Cost comparison of predictive genetic testing versus conventional clinical screening for familial adenomatous polyposis

B Bapat, H Noorani, Z Cohen, T Berk, A Mitri, B Gallie, K Pritzker, S Gallinger, A S Detsky

Abstract

Background—Mutations of the APC gene cause familial adenomatous polyposis (FAP), a hereditary colorectal cancer predisposition syndrome.

Aims—To conduct a cost comparison analysis of predictive genetic testing versus conventional clinical screening for individuals at risk of inheriting FAP, using the perspective of a third party payer.

Methods—All direct health care costs for both screening strategies were measured according to time and motion, and the expected costs evaluated using a decision analysis model.

Results—The baseline analysis predicted that screening a prototype FAP family would cost $4975/£3109 by molecular testing and $8031/£5019 by clinical screening strategy, when family members were monitored with the same frequency of clinical surveillance (every two to three years). Sensitivity analyses revealed that the genetic testing approach is cost saving for key variables including the kindred size, the age of screening onset, and the cost of mutation identification in a proband. However, if the APC mutation carriers were monitored at an increased (annual) frequency, the cost of the genetic screening strategy increased to $7483/£4677 and was especially sensitive to variability in age of onset of screening, family size, and cost of genetic testing of at risk relatives.

Conclusions—In FAP kindreds, a predictive genetic testing strategy costs less than conventional clinical screening, provided that the frequency of surveillance is identical using either strategy. An additional significant benefit is the elimination of unnecessary colonic examinations for those family members found to be non-carriers.

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Keywords: familial adenomatous polyposis; adenomatous polyposis coli gene; cost analysis; genetic testing

In recent years, the genes responsible for a number of adult onset hereditary disorders, including breast and colon cancer and Alzheimer’s disease, have been identified. The cloning of these disease genes, coupled with sensitive and reliable genetic mutation characterisation techniques, has made it possible to identify individuals who have inherited a high risk of developing disease later in life. Predictive genetic testing is thus opening a whole new era of medicine where individuals in high risk families can be screened and counselled before they develop disease. Presymptomatic DNA testing also offers the opportunity for disease prevention by identifying individuals with elevated risk who can benefit from improved surveillance regimens. The potential for cost savings and clinical benefits is significant, particularly as the cost of DNA testing decreases with improvements in the technology.

In this study, we have conducted a cost comparison analysis of predictive DNA testing versus conventional clinical screening for individuals with a family history of familial adenomatous polyposis (FAP). This rare, hereditary, preneoplastic syndrome occurs with a population frequency of one in 10 000.4 The hallmark of FAP is the development of multiple colorectal adenomatous polyps, typically from the age of puberty onwards. An attenuated variant form, known as AAPC, is characterised by either a later age of onset and/or less florid polyposis. The adenomatous polyps progress to malignancy over a variable time period of 5–10 years.4,5 FAP is an autosomal dominant condition associated with a high penetrance and first degree relatives of affected individuals have a 50% risk of inheriting the disease.4,5 Prior to the advent of predictive genetic testing, screening for the appearance of multiple colorectal adenomatous polyps has been the most effective method to identify high risk members of FAP families. Such conventional screening regimens involve frequent colonic examinations by either flexible sigmoidoscopy or colonoscopy, repeated at regular time intervals. Guidelines for screening asymptomatic patients were established by an international consortium which recommended initiation of flexible sigmoidoscopy from age 10–14 years, repeated every two years until age 40, and every three to five years thereafter until age 60.1

In 1991, the genetic defect responsible for FAP was identified and shown to be due to mutations in the adenomatous polyposis coli (APC) gene, a tumour suppressor gene that...
Cost comparison analysis for FAP screening

We evaluated the costs of identifying a germline \( AP\)-mutation in blood lymphocytes of FAP patients, using molecular diagnostic technology currently in use in our laboratory. The direct costs for genetic testing included technologists’ labour time, data interpretation and reporting by a trained scientific or clinical professional, genetic counselling, laboratory supplies, equipment, and overheads. Sample analysis was based on detailed monitoring of all screen tests. Supplies (for example, chemicals and reagents, disposable) were valued based on the replacement prices and also included an estimate of wastage. All essential laboratory equipment (for example, centrifuges, gel electrophoresis apparatus, etc.) were valued using current replacement costs, on an “annualised” basis using a 5% discount rate, and with an assumed working life of five years. Equipment costs per sample were derived by estimating the optimal laboratory caseload. Twenty per cent of total testing costs were allocated to overheads, accounting for laboratory quality assurance services, general utilities, and other operating inputs not identified above, including freight. Two technologists each devote one half of their time to the genetic analysis, and labour costs were based on the technologists’ actual gross annual earnings including benefits, and adjusted to account for holiday and sick leave. Molecular diagnostic test design, data interpretation, and reporting were estimated to be one hour for proband and a half an hour for each at risk relative. Genetic counselling was two and a half hours of contact time per proband, and three hours for each at risk relative. Counselling time was based on both direct (for example, pretest explanation, discussion of results) and indirect (phone correspondence, paperwork) communication with each family member, and valued using the (adjusted) salary grade for genetic counsellors.

