# Probabilistic Cost-Effectiveness Comparison of Screening Strategies for Colorectal Cancer

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A stochastic discrete-event simulation model of the natural history of Colorectal Cancer (CRC) is augmented with screening technology representations to create a base for simulating various screening strategies for CRC. The CRC screening strategies recommended by the American Gastroenterological Association (AGA) and the newest screening strategies for which clinical efficacy has been established are simulated. In addition to verification steps, validation of screening is pursued by comparison with the Minnesota Colon Cancer Control Study. The model accumulates discounted costs and quality-adjusted life-years. The natural variability in the modeled random variables for natural history is conditioned using a probabilistic sensitivity analysis through a two-stage sampling process that adds other random variables representing parametric uncertainty. The analysis of the screening alternatives in a low-risk population explores both deterministic and stochastic dominance to eliminate some screening alternatives. Net benefit analysis, based on willingness to pay for quality-adjusted life-years, is used to compare the most cost-effective strategies through acceptability curves and to make a screening recommendation. Methodologically, this work demonstrates how variability from the natural variation in the development, screening, and treatment of a disease can be combined with the variation in parameter uncertainty. Furthermore, a net benefit analysis that characterizes cost-effectiveness alternatives can explicitly depend on variation from all sources producing a probabilistic cost-effectiveness analysis of decision alternatives.

Categories and Subject Descriptors: I.6.3 [**Simulation and Modeling**]: Applications; I.6.5 [**Simulation and Modeling**]: Model Development; I.6.4 [**Simulation and Modeling**]: Model Validation and Analysis

This research was supported in part by grant RO1CA92653 from the National Cancer Institute.
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DOI 10.1145/1502787.1502789 http://doi.acm.org/10.1145/1502787.1502789

General Terms: Design, Measurement, Verification

Additional Key Words and Phrases: Cost-effectiveness analysis, probabilistic sensitivity analysis, net benefit analysis, acceptability curves, colorectal cancer screening strategies, medical decision-making

**ACM Reference Format:**

Tafazzoli, A., Roberts, S., Klein, R., Ness, R., and Dittus, R. 2009. Probabilistic cost-effectiveness comparison of screening strategies for colorectal cancer. ACM Trans. Model. Comput. Simul., 19, 2, Article 6 (March 2009), 29 pages. DOI = 10.1145/1502787.1502789 http://doi.acm.org/10.1145/1502787.1502789

## 1. INTRODUCTION

ColoRectal cancer (CRC) is the second leading cause of cancer death in the United States. The only effective treatment that permits long-term survival is surgical resection of the cancer when at an early stage. Therefore, early detection and surgical excision of the cancer at an early stage or during its precancerous stages is the critical element of a strategy to reduce CRC-related mortality. Indeed, evidence from several studies suggests that screening for colorectal cancer and precancerous adenomatous polyps and their subsequent removal can reduce both the incidence of and mortality associated with CRC [Hardcastle et al. 1996; Kewenter et al. 1994; Kronborg et al. 1996; Mandel et al. 2000, 1993]. Several diagnostic tests have been developed and are recommended for the early detection of CRC and its precursor lesions. These tests vary widely in sensitivity, specificity, invasiveness, and cost [Pignone et al. 2002]. In addition, these tests can be implemented in a wide variety of strategies that involve one or more tests at varying intervals of time. It is not feasible to conduct clinical trials of all possible screening strategies for CRC. However, simulation models offer an alternative means to evaluate and compare screening strategies [Caro 2005].

We employ the Vanderbilt/NC State (V/NCS) stochastic discrete-event simulation model of the natural history of CRC, which is capable of modeling a population over time and may include a mixture of patients with different birth years, races, genders, and family histories of colorectal neoplasia [Cubbage 2003; Roberts et al. 2008]. Exploiting the object-oriented structure of the model, a screening structure was added to perform deterministic and probabilistic cost-effectiveness analyses of the screening strategies recommended by the clinical guidelines provided by the American Gastroenterological Association (AGA) [Winawer et al. 2003] and some potential strategies employing more recently developed screening modalities. The enhanced model can simulate the effects of various screening, surveillance, and treatment interventions on the morbidity and mortality of CRC in the U.S. general population or in selected subsets over time. This model produces discounted costs and quality-adjusted life-years (QALYs) [Ness et al. 2000] for screening decisions as the primary outcomes, although various natural history data may also be collected and reported.

This research reports on the cost-effectiveness analysis of CRC screening alternatives in a population without a family history of colorectal neoplasia, generally considered low-risk for CRC. Common screening strategies are described

in Section 2, noting recommended screening guidelines and the important role of compliance. The enhancements to the existing V/NCS model for screening are described in Section 3, giving special attention to the parameterization of the screening model components. In Section 4 an effort is made to verify and validate the simulation model with screening. Although the statistical parameters of the natural history model represent the natural variability in the simulated population, there are important parameters related to the screening strategies that are uncertain. Both a deterministic (expected value) and probabilistic sensitivity analysis (Sections 5 and 6) are used to examine alternative screening strategies for populations with low risk of developing CRC. The most cost-effective strategies are compared in a net benefit analysis in Section 7 that produces acceptability curves. Recommendations for screening are thus conditioned on a ceiling ratio. In the final section (Section 8) we argue that the methodology used for this analysis has broader application.

## 2. CRC SCREENING AND SURVEILLANCE STRATEGIES

CRC screening strategies begin with an initial screening test followed by colonoscopy for positive tests. Strategies can be categorized into two groups, depending on whether the initial test is endoscopic or nonendoscopic. Endoscopic tests provide direct views of the lining of the colon. The two types of endoscopy employed in CRC screening are sigmoidoscopy (evaluation of the colon distal to the splenic flexure) and colonoscopy (evaluation of the entire colon).

Nonendoscopic methods may rely on consequences of adenomas or cancers present in the colon or on techniques to indirectly image the colon. Tests, such as the fecal occult blood test or fecal DNA test, indirectly check the colon for abnormalities through examination of the stool. A second type of nonendoscopic test, including virtual colonoscopy and double contrast barium enema applies radiographic techniques to visualize the colon less invasively than colonoscopy.

Screening tests are administered to asymptomatic individuals who are at potential risk for developing colorectal cancer. The tests are used to detect colorectal adenomas or cancer. Sensitivity of a test is its ability to identify true disease, which in the present case refers to colorectal adenoma or cancer. A screening test is highly sensitive if it has few false negatives (missing of an existing adenomatous polyp) and many true positives (detecting of an existing adenomatous polyp) in its results. Specificity is the test's ability to determine there is no disease. High specificity for a screening test means that it generates few false positives ("detecting" a nonexistent adenomatous polyp) and many true negatives (detecting no adenomatous polyp in a normal colon). Since many of the tests have low sensitivity, they miss detecting adenomatous polyps and need to be repeated frequently. Although their specificities are relatively high, the prevalence of colorectal cancer is low in a general screening population, and screening tests can generate many false positive results.[1]

CRC surveillance refers to the follow-up examination of the colon in patients with a prior history of colorectal adenomas or cancer. Because a history

[1]For examples of sensitivity and specificity calculations, see http://www.poems.msu.edu/EBM/Diagnosis/SensSpec.htm.

of colorectal adenomas or cancer is a risk factor for future colonic neoplasia, surveillance regimens are more aggressive than standard screening strategies, meaning the frequency of testing is increased (from http://www.cancer.org).

The most recently updated guideline for colorectal cancer screening and surveillance strategies was released in 2003 by the American Gastroenterological Association [Winawer et al. 2003]. Based on new evidence and experienced judgment, clinical guidelines include different recommendations for people at low and high risk. In this article, the screening strategies studied focus on low-risk (no family history) populations including those recommended in the AGA's clinical guidelines. In addition, six newly proposed screening strategies based on virtual colonoscopy or fecal DNA tests were also examined to compare them with current strategies. The virtual colonoscopy strategies differ in their frequency and the test sensitivity and specificity found in the respective clinical trials [Kay et al. 2000; Pickhardt et al. 2003]. Specifically, the strategies are summarized as:

—No screening;
—Fecal Occult Blood Test every year (FOBT);
—Double Contrast Barium Enema every five years (DCBE);
—Sigmoidoscopy every five years (Sig);
—FOBT every year combined with Sigmoidoscopy every 5 years (Sig & FOBT);
—Colonoscopy every 10 years (Colon 10);
—Virtual colonoscopy Pickhardt every 5 years (Pickhardt 5);
—Virtual colonoscopy Pickhardt every 10 years (Pickhardt 10);
—Virtual colonoscopy Cotton every 5 years (Cotton 5);
—Virtual colonoscopy Cotton every 10 years (Cotton 10);
—Fecal DNA every 3 years (FDNA 3); and
—Fecal DNA every 5 years (FDNA 5).

## 3. EXTENDING THE VANDERBILT/NC STATE MODEL

The Vanderbilt/NC State (V/NCS) model is a stochastic, discrete-event simulation model constructed on an object-oriented simulation platform that has been specialized to model the natural history of CRC in individuals [Roberts et al. 2008]. The discrete-event representation of the natural history models changes in the CRC state (if any) of an individual throughout his/her natural lifetime. Screening can intervene in the CRC process by detecting adenomas and early cancers. Removing these neoplasia changes the future outcomes, thus potentially extending life. The simulation is able to model multiple adenoma life cycles simultaneously for a single individual and to update simulation time only to the next event, providing a variable time update scheme that does not create event collisions within some fixed time increment. Furthermore, unlike strict stochastic process models such as Markov models, arbitrary statistical behavior and complex structure may be incorporated.

