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As Tests Evolve and Costs of Cancer Care Rise: Reappraising Stool-Based Screening for Colorectal Neoplasia

Murtaza Parekh, M.D., M.P.H.[1,2], **A. Mark Fendrick, M.D.**[3,4,5], and **Uri Ladabaum, M.D., M.S.**[1,2]

[1]Division of Gastroenterology, University of California, San Francisco

[2]Department of Medicine, University of California, San Francisco

[3]Department of Internal Medicine, University of Michigan, Ann Arbor

[4]Department of Health Management and Policy, School of Public Health, University of Michigan, Ann Arbor

[5]Consortium for Health Outcomes, Innovation, and Cost-Effectiveness Studies (CHOICES), University of Michigan, Ann Arbor

Abstract

Background—Colorectal cancer (CRC) screening and treatment are rapidly evolving.

Aims—To reappraise stool-based CRC screening in light of changing test performance characteristics, lower test cost, and increasing CRC care costs.

Methods—Using a Markov model, we compared fecal DNA testing every 3 years (F-DNA), annual fecal occult blood testing (FOBT) or immunochemical testing (FIT), and colonoscopy every 10 years (COLO).

Results—In the base case, FOBT and FIT gained life-years/person and cost less than no screening. F-DNA version 1.1 at $300 (the current PreGen Plus test) gained 5,323 life-years/100,000 persons at $16,900/life-year gained, and F-DNA version 2 (enhanced test) gained 5,795 life-years/100,000 persons at $15,700/life-year gained *vs.* no screening. In the base case and most sensitivity analyses, FOBT and FIT were preferred over F-DNA. F-DNA version 2 cost $100,000/life-year gained *vs.* FIT when per-cycle adherence with FIT was 22%. FIT with excellent adherence was superior to COLO.

Conclusions—As novel biological therapies increase CRC treatment costs, FOBT and FIT could become cost-saving. The cost-effectiveness of F-DNA compared with no screening has improved, but FOBT and FIT are preferred over F-DNA when patient adherence is high. FIT may be comparable to COLO in persons adhering to yearly testing.

INTRODUCTION

Colorectal cancer (CRC) affects up to 6% of the population and is the second leading cause of cancer-related death in the U.S.(1) Each year, approximately 145,000 new cases of CRC

Corresponding author/reprint requests: Uri Ladabaum, M.D., M.S., Division of Gastroenterology, S-357, Box 0538, University of California, San Francisco, 513 Parnassus Avenue, San Francisco, CA 94143-0538, Tel: 415-514-0591, Fax: 415-502-6714, uri.ladabaum@ucsf.edu.

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are diagnosed and approximately 55,000 deaths are attributed to CRC in the U.S.(2) Screening decreases CRC incidence and mortality and is cost-effective,(3–13) but only a minority of the population has been screened.(14, 15) Patient preferences for invasive *vs.* non-invasive screening tests vary,(16–18) and the availability of some tests may be limited. (19)

In 2004, we first explored the potential role of fecal DNA testing in average-risk persons. (20) We concluded that it could not be considered a substitute for traditional screening methods, but that it could have an important impact if it attracted persons who are not currently screened for CRC.(20) A prospective trial of the original PreGen Plus fecal DNA test (Exact Sciences Corporation, Marlboro, MA and LabCorp, Burlington, NC) subsequently found the test to be superior to fecal occult blood testing in detecting CRC and large adenomas,(21) but its performance was inferior to our original estimates and its projected effectiveness and cost-effectiveness declined.(22).

CRC screening is a rapidly evolving field and key variables that affect estimates of effectiveness and cost-effectiveness are changing, including test performance characteristics and cost, and costs of CRC care. Technical advances in DNA stabilization,(23) DNA extraction from stool,(24) and use of gene-specific methylation(25) have improved the fecal DNA test.(26) Test cost has decreased to approximately $300 after write-offs (personal communication, Barry Berger, Exact Sciences Corporation). At the same time, bevacizumab (an antibody targeting vascular endothelial growth factor, a known regulator of tumor cell angiogenesis) and cetuximab (an antibody targeting the epidermal growth factor receptor, a tyrosine kinase important in the regulation of growth and survival pathways in CRC cells) (27–29) have emerged as novel treatments that enhance the efficacy of chemotherapy for advanced CRC,(28, 30) but also markedly increase treatment costs.(31)

Our aims were to reappraise noninvasive stool-based screening for colorectal neoplasia in persons unwilling or unable to undergo invasive screening with sigmoidoscopy or colonoscopy in light of changing fecal DNA test performance characteristics,(21, 26) lower test cost, and increasing costs of CRC care. We compared fecal DNA testing, guaiac-based fecal occult blood testing, and fecal immunochemical testing. Because adherence with yearly guaiac-based fecal occult blood testing is poor,(15, 32–44) we examined in detail the potential impact of imperfect adherence on the effectiveness and cost-effectiveness of screening strategies. We have previously examined the cost-effectiveness of other modalities, including colonoscopy.(11, 20, 22, 45) While here we focus on stool-based testing, we report results for screening colonoscopy for purposes of comparison.

MATERIALS AND METHODS

Literature Review and Data Sources

The sources for most model inputs have been described previously.(11, 20, 22, 45) For updated clinical information on fecal DNA testing and FIT, we searched PubMed using the terms *fecal DNA*, *colorectal cancer, fecal immunohistochemistry*, *detection*, *sensitivity*, *specificity*, and *test performance*, we reviewed national meeting abstracts, and we obtained data from EXACT Sciences Corporation (Marlboro, MA) and FDA submission data from Enterix Inc. (Edison, NJ), maker of InSure FIT. For updated cost data, we searched PubMed using the terms *colorectal cancer*, *chemotherapy*, and *cost*, we reviewed national meeting abstracts, we obtained data from EXACT Sciences Corporation, and we used 2006 Medicare fee schedules, as detailed below.(46)

Decision Analytic Model

Our decision analytic model and its calibration and validation have been described in detail.(11, 20, 22, 45, 47) The model is constructed in TreeAge (TreeAge Software, Inc., Williamston, MA) and the Natural History model is calibrated to reproduce the natural history and age-specific incidence and prevalence of colorectal adenomas and CRC in the U.S. without screening.(11, 20, 22, 45, 47) Screening strategies are then superimposed on the Natural History model. As described in detail previously, the model's predictions for conventional strategies are consistent with available clinical data.(11, 20, 22, 45, 47) For the current analysis, the model was modified to allow variable adherence rates every time a screening test was offered. To validate this modification, we have modeled a cohort representing the one studied by Mandel *et al*.(32, 33) with FOBT offered and followed up as in that study.(22) Our model predicts a 21% reduction in CRC incidence over 18 years *vs.* 20% observed in the study,(33) and a 36% reduction in CRC mortality over 16 years *vs.* 33% observed in the study.(32)

Natural History—The principal health states in the model are (Figure 1): normal; small (<10 mm) adenomatous polyp; large (≥10 mm) adenomatous polyp; localized, regional, or distant CRC; and dead. Approximately 85% of CRCs develop through a polypoid adenoma. In the Natural History model, CRCs are diagnosed with colonoscopy once they lead to symptoms. Diagnosed CRCs are treated, resulting in stage-specific survival.(11, 20, 28, 30, 45, 48–51) Persons surviving CRC treatment enter surveillance (see below). Beginning at age 50 years, average-risk persons progress through the model for 50 1-year cycles, until age 100 years or death. Age-specific non-CRC mortality rates reflect U.S. life table data.(52) Model inputs are shown in Table 1.

Screening Strategies and Surveillance—We compared Natural History, fecal DNA testing (F-DNA), annual guaiac-based fecal occult blood testing (FOBT) and annual fecal immunochemical testing (FIT). First, a screening interval for F-DNA was selected that could be considered cost-effective compared to a shorter screening interval, as described below. Because our focus was noninvasive stool-based screening strategies, flexible sigmoidoscopy and colonoscopy are not presented as alternatives.

