Review and Analysis of Cost-Effectiveness Analyses for Two Medicare-Covered Services

A study conducted by staff from the Institute for Clinical Research and Health Policy Studies at the New England Medical Center for the Medicare Payment Advisory Commission

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1 Introduction

The objective of this project has been to review the methodologies and assumptions used in selected cost-effectiveness studies published in peer-reviewed journals for two Medicare-covered services.

In order to facilitate identification of these two covered services, the Tufts New England Medical Center (NEMC) research team (formerly at the Harvard Center for Risk Analysis) submitted to MedPAC in November 2005 a preliminary analysis of four candidate services that included pharmaceuticals, medical devices, surgical procedures, diagnostic procedures, and cognitive services covered by Medicare. The four services identified for this purpose were implantable cardioverter defibrillators (ICDs); colorectal cancer (CRC) screening alternatives; positron emission tomography (PET) for Alzheimer's disease; and erythropoietin for cancer patients undergoing chemotherapy. These services were selected because they represent a diverse group with respect to type of intervention (i.e., medical devices, pharmaceuticals, procedures), and because they represent important interventions for the Medicare population in terms of their impact on beneficiary health and their impact on Medicare spending.

Following submission of our November, 2005 review, MedPAC selected CRC screening and ICDs as the two services for the analysis described in the present report. These services were selected because we identified a large number of studies that assessed their cost-effectiveness in the health economics literature. For this deliverable, per the scope of work, for each of these two services, we first summarize characteristics for each identified study, including 1) the type of model used; 2) the model's perspective; 3) the study funding source; 4) the modeling software used; 5) cost categories included; 6) discount rates used; 7) outcome measures (e.g., life years, quality adjusted life years, etc.); 8) type of sensitivity analysis conducted; and 9) adherence to criteria specified by the Panel on Cost-Effectiveness in Health and Medicine (1).

Second, we discuss the extent to which the studies for each of these two services are in accordance with respect to their assumptions, methods, and results.

Third, we attempt to identify factors that most explain the differences in results across studies.

Finally, we are in the process of contacting the lead authors of each study to see if they would be amenable to providing their modeling software for a more comprehensive evaluation of the literature and to gather their comments on the analysis described in this report.

The remainder of this report has three sections. Section 2 discusses the CRC literature. Section 3 discusses the ICD literature. Finally, we provide our conclusions in Section 4.

2 Studies of the Cost-Effectiveness of Colorectal Cancer (CRC) Screening

We eliminated from consideration two of the 28 studies identified in the November, 2005 report to MedPAC. We eliminated Sorentino et al. (2) because we were unable to obtain a manuscript for this study. We eliminated Tarraga Lopez et al. (3) because of problems interpreting the methodology and results of the study.

2.1 Model Design, Methodology, and Assumptions

The Appendix tables summarize model design, methodology, and assumptions (see Tables 1a and 1b in the Appendix). Note that these studies fall into two categories. Of the 26 studies, 22 evaluated screening programs designed to identify cancer or indications of precancer in asymptomatic individuals. The remaining four studies (4-7) evaluated screening programs designed to identify individuals with a genetic predisposition to develop CRC. For the purpose of the following discussion in this section, these two sets of studies are aggregated. As is evident from the discussion in Section 2.2, none of the studies alone addresses the full range of interventions available. However, collectively, the literature addresses this set of interventions.

2.1.1 Funding Source

Of the 26 studies included in our analysis, 18 clearly specified their funding source. Of these, six listed a foundation (or what appeared to be a foundation) as their sole source of financial support, nine listed government as their sole source of support, two listed both government and foundation support, and one listed professional society support.

2.1.2 Model Type[1]

Of the 26 studies, 11 studies indicated the use of a Markov model, and one other indicated use of discrete event simulation. Five others indicated the use of a decision analytic model, but did not clearly describe what type (discrete event simulation, Markov simulation, or some other type of simulation). Of the remaining nine studies, four statistically compared two groups, and five used a "static" model, which is essentially a closed form equation that specifies the benefits and costs of each intervention.

2.1.3 Software

For Markov models (N=11), four studies used TreeAge DATA , two used Microsoft Excel, one used SML Tree , and one used Decision Maker. The three remaining Markov study papers did not specify what software they used. The six other decision model papers (including one that reported use of discrete event simulation) reported use of MISCAN-COLON in one case (apparently special purpose software), Insight version 5.4 in one case, and Decision Maker in one case. The other three decision models did not specify the type of software used. Of the four papers using statistical comparisons, one reported use of published results, while the other three did not report the underlying software used. Finally, this issue is not applicable to the static models, as no specialized software is needed to implement the needed calculations.

2.1.4 Perspective

Just under half the studies (N=12) provided an explicit indication of the study perspective. Of these, nine indicated that the analysis was conducted from the perspective of the health care payer, while the other three explicitly stated that the analysis was conducted from a societal perspective.

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[1] Researchers use a variety of approaches to evaluate the cost effectiveness of medical interventions. Perhaps the most straight-forward approach is the direct comparison of empirically recorded costs and therapeutic benefits for two groups receiving alternative treatments. This report refers to this approach as a "statistical comparison." In order to extrapolate beyond the period during which data were collected, or to extend results to a broader population, researchers develop various types of "decision analytic policy models" that combine empirically recorded results with other assumptions. A Markov model specifies a set of health states (e.g., healthy, early cancer, late cancer, dead) and uses empirical information to quantify the probability that individuals will move from one state to another during a fixed period of time (e.g., one month or one year). By assigning costs and benefits to each of these states, Markov models can tabulate costs and therapeutic effectiveness for the population over time. Discrete event simulations are a different type of computer model, allowing for greater flexibility than Markov models (because they do not limit characterization of disease progression to a fixed number of states) but typically this flexibility is gained at the cost of greater computational complexity. At the other end of the complexity spectrum are so-called "static models" that quantify benefits and costs for alternative treatments using formulas that can be implemented in a conventional spreadsheet program, such as Excel.

Nonetheless, it is not clear what authors really mean when they indicate use of the societal perspective. For example, none of the three studies stating that they used the societal perspective indicated inclusion of out-of-pocket expenses (e.g., lost wages, time spent by the patient, and so forth). Nor was it typically clear if the costs were net of co-payments made by the patient. We therefore concluded that only one of the 26 studies used the societal perspective (and that study did not even specify the perspective it used). Among the other 25 studies, it was generally unclear what fraction of the health care costs were accounted for in the analysis. Hence, the extent to which the payer's perspective was reflected in these analyses was not always clear.

2.1.5 Costs

All of the studies included health care costs, although at least one study included what was in our judgment clearly a limited subset of these costs (8). Only one study (9) indicated incorporation of out of pocket costs into the analysis. No studies indicated inclusion of lost productivity costs.

2.1.6 Discounting

Of the 26 studies, five did not indicate whether they discounted either costs or benefits. An additional study reported discounting of costs (at 5% annually), but did not indicate whether benefits were also discounted. Three studies explicitly stated that they did not discount costs or benefits. One study reported discounting costs at 5% annually but indicated that benefits were not discounted. Of the remaining 16 studies, the most commonly used annual discount rate was 3% for both costs and benefits (N=10). Another five studies discounted both costs and benefits at 5% annually, while the last study discounted both costs and benefits at 4% annually.

2.1.7 Outcome Measures

Most studies quantified benefits in terms of life years only (N=14). Two studies quantified benefits in terms of quality adjusted life years (QALYs) only. Six studies quantified benefits in terms of a natural unit (deaths prevented, cases detected, or genetically susceptible patients identified, or adenomas detected). The remaining four studies quantified benefits in terms of both life years and natural units.

2.1.8 Sensitivity Analysis

All but three studies conducted univariate sensitivity analyses. All of these analyses were "bounding" analyses, meaning that they explored the impact on the CE ratio of varying assumptions from their base case value to some extreme value, one at a time. They did not assign any relative probability to the CE values within the identified range of plausible values.

Only a single study conducted a multivariate sensitivity analysis, more properly referred to as an uncertainty analysis. This analysis evaluated the impact of simultaneous deviations of multiple assumptions from their base case values. Because the alternative values were identified probabilistically, the resulting alternative CE ratios could be assigned relative probabilistic weights.

2.1.9 Adherence to Cost-Effectiveness Panel Criteria

In some respects, the studies described here generally adhere to the Cost-Effectiveness Panel criteria. The vast majority of studies discount benefits and costs, for example. On the other hand, only a minority even claim to report cost-effectiveness from a societal perspective. We judged even those that did make this claim to have been conducted essentially from a healthcare payer perspective. In addition, most of the studies used life years as the outcome measure, rather than QALYs.

For this particular intervention, we believe that of these deviations, the omission of patient-incurred costs may have had the greatest impact on the study results. In particular, it is conceivable that a non-trivial proportion of CRC cases may result in substantial productivity losses as a result of illnesses that might occur prior to retirement. Other deviations (e.g., use of life years) may not have as important an effect because it is likely that the majority of the QALY losses associated CRC reflect changes in life expectancy anyway.

2.2 Concordance of Assumptions, Methods, and Results Across Studies

In some respects, the studies described above often used similar assumptions. In particular, they typically used a 3% discount rate and conducted their analyses from the perspective of the health care payer. Beyond these limited similarities, however, study

methodologies and assumptions differed substantially. Although 11 analyses developed Markov models, the remaining 15 included a range of other types of models, including statistical comparisons of different groups. The vastly different nature of the underlying models alone complicates comparison of assumptions across studies.

Assessing concordance of results across evaluations of CRC interventions is complicated by the diverse range of interventions, comparators, populations analyzed, and units used to quantify benefits. In order to conduct this assessment, we limited attention to CE ratios that compared a strategy of screening asymptomatic individuals for CRC to conducting no screening in this population. This criterion eliminated four studies (4-7) that evaluated strategies designed to identify individuals at high genetic risk for CRC. Among the remaining studies, requiring a "no-screening" comparator eliminated 23 of the 92 reported CE ratios.

The remaining 69 CE ratios quantified benefits in terms of cancer cases detected (N=7), fatalities avoided (N=5), life years (N=53), and QALYs (N=4). Given the dominance of the life year metric, we eliminated from consideration CE ratios that used other benefit measures.

Next, within each study, we consolidated multiple CE ratios that evaluated the same technology applied at the same frequency, but to different populations. This consolidation aimed to mitigate the potential of assigning excess weight to studies reporting multiple CE ratios that effectively represent very similar underlying analyses. For example, Theuer et al. (10) reported four CE ratios for the use of colonoscopy to screen for CRC every ten years (starting at age 50), one each for the Asian, Black, Latino, and White populations. Because the CE ratios were similar for these populations, we averaged these values to produce a single estimate of the cost-effectiveness of screening 50-year olds once every 10 years using colonoscopy, compared to conducting no CRC screening at all. In addition to replacing the four CE ratios from the Theuer et al. study with one ratio, this step replaced four other CE ratios from this study (for use of both fecal occult blood testing and sigmoidoscopy in four populations) with a single ratio, and five ratios from Gyrd-Hansen et al. (11) with a single ratio (for use of fecal occult blood testing every 1.5 years or every 2 years in various age groups). In summary, this step replaced 13 CE ratios with 3 CE ratios, decreasing the total number CE ratios to 43.

Finally, Sonnenberg et al. reported the same CE ratio in two papers (12;13) comparing colonoscopy screening every 10 years to no screening. Eliminating this redundancy reduced the

number of CE ratios for our analysis to 42. These values, which are summarized in Table 2-1 (converted to 2004 U.S. dollars), cover 5 distinct screening technologies (colonoscopy, catscan colonoscopy, double barium contrast enema, fecal occult blood testing, and sigmoidoscopy) and two sets of combined uses of these technologies (fecal occult blood testing and sigmoidoscopy, and fecal occult blood testing and double contrast barium enema). For some of these technologies, there are CE ratios evaluating more than one screening frequency.

Table 2-1
CE Ratios for CRC Screening Strategies:
Ratios Using Life Years and Comparing Screening to No Screening

Intervention Technology	Intervention Frequency	Study	CE 2004 US $/LY
COL	Every 3 yr	Glick et al. (14)	21,763
	Every 5 yr	Glick et al. (14)	17,316
		Khandker et al. (15)	36,612
	Every 10 yr	Glick et al. (14)	26,693
		Khandker et al. (15)	22,556
		O'Leary et al. (16)	10,633
		Sonnenberg et al. (12;13)	12,728
		Theuer et al. (10)	17,041
CAT COL	Every 10 yr	Sonnenberg et al. (17)	13,309
DCBE	Every 3 yr	Glick et al. (14)	16,010
	Every 5 yr	Glick et al. (14)	16,247
		Khandker et al. (15)	22,374
	Every 10 yr	Glick et al. (14)	26,351
FOBT	Every yr	Glick et al. (14)	16,351
		Gyrd-Hansen et al. (11)	4,643
		Helm et al. (18)	24,127
		Khandker et al. (15)	18,347
		Salkeld et al. (19)	22,996
		O'Leary et al. (16)	25,860
		Sonnenberg et al. (12)	11,247
	Every 2 yr	Gyrd-Hansen et al. (11)	7,446
		Helm et al. (18)	2,942
		Lejeune et al. (20)	9,185
		O'Leary et al. (16)	10,861
FOBT + DCBE	Every 3 yr	Glick et al. (14)	19,462
	Every 5 yr	Glick et al. (14)	17,060
	Every 10 yr	Glick et al. (14)	18,860
FOBT + SIG	Every 3 yr	Glick et al. (14)	18,050
		Khandker et al. (15)	25,918
	Every 5 yr	Glick et al. (14)	16,421
		Khandker et al. (15)	23,203
		Theuer et al. (10)	18,877
	Every 10 yr	Glick et al. (14)	17,468
SIG	One time	Frazier et al. (21)	1,391
	Every 3 yr	Glick et al. (14)	16,318
		Khandker et al. (15)	20,727
	Every 5 yr	Glick et al. (14)	14,384
		Khandker et al. (15)	16,106
		Loeve et al. (22)	Dominates (b)
		Sonnenberg et al. (12)	42,310
	Every 10 yr	Glick et al. (14)	24,226
		O'Leary et al. (16)	9,264

Abbreviations: COL (colonoscopy), CAT COL (cat scan, i.e., virtual, colonoscopy), DCBE (double barium contrast enema), FOBT (fecal occult blood testing), SIG (sigmoidoscopy).

(a) Average CE ratio for 50 year-old Asian, Black, Latino, and White populations

(b) Screening strategy produces more health (life years) and costs less than the alternative (no screening).

Visual inspection of the values listed in Table 2-1 reveals that the degree of agreement within each of the groups varies. Developing a summary measure of agreement is helpful only if there are more than a limited number of measurements. For the purpose of describing within-group variation, consider the coefficient of variation (CV), defined as the ratio of the standard deviation divided by the mean. We report the CV for the three groups that include at least four CE ratios: for colonoscopy screening every 10 years, CV=0.37 (N=5); for fecal occult blood test screening conducted annually, CV = 0.44 (N=7); and for fecal occult blood test screening conducted every two years, CV = 0.45 (N=4). It must be emphasized that even in these groups, the number of observations is limited, so the CV values are only indicative of the degree of spread. Nonetheless, they indicate reasonable agreement.

The degree of agreement can be viewed more qualitatively, as well. For example, the potential range of CE values can be divided into qualitative but generally accepted categories. Such categories might include 1) screening dominates the no screening alternative (i.e., it produces more health measured in life years and costs less than the alternative); 2) screening is "inexpensive" (CE ratio < $50,000/LY) (e.g., see (23)); 3) screening is expensive (CE ratio > $50,000/LY); 4) screening is dominated by the no screening alternative (i.e., it produces less health measured in life years and costs more than the alternative). From this perspective, the CE ratios in each of the groups listed in Table 2-1 are generally consistent.

To the extent that the CE ratios from various studies differ, it is difficult to attribute these differences to the nature of the populations studied. The populations reflected in these evaluations typically include asymptomatic individuals between the ages of approximately 50 and

80 years. More specific characterizations of these populations are typically not possible because the assumptions for these studies are often drawn from multiple sources.

2.3 Identifying Influential Assumptions

Influential assumptions can in principle be identified in either of two ways. First, sensitivity analyses conducted in each of the studies can be reviewed and the most influential assumptions catalogued. This approach is complicated by the fact that the studies review a widely varying set of assumptions, even those that evaluate the same technologies. Consider, for example, the five studies that evaluated use of colonoscopy screening. The assumptions reviewed as part of sensitivity analysis in these studies were:

- Glick et al. (14): Test sensitivity for detection of polyps, test sensitivity for detection of cancer, test specificity, polyp prevalence, polyp incidence, annual cancer incidence, polyp dwell time, CRC survival rates, surgical mortality (colonic resection), lifetime prevalence and incidence of cancer, cost assumptions;
- Khandker (15): Polyp dwell time, screening compliance rates, test sensitivity;
- O'Leary (16): Probability that adenomas > 10 mm will progress to cancer, discount rate, costs;
- Sonnenberg (12): Screening compliance rates, test sensitivity and specificity;
- Theuer (10): Polyp dwell time.

The fact that some assumptions (e.g., polyp dwell time and test specificity and sensitivity) are analyzed in multiple studies suggests that they are likely to be important. Because the lists of assumptions evaluated are so diverse, however, it is difficult to use the sensitivity analysis results in a more rigorous manner to comprehensively evaluate the relative importance of various assumptions.

A second approach that might be used to evaluate the relative importance of alternative assumptions would attempt to associate differences in CE ratio values across studies with assumptions made in those studies. For CRC, such an approach in practice is not feasible because the number of CE ratios that can be directly compared in this manner is limited (as discussed earlier), while the number of assumptions are relatively numerous.

2.4 Obtaining Model Software from Study Authors

We requested a copy of software used in each study, with the exception of those studies that indicated use of a static model (see discussion above). We are currently waiting for responses to this request from lead authors of the studies.

3 Studies of Implantable Cardioverter Defibrillators (ICDs)

This assessment includes 15 of the 16 studies identified in the November, 2005 report to MedPAC. We eliminated one study (24) because it quantifies benefits in terms of a relative risk reduction for mortality, not in terms of additional survival. We combined two studies (25;26) because they describe two applications of the same model. These revisions leave a total of 14 distinct studies.

3.1 Model Design, Methodology, and Assumptions

The appendix tables summarize model design, methodology, and assumptions (see Tables 2a and 2b in the Appendix). Because the set of interventions for this technology is limited (compared to the wide range of interventions available for CRC screening), many studies analyze the most relevant comparison – i.e., between ICD use and pharmaceutical treatment.

3.1.1 Funding Source

Of the 14 studies included in our analysis, 11 clearly specified their funding source. Of these, six listed government agencies as their sole source of funding, two listed institutional sources (i.e., they indicated that the research time was funded the researchers' home institutions), and two listed corporations as their sole source of support. The final study identified both government and corporate (insurance company) support.

3.1.2 Model Type

Eight of the 14 studies developed cost-effectiveness ratios by statistically comparing the experience of cohorts receiving ICDs to the experience of control groups. Five of the remaining studies developed Markov models. The final study developed a static model, which is essentially a closed form equation that specifies the benefits and costs of each intervention.

3.1.3 Software

All five Markov models were developed in SMLTree. Only one of the eight studies that statistically compared ICD and non-ICD intervention groups identified the software used (SAS). Finally, this issue is not applicable to the static models, as no specialized software is needed to implement the needed calculations.

3.1.4 Perspective

Of the 14 studies, 11 provided a clear indication of the analytical perspective, of which seven indicated they took a societal perspective. We judged that only one of these seven actually did take a societal perspective, and that the other six took the perspective of the payer. As in the case of the CRC studies, the omission of expenses incurred by parties other than the health care payer (e.g., productivity losses, time spent by the patient, and so forth) lead us to disagree with the societal perspective designation reported by the authors. The four studies that indicated that they took the perspective of the payer were consistent with our own evaluation of the perspective for these studies.

Of the three studies that did not clearly indicate the authors' intended analytical perspective, we judged two as taking the payer's perspective. We could not determine the perspective of the last study. In total, we concluded that 12 of the 14 studies took the payer's perspective, one took a societal perspective, while the perspective of one study could not be determined.

3.1.5 Costs

Thirteen of the 14 studies included health care costs, while the remaining study did not clearly indicate what costs were included in the analysis. Only one study reported accounting for any patient costs (time). Whether patient costs were included could not be determined for two studies.

3.1.6 Discounting

Of the 14 studies, one discounted both costs and benefits at a 5% annual rate. In addition, two studies did not clearly indicate whether they discounted either costs or benefits. All of the 11

remaining studies discounted costs at a 3% annual rate. Ten of these also discounted benefits at 3% annually. The eleventh study did not clearly indicate whether it discounted benefits.

3.1.7 Outcome Measures

Most studies quantified benefits in terms of life years only (N=8). Tow studies quantified benefits in terms of QALYs only. Two studies quantified benefits in terms of both QALYs and life years. Finally, one study quantified benefits in terms of natural units (the number of hospital days avoided).

3.1.8 Sensitivity Analysis

Four of the 14 studies conducted no sensitivity analyses. Seven studies conducted a univariate sensitivity analysis (a non-probabilistic analysis in all cases), while two conducted both a univariate and multivariate sensitivity analysis. In both cases, the univariate analyses were non-probabilistic. One of the two multivariate analyses was non probabilistic, while the other included a multivariate probabilistic analysis. The last study conducted a non-probabilistic multivariate sensitivity analysis but no univariate analysis.

3.1.9 Adherence to Cost-Effectiveness Panel Criteria

Adherence to the Cost-Effectiveness Panel criteria for the studies of ICD cost-effectiveness was similar to the adherence for the CRC studies. The major deviation we identified was the omission of costs absorbed by parties other than the health care system, and in particular, costs associated with lost productivity (due to mortality occurring before the age of retirement). Even if most mortality results from deaths that occur after the typical retirement age, the substantial productivity costs associated with those that occur earlier might conceivably be sufficiently large to substantively affect the cost-effectiveness estimates.

3.2 Concordance of Assumptions, Methods, and Results Across Studies

As with the studies evaluating the cost-effectiveness of CRC screening, the methodologies used in studies evaluating the cost-effectiveness of ICDs differed substantially. While assumptions were similar for discounting and analytical perspective, model types differed, with eight studies relying on statistical comparisons, five using Markov models, and one using a

closed form equation. In the case of ICDs, the substantial number of well-conducted randomized controlled trials (for example, see Sanders et al. (27)) has meant that study authors have had a wide range of data to choose from. As described below, study population differences can have an important impact on the results.

To assess concordance of results across studies, we divided ratios into three categories based on the intervention and comparator (ICD vs. pharmaceutical therapy; ICD vs. no treatment; and pharmaceutical treatment vs. no therapy), and then further divided these categories into two groups each based on the units used to quantify benefits (life years or QALYs). This classification yielded 39 ratios comparing ICDs and pharmaceutical therapy (22 life year and 17 QALY ratios); 7 ratios comparing ICDs to no treatment (4 life year and 3 QALY ratios); and 7 ratios comparing pharmaceutical treatment to no treatment (4 life year and 3 QALY ratios). In addition to these categories, we identified 11 ratios comparing other interventions, such as a comparison of different types of ICD technology (28), a comparison of (at the time) state of the art ICD technology and less advanced ICD technology (29), and an evaluation of a hybrid strategy that involves potentially switching from pharmaceutical treatment to ICDs if warranted by health considerations (30). As in our analysis of CRC CE ratios, we first converted all currency values to 2004 U.S. dollars. Tables 3-1 and 3-2 summarize the resulting ratios. Note that these tables also quantify the ratio denominator (incremental costs) and denominator (incremental benefits).

Table 3-1
CE Ratios for ICD and Corresponding Pharmaceutical Strategies:
Ratios Using Life Years

Author	Incremental Costs	Incremental Benefits	CE Ratio 2004 US $/LY
	ICD vs. Pharmaceutical Treatment		
Al-Khatib et al. (31)	$95,373	1.8	$53,026
Larson et al. (32)	$16,596	0.21	$78,464
McGregor et al. (33)	NA	NA	$49,832
Mushlin et al. (34)	$25,399	0.8	$31,778
Owens et al. (30)	$46,357	0.69	$66,933
	$48,465	0.69	$69,412
Sanders et al. (35)	$42,520	0.59	$71,773
	$39,231	0.2	$196,610
	$43,427	0.08	$568,628
Sanders et al. (27)	$89,072	3.64	$24,468
	$53,965	-0.4	Dominated[(a)]
	$98,162	4.14	$23,694
	$76,789	2.04	$37,718
	$97,195	2.72	$35,590
	$56,963	-0.48	Dominated[(a)]
	$66,054	1.87	$35,300
	$68,665	1.4	$49,033
Sheldon et al. (26) and O'Brien et al. (25)	$37,395	-0.4	Dominated[(a)]
	$40,035	0.22	$181,954
	$32,656	0.44	$73,822
	$30,246	1.7	$17,818
Weiss et al. (36)	$47,055	0.5	$88,894
	ICD vs. No Treatment		
Hauer et al. (29)	-$24,178	0.41	Dominates[(b)]
Sanders et al. (35)	$60,775	1.01	$59,754
	$60,208	0.51	$116,560
	$67,804	0.26	$258,292
	Pharmaceutical Treatment vs. No Treatment		
Hauer et al. (29)	$82,400	1.98	$41,512
Sanders et al. (35)	$18,255	0.42	$42,860
	$20,976	0.31	$66,104
	$24,378	0.18	$131,073

NA – Information not available.

Notes:

(a) Use of ICDs produces less health (life years) and costs more than the use of pharmaceuticals.

(b) Use of ICDs produces more health (life years) and costs less than no treatment.

Table 3-2
CE Ratios for ICD and Corresponding Pharmaceutical Strategies: Ratios Using QALYs

Author	Incremental Costs	Incremental Benefits	CE Ratio 2004 U.S. $/QALY
	ICD vs. Pharmaceutical Treatment		
Chen et al. (37)	$102,613	0.9986	$102,790
Owens et al. (30)	$46,357	0.5	$92,219
	$48,465	0.51	$95,194
Owens et al. (38)	NA	NA	$55,219
	NA	NA	$50,910
	NA	NA	$60,094
Sanders et al. (35)	$42,520	0.52	$81,411
	$39,231	0.18	$221,895
	$43,427	0.06	$632,577
Sanders et al. (27)	$89,072	2.64	$33,752
	$53,965	-0.29	Dominated
	$98,162	2.99	$32,882
	$76,789	1.47	$52,321
	$97,195	1.96	$49,613
	$56,963	-0.34	Dominated
	$66,054	1.36	$48,646
	$68,665	1.01	$67,892
	ICD vs. No Treatment		
Sanders et al. (35)	$60,775	0.89	$67,804
	$60,208	0.45	$132,434
	$67,804	0.23	$293,441
	Pharmaceutical Treatment vs. No Treatment		
Sanders et al. (35)	$18,255	0.37	$48,869
	$20,976	0.27	$75,401
	$24,378	0.17	$150,236

Unlike in the case of CRC, we have in the case of ICDs retained multiple CE ratios from several studies for the same intervention. For example, Sanders et al. (27) contributes eight values to the list of life year CE ratios that compare ICDs to pharmaceutical treatment. In the

case of CRCs, the CE ratios were similar for different populations. On the other hand, population characteristics (e.g., baseline mortality rate and ratio of sudden to non-sudden deaths) have a substantial influence on CE ratios for ICDs (see discussion below). Qualitatively, the cost-effectiveness ratios also diverge. For example, for QALY CE ratios comparing ICDs to pharmaceutical treatment, four ratios fall below the $50,000/QALY threshold, eight are between $50,000/QALY and $100,000/QALY, and the remaining three range from just over $100,000/QALY to more than $600,000/QALY.

3.3 Identifying Influential Assumptions

The fact that there are a relatively large number of comparable CE ratios (19 positive values for the life year ratios) facilitates an analytical evaluation of why they differ. Because $CE = \frac{\Delta Cost}{\Delta Benefits}$, it follows that $\log(CE) = \log(\Delta Cost) - \log(\Delta Benefits)$. Based on this relationship, we can regress the log of the CE ratio against the log of the incremental costs and incremental benefits to determine which of these two factors contributes the most to the CE ratio's variability. The proportion of variation explained by each of these terms serves as an indicator of the degree of variation explained[2]. As expected, very close to 100% of the variation is explained by $\log(\Delta Benefit)$ and $\log(\Delta Cost)$ (the model $R^2 > 99.9\%$, with the shortfall appears to reflect errors introduced by the rounding of reported values). Of the total variation in $\log(CE)$, $\log(\Delta Benefit)$ explains 90% and $\log(\Delta Cost)$ explains approximately 20%[3].

The implication of this analysis is that differences in the CE ratio values reported across studies are due to factors affecting estimated benefits, and not for the most part due to factors that influence cost estimates. Factors that might have a substantial impact on estimated benefits include 1) the baseline mortality rate (i.e., the mortality rate among individuals who do not receive ICDs); and 2) the mortality relative risk associated with ICDs.

Differences in the baseline mortality rate and estimated relative risk for ICDs may be due to different results from randomized controlled trials (RCTs). Figure 2 in Sanders et al. (27)

[2] The values reported here are based on the Type III sums of squares computed using SAS procedure GLM (version 9, SAS Institute, Cary, NC. The proportion of variation is the Type III sums of squares divided by total sums of squares.

[3]). If the two explanatory variables were statistically independent, the proportion of variation explained would sum to 100%. Because they are modestly correlated, there is some overlap in their explanatory power, and as a result, these proportions sum to more than 100%.

shows the degree to which both of these factors vary across studies. The figure suggests that mortality relative risk ranges from approximately 0.45 to more than 1.0 and that baseline annual mortality ranges from as little as approximately 7.5% to nearly 20%. Goldberger and Lampert (39) reviewed these studies. They concluded that mortality relative risk exceeded unity in two studies (DINAMIT and CABG) because the baseline mortality risk in those two studies was relatively low (see pp 812-13 in that review). On the other hand, Sanders et al. (27) noted that the DEFINITE trial reported that ICDs substantially reduce mortality even though the baseline mortality risk for that study's cohort was already low (see their Figure 2). In any case, differences in the results reported by RCTs do not explain all differences in CE ratio estimates. Based on the six RCTs reporting relative risks below unity (i.e., among those studies that found ICDs reduce risk), Sanders et al. (27) estimated that incremental life expectancy ranged from 1.40 to 4.14 life years. Other CE ratio studies report substantially smaller (although still positive) incremental life expectancy estimates (see Table 3-1).

A further assumption that may be important is the estimated ratio of sudden cardiac mortality (which can be prevented by an ICD) to non-sudden cardiac mortality (which cannot). Owens et al. (38) demonstrated that the ratio of these two mortality rates can substantially influence the CE ratio, even if total mortality remains unchanged. For example, Owens et al. estimated the cost effectiveness of ICDs relative to pharmaceutical treatment to be $29,800 if the ratio of sudden to non-sudden cardiac death is 15. If, on the other hand, the ratio of non-sudden to sudden cardiac mortality is assumed to be 15, the cost-effectiveness ratio is nearly an order of magnitude greater ($236,000/QALY).

It is also true that the benefit afforded by ICDs depends on patient baseline health. For example, results reported by Sanders et al. (35) indicate that ICDs offer the greatest advantage over pharmaceutical treatment for patients with a low ejection fraction (EF). For patients with EF <= 0.3, ICDs extend life expectancy by 0.59 years compared to pharmaceutical treatment. For patients with EF > 0.4, the corresponding improvement is only 0.08 years. Sheldon et al. (26) estimated cost-effectiveness after stratifying patients according to the number of risk factors they had (factors were age >= 70, left ventricle ejection fraction <= 35%, New York Heart Association risk class III). For patients with none of these risk factors, ICDs reduced life expectancy, compared to treatment with pharmaceuticals. For patients having 1, 2, or 3 risk factors, ICDs increased life expectancy by 0.22, 0.44, and 1.70 life years, respectively. Unfortunately, many of

the CE studies described here do not evaluate the impact of baseline risk on the CE ratio. The results described here indicate, however, that baseline risk plays an important role.

Although differences in cost-effectiveness results for ICDs cannot be completely explained, this analysis has shown that the major factors can be identified.

3.4 Obtaining Model Software from Study Authors

For each study, we sent a request to the first author requesting a copy of the software used to implement the paper's model. An initial email request was sent to the author on April 13, 2005, with follow-up requests sent on May 11. Table 3-3 summarizes the responses received through May 24, 2006 for the 40 studies retained for the analysis in this report.

Table 3-3
Author Responses to Requests for a Copy of Their Model Software[(a)]

Response Category	Number of Responses	Percent
Unable to locate lead author or author deceased.	5	12.5
Emailed author but did not receive a response within one month and following two emails.	17	42.5
Forwarded our request to another author or directed us to contact someone else.	7	17.5
Replied that no model software was used - just arithmetic (e.g., Excel), statistical analysis, or something similar.	5	12.5
Author not willing to provide model details (e.g., because of ongoing work) or because model is difficult to interpret by others and author is afraid it will be misinterpreted	6	15

Notes: (a) Responses from authors listed on multiple studies are recorded once for each study they were contacted for, even if they responded only once to our inquiry.

4 Conclusions

Our review indicates that for high profile and potentially high-cost Medicare-reimbursed services, such as ICDs and CRC screening, there are numerous cost-effectiveness analyses in the

medical literature. Many of the studies measure outcomes in terms of costs per life year or QALY gained, hence providing a convenient basis for comparison. In some respects, such as the discounting of costs and benefits, the studies we reviewed adhered to key criteria specified by the Panel on Cost-Effectiveness in Health and Medicine (1). The use of QALYs to quantify benefits was less common than the use of life years. However, the fact that mortality is likely to account for vast majority of the QALY loss associated with the relevant health effects means that this deviation from the Cost-Effectiveness Panel criteria is unlikely to be important for these particular interventions. For these reasons, the literature provides a rough estimate of the net costs and clinical effects for the two interventions we reviewed. Collectively, the literature also helps to shed light on key areas of uncertainty where additional data collection might be most fruitful.

To be sure, relying on the literature to rigorously evaluate specific policy issues poses a number of challenges. First, few studies take into account costs beyond those incurred by the health care payer. To the extent that policy makers wish to include other costs (most notably, lost productivity costs) in their assessments, the literature would be inadequate. Second, cost effectiveness analyses use a wide range of assumptions. Where there are multiple effectiveness studies available (as is clearly evident in the case of ICDs), this issue can cause substantial divergence in cost-effectiveness estimates. Those studies can produce different results for a variety of reasons, some of which may be related to the nature of the populations included. Third, studies can differ in terms of the specific interventions evaluated. This issue was particularly evident in the case of CRC screening, where there were many combinations of screening technologies and screening frequencies that could be evaluated. Finally, comparisons across studies can be complicated by different approaches to the analysis. For example, some studies relied essentially on statistical comparisons of survival, while others extrapolated beyond what was observed through the use of decision analytic simulation models.

Despite these challenges, the literature offers a useful guide for identifying the most promising interventions, and in providing a ballpark estimate of the net costs and clinical effects for the two interventions. It is also important to keep in mind that much of the variation across cost-effectiveness analyses in terms of the populations addressed and the comparators analyzed is not unique to CEAs. Randomized clinical trials of the same intervention typically differ across these dimensions as well (as is evident in the case of the trials evaluating ICDs). To the extent that policy makers are interested in evaluating specific interventions and understanding the

implications of different assumptions on cost-effectiveness ratios, they may wish to conduct or contract for additional analyses of the published estimates.

Appendix – Summary of Study Design, Methodology, and Assumptions

Table 1a
CRC Screening: Model Design, Methodology and Assumptions – Part 1 of 2

				Perspective		Costs	
Study	**Funding**	**Model Type**	**Software**	**Author**	**Reader**	**Health Care**	**Out of Pocket**
Berchi et al. (40)	Foundation?	Markov	DATA	Payer	Payer	Yes	No
Frazier et al. (21)	Government	Markov	SMLTREE	Not stated	Payer	Yes	No
Glick et al. (14)	Not stated	Decision Model	Not stated	Not stated	Payer	Yes	No
Gyrd-Hansen et al. (11)	Not stated	Static Model	Not applicable	Payer	Payer	Yes	No
Heitman et al. (41)	Foundation	Markov	DATA	Payer	Payer	Yes	No
Helm et al. (18)	Government + Foundation	Statistical comparison	Used Published Results	Not stated	Payer	Yes	No
Khandker et al. (15)	Government	Markov	Decision Maker	Not stated	Payer	Yes	No
Kievit et al. (4)	Foundation?	Markov	DATA	Payer	Payer	Yes	No
LeJeune et al. (20)	Government	Markov	Not stated	Payer	Payer	Yes	No
Lieberman et al. (42)	Not stated	Static formula	Not applicable	Not stated	Payer	Yes	No
Loeve et al. (22)	Government	Simulation - Type unclear	MISCAN-COLON	Not stated	Payer	Yes	No
Nakama et al. (8)	Government	Statistical comparison	Not stated	Not stated	Payer	Some	No
Ness et al. (43)	Professional Association (Am. Coll. Of Gastroenterology)	Discrete Event Simulation	Insight 5.4	Societal	Payer	Yes	No
O'Leary et al. (16)	Not stated	Markov	DATA	Payer	Payer	Yes	No
Ramsey et al. (5)	Government	Static Model	Excel and @Risk	Societal	Payer	Yes	No
Reyes et al. (6)	Foundation	Decision Model (type not clear)	Not stated	Societal	Payer	Yes	No
Robinson et al. (44)	Government	Statistical comparison	Not stated	Not stated	Payer	Yes	No
Salkeld et al. (19)	Not stated	Static model	Not applicable	Not stated	Payer	Yes	No
Sieg et al. (9)	Not stated	Static model	Not applicable	Not stated	Societal	Yes	Yes
Sonnenberg et al. (17)	Foundation	Markov	Not stated	Payer	Payer	Yes	No
Sonnenberg et al. (12)	Government Foundation	Markov	Excel	Payer	Payer	Yes	No
Sonnenberg et al. (13)	Not stated	Markov	Excel	Not stated	Payer	Yes	No
Theuer et al. (10)	Government	Decision Model	Not stated	Not stated	Payer	Yes	No
Vasen et al. (7)	Not stated	Decision Model	Decision Maker	Not stated	Payer	Yes	No
Whynes et al. (45)	Foundation	Markov	Not stated	Payer	Payer	Yes	No
Yamamoto et al. (46)	Government	Statistical comparison	Not stated	Not stated	Payer	Yes	No

Table 1b
CRC Screening: Model Design, Methodology and Assumptions – Part 2 of 2

	Discounting		Outcome Measures			Sensitivity Analysis	
Study	**Costs**	**Outcomes**	**QALYs**	**LYs**	**Other**	**Univariate**	**Multivariate**
Berchi et al. (40)	5%	None	No	Yes		Bounding	None
Frazier et al. (21)	3%	3%	No	Yes		Bounding	None
Glick et al. (14)	5%	5%	No	Yes		Bounding	None
Gyrd-Hansen et al. (11)	5%	5%	No	Yes		Bounding	None
Heitman et al. (41)	3%	3%	No	Yes	Perforations of the colon, adenomas removed	Bounding	None
Helm et al. (18)	None	None	No	Yes		Bounding	None
Khandker et al. (15)	3%	3%	No	Yes		Bounding	None
Kievit et al. (4)	4%	4%	No	Yes	Cases detected	Bounding	None
LeJeune et al. (20)	3%	3%	No	Yes		Bounding	None
Lieberman et al. (42)	Not stated	Not stated	No	No	Death prevented	Bounding	None
Loeve et al. (22)	3%	3%	No	Yes		Bounding	None
Nakama et al. (8)	None	None	No	No	Case Detected	None	None
Ness et al. (43)	Not stated	Not stated	Yes	No		Bounding	None
O'Leary et al. (16)	5%	5%	No	Yes		Bounding	None
Ramsey et al. (5)	3%	3%	No	Yes	Carrier detected	Bounding	Probabilistic
Reyes et al. (6)	None	None	No	No	Carrier detected	Bounding	None
Robinson et al. (44)	Not stated	Not stated	No	No	Detected adenomas > 1 cm	None	None
Salkeld et al. (19)	5%	5%	No	Yes		Bounding	None
Sieg et al. (9)	Not stated	Not stated	No	No	Cases detected	None	None
Sonnenberg et al. (17)	3%	3%	No	Yes		Bounding	None
Sonnenberg et al. (12)	3%	3%	No	Yes		Bounding	None
Sonnenberg et al. (13)	3%	3%	No	Yes		Bounding	None
Theuer et al. (10)	5%	5%	No	Yes		Bounding	None
Vasen et al. (7)	5%	Not stated	No	Yes		Bounding	None
Whynes et al. (45)	3%	3%	Yes	No		Bounding	None
Yamamoto et al. (46)	Not stated	Not stated	No	No	Cases detected	None	None

Table 2a
ICDs: Model Design, Methodology and Assumptions – Part 1 of 2

				Perspective		Costs	
Study	Funding	Model Type	Software	Author	Reader	Health Care	Out of Pocket
Al-Khatib et al. (31)	Corporate (device maker)	Statistical Comparison	Not stated	Societal	Payer	Yes	No
Cardinal et al. (28)	Not stated	Statistical Comparison	Not stated	Not Stated	Payer	Yes	No
Chen et al. (37)	Institutional	Static Model	Not applicable	Societal	Societal	Yes	Yes (Time)
Hauer et al. (29)	Not stated	Statistical Comparison	Not stated	Payer	Payer	Yes	No
Kupersmith et al. (47)	Not stated	Markov	SMLTree	Payer	Payer	Yes	No
Larson et al. (32)	Government	Statistical Comparison	Not stated	Societal	Payer	Yes	No
McGregor et al. (33)	Institutional	Statistical Comparison	Not stated	Payer	Payer	Yes	No
Mushlin et al. (34)	Corporate (device maker)	Statistical Comparison	Not stated	Not Stated	Payer	Yes	Not Clear
Owens et al. (30)	Government	Markov	SMLTree	Societal	Payer	Yes	No
Owens et al. (38)	Government	Markov	SMLTree	Societal	Payer	Yes	No
Sanders et al. (35)	Government	Markov	SMLTree	Societal	Payer	Yes	No
Sanders et al. (27)	Government; Corporate (Insurance co.)	Markov	SMLTree	Societal	Payer	Yes	No
Sheldon et al. (26); O'Brien et al. (25)	Government	Statistical Comparison	Not stated	Payer	Payer	Yes	No
Weiss et al. (36)	Government	Statistical Comparison	SAS	Not Stated	Not Clear	Not Clear	Not Clear

Table 2b
ICDs: Model Design, Methodology and Assumptions – Part 2 of 2

	Discounting		Outcome Measures			Sensitivity Analysis	
Study	Costs	Outcomes	QALYs	Lys	Other	Univariate	Multivariate
Al-Khatib et al. (31)	3%	3%	No	Yes		None	Bounding
Cardinal et al. (28)	Not stated	Not stated	No	No	Hospital Stay (days)	None	None
Chen et al. (37)	3%	3%	Yes	No		Bounding	None
Hauer et al. (29)	Not stated	Not stated	No	Yes		None	None
Kupersmith et al. (47)	5%	5%	No	Yes		None	None
Larson et al. (32)	3%	3%	No	Yes		Bounding	None
McGregor et al. (33)	3%	3%	No	Yes		Bounding	None
Mushlin et al. (34)	3%	3%	No	Yes		Bounding	None
Owens et al. (30)	3%	3%	Yes	Yes		Bounding	None
Owens et al. (38)	3%	3%	Yes	No		Bounding	Bounding
Sanders et al. (35)	3%	3%	Yes	Yes		Bounding	Probabilistic
Sanders et al. (27)	3%	Not Clear	Yes	Yes		Bounding	None
Sheldon et al. (26); O'Brien et al. (25)	3%	3%	No	Yes		Bounding	None
Weiss et al. (36)	3%	3%	No	Yes		None	None

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