed line is the efficient frontier, representing sequential strategies, starting from the origin, with the greatest gain of QALYs per incremental cost. Strategies to the southeast of the efficient frontier are referred to as dominated. The inverse of the slope of the efficient frontier is the incremental cost-effectiveness ratio, representing the incremental cost per QALY compared with the next best strategy on the efficient frontier (see text). (◇ not shown in A due to scale, but data are reported in Table 3). B, average cost per QALY of 20 screening strategies for Lynch syndrome as functions of age, compared with current practice.

ceding risk assessment. The $PREMM_{126}$ model was chosen for risk assessment because it is usable for individuals who have not necessarily developed malignancies (20% of the development cohort were unaffected by cancer). Furthermore, it was built from a racially diverse group of individuals referred for genetic testing and externally validated against an independent cohort of individuals with colorectal cancer recruited through the Colon Cancer Family Registry (CCFR). In clinical practice, however, clinicians may use other means to quantify risk for individuals without malignancy such as MMRpro (available at www4.utsouthwestern.edu/breasthealth/cagene/).

In the primary screening groups, individuals with negative genetic test results were presumed not to carry a mutation and received future screening for sporadic colorectal cancer according to National Comprehensive Cancer Network (NCCN) Practice Guidelines (33). Individuals with positive genetic test results were thereafter screened annually with colonoscopy and with endometrial biopsy and transvaginal ultrasound, or were given prophylactic

Table 2. Health outcomes among probands exposed to primary genetic screening strategies relative to current practice patterns

	Screening strategy		Reduction of colorectal cancer incidence in carriers exposed to screening strategy (%)	Reduction of endometrial cancer incidence in carriers exposed to screening strategy (%)	Absolute life-years saved per carrier exposed to screening strategy (y)
Strategy	Screening start-age (y)	Risk threshold (%)			
1	20	0.0	43.9	39.6	4.07
2	25	0.0	43.6	39.2	3.99
3	30	0.0	42.8	38.8	3.81
4	35	0.0	39.5	38.2	3.48
5	40	0.0	33.2	37.5	2.94
6	20	2.5	24.2	17.2	2.00
7	25	2.5	23.6	17.0	1.95
8	30	2.5	22.6	16.6	1.87
9	35	2.5	21.2	15.8	1.74
10	40	2.5	19.3	14.6	1.56
11	20	5.0	13.8	9.2	1.11
12	25	5.0	13.5	9.0	1.09
13	30	5.0	13.0	8.7	1.07
14	35	5.0	12.2	8.1	0.99
15	40	5.0	11.0	7.3	0.88
16	20	10.0	7.0	4.7	0.56
17	25	10.0	6.9	4.6	0.54
18	30	10.0	6.6	4.5	0.52
19	35	10.0	6.1	4.1	0.47
20	40	10.0	5.3	3.6	0.41

TAHBSO as described in Table 12 of the Appendix. Individuals who were not genetically tested (i.e., failure to exceed the risk threshold for genetic testing) received future screening for sporadic colorectal cancer according to NCCN Practice Guidelines. However, as these simulated individuals aged, their family histories of cancer in first- and second-degree relatives evolved naturally. Individuals in the simulation became aware of these updates in cancer diagnoses among relatives at rates described in the literature and sought physician reassessment of their own updated risks (with PREMM$_{126}$) as appropriate (34, 35).

In the current practice group (control arm), cloned cohorts were given current care in which testing was performed in individuals with appropriate clinical risk factors after a malignancy was detected (33). Individuals with colorectal or endometrial cancer meeting certain clinical criteria (colorectal or endometrial cancer at age <50, or ≥2 Lynch syndrome-associated cancers in the same proband, or a proband with ≥2 first- or second-degree relatives with Lynch syndrome-associated cancers) were offered either tumor testing by IHC, followed—when positive—by single-gene testing, or direct genetic testing for *MLH1*, *MSH2*, and *MSH6*, followed optionally by *PMS2*, at utilization rates reflective of current practice (Fig. 19 in the Appendix and Grover et al. (6)). When genetic testing demonstrated the presence of a mismatch repair mutation in the proband, testing was extended to at-risk relatives.

In both the primary screening groups and the current practice group, individuals testing positive at the time of a malignancy were offered appropriate surgical and/or medical intervention and ongoing surveillance. In addition, single-site (mutation-specific) testing was performed on first-degree relatives of known mutation carriers at reported compliances (Table 1).