### 3.1 Natural Variability in the Simulation Model

The simulation model of the natural history of CRC is composed of over 100 random variables to represent the natural variability expected in any studied population. Time-independent random variables are generally modeled with bounded Johnson distributions [Hahn and Shapiro 1967] and empirical continuous distributions for continuous random variables and with empirical discrete distributions for empirically-based discrete random variables. The choice of the bounded Johnson was based on the flexibility of two shape parameters along with bounded support (lower and upper limit), which conforms to the expected biomedical phenomena being modeled. The time-dependent processes were generally modeled with a Non-Homogeneous Poisson Process [Law and Kelton 2000] having linear rate functions that could be easily parameterized. Empirical estimates of distribution parameters are based on clinical reports, literature, and expert opinion.

Each random variable was parameterized for personal characteristics so that individuals from any population had individualized realizations for each random variable. Because each source of variation in the simulation model had its own random number seed and because each random number obtained was transformed to a single random variate, populations with identical characteristics could be defined for different scenarios. Some of the more prominent random variables included the risk of CRC, the incidence of nonvisible adenomas, the distribution of adenomas within the colon, the rate and progression time of adenomas to cancer based on histopathology, the stage-based transition times toward cancer, and time from cancer to death.

### 3.2 Importance of a Valid Stochastic Model of Natural History

Extensive calibration of the natural history model input was based not only on average or expected outcomes, but also on the range of outcomes produced. In the case of time-dependent outcomes, the character of the time series was carefully examined to insure appropriate patterns such as trends and abrupt changes. The result of these efforts provides strong evidence that the model of natural history is an appropriate approximation of the CRC process. Furthermore, the outcomes from the model not only yield approximate expected values but, as importantly for this analysis, appropriate distributions of these outcomes. Nevertheless, it is important to understand that estimates of output are numerically based and thus require statistical estimation.

### 3.3 Adding Screening and Surveillance

Screening and surveillance variables were added to the original model of the natural history. Each screening test had associated sensitivity and specificity for adenomas and CRC based on adenoma histology at the time of screening (see Tables V and VI in Appendix A). Some modification to the objects and events in the natural history simulation was needed to accommodate screening. Each neoplasm has a separate event calendar that stores all future events associated with it. This design improved simulation efficiency. Since physically removing a neoplasm eliminates all future consequences, the dedicated

event calendar allows removal of all the events related to that neoplasm at once. The scenario object was expanded to include the screening options and parameters. New events were added to the event graph to handle screening events, diagnostic colonoscopy events, surveillance events, and modifications to other events affected by screening and surveillance (see Tafazzoli [ 2004] for details).

### 3.4 Modeling Compliance

For any screening test to be effective, patients must be willing to have the test performed. In the model, CRC screening compliance is defined as a person-specific characteristic that determines the maximum acceptable screening frequency for any given screening modality. The model uses a multinomial distribution to assign a value to the compliance variable. This variable governs whether or not the person is adherent with a given screening test and, if adherent, at what maximum frequency (e.g., a person may be adherent with FOBT but only at a maximum frequency of one time in three years). A binomial distribution controls adherence with colonoscopy to follow-up from a positive screening test and for surveillance.

In our model the computed compliance frequencies for a person are correlated but vary based on the invasiveness of the underlying screening tests. We assumed that the compliance frequency of a person to a more invasive screening modality is always less than or equal to the compliance frequency for a less invasive screening modality. For example, if a person is never compliant to the FOBT screening test (which is not very invasive), then this person will also be considered never compliant to modalities such as colonoscopy and sigmoidoscopy (which are more invasive). This was a clinical judgment provided by our physician coauthors.

## 4. MODEL VERFICATION AND VALIDATION

The verification of the model used procedures to ensure that all portions of the model worked as expected; the validation included examinations to ensure that the model output matched targets obtained from the medical literature. Earlier verification and validation addressed the natural history without screening [Cubbage 2003]. The analysis here compares the simulation output to the Minnesota Colon Cancer Control Study clinical trial results [Mandel et al. 1993].

### 4.1 General Verification

The main purpose of the verification was to ensure that the screening and surveillance models worked as intended. The screening model is programmed using the .NET Visual Studio interactive development environment [Griffiths et al. 2003] that provides a very flexible setting for constructing, compiling, as well as testing and executing code. Taking advantage of these tools and other techniques, two methods were employed to verify the model: (1) stepping through the screening source code line-by-line and routine-by-routine to verify the general program flow, while watching the key variables, and (2) creating and examining an output trace file.

Table I. CRC Death in the Control and Annual Groups of the Simulated Model and Trial Together with the 95% Confidence Intervals

| | Simulation Cancer Death | | | | |
|---|---|---|---|---|---|
| Strategy | Mean | Standard Deviation | Lower Bound | Upper Bound | Trial Cancer Death |
| Control Group | 125 | 13.63 | 121 | 130 | 121 |
| Annual Group | 89 | 9.37 | 86 | 92 | 82 |

The most comprehensive verification occurred when the Visual Studio debugger was used to check the key variables, which were discounted costs and QALYs. These two values are critical to the eventual cost-effectiveness analysis; therefore exact manual verification was done to check that costs and utilities are collected and discounted properly.

### 4.2 Model Validation

A comparison of the Minnesota Colon Cancer Control Study was made to a simulation of that population in order to validate the ability of the V/NCS model to simulate screening strategies over a specific period of time. The Minnesota study population compared the effectiveness of annual and biennial FOBT screening strategies in reducing CRC mortality to a "no screening" program. This trial was chosen because it is the only fully reported, large clinical trial performed within the United States. Other models have used it for validation purposes, since it provides comprehensive output not found in other randomized trials [Pignone et al. 2005].

The Minnesota study was initiated by recruiting 46,551 male and female volunteers ages 50 to 80 from 1975 through 1977 and randomly assigning them to three groups: annual screening, biennial screening, and control (no screening). The participants in these three groups were followed until 1991. During this interval the CRC incidence and mortality were accumulated for all three groups. The final report of this randomized trial revealed a 33% decrease in CRC mortality within the annual FOBT screening group when compared to the control group.

To replicate the population in the Minnesota study, the enhanced V/NCS model was redesigned and a series of Minnesota study-specific parameter values was used. The parameters for age distribution, gender, compliance rate to FOBT and follow-up colonoscopy tests, natural death, and five-year survival of the original simulation model were recalculated to match the inputs reported in the Minnesota study.

The results generated from the V/NCS model are shown in Table I. The CRC mortality in the actual study falls within the 95% confidence interval of the CRC death for the control group of the simulation model as it is shown in Table I. For the annual group this argument is not exactly true but can be satisfied for a slightly smaller confidence value (around 90%). All simulation outcomes were somewhat higher than the actual trial. This result may reflect a higher risk for CRC in the modeled population compared to the actual trial population (which may have been "healthier"). However, the percent decrease in CRC mortality, which was the main result of the Minnesota trial ($\sim$33%) falls

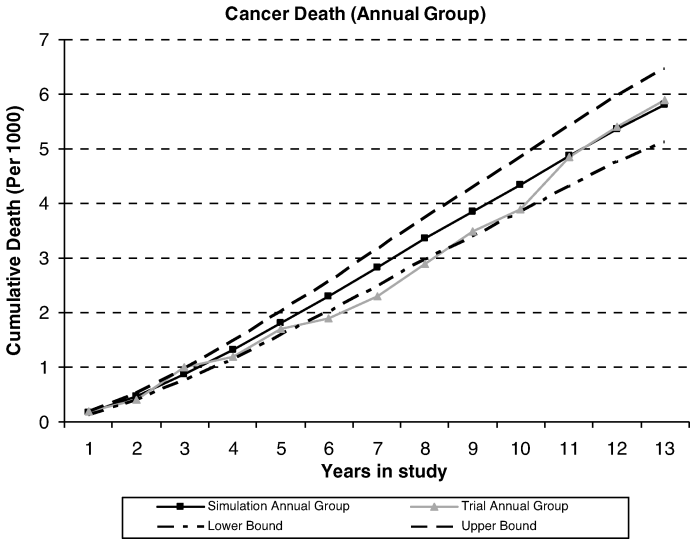


Fig. 1. Actual and simulated CRC mortality together with 95% confidence bounds of the simulated CRC mortality in the annual group.

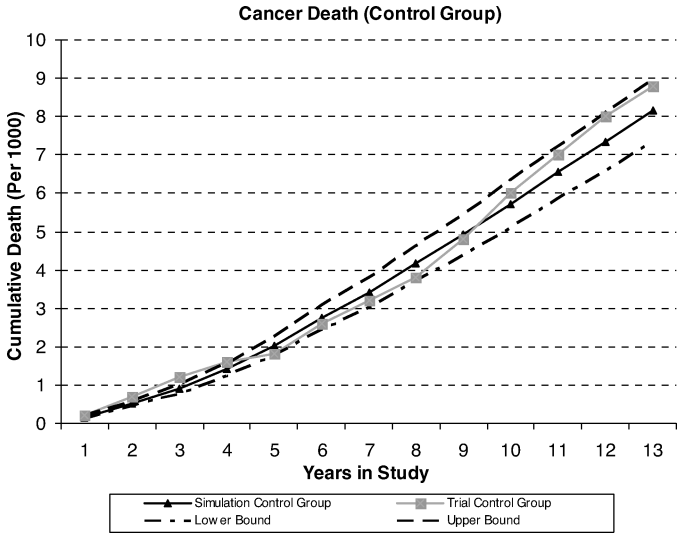


Fig. 2. Actual and simulated CRC mortality together with 95% confidence bounds of the simulated CRC mortality in the control group.

within the expected decrease in death of the simulation model (24% to 34%). This result adds substantial validation to the V/NCS model.