Screening strategies were superimposed on the Natural History model. In the base case, in all strategies, screening and surveillance with perfect adherence were performed up to and including age 80. Variable adherence was a principal focus of sensitivity analyses. After age 80, colonoscopy was performed only to evaluate symptoms. With colonoscopy, polyps were removed and CRCs were biopsied if detected. If F-DNA, FOBT or FIT were positive then colonoscopy followed with polypectomy and biopsy as necessary. If colonoscopy was normal after a positive noninvasive test, the noninvasive test was assumed to be a false-positive and screening resumed in 10 years with the primary screening strategy. CRC was managed, and symptomatic CRC could be detected, as in the Natural History model.

In all strategies, after adenoma detection, patients underwent surveillance colonoscopy every 5 years.(53, 54) Persons developing CRC underwent colonoscopy at diagnosis, 3 years later and then every 5 years thereafter.(53, 54)

Fecal Occult Blood Testing and Fecal Immunochemical Testing—In the FOBT strategy, annual testing(3, 53, 55) was offered with test performance characteristics as modeled previously (Table 1).(22) FIT was evaluated with annual testing and test performance characteristics based on available literature(56–66) and FDA submission data from Enterix Inc. (Edison, NJ), maker of InSure FIT.(67) Reported FIT sensitivities range from 30–100% for CRC and 20–71% for large adenoma, with specificities of 86–99%.(56–

66) In the base case for FIT, we assumed sensitivity of 76% for CRC, 40% for large adenoma, and specificity of 91%.

Fecal DNA Testing—F-DNA version 1 was defined as the strategy using the prototype test evaluated by Imperiale *et al.*(21) This test had sensitivities of 52% for CRC and 18% for large adenoma, and specificity of 94%.(21) F-DNA version 2 was defined as the strategy using the test recently reported by Itzkowitz *et al.*(26) This test represents the optimal marker combination of vimentin methylation and a DNA integrity assay, with sensitivity of 88% for CRC, and specificity of 82%.(26) The sensitivity of F-DNA version 2 for large adenoma has not been reported formally. We assumed that the sensitivity for large adenoma of F-DNA version 2 was 18%, the same as for version 1. For F-DNA versions 1 and 2, we assumed that F-DNA could not distinguish normal from small adenoma. Thus, F-DNA was positive when the most advanced lesion was a small adenoma at a rate defined as (100%-specificity).

The test currently available on the market is version 1.1 (PreGen Plus, LabCorp, Burlington, NC). Compared with version 1, version 1.1 includes a DNA stabilization buffer and an improved gel capture method for isolating DNA.(18, 23–25). When the version 1 test was enhanced in these ways in the recent study by Itzkowitz *et al.*, sensitivity for CRC was 73% and specificity was 89%.(26) We assumed that the sensitivity for large adenoma of F-DNA version 1.1 was 18%, the same as for the other versions of the test.

Before evaluating fecal DNA testing strategies, an appropriate screening interval was selected. As described previously,(20) we examined F-DNA at progressively shorter screening intervals ranging from 1 to 5 years. Screening at a given interval (*e.g.* 4 years) was compared to screening at a longer interval (*e.g.* 5 years), yielding the incremental cost per life-year gained when shortening the interval. For the base case, we selected a screening interval consistent with the commonly accepted “willingness to pay” threshold of $50,000/life-year gained.(68–70) Thus, in the base case fecal DNA testing was offered every 3 years (see Results).

Screening Colonoscopy—The screening colonoscopy strategy included colonoscopy every 10 years if no adenomas were detected (COLO). Polyps were removed upon detection and masses underwent biopsy. Test performance characteristics and costs are presented in Table 1. After detection of adenomas, surveillance was performed as described for all strategies above.

Cost Inputs—Procedure cost estimates ranged from those derived from Medicare fee schedules (including professional fees and procedure reimbursement) to those reported from a health maintenance organization.(7–13, 20, 47) Based on Medicare schedules, we assumed a base case cost of $15 for each cycle of FOBT and $22 for each cycle of FIT.(46) The PreGen Plus test list price is $495 (LabCorp, Burlington, NC; test number 512094), but the average reimbursement for the test is approximately $300 after write-offs (personal communication, Barry Berger, Exact Sciences Corporation). In the base case, we assumed a cost of $300 for each fecal DNA test. Complication costs were derived from relevant diagnostic related groups (DRG 148, major small and large bowel procedures). (9, 11, 20, 47, 71, 72)

Stage-specific costs of care for CRC were taken from published reports and available data on the costs of newer therapies for advanced CRC.(5, 9, 11, 20, 31, 47, 73–75) Our Natural History model is calibrated to SEER data on CRC stage distribution of 39% localized, 39% regional and 22% disseminated CRC.(22) After comparisons with data on CRC TNM stage distribution, we assumed that disseminated CRC in our model represented TNM Stage IV

disease and that 2/3 of patients with regional CRC in our model had TNM Stage III disease.(76, 77) To account for the increasing costs of CRC care for advanced disease, we assumed that patients with TNM Stage III disease received three 8-week cycles of FOLFOX (oxaliplatin, infusional fluorouracil and leucovorin) chemotherapy,(78) resulting in an increased cost of $34,800 over the costs assumed in our previous analyses.(31) We assumed that patients with TNM Stage IV disease received four to six cycles of treatment including the emerging biological agents bevacizumab and cetuximab,(28, 30, 48–51, 78, 79) resulting in an increased cost to $200,000.(31) Base case cost inputs incorporate these assumptions (Table 1).

Costs were updated to 2006 dollars as necessary, using the medical services component of the consumer price index.(80) For each base case cost input, we used the average of the published values. Indirect costs were not included. We used a third-party payer perspective.

Clinical and Economic Outcomes

For each strategy, we determined CRC cases by stage in a cohort of 100,000 persons, deaths by cause, and average life-years and costs per person (both discounted at 3% annually).(81)

Cost-Effectiveness of Screening Strategies

If one strategy afforded more life-years than another at higher expense, an incremental cost-effectiveness ratio was calculated. One-way sensitivity analyses were performed on all model inputs, including test performance characteristics and costs. Two-way sensitivity analyses were performed on variables determined to be influential on one-way sensitivity analyses. Threshold analyses were performed to identify critical values for variables at which specific conditions of interest were met (*e.g.* clinical equivalence, or cost-effectiveness at a willingness to pay of $50,000–$100,000/life-year gained). A Monte Carlo simulation with 1,000 trials was performed with sampling for the test performance characteristics for FOBT, FIT, and F-DNA versions 1, 1.1 and 2 from uniform distributions representing the 95% confidence interval ranges reported in the literature (Table 1).

In controlled trials of FOBT, adherence has been less than perfect.(32, 33, 36, 38) Initial screening rates have ranged from 53% to 78%(32, 33, 36, 38) and repeat screening has ranged from 77%(82) to 94%.(38) Adherence is lower outside of controlled trials. Data from the Behavioral Risk Factor Surveillance System (BRFSS) in 2001 reported that 45% of adults aged 50 or greater had ever had FOBT and 24% had FOBT within the past 12 months.(15) Others have reported initial rates of screening with FOBT from 35% to 47%(34, 41–43, 61) and rates of FOBT within one year (considered up to date) from 10% to 26%.(37, 39, 40, 43, 44) Data on annual follow up, or serial screening, are very limited. Myers *et al.* reported initial response to a screening program of 41% (647 of 1,565 subjects) and then subsequent serial screening by 56% of initial responders (362 of 647).(42) Using data from Liang *et al.*, adherence to annual screening can be estimated at 61%.(39) Thus, imperfect adherence was explored in detail in sensitivity analyses.

In the base case, we assumed perfect adherence for all strategies. This reflects the optimal possible “efficacy” of the strategies. The results are useful because they reflect a strategy’s impact in persons who adhere to it. Because imperfect adherence limits true “efficacy” in larger cohorts, we performed extensive sensitivity analyses on adherence in order to estimate real-world “effectiveness” with imperfect adherence.

RESULTS

Base Case

Selection of Screening Interval for F-DNA—F-DNA version 1 every 3 years compared with every 4 years cost $39,200/life-year gained, and every 2 years compared with every 3 years it cost $52,600/life-year gained (Table 2). Similarly, F-DNA version 2 every 3 years compared with every 4 years cost $47,700/life-year gained, and every 2 years compared with every 3 years it cost $57,100/life-year gained. Therefore, we selected a screening interval of 3 years for F-DNA.