**Methods**

**PATIENT ACCRUAL**

Patients with FAP and their families were identified through a familial Gastrointestinal Cancer Registry located at the Mount Sinai Hospital, University of Toronto. To date, 257 unrelated FAP families have been registered. Patient specimen and data accrual described in this study were carried out according to a protocol approved by the Human Ethics Committee, University of Toronto.

**GENETIC TESTING**

A genetic testing algorithm has been established in our laboratory and employs initial screening for the two most frequent mutations, at \( AP\) codons 1061–1063 and 1309–1311 by heteroduplex analysis (HDA). If mutations are not detected by this screen, the \( AP\) gene is analysed by protein truncation test (PTT) assay as described previously. For PTT assay, the entire coding region of the \( AP\) gene is divided into six overlapping segments and sequentially analysed. To date, 124 FAP families have been screened by PTT analysis of the entire coding region of the \( AP\) gene and truncating mutations have been identified in 92 families, indicating a 74% (92/124) sensitivity for the PTT assay.
per cent of the total costs for each procedure was allocated to overheads, accounting for administrative and support services, utilities, and cost for use of the clinic space.

Figure 1  Decision model used in the cost comparison analysis of predictive genetic versus clinical screening strategy. The two options, genetic versus clinical screening, are indicated by the shaded square on the left. Each shaded circle represents chance events; rectangles on the extreme right represent outcomes corresponding to that path in the decision tree; *complementary probability.

### Table 1  Baseline estimates used in the decision model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interpretation</th>
<th>Baseline value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>pSens</td>
<td>Sensitivity of genetic strategy for APC mutation in proband</td>
<td>0.74</td>
<td>18, 23</td>
</tr>
<tr>
<td>p15</td>
<td>Proportion of relatives ages 10 and 20 years</td>
<td>0.60</td>
<td>†</td>
</tr>
<tr>
<td>p25</td>
<td>Proportion of relatives ages 20 and 30 years</td>
<td>0.20</td>
<td>†</td>
</tr>
<tr>
<td>p35</td>
<td>Proportion of relatives ages 30 and 40 years</td>
<td>0.20</td>
<td>†</td>
</tr>
<tr>
<td>pCarry</td>
<td>Risk of carrying APC mutation</td>
<td>0.50</td>
<td>†</td>
</tr>
<tr>
<td>pExp</td>
<td>Degree of expression of APC mutation</td>
<td>0.90</td>
<td>23</td>
</tr>
<tr>
<td>p20</td>
<td>Detection of FAP polyps ages 15 and 25 years</td>
<td>0.90</td>
<td>†</td>
</tr>
<tr>
<td>p30</td>
<td>Detection of FAP polyps ages 25 and 35 years</td>
<td>0.99</td>
<td>†</td>
</tr>
<tr>
<td>p40</td>
<td>Detection of FAP polyps ages 35 and 50 years</td>
<td>1.00</td>
<td>†</td>
</tr>
</tbody>
</table>

†Authors’ estimates.
Cost comparison analysis for FAP screening

Table 3  Clinical screening costs

<table>
<thead>
<tr>
<th>Input</th>
<th>Cost/examination ($/£)</th>
<th>Recommended no of examinations</th>
<th>Cost/patient ($/£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician fees</td>
<td>129.55/80.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other personnel</td>
<td>69.72/43.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other recurrent/ flexible sigmoidoscopy</td>
<td>14.42/9.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% overhead</td>
<td>42.74/26.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic assessment</td>
<td>256.43/160.71</td>
<td>17</td>
<td>2182.35/1363.97*</td>
</tr>
<tr>
<td>Subtotal</td>
<td>42.74/26.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2238.25/1398.91</td>
<td></td>
<td>2238.25/1398.91</td>
</tr>
</tbody>
</table>

Patients aged 10–50 years. *5% discount rate.