Figures 1 and 2 compare the cumulative CRC mortality during the study years between the actual trial and simulated model for control and annual groups. It is easily seen from these curves that both the annual and control group's mortality curves in the actual trial are almost always within the simulated model confidence limits for the cancer death.

## 5. DETERMINISTIC COST-EFFECTIVENESS ANALYSIS

From an economic viewpoint, cost-effectiveness analysis (CEA) is considered the most appropriate method of comparing preventive health services [Briggs et al. 2002b; Gold et al. 1996]. Its basic purpose is to assess the cost of health care resources dedicated to a health care intervention relative to the health care benefits that are produced by that same intervention.

The central measure in CEA of health care interventions is the (incremental) cost-effectiveness ratio ($CE$), which is the difference in the costs ($C$) of two alternatives divided by the difference in their effectiveness ($E$).

$$CE = \frac{\Delta C}{\Delta E}. \tag{1}$$

The CE ratio is essentially the incremental price of obtaining a unit health effect from a given health intervention when compared with an alternative. If an intervention under study is both less costly and more effective than the alternative, this intervention is said to dominate the alternative and there is no need to calculate a CE ratio. Therefore, CE analysis is performed only in circumstances where the intervention is both more costly and more effective than the alternative. So if $C_B$and $E_B$ represent the cost and effect of the base policy while $C_A$ and $E_A$ represent cost and effect of an alternative policy, the cost-effectiveness ratio is

$$CE = \frac{C_A - C_B}{E_A - E_B}. \tag{2}$$

Interventions that have a relatively low ratio would typically have high priority for resources.

CEA can also reveal trade-offs in choosing among various interventions. Consequently, as the first step, we performed a "deterministic" cost-effectiveness analysis to compare the expected outcomes from the simulations of competing screening alternatives when the best estimates of model parameters were applied (base-case analysis). Thus, the incremental cost-effectiveness ratio (ICER) is estimated from the average of the individual costs and effectiveness (potentially discounted) from the simulation of the base and alternative policies as

$$\widehat{ICER} = \frac{\overline{C}_A - \overline{C}_B}{\overline{E}_A - \overline{E}_B}. \tag{3}$$

The cost of a screening policy includes all direct costs associated with the screening and any related direct medical cost, while "effect" is quality-adjusted life-years (QALYs) observed (for details on these calculations within the simulation, see Roberts, et al. [2008]).

### 5.1 Base Case

Base-case simulations were done using the low-risk population. This population contains one million 50 year-old individuals with no family history of colorectal cancer. In order to resemble the U.S. population, demographic characteristics in this study have the same gender and race proportions reported for the U.S. population in year 2004 (i.e., female: 0.513; fraction white female: 0.883; male: 0.487; fraction white male: 0.899) [U.S.Census Bureau 2004].

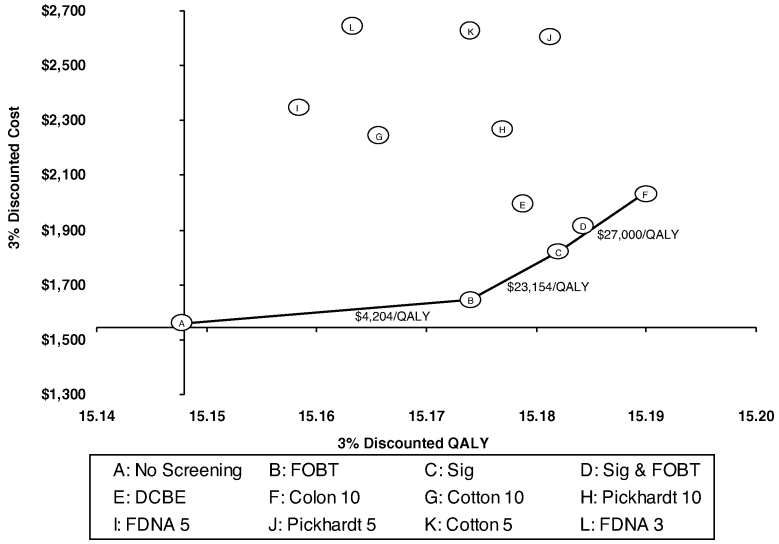


Fig. 3. Baseline cost-effectiveness results on the cost-effectiveness plane for the low-risk population showing the "efficient frontier."

The screening starting age for this population was set to be 50 years. The individuals previously screened for or diagnosed with colorectal cancer before their screening start age were excluded from the population to avoid including costs and QALYs that occur outside the model's time frame. Screening was stopped at age 80 but surveillance continued until life's end.

### 5.2 Results of the Deterministic Cost-Effectiveness Analysis

The results of the deterministic cost-effectiveness analysis are presented on the cost-effectiveness plane in Figure 3, which also shows the efficiency frontier for nondominated strategies. The efficiency frontier is formed by creating linear combinations of screening alternatives with the lowest incremental cost-effectiveness ratios, starting with "no screening" as the initial base. Costs and QALYs were discounted at 3%. The incremental cost-effectiveness ratios were calculated by comparing each strategy to the next less costly and less effective strategy. These results are shown in Table II.

Closer examination of Table II reveals that the DCBE, virtual colonoscopy, and fecal DNA are clearly (or simply) dominated by other choices whose cost is lower and whose QALYs are higher. Sig & FOBT could be eliminated by extended dominance, which means a linear combination of two other choices has a lower cost and higher QALY.

Overall, this analysis showed that No Screening, FOBT, Sig, and Colon 10 strategies are candidate choices depending on the maximum acceptable marginal cost effectiveness in the population. At a commonly estimated acceptable cost-effectiveness ratio (in the U.S.) of $50,000 per QALY, the most cost-effective strategy would be colonoscopy at ten-year intervals. However, a policy maker may also consider clinical, social, and supply issues.

Table II. ICER of Different Screening Strategies for Low-Risk Population

| Rank | Strategy | Lifetime Cost Discounted 3% | QALYs Discounted 3% | ICER ($ per QALY Gained) |
|---|---|---|---|---|
| | SIG & FOBT | $1,915 | 15.1845 | Dominated (Extended) |
| | DCBE | $2,990 | 15.1791 | Dominated (Simple) |
| | Cotton 10 | $2,243 | 15.1657 | Dominated (Simple) |
| | Pickhardt 10 | $2,271 | 15.1773 | Dominated (Simple) |
| | FDNA 5 | $2,343 | 15.1580 | Dominated (Simple) |
| | Pickhardt 5 | $2,610 | 15.1814 | Dominated (Simple) |
| | Cotton 5 | $2,631 | 15.1741 | Dominated (Simple) |
| | FDNA 3 | $2,645 | 15.1632 | Dominated (Simple) |

Note: QALY: Quality-Adjusted Life-Year; ICER: Incremental Cost-Effectiveness Ratio.

## 6. DEALING WITH PARAMETER UNCERTAINTY

A deterministic analysis is vulnerable to questions such as: "How robust are these conclusions to the uncertainty in parameters that influence these results?" and "Is it prudent for medical decision makers to simply rule out the dominated strategies?" For example, a close examination of the cost-effectiveness plane and the efficiency frontier reveal that the Sig & FOBT strategy could have formed a part of the frontier line if its cost was slightly less or its effectiveness more. Thus rejecting this strategy, knowing that uncertainty exists in the perceived values of many cost and effectiveness parameters of this model, would be premature.

Conventional univariate sensitivity analysis is likely to misestimate uncertainty because only individual variables are varied while maintaining all remaining parameters at their baseline [Manning et al. 1996]. Clearly, many parameters are correlated and will therefore not vary in isolation. In principle, N-way sensitivity analysis varies parameters together but it is usually not clear how to choose N and how to coordinate such parameter changes [O'Brien et al. 1994].

Probabilistic sensitivity analysis (PSA) will engender a more realistic representation of uncertainty in a model's results [Claxton et al. 2005; Doubilet et al. 1985; Glick et al. 2001]. It requires that joint statistical distributions for model parameters be specified to represent the uncertainty in their estimation and it employs distribution sampling to select values at random from these distributions before conducting the simulation. Outcomes are obtained from multiple simulations based on selections of parameters. Therefore, probabilistic models allow the effects of joint uncertainty across all the parameters of the model to be considered.

### 6.1 Candidate Parameters

In this simulation model there are three types of model parameters that might be subjected to sensitivity analysis:

(1) natural variability parameters used in the creation of the natural history model (e.g., the distribution of the lifetime CRC risk within a population);

(2) cancer control strategy parameters (e.g., colonoscopy test characteristics); and
(3) economic parameters used in the analysis (e.g., cancer care costs or health state utilities).

All the natural variability parameters are intimately linked to the calibration of the natural history model and such parameters are mostly distribution parameters. Alternation of these parameters would result in a new CRC natural history model that would potentially violate calibration and validation of the basic model. Furthermore, as distribution parameters, they cannot be individually changed arbitrarily and since the data comes mostly from registries, uncertainty is small. Therefore, natural history parameters were not included in the PSA.

