Family History Assessment to Detect Increased Risk for Colorectal Cancer: Conceptual Considerations and a Preliminary Economic Analysis

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Abstract

Background: Although the rationale for earlier screening of persons with a family history of colorectal cancer is plausible, there is no direct evidence that earlier assessment is either effective or cost-effective.

Objective: To estimate the clinical and economic effect of using family history assessment to identify persons for colorectal cancer screening before age 50.

Methods: We developed a decision model to compare costs and outcomes for two scenarios: (a) standard population screening starting at age 50; (b) family history assessment at age 40, followed by screening colonoscopy at age 40 for those with a suggestive family history of colorectal cancer. The analysis was conducted using the health insurer perspective.

Results: Using U.S. population estimates, 22 million would be eligible for family history assessment, and one million would be eligible for early colonoscopy; 2,834 invasive cancers would be detected, and 29,331 life years would be gained. The initial program cost would be $900 million. The discounted cost per life year gained of family history assessment versus no assessment equals $38,228. The results were most sensitive to the life expectancy benefit from earlier screening, the cost of colonoscopy, and the relative risk of colon cancer in those with a family history.

Conclusions: The cost-effectiveness of family history assessment for colorectal cancer approaches that of other widely accepted technologies; yet, the results are sensitive to several assumptions where better data are needed. Because of the relatively high prevalence of family history in the population, careful analysis and empirical data are needed. (Cancer Epidemiol Biomarkers Prev 2005;14(11):2494–500)

Introduction

Family history assessment is a potentially valuable tool for reducing the burden of colorectal cancer. People with a first-degree relative (parent, sibling, or child) with colon cancer diagnosed at age <60 years or with more than one first-degree relative diagnosed with colorectal cancer at any age are at increased risk for developing cancer and are more likely to be diagnosed at an earlier age (1). Traditional ascertainment of family history in practice is a gateway to find families at high risk for rare single-gene Mendelian disorders. Moreover, family history is also an independent risk factor, reflecting multiple genes of higher prevalence and environmental exposures that are as yet poorly characterized. More than identifying relatively rare families with extreme cancer risk, family history assessment’s major potential benefit may thus lie in identifying large numbers of persons who are at moderately increased risk for developing colorectal cancer. Accordingly, several clinical practice guidelines recommend that persons meeting family history criteria should be advised to begin colon cancer screening at an earlier age than the general population (2-5).

Although the epidemiologic and biological rationale for earlier screening of persons with a family history is plausible, there is no direct evidence that earlier screening is either effective or cost-effective. Family history assessment is not uniformly practiced in clinical settings, and there are no specific programs under way to increase family history assessment in the general population. Additionally, many more people in the population have suggestive family histories than those who carry single-gene disorders for major cancer susceptibility; thus, any assessment program will result in many more false than true positives. The clinical and economic implications of promoting population-wide family history assessment are great: tens of millions of adults would be assessed, and 10% to 15% of those evaluated would likely meet criteria for more aggressive screening programs (2, 3). Implementing such programs would also greatly affect primary care physicians, specialists, and public and private health care payers.

To better evaluate these issues, we developed a decision model to characterize the clinical and economic implications of implementing family history assessment programs in primary care settings to identify persons at increased risk for developing colorectal cancer. Our model addresses people at “moderate” risk of colorectal cancer because of their family history and does not address the costs and benefits of assessment for rare Mendelian disorders, such as familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer, as they have been discussed elsewhere (6-9).

Materials and Methods

Conceptual Issues. The preclinical course of colorectal cancer in persons with a family history of colorectal cancer but do not carry high-risk mutations is not well known. There is widespread agreement that most colorectal cancers develop from adenomatous polyps, although the true proportion is a source of some debate (10, 11). Persons with a family history of colorectal cancer are more likely to develop cancer at a
For decision modeling, it is important to be precise in defining the family history criteria, as well as the age at onset, mode, and frequency of screening of persons with a “positive” family history. It is also necessary to make certain simplifying assumptions to make the modeling exercise tractable and to convey important concepts with clarity. We know that a certain fraction of healthy individuals in a population will develop colorectal polyps, and that the number of polyps observed in a given population increases with the age of the cohort. In the absence of screening, a fraction of the polyps that develop will transform into invasive cancers; current estimates suggest that about 5% will do so (15-17). The sojourn time from polyp onset to invasive cancer will vary but on average may be 5 to 10 years (13, 18, 19). Figure 1A displays this concept of polyp development and transformation. Polyp behavior may be different in persons who, because of their family history, are at increased risk for colorectal cancer. Below, we outline two possible approaches to characterizing polyp development and transformation in those with a family history.