Clinical Outcomes with Perfect Adherence—Compared with no screening, all strategies reduced CRC incidence and mortality (Table 3). FIT yielded the greatest number of discounted life-years/person, followed by COLO, F-DNA version 2, FOBT, F-DNA version 1.1 and F-DNA version 1. Without screening, a cohort of 100,000 persons experienced 5,927 CRC cases, and CRC accounted for 2.4% of deaths. Compared with no screening, F-DNA version 1 decreased CRC incidence by 33% and CRC-related mortality by 49%, F-DNA version 1.1 decreased CRC incidence by 37% and CRC-related mortality by 57%, FOBT decreased CRC incidence by 49% and CRC-related mortality by 66%, F-DNA version 2 decreased CRC incidence by 43% and CRC-related mortality by 63%, COLO decreased CRC incidence by 73% and CRC-related mortality by 80%, and FIT decreased CRC incidence by 66% and CRC-related mortality by 78%.

Cost-Effectiveness with Perfect Adherence—Compared with no screening, all screening strategies increased life expectancy at reasonable costs (Table 3). FOBT and FIT yielded more average life-years per person than no screening, and achieved this at a lower cost—that is, they were dominant compared with no screening. Compared with no screening, F-DNA version 1 gained 4,466 life-years/100,000 persons at an incremental cost of $21,200/life-year gained, F-DNA version 1.1 gained 5,323 life-years/100,000 persons at an incremental cost of $16,900/life-year gained, and F-DNA version 2 gained 5,795 life-years/100,000 persons at an incremental cost of $15,700/life-year gained. COLO gained 6,185 life-years/100,000 persons at an incremental cost of $9,200/life-year gained.

FOBT and FIT were preferred over all F-DNA versions. F-DNA versions 1 and 1.1 were dominated by FOBT and FIT. F-DNA version 2 was slightly more effective than FOBT, but at a very high incremental cost of $669,000/life-year gained. FIT was dominant over all other strategies, including F-DNA version 2 (Table 3). COLO was dominated by FIT and it cost $144,000/life-year gained compared to FOBT.

One-way and Two-way Sensitivity Analyses

Changes in most variables did not significantly affect the comparisons between the F-DNA strategies and FOBT or FIT (Table 4). If we assumed significantly worse test performance characteristics for FOBT than in the base case, the F-DNA strategies compared more favorably but still cost >$50,000/life-year gained compared with FOBT. When we examined the low end of reported values for FIT test performance, it was still dominant over the F-DNA strategies. If FIT test cost increased to $95, the strategy was no longer cost-saving compared with no screening (it cost $8,300/life-year gained) and it cost $135,000/life-year gained compared with FOBT, but it was still dominant over the F-DNA strategies. Changes in colonoscopy test performance, complication rate, and costs did not affect the results significantly.

As the sensitivity for large adenoma of the F-DNA version 2 test improved, this strategy became progressively more effective than FOBT (Figure 2A). With a sensitivity for large

adenoma of 80%, F-DNA version 2 cost $87,500/life-year gained compared with FOBT, but this incremental cost/life-year gained rose sharply as sensitivity for large adenoma decreased (Figure 2B). At a test cost of $200, F-DNA version 2 cost <$50,000/life-year gained compared with FOBT when F-DNA test sensitivity for large adenoma was >60% (Figure 2B).

If we assumed lower CRC care costs because the novel, costly therapies were not used, no screening strategy was cost-saving anymore. Compared with no screening, FOBT cost $8,000/life-year gained, FIT cost $4,3000/life-year gained, F-DNA version 1 cost $33,100/life-year gained, F-DNA version 1.1 cost $28,800/life-year gained, and F-DNA version 2 cost $27,700/life-year gained. However, the incremental cost-effectiveness ratios comparing the F-DNA strategies to FOBT and FIT were not affected significantly (Table 4).

Threshold Analyses on F-DNA Test Cost

F-DNA test cost would need to be significantly lower than the $300 assumed in the base case in order to make any of the F-DNA strategies competitive with FOBT. F-DNA test cost would need to fall to $40 for FOBT to cost >$50,000/life-year gained compared to F-DNA version 1.1. F-DNA test cost would need to fall to $60 for F-DNA version 2 to cost < $50,000/life-year gained compared to FOBT.

Even when the F-DNA test was assumed to be free, FIT cost only $9,200/life-year gained compared to F-DNA version 1 and $8,100/life-year gained compared to F-DNA version 1.1, and it still dominated F-DNA version 2.

Monte Carlo Simulation Focusing on Test Performance Characteristics

When test performance characteristics for all stool-based tests were varied within the ranges reported in the literature (Table 1), FOBT was dominant over no screening in >95% of iterations, and FIT was dominant over no screening in 100% of iterations. Compared with no screening, the mean (and 95% confidence interval) for the cost/life-year gained was $21,500 ($16,000–$29,200) for F-DNA version 1, $17,600 ($13,900–$21,700) for F-DNA version 1.1, and $16,500 ($13,700–$19,200) for F-DNA version 2.

Compared with F-DNA version 1.1, FOBT was dominant in 88% of iterations, it cost between $100,000 and $1,000,000/life-year gained in 18% of iterations, and it was more costly in the remainder. Compared with FOBT, F-DNA version 2 was dominant in 64% of iterations, it cost <$100,000/life-year gained in 1% of iterations, it cost between $100,000 and $1,000,000/life-year gained in 28% of iterations, and it was more costly in the remainder. Compared with F-DNA version 2, FIT was dominant in 100% of iterations.

Sensitivity Analyses on Adherence with Testing

As the per-cycle (per-year) adherence with testing decreased with FOBT and FIT, the effectiveness of FOBT decreased steadily, and the effectiveness of FIT began to decrease significantly when the per-cycle adherence fell below approximately 60% (Figure 3).

F-DNA version 1.1 (with 100% adherence) became more effective than FOBT when the per-cycle adherence with FOBT fell below 85%. F-DNA version 1.1 cost $100,000/life-year gained compared with FOBT when per-cycle adherence with FOBT was 49%, and $50,000/life-year gained when the per-cycle adherence with FOBT was 31% (Figure 4).

F-DNA version 2 (with 100% adherence) became more effective than FIT when the per-cycle adherence with FIT fell below 50%. F-DNA version 2 cost $100,000/life-year gained

compared with FIT when per-cycle adherence with FIT was 22%, and $50,000/life-year gained when the per-cycle adherence with FIT was 13% (Figure 5).

Imperfect adherence with F-DNA affected the comparisons with FOBT and FIT. To illustrate, when the per-cycle adherence with F-DNA version 1.1 was 50%, F-DNA version 1.1 became more effective than FOBT when the per-cycle adherence with FOBT fell below 35% and it cost $100,000/life-year gained compared with FOBT when per-cycle adherence with FOBT was 26. Similarly, when the per-cycle adherence with F-DNA version 2 was 50%, F-DNA version 2 became more effective than FIT when the per-cycle adherence with FIT fell below 19% and it cost $100,000/life-year gained compared with FIT when per-cycle adherence with FIT was 12%.

DISCUSSION

CRC screening and treatment are rapidly evolving fields, necessitating reappraisal of the effectiveness and cost-effectiveness of screening strategies as key variables change. Our current analyses focused on the latest test performance characteristics and costs of noninvasive, stool-based tests, and the increasing costs of care for advanced CRC. Our results lead to four major conclusions. First, if CRC treatment costs increase significantly due to the use of novel biological therapies, FOBT and FIT could improve clinical outcomes while also achieving cost savings. Second, recent improvements in test performance and lower test cost have translated into enhanced cost-effectiveness for F-DNA compared with no screening, but FOBT and FIT are likely to be preferred over F-DNA when patient adherence with yearly testing is high. Third, adherence over time is a key determinant of the effectiveness of strategies that rely on frequent testing, and F-DNA with screening every 3 years could be cost-effective compared with FOBT and FIT in populations with poor adherence to yearly testing. Fourth, in persons who can adhere to yearly testing, highly sensitive and relatively inexpensive stool-based testing such as FIT may be comparable to screening colonoscopy every 10 years.

