

Lynch Syndrome Screening Implementation: Business Analysis by a Healthcare System

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Objective: To characterize the current state of evidence and apply simulation modeling to support decision making about provision and coverage of a Lynch syndrome (LS) screening program among colorectal cancer (CRC) patients in our integrated healthcare delivery system.

Study Design: Application of multiple methods for synthesizing evidence guided by needs of our clinical and administrative decision makers.

Methods: Narrative and focused reviews, computerized simulation models of multiple screening options, queries of our electronic data warehouse, and extensive communication with decision makers.

Results: Review of published evidence at the time of the study period revealed that screening unselected CRC patients for LS would likely cost less than \$25,000 per life-year saved (compared with no screening) and that screening with immunohistochemistry is substantially more efficient than other options. Our simulation models suggest that not only does including BRAF mutation testing substantially improve efficiency but that adding methylation testing improves it further. We characterized a variety of other metrics that contributed not only to local decisions but to the broader evidence base on this topic.

Conclusion: The current state of evidence at the time of the study period suggests an LS screening program can be both effective in reducing mortality from CRC and cost-effective. However, direct evidence remains limited and multiple factors could threaten success of such a program. We have identified opportunities for optimizing the efficiency of available screening protocols. While there was enough evidence for our system to proceed with an LS screening program, we recognize the threats to program success and will prospectively collect outcome data supporting empirical examination of the program.

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For author information and disclosures,
see end of text.

Colorectal cancer (CRC) is one of the most common cancers worldwide, with more than a million cases detected and half a million who die from the disease annually.^{1,2} Approximately 5% to 10% of CRC is familial, reflecting shared genetic and environmental predisposition.³ However, some CRC is due to mutations in highly penetrant genes such as *APC*, *MYH*, and *PTEN*, as well as the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*. These are referred to as hereditary CRC to distinguish them as single gene disorders.⁴ Between 2% and 5% of all CRC is due to genetic mutations in MMR genes, collectively known as Lynch syndrome (LS), previously referred to as hereditary non-polyposis colorectal cancer.⁵ Individuals with LS have a lifetime risk of CRC as high as 70% to 80% as well as higher risk of endometrial, ovarian, pancreatic, and urologic cancers.⁶

Importantly, risk for CRC can be dramatically lowered by intensive surveillance of LS mutation carriers, principally colonoscopy beginning at an early age and at increased frequency.^{7,8} This can be achieved by identifying MMR mutations in index cases and if a mutation is identified, performing family-specific mutation analysis on at-risk relatives. Relatives who test negative revert to routine population screening for CRC.

The optimal way to identify index cases remains undetermined. Family history was initially the recommended screening approach, but recent evidence has suggested substantial deficiencies in this approach. Emerging evidence suggested that tumor-based testing might be a clinically effective and cost-effective alternative to family history. However, multiple approaches could be used to identify individuals at risk, about which evidence was immature.

The goals of this study were 3-fold. The first goal was to thoroughly understand the current evidence base on the effectiveness and “value” of the different LS screening approaches. Based on the results of the first goal, the second goal was to make decisions about the details required for simulation models and construct appropriate models that would address screening efficiency and other questions from the perspective of our healthcare system. The third goal was to communicate the results to our clinical and administrative leaders to inform decisions on implementation of a screening program.

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STUDY DESIGN

To address our first goal, we performed a series of narrative or qualitative reviews, which shaped our strategies for addressing the layers of questions important to remaining goals. The qualitative reviews were followed by more focused reviews, including review of unpublished data when available to provide data and summary statistics for the simulation models. Queries of our electronic data warehouse were performed to determine system-specific statistics for the models.

METHODS

Narrative reviews were chosen for their flexible nature, both to extract the background information needed to understand the subject area and allow for incorporation of new data in a rapidly evolving field.⁹ The evidence base searched was PubMed, augmented by hand searches, the expertise of our team, contact with Hampel and colleagues of the Ohio State University LS research group, and information garnered from professional meetings.

As the nature and scope of the important questions to be addressed became clear from the narrative reviews, more focused reviews were used to address the questions. The first was the clinical effectiveness of available methods for LS case finding among CRC patients. The second, given our commitment to bringing value to our integrated system, was the cost-effectiveness of these different approaches. Finally, the task of identifying numerical parameters to populate the analytic models involved both focused reviews and expert opinion.

The primary study period was mid-2007 to fall 2009, with final updates made up to fall 2010 in order to rerun the model with the most recent data available. All searches and analyses were performed by the first author (JMG); input was provided by all co-authors as well as other sources.

The computer simulation models were theoretic models, thus exempt from institutional review board approval. Our theoretic cohort consisted of new CRC patients expected to be diagnosed and treated within our delivery system. The models were constructed in TreeAge Pro software (Williamstown, Massachusetts) and Excel software (Microsoft; Redmond, Washington) using @Risk software as a decision analysis “add-on” (Palisade, Ithaca, New York). Final model constructs were constructed in both platforms for validation purposes.

Model structures were constructed to estimate a combination of budget impact and cost-consequences analyses.^{10,11} The primary outcomes included the absolute and relative ef-

Take-Away Points

Our study summarizes the evidence on the cost-effectiveness of Lynch syndrome (LS) screening in colorectal cancer (CRC) populations and, through computer simulation models, extended the evidence base to address the specific information needs of decision makers in our integrated healthcare system.