“Polyp Age Shift” Hypothesis. One plausible scenario is that persons with a family history develop more polyps at an earlier age. In this case, rate of development and risk of transformation into invasive cancer are the same as for those without a family history but because individuals have more polyps, more are available to transform into cancers at a younger age. (Fig. 1B) The rare inherited condition familial adenomatous polyposis, caused by a mutation in the adenomatous polyposis coli (APC) gene, is often offered as biological support of this hypothesis. Persons with familial adenomatous polyposis develop thousands of polyps throughout their colon at a very young age, and although the risk of any one polyp progressing to colorectal cancer is very modest, the sheer number of polyps results in affected persons having a near 100% chance of developing colon cancer before age 60 (20). Other evidence can be found in an analysis of two large cohorts involving >840,000 patient-years of follow-up, where a family history of colorectal cancer was associated with a significant increase in risk in younger persons (1.7- to 4-fold increase between ages 40 and 60 years) but not with a significantly increased risk for persons older than age 60 (21).

“Aggressive Polyp” Hypothesis. Another plausible scenario is that persons with a family history develop polyps at the same rate as those without family history, but the risk of transformation into invasive cancer is greater (Fig. 1C). In addition to higher rates of transformation, the dwell times for “aggressive polyps” may be shorter than polyps in those without a family history. There is some biological evidence that polyps behave more aggressively in persons with a family history. Expansion of the proliferative compartment of epithelial cells in colonic crypts and colonic adenomas have been described in individuals from families with high rates of colon cancer (22). It has been noted that DNA methylation is a common characteristic in colorectal tumors, and that patients with extensively methylated tumors are also more likely to have early onset cancer and affected family members (23-25). Epidemiologic studies have shown that adenomatous polyps diagnosed in a first-degree relative before age 60 increases the risk of colorectal cancer (1). This evidence suggests that genetic factors may predispose persons to such problems as DNA methylation and thus higher risk for neoplastic transformation, even if the number of adenomatous polyps that develop are similar to those without a family history.

The true pathophysiology of colorectal cancer in persons with a family history is likely to be a hybrid of both the stage shift and aggressive polyp hypotheses. Discovering this process (as well as the degree of heterogeneity) is critical to devising an efficient assessment strategy for this population.

Table 1. Recommendations regarding use of family history to assess risk of colorectal cancer

<table>
<thead>
<tr>
<th>Source</th>
<th>Risk categories</th>
<th>Screening schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Cancer Society (34)</td>
<td>CRC or AdP in ≥1 first-degree relative before age 60 or ≥2 first-degree relatives at any age (excluding HNPCC and FAP)</td>
<td>Colonoscopy every 5-10 y, starting at age 40</td>
</tr>
<tr>
<td>American Gastroenterological Association (2)</td>
<td>≥2 first-degree relatives with CRC/AdP, or ≥1 first-degree relative affected before age 60, 1 first-degree relative affected with CRC/AdP at or after age 60</td>
<td>Colonoscopy every 5 y, beginning at age 40 or 10 y before youngest diagnosis in family, whichever came first</td>
</tr>
<tr>
<td>Canadian Task Force on Preventive Health Care (35)</td>
<td>1 or 2 first-degree relatives with CRC, &gt;2 relatives with CRC</td>
<td>Same as average risk, but beginning at age 40</td>
</tr>
<tr>
<td>U.S. Preventive Services Task Force</td>
<td>≥1 first-degree relative with CRC onset before age 60</td>
<td>Same as average risk</td>
</tr>
</tbody>
</table>

Abbreviations: AdP, adenomatous poly; CRC, colorectal cancer; FOBT, fecal occult blood testing; Flex sig, flexible sigmoidoscopy; HNPCC, hereditary nonpolyposis colorectal cancer; FAP, familial adenomatous polyposis.