Before the current era of novel but costly treatments for advanced CRC, multiple analyses concluded that CRC screening is cost-effective.(3–13, 20, 22) Screening had been estimated to be cost-saving only when very low screening costs were assumed.(83) Our current analyses demonstrate how FOBT and FIT could not only decrease CRC incidence and mortality, but could actually decrease total overall CRC-related costs (screening, testing, complications and CRC care) if advanced CRC is treated with novel, costly therapies.(28, 30, 31, 48–51, 78, 79) It is rare for medical interventions to improve outcomes as well as decrease costs. Therefore, the question is often whether an intervention is “cost-effective.” We have previously estimated that screening 75% of the U.S. population with conventional methods could increase overall CRC-related costs by $1–3 billion/year, accounting for savings in CRC care.(22) However, if costly therapies for advanced CRC become widely used, the economic benefit of prevention and early detection may become large enough that overall savings could be realized by screening.

With current test cost of $300, F-DNA version 1.1 (the currently available test PreGen Plus, LabCorp, Burlington, NC) and F-DNA version 2 (the refined test as in Itzkowitz *et al.*(26)) were both cost-effective compared with no screening. Assuming the high advanced CRC care costs associated with novel biological therapies, these strategies cost approximately $17,000/life-year gained (upper 95% confidence interval of approximately $22,000/life-year gained). Without the use of novel therapies for advanced CRC, these strategies were still cost-effective compared with no screening (<$30,000/life-year gained). However, FOBT and FIT were preferred over all F-DNA strategies when they were not compromised by poor adherence.

With current test performance characteristics and good adherence, substantial decreases in test cost would be required for any F-DNA test to become cost-effective compared with FOBT. F-DNA test cost would need to be $40–60 for F-DNA versions 1.1 and 2 to compare favorably with FOBT at a threshold of $50,000/life-year gained. More dramatically, FIT dominated F-DNA strategies in most sensitivity analyses, and it was preferred even when the F-DNA test was assumed to be free.

Early detection of CRC as well as CRC prevention through removal of adenomas underlie the benefit of screening. In the base case, we assumed low F-DNA sensitivity for large adenoma. Better sensitivity for large adenoma would improve F-DNA's effectiveness (Figure 2A), but the effect appears less dramatic than we expected initially. This result depends on the assumption that most CRCs remain localized or regional for several years, and can therefore be detected at a high rate with a relatively sensitive test that is performed every 3 years. Similarly, for adenomas that "dwell" for many years, repeated testing with only a fair test has a reasonably high cumulative sensitivity. Our model's predictions for FOBT's effectiveness are very close to the results of clinical trials,(22, 32, 33) giving us confidence regarding our predictions for F-DNA. However, if the fraction of rapidly advancing adenomas or tumors is higher than reflected in our current model, the benefit of improved sensitivity for large adenoma may be underestimated.

Not surprisingly, we found that adherence over time is a key determinant of the effectiveness of strategies that rely on frequent testing (Figure 3). Even in the idealized setting of a controlled trial, adherence with annual or biannual FOBT is less than ideal.(32, 33, 36, 38) In clinical practice, it has been difficult to achieve ongoing high rates of adherence with FOBT,(39, 42) and the follow-up of abnormal tests is difficult to ensure.(32, 33, 36, 38, 41, 61) Furthermore, patient preferences for screening options vary.(16, 84–90) Because changing the adherence rates of multiple strategies simultaneously is cumbersome, we compared F-DNA with perfect adherence against FOBT and FIT with imperfect adherence (Figures 4 and 5). It is conceivable that F-DNA could be considered cost-effective compared with FOBT or FIT in populations that demonstrate good to excellent adherence with testing every 3 years, but who would otherwise have very poor adherence with yearly testing. Further study is required in this area.

In persons adhering perfectly with screening, which reflects optimal efficacy, screening colonoscopy every 10 years decreased CRC incidence more than annual FIT, but the average life-expectancy with FIT was higher than with screening colonoscopy. This is explained by the fact that most CRCs were diagnosed at treatable stages. The generalizable conclusion is that among persons who can comply with frequent testing, highly sensitive and inexpensive non-invasive testing may be comparable to much less frequent screening with colonoscopy.

The current reappraisal raises important points when compared with our first analysis of F-DNA.(20) As F-DNA's test performance has improved and its cost has decreased, it has become more cost-effective when compared with no screening, an effect that is accentuated as the cost of CRC care increases. However, colonoscopy remains preferred over F-DNA with current parameters. In our first analysis, we did not focus on the comparison between stool-based tests, which is the principal subject of our current reappraisal. Our current results highlight that, in the setting of good adherence, FOBT and FIT are likely to be preferred over F-DNA.

Our analysis has some limitations. Indirect costs were not included. Patterns of adherence over time are likely to be complex, and such considerations are beyond the scope of the current analyses. Finally, as in all decision analytic exercises, there is uncertainty

surrounding important inputs. However, we have addressed the key variables in extensive sensitivity analyses in order to be able to draw conclusions that may focus future clinical research and inform policy decisions.

In conclusion, our analyses suggest that as the costs of care for advanced CRC increase due to use of novel but costly biological therapies, screening with reasonably effective and inexpensive methods such as FOBT and FIT could be not only cost-effective, but potentially cost-saving. The evolution of test performance characteristics and decrease in test cost for F-DNA have translated into improved cost-effectiveness for F-DNA compared with no screening, but presently FOBT and FIT remain preferred over F-DNA in populations with high adherence to yearly testing. F-DNA with excellent adherence could be considered cost-effective compared with FOBT or FIT in populations with very poor adherence to yearly testing. With excellent annual adherence, sensitive and inexpensive stool-based testing such as FIT may be comparable to screening colonoscopy.