- Published evidence suggests that LS screening in unselected CRC population is cost-effective.
- Our simulation models have identified the most efficient screening protocol as well as other decision metrics.
- While LS screening offers promise in reducing morbidity and mortality from CRC, important questions remain about implementation of such programs.

fectiveness and costs of the screening protocols, including total costs of testing, number of cases detected, cost per case detected, and the incremental differences between the different protocols. Secondary outcomes were defined by decision makers as we proceeded through decision making, which we describe in the Results section.

Sensitivity analyses (SAs) were performed to test the models as well as examine their output. The influence of model variables on outcomes was explored via multiple 1-way SAs. Calculation of point estimates and plausible ranges of outcomes was performed by Monte Carlo analysis.

Data Sources for Models

Test performance values, except those of methylation testing, were taken largely from the recent Hampel et al and Palomaki et al studies.^{5,8,12} Methylation testing performance values, including conditional dependence (CD) with the BRAF test, were extracted from recent studies.^{13,14} When gaps in published data were identified, we contacted outside investigators to obtain unpublished data. Sensitivity and specificity values were based on clinical validity (ie, the tests’ abilities to detect the presence or absence of LS). See **Table 1** for primary model input.

Costs of tests were obtained from our reference laboratory, based on prices available to our healthcare system (current as of fall 2010), plus a \$30 charge by our pathology department when applicable. At the time of completion of this study, there were no other labs in the United States that offered all the tests (with all 4 MMR proteins and genes) considered in the models.

RESULTS

Literature Review

The preponderance of evidence identified by our review suggested that screening unselected CRC patients for LS index cases with systematically applied tumor-based testing protocols could lead to a substantial reduction in CRC mortality in our patient population.^{7,8} The early modeling studies provided preliminary evidence suggesting that tumor-based LS

■ **Table 1.** Epidemiologic and Cost Assumptions for Model Variables

Variable Description	Base	Range	Reference	Cost
IHC sensitivity	.94	.90-.98	8 ^a	\$230 ^{b,c}
IHC specificity	.88	.84-.92	8 ^a	—
BRAF sensitivity	.995	.98-1.0	12 ^a	\$305 ^b
BRAF specificity	.69	.59-.79	12 ^a	—
BRAF sensitivity-2 (after methyl)	.998	.995-1.0	References 13, 14 as basis for estimates	\$305 ^b
BRAF specificity-2 (after methyl)	0.50	.35-.65	References 13, 14 as basis for estimates	—
Seq-Rearr sensitivity	.99	.98-1.0	Our reference laboratory and others	\$1355 ^b
Seq-Rearr specificity	.99	.98-1.0	Our reference laboratory and others	—
Methylation sensitivity	.93	.90-.96	13, 14	\$295 ^b
Methylation specificity	.985	.97-1.0	13, 14	—
Methyl sensitivity-2 (after BRAF)	.938	.908-.968	References 13, 14 as basis for estimates	\$295 ^b
Methyl specificity-2 (after BRAF)	.975	.960-.990	References 13, 14 as basis for estimates	\$295 ^b
Prevalence of LS among unselected CRC cases	0.036	.028-.044	8 ^a	—
Probability of MLH1 defects among abnormal IHC given presence of LS	0.2450	.1461-.3535	Calculated from references 5 and 8	—
Probability of MLH1 defects among abnormal IHC given absence of LS	0.8220	.7013-.8936	Calculated from references 5 and 8	—

CRC indicates colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome; methyl, methylation of the MLH1 promoter; Seq-Rearr, sequencing-rearrangement analysis.
^aAnd expert opinion.
^bOur reference laboratory.
^cIncludes additional charge for specimen handling.

screening protocols can provide good economic value at the societal level on the order of \$5000 to \$10,000 per life-year (LY) saved.^{13,15-22} A recent modeling study by Mvundura et al, using conservative baseline estimates and modeling more contemporary screening protocols, provided further evidence of the value of this screening; it demonstrated a cost-effectiveness ratio of about \$22,500 per life-year saved (using an immunohistochemistry-first [IHC-first] approach) compared with no LS screening.²³

The review also established that family history approaches have poor sensitivity or specificity for LS case finding under ideal circumstances.^{24,25} Performance in real-world practice would be far less than ideal because of barriers in the collection and interpretation of family history data.²⁶

Limiting screening of CRC cases to persons under 50 years of age, while decreasing the cost of the screening program, would miss approximately 50% of LS cases; thus this approach was judged not sufficiently sensitive for our purposes.^{23,27} There is early evidence that using a prediction algorithm combining pathology and other features might efficiently predict a positive microsatellite instability (MSI) test as a marker for the presence of LS.²⁸ This screening method requires validation, as its performance is likely operator dependent.