*Used for the current analysis.
effectiveness of new therapy compared with the existing therapy. The difference in costs over the difference in effectiveness of family history assessment versus standard care, known as the incremental cost-effectiveness of family history assessment, can be derived using the following formula:

\[
\text{Incremental Cost - effectiveness Ratio (ICER)} = \frac{C_{\text{FmHx}} - C_{\text{SC}}}{E_{\text{FmHx}} - E_{\text{SC}}}
\]

where \(C_{\text{FmHx}}\) and \(C_{\text{SC}}\) refer to average total costs, and \(E_{\text{FmHx}}\) and \(E_{\text{SC}}\) refer to average total effectiveness for the family history assessment and standard care arms, respectively. In the family history assessment arm, individuals incur screening costs (and polypectomy costs) but are spared from the treatment costs of colon cancer. In the standard care arm, no screening costs are incurred, but care costs are incurred for those who present as clinically diagnosed colorectal cancers before age 50. Effectiveness can be defined as polyps detected, invasive cancers prevented, life years gained, or quality-adjusted life years gained. Costs and benefits are considered as they accrue over a lifetime starting from the point of assessment (or no assessment) family history.

**Model Assumptions.** Our model is designed to compare two scenarios: (a) population screening using colonoscopy beginning at age 50 (standard care); (b) family history assessment at age 40, with stratification into those who begin screening with colonoscopy at age 40 (“positive family history”) and the remainder who would begin screening at age 50 (Fig. 2). Models must make assumptions about the disease, the setting in which assessment for the disease will take place, and the perspective of the analysis; that is, from what (or who’s) point of view the analysis is structured. Our model starts with the assumption that disease progression follows the “polyp age shift” hypothesis, because this idea seems to underlie the majority of screening guidelines for persons with a family history. Specifically, the model characterizes persons with a suggestive family history of colon cancer as having a higher than average risk of developing a polyp at age 40 than an average risk person (no family history). We will later analyze the cost-effectiveness of assessment guidelines under the “aggressive polyp” hypothesis. In the aggressive polyp scenario, the model assigns a higher risk of malignant transformation for each polyp. Polyp sojourn times are based on estimates in the published literature. The setting includes all U.S. residents ages 40 to 45 years with a “positive” family history and therefore would be eligible for screening. In accordance with current guidelines, those with one or more first-degree relatives who were diagnosed with colorectal cancer before age 60 years or with two first-degree relatives diagnosed at any age are considered “positive” and therefore eligible for screening (2). We exclude those with histories suggestive of familial cancer syndromes (e.g., hereditary nonpolyposis colorectal cancer and familial adenomatous polyposis), as they are a small proportion of those having close relatives with colon cancer, screening guidelines are quite different (7, 27), and cost-effectiveness analyses have already been conducted for these syndromes (6, 8). Following guideline specifications for screening frequency for persons with the family history noted above, we assume that those who are eligible begin colonoscopy at age 40 are screened every 10 years thereafter (2).

Many epidemiologic and clinical factors will determine the efficacy and cost-effectiveness of family history assessment, and we must make assumptions about these for our base case. For example, the accuracy with which family histories are elicited and the choice of the screening modality and accuracy of that modality; individual adherence to screening recommendations, the clinical benefits for those who are

<table>
<thead>
<tr>
<th>Age</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel A</td>
<td>No Family History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panel B</td>
<td>Family History</td>
<td>Age-shift</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panel C</td>
<td>Family History</td>
<td>Aggressive polyp</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
screened (compared with no screening) in terms of number of advanced malignancies prevented, and years of life saved through screening. Table 2 lists factors that were explicitly considered for the model and values and ranges chosen for those factors. The analysis takes the perspective of assessment from a ‘best case’ perspective (i.e., with variables that are generally favorable to assessment). If family history assessment is not cost-effective under favorable assumptions, it is unlikely to improve under less favorable (more realistic) assumptions. This is done to focus the analysis on the incremental benefits of having a national policy of beginning colon cancer assessment at age 40 (through risk stratification) rather than age 50. Later in the sensitivity analysis, we vary these estimates across a range of plausible values and determine how these changes influence the outcome of the analysis.

Sensitivity Analysis. Sensitivity analysis tests the robustness of the model to changes in values for input variables. We performed one-way sensitivity analysis on all variables in the model and then arranged them in order based on the variables that had the greatest effect on the overall cost-effectiveness of the model. Ranges for each variable were based on 95% confidence intervals if available from the source data or by expert opinion.