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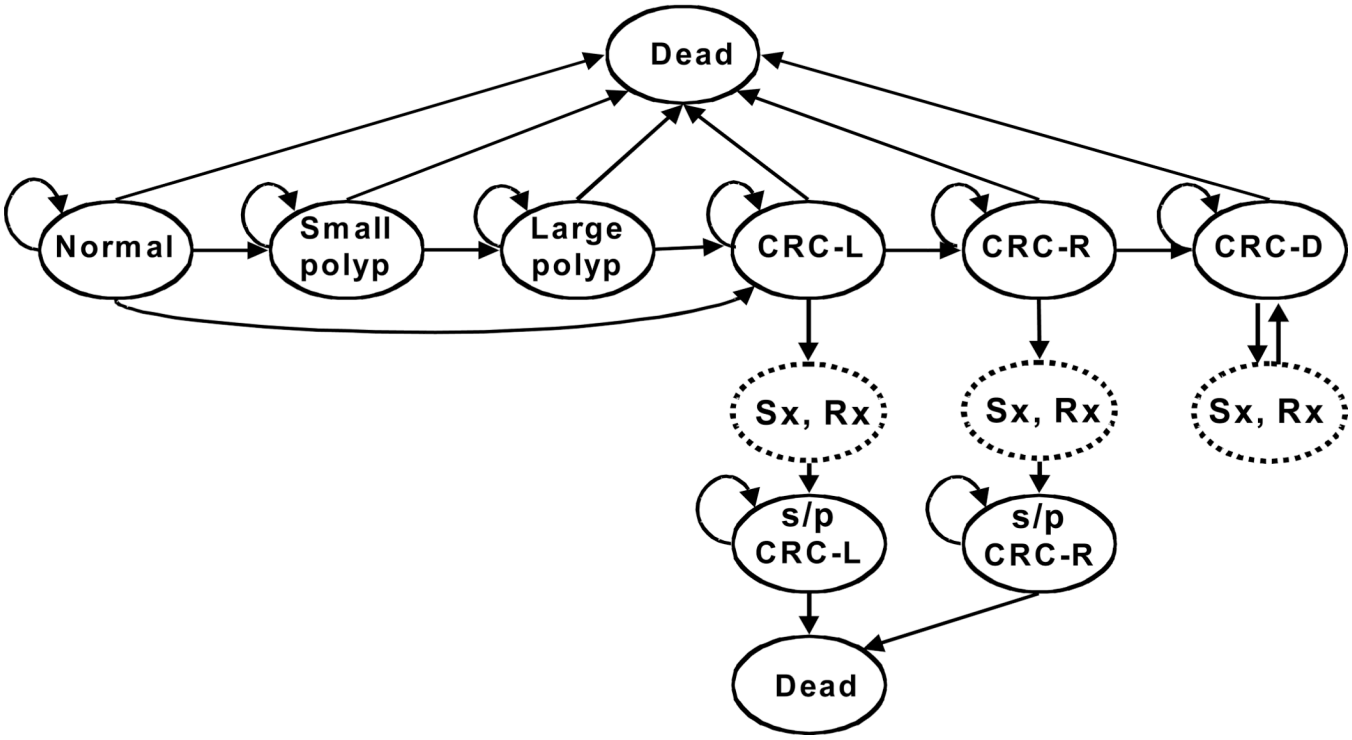
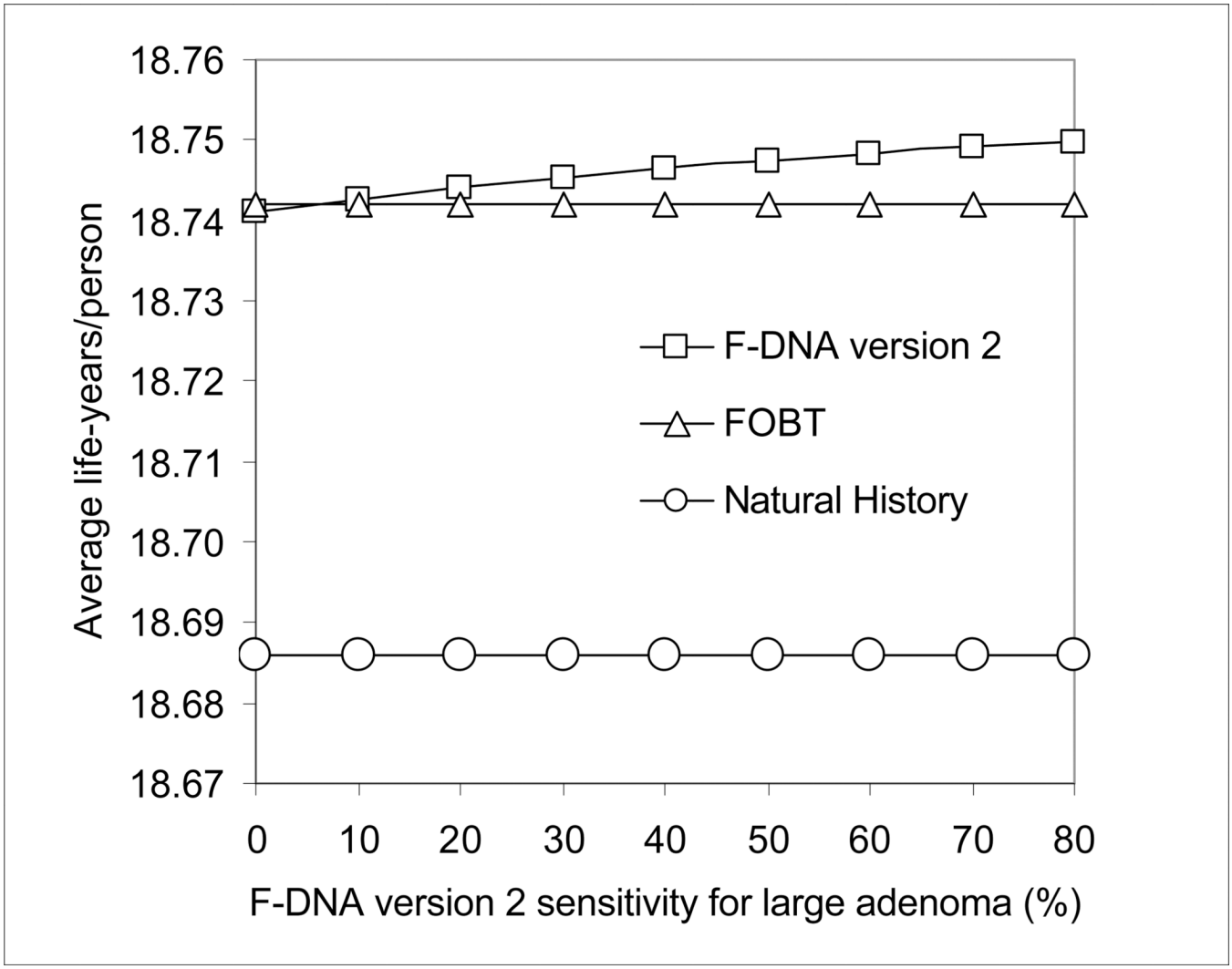


Figure 1.
Markov states in the natural history model. Persons cycle between states every year from age 50 to 100. Screening strategies were superimposed on the natural history model.



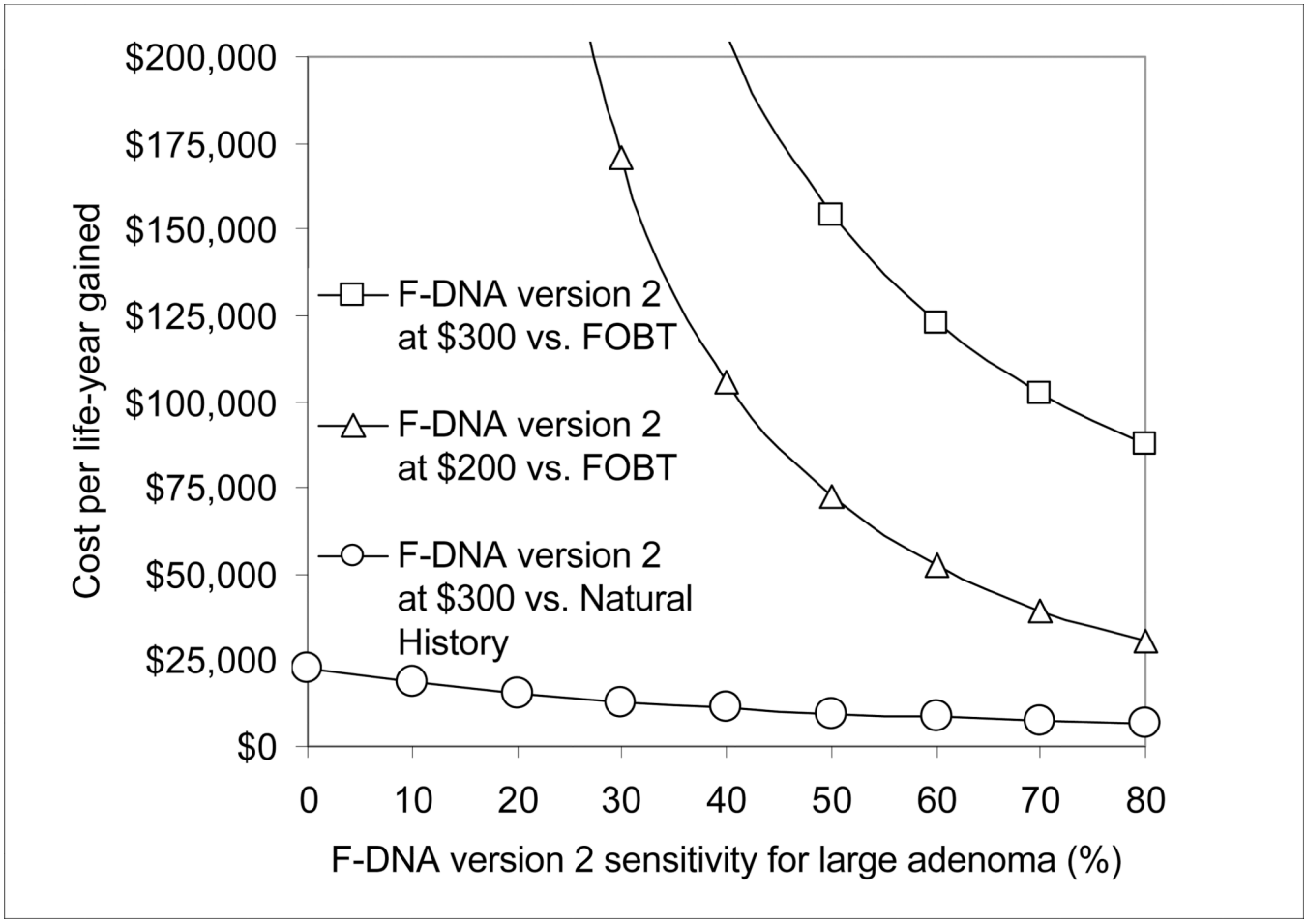


Figure 2.