Table 4  One way sensitivity analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interpretation</th>
<th>Baseline value</th>
<th>Range of values</th>
<th>Threshold value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>pSens</td>
<td>Sensitivity of genetic strategy for APC mutation in proband</td>
<td>0.74</td>
<td>0.00–1.00</td>
<td>0.10</td>
</tr>
<tr>
<td>p15</td>
<td>Proportion of relatives between ages 10 and 20 years</td>
<td>0.60</td>
<td>0.00–1.00</td>
<td>§</td>
</tr>
<tr>
<td>p25</td>
<td>Proportion of relatives between ages 20 and 30 years</td>
<td>0.20</td>
<td>0.00–1.00</td>
<td>§</td>
</tr>
<tr>
<td>p35</td>
<td>Proportion of relatives between ages 30 and 40 years</td>
<td>0.20</td>
<td>0.00–1.00</td>
<td>§</td>
</tr>
<tr>
<td>pCarry</td>
<td>Risk of carrying APC mutation</td>
<td>0.50</td>
<td>0.00–1.00</td>
<td>0.84</td>
</tr>
<tr>
<td>pExp</td>
<td>Degree of expression of APC mutation</td>
<td>0.90</td>
<td>0.00–1.00</td>
<td>§</td>
</tr>
<tr>
<td>p20</td>
<td>Detection of FAP polyps between ages 15 and 25 years</td>
<td>0.90</td>
<td>0.00–1.00</td>
<td>§</td>
</tr>
<tr>
<td>p30</td>
<td>Detection of FAP polyps between ages 25 and 35 years</td>
<td>0.99</td>
<td>0.00–1.00</td>
<td>§</td>
</tr>
<tr>
<td>p40</td>
<td>Detection of FAP polyps between ages 35 and 50 years</td>
<td>1.00</td>
<td>0.00–1.00</td>
<td>§</td>
</tr>
<tr>
<td>N</td>
<td>Number of relatives in a family</td>
<td>6</td>
<td>1–10</td>
<td>§</td>
</tr>
<tr>
<td>cProb</td>
<td>Cost for genetic testing for APC mutation in proband</td>
<td>420</td>
<td>100–2500</td>
<td>851</td>
</tr>
<tr>
<td>cRel</td>
<td>Cost for genetic testing of each relative</td>
<td>252</td>
<td>100–2500</td>
<td>§</td>
</tr>
</tbody>
</table>

*The threshold* value is a value where the two screening strategies have equal expected costs. If a given variable has a value less than the threshold value, then one strategy is cheaper; if the variable has a value greater than the threshold, then the alternative strategy is cheaper. 

†Assuming the same frequency of clinical screening for both strategies (FAP model A).

‡Assuming annual screening for relatives testing positive for the APC mutation under genetic route (FAP model B).

§The genetic strategy is less expensive than the clinical one over all the given range of values (no threshold).

Sensitivity analysis

All variables of the decision analysis model were examined over a wide range of values in one way sensitivity analyses. The threshold (that is, the point at which two screening strategies have equal expected costs) was determined for each of the variables in order to evaluate the robustness of the results of the baseline analyses under FAP models A and B as described above.

Results

GENETIC TESTING COSTS

The direct cost of genetic testing for the proband was almost twofold more than the cost of subsequent testing of each at risk family member (table 2). Technologist labour and supplies constituted over 50% of the proband costs.

CLINICAL SCREENING COSTS

At our Registry, conventional clinical screening of first degree relatives of FAP patients consists of a baseline flexible sigmoidoscopy at 10 years of age, and follow up every two years to age 35 and every three to five years to age 50 (17 examinations in total). These guidelines are in accordance with internationally accepted protocols of the Leeds Castle Polyposis Group. Table 3 shows the direct costs of clinical screening for each at risk relative up to the fifth decade of life. Physician fees make up 50% of the total costs for each sigmoidoscopic examination.

DECISION ANALYSIS

For our baseline variables under FAP model A, predictive genetic testing strategy for a prototype FAP family is expected to cost $4975/£3109 while clinical screening is expected to cost $8031/£5019. Assuming that each of the remaining baseline variables are constant, the genetic strategy was less expensive over the full range of values for the proportion of relatives in different subgroups of age of screening onset, the degree of expression of the APC mutation, the probabilities of detecting adenomatous polyps within the three age categories, the number of at risk relatives in an FAP family, and the cost of APC mutation identification in the proband. The sensitivity of PTT assay varies from 74% as observed in our laboratory to 85% as reported previously. Decision analysis (table 4) has shown the genetic route to be robust over a wide range of sensitivities (32–100%). In other words, the genetic route will cease to be cost saving only if the sensitivity of the PTT assay for the proband decreases to 0.10 or less (model A). For the same family, under FAP model B, predictive genetic testing costs $7483/£4677 while clinical screening costs $8031/£5019. The genetic route ceases to be cost saving when: (a) the test sensitivity for the proband decreases to less than 0.31; (b) the proportion of subsequent testing of each at risk family member (table 2). Technologist labour and supplies constituted over 50% of the proband costs.
of at risk relatives is 37% instead of 60% for the age of screening onset group 10–20 years; (c) the degree of expression of the APC mutation, defined as the probability of occurrence of adenomatous polyps, decreases to 0.71; and (d) the probability of detection of adenomatous polyps between ages 15 and 25 years falls from 0.90 to 0.20.