Strategic and economic parameters are good candidates for PSA, since their input values usually have no default variability but their values are not known with certainty. Typically, a single point estimate of these parameters is given along with a range of variation (95% tolerance intervals) which can be used to guide a one-way or multiway sensitivity analysis. Furthermore, parameters like cost and utility components do not affect natural history.

In PSA, instead of assigning an estimated value to a strategic or economic parameter, it is preferred that each uncertain parameter be described by a probability distribution to reflect the uncertainty in its value, and this value is propagated throughout the simulation replications. This description entails assigning a prior probability distribution to each of these input parameters. These prior distributions reflect all prior available information and prior beliefs about the parameters' true values. If collected data becomes available for a specific parameter, the likelihood function of the data could be used to define a proper posterior distribution applying Bayesian methods [Briggs 1999; Eddy et al. 1990a, 1990b]. Therefore the CRC model parameters that were fixed in the deterministic model are now being treated as random variables.

Using data from literature along with recommendations offered by the clinical investigators in this project, the prior distributions were developed. Tables IV through IX in Appendix A contain the parameters used in the deterministic analysis, along with the distributions which were assigned to them for the PSA. Although it is preferred that joint distributions be used to specify parameter uncertainty in PSA, we used a combination of marginal distributions and correlations to approximate these joint distributions, since much of valuation was based on very limited data and clinical judgment (see the NORTA (NORmal-To-Anything) description in Law and Kelton [2000]). Furthermore, Monte Carlo sampling from arbitrary joint distributions remains problematic.

6.1.1 *Cost Parameters.* In PSA, different cost variables were sampled from different multivariate Beta distributions (marginal Betas with bivariate correlations). Beta distributions were chosen for cost variables because this distribution provides a very flexible model of bounded random variables thought to best describe the cost uncertainty. Furthermore, information existed for a minimum value, a maximum value, and most likely value for these variables.

The standard deviation of the distribution was estimated from the assumption that it was one-sixth of the range. Together, these statistical quantities were used to form the parameters of the four-parameter Beta. Costs for different components for a person are typically positively correlated and thus, we used 0.5 as the value of correlation coefficients between all pairs of cost variables. This choice was made because 0.5 is a compromise of no correlation and perfect positive correlation, and we had no reason to be biased towards either way.

The parameters for each Beta distribution were derived using the locally developed VIM (Visual Interactive Modeling) program [Roberts 2004]. This program allowed us to fit a desired distribution to certain statistical characteristics such as mean, mode, minimum, maximum, standard deviation, etc., although commercial software exists that will perform similar functions.

6.1.2 *Screening Characteristics Parameters.* Sensitivity and specificity parameters of all screening modalities along with procedure complication parameters were also considered in the probabilistic sensitivity analysis. Using literature available on characteristics of screening tests, we defined a range of variation for each of these parameters, as well as a most likely value.

All of these parameters provide the model with a true or false response. As in the case of complication parameters, they either show a complication, such as hemorrhage, after a screening test or not. Therefore, they can be considered as independent Bernoulli trials leading to a binomial form of the data likelihood. With such data, it is natural to use the proportion of the true responses as the estimate of the corresponding probability in the model.

Fortunately, Bayesian methods provide a straightforward method for assigning prior knowledge to the parameter of the binomial likelihood. The Beta distribution is a continuous distribution on the interval 0-1 and is a conjugate family for the binomial likelihood. Hence, the ease of updating the Beta prior to a Beta posterior, when supplied with additional data, is one of the main advantages of using a Beta prior for the parameter of the binomial distribution [Gelman et al. 2004].

For these reasons, prior Beta distributions were fitted to these parameters based on existing statistics. The advantage of this distribution is that by varying its two shape parameters, a wide variety of possible shapes to the distribution over the interval can be obtained to conform to clinical experience and judgment.

Based on recommendations from the clinical investigators, a correlation coefficient of $+1$ was used between all the pairs of sensitivity variables of a screening test, since they are fully correlated. Also between the specificity and each of the sensitivity parameters of the screening tests, a correlation coefficient of $-1$ was specified. The reason for this specification is that specificity and sensitivity of a test inversely affect each other and as one decreases the other will increase.

6.1.3 *Utility Parameters.* Unfortunately, except for a point estimate, very little is known regarding the distributional characteristics of utilities associated with CRC outcome states, but we elected to incorporate skewed Beta distributions for these utilities. The maximum utility was set to the age-specific utility the person would have in the absence of cancer (when the person is

healthy). The minimum was obtained by multiplying the estimated utility value for the health state by the maximum utility value. The mode is then the estimated utility value for the health state. The standard deviation of the Beta distribution was, as before, assumed to be one-sixth of the utility range. Thus, the Beta distribution is highly skewed toward the maximum value, since the minimum value usually was very close to the mode.

6.1.4 *Compliance Parameters.* For a screening modality, different levels of compliance are assumed, such as never-compliant, one-time compliant, etc. For a particular modality, a person may have any one of these compliance levels with a specific probability. Therefore, in general, if there are $k$ levels of compliance, a multinomial distribution with parameters $p_1, p_2, \ldots, p_k$ is a reasonable distribution to model the compliance level of a person, where $p_i$ is the probability that the person has compliance level $i$.

For a complete probabilistic sensitivity analysis, it was decided to assign probability distributions to parameters of this multinomial distribution, namely $p_1, p_2, \ldots, p_k$. It should be noted that since the sum of these probabilities must be equal to 1, they are not independent and as a result, it is not possible to assign independent distributions to each of them. In Bayesian theory a conjugate family for the multinomial distribution is the Dirichlet distribution. This distribution was used in sensitivity analysis to draw samples for $p_1, p_2, \ldots, p_k$ [Devroye 1986].

## 6.2 Probabilistic Sensitivity Analysis

The inputs to the simulation were thus partitioned into two sets of random variables: $\{\zeta\}$, which are used in specifying the natural history and $\{\eta\}$, which describe the cost, screening, utilities, and compliance. Having specified distributions for all of the relevant parameter uncertainties in the model, the probabilistic sensitivity analysis was performed by randomly sampling from each of the parameter distributions and calculating the discounted expected cost and discounted expected QALYs for that combination of parameter values, using the simulation model. This process forms a single replication of the model results for a specific screening strategy within a population. The algorithm can be described as follows.

```
For a given screening policy
For 1 to Replications
    Establish costs, screening, utilities, and compliance by a sample from {η}
    For 1 to Number of Patients
        Simulate life-time of patient by sampling from {ζ}
        Save discounted total costs and discounted QALY for patient
    Next Patient
    Compute average discounted total costs and QALY for the replication
    Save average costs, QALY, and cost-effectiveness ratio for replication
Next Replication
```

It is important to note that individual patients are being independently simulated and that this algorithm is applied to each screening policy. Each screening

alternative has recorded the average costs, QALY, and cost-effectiveness rations for every replication.

It should be noted that DCBE, fecal DNA, and virtual colonoscopy strategies were not considered in the probabilistic sensitivity analysis for two reasons. First, they were simply dominated by the other strategies on the frontier line in the base-case analysis. Second, they had almost no chance to compete with other strategies in the probabilistic analysis because of their distance from the frontier, that is, they had very low effectiveness and high cost.

6.2.1 *Population Size.* After observing several simulation outputs, it was determined that the mean estimates of QALYs had a much smaller range among the different screening strategies then the cost values. The magnitude of the difference in QALYs was in the thousandths. Therefore, to obtain a valid result, the variance of QALYs should be lowered to an extent that their confidence intervals do not overlap when comparing any two strategies. In other words, the population size of compared screening strategies should be large enough so that the confidence interval on the mean difference of their QALYs would not include the value zero. By achieving the desired amount of precision on QALYs, the necessary precision for cost would certainly be provided [Al et al. 1998].

Applying the concept of "common random numbers" to the V/NCS model, it was possible to simulate different screening strategies on an identical population. Therefore, differences in mean performances, such as cost and QALYs, between various screening strategies are estimated more precisely than absolute mean performances of an individual strategy [Kelton et al. 2004].

To estimate the proper model size, first a sample population of size 20,000 was simulated under the Colon 10 and Sig & FOBT strategies and the 3% discounted QALYs for each person were computed. The 95% confidence interval on the average difference in QALYs was computed as [−0.0202,0.0068]. The half-width of the difference in QALYs for a population of size 20,000 was about 0.0135 years. A margin of error of ±0.005 years (less than 2 days) with 95% confidence interval was selected to satisfy our required precision. The total population necessary to be simulated to achieve the assigned precision was therefore computed as 145,000. Based on this output, a population size of 150,000 patients was assigned for each replication of the screening strategies and 1,000 replications were performed to examine the distributions of the resulting costs and outcomes for each screening strategy.

