Colorectal Cancer Screening: Technical Report Prepared for the National Commission on Prevention Priorities

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A. USPSTF Recommendation

The USPSTF strongly recommends that clinicians screen men and women 50 years of age or older for colorectal cancer (A recommendation).[1] The USPSTF evidence review found good, direct evidence of the effectiveness of fecal occult blood testing (FOBT); fair, direct evidence for the effectiveness of flexible sigmoidoscopy; and indirect evidence for combined FOBT & flexible sigmoidoscopy, colonoscopy alone, and double contrast barium enema. The USPSTF recommends that the choice among screening strategies be made according to individual patient circumstances and preferences. The USPSTF does not specify appropriate screening intervals.

B. Choice of Screening Tools and Intervals

We based our estimates on FOBT, flexible sigmoidoscopy, and colonoscopy because the evidence is strongest for these screening tools, and the available evidence on delivery rates suggests that the majority of screening is currently performed by one of these tests. Our estimates of the CPB (clinically preventable burden) and CE (cost effectiveness) of colorectal cancer screening are weighted estimates of the value of FOBT, flexible sigmoidoscopy, and colonoscopy, where the weights are based on the current delivery rates for these services.

The evidence does not clearly indicate whether annual FOBT provides a substantial benefit over biennial FOBT, or whether flexible sigmoidoscopy screening every 10 years provides less benefit than screening every 5 years. Our estimates are based upon the most commonly recommended intervals by other organizations:[2] annual FOBT, flexible sigmoidoscopy every 5 years, or colonoscopy every 10 years.

C. Literature Search and Abstraction

SEER (Surveillance, Epidemiology and End Results) cancer statistics are a well-known, highly regarded source of cancer mortality data.[3] Therefore, an extensive search for cancer mortality data was not necessary. We performed a Level I search[4] for quality of life data, effectiveness, adherence, delivery rates, and cost-effectiveness. The search found 543 articles.

C1. Effectiveness Literature:

From these articles, we identified 23 articles reporting the effectiveness of colorectal cancer screening in preventing colorectal cancer mortality.[5-27] Eight of these studies were excluded, either because participants were not compared to a group without screening[5;25] or because a more recent article on same study with longer follow-up was available.[6;8;10;11;14;27] After this literature was reviewed, modeled estimates of the mortality reduction obtainable with screening from sigmoidoscopy and colonoscopy[28-30] were added to our evidence base due to the scarcity of direct evidence for these screening tools.

C2. Cost Effectiveness Literature:

The search identified 10 articles on cost-effectiveness that expressed results in terms of dollars per life years saved.[28-37] We abstracted seven of these articles[28-32;34-36] after excluding three studies because more recent estimates were available using essentially the same model,[33] the model was estimated with substantially older data than more recent estimates,[37] or the age group for screening was too limited.[35]

We reviewed, but did not formally abstract, 53 published articles containing estimates of adherence with screening or follow-up procedures,[7-11;14;15;18;25;38-81] and 6 articles examining national delivery rates of FOBT and proctoscopy (variously defined).[82-87]

D. Clinically Preventable Burden (CPB) Estimate

Conceptually, CPB is the burden addressed by the service multiplied by the effectiveness of the service. Table 1 shows the summary calculations for CPB. Some of the data points in Table 1 are estimates from the literature and others are calculated based upon other data in the table. The "Data Source" column in Table 1 shows either the references for estimates or the formula used to calculate the variable. The letters in the formulas refer to the row labels (left most column) for the data on which the calculation is based. The "Base Case" column shows the best available estimate for each variable that was used in our calculation of CPB, and the "Range" column shows the range over which the point estimates were varied in our sensitivity analysis.[4] We created additional tables (not shown) to summarize the evidence and perform supporting calculations. Their contents are described below.

D.1 Burden of Disease:

Colorectal Cancer Mortality and Life Expectancy at Age of Death: Rows a and b.

CPB is based on delivery of the service to a one-year U.S. birth cohort (the size of which is defined consistently in this study as 4 million) over the age range for which the service is recommended by the USPSTF. There would be 90,800 colorectal cancer deaths after the age of 50 in a US birth cohort of 4,000,000 individual (row a) given current rates of colorectal cancer screening, current colorectal cancer mortality rates,[3] and current life-expectancy after the age of 50.[88] This is higher than the 54,156 deaths observed in 2000 for the cross-section of individuals age 50 and above[3] because the 2000 total largely reflects pre-baby boom birth cohorts of less than 4,000,000. We calculated the average life expectancy (LE) at the age of premature death (row b) as the weighted average of LE in 5-year age groups by using LE estimates from life-tables[88] and age at death for cancer deaths.[3]

Delivery Rates: Rows c-f.

They enter into the calculations of CPB at two points:

1. to calculate a weighted average of the benefits of FOBT, sigmoidoscopy, and colonoscopy (row j); and
2. to calculate predicted deaths in the absence of screening (row k).

For each service, CPB is estimated independently of current delivery rates to indicate each service's total value, rather than the value of improving delivery rates over current levels for the U.S. population. Delivery rate estimates are based on six reports of two national surveys conducted at various times from 1992 – 2001. Four reports[84-87] summarized screening rates from the Behavioral Risk Factor Surveillance Survey (BRFSS) in 1992, 1997, 1999, and 2001, and two reports[82;83] summarized screening rates from the National Health Interview Survey (NHIS) in 1992, 1998 and 2000. The questions in these surveys were not consistent over time, but the responses appear to indicate a slow upward trend in use of FOBT and endoscopy since 1992 (although the wording 'proctoscopy' was used in most of these surveys).

It is necessary to use earlier delivery rates to estimate what the total mortality attributable to cancer would have been in the absence of screening in 2000 (row k) because screening impacts mortality for several years following screening. From data reported by Nadel,[82] we

estimate that 17.6% of the US population greater than 50 years of age received some sort of screening for colorectal cancer in 1992. We estimate this based on the reported use of home FOBT kits for screening purposes and on an estimate of the use of proctoscopy for screening purposes in 1992. The portion of proctoscopy that was performed for screening purposes in 1992 is not available. Therefore, we applied the portion of all proctoscopy that was performed for screening in 1998 to total proctoscopy use in 1992. Finally, only more recent NHIS questions distinguish between screening by sigmoidoscopy versus colonoscopy. Therefore we use the relative portion of screening by home FOBT, sigmoidoscopy, and colonoscopy as recently reported by Subramanian[83] from the 2000 NHIS (rows d-f). Combining survey responses from various years in this manner produces an imperfect estimate of screening rates for colorectal cancer in 1992. However, we use this mix of estimates rather than using data from 2000 for both the mix of screening tools and the overall screening rate, because using the higher screening rates from 2000 will cause us to overstate the number of deaths that have been prevented by screening.

Finally, to estimate the weighted efficacy of screening given the current mix of screening tools in use, we tabulate the use of procedures for screening purposes from the most recently available NHIS public use data set (2003).[89] 2.4% of respondents (as tabulated with sample weights) were up-to-date on both FOBT and one of sigmoidoscopy or colonoscopy. We assign these individuals to the FOBT category.

D.2 Effectiveness of Screening:

The primary distinction we make between efficacy and effectiveness is that effectiveness reflects the level of patient adherence that can be expected in every-day practice, while efficacy reflects 100% patient adherence.[4] CPB is based on effectiveness, where patient adherence is defined as the percent who accept the service once offered and adhere with follow-up treatment or advice to change behavior.

D.2.1 Effectiveness Literature:

Twelve of the effectiveness studies that were included examined FOBT screening, including 3 randomized controlled trials,[9;15;21] one quasi-randomized trial[18] and 8 case-control studies.[7;12;13;19;20;23;24;26] Four case-control studies examined flexible sigmoidoscopy.[16;17;20;22] Because the evidence base for quantifying the effectiveness of flexible sigmoidoscopy and colonoscopy in reducing mortality is very limited, we also included modeled estimates of mortality reduction,[28-30] and we checked our base-case estimates of mortality reduction against available estimates of the reduction in cancer cases achieved by sigmoidoscopy and colonoscopy screening.[90-92]

D.2.2 Efficacy of FOBT: Row g.

We found only one estimate in the literature that reports the mortality reduction among those who completed (i.e., both offered and adhered with) an entire series of screens. In this study, Faivre et al. reported a 70% reduction in colorectal cancer mortality among people who completed all four in a series of biennial FOBT screens.[7] However, the confidence interval for the odds ratio was very wide (.12 to .76). In addition, comparing those who completed all screens to a control group would produce biased estimates of effectiveness if the self-selected group who completed all screening had different baseline cancer risks than the control group. Therefore, we increased our evidence-base for estimating the efficacy of a series of FOBT screens by calculating efficacy using adherence and effectiveness from 4 controlled trials[9;15;18;21] (efficacy =

effectiveness / adherence). We made similar approximations using the results of 8 case-control studies[7;12;13;19;20;23;24;26] by assuming that people who had at least one screen were 80% adherent with recommended screening intervals.[7] This produces a range of efficacy for FOBT of 13% to +60% in reducing colorectal cancer morality. The mean of all studies for our base-case estimate is 38%. Our range in sensitivity analysis reflects the fact that 10 of 12 estimates clustered between 25% and 60%.

D.2.3 Efficacy of Flexible Sigmoidoscopy: Row h.

The evidence base for the effectiveness of flexible sigmoidoscopic screening was limited. Four case-control studies[16;17;20;22] yielded estimates of 5%, 11%, 34% and 79% reductions in colorectal cancer mortality (from both proximal and distal cancers). The two lowest estimates were based on odds ratios that were not statistically different from zero. Due to the variable nature of retrospective case-control study interventions, screening sigmoidoscopy is defined as having at least one test. These studies did not report how frequently screening was received in the past, but the use of prior screens may be less important to the estimated effect size of sigmoidoscopy than to that of FOBT because sensitivity of the screen is substantially higher for adenomas within reach of the sigmoidoscope. Therefore, we assume that these four case-control studies provide a better estimate of efficacy than effectiveness, although one-time screening does not reflect the benefit of false-negatives that are corrected in subsequent screenings or the benefit of follow-up colonoscopies after abnormal findings on subsequent screenings.

Due to the small number and wide range of the four estimates noted above, we also considered two other sources of information on screening effectiveness: case-control studies of colorectal cancer cases (not deaths) and modeled estimates of reductions in colorectal cancer deaths. Using the same population (Veterans Administration patients) that generated the 5% estimate of effectiveness in reducing mortality above, the authors reported a separate case-control study in which cases were defined as cases of colorectal cancer (not deaths).[90] They reported odds ratios of 0.56 and 0.61 for colon and rectal cancer respectively with the use of flexible sigmoidoscopy as the most recent screening tool. Similarly, using cases drawn for SEER registries in Washington and Utah, Slattery et al. reported adjusted odds ratios of 0.6 for men and 0.5 for women for cancers associated with having ever received "sigmoidoscopy for check-up".[92] Newcomb et al. reported odds ratios of 0.24 and 0.89 for incident distal and proximal cancers respectively for those having at least one sigmoidoscopy exam 1 year prior to diagnosis of the case.[91] These odds ratios indicated an effectiveness of sigmoidoscopy in preventing all colorectal cancer cases of about 45% when using odds ratios to approximate relative risk and assuming that 55% of cancers are distal.

Cost-effectiveness studies that reported the percent reduction in colorectal cancer deaths as a result of a model that assumes 100% compliance have estimated reduction in deaths with the use of flexible sigmoidoscopy every 5 years of 53%,[29] 66%,[30] and 68%.[28]

Among both case-control studies and modeled estimates, reductions in colorectal cancer mortality were 5%, 11%, 34%, 53%, 66%, 68%, and 77%, with a mean and median of 45% and 53% respectively. It is difficult to objectively define a base-case estimate for the effectiveness of flexible sigmoidoscopy because this range is wide, there is no apparent cluster of estimates within the range, and each estimate had moderate limitations. We assign 50% as our base-case estimate for mortality reduction, because it lies between the mean and the median and it is consistent with reductions in colorectal cancer cases reported from the two case-control studies summarized above.

We use a range of 25% to 75% efficacy of sigmoidoscopy in sensitivity analysis. The base case estimate of 50% is consistent with nearly 100% efficacy in the prevention of mortality from cancers within reach of the sigmoidoscope, and estimates above 50% are feasible because follow-up colonoscopy detects and treats polyps outside the reach of the sigmoidoscope. Both Selby et al.[22] and Newcomb et al.[17] reported non-statistically significant reductions in mortality from cancers outside the reach of the sigmoidoscope.

D.2.4 Efficacy of Colonoscopy: Row i.

We identified only one observational estimate, and no controlled trials, of the efficacy of colonoscopy in preventing colorectal cancer mortality. In a case-control study among Veterans Administration patients, Muller and Sonnenberg reported adjusted odds ratios of 0.45 for colorectal cancer death associated with the use of colonoscopy without tissue removal as the most recent colorectal procedure.[16] Using this odds ratio to approximate relative risk, this study implies an effectiveness of 55% in reducing colorectal cancer mortality. Muller and Sonnenberg also reported odds ratios of 0.47 and 0.61 for incident colorectal cancer cases associated with the use of colonoscopy without polypectomy as the most recent colorectal procedure.[90] As noted by the authors, the mortality and case reduction estimates from these reports was limited by incomplete data capture outside of the VA system and categorization of patients by most recent type of endoscopic procedure.[16;90]

In another case-control study in Germany that did not distinguish between endoscopy by colonoscopy or flexible sigmoidoscopy, Brenner et al. reported an adjusted odds ratio of 0.28 with any history of endoscopy and odds ratios for colorectal cancer deaths of 0.20 and 0.23 with any endoscopy within the last 5 years and last 5-10 years respectively.[93] In addition to not distinguishing between types of endoscopy, this study did not distinguish between endoscopies that did and did not follow FOBT screenings, and therefore may not accurately reflect the efficacy of endoscopy as a primary screening tool.

The same cost-effectiveness studies that reported modeled estimates of effectiveness for sigmoidoscopy screening in reducing colorectal cancer mortality, reported modeled estimates of 68%,[29] 78%,[30] and 90%[28] reductions in mortality with screening by colonoscopy in 10-year intervals with 100% compliance.

The overall mean and median of the four estimates for reductions in colorectal cancer deaths (excluding the study that did not distinguish by endoscopy type) from the single case-control study and three modeled estimates are 73% and 74%. As with sigmoidoscopy, it is difficult to assign a base-case estimate for the efficacy of colonoscopy from these data. Furthermore, because there is only one direct estimate, these summary measures are heavily influenced by the three modeled estimates. We assign a base-case estimate of 70% on the assumptions that colonoscopy views approximately 85% of the colon and that cancers are evenly distributed through the colon with the same case-fatality rate when not detected early. This base-case estimate of 70% efficacy implies that colonoscopy is approximately 83% effective in preventing deaths from cancers within reach of colonoscopy.

D.2.5 Patient Adherence: Row l.

The RCT and case-control study results reflect adherence with follow-up treatment. However, we needed to incorporate estimates of patient adherence with the screens once they are offered. We found estimates of adherence with offers for FOBT screens in 36 studies.[7-11;15;18;25;38-65] Eleven studies were excluded because they were earlier reports of populations

whose adherence is reported in another included study.[10;11;15;58-65] We excluded 9 additional studies from our evaluation because the populations appeared to be too selective to provide generalizable estimates of adherence.[25;38;42;44;45;47;49;50;56] Most of the excluded populations were individuals who had previously consented to participate in a screening trial. Most of the included studies are from European countries; most report adherence with one screen rather than a series of screens; and most report adherence with offers that were sent by mail rather than in a clinical setting. There are too few studies of US populations, of offers of a series of screens, or of offers in a clinical setting to determine whether their results might differ from these findings. Therefore we calculated averages across all included studies. The vast majority of mailed invitations included an FOBT kit with instructions, and most invitations were followed by reminder calls. The mean and median adherence with offers for FOBT screening in the 16 included studies[7-9;18;39-41;43;46;48;51-55;57] were 50% and 47% respectively. The minimum and maximum estimates for these 15 populations were 20% and 75%.

Similarly, we identified estimates of adherence with sigmoidoscopy among 18 studies,[25;39;44;51;55;66-78] and excluded nine of these[25;44;69;72;73;75-78] from our evaluation due to concerns about generalizability. Three additional studies were excluded because they were earlier reports of one of 16 populations covered by the 18 reports.[66-68] As with FOBT screening, a large portion (3 of 6) were from European countries, and they reported adherence with a single screen that was offered through a mailed invitation. The mean and median adherence in the 6 included studies[39;51;55;70;71;74] were 54% and 46%, and the minimum and maximum estimates were 39% and 81%.

A recent study reported of referrals for colonoscopy in an unselected population found that 50% of individuals completed screening.[94] Three studies in selected populations (individuals at high risk, consented to randomization, or scheduled an initial screen) reported acceptance of screening greater than 60%.[75;76;79]

Our evidence summary shows no apparent difference in adherence between the FOBT and sigmoidoscopy. Given the available evidence, a reasonable adherence estimate for offers of one FOBT or sigmoidoscopy is 50%. This estimate may slightly understate adherence in the general population because some of the studies in this summary excluded individuals who were already up-to-date on screening. However, the impact is likely to be small because screening rates have been and remain lower for colorectal cancer screening than for other recommended cancer screenings. In addition, the USPSTF recommends offering screening choices to patients and some[33] have suggested that offering more than one test may increase acceptance of screening because those who reject one type of screening may accept another. The literature we reviewed showed some evidence of this,[39;51;55] but the evidence is insufficient to quantify the effect of offering more than one type of screening. Based on the estimate of 50% adherence with an offer for a single type of screening, we assume adherence among those offered a range of screening options would be 60% for our base-case (row n), and use a range of 40% to 75% in our sensitivity analysis. Because our estimates of the percent reduction in colorectal cancer mortality (rows d-f) reflect the rates of adherence with follow-up in the RCTs and case-control studies, adherence with follow-up diagnostics and treatment are not added to the calculation of CPB in Table 1. Our review did find 5 estimates of adherence with diagnostic follow-up following a positive test, with an average adherence of 84%.[11;25;38;40;80] One study reported adherence with surveillance of 83% after a positive or suspicious screen (average of a variety of risk-level groups).[81]

D.3 CPB Estimate: Rows q and r.

Based on the data points, assumptions, and calculations described above, colorectal cancer screening will prevent more than 31,000 deaths in a birth cohort (row q) and the base case estimate for the CPB of colorectal cancer screening is 337,556 life years saved (row r). As discussed in the sensitivity analysis section following, this estimate is approximately equivalent to the reduction in quality adjusted life years saved (QALYs saved), and thus is comparable to CPB as measured in QALYs saved for other services in the Prevention Priorities study.

D.4 Sensitivity Analysis for CPB.

In single-variable sensitivity analysis, CPB is most sensitive to the number of deaths attributable to colorectal cancer, the life expectancy at death, the efficacy of colonoscopy in preventing deaths, and the adherence with screening (rows a, b, i, & p in Table 1). For these variables, CPB changes by -33% to +25% within the ranges specified for each variable in Table 1. CPB is also moderately sensitive to the estimate of the portion of screening that occurs by FOBT versus colonoscopy. Changing three of the most influential variables simultaneously in the same direction produces our lower and upper CPB estimates of 134,000 and 623,000 QALYs saved.

Our base-case estimate of CPB may overstate the true value of screening if our inclusion of trial data has caused us to estimate adherence with screening or with follow-up diagnostic tests and treatments at a higher rate than can be expected in typical practice.

Our base-case estimate may also overstate CPB if we have overestimated the gains in life-expectancy. If, on average, individuals whose colorectal cancer deaths were prevented die sooner than the general population for other reasons, then we have overestimated average life-expectancy per colorectal cancer death prevented. As possible evidence of this, the two studies which report all-cause mortality found no difference between screened and unscreened groups. One randomized controlled trial of FOBT screening showed a non-statistically significant 1% reduction in all-cause mortality at 10 years follow-up (from year of study initiation),[11] and no reduction at 13 years follow-up.[9] A second FOBT trial showed no reduction in all-cause mortality at both 13 and 18 years follow-up.[14;15] These studies did not have adequate power to fully evaluate all-cause mortality. In any case, to avoid building-in implicit discrimination against subpopulations with lower than average life-expectancy, our study methodology requires the use of average life-expectancy for all individuals in the analysis of all services.

Our estimate also excludes complications from screening and adjustments for effects on quality of life. Major complications are rare. Data on the frequency of events, quality of life, and the duration of impaired or improved quality of life are not sufficient to produce accurate adjustments to life years saved. In Table 2 we provide a very rough estimate of what the adjustments to our estimate of CPB (337,500 LYS, Table 1) might be if all quality of life and complications were included. Columns a and b describe the events and potential quality of life issues associated with the events. Column c provides an estimate of the lifetime incidence of each event in a cohort of 3,740,000 -- the portion of a birth cohort of 4,000,000 that is still alive at the initial screening age of 50. Most of the incident estimates in column c are based upon the results of a high-quality cost-effectiveness study that reported relatively detailed results.[32] Column d and e provide our assumptions on the quality of life impact and duration of impact for each event. A negative number in column d reflects an adverse impact on quality of life. The weights are relative to 1.0 for perfect health, so a quality of life weight of -0.05 over 20 years is mathematically equivalent to a loss of one full year of perfect health. However, the quality of life

weights and durations are not data-driven. Their values were chosen to be reasonably consistent with the quality of life weights and durations used elsewhere in the Prevention Priorities Study. Column f is calculated by multiplying column d by the year-equivalents of column e. Total QALYs (column g) is the product of incidence, duration, and quality of life weight.

In this example, our estimate of 337,500 years of life saved (Table 1) will increase by about 6,800 quality-adjusted life-year equivalents (2.0%). The margin of error of this estimated adjustment is very large. For example, simply reducing the assumed values of the annual quality of life reduction for cases of cancer prevented from 0.20 to 0.15 changes the adjustment from a positive 6,800 to a negative 1,200. Due to the large potential for error relative to small impact on CPB, we have not incorporated such an estimate into our CPB estimate.

E. Cost-Effectiveness Estimate

We used the same methods for producing estimates of CE across preventive services.[95;96] These methods are consistent with the 'reference case' of the Panel and Cost-Effectiveness in Health and Medicine.[97] Our methods include the use of a 3% discount rate for both cost and health benefits, the exclusion of productivity losses from disease costs, and the exclusion of medical costs that are not related to the conditions prevented by the service. We use year 2000 dollars for all cost data.

E.1 Cost-effectiveness Literature.

We abstracted seven CE studies that estimated the cost per life-year saved of FOBT screening, sigmoidoscopy screening, or colonoscopy for a birth cohort of persons 50+ years of age to at least age 80.[28-34] As described above, we excluded three other studies that were identified in the search.[35-37] No studies measured health outcomes in terms of QALYs, and none used a societal perspective in estimating net costs.

Six of the seven studies reported the CE of annual FOBT screening.[28-33] They either reported the CE of annual FOBT relative to no screening, or reported results in sufficient detail to allow calculation of the CE of screening relative to no screening. The range of base-case estimates for these five studies, adjusting to year 2000 dollars, is $6,300/LYS to $19,700/LYS.

Six of the seven abstracted studies reported CE ratios of screening by flexible sigmoidoscopy every five years compared to no screening, or reported data in sufficient detail to allow calculation of such CE ratios.[28-33] Adjusting to year 2000 dollars, the range of base-case estimates for these six studies is $13,600/LYS to $36,300/LYS. However, only one study[32] had a base-case estimate above $18,000/LYS. That estimate appears to be largely due to the use of a high unit cost of sigmoidoscopy. With the exception of this highest estimate, the range of CE for screening by flexible sigmoidoscopy every 5 years is similar to the range for annual FOBT.

All seven of the abstracted studies also reported the CE of screening by colonoscopy compared to no screening or reported results in sufficient detail to allow calculation of such CE ratios. Adjusting to year 2000 dollars, the range of base-case estimates for these six studies is $7,300/LYS to $22,000/LYS.

E.2 Adjusted CE ratio.

We based our CE estimates on a study by Vijan et al.[29] that most adequately modeled two important variables: adherence with screening and follow-up diagnostic tests, and the costs of screening. Vijan et al. accounted for incomplete adherence with all screens and with follow-up studies after positive tests. They also had the most complete consideration of the costs of

screening, and used estimates that were in the mid-range of those used by the other studies. Vijan et al. present estimates with varying levels of adherence. We base our CE scores on their estimates with 75% adherence.

One weakness of the study by Vijan et al for our purposes was that colonoscopy was modeled as two screens at either ages 50 and 60 or at ages 55 and 65. Although this was a 10-year interval, no screening at older ages was included. The impact on the CE ratio of excluding screenings in older ages is difficult to predict. The annual risk of colorectal cancer mortality increases substantially with age from about 5 per 10,000 in ages 60-69 to about 20 per 10,000 in ages 80 and older. However, decreasing life expectancy at later ages limits the impact of screening, both by reducing the years of life at risk for colorectal cancer death and by reducing the number of years of life gained from avoiding a colorectal cancer death.

E.2.1 Adjustment of Patient Time Costs.

The CE estimate is shown in Table 3. In order to make adjustments for the cost of patient time for screening and follow-up tests, we rely on the more detailed results on the frequency of follow-up studies that were provided by Sonnenberg et al.[32] We also made adjustments to Sonnenberg et al's frequencies to account for incomplete adherence with screening and follow-up diagnostic tests. We use average hourly earnings plus benefits in 2000[98] to estimate the value of patient time. From these, we derive estimates of $109, $108, and $55 per targeted individual for annual FOBT, 5-year flexible sigmoidoscopy and 10-year colonoscopy respectively (rows f, n, and v in Table 3; expressed in year 2000 dollars and discounted back to the 1st year of screening). This adds approximately $5,000/LYS to the CE of annual FOBT screening, $4,000/LYS to the CE of 5-year sigmoidoscopy screening, and $1,300/LYS to the CE of colonoscopy.

E.2.2: Weighted Adjusted CE ratio.

Adding these to the estimates of Vijan et al, CE of annual FOBT in year 2000 dollars is $13,300/LYS, the CE of flexible sigmoidoscopy every 5 years is $18,900/LYS, and the CE of colonoscopy at ages 50 and 60 is $8,800/LYS (rows h, p, and x of Table 3). Weighting these three estimates by the estimated proportion of the population currently accepting each type of screening (rows y-aa in Table 3), gives us our base-case estimate of $11,900/LYS.

E.3 Sensitivity Analysis for CE.

The intent of most CE studies is to inform decisions about the choice and frequency of screening technology, so their sensitivity analyses focus on the impact of different variable estimates on the incremental CE ratios. For our purposes, however, we needed to focus on the average CE ratio (screening compared to no screening given the current mix of screening technologies). The variables which are influential for the incremental CE ratio are likely to be different from those that are influential for the average CE ratio. Therefore, the reported sensitivity analyses in the published studies are of limited usefulness for our purposes.

Our ability to conduct additional sensitivity analysis was limited by the lack of detail in reported CE studies. As with other services where our estimates are based upon published CE studies, our range for sensitivity analysis is based on changes in the two most influential 'aggregate variables'.[4] Using the results of Vijan, we are able to explore the impact of independent changes in discounted years of life gained (+/- 25%), discounted net costs (+/- 40%), an alternative estimate of adherence with screenings and follow-up (50% rather than the

75% used in the base case), and the mixture of screening technologies used in current practice. We find that the change in adherence and changes in the mixture of screening technologies to be less influential than the change in gains in life expectancy and net costs. Therefore we calculate a range based on simultaneous changes to LE and net costs and obtained a range of $5,700 to $22,000 per LY saved.

CE studies are not consistent in their determination of which screening strategy is the most cost-effective.[99;100] Although Song et al.[30] did not model incomplete adherence, they, like Vijan et al., used cost-estimates based upon a thorough review of available data. While Vijan et al. found colonoscopy to be the most cost-effective of the three strategies included in our weighted estimate, Song et al. found annual FOBT to be the most cost-effective screen. However, when we recalculate our adjusted, weighted CE ratio based upon the estimates of Song et al. we find our estimate changes by only $200/LYS ($12,100 based upon Song et al. compared to $11,900 based upon Vijan et al.).

F. Scoring

We ranked services in the Prevention Priorities Study based upon scores for CPB and CE rather than point estimates.[4;96] For each measure, we assigned scores according to the quintile in which the service's CPB and CE estimates fall among all services included in the study. Services having the highest CPB or best-cost-effectiveness received a score of 5.

For colorectal cancer screening the CPB estimate resulted in a CPB score of 4. Sensitivity analysis produced some estimates that would have resulted in CPB scores of 5. In these scenarios, the CPB estimate for colorectal cancer would be among the lowest of services receiving a CPB score of 5. The lower-bound score from sensitivity analysis produced by simultaneously changing the three most sensitive variables in a less favorable direction would produce a CPB point estimate that remains consistent with a CPB score of 4.

The CE estimate also resulted in a score 4, and sensitivity analysis indicated that a score of 3 was possible, but that a score of 5 was not. Colorectal cancer screening would need to be cost-saving to obtain a CE score of 5, and there was no indication that this was possible when analyzing the service using a birth cohort approach as was done for this and every other service in the ranking. One previous study which simulated endoscopy screening in a cross-section of the 1993 US population with additional screens over time found cost-savings in the base-case.[36] We did not find savings when the model was re-estimated using a birth-cohort approach.[100].

The resulting total score for this service was 8. The sensitivity analysis described above indicated that total scores of 7 and 9 are possible.

G. Limitations

Relative to other services in this ranking, there were few limitations for this service that have the potential to impact the scoring for the service. Although there was uncertainty in each data point entered into the model, no reasonable change to any variable would by itself changed the total score for this service. CPB, for example, was very sensitive to the estimates of efficacy for colonoscopy, and there was very little data on which to base the estimate for this variable. However, reducing the efficacy of colonoscopy to its lower bound did not change the score of CPB.

The lack of data on quality of life was a substantial limitation. Our sensitivity analysis indicated that it is unlikely that adjustments for quality of life would substantially impact the

CPB estimate, and, by extension, CE estimates. However it was always possible that more complete data would reveal unanticipated quality of life effects in either direction.

The estimates of CPB and CE were limited to three screening strategies for which data were most complete: FOBT alone, flexible sigmoidoscopy alone, and colonoscopy. The USPSTF recommendation indicated that effective screening options include combined FOBT and flexible sigmoidoscopy as well as double-contrast barium enema. In effect, the screenings that would occur using one of these strategies were represented in our estimates by the weighted averages for the three included strategies. Therefore, excluding these scenarios resulted in substantial bias to our estimates only if the strategies would be frequently used and they had substantially different efficacy and cost-effectiveness than the weighted average of the included strategies. There was little reason to believe that either strategy produces substantially greater mortality reductions or was substantially more or less cost-effective than the included studies.[100]

Table 1. Summary of Clinically Preventable Burden (CPB) Estimate for Colorectal Cancer Screening				
Row Label	**Variable**	**Data Source**	**Base Case**	**Range**
a	2000 Colorectal cancer deaths ages 50+	[3;88]	90,785	+/- 20%
b	Weighted life expectancy at death	[3;88]	10.72	+/- 20%
c	Delivery rate for any recommended screening	[82]	17.6%	15% to 25%
d	Percent of screening by FOBT in 1990's	[83]	47.8%	30% to 70%
e	Percent of screening by sigmoidoscopy in 1990's	[83]	19.1%	15% to 30%
f	Percent of screening by colonoscopy in 1990's	= 1 – d - e	33.1%	
g	Efficacy of FOBT	[7;9;12;13;15;17-21;23;24;26]	37.8%	25% to 60%
h	Efficacy of sigmoidoscopy	[16;17;20;22;28-30]	50.0%	25% to 75%
i	Efficacy of colonoscopy	[16;28-30]	70.0%	40% to 85%
j	Weighted efficacy of screening in 1990's	= g*d + h*e + i*f	50.8%	
k	Percent of screening by FOBT in 2003	[89]	48.4%	30% to 70%
l	Percent of screening by sigmoidoscopy in 2003	[89]	8.7%	5% to 15%
m	Percent of screening by colonoscopy in 2003	[89]	42.8%	
n	Weighted efficacy of screening in 2003	= g*k + h*l + i*m	52.6%	
o	Predicted deaths in the absence of screening	= a/(1-c*j)	99,668	
p	Adherence with offers to receive screening	[7-9;18;39-41;43;46;48;51-55;57;70;71;74]	60.0%	40% to 75%
q	Deaths prevented	= o*n*p	31,481	
r	**Life years saved (CPB)**	= q * b	**337,556**	

Table 2. Net Change in QALYS from Screening, Diagnostic Tests, Treatment, and Complications							
Event	**Possible Quality of Life Impact**	**Number in 3,740,000 Lifetimes***	**Quality of Life Weight**	**Duration of Effect on Quality of Life**	**QALYs per Occur-rence (= d x e)**	**Total QALYs (= c x f)**	**Notes on estimate of lifetime incidence of screening, treatment or events (Column c)**
a	**b**	**c**	**d**	**e**	**f**	**g**	**h**
FOBT Screens	Discomfort, Anxiety	26,436,153	-0.05	2 days	-0.00027	-7,243	Based on Sonnenberg, 2000 model results.[32]
Sigmoidoscopy Screens	Discomfort, Anxiety	2,672,762	-0.05	2 days	-0.00027	-1,465	Based on Sonnenberg, 2000 model results.[32]
Colonoscopy Screens, Diagnostics, and Polypectomies	Discomfort, Anxiety	3,407,062	-0.30	4 days	-0.00027	-11,201	Based on Sonnenberg, 2000 model results.[32]
Cancers Prevented	Treatment & Recovery Discomfort, Anxiety	42,208	0.2	3.9 years	0.7800	32,142	Based on cancers prevented in Sonnenberg 2000.[32] Assume polypectomies 90% effective in avoiding cancer treatments
Bleeding Complications	Treatment & Recovery Discomfort, Anxiety	10,354	-0.3	1 month	-0.02500	-259	Based on Sonnenberg, 2000 model results.[32]
Perforation Complications	Treatment & Recovery Discomfort, Anxiety	6,318	-0.5	3 months	-0.12500	-790	Based on Sonnenberg, 2000 model results.[32]
Deaths from Complications	Death	290	-1.0	15 years	-15	-4,353	Based on Sonnenberg, 2000 model results.[32]
					Approximate Net QALYs:	**-6,832**	
*Adjusted to reflect incomplete adherence and portion choosing FOBT, Sigmoidoscopy, and Colonoscopy for screening from rows d-f of Table 1.							

Table 3. Summary of Cost Effectiveness (CE) Estimate for Colorectal Cancer Screening				
Row Label	**Variable**	**Data Source**	**Base Case**	**Range**
Annual FOBT, all estimates are per person				
a	Discounted days of gained LE	[29]	8.0	+/- 25%
b	Discounted net costs	[29]	$170	+/- 40%
c	Original average CE	= b / (a/365)	$7,756/LYS	
d	Discounted net costs adjusted to $2000	= b / 0.9283	$183	
e	Inflation adjusted avg. CE	= d / (a/365)	$8,355/LYS	
f	Personal time costs of screening	[32;98]	$109	+/- 75%
g	Discounted net costs w/ time adjustment	= d + f	$292	
h	Adjusted CE	= g / (a/365)	$13,334/LYS	
Flexible Sigmoidoscopy every 5 years				
i	Discounted days of gained LE	[29]	10.7	+/- 25%
j	Discounted net costs	[29]	$430	+/- 40%
k	Original avg. CE	= j / (i/365)	$14,668/LYS	
l	Discounted net costs adjusted to $2000	= j / 0.9283	$463	
m	Inflation adjusted avg. CE	= l / (i/365)	$15,801/LYS	
n	Personal time costs of screening	[32;98]	$108	+/- 75%
o	Discounted net costs w/ time adjustment	= l + n	$571	
p	Adjusted CE	= o / (i/365)	$19,482/LYS	
Colonoscopy every 10 years				
q	Discounted days of gained LE	[29]	15.6	+/- 25%
r	Discounted net costs	[29]	$300	+/- 40%
s	Original average CE	= r / (q/365)	$7,019/LYS	
t	Discounted net costs adjusted to $2000	= r / 0.9283	$323	
u	Inflation adjusted avg. CE	= t / (q/365)	$7,561/LYS	
v	Personal time costs of screening	[32;98]	$55	+/- 75%
w	Discounted net costs w/ time adjustment	= t + v	$378	
x	Adjusted CE	= w / (q/365)	$8,840/LYS	
Weighted Average CE ratio				
y	Percent of screening by FOBT in 2003	Table 1, row k	48.4%	30% to 70%
z	Percent of screening by sigmoidoscopy in 2003	Table 1, row l	8.7%	15% to 30%

aa	Percent of screening by colonoscopy in 2003	Table 1, row m	42.8%	Varies with y and z
bb	Weighted CE (based on current delivery patterns)	= h*y + p*z + x*aa	$11,947/LYS	

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