A. Impact of sensitivity for large adenoma on the effectiveness of F-DNA. The effectiveness of F-DNA increases as sensitivity for large adenoma improves.

B. Impact of sensitivity for large adenoma and test cost on the cost-effectiveness of F-DNA. At a test cost of $200 and test sensitivity for large adenoma of >60%, F-DNA version 2 cost <$50,000/life-year gained compared with FOBT.

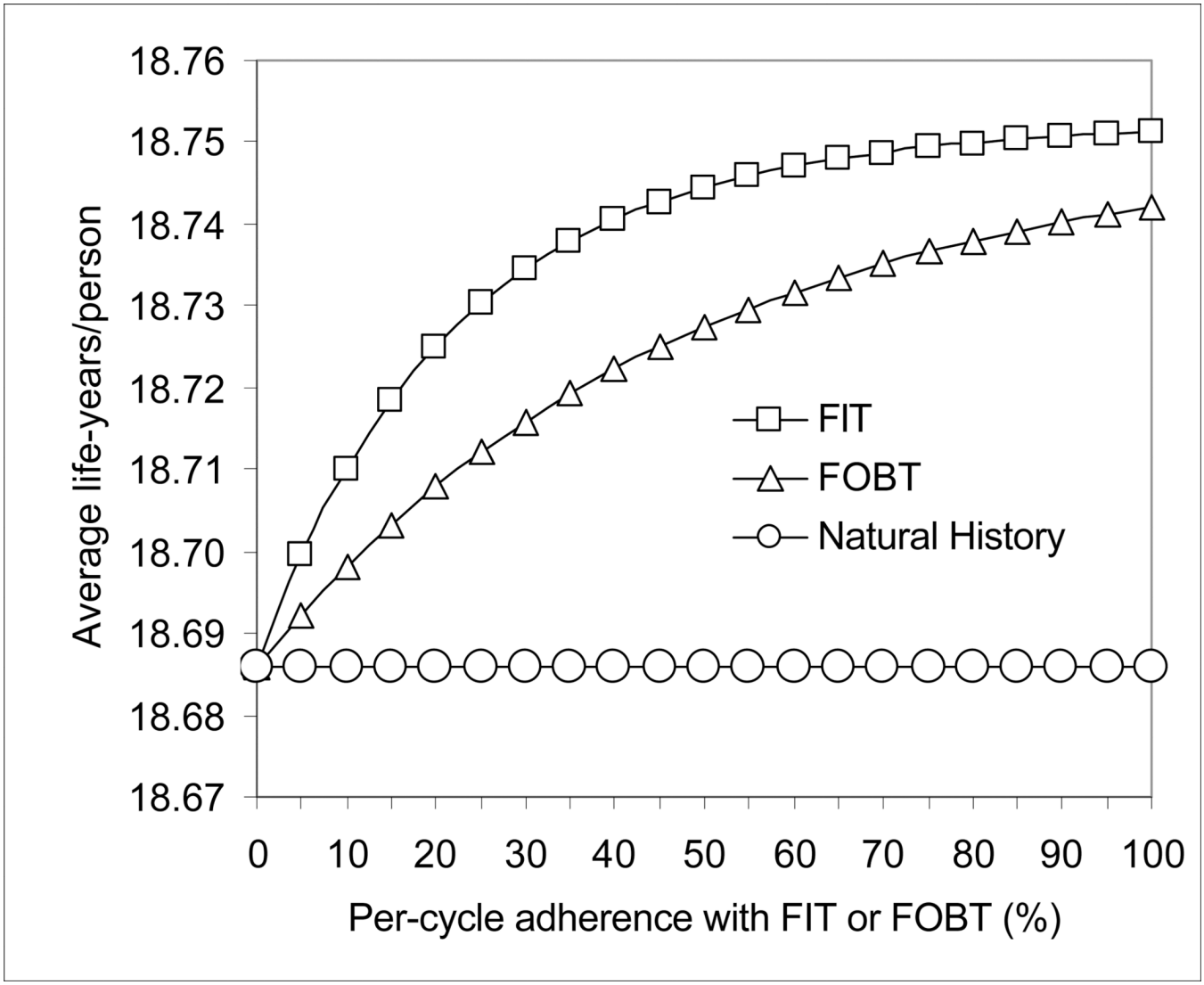


Figure 3.
Impact of adherence on the effectiveness of FOBT and FIT. As adherence with yearly testing decreased, the effectiveness of FOBT decreased steadily, and the effectiveness of FIT decreased significantly with per-cycle adherence below 60%.

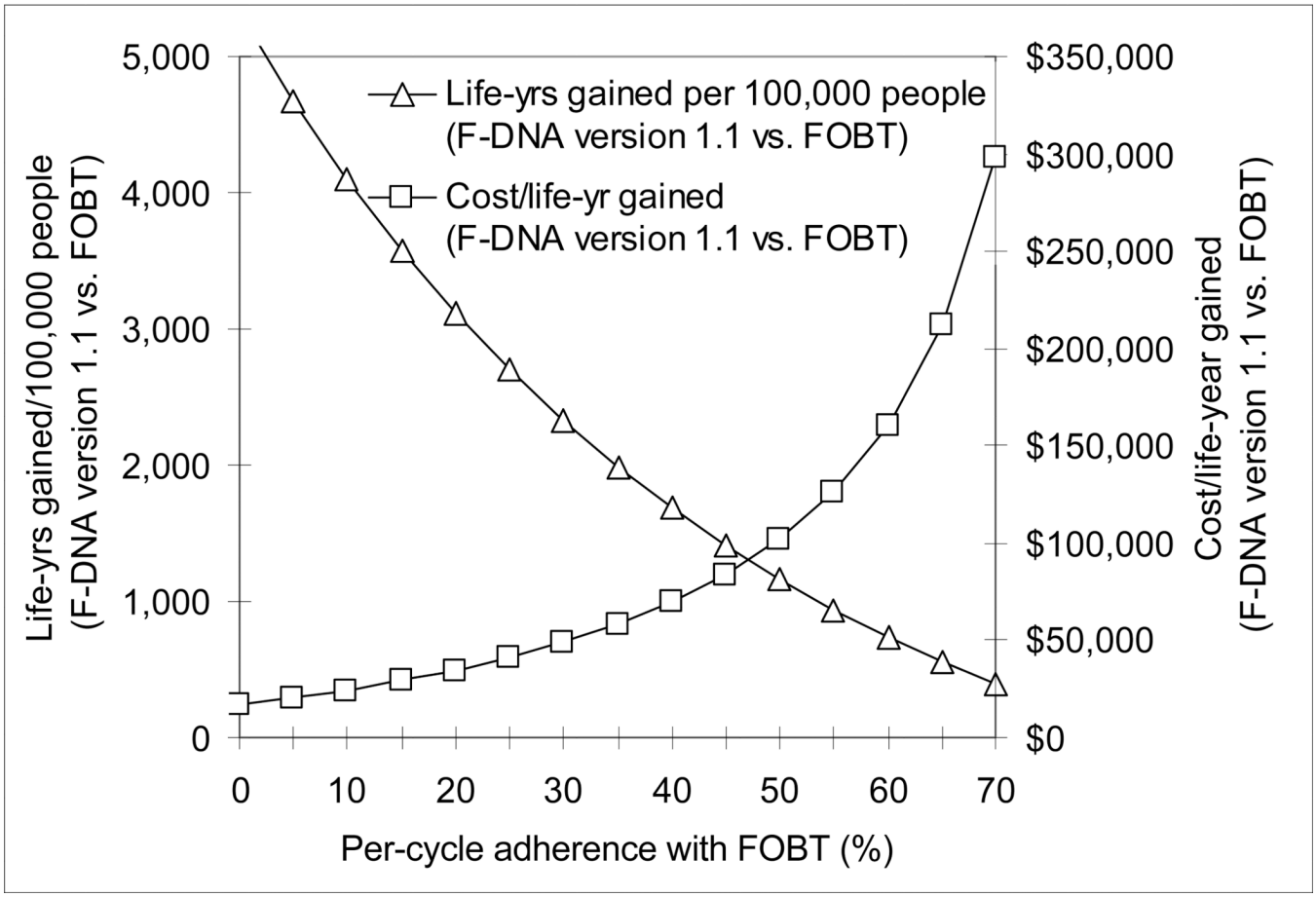


Figure 4.
Impact of adherence on the effectiveness and cost-effectiveness of F-DNA version 1.1 compared with FOBT. F-DNA version 1.1 became more effective than FOBT when the per-cycle adherence with FOBT fell below 85%, and it cost an incremental $50,000/life-year gained when the per-cycle adherence with FOBT was 31%.

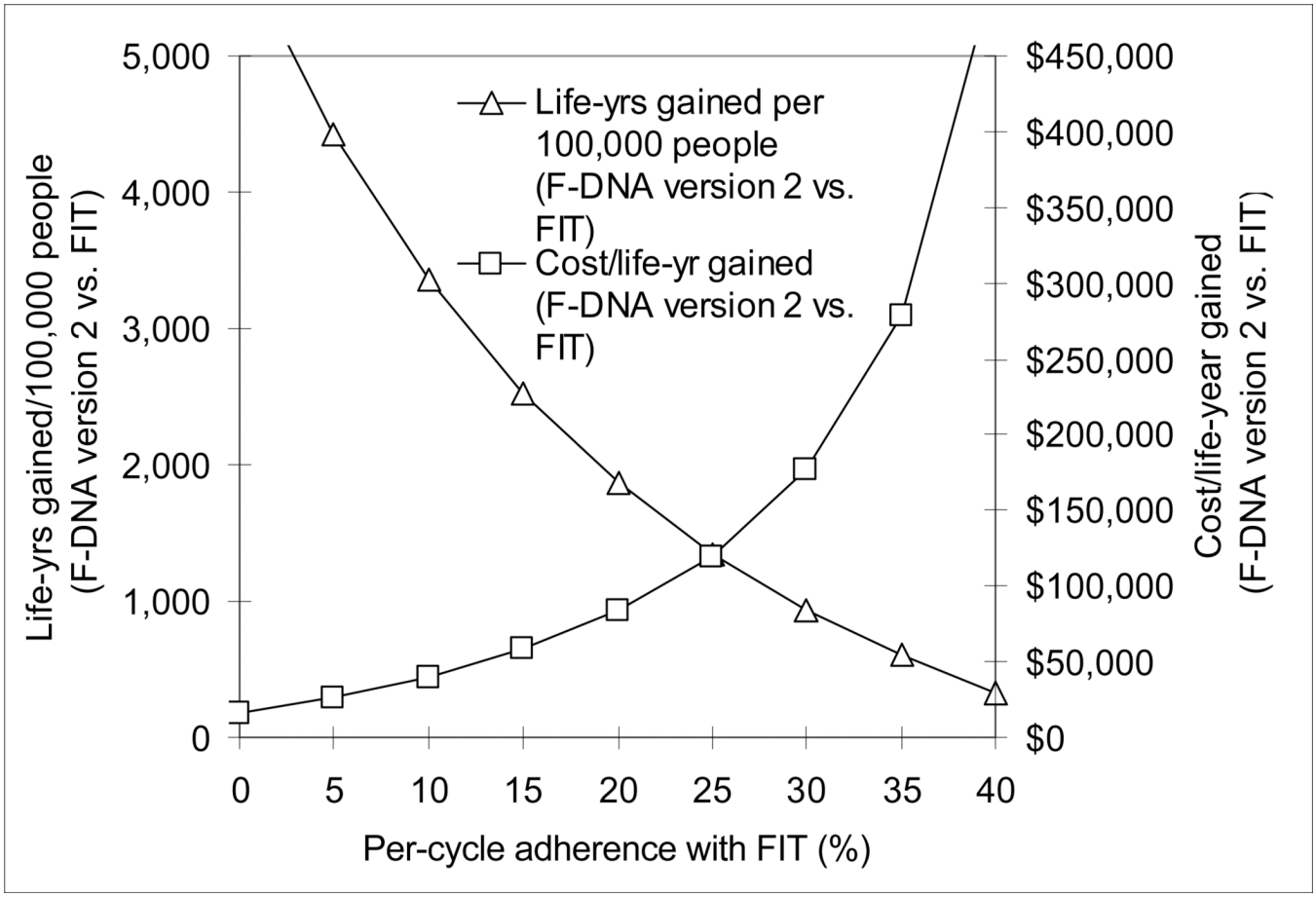


Figure 5.
Impact of adherence on the effectiveness and cost-effectiveness of F-DNA version 2 compared with FIT. F-DNA version 2 became more effective than FIT when the per-cycle adherence with FIT fell below 50%, and it cost an incremental $100,000/life-year gained when per-cycle adherence with FIT was 22%

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Table 1

Inputs in the Cost-Effectiveness Model

Variable	Base Case Value (Range)*	References
Clinical		
Polyp prevalence at age 50, %†	15	(91–93)
small polyp, % †	95	(93–95)
large polyp % †	5	(93–95)
Annual transition rate to small polyp from normal, %†	Age specific, 1.1–1.9	(91–95)
Annual transition rate to large polyp from small polyp, %†	1.5	(93–96)
Annual transition rate to cancer without polypoid precursor, %†	Age specific, 0.006–0.086	(9, 91–93, 97)
Annual transition rate to cancer from large polyp, %†	5	(9, 91–93, 97)
Symptomatic presentation of localized cancer, %†	22/y over 2y	(97)
Symptomatic presentation of regional cancer, %†	40/y over 2y	(97)
Mortality rate from treated localized cancer, %¶	1.74/y in first 5y	(97)
Mortality rate from treated regional caner, %¶	8.6/y in first 5y	(97)
Mean survival from distant cancer, y	1.9	(28, 30, 31, 48–51, 78, 79, 97)
Mortality rate from cancer treatment, %	2	(9, 10)
Fecal occult blood testing sensitivity for cancer, %	40 (30–60)	(9, 10)
Fecal occult blood testing sensitivity for large polyp, %	10 (5 – 15)	(9, 10)
Fecal occult blood testing specificity, %‡	92 (90–97)	(9, 10)
FIT testing sensitivity for cancer, %	76 (62–88)	(56–66)
FIT testing sensitivity for large polyp, %	40 (20–67)	(56–66)
FIT testing specificity, %‡	91 (86–98)	(56–66)
Fecal DNA version 1 testing sensitivity for cancer, %	52 (35–68)	(21)
Fecal DNA version 1 testing sensitivity for large polyp, %	18 (14–22)	(21)
Fecal DNA version 1 testing specificity, %‡	94 (93–96)	(21)
Fecal DNA version 1.1 testing sensitivity for cancer, %	73 (57–84)	(26)

Variable	Base Case Value (Range)*	References
Fecal DNA version 1.1 testing sensitivity for large polyp, %	18 (14–22)	(26)
Fecal DNA version 1.1 testing specificity, %‡	89 (83–94)	(26)
Fecal DNA version 2 testing sensitivity for cancer, %	88 (74–95)	(26)
Fecal DNA version 2 testing sensitivity for large polyp, %	18 (14–22)	(26)
Fecal DNA version 2 testing specificity, %‡	82 (74–88)	(26)
Colonoscopy sensitivity for cancer, %	95 (90–97)	(9, 10)
Colonoscopy sensitivity for large polyp, %	90 (85–95)	(9, 10)
Colonoscopy sensitivity for small polyp, %	85 (80–90)	(9, 10)
Colonoscopy major complication rate, %	0.1 (0.05–0.5)	(9, 10)
Colonoscopy mortality rate, %	0.01 (0.005–0.03)	(9, 10)
Cost, $		
Fecal occult blood testing	15 (15–56)	(46)
FIT testing	22 (22–95)	(46)
Fecal DNA testing	300 (300–495)	#
Colonoscopy	920 (710–1350)	(7, 9, 11, 20, 47, 98)
Colonoscopy with lesion removal	1350 (990–2030)	(7, 9, 11, 20, 47, 98)
Endoscopy complication	29,000 (16,000 – 43,000)	(71, 72)
Colorectal cancer care by stage§		
Localized	51,000 (40,000–62,000)	(5, 73–75)
Regional	98,000 (85,000 – 105,000)	(5, 28, 30, 31, 48–51, 73–75, 78, 79)
Distant	200,000 (175,000 – 230,000)	(5, 28, 30, 31, 48–51, 73–75, 78, 79)

*Range for test sensitivity and specificity used in Monte Carlo simulation

†Derived from epidemiologic and autopsy data

¶The annual mortality rate applies to those surviving to the beginning of each year, reflecting exponential decay since the fraction of persons surviving decreases at a rate proportional to its value

‡Sensitivity for small polyp set at (1-specificity)

§Derived from Centers for Medicare and Medicaid Services and published data

#Derived from LabCorp list price and average reimbursement (personal communication, Barry Berger, Exact Sciences Corp.)

Table 2

Effectiveness, Cost and Incremental Cost-Effectiveness of F-DNA version 1 at progressively shorter intervals.

F-DNA Interval	Discounted Life-Years/Person	Discounted Cost/Person	Incremental Cost/Life-Year Gained compared to next shorter interval
5 years	18.7197	$3,531	--
4 years	18.7244	$3,627	$20,400
3 years	18.7305	$3,867	$39,200
2 years	18.7394	$4,339	$52,600
1 year	18.7478	$5,658	$158,000

Table 3

Base case clinical and economic results and incremental cost-effectiveness ratios

	Natural History	F-DNA version 1	F-DNA version 1.1	FOBT	F-DNA version 2	Colonoscopy	FIT
CRC cases per 100,000 persons from age 50 to 100 years	5,927	3,989	3,711	3,009	3,403	1,584	2,015
CRC stage							
Local	2,373	2,191	2,231	1,876	2,148	882	1,291
Regional	2,210	1,266	1,086	813	943	509	504
Distant	1,345	532	393	320	312	193	220
Deaths attributable to CRC	2.4%	1.2%	1.0%	0.8%	0.9%	0.5%	0.5%
Life yrs/person[†]	18.686	18.730	18.739	18.742	18.744	18.748	18.751
Cost/person[†]	$2,921	$3,867	$3,821	$2,683	$3,833	$3,489	$2,428
Incremental life-yrs gained per 100,000 persons compared to:							
Natural History	-	4,466	5,323	5,623	5,795	6,185	6,542
F-DNA version 1	-	-	857	1,157	1,329	1,719	2,076
F-DNA version 1.1	-	-	-	300	472	862	1,219
FOBT	-	-	-	-	172	562	919
F-DNA version 2	-	-	-	-	-	390	747
Colonoscopy	-	-	-	-	-	-	357
Increment cost per life-yr gained compared to:							
Natural History	-	$21,200	$16,900	Dominates[‡]	$15,700	$9,200	Dominates[‡]
F-DNA version 1	-	-	Dominates[‡]	Dominates[‡]	Dominates[‡]	Dominates[‡]	Dominates[‡]
F-DNA version 1.1	-	-	-	Dominates[‡]	$2,700	Dominates[‡]	Dominates[‡]
FOBT	-	-	-	-	$669,000	$144,000	Dominates[‡]
F-DNA version 2	-	-	-	-	-	Dominates[‡]	Dominates[‡]
Colonoscopy	-	-	-	-	-	-	Dominates[‡]

CRC=Colorectal cancer; F-DNA=Fecal DNA testing every 3 years; FOBT=Annual guaiac-based fecal occult blood testing; FIT=Annual fecal immunochemical testing

[†]Discounted at 3% per year

‡Strategy in top row is more effective and less costly than strategy in left column to which it is being compared

Table 4

One-way sensitivity analyses

Subject of sensitivity analysis	Base case value(s)	Value(s) in sensitivity analysis	FOBT vs. F- DNA version 1		FOBT vs. F-DNA version 1.1		F-DNA version 2 vs. FOBT		FIT vs. F- DNA version 2	
			Life-yrs gained per 100,000 persons	Cost/life-yr gained	Life-yrs gained per 100,000 persons	Cost/life-yr gained	Life-yrs gained per 100,000 persons	Cost/life-yr gained	Life-yrs gained per 100,000 persons	Cost/life-yr gained
Fecal DNA test										
Cost	$300	$200	1,157	Dominates	300	Dominates	172	$410,000	747	Dominates
		$495	1,157	Dominates	300	Dominates	172	$1,170,000	747	Dominates
Colonoscopy										
Sensitivity for CRC	95%	90%	1,136	Dominates	273	Dominates	192	$596,000	720	Dominates
		97%	1,156	Dominates	242	Dominates	240	$474,000	612	Dominates
Sensitivity for large polyp	90%	85%	1,157	Dominates	289	Dominates	194	$592,000	658	Dominates
		95%	1,166	Dominates	313	Dominates	154	$745,000	818	Dominates
Sensitvity for small polyp	85%	80%	1,135	Dominates	286	Dominates	178	$647,000	745	Dominates
		90%	1,168	Dominates	308	Dominates	167	$688,000	748	Dominates
Probability of complication	0.1%	0.05%	1,157	Dominates	300	Dominates	172	$670,000	747	Dominates
		0.5%	1,157	Dominates	300	Dominates	172	$663,000	747	Dominates
Probability of death related to colonoscopy	0.01%	0.005%	1,204	Dominates	328	Dominates	169	$690,000	761	Dominates
		0.05%	751	Dominates	61	Dominates	217	$531,000	632	Dominates
Cost (diagnostic/with lesion removal)	$920/$1350	$710/$990	1,157	Dominates	300	Dominates	172	$688,000	747	Dominates
		$1350/$2030	1,157	Dominates	300	Dominates	172	$632,000	747	Dominates
Cost of complication	$29,000	$16,000	1,157	Dominates	300	Dominates	172	$669,000	747	Dominates
		$43,000	1,157	Dominates	300	Dominates	172	$668,000	747	Dominates
FOBT										
Sensitivity for CRC/large polyp/small polyp/Specificity	40%/10%/8%/92%	30%/5%/3%/97%	527	Dominates	−330(F-DNA version 1.1 is more effective)	$385,000(F-DNA version 1.1 vs. FOBT)	802	$160,000	747	Dominates

Subject of sensitivity analysis	Base case value(s)	Value(s) in sensitivity analysis	FOBT vs. F- DNA version 1		FOBT vs. F-DNA version 1.1		F-DNA version 2 vs. FOBT		FIT vs. F- DNA version 2	
			Life-yrs gained per 100,000 persons	Cost/life-yr gained	Life-yrs gained per 100,000 persons	Cost/life-yr gained	Life-yrs gained per 100,000 persons	Cost/life-yr gained	Life-yrs gained per 100,000 persons	Cost/life-yr gained
		60%/15%/10%/90%	1,747	Dominates	890	Dominates	−418 (FOBT is more effective)	$286,000 (FOBT vs. F-DNA version 2)	747	Dominates
		13%/11%/5%/95%(as in Imperiale *et al.* (21))	−407 (F-DNA version 1 is more effective)	$303,000 (F-DNA version 1 vs. FOBT)	−1,264 (F-DNA version 1.1 is more effective)	$94,000 (F-DNA version 1.1 vs. FOBT)	1,736	$69,000	747	Dominates
Cost	$15	$56	1,157	Dominates	300	Dominates	172	$413,000	747	Dominates
FIT										
Sensitivity for CRC/large polyp/small polyp/ specificity	76%/40%/91%	62%/20%/14%/86%	1,157	Dominates	300	Dominates	172	$669,000	385	Dominates
Cost	$22	$95	1,157	Dominates	300	Dominates	172	$669,000	747	Dominates
CRC care costs										
Local/regional/distant	$51,000/98,000/200,000	$40,000/85,000/175,000	1,157	Dominates	300	Dominates	172	$657,000	747	Dominates
		$62,000/105,000/230,000	1,157	Dominates	300	Dominates	172	$678,000	747	Dominates
		$51,000/75,000/78,000 (without use of novel chemotherapy)	1,157	Dominates	300	Dominates	172	$674,000	747	Dominates

CRC=Colorectal cancer; F-DNA=Fecal DNA testing every 3 years; FOBT=Annual guaiac-based fecal occult blood testing; FIT=Annual fecal immunochemical testing

"Dominates" denotes situation where first strategy is more effective and less costly than second strategy