6.2.2 *Results of the Probabilistic Analysis.* The two-stage sampling process is adopted in order to condition the results of the discrete-event simulation on the parameter uncertainty. The results of the 1,000 samplings from each uncertain parameter, where each sampling is followed by a discrete-event simulation of a unique randomly generated population of size 150,000 (demographically proportional to the U.S. population), are obtained. The 1,000 averages from each 150,000 patients are presented on the cost-effectiveness plane in Figure 4, together with the baseline estimate of the efficient frontier (shown as the piecewise line). This figure shows the empirical distribution of

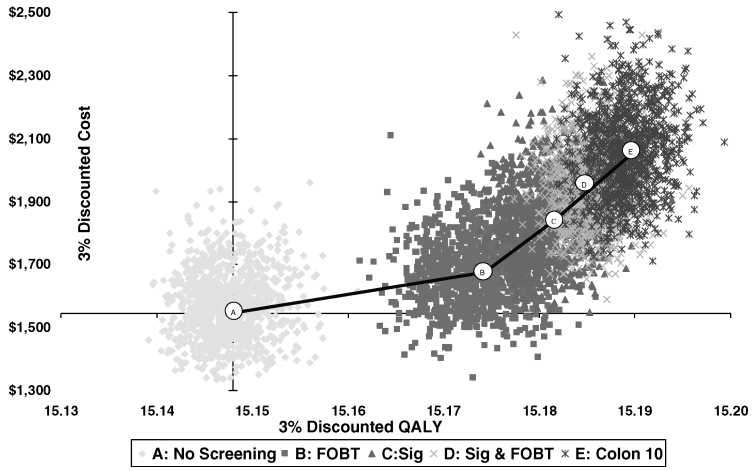


Fig. 4. Results for 1,000 replications of screening strategies for low-risk population presented on the cost-effectiveness plane.

Table III. Percentage of Time Each Screening Strategy Formed Part of the Frontier Line along with 95% Confidence Bounds for Low- Risk Population

| Strategy | % Formed Part of Frontier Line | 95% Lower Bound | 95% Upper Bound |
|---|---|---|---|
| No Screening | 100% | 100% | 100% |
| FOBT | 100% | 100% | 100% |
| Sig | 46% | 43% | 49% |
| Sig & FOBT | 46% | 43% | 49% |
| Colon 10 | 99% | 98.4% | 99.6% |

cost-effectiveness ratios for different screening strategies. For each of the individual replication averages for all screening alternatives, an efficient frontier could be calculated together with the incremental cost-effectiveness ratios for strategies on the frontier, since the replications are driven by common random variables. In particular, this figure shows that it may not be a good decision to rule out the Sig & FOBT strategy, since it forms part of the frontier in many replications. However, it is not possible to gain a clear view from Figure 4 as to how often this strategy forms part of the frontier because the frontier strategies are not marked out for each separate replication.

As the next step of the analysis, we determined how often a given screening strategy formed part of the frontier line in the 1,000 replications for each alternative strategy. These proportions, shown in Table III, indicate that Sig & FOBT formed part of the frontier line in 46% of the simulations, which is the same as the Sig strategy.

However, even knowing the proportion of times a strategy forms part of the efficient frontier, it is not clear how decision makers would interpret this result. If the shadow price for an extra QALY (i.e., the maximum willingness to pay or "ceiling ratio") were known, it would be possible to compare between all of the screening strategies, not just identify those that form the efficient frontier.

## 7. COST-EFFECTIVENESS ACCEPTABILITY CURVES

Decision-making in health care is undertaken in a context of uncertainty concerning the effectiveness and costs of health care interventions. One method that has been suggested to represent this decision uncertainty, particularly when more than two options are compared, is cost-effectiveness acceptability curves (CEACs) [Fenwick et al. 2001; Fenwick et al. 2004; Lothgren and Zethraeus 2000]. These curves present the probability that (proportion of simulations in which) a given intervention is more cost effective than the alternatives for a range of maximum thresholds regarding the willingness to pay for an additional QALY.

The net health benefits framework was used to generate the CEACs [Stinnett and Mullahy 1998]. This approach offers many advantages for handling uncertainty in cost-effectiveness analysis and overcomes the particular problem associated with negative incremental cost-effectiveness ratios.

### 7.1 Net Health Benefits

For a medical intervention $A$,the average net health benefit (NHB) is defined as

$$NHB = E_A - C_A/\lambda, \tag{4}$$

where $C_A$ and$E_A$represent the mean cost and the mean health effect, respectively, of alternative A, and threshold ratio $\lambda$ is defined as society's willingness to pay for an incremental gain in health. The first part of the preceding equation is simply the health effect associated with intervention $A$ and the second part of the expression represents the health gain that could have been attained by instead investing the resources consumed by $A$ in a marginally cost-effective program. Thus, the average NHB of an intervention is interpreted as the net benefit (measured in units of health) of investing resources in $A$ rather than investing these resources in a marginally cost-effective program.

The incremental NHB of $A$compared with $B$ is

$$(E_A - C_A/\lambda) - (E_B - C_B/\lambda) = (E_A - C_B/\lambda) - (E_A - C_B/\lambda), \tag{5}$$

where this expression can be interpreted as the net benefit of investing resources in $A$ rather than implementing $B$ and investing the leftover $(C_A - C_B)$ resources in a marginally cost-effective program. For $NHB > 0$, $A$ is deemed cost effective and should be selected for implementation. For $NHB < 0$, more health improvement can be attained by forgoing the intervention in question and investing resources elsewhere; $A$ is therefore deemed cost ineffective and should not be selected for implementation.

In other words, an intervention's average NHB compares the effectiveness of that intervention with the minimum health effect that society would demand in return for its investment, which is equal to $C_A/\lambda$. The incremental NHB of $A$relative to $B$ compares the difference in the two programs' health effects with the minimum difference in the health effects society would demand in order to justify the additional expenditure required to implement $A$ rather than $B$.

### 7.2 Stochastic Net Health Benefit Analysis

In the context of a stochastic health process, it is necessary to estimate the distribution of NHB for the intervention alternatives. For any given value of variability alone permits different screening alternatives to be the most cost effective. Therefore, estimation of the most cost-effective alternative requires that all alternatives be considered simultaneously. The following algorithm was used.

```
For every value of λ
    For each replication
        Compute the NHB for every screening alternative
        Choose that screening alternative with the highest NHB
    Next replication
    For each screening alternative
        Compute proportion of replications in which this was highest
    Next screening alternative
Next λ
Plot highest NHB for each value of λ
```

The average NHB for all the strategies in Figure 4 was computed for each replication of the probabilistic model using each specified shadow price $\lambda$ In each replication, the strategy of choice for a given $\lambda$ was the one with the greatest average NHB. This must be the case, as only that strategy had a positive incremental NHB when compared to every other alternative. The proportion of times a strategy had the highest average NHB among the 1,000 replications of the probabilistic model for a specific shadow price gave the strength of evidence in favor of that strategy being cost effective.

Since the shadow price of an extra QALY is not known, by plotting all possible values of the ceiling ratio, the proportion of times an intervention is the strategy of choice was determined for each value of $\lambda$. Figure 5 shows the acceptability curves developed for the target population. For ($\lambda \leq \$4{,}100/$ QALY) No Screening is the strategy of choice. The FOBT strategy should be chosen if ($\$4,100/\text{QALY} \leq \lambda \leq \$25,300/$ QALY). For ($\lambda \geq \$25{,}300/$ QALY) Colon 10 should be considered. One of the advantages of this approach is its ability to handle multiple mutually exclusive strategies.

Sig, Sig & FOBT strategies appear in Figure 5, although they never achieve the most likely cost-effective strategy. In these situations, Stinnett and Mullahy [1998] suggested that the principle of stochastic dominance be applied in order to rule out interventions. In Figure 6, we take the value of the ceiling ratio at the point it seems the curves for FOBT and Sig strategy in Figure 5 become tangent to each other. Then we plot the cumulative density functions of FOBT, Sig, Sig & FOBT, and Colon 10 strategies over net health benefit values to check for the first-order dominance. Neither the Sig nor Sig & FOBT strategies can be ruled out under first-order stochastic dominance.

In general, CEACs figures can be used by decision makers in providing new CRC clinical recommendations based on the money society is willing to pay to gain a QALY. However, exactly how decision makers should use the information from the acceptability curves to choose between the strategies remains controversial. One approach (as discussed for Figure 5) would be to say that, for any

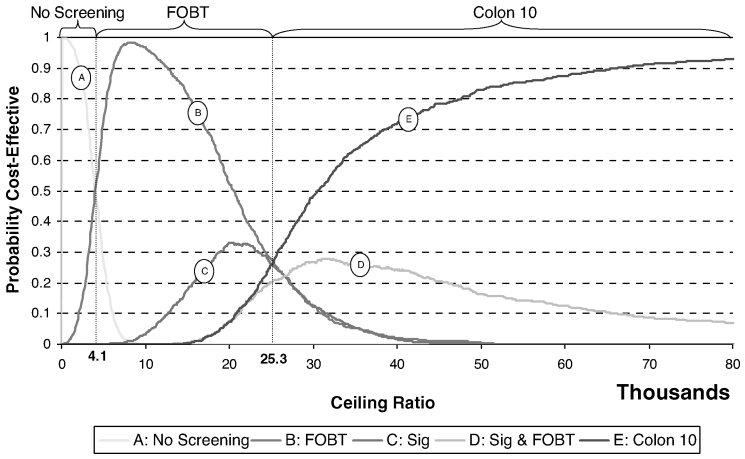


Fig. 5. Acceptability curves for the choice of screening strategy for the low-risk population displaying "most likely" to be a cost-effective strategy.