Simulation Models

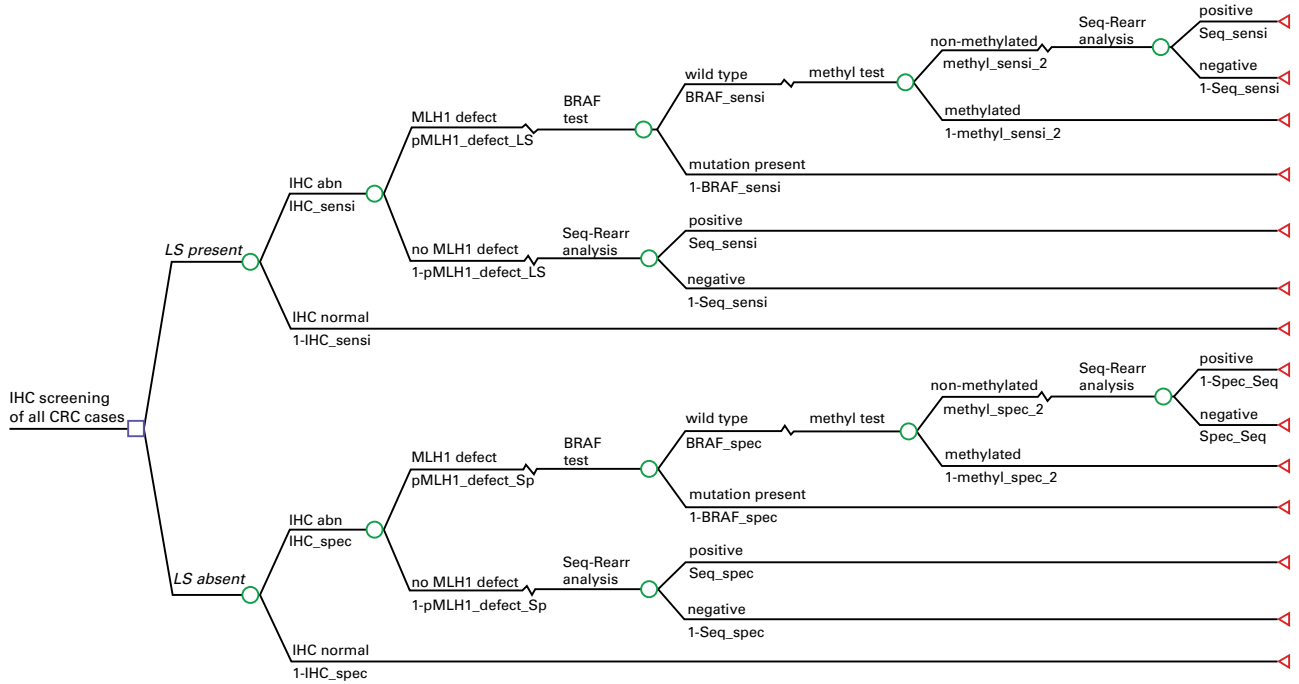
The tests determined to be candidates for initial screening of tumors and thus represented in our simulation models included IHC staining for the 4 MMR proteins, MSI, BRAF mutation, and MMR gene sequencing/rearrangement (ie, deletion/duplication) analyses (Seq-Rearr). Reflex testing after a positive screening test included various combinations of these tests, always finishing with confirmatory Seq-Rearr. Seq-Rearr tests are bundled by our reference lab and thus are treated as a single test in our models. In the final months of the study, evidence regarding the utility of an additional test emerged: methylation of the *MLH1* promoter (methyl), which was added to the models.

Based on published evidence, several options were eliminated early. Screening by Seq-Rearr was not viable due to poor cost-effectiveness.^{16,23} Initial screening by BRAF analysis was ruled out given its low prevalence in the CRC population. MSI-first screening was removed from the final models as evidence emerged that it would be substantially less cost-effective than IHC-first screening because of its inability to target subsequent sequencing with equivalent sensitivity.^{5,7,12,23}

With the decision that only an IHC-first screening approach would be used in our final models, it was recognized that multiple options could be applied after IHC testing. Fol-

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■ **Figure 1.** Model of Our Reference Laboratory’s Lynch Syndrome Screening Protocol



Abn indicates abnormal; CRC, colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome; methyl, methylation of the MLH1 promoter; seq, sequencing; Seq-Rearr, sequencing-rearrangement analysis; sp, sporadic; spec, specifically.

lowing is a list of the final screening protocols identified by our group as viable given currently available tests and evidence. (See **Figure 1** for a schematic of the model structure of the “IHC with BRAF then methyl” protocol.)

- IHC direct to sequencing
- IHC with BRAF
- IHC with methyl
- IHC with BRAF then methyl
- IHC with methyl then BRAF

The BRAF and methyl tests both identify somatic changes in tumors with abnormal IHC for MLH1, which when positive rules out the presence of LS. Their comparative performance has not been well characterized. Combining data from 2 studies identified late during our study period revealed the performance of these tests (**Table 2**),^{13,14} suggesting why the tests would be expected to make different contributions to overall LS screening/testing performance.

The aforementioned studies performed both tests on cases with and without LS, which enabled us to use the data as the basis for estimation of the correlation or dependence of sensitivity and specificity pairs, referred to as CD. When statistically significant, these relationships alter the

sensitivity and/or specificity of the second test when used in sequence.²⁹ The revised test performance parameters were used to adjust for the CD phenomena in 2 of the 5 testing protocols.

Table 3 provides best estimates of the primary outcomes of the 5 protocols, with 95% confidence intervals for total program costs and number of LS cases expected to be identified in a cohort of 100 CRC cases, calculated by Monte Carlo simulation and modeled at baseline conditions defined in this study, with adjustment for CD of BRAF and methyl tests. IHC with methyl is dominated by IHC with BRAF then methyl (ie, it is both less effective at case finding and more expensive). The IHC straight to sequencing protocol was the most effective of the modeled protocols at finding LS cases, but the expected cost to find 1 additional LS case was more than \$1.5 million over that of the next most efficient protocol.

■ **Table 2.** BRAF and Methylation Test Performance Characteristics

Test	Sensitivity	Specificity
BRAF	1.00	0.692
Methylation	0.931	1.00

■ **Table 3.** Primary Outcomes of Simulation Models

Screen/ Test Protocol	Mean (95% CI) Cost to Test Cohort of 100 CRC Cases ^a	Incremental Cost to Screen ^b	Mean (95% CI) Number of LS Cases Detected ^a	Incremental Increase in Number of LS Cases Detected ^b	Average Cost per Case Detected ^b	Cost to Detect 1 Additional LS Case ^b	Sensitivity of Screening Protocol ^b
IHC with methyl + BRAF	\$34,055 (\$32,332-\$35,744)	—	3.283 (2.75-3.82)	—	\$10,369	—	91.26%
IHC with BRAF + methyl	\$35,025 (\$33,098-\$36,965)	\$972	3.29 (2.75-3.82)	0.0045	\$10,693	\$216,498	91.39%
IHC with methyl (no BRAF)	\$37,020 (\$34,645-\$39,404)	\$1997	3.285 (2.75-3.82)	-0.0027	\$11,266	Dominated	91.25%
IHC with BRAF (no methyl)	\$38,073 (\$35,252-\$41,040)	\$3126	3.3404 (2.79-3.88)	0.0506	\$11,467	\$61,834	92.79%
IHC straight to sequencing	\$44,249 (\$39,958-\$48,505)	\$6360	3.342 (2.79-3.88)	0.0041	\$13,355	\$1,552,345	92.90%

CI indicates confidence interval; CRC, colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome; methyl, methylation of the MLH1 promoter.

^aBy Monte Carlo simulation.

^bBy deterministic analysis.

Local decision makers were interested in additional metrics to help them determine the impact on clinical resources and budget, including the number of CRC patients treated annually within our delivery system for whom tumor tissue was expected to be available for testing (about 335). Our models allowed us to estimate the percentage of total test costs that would fall under Diagnosis-Related Group payment (about 69%) and the percentage of screened patients who would be eligible for sequencing, thus requiring genetic counseling (5%-6%).

From a separate simulation model we determined the impact of compliance in screened CRC patients eligible for Seq-Rearr testing (assumed to be 100% in our primary models). At 50% compliance, for the protocol currently provided by our reference lab, the total cost to screen/test would decrease by about 11% and the cost per case detected would increase by about 79%.

Figure 2 illustrates the 8 variables with the most influence on screening efficiency, based on a 1-way SA. See the **Appendix** for more details.

DISCUSSION

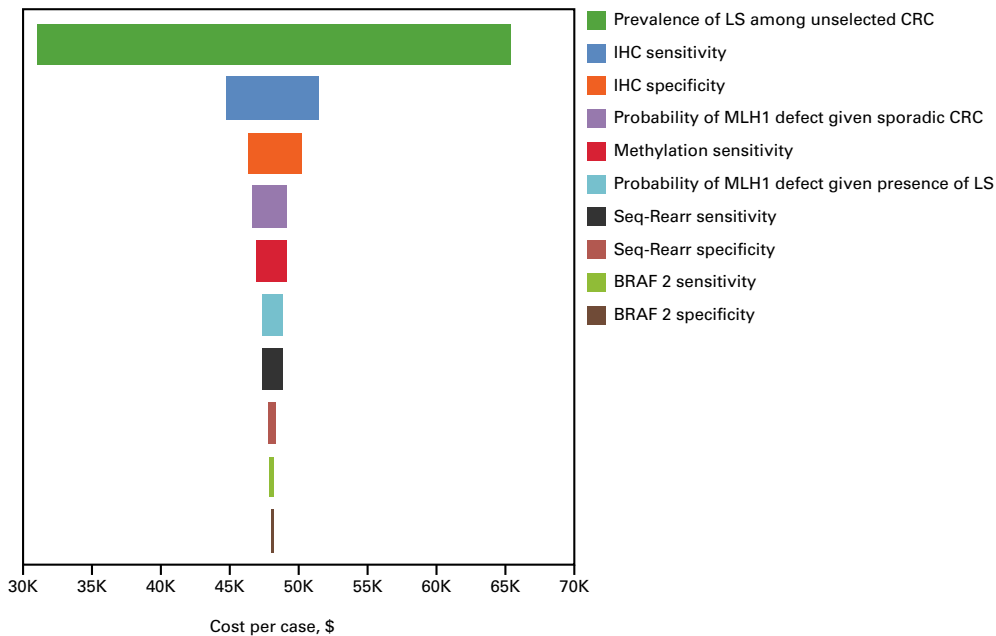
In this study, review and presentation of the evidence led to deliberation by appropriate decision makers within our healthcare system about providing and covering tumor-based LS screening. The review also provided sufficient evidence to rule out multiple screening alternatives, permitting us to focus only on tumor-based protocols that began with IHC testing. Simulation models of the protocols provided point estimates

and plausible ranges of various screening efficiency and business impact metrics of interest to decision makers.

From the results presented in Table 3 it is apparent that, with the exception of the IHC with methyl protocol, the more money spent, the more LS cases can be identified. Performing sequencing on all screen-positive IHC cases, while most effective, is substantially more expensive than the alternatives. The dramatic increase in cost to attain a small increase in detection is difficult to justify from a societal perspective. That left only 3 protocols for us to consider for implementation. Our models suggest that IHC with BRAF then methyl, the standard protocol currently offered by our reference lab, is not the most efficient option. Thus, we must reconcile the high cost to detect 1 additional LS case (best estimate of \$216,498) with the more efficient IHC with methyl then BRAF protocol (not currently available from any commercial lab).

This story is incomplete, however, without considering the uncertainty in the point estimates, reflected by the ranges reported on the 2 key outcomes in Table 3. One-way SA identified that LS prevalence has the biggest impact on the model. The uncertainty associated with this variable can only be substantially reduced by measuring or (validly) estimating the LS prevalence in the population of interest. In our case, we will estimate the LS prevalence in our CRC population via the screening program, with the recognition that we will only be performing the gold standard testing (ie, Seq-Rearr) on cases that screen positive by IHC, with its imperfect sensitivity, and survive the BRAF and methyl rule-out tests. We are currently collecting these follow-up data (see Appendix).

■ **Figure 2.** Multiple 1-Way Sensitivity Analysis (Tornado Diagram) on Cost-Effectiveness



CRC indicates colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome; Seq-Rearr, sequencing-rearrangement analysis.

IHC test performance was the second most influential variable. For our simulation models we used results from the latest study from the Ohio State group⁸ and expert opinion for plausible ranges, because our reference lab could not provide us with estimates of these figures, reflecting the lack of proficiency testing for this assay during our study period. As LS screening involving the IHC assay continues to disseminate, appropriate proficiency testing may become available, thus reducing uncertainty about test performance. Of course, the true value of these test parameters may be lower or higher than our estimates. Our data tracking system may allow us to improve IHC test performance by addressing preanalytic issues (eg, sample preparation and transport) as well as collecting data on uninformative results—a data element that was not modeled.

Consideration of Patient and Family Outcomes

Identification of a patient with LS can have a profound effect on patients and their families. The importance of genetic counseling for patients and family members who were identified to be at risk prior to initiation of the screening program (either on the basis of family history or tumor screening ordered by the treating physician) was already recognized by the organization. Systems were in place to ensure access to these services. The primary question for this analysis was whether the systematic application of tumor-based screening raised issues different from those in existing care practices.

The 2 issues that were identified were whether the tumor screening represented a “genetic test” and whether informed consent beyond that already obtained for the surgical procedure would be required to perform the screening. A group of internal and external experts including medical ethicists was convened to address these issues. The conclusions were that because the test was a screen that required confirmatory molecular testing, the screening itself did not constitute a genetic test; thus, formal consent for the screening was not required. The group also noted that more and more molecular tests are being applied to tumors, and while most do not provide information about a possible germ-line genetic mutation, they are increasingly used to assess prognosis and treatment. To require patients to consent to each of these molecular diagnostics was thought to be unsustainable. It was recommended that educational materials be prepared and distributed to patients prior to surgery, which was done. A number of other healthcare systems that had already embarked on an LS tumor screening program were contacted regarding the consent issue. While some had decided to formally get consent from patients, the majority were not obtaining consent for the screening, but were providing educational materials and using genetic counselors to follow all screen-positive patients.

In order to ensure that outcomes of a positive screen could be appropriately addressed, the screening program was de-

signed so the oncology genetic counselor reviewed all screening results. The genetic counselor was given the responsibility of following up with all screen-positive patients so the concerns of the patients and their families would be addressed in a manner consistent with current practice. The systematic application of this intervention was endorsed by oncology care providers, who recognized that depending on referrals to genetic counseling could result in haphazard follow-up and poor clinical and psychological outcomes.

Policy Implications

It can be quite challenging for a private healthcare system in the United States to base clinical policy decisions on evidence of cost-effectiveness determined from a national perspective. In most cases published models have been structured or framed differently from local care delivery environments and populated with “average” data that are valid for no specific institution, thereby limiting their relevance. However, existing evidence can be used to customize models to answer local questions, as suggested by Sculpher et al.³⁰

Limitations of Study

Our study has several limitations. Our literature searches were limited to those indexed in PubMed and excluded studies not published in English. However, interaction with groups actively collecting data relevant to screening allowed incorporation of the most recent and relevant data prior to its publication, allowing refinement of the model using the most up-to-date information, an approach endorsed by Gudgeon et al.³¹

The conclusion that LS case finding by tumor-based screening results in improvement in health outcomes is, according to the recent EGAPP report, “limited but promising.”⁷ Although the more recent modeling study by Mvundura et al²³ provides additional evidence that LS screening is cost-effective, as a simulation model it cannot be considered high-level evidence. Given that LS screening is rapidly emerging into clinical practice, decisions should be based on the best possible evidence, which simulation modeling can augment.

The results of our internal studies will have limited relevance to some healthcare systems or insurers due to population or operational differences. However, the methods described here could be used to develop customized approaches appropriate to local decision needs.

Future Studies

Given that the primary issue is the impact of LS screening on CRC-related morbidity and mortality of family members of LS probands and that the evidence remains “limited but promising,” the focus of research should be on answering questions at this level. Mvundura et al and Hall discuss the

barriers to successful implementation of LS screening,^{23,32} not least of which are issues related to acceptance of and compliance with testing and CRC surveillance, which are currently not well understood.

Given these knowledge gaps, it is important for systems that do implement LS screening to prospectively collect data on important outcomes. Monitoring outcomes can address many issues, including identification of process failures resulting in errors and missed opportunities. Outcome capture is ongoing in our system.

CONCLUSION

The results of our modeling efforts were useful to internal decision makers and led to implementation of tumor-based screening for LS within our delivery system. This is the first time that a formal decision analysis has been used to guide implementation of clinical services on a systemwide basis within Intermountain Healthcare.

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■ **Appendix. Lynch Syndrome Screening Implementation: Business Analysis by a Healthcare System**

The following information is provided for those interested in additional details about the study, arranged by section to which the comments best apply.

METHODS

We determined **expected annual number of colorectal cancer (CRC) cases within our system** by electronic queries of our internal cancer registry for the years 2002 to 2008, defining colorectal cancer cases as those with a diagnosis that had an ICD-O-3 primary site code of C18.X (colon), C19.X (rectosigmoid junction), or C20.X (rectum), which is the same method used by our state cancer registry. We further refined our estimate of expected cases for screening by determining which of the CRC cases had a surgical resection and pathology specimen, since both the immunohistochemistry (IHC) and microsatellite instability (MSI) assays require a tumor specimen. In the final analyses we used only data from 2005 to 2008 as the basis for estimates of expected CRC cases available for screening, to reflect a change in our oncology services that occurred at the beginning of 2005.

The mean number of CRC cases created annually within our system from 2005 to 2008 was 415. Of these, a mean of 334 tumor specimens (80% of the total) were collected and recorded by our registry. Thus, we took 334 as our best estimate for number of CRC cases expected to be available for IHC screening in a near-term 12-month period within our system.

Assumptions

The baseline prevalence of Lynch syndrome (LS) in the final analytic models among unselected CRC cases was taken to be 3.6%, based on the most recent report by Hampel et al and limited to their most recent cohort of 500 CRC cases.¹ We believe this represents the best estimate for our population based on current case finding methods and in a population with demographics similar to our own. The mean prevalence in the larger Hampel data set (N = 1566),² 2.8%, was chosen to represent a minimum prevalence for the pur-

poses of sensitivity analysis. A value of 4.4% was assigned for symmetry as the upper limit, which falls within the prevalence estimates published in the literature. In addition, the Hampel group identified and reported 13 missense mutations (among the smaller cohort) that were not able to be definitively classified as disease causing at the time of the report.¹ Some of these are likely to be reclassified as disease causing, which would increase the estimated prevalence, meaning that our prevalence estimates are conservative.

The **sensitivity and specificity (s/s) of IHC testing** were also taken from the most recent Hampel et al report.¹ These values were used because they best reflected IHC testing performance with current methodologies in an experienced laboratory. The s/s of sequencing-rearrangement analysis (Seq-Rearr) was taken from values provided by our reference laboratory and was consistent with published data. The s/s of MSI and BRAF testing was taken from Palomaki et al³ and the latter was confirmed by more recent reports.^{4,5} **Sensitivity** of both these tests was defined as the probability of the test result being consistent with the presence of LS. For BRAF, this was based on the presence of BRAF wild type (ie, no BRAF mutation) and for methylation testing on the absence of hypermethylation of the MLH1 promoter (methyl) in known LS cases. Similarly, **specificity** of BRAF or methylation was based on the presence of a BRAF mutation or hypermethylation of the MLH1 promoter in CRC cases without LS (sporadic CRC).

A related issue is the uncertainty in s/s due to test dependence or interaction, referred to as **conditional dependence (CD)** and expressed mathematically as conditional covariance.^{6,7} Among the tests considered in our study, the tests most likely to be conditionally dependent are BRAF and methylation (of MLH1 promoter). Late in the study we were able to identify 2 studies that provided data,^{4,5} combined in **Appendix Table 1**, enabling us to (1) confirm the estimates of BRAF s/s calculated by Palomaki et al,³ thereby also validating this new data set; and (2) provide the basis for estimating CD parameters using the CD calculator developed by Gardner et al.⁶ This was

■ **Appendix Table 1. Test Performance Data of BRAF and Methylation Testing From Published Literature**

LS Present	Methylation Test		LS Absent	Methylation Test		
	Positive (Not Hyper-methylated)	Negative (Hyper-methylated)		Positive (Not Hyper-methylated)	Negative (Hyper-methylated)	
BRAF Test	Positive (wild-type)	27	2	Positive (wild-type)	0	8
	Negative (mutation)	0	0	Negative (mutation)	0	18

LS indicates Lynch syndrome.

an important development, enabling us to model 2 additional screening protocols, 1 of which represented the protocol offered by our reference laboratory, which had recently added methylation testing to its testing cascade. These were “IHC with BRAF then methyl” (our reference lab’s protocol) and “IHC with methyl then BRAF.” The CD calculator matched precisely the point estimates of Palomaki et al³ (sensitivity = 1.00 and specificity = 0.69) when *s/s* definitions were reconciled.

By definition, when either the sensitivity or specificity of 1 or more of the test pairs is 100%, as was the case in this data set (BRAF sensitivity, methyl specificity), CD cannot be calculated and thus is considered not to exist for that test performance parameter (eg, sensitivity). To explore the possibility of CD between the 2 tests and because we believed that as more data become available, the perfect performance of BRAF sensitivity and methyl specificity will disappear (as has turned out to be the case with BRAF), we created a virtual population by multiplying the observed table values by 5 and then moving 1 subject into the false-negative cell (with zero counts) for sensitivity and 1 into each of the zero count cells in the positive methyl result cells in such a way as to be consistent with the observed sample and to yield calculated sensitivity values fully consistent with published values. This gave nonzero estimates for *s/s* while retaining the overall relationship seen in the sample. Proportions from this virtual population were then used in the CD calculator to determine whether CD existed in the virtual population and, if so, how the performance of these 2 tests would be affected when used serially. The CD calculator yielded “virtual” sensitivities, adjusted for CD, for BRAF of 1.00 (no decrement) and for methyl of 0.938 (vs 0.931), and adjusted specificities for BRAF of 0.50 (vs 0.693) and for methyl of 0.975 (vs 0.985). Conclusions drawn from this use of limited data must be tempered, of course. However, it allowed us to explore the possible impact of CD between 2 tests that are generally believed to measure the same biologic phenomena, while awaiting the availability of more data. The test performance characteristic that changed most as a function of its CD (with methyl) was BRAF specificity.

An additional source of uncertainty in modeling is **correlation between variables**, such as the multiple tests in this analysis. Correlation is where change in 1 variable predicts the direction of change in another, and assignment of correlation coefficients also specifies the magnitude of change of the correlated variable. The classic correlation between *s/s* of tests is inverse (<0 to -1.0), reflecting the trade-off between the true-positive and false-positive rates in receiver operating curve analysis. This classic inverse correlation is based on analytic validity of tests (ie, the accuracy with which a particular [genetic] characteristic or marker can be identified in a given laboratory test). The *s/s* of tests in our models were based on

the tests’ clinical validity (ie, the accuracy with which a test identifies or predicts the presence or absence of LS). We ran model simulations both ways, which had no influence on our conclusions. Since we were unable to confidently establish these relationships from available data, we took a conservative approach to this issue and left these variables uncorrelated. If there is, in fact, a strong inverse correlation between *s/s* pairs, the range of outcomes would be compressed, reflecting a reduction of uncertainty. We encourage others to examine this relationship in available data sets if possible, especially in those variables with substantive impact on outcomes.

We are also aware that problems with the **technical performance of the tests** (eg, test failure rate, preanalytic issues) will impact the effectiveness and costs of such a screening program. We did not attempt to model such factors due to their complexity and the lack of available data, but will monitor them as we proceed with the program.

The **costs associated with Seq-Rearr analysis** may, in reality, be somewhat higher in practice due to the fact that abnormal IHC staining patterns often involve 2 mismatch repair (MMR) proteins and the first Seq-Rearr testing effort may fail to identify a mutation, thus requiring a second test to identify the mutated MMR gene. We had no data upon which to base modeling of these events, so our model output reflects only 1 Seq-Rearr test per patient (of those who get to this point in the protocol). We may revisit this variable after we collect enough follow-up data.

The **probabilities representing the proportion of MLH1 defects** among abnormal IHC given the presence or absence of LS were calculated from the most recent Hampel data set (N = 500),¹ the most complete data available to us. We validated these calculations by extending them to the large Hampel data set (N = 1566),² which provided excellent agreement in these proportions. Additionally, we constructed and tested the final models in 2 different software platforms using different modeling structures. For example, the Excel models were structured both by disease (LS) presence/absence and by test (IHC) results first. These represent the 2 primary structures for constructing a diagnostics-based model. The different modeling structures required calculating different parameters (from the source data) in order to populate the models. All 3 modeling structures (the 2 Excel models and the TreeAge model) yielded point estimates of our primary outcomes that were virtually identical (data not presented).

Sensitivity Analysis

There are multiple ways to perform sensitivity analysis; however, the choice of method(s) should be determined by the information needs of decision making.⁸ For this project,

■ **Appendix Table 2. Follow-up Measures**

Measure	Type of Measure	System Level
No. of CRC cases	Process	Macro
By hospital	Process	Macro
No. of CRC cases sent for IHC	Process	Meso
IHC normal	Process	Macro
IHC abnormal	Process	Macro
<i>MSH2, MSH6, PMS2</i> abnormal	Process	Macro
No. of MLH1 abnormal BRAF +	Process	Macro
No. of MLH1 abnormal promoter methylation +	Process	Macro
No. of MLH1 abnormal, BRAF and methylation –	Process	Macro
No. of true-positive patients contacted by CGC	Access/process	Macro
No. of true-positive patients’ physicians contacted by CGC	Process	Macro
Physicians’ reactions to information	Experience	Individual
No. of patients attending counseling session	Access/process	Macro
No. of patients declining counseling (reason)	Outcome/experience	Individual/macro
No. of patients pursuing confirmatory genetic testing	Outcome/experience	Individual/macro
No. of patients declining confirmatory testing (reason)	Outcome/experience	Individual/macro
No. of patients tested with mutation found	Outcome/experience	Individual/macro
No. of patients tested with no mutation found	Outcome	Individual/macro
Insurance coverage for testing	Access	Macro
For mutation + patients and their relatives		
No. of at-risk relatives	Process	Macro
No. of relatives presenting for counseling	Access/process	Macro
No. of relatives pursuing familial mutation testing	Process/experience	Individual/macro
Mutation +	Outcome	Individual/macro
Mutation –	Outcome	Individual/macro
No. of relatives declining testing (reason)	Outcome/experience	Individual/macro
No. of relatives pursuing risk-appropriate surveillance	Outcome	Individual/macro
Mutation +	Outcome	Individual/macro
Mutation –	Outcome	Individual/macro
Mutation unknown	Outcome	Individual/macro
No. of patients with polyps	Outcome	Individual/macro
No. of patients with CRC	Outcome	Individual/macro
Stage	Outcome	Individual/macro
No. of patients with endometrial or other LS tumor	Outcome	Individual/macro
Stage	Outcome	Individual/macro

CGC indicates certified genetic counselor; CRC, colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome; macro level, policy; meso level, healthcare organization; micro level, patient.

that meant applying only relatively simple methods to help bring clarity and confidence to the questions asked by our decision makers and not to apply many of the more complex methods available.

As indicated in the article, we performed multiple 1-way sensitivity (tornado) analyses, both to better understand the variability and uncertainty in the models and to explore the features of the 2 software platforms we were using. Figure 2 in the article is a Tornado diagram that we thought best rep-

resented our series of 1-way sensitivity analyses. This helped us understand where to focus our attention with regard to optimizing the performance of the screening program.

For the purposes of performing model (Monte Carlo) simulations and probabilistic sensitivity analysis (PSA), probability distributions were assigned for all variables with variability or spread. After considerable exploration of the issue, in the end we assigned “triangular” distributions for test performance characteristics and “beta” distributions for

the other probabilities. Both distribution types are considered preliminary distributions, reflecting the nature of available data,⁹ and served our analytic and decision needs. As we revisit our models, using data obtained from follow-up of our program, we will reexamine the selection and parameterization of key variable distribution types. In particular, if we are able to establish data sets we believe represent the variables that substantially impact outcomes, we will develop empirical distribution functions, which capture all the information within the data set and would be expected to best represent a given variable for the purposes of simulation.⁸

The usefulness of PSA was limited to the degree that our PSA told us that we could not be highly (eg, >95%) confident that the differences between the different screening protocols, as expressed by the point estimates, would hold up given the plausible ranges of the model variables. However, our primary decision needs were related more to most likely outcomes than to extreme but plausible outcomes. Therefore, the best estimates, combined with information about the most influential variables on the most relevant outcomes (which varied from one stakeholder to another), potential impact of changing the order of BRAF and methylation testing, and better understanding of their CD has shaped our information/data needs for the future, including what data we will ask our reference lab to provide.

RESULTS

Although we determined through our review of the literature that screening beginning with MSI testing was unlikely to yield a cost-effective protocol, we acknowledge that it could be a viable option under some circumstances, especially when IHC testing from a quality laboratory provider is not available. The decision analytic study of Mvundura et al demonstrated that this option has a cost-effectiveness ratio, compared with no screening program, of just under \$50,000 per life-year saved.¹⁰ Given the conservative nature of this modeling study, it may be that this option could be substantially more cost-effective in a best-case scenario. However, it is unlikely to compare well with screening using the IHC test without some fundamental change in technologies or costs.

DISCUSSION

The Decision-Making Process

In summary, it was determined through our Genetic Testing Practice Council (GTPC) routine horizon scan efforts that screening for LS was emerging as an important way to reduce CRC burden with apparently favorable cost-effectiveness. We performed an in-depth review of the literature to confirm our

initial impression about the issue and presented our findings to our internal Guidance Council.

The Guidance Council supported proceeding with fully characterizing the current state of the evidence and developing decision models to determine the expected performance characteristics of LS screening algorithms and costs. Results from modeling were subsequently brought back to the Guidance Council for review, comment, and ultimately their recommendation to continue to proceed with implementation.

The GTPC leadership then convened an ad hoc group of senior administrative leaders (medical, financial, and health plans) and relevant clinical leaders (surgery, oncology, pathology, primary care) to present the various approaches to LS screening and to make the final case for implementation of LS screening. This group also endorsed implementation of the screening program.

At this point GTPC needed to understand the process to deploy screening, including determining all the providers who would be impacted by the program in order to educate them about the project according to each provider group's role in the process to ensure buy-in and participation. This goal was accomplished by working in concert with champions from each of the clinical groups. The most crucial issue identified was follow-up of patients who screened positive. This barrier was overcome by developing systems to alert the oncology genetic counselor to all positive screening results. The counselor (JLW, who is a member of the GTPC and was involved in this process from the outset) will be responsible for follow-up and counseling of all patients who screen positive. This process took several months and resulted in a pilot program beginning in 2 hospitals that has expanded to most of the delivery system at the time of this writing.

Follow-up Measures to Monitor Screening Program

Appendix Table 2 shows the list of measures we have been collecting since initiating our LS screening program. At the time of this writing (April 2011) the program has been operational for approximately 18 months but has not been put in place by all hospitals. Examination of the data will allow us to determine how well the program is working, weaknesses in the process, and ultimately, whether to continue the program, including extending to all hospitals.

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