Discussion

We performed a detailed comparison of all direct health care costs for genetic or conventional clinical screening for FAP. The predictive genetic testing approach costs about one third to one thirteenth less than that of the conventional clinical strategy over a wide range of variables. Thus, on the basis of economic variables alone, molecular genetic testing was the method of choice. A significant finding of this study was that the predictive genetic testing strategy saved substantial costs only if the sigmoidoscopic surveillance regimens for APC mutation carriers remained the same as for conventional clinical screening. FAP is a paradigm for cancer prevention based on the known adenoma–carcinoma sequence which occurs over an average of 5–10 years. Prophylactic colectomy in affected individuals essentially eliminates risk of colon cancer, although individuals may still be at risk of rectal cancer depending on the specific prophylactic operation performed and subsequent screening of the remaining rectum, and for other extracolonic manifestations associated with FAP. Clinical screening regimens have been established to ensure that at risk offspring and siblings of FAP patients benefit from early diagnosis and treatment. Interestingly, several registries have now advocated annual flexible sigmoidoscopy for presymptomatic family members known to carry an APC mutation.\(^6-27\)

The efficacy of increasing surveillance frequency from a biennial to annual time interval for APC mutation carriers is not yet proved, especially in the absence of histological or clinical data to support such findings. Early studies by Morson (1974) found an average 5% malignancy rate for adenomas over a life span and showed that only a few adenomas in FAP ever become malignant.\(^7\) The minimal interval of five years for such a transition would suggest the lack of an accelerated evolution process, such as that indicated for colorectal adenomas associated with hereditary nonpolyposis colorectal cancer (HNPCC).\(^28\)

The decision analysis carried out in this study was conservative for several reasons. Firstly, if a germline APC mutation is not detected by HDA and/or PTT assay, molecular linkage analysis using intragenic and closely linked polymorphic DNA markers can achieve predictive carrier risk estimates with greater than 99% accuracy in informative families.\(^5\)\(^9\)\(^10\) For families with a suitable pedigree structure, the inclusion of linkage based testing would result in greater cost savings under the genetic route. Several different molecular diagnostic techniques can be used for predictive genetic testing of FAP.\(^6\)\(^9\)\(^17\)\(^27\) The choice of optimal technique(s) is largely dependent on the nature of mutations and the frequency of specific mutations. We chose PTT for mutation analysis as the majority of germline APC mutations are truncating in nature. Another assumption regarding the time span for conventional clinical screening is also conservative as at risk relatives continue to be examined after age 50 years, albeit at a low frequency.\(^4\) Given, however, that the costs for each subsequent procedure following the baseline endoscopy were discounted at a rate of 5% per year to their present values, extension of the screening time frame would not significantly affect our analytical result. Finally, the cost comparison analysis was done with the perspective of a third party payer, and therefore, only the costs directly related to the comparative strategies were considered. Inclusion of direct personal and indirect costs, such as lost productivity of patients and accompanying family members during each clinic visit for a sigmoidoscopic examination, would result in further cost savings under the genetic route.

What are the implications of such a cost analysis for screening members of FAP families? Apart from the lower cost, the genetic route is less invasive, needs to be performed only once, and can be carried out early in life, thereby significantly modifying the inherent risk of FAP in at risk relatives.\(^4\)\(^5\) In individuals identified as high risk, surveillance regimens can also be initiated for extracolonic manifestations such as upper gastrointestinal polyps and cancer. Because the age of onset of FAP adenomas is variable, patient compliance with screening regimens remains an important factor for the optimal management of this disorder. On the other hand, a reduced genetic risk will relieve anxiety associated with frequent colonic examination\(^1\); clinicians can now focus on those asymptomatic patients identified as “high risk” by genetic testing but for whom one cannot predict the clinical sequelae. More importantly, family members identified to be non-mutation carriers can be released from unnecessary clinical surveillance. From the analysis presented here, we conclude that substantial direct cost savings could result from the adoption of a genetic screening strategy for FAP, but only if the frequency of sigmoidoscopic screening is not increased for asymptomatic patients carrying the APC mutation. Given the limited health care resources available, not only to screen and treat but also to counsel affected FAP families, it would seem prudent to remain focused on a biennial screening regimen.

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