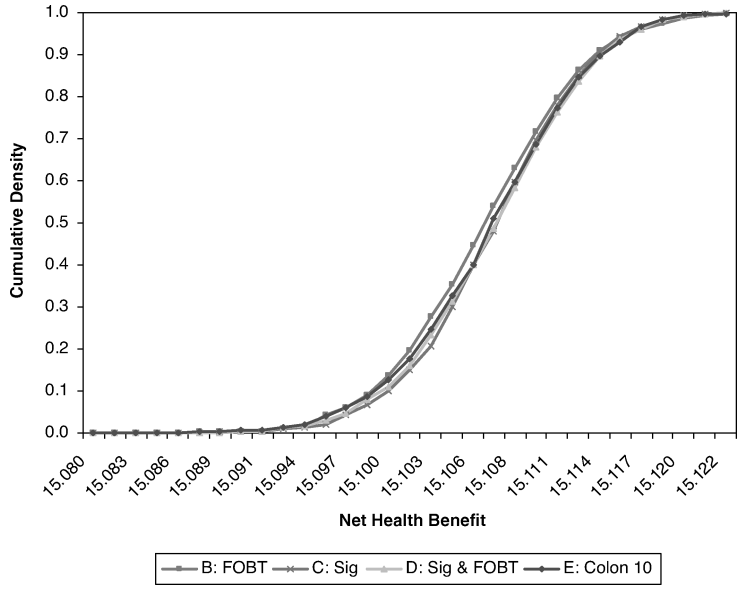


Fig. 6. Cumulative density functions over net health benefit for low-risk population (ceiling ratio = $25,000/QALY).

given value of the ceiling ratio, the decision would be to choose the strategy that is most likely to be cost effective. Interestingly, for this case, this decision rule gives almost the same recommendations as the deterministic analysis provided in Figure 3, where uncertainty was not considered.

Briggs [2002a] has suggested using a conventional statistical decision-making approach by adopting a 5% Type I error rate interpretation of the results. This decision rule implies that a more effective and more expensive strategy should replace the currently provided strategy only if it can be shown

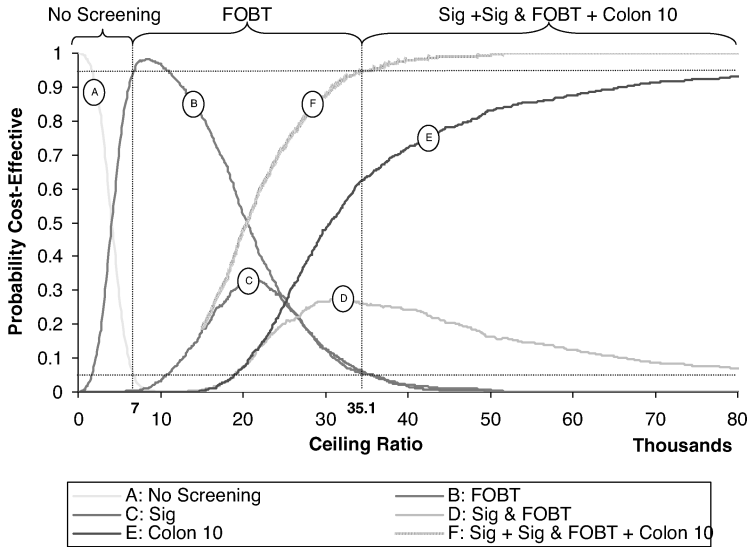


Fig. 7. Decision-making assuming more expensive strategies have to be shown to be significantly more cost effective than the current strategy for low-risk population (at conventional 5% level).

to be significantly more cost effective. Figure 7 illustrates the results of applying this decision rule to our model. As can be seen, it provides quite different cutoff points for the decision maker's ceiling ratios for the different strategies to be considered cost effective.

Note that under a 5% significance decision rule, none of Sig, Sig & FOBT, and Colon 10 strategies would be considered significantly cost effective to be a clear decision choice. If the shadow price of an additional QALY is above $35,100/QALY, we should adopt a decision that considers one or more of these three strategies. While it never quite reaches a 5% threshold, Colon 10 appears most likely to be more cost effective at high willingness-to-pay values.

It is important to recognize, however, the arbitrary nature of the conventional decision rule. Consider if instead of placing the "burden of proof" for cost effectiveness on more expensive and more effective strategies, it is the less expensive but less effective strategies that would be used only if they were shown to be significantly cost effective. The results for this assumption are not shown in Figure 7, but clearly this change in the decision rule would result in a new set of threshold values. Colon 10 would then be the strategy of choice unless the shadow price were below $19,000/QALY; between $1,800/QALY and $19,000/QALY, either the Sig or FOBT strategy would be considered; and below a shadow price of $1,800/QALY the No Screening strategy would be the strategy of choice.

## 8. CONCLUSION

The CRC stochastic simulation model reflects the observed variability inherent in the natural history of CRC and in the procedures being used to screen for

CRC. Natural variability in a model must be verified and validated. However, there are other important input parameters whose true values are unknown. Estimates of these parameters are therefore uncertain. If uncertain parameters are treated as certain (such as using some empirical average), then their uncertainty is ignored and any analysis based on the model is suspect. The parameter uncertainty may be modeled with statistical distributions (either directly or using Bayesian methods); however, doing so increases the variability in the model and further complicates the cost-effectiveness analysis. Deterministic cost-effectiveness analysis based on expected values ignores variation. To incorporate both natural variation and parameter uncertainty, we employ a two-stage sampling algorithm. The values for the parameters are sampled first, and then using these values, the discrete-event simulation is executed. This procedure effectively conditions the output from the simulation on the uncertainty in the parameters and uses the simulation to conduct a probabilistic sensitivity analysis. The distribution of the most cost effective outcomes is compared using CEAC, which parameterizes the choice with a ceiling ratio based on a net health benefits ratio. The combination of probabilistic sensitivity analysis and CEACs have gained widespread acceptance and are now being recommended for the NICE reference case [Claxton et al. 2005].

The essential value of CEAC is that the distribution (not just the means) of cost effectiveness for alternatives is being compared and thus a full representation of all sources of variation is needed. Simulation appears to be the only method able to incorporate all sources of variation. In a discrete-event simulation, natural variability plays a central role, representing the person-to-person variation that is directly observed. The simulation provides an implicit joint distribution of the many random variables, both in sampling and through event processing, which incorporates the natural history of CRC and the screening options. The costs and effectiveness are then conditioned on the joint distribution of uncertain parameters. This article describes how these analyses are implemented in the analysis of multiple screening strategies for CRC.

Most of the literature to date has confined itself to discussing CEAC largely in the context of decisions involving two interventions. Their use in a complex discrete-event simulation modeling of natural variability has been limited. This is likely due to complexities associated with the stochastic analysis of incremental cost-effectiveness ratios for decisions involving multiple comparators. This article provides an additional case of multiple comparators for CEAC and, importantly, offers the first case of applying probabilistic cost-effectiveness analysis to CRC screening for low-risk patients (although the same methodology can be applied to analysis of screening for the high-risk patient).

## APPENDIX A: PARAMETERS USED IN THE DETERMINISTIC ANALYSIS ALONG WITH THE DISTRIBUTIONS WHICH WERE ASSIGNED TO THEM FOR THE PROBABLISTIC SENSTIVITY ANALYSIS

Table IV. Cost Parameters Used in the Deterministic Analysis and the Distribution Assigned to Them for the Probabilistic Analysis

| | Deterministic Analysis | Probabilistic Sensitivity Analysis | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cost Category | Parameter Value | Distribution Type | Mode | SD | Min | Max | Alph | Beta |
| Cancer: Initial Local (within 6 months of CRC diagnosis) | $20,323 | MVBeta | $20,323 | $1,829 | $16,258 | $32,517 | 4.261 | 10.781 |
| Cancer: Initial Regional (within 6 months of CRC diagnosis) | $23,368 | MVBeta | $23,368 | $2,103 | $18,694 | $37,389 | 4.261 | 10.781 |
| Cancer: Initial Distant (within 6 months of CRC diagnosis) | $26,708 | MVBeta | $26,708 | $2,404 | $21,366 | $42,733 | 4.261 | 10.781 |
| Cancer: Continuing Local/Year | $539 | MVBeta | $539 | $49 | $431 | $862 | 4.261 | 10.781 |
| Cancer: Continuing Regional/Year | $2,461 | MVBeta | $2,461 | $221 | $1,969 | $3,938 | 4.261 | 10.781 |
| Cancer: Continuing Distant/Year | $26,855 | MVBeta | $26,855 | $2,417 | $21,484 | $42,968 | 4.261 | 10.781 |
| Cancer: Terminal (within 6 months of scheduled cancer death) | $21,172 | MVBeta | $21,172 | $1,905 | $16,938 | $33,875 | 4.261 | 10.781 |
| Screening Colonoscopy | $614 | MVBeta | $614 | $55 | $491 | $982 | 4.261 | 10.781 |
| Diagnostic Colonoscopy | $661 | MVBeta | $661 | $59 | $529 | $1,058 | 4.261 | 10.781 |
| Colonoscopy with Polypectomy | $745 | MVBeta | $745 | $67 | $596 | $1,192 | 4.261 | 10.781 |
| Post-Polypectomy Hemorrhage | $5,004 | MVBeta | $5,004 | $450 | $4,003 | $8,006 | 4.261 | 10.781 |
| Screening Sigmoidoscopy | $210 | MVBeta | $210 | $19 | $168 | $336 | 4.261 | 10.781 |
| Diagnostic Sigmoidoscopy | $276 | MVBeta | $276 | $25 | $221 | $442 | 4.261 | 10.781 |
| Perforation: Colonoscopy | $16,088 | MVBeta | 16,088 | $1,448 | $12,870 | $25,741 | 4.261 | 10.781 |
| Perforation: Sigmoidoscopy, DCBE, Virtual Colonoscopy | $16,088 | MVBeta | 16,088 | $1,448 | $12,870 | $25,741 | 4.261 | 10.781 |
| Pathology per Polypectomy | $67 | MVBeta | $67 | $6 | $54 | $107 | 4.261 | 10.781 |
| Pathology per Biopsy | $67 | MVBeta | $67 | $6 | $54 | $107 | 4.261 | 10.781 |
| Sigmoidoscopy with Biopsy | $288 | MVBeta | $288 | $26 | $230 | $461 | 4.261 | 10.781 |
| Post-Biopsy Hemorrhage | $5,004 | MVBeta | $5,004 | $450 | $4,003 | $8,006 | 4.261 | 10.781 |
| Fecal DNA Test | $400 | MVBeta | $400 | $36 | $320 | $640 | 4.261 | 10.781 |
| FOBT | $5 | MVBeta | $4.54 | $0 | $4 | $7 | 4.261 | 10.781 |
| DCBE Test | $192 | MVBeta | $192 | $17 | $154 | $307 | 4.261 | 10.781 |
| Virtual Colonoscopy Test | $614 | MVBeta | $614 | $55 | $491 | $982 | 4.261 | 10.781 |

Note: MVBeta: Multivariate Beta Distribution, SD: Standard Deviation.