Screening strategies were compared with control groups in three ways. First, as a policy study, screening strategies were compared with current practice patterns to demonstrate the care gap between current health care and the gains that stand to be achieved with wide adoption of the new strategy (Tables 2 and 3). This policy-approach indicates the upper limit of the total disease burden that the new intervention could alleviate if it were to be widely adopted, and the cost-effectiveness, if any, associated with this approach. Second, to compare wide adoption of screening to wide adoption of current policy (i.e., the assumption that 100% of physicians adhere to current guidelines for testing at-risk probands with tumors), a sensitivity analysis was conducted as shown in Figure 2. Third, to compare the screening strategy under a broad range of adoption rates (0%, 33%, 67%, 100%) to current rates of physician adoption of testing at-risk probands with tumors, we calculated health outcomes for a subset of strategies from Tables 2 and 3 (strategies 12–14) that were found to offer a balanced combination of health improvement and cost-effectiveness (Table 4).

Table 3. Health and economic outcomes of 100,000 simulated individuals in the general population plus first-degree relatives of mutation carriers exposed to primary genetic screening strategies

	Screening strategy		Number of 4-gene tests offered per 100,000 simulated individuals in the general population	Number of first-degree relatives tested per 100,000 simulated individuals in the general population	Average number of 4-gene tests needed to identify an additional mutation carrier	QALYs gained per 100,000 simulated individuals in the general population relative to current practice	Increase in cost relative to current practice ($ million)	Average cost-effectiveness ratio ($/QALY)	Incremental cost-effectiveness ratio ($/QALY)
Strategy	Screening start-age (y)	Risk threshold (%)							
1	20	0.0	100,000	885	140.4	933	374.2	401,019	7,008,872
2	25	0.0	99,999	837	141.0	925	318.1	343,870	490,315
3	30	0.0	99,997	821	141.3	800	268.7	335,900	-
4	35	0.0	99,352	790	143.8	675	227.0	336,253	-
5	40	0.0	98,566	754	144.0	546	193.9	355,191	-
6	20	2.5	6,159	499	16.8	313	18.6	59,357	-
7	25	2.5	6,095	465	17.1	311	17.0	54,748	92,555
8	30	2.5	6,003	444	17.3	288	14.9	51,774	-
9	35	2.5	5,995	436	17.2	266	12.9	48,352	74,023
10	40	2.5	5,984	422	17.2	220	11.8	53,770	-
11	20	5.0	1,546	349	7.29	151	4.7	31,241	-
12	25	5.0	1,511	318	7.31	147	4.1	27,571	44,537
13	30	5.0	1,475	298	7.41	135	3.5	26,229	-
14	35	5.0	1,459	287	7.51	125	3.1	24,585	40,645
15	40	5.0	1,419	271	7.6	102	2.7	26,662	-
16	20	10.0	287	253	2.63	69	0.9	13,300	-
17	25	10.0	269	225	2.60	67	0.7	10,682	37,268
18	30	10.0	259	205	2.56	63	0.6	8,994	14,922
19	35	10.0	252	190	2.55	56	0.5	8,253	10,331
20	40	10.0	247	173	2.56	45	0.3	7,745	7,745

NOTE: Average cost-effectiveness ratio is relative to current practice. Incremental cost-effectiveness ratio is relative to the adjacent screening strategy on the efficient frontier (Fig. 1A). Dashes (–) in the table represent dominated strategies (those below the efficient frontier).

Table 4. Health and economic outcomes of several primary genetic screening strategies with varying levels of adoption relative to current practice patterns

Screening strategy			Percentage of population adopting primary genetic screening (%)	Reduction of colorectal cancer incidence in carriers exposed to screening strategy (%)	Reduction of endometrial cancer incidence in carriers exposed to screening strategy (%)	Absolute life-years saved per carrier exposed to screening strategy (y)	Average cost-effectiveness ratio ($/QALY)
Strategy	Screening start-age (y)	Risk threshold (%)					
12	25	5.0	100%	13.5	9.0	1.09	27,571
			67%	9.1	6.0	0.73	27,535
			33%	4.5	3.0	0.36	27,580
13	30	5.0	100%	13.0	8.7	1.07	26,229
			67%	8.7	5.8	0.71	26,351
			33%	4.3	2.9	0.35	26,177
14	35	5.0	100%	12.2	8.1	0.99	24,585
			67%	8.2	5.4	0.66	24,602
			33%	4.0	2.7	0.33	24,511

Parameters and assumptions

Parameters, base case values, and assumptions used to inform the model were drawn from the literature and publicly available data sets to the greatest extent possible (Table 1 in the manuscript and Table 12 in the Appendix). When data were lacking, these values were estimated by consensus among the study authors with clinical expertise in Lynch syndrome, and appropriate sensitivity analyses were performed. The model validated well against studies with mutation carriers describing (i) incidence of adenomas (36), (ii) effects of colonoscopic surveillance on incidence of colorectal cancer (37), and

(iii) effects of hysterectomy on incidence of endometrial cancer (9).