We also did a multiway sensitivity analysis of the model. This was done by creating probability density functions for each variable and then randomly drawing observations from those distributions and rerunning the analysis while tracking descriptive statistics (mean, SD) of several key outputs. When these statistics converged (did not change more than +1.5% between successive simulations), we halted the simulations. In cases where the distributions were unknown, we created triangular distributions with mean values equal to the base case value for the model, and the extremes at either end of the ranges used in the one-way analysis. The array of cost-effectiveness outcome points were then mapped onto a cost-effectiveness plane and 95% confidence intervals were tabulated.

Results

Among the 22 million persons ages 40 to 44 years, we assume half would receive family history assessment during a visit to physician offices. Family history assessment would identify

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**Table 2. Data used to inform the decision model**

<table>
<thead>
<tr>
<th>Item</th>
<th>Input</th>
<th>Low</th>
<th>High</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of family history screen</td>
<td>1st/3rd of level III office visit, new patient ($40)</td>
<td>32</td>
<td>100</td>
<td>HCPC 99204 (36)</td>
</tr>
<tr>
<td>No. eligible screenees, U.S.</td>
<td>Adults age 40-44: 22,441,863</td>
<td>—</td>
<td>—</td>
<td>U.S. Census (37)</td>
</tr>
<tr>
<td>Proportion assessed for family history at age 40</td>
<td>50%</td>
<td>30%</td>
<td>70%</td>
<td>Estimate</td>
</tr>
<tr>
<td>Proportion with positive FmHx</td>
<td>9%</td>
<td>8%</td>
<td>15%</td>
<td>PLCO trial (38)</td>
</tr>
<tr>
<td>Lead time for polyps</td>
<td>6.4 y</td>
<td>4 y</td>
<td>9 y</td>
<td>Moss et al. (39), Launoy et al. (40)</td>
</tr>
<tr>
<td>Proportion of polyps that do not progress</td>
<td>0.95</td>
<td>0.8</td>
<td>0.99</td>
<td>Shinya et al. (15), Rex et al. (16), Gschwanter et al. (17)</td>
</tr>
<tr>
<td>Risk of perforation, screening colonoscopy</td>
<td>1.96 per 1,000</td>
<td>0.5 per 1,000</td>
<td>2.5 per 1,000</td>
<td>Gatto et al. (41), Gschwanter et al. (17)</td>
</tr>
<tr>
<td>Screening colonoscopy cost</td>
<td>$723</td>
<td>$600</td>
<td>$1,500</td>
<td>HCPC G0105* (36, 42)</td>
</tr>
<tr>
<td>Proportion of positives receiving colonoscopy (adherence)</td>
<td>75%</td>
<td>50%</td>
<td>100%</td>
<td>Estimate</td>
</tr>
<tr>
<td>Relative risk of developing colorectal cancer in person with family history, age 40-50</td>
<td>2.25</td>
<td>1.8</td>
<td>2.7</td>
<td>Johns et al. (43)</td>
</tr>
<tr>
<td>Probability of developing colorectal cancer, age 40-50</td>
<td>0.185%</td>
<td>0.148%</td>
<td>0.222%</td>
<td>SEER STAT (44)</td>
</tr>
<tr>
<td>Life expectancy benefit for avoidance of colorectal cancer age 40-50</td>
<td>10.35</td>
<td>5</td>
<td>12</td>
<td>Calculated (see article), Sonnenberg et al. (45)</td>
</tr>
<tr>
<td>Cost of treating perforation</td>
<td>$15,684</td>
<td>$10,000</td>
<td>$20,000</td>
<td>HCPC 45385, 88305* (36, 42)</td>
</tr>
<tr>
<td>Cost of polypectomy and pathologic evaluation</td>
<td>$1,036</td>
<td>$800</td>
<td>$1,500</td>
<td>Brown et al. (46)</td>
</tr>
<tr>
<td>Lifetime cost of treatment for colorectal cancer in age 40-50</td>
<td>$51,600</td>
<td>$40,000</td>
<td>$60,000</td>
<td>Estimate</td>
</tr>
<tr>
<td>Efficacy of colonoscopy for removing precancerous polyps</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discount rate for future costs and life years</td>
<td>3% per annum</td>
<td></td>
<td></td>
<td>Gold et al. (47)</td>
</tr>
</tbody>
</table>

*HCPC G0105 screening colonoscopy, high-risk individual (physician fee, $390; facility fee, $333).
†HCPC 45385 lesion removal colonoscopy (physician fee, $599; facility fee, $333); 88305 Tissue exam by pathologist ($104).

Abbreviations: HCPC, Healthcare Common Procedure Code; PLCO, prostate, lung, colon, and ovary.

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Sensitivity Analysis. We varied individual inputs into the model to determine their effect on the overall cost-effectiveness of the assessment strategy. Figure 3 shows the results for the 15 variables that had the greatest effect on the outcome. By far the most important variable was the survival gain among those who have precancerous polyps removed. The next most influential factors, in declining order of importance, are the cost of colonoscopy, and the baseline risk of colorectal cancer between ages 40 to 49 in the average risk population.

We conducted an n-way probabilistic sensitivity analysis, based on replications of the analysis with values drawn from distributions for the 15 most sensitive variables from the one-way analysis. This analysis shows a mean cost-effectiveness of $94,428 per life year gained (median = $87,675), and a 90% confidence interval range from $53,705 per life year gained to $152,655 per life year gained. Based on these results, Fig. 4 shows a cost-effectiveness acceptability curve for family history assessment.

Outcomes Under an Aggressive Polyp Scenario. Under the aggressive polyp scenario, most polyps arise after age 40, but a higher proportion transform into invasive cancers. In this case, screening colonoscopy at age 40 for those with suggestive family histories will identify fewer polyps that are destined to become invasive cancers. If we assume that 50% fewer polyps destined to become cancers are not detected at age 40 because they would develop after the initial screening but prior to age 50, the cost-effectiveness of assessment decreases to $121,922/ life year saved.

Discussion

Family history assessment for colorectal cancer susceptibility is a costly but potentially beneficial intervention that has feasibility for implementation in clinical practice. We built a decision model to evaluate the cost-effectiveness of implementing such a program. Under generally favorable assumptions towards family risk assessment and using the early-onset hypothesis of polyp behavior in persons with family history, family history assessment may be modestly cost-effective. The most important factors influencing the outcome are the life expectancy gain for persons who undergo regular colonoscopy screening and the cost of colonoscopy. If polyp behavior is substantially different than theorized, simply shifting screening to an earlier age is much less cost-effective. Additional research that better defines the benefits of colonoscopy in 40-year-olds with suggestive family histories and clearer delineation of polyp behavior are the most critical information that is needed to better define the cost-effectiveness of assessment.

Our model does not address several other issues that ultimately will determine the success and cost-effectiveness of family history assessment. First, it is not clear how many individuals visit primary care physicians for preventive care near age 40, particularly men. Second, individuals need to have an opportunity to receive family history assessment. Acute care visits for acute or chronic medical care needs are underused in the United States (28). Studies suggest that risk counseling can improve use of screening services both in those at increased and average risk for colorectal cancer (29-31); yet, it is not known whether counseling at age 40 would translate into higher rates of screening 10 years hence (for those at average risk). This model does not quantify the costs and benefits of identifying those who carry rare mutations with
Figure 4. Cost-effectiveness acceptability curve for family history assessment. Probability that family history assessment is associated with a cost per life year gained that is lower than the corresponding cost-effectiveness ratio (x-axis). The value of the ceiling ratio at a probability of 0.5 is the expected cost per quality-adjusted life years for family history assessment.

Health plans might argue that such payment is not justified until we have direct evidence of benefit, as was obtained for other screening procedures like mammography and colorectal cancer screening after age 50. Certainly, a prospective controlled trial of family history assessment combined with early colonoscopy for those with a suggestive family history would be costly, time consuming, and challenging to implement on a population level. As costly as such trials are in prevention, our analysis suggests that such an investment may be worthwhile, given the substantial potential costs and benefits involved in such programs.

This analysis considers guidelines and screening practices that are widely agreed upon in the United States. Other countries with greater resource constraints on health care expenditures might consider less costly screening modalities (e.g., fecal occult blood testing and flexible sigmoidoscopy) or screening schedules. Simulation models can address the tradeoffs between cost, sensitivity, specificity, and feasibility in these situations.

Acknowledgments

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References

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