Table V. Test Characteristics Parameters Used in the Deterministic Analysis and the Distribution Assigned to Them for the Probabilistic Analysis

| Screening Test | Test Characteristics | Deterministic Analysis | | Probabilistic Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Parameter Value | Distribution Type | Mode | SD | Min | Max | Alpha | Beta |
| Colonoscopy | Sensitivity for Cancer | 0.95 | MVBeta | 0.95 | 0.0167 | 0.9 | 1 | 3.982 | 3.98 |
| | Non-Advanced Adenoma Sensitivity | 0.77 | MVBeta | 0.77 | 0.0167 | 0.7 | 0.8 | 4.65 | 2.56 |
| | Advanced Adenoma Sensitivity | 0.84 | MVBeta | 0.84 | 0.0167 | 0.8 | 0.9 | 3.307 | 4.46 |
| | Neoplasia Specificity | 0.79 | MVBeta | 0.79 | 0.0217 | 0.74 | 0.87 | 3.196 | 4.51 |
| | Mortality | 0.0001 | Beta | 0.0001 | 0.0000125 | 0.000025 | 0.0001 | 3.871 | 1 |
| | Perforation | 0.002 | Beta | 0.002 | 0.00025 | 0.0005 | 0.002 | 3.872 | 1 |
| | Post-Polypectomy Hemorrhage | 0.009 | Beta | 0.009 | 0.00075 | 0.0045 | 0.009 | 3.872 | 1 |
| Sigmoidoscopy | Sensitivity for Cancer | 0.95 | MVBeta | 0.95 | 0.0167 | 0.9 | 1 | 3.982 | 3.98 |
| | Non-Advanced Adenoma Sensitivity | 0.77 | MVBeta | 0.77 | 0.0167 | 0.7 | 0.8 | 4.65 | 2.56 |
| | Advanced Adenoma | 0.84 | MVBeta | 0.84 | 0.0167 | 0.8 | 0.9 | 3.307 | 4.46 |
| | Neoplasia Specificity | 0.83 | MVBeta | 0.83 | 0.0167 | 0.79 | 0.89 | 3.307 | 4.46 |
| | Mortality | 0.000045 | Beta | 0.000045 | 0.000004 | 0.000025 | 0.00005 | 4.984 | 2 |
| | Perforation | 0.0009 | Beta | 0.0009 | 0.000083 | 0.0005 | 0.001 | 4.604 | 1.9 |
| FOBT | Colorectal Cancer Sensitivity | 0.21 | MVBeta | 0.21 | 0.0667 | 0.1 | 0.5 | 2.39 | 4.67 |
| | Non-Advanced Adenoma Sensitivity | 0.06 | MVBeta | 0.06 | 0.0167 | 0.05 | 0.15 | 1.36 | 4.24 |
| | Advanced Adenoma Sensitivity | 0.09 | MVBeta | 0.09 | 0.0417 | 0.05 | 0.3 | 1.657 | 4.45 |
| | Neoplasia Specificity | 0.95 | MVBeta | 0.95 | 0.0133 | 0.9 | 0.98 | 4.584 | 3.15 |

Note: MVBeta: Multivariate Beta Distribution; SD: Standard Deviation.

Table VI. Test Characteristics Parameters Used in the Deterministic Analysis

| | | Deterministic Analysis |
|---|---|---|
| Screening Test | Test Characteristics | Parameter Value |
| DCBE | Sensitivity for Cancer | 0.77 |
| | Non-Advanced Adenoma Sensitivity | 0.33 |
| | Advanced Adenoma Sensitivity | 0.33 |
| | Neoplasia Specificity | 0.79 |
| | Mortality Rate | 0.000003 |
| | Perforation Rate | 0.00006 |
| Fecal DNA | Sensitivity for Cancer | 0.46 |
| | Non-Advanced Adenoma Sensitivity | 0.06 |
| | Advanced Adenoma Sensitivity | 0.1 |
| | Neoplasia Specificity | 0.94 |
| Virtual Colonoscopy Pickhardt | Sensitivity for Cancer | 1 |
| | Non-Advanced Adenoma Sensitivity | 0.45 |
| | Advanced Adenoma Sensitivity | 0.89 |
| | Neoplasia Specificity | 0.81 |
| | Mortality | 0.000003 |
| | Perforation | 0.00006 |
| Virtual Colonoscopy Cotton | Sensitivity for Cancer | 0.75 |
| | Non-Advanced Adenoma Sensitivity | 0.18 |
| | Advanced Adenoma Sensitivity | 0.51 |
| | Neoplasia Specificity | 0.93 |
| | Mortality | 0.000003 |
| | Perforation | 0.00006 |

Table VII. Utility Parameters Used in the Deterministic Analysis and the Distribution Assigned to Them for the Probabilistic Analysis

| | Deterministic Analysis | | Probabilistic Analysis (Beta Distribution) | | | | | |
|---|---|---|---|---|---|---|---|---|
| Utility Category | Parameter Value | Distribution Type | Mode | SD | Min | Max | Alpha | Beta |
| Local Colon Cancer (44-54)* | 0.74 | Beta | 0.74 | 0.0403 | 0.688 | 0.9 | 1.98 | 4.6 |
| Local Colon Cancer (54-64) | 0.74 | Beta | 0.74 | 0.0399 | 0.681 | 0.9 | 2.197 | 4.64 |
| Local Colon Cancer (64-74) | 0.74 | Beta | 0.74 | 0.0386 | 0.659 | 0.9 | 2.955 | 4.6 |
| Local Colon Cancer (74+) | 0.74 | Beta | 0.74 | 0.0377 | 0.644 | 0.9 | 3.504 | 4.38 |
| Local Rectal Cancer (44-54) | 0.74 | Beta | 0.74 | 0.0403 | 0.688 | 0.9 | 1.98 | 4.6 |
| Local Rectal Cancer (54-64) | 0.74 | Beta | 0.74 | 0.0399 | 0.681 | 0.9 | 2.197 | 4.64 |
| Local Rectal Cancer (64-74) | 0.74 | Beta | 0.74 | 0.0386 | 0.659 | 0.9 | 2.955 | 4.6 |
| Local Rectal Cancer (74+) | 0.74 | Beta | 0.74 | 0.0377 | 0.644 | 0.9 | 3.504 | 4.38 |
| Local High Rectal Cancer (stage II)(44-54) | 0.59 | Beta | 0.59 | 0.0636 | 0.549 | 0.9 | 1.392 | 4.22 |
| Local High Rectal Cancer (stage II)(54-64) | 0.59 | Beta | 0.59 | 0.0629 | 0.543 | 0.9 | 1.475 | 4.32 |
| Local High Rectal Cancer(stage II)(64-74) | 0.59 | Beta | 0.59 | 0.0608 | 0.525 | 0.9 | 1.76 | 4.51 |
| Local High Rectal Cancer (stage II) (74+) | 0.59 | Beta | 0.59 | 0.0595 | 0.513 | 0.9 | 1.983 | 4.59 |
| Local Low Rectal Cancer (stage II)(44-54) | 0.5 | Beta | 0.5 | 0.0775 | 0.465 | 0.9 | 1.253 | 4.11 |

*Continued on next page*

Table VII. Continued

| | Deterministic Analysis | | Probabilistic Analysis (Beta Distribution) | | | | | |
|---|---|---|---|---|---|---|---|---|
| Utility Category | Parameter Value | Distribution Type | Mode | SD | Min | Max | Alpha | Beta |
| Local Low Rectal Cancer (stage II)(54-64) | 0.5 | Beta | 0.5 | 0.0767 | 0.46 | 0.9 | 1.262 | 4.15 |
| Local Low Rectal Cancer (stage II)(64-74) | 0.5 | Beta | 0.5 | 0.0742 | 0.445 | 0.9 | 1.473 | 4.36 |
| Local Low Rectal Cancer (stage II) (74+) | 0.5 | Beta | 0.5 | 0.0725 | 0.435 | 0.9 | 1.601 | 4.42 |
| Regional Colon Cancer (no chemoRx complications)(44-54) | 0.7 | Beta | 0.7 | 0.0465 | 0.651 | 0.9 | 1.746 | 4.5 |
| Regional Colon Cancer (no chemoRx complications)(54-64) | 0.7 | Beta | 0.7 | 0.0460 | 0.644 | 0.9 | 1.909 | 4.57 |
| Regional Colon Cancer (no chemoRx complications)(64-74) | 0.7 | Beta | 0.7 | 0.0445 | 0.623 | 0.9 | 2.489 | 4.67 |
| Regional Colon Cancer (no chemoRx complications) (74+) | 0.7 | Beta | 0.7 | 0.0435 | 0.609 | 0.9 | 2.937 | 4.62 |
| Regional Colon Cancer (chemoRx complications)(44-54) | 0.63 | Beta | 0.63 | 0.0574 | 0.586 | 0.9 | 1.492 | 4.35 |
| Regional Colon Cancer (chemoRx complications)(54-64) | 0.63 | Beta | 0.63 | 0.0567 | 0.58 | 0.9 | 1.595 | 4.43 |
| Regional Colon Cancer (chemoRx complications)(64-74) | 0.63 | Beta | 0.63 | 0.0549 | 0.561 | 0.9 | 1.956 | 4.59 |
| Regional Colon Cancer (chemoRx complications) (74+) | 0.63 | Beta | 0.63 | 0.0537 | 0.548 | 0.9 | 2.245 | 4.65 |
| Regional High Rectal Cancer (44-54) | 0.59 | Beta | 0.59 | 0.0636 | 0.549 | 0.9 | 1.392 | 4.22 |
| Regional High Rectal Cancer (54-64) | 0.59 | Bata | 0.59 | 0.0629 | 0.543 | 0.9 | 1.475 | 4.32 |
| Regional High Rectal Cancer (64-74) | 0.59 | Beta | 0.59 | 0.0608 | 0.525 | 0.9 | 1.76 | 4.51 |
| Regional High Rectal Cancer (74+) | 0.59 | Beta | 0.59 | 0.0595 | 0.513 | 0.9 | 1.983 | 4.59 |
| Regional Low Rectal Cancer (44-54) | 0.5 | Beta | 0.5 | 0.0775 | 0.465 | 0.9 | 1.253 | 4.11 |
| Regional Low Rectal Cancer (54-64) | 0.5 | Beta | 0.5 | 0.0767 | 0.46 | 0.9 | 1.262 | 4.15 |
| Regional Low Rectal Cancer (64-74) | 0.5 | Beta | 0.5 | 0.0742 | 0.445 | 0.9 | 1.473 | 4.36 |
| Regional Low Rectal Cancer (74+) | 0.5 | Beta | 0.5 | 0.0725 | 0.435 | 0.9 | 1.601 | 4.42 |

*Continued on next page*

Table VII. Continued

| | Deterministic Analysis | | Probabilistic Analysis (Beta Distribution) | | | | | |
|---|---|---|---|---|---|---|---|---|
| Utility Category | Parameter Value | Distribution Type | Mode | SD | Min | Max | Alpha | Beta |
| Distant? Terminal Cancer (within 18 months of scheduled cancer death)(44-54) | 0.25 | Beta | 0.25 | 0.1163 | 0.233 | 0.9 | 1.076 | 3.96 |
| Distant? Terminal Cancer (within 18 months of scheduled cancer death)(54-64) | 0.25 | Beta | 0.25 | 0.1150 | 0.23 | 0.9 | 1.089 | 3.98 |
| Distant? Terminal Cancer (within 18 months of scheduled cancer death)(64-74) | 0.25 | Beta | 0.25 | 0.1113 | 0.223 | 0.9 | 1.13 | 4.03 |
| Distant? Terminal Cancer (within 18 months of scheduled cancer death) (74+) | 0.25 | Beta | 0.25 | 0.1088 | 0.218 | 0.9 | 1.16 | 4.06 |
| Colonoscopy Complication (6 weeks) (44-54) | 0.74 | Beta | 0.74 | 0.0403 | 0.688 | 0.9 | 1.98 | 4.6 |
| Colonoscopy Complication (6 weeks) (54-64) | 0.74 | Beta | 0.74 | 0.0399 | 0.681 | 0.9 | 2.197 | 4.64 |
| Colonoscopy Complication (6 weeks) (64-74) | 0.74 | Beta | 0.74 | 0.0386 | 0.659 | 0.9 | 2.955 | 4.6 |
| Colonoscopy Complication (6 weeks) (74+) | 0.74 | Beta | 0.74 | 0.0377 | 0.644 | 0.9 | 3.504 | 4.38 |
| Sigmoidoscopy Complication (6 weeks) (44-54) | 0.74 | Beta | 0.74 | 0.0403 | 0.688 | 0.9 | 1.98 | 4.6 |
| Sigmoidoscopy Complication (6 weeks) (54-64) | 0.74 | Beta | 0.74 | 0.0399 | 0.681 | 0.9 | 2.197 | 4.64 |
| Sigmoidoscopy Complication (6 weeks) (64-74) | 0.74 | Beta | 0.74 | 0.0386 | 0.659 | 0.9 | 2.955 | 4.6 |
| Sigmoidoscopy Complication (6 weeks) (74+) | 0.74 | Beta | 0.74 | 0.0377 | 0.644 | 0.9 | 3.504 | 4.38 |
| DCBE Complication (6 weeks) (44-54) | 0.74 | Beta | 0.74 | 0.0403 | 0.688 | 0.9 | 1.98 | 4.6 |
| DCBE Complication (6 weeks) (54-64) | 0.74 | Beta | 0.74 | 0.0399 | 0.681 | 0.9 | 2.197 | 4.64 |
| DCBE Complication (6 weeks) (64-74) | 0.74 | Beta | 0.74 | 0.0386 | 0.659 | 0.9 | 2.955 | 4.6 |
| DCBE Complication (6 weeks) (74+) | 0.74 | Beta | 0.74 | 0.0377 | 0.644 | 0.9 | 3.504 | 4.38 |
| Virtual Colonoscopy Complication (6 weeks)(44-54) | 0.74 | Beta | 0.74 | 0.0403 | 0.688 | 0.9 | 1.98 | 4.6 |

*Continued on next page*

Table VII. Continued

| | Deterministic Analysis | | Probabilistic Analysis (Beta Distribution) | | | | | |
|---|---|---|---|---|---|---|---|---|
| Utility Category | Parameter Value | Distribution Type | Mode | SD | Min | Max | Alpha | Beta |
| Virtual Colonoscopy Complication (6 weeks)(54-64) | 0.74 | Beta | 0.74 | 0.0399 | 0.681 | 0.9 | 2.197 | 4.64 |
| Virtual Colonoscopy Complication (6 weeks)(64-74) | 0.74 | Beta | 0.74 | 0.0386 | 0.659 | 0.9 | 2.955 | 4.6 |
| Virtual Colonoscopy Complication (6 weeks)(74+) | 0.74 | Beta | 0.74 | 0.0377 | 0.644 | 0.9 | 3.504 | 4.38 |

Note: MVBeta: *: Determines the age period for a specific utility value; SD: Standard Deviation.

Table VIII. Compliance Rate Parameters Used in the Deterministic Analysis and the Distribution Assigned to Them for the Probabilistic Analysis

| | Deterministic Analysis | | Probabilistic Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|
| Compliance Category | Parameter Value | Distribution Type | Mode | SD | Min | Max | Alpha | Beta |
| Surveillance | 0.8 | Beta | 0.8 | 0.0333 | 0.8 | 1 | 1 | 3.935 |
| Post Positive FOBT | 0.7 | Beta | 0.7 | 0.0500 | 0.7 | 1 | 1 | 3.872 |
| Post Positive Fecal DNA | 0.7 | Beta | 0.7 | 0.0500 | 0.7 | 1 | 1 | 3.872 |
| Post Positive Sigmoidoscopy | 0.8 | Beta | 0.8 | 0.0333 | 0.8 | 1 | 1 | 3.935 |
| Post Positive DCBE | 0.8 | Beta | 0.8 | 0.0333 | 0.8 | 1 | 1 | 3.935 |
| Post Positive Virtual Colonoscopy | 0.8 | Beta | 0.8 | 0.0333 | 0.8 | 1 | 1 | 3.935 |

SD: Standard Deviation.

Table IX. Compliance Rate Parameters Used in the Deterministic Analysis and the Distribution Assigned to Them for the Probabilistic Analysis

| | | Deterministic Analysis | | Probabilistic Analysis | |
|---|---|---|---|---|---|
| Screening Test | Compliance Category | Parameter Value | Distribution Type | Distribution Parameter | Value |
| Colonoscopy, Sigmoidoscopy, DCBE, Virtual Colonoscopy | Every 5 Years | 0.54 | Dirichlet | 0 | 136 |
| | One Time Compliant | 0.16 | Dirichlet | 1 | 77 |
| | Never Compliant | 0.30 | Dirichlet | 2 | 241 |
| FOBT | Every 1 Year | 0.29 | Dirichlet | 0 | 128 |
| | Every 2 Year | 0.11 | Dirichlet | 1 | 48 |
| | Every 5 Years | 0.11 | Dirichlet | 2 | 48 |
| | One Time Compliant | 0.09 | Dirichlet | 3 | 40 |
| | Never Compliant | 0.40 | Dirichlet | 4 | 176 |
| Fecal DNA | Every 3 Year | 0.48 | Dirichlet | 0 | 137 |
| | Every 5 Year | 0.11 | Dirichlet | 1 | 50 |
| | One Time Compliant | 0.11 | Dirichlet | 2 | 219 |
| | Never Compliant | 0.30 | Dirichlet | 3 | 50 |

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Received March 2007; revised October 2007, April 2008; accepted May 2008