Results

Table 2 summarizes the health outcomes and life-years gained for probands exposed to the various screening strategies. Table 3 summarizes health outcomes and cost-effectiveness for probands and first-degree relatives exposed to each screening strategy.

Universal primary genetic screening (0% pretest probability), starting at age 20 (Strategy 1), reduced colorectal
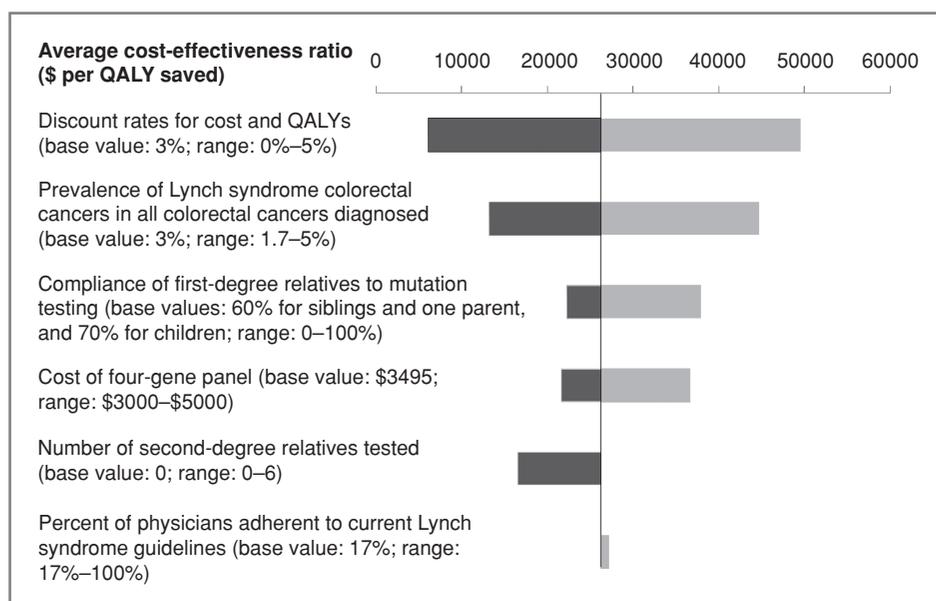

Figure 2. One-way sensitivity analysis of Strategy 13 (Tables 2–4). Sensitivity of the average cost-effectiveness ratio as each parameter varies within the specified range.

and endometrial cancer incidence in mutation carriers relative to current practice by 43.9% and 39.6%, respectively. In the simulated population of 100,000 individuals, this strategy identified 336 mutation carriers in probands (approximately 86% of the total number of probands with mutations). Single-site testing was offered to 1,351 first-degree relatives of these probands, 885 of whom complied with testing, and 428 of whom were found to be mutation carriers. This strategy resulted in the identification of 712 additional mutation carriers relative to the current practice arm. Total treatment costs of colorectal and endometrial cancer for mutation carriers were reduced by 39%, and absolute life expectancy per mutation carrier increased by 4.07 years. The cost savings of cancer treatment were partially offset by the costs of surveillance, prophylactic procedures, and notably by the costs of genetic testing, as one hundred forty 4-gene tests were needed to identify one additional mutation carrier. This screening strategy resulted in a gain of 933 QALYs with an additional cost of $374 million compared with current practice patterns, at an average cost-effectiveness ratio of $401,019 per QALY gained.

As the risk threshold for genetic testing was increased, fewer people received primary genetic screening. For a 5% risk threshold in which screening started at age 30, as in Strategy 13 (Table 3), 1,475 probands were offered 4-gene panels, resulting in 199 additional mutation carriers identified (7.41 tests per identified mutation carrier), and a gain of 135 QALYs at an average cost-effectiveness ratio of $26,229 per QALY gained. At a 10% threshold for testing initiated at age 30, as in Strategy 18, 259 people were offered 4-gene panels, resulting in the identification of 101 additional mutation carriers (2.56 tests per identified mutation carrier), a gain of 63 QALYs, at an average cost-effectiveness ratio of $8,994 per QALY gained.

Corresponding to the values in Table 3, Figure 1A plots QALYs gained versus increase in cost for each primary screening strategy. QALYs gained and cost depended strongly on risk thresholds, and weakly on initial screening age. The average cost-effectiveness ratio as a function of initial screening age is shown in Figure 1B. For risk thresholds of 2.5% and 5.0%, screening started at age 35 offered the lowest average cost-effectiveness ratios, although the incremental magnitudes of these optima relative to other ages were small.

Figure 2 shows the influence of several parameters in a one way sensitivity analysis of Strategy 13. This strategy was chosen for sensitivity analysis because it was in the center of a cluster of three strategies with similar average and incremental cost-effectiveness ratios under $50,000 per QALY (12–14). Cost-effectiveness was most sensitive to discount rate and the prevalence of Lynch syndrome-associated colorectal cancer, and incrementally less sensitive to compliance of first-degree relatives with testing, physician adherence to current guidelines in the current practice group, and to the cost of the 4-gene panel.

Inspecting this same cluster of strategies (12–14), Table 4 indicates the degree to which the overall impact of genetic screening on Lynch syndrome cancer outcomes depends on the combined adoption of this screening approach by physicians and patients. In strategy 13, for instance, if the rate of physician–patient adoption of the screening strategy was reduced from 100% to 67% and to 33%, then the absolute life-years saved per carrier exposed to screening were reduced from 1.07 to 0.72 and to 0.35, respectively. Despite reduction in both life-years saved and in cost incurred with imperfect adoption levels, the cost-effectiveness ratios of these strategies in Table 4 were the same as for those strategies in Table 3 in which full adoption was modeled.

Discussion

By examining primary genetic screening to detect mismatch repair mutation carriers prior to malignancy, and by capturing the important familial factors in risk assessment and in posttest screening of first-degree relatives of mutation-carrying probands, this study enabled the identification of strategies to cost-effectively reduce the burden of Lynch syndrome. This primary screening approach is distinct from current guidelines which recommend clinically informed genetic testing in individuals who have already developed malignancies.

From a clinical perspective, universal screening (0% risk threshold) starting at age 20 reduced the incidence of colorectal and endometrial cancer in mutation carriers compared with current practice (control) the greatest (43.9% and 39.6% respectively), and substantially increased the average life-years per mutation carrier (4.07 years gained), as shown in Table 2. As the risk threshold for genetic testing was increased, and fewer people qualified for testing (as in Strategy 20), the reductions in colorectal and endometrial cancer incidence were minimized (5.3% and 3.6%, respectively), as were life-years gained per mutation carrier (0.41 years).

From a cost-effectiveness perspective, although universal screening offered the greatest benefit in clinical outcomes, it did so at the least attractive cost-effectiveness ratios. Furthermore, universal screening required the largest number of tests—over 140—to identify one additional mutation carrier. However, as the risk threshold for genetic testing was set to 5.0% and 10%, the cost-effectiveness values fell below the benchmark of $50,000 per QALY, and the number of tests needed to identify one additional mutation carrier dropped to 7–8, and 2–3, respectively. Although the health outcomes in Table 2 were sensitive to both screening age and risk of carrying a mutation, sensitivity of cost-effectiveness was dominated by the latter (Table 3 and Figs. 1A and B).

Between the extremes of universal testing and a strategy involving a high threshold for testing were strategies, such as 12, which achieved reductions in colorectal and endometrial cancer incidence of 13.5% and 9.0% respectively, at an average cost-effectiveness ratio of $27,571 per QALY and an incremental cost-effectiveness ratio of $44,537 per

QALY. As the age at which to start screening increased from 25 to 35 (e.g., strategies 12, 14), screening had less of an effect on the reduction of colorectal cancer incidence (13.5% vs. 12.2%), and on the reduction of endometrial cancer incidence (9.0% vs. 8.1%), but improved cost-effectiveness ($44,537 per QALY vs. $40,645 per QALY). On the basis of the values in Table 3, several effective primary genetic screening strategies exist for start ages of 25 to 35, with a risk threshold of 5%. Cost per QALY of strategies 12 and 14, for example, are below the cost-effectiveness benchmark and are comparable to values of other accepted prevention activities described by Maciosek et al. (38) including colorectal cancer screening (<$14,000 per QALY), cervical cancer screening ($14,000–$35,000 per QALY), and breast cancer screening ($35,000–$165,000 per QALY). Furthermore, relative to the other screening strategies studied, strategies 12 and 14 concomitantly achieved modest gains in absolute life-years and modest reductions in the incidence of colorectal and endometrial cancer.

As suggested in Table 4, the absolute benefits in health outcomes in strategies 12 to 14 depended on the projected adoption rates of the screening strategies. However, with the exception of slight variation due to random sampling, the cost-effectiveness ratio itself did not vary as a function of adoption rate, a finding which is consistent with similar observations described elsewhere (39). Of note is that adoption of the proposed screening strategy is a dual function of individuals visiting with their physicians and physicians implementing the strategy. Although younger patients may be less likely to visit with their physicians, the modeled screening strategies indicate a start-age and not a single age for risk assessment. Because the simulated patients may return to their physicians for physical exams and for risk reassessments as their first- and second-degree relatives age and develop disease over time, a 25-year-old, for example, who does not comply with visiting his or her physician is not an opportunity lost, but merely an opportunity delayed. Ultimately, as adoption improves over time, exemplified by the successful and widespread adoption of history- and genetic-based screening strategies associated with *BRCA1/2*, benefits in health outcomes will rise accordingly.

This analysis was based on a number of important but generally conservative assumptions. First, although we assumed that single-site testing was only offered to first-degree relatives of probands, in clinical practice efforts are commonly made to offer single-site tests to second-degree relatives as well. For example, in the study by Hampel, five to six relatives were tested per proband on the basis of cascade testing of family members beyond first-degree relation (40). An estimate of the benefit of extending testing to second-degree relatives in whom mutation prevalence of 25% was assumed, resulted for strategy 13 in an average cost-effectiveness ratio of $16,564 per QALY if six second-degree relatives were tested. Second, the current study used an annual discount rate of 3% for both cost and QALYs in the base case

calculation. It is possible that this approach is conservative over lifetime horizons in which testing costs are incurred upfront whereas treatment and QALY savings at substantial discounts are realized later. Third, we used conservative estimates related to diagnostic testing. We set the analytic sensitivity of genetic tests at 90% for *MLH1*, *MSH2*, and *MSH6*, and 62% for *PMS2*. These values are below subjective levels cited in the literature (e.g., 99.5%; 1), but allowed us to account for effects of such factors as genetic variants of uncertain significance known to occur in the genes modeled. Ongoing advances in testing techniques as well as emerging tests for BRAF and TAC/STD1 will likely lead to higher sensitivities. We also estimated that in current practice, when taking the entire U.S. population into account, approximately 30% of individuals diagnosed with colorectal cancer have access to MSI and IHC testing. Although nearly all individuals diagnosed with and treated for colorectal cancer in academic and institutional clinical settings have access to these testing modalities, most individuals are diagnosed and treated at community hospitals where protocols for routine processing of tumors for MSI and IHC are not yet widely implemented. We acknowledge that this may change over time, with MSI increasingly recognized as a prognostic factor for survival and as a predictive factor for sensitivity to specific chemotherapies. Fourth, the costs of colorectal cancer treatment were based on SEER Medicare data from 1998 to 2003 (20), rather than the much higher costs of recently available molecular-targeting agents. This approach was taken to minimize the favorable bias on outcomes that the uniform use of these high-cost agents in the control group would introduce. Had updated estimates of the costs of colorectal cancer treatment been implemented, the cost-effectiveness of primary genetic screening would have been further enhanced.

In summary, primary genetic screening for mutations in mismatch repair genes, with a screening start age between 25 and 35, and a risk threshold of 5%, leads to improvements in health outcomes among carriers and families with these mutations and is cost-effective relative to the common criterion of $50,000 per QALY. In the simulation, approximately 1% of the general population had risk in excess of the aforementioned 5% threshold, emphasizing the scope of the public health issue that could be addressed by such a screening strategy. This finding supports the concept that genetic screening of unaffected at-risk individuals, when conducted in association with appropriate risk assessment, and when followed by surveillance for colorectal and endometrial cancer would cost-effectively improve health outcomes. Furthermore, it offers an evidence-based justification for a shift in the clinical approach to Lynch syndrome from one that is reactive to one that is proactive. By providing clinicians with a simple and easily employed means of determining an individual's future risk of developing Lynch syndrome, the primary care practitioner may now participate with the oncologic and surgical specialists in the fundamental roles of prevention, surveil-

lance, and management of patients with Lynch syndrome mutations.

Disclosure of Potential Conflicts of Interest

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Health Benefits and Cost-Effectiveness of Primary Genetic Screening for Lynch Syndrome in the General Population

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