INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

FINAL APPRAISAL DOCUMENT

CT COLONOGRAPHY
FOR COLORECTAL CANCER SCREENING

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EXECUTIVE SUMMARY

Introduction

Computed tomography colonography (CT colonography or CTC) is a minimally invasive radiological technique used to provide images of the colon and rectum. CTC has been suggested as an alternative or as complementary to conventional colonoscopy and other population-based screening methods for colorectal cancer. Given that only 40%-60% of eligible patients undergo recommended screening for colorectal cancer, some commentators have suggested that the speed and relative ease of CTC compared to conventional colonoscopy might enhance patient compliance with screening recommendations. After more than a decade of research on CTC, however, questions remain about several important issues:

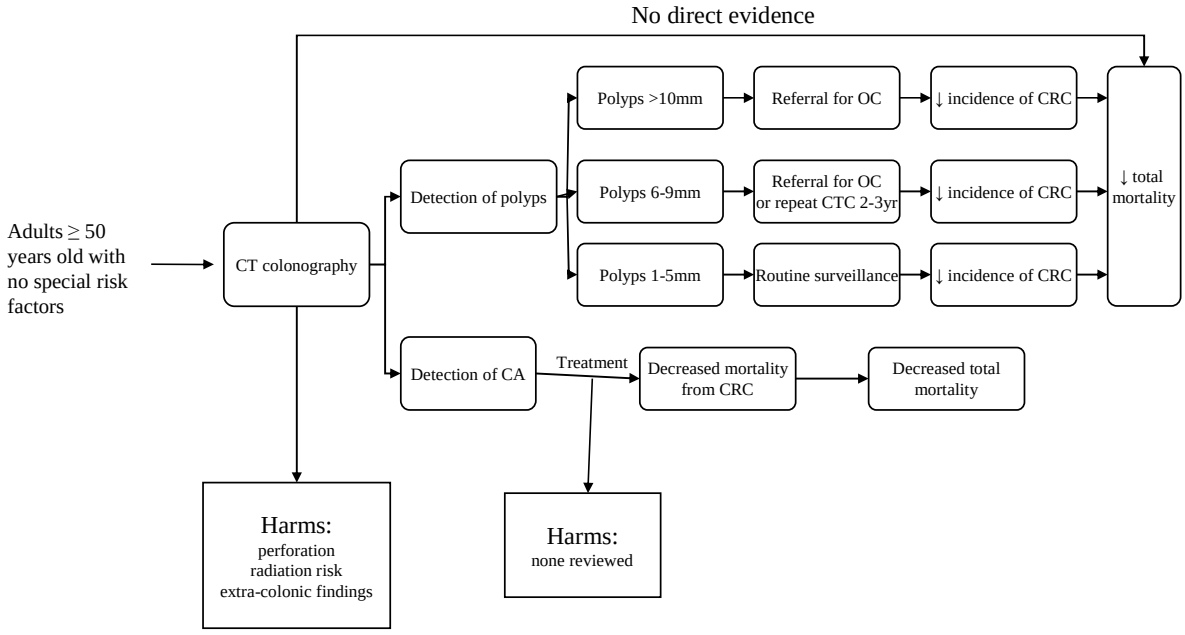
1) The sensitivity and specificity of CTC compared to conventional colonoscopy
2) Variation in performance across different providers and imaging modalities
3) Likely impact of CTC on population screening rates
4) Linkages between CTC and colonoscopy for removal of identified polyps
5) The impact on outcomes and costs of incidental "extracolonic" findings
6) Cost and cost-effectiveness of CTC

Given the possible benefits of introducing a widely available minimally-invasive option for colorectal cancer screening, there is considerable interest in CTC. That interest is colored by uncertainty over the evidence on the accuracy of CTC, and by questions about the potential impact broad adoption of CTC would have on systems of care and on health care costs. With these issues and questions in mind, ICER selected CTC as an important technology for which decision-makers would benefit from a thorough review of its clinical effectiveness and value compared to colonoscopy and other accepted screening methods for colorectal cancer.

Analytic Framework for Evaluation of CT Colonography

The analytic framework for this evaluation is shown in the Figure at the top of the next page. As is the case for many screening interventions, including optical colonoscopy, there are no data directly demonstrating its beneficial impact on all-cause mortality, and judgments about the effectiveness of the intervention must rest upon consideration of the strength of sequential conceptual links. For the evaluation of CTC the primary conceptual links are those between polyp detection and removal, disease-specific mortality, and overall mortality.

Analytic Framework: CT Colonography screening for colorectal cancer



Colorectal Cancer Screening and Polyp Size

Colorectal cancers most commonly develop from adenomatous polyps which arise from the mucosal lining of the large bowel. The interval from the development of an adenomatous polyp to transformation into cancer is estimated to be approximately 10 years (Winawer, 2003), although only a minority of all polyps progress to cancer (Stryker, 1987). The probability of progression to cancer is related to the size of the polyp. It has been estimated that 1% of polyps greater than or equal to 10mm will progress to cancer each year (Stryker, 1987; Van Dam, 2004). For polyps 5mm or less in size the risk of 10-year progression to cancer is considerably less than 1%, and may be as low as 0.25%. (Tsai, 1995). Guidelines for colorectal cancer screening programs and for the management of colorectal polyps have recommended that patients with polyps greater than or equal to 10mm and all patients with three or more smaller polyps should have the polyp(s) removed for histological examination. Although the natural history of smaller polyps is not known with certainty, and despite the fact that many clinicians in practice remove polyps of any size, the consensus among experts in this field is that the identification and biopsy of lesions ≤5mm are generally unnecessary unless the patient has three or more lesions.

Following the guidance of the ICER Evidence Review Group (see section on Evidence Review Group starting on page 17) the clinical effectiveness of CTC for this review was evaluated by examining data separately on its test characteristics for polyps ≥10mm and for polyps 6-9mm, since some policy makers will want to assign differential importance to CTC performance in

these two categories. This review did not evaluate the performance of CTC for polyps ≤5mm as the clinical community does not assign significant importance to identification of these lesions and, in fact, recent articles have argued that greater harm than good arises from the biopsy of such "diminutive" lesions (Pickhardt, 2007).

Summary of Literature Review on Comparative Clinical Effectiveness

The accuracy of CTC has varied significantly in published studies over the years. In particular, the wide range of sensitivities (50%-90%) for medium and large polyps has led many commentators and previous health technology assessment bodies to judge the evidence base for CTC inadequate to support broad adoption of CTC for population-based screening. The best results in the literature have been those reported in a large study by Pickhardt in 2003, in which CTC was found to have comparable sensitivity with colonoscopy in the detection of both large and medium-sized polyps. Inferior results, however, were subsequently published by Cotton (2004), whose study reported that CTC detected only 23% of medium-sized lesions and 52% of larger polyps. Relatively poor results were also described by Rockey in 2005. The two latter studies, however, although published after Pickhardt, were actually performed prior to the Pickhardt study, and significant questions have been raised among clinical experts and in published commentaries regarding the adequacy of radiologist training and the quality of the CTC protocol used in these studies. For example, in the Cotton study radiologists reading the CTC in 8 of 9 centers were only required to have read 10 prior CTC studies, and the CTC results from the one center where radiologists had better training were significantly better than all others. Pickhardt's study required a minimum of 25 prior readings, whereas more recent guidelines suggest a minimum of 50-75. The deficiencies in many studies related to radiologist training and in other technical standards of CTC led our clinical experts to assert that Pickhardt's data are more representative of the performance of CTC as it would be practiced in the community today.

The ICER systematic review, guided by input from clinical experts, established minimum criteria for radiologist training and CTC technical specifications that had to be met for inclusion in our review. We identified four components of CT colonoscopy that we used to score studies using current best technology and performance standards versus studies using outdated technology or including sub-standard performance attributes. The four items include the following:

1. Multi-detector CT scanners with collimation < 5 mm;
2. Scan acquired within a single breath hold of ≤ 30 seconds;
3. Reference standard of combined CT colonoscopy and colonoscopy results (i.e., segmental unblinded colonoscopy or second look colonoscopy)
4. Trained readers by virtue of having read least 30 CT scans or undergone training before study start.

As shown in Tables 5-8 in the Tables section of this review, the data from our pooled analysis of studies that met these criteria demonstrated that the sensitivity and specificity of CTC for polyps ≥ 10mm was over 90%, very similar to that of colonoscopy. Pooled estimates of CTC sensitivity and specificity for all lesions ≥ 6mm are lower (86% and 81% respectively), but a judgment of these numbers must be made in light of the uncertainty among clinicians over the clinical significance of and best management strategies for these medium-sized polyps, and the proposed CTC screening strategy of rescreening every five years instead of every ten years, as is generally recommended for colonoscopy.

Using our pooled data on test characteristics from studies of "high-quality" CTC, the following estimates are obtained if one assumes that optical colonoscopy is a perfect reference standard:

- For every 1,000 patients screened by CTC and referred for colonoscopy for a finding of a lesion ≥ 6mm there will be:
  - 855 patients who have a true negative test
  - 15 patients who have a false negative test
  - 85 patients who have a true positive CTC (confirmed on colonoscopy)
  - 45 patients who have a false positive CTC (no polyp found on colonoscopy)

Potential Harms

Review of the evidence confirmed clinical expert opinion that CTC is a very safe procedure, with a far lower rate of complications than colonoscopy due to the virtual absence of risk for perforation when delivered in modern protocols. The potential for harm from radiation is more difficult to assess given the uncertainty of true risks of low levels of radiation exposure, but in the best empirical attempts to quantify the risk, it appears very low, less than the estimated attributable death rate from a colonoscopy with polypectomy, and clinically acceptable given the age of patients undergoing screening (>50) and the countervailing benefit of reducing the risk of cancer death conferred by screening for colorectal cancer.

The relative benefits and harms of extracolonic findings on CTC are also difficult to judge empirically. Studies suggest that approximately 6-8% of asymptomatic adults will have an extracolonic finding with a recommendation for follow-up of some kind. Were CTC to be adopted broadly, this rate of extracolonic findings would generate significant numbers of patients requiring further investigation. Upon further investigation some of these findings will be judged to have brought clinical benefit to the patient, most often either by early detection of a repairable abdominal aortic aneurysm, or by detection of an early stage cancer. However, previous total body CT screening experience suggests that most abnormalities found among asymptomatic adults will be proven clinically insignificant, while additional risks, anxieties, and costs are generated by follow-up investigations. The additional cost per patient for these follow-up investigations has been found to be in the range of $2-$34, but these estimates are based on relatively small samples and further study will be required to arrive at a greater understanding of the net health benefit and costs of CTC extracolonic findings. From both a clinical and a health systems' perspective, this is one of the most important uncertainties regarding CTC. The determination of net health benefit for CTC may hinge on decision-makers interpretation of the boundaries of risk, benefit, and cost of extracolonic findings. As with judgments of all the potential benefits and harms of CTC, a decision on net health benefit may depend on whether CTC is viewed as an intervention among patients who otherwise would not receive colorectal cancer screening, or as an option for patients who would otherwise receive colonoscopy or some other accepted form of screening.

Patient Acceptance

The literature is somewhat inconsistent due to variations in the protocols for CTC and colonoscopy, but the preponderance of the data suggests that among patients who experienced both CTC and colonoscopy, a small majority preferred CT colonoscopy.

Impact on Population Screening Rates
It is unclear whether the preference elicited among some patients for CTC would result in a larger number of unscreened individuals in a population becoming screened. No study to date has examined whether the availability of CT colonography results in increased numbers of individuals being screened within a population.

Comparing CTC to screening modalities other than optical colonoscopy
This review did not undertake a formal systematic review of the literature on all colorectal screening methods, but the scoping committee expressed the desire to view the performance of CTC in relation to other accepted modalities such as fecal occult blood tests (FOBT), fecal immunochemical tests (FIT), and flexible sigmoidoscopy (SIG). In the Table on the following page we present a comparison based on single source estimates of test characteristics. In this simplistic comparison of sensitivities and specificities, in which major assumptions are made regarding the relationship of test characteristics for adenomas and those for cancer, CTC is estimated to have superior sensitivity and similar specificity compared to other non-invasive approaches.

Test characteristics of CTC in comparison to other accepted modalities

Test	Sensitivity for Adenomas, by Size			Sensitivity for Cancer	Specificity	Reach	Source
	≤ 5 mm	6-9 mm	10+ mm				
FOBT[1]	0.046	0.063	0.107	0.129	0.954	Whole colorectum	Imperiale 2004
FIT[2]	0.045	0.11	0.224	0.658	0.955	Whole colorectum	Morikawa 2005
COL*	0.74	0.85	0.95	0.95†	0.9	98% to end of cecum	van Rijn 2006
SIG*	0.74	0.85	0.95	0.95†	0.92	80% to end of sigmoid colon; 40% to end of descending colon	Frazier, 2000, Expert opinion
CTCL	--	--	0.938	0.96†	0.92‡	Whole colorectum	ICER pooled estimate

[1]FOBT: Fecal occult blood test (Hemoccult II®)
[2]FIT: Fecal immunochemical test
COL: Colonoscopy
SIG: Flexible sigmoidoscopy
CTCL: Computed tomographic colonography with a positivity criterion of a large lesion (i.e., 10+mm)
*Sensitivity estimates are per lesion and are defined within reach of the scope
†Sensitivity for cancer assumed to equal that for large adenomas
‡Probability that CTC correctly finds a person to be free of an adenoma larger than the positivity criterion

Summary of Findings of Comparative Value:

CTC vs. no screening for population screening for colorectal cancer
The following numbers represent the base case analysis and compare *no screening* to a strategy of screening with CTC every five years and referring for colonoscopy all lesions ≥ 6mm.

- Cost of CTC = $523
- CTC cost to prevent one case of cancer *vs. no screening* = $19,000
- CTC cost to prevent one death *vs. no screening* = $37,000
- CTC cost per life-year gained *vs. no screening* = $1,500

CTC vs. colonoscopy for population screening for colorectal cancer
In direct comparison to colonoscopy, CTC every ten years is more expensive and marginally less effective in preventing cases of cancer (47 vs. 52 in a lifetime cohort of 1,000 individuals) and cancer deaths (24 vs. 26). Only one CTC screening strategy is more effective than colonoscopy every ten years, and that strategy is to perform CTC every five years with colonoscopy referral for polyps ≥ 6mm. For this strategy the cost-effectiveness is:

- Cost of CTC = $523
- Cost of colonoscopy = $522
- The cost per life-year gained for CTC *vs. colonoscopy* = $630,700

We also performed threshold analyses on the reimbursed price of CTC within the five-year strategy (the only CTC strategy we evaluated that was more effective than colonoscopy) to determine the CTC-to-colonoscopy-without-polypectomy cost ratio (i.e., "procedure cost ratio") that would produce incremental cost per life-year-saved at boundaries familiar to policy-makers.

- **To achieve Cost/Life-Year Saved = $150,000**
  Cost ratio CTC/colonoscopy = 0.52
  If colonoscopy cost = $522, CTC cost must = $272

- **To achieve Cost/Life-Year Saved = $100,000**
  Cost ratio CTC/colonoscopy = 0.47
  If colonoscopy cost = $522, CTC cost must = $246

- **To achieve Cost/Life-Year Saved = $50,000**
  Cost ratio CTC/colonoscopy = 0.42
  If colonoscopy cost = $522, CTC cost must = $219

Evidence Review Group Deliberation

The Evidence Review Group deliberation (see section starting on page 18 for membership and details) focused on many important issues regarding the evidence provided by the ICER review. Major points of discussion are shown in the numbered points below.

1) *Criteria for selection of relevant articles judged critical to review findings and was considered appropriate.*
   Like many diagnostic technologies, CTC has evolved in two aspects: technical, as the CT scanners, scanning software, bowel preps, and other technical aspects change; and interpretation, as the experience and standards for training of clinicians interpreting the results change. The ERG acknowledged that CTC remains in evolution, and that the criteria set for inclusion in our set of evaluated studies may not be applicable everywhere in the US. Nonetheless, the input of our clinical experts and health plan representatives suggested that the criteria selected were reasonable and that these standards could be widely achieved in the general community.

2) *Data on alternative colorectal cancer screening methods come from studies of their sensitivity/specificity for cancer detection, not polyp detection, so it is difficult to compare the evidence on FOBT and FIT to colonoscopy and CTC.*

3) *Colonoscopy is often considered the "gold standard," especially in comparison to CTC, but evidence demonstrates that colonoscopy also misses a fair number of medium and even large-sized polyps.*

4) *A key issue influencing the review of evidence is whether the benefits and harms of CTC should be viewed in comparison to optical colonoscopy, to other accepted modalities of colorectal cancer screening, or to no screening at all.*
   From a population perspective there are not nearly enough gastroenterologists available to perform needed colonoscopies, and if CTC can increase population-based screening its benefits and its cost-effectiveness are likely to be judged quite favorably. Others argued that there is no hard evidence to suggest that CTC would increase screening among those who would not have received screening another way; in addition, there are other non-invasive methods, such as FIT, that might be preferred by some systems of care. Some voiced concern that an increase in screening through CTC would only exacerbate the difficulty in obtaining timely gastroenterologist follow-up, and that broad considerations of capacity and professional training need to be done when considering adoption of CTC.

5) *On the horizon there is a new method of bowel prep for CTC that is non-cathartic, and if this method is demonstrated to provide the same sensitivity/specificity as current CTC, patient acceptance of CTC is likely to be much higher than for colonoscopy.*
   Our clinical experts estimated that evidence on the performance of non-cathartic prep would be available within the next 9-12 months.

6) *Judgments of the comparative clinical effectiveness and value of CTC may hinge on better understanding of the impact of extracolonic findings and the radiation risk.*
   Several ERG members expressed the opinion that extracolonic finding rates near 8% would drive a large number of follow-up investigations of highly dubious clinical value. Other

members of the ERG were more sanguine about the potential clinical benefits of early detection of significant extracolonic lesions, particularly if reporting of these lesions is guided by recently published ACR standards. The appraisal document has been revised to include significantly expanded examination of the evidence on radiation risk and on the published data on extracolonic findings.

7) *The economic model has several limitations but overall was viewed as a very useful tool for providing evidence on the clinical and cost-effectiveness of CTC.*
Some of the ERG participants would have liked the modeling to have included other possible CTC screening options, particularly one in which patients with medium-sized polyps are offered the option of immediate referral for colonoscopy vs. repeat CTC in 1-2 years. The decision model used for this appraisal could not evaluate this CTC surveillance strategy because the model does not explicitly simulate hyperplastic polyps. Data from the University of Wisconsin Medical School on the outcomes of individuals opting for CTC surveillance of medium-sized polyps are likely to be available in coming years and may help inform whether this is a reasonable strategy.

The specific discussion of the assignment of ICER ratings for comparative clinical effectiveness and for comparative value was preceded by the presentation of ICER's draft recommendations for ratings in two frameworks: 1) CTC vs. no screening; and 2) CTC vs. optical colonoscopy. There was unanimous consensus that, compared to no screening, CTC should be rated "Superior" in comparative clinical effectiveness, and "High Value" in comparative value. When rating CTC vs. colonoscopy there was some concern that the uncertainty regarding the impact of extracolonic findings made it difficult to have high confidence in any degree of net health benefit for CTC, but a majority (8/11) voters recommended a rating of "Comparable;" two voters recommended "Insufficient," and one voter recommended that CTC be rated as having "Incremental" comparative clinical effectiveness compared to colonoscopy.

Given that CTC is not covered by insurers for screening, the comparative value of CTC vs. colonoscopy was presented in draft form to the ERG in three versions according to three different possible scenarios of the potential reimbursement ratio between CTC and colonoscopy. A majority of voting ERG members (7/11) felt this was the best way to present the comparative value, but 4/11 felt that it would be preferable to label CTC only as "low value" according to the base case estimates of reimbursed price for CTC (equal to that of colonoscopy). The final ICER ratings are shown on the following pages, with background on the rating methodology immediately afterward.

ICER Integrated Evidence Rating™: CTC vs. NO SCREENING

The Comparative Clinical Effectiveness of CT colonography for colorectal cancer screening vs. NO SCREENING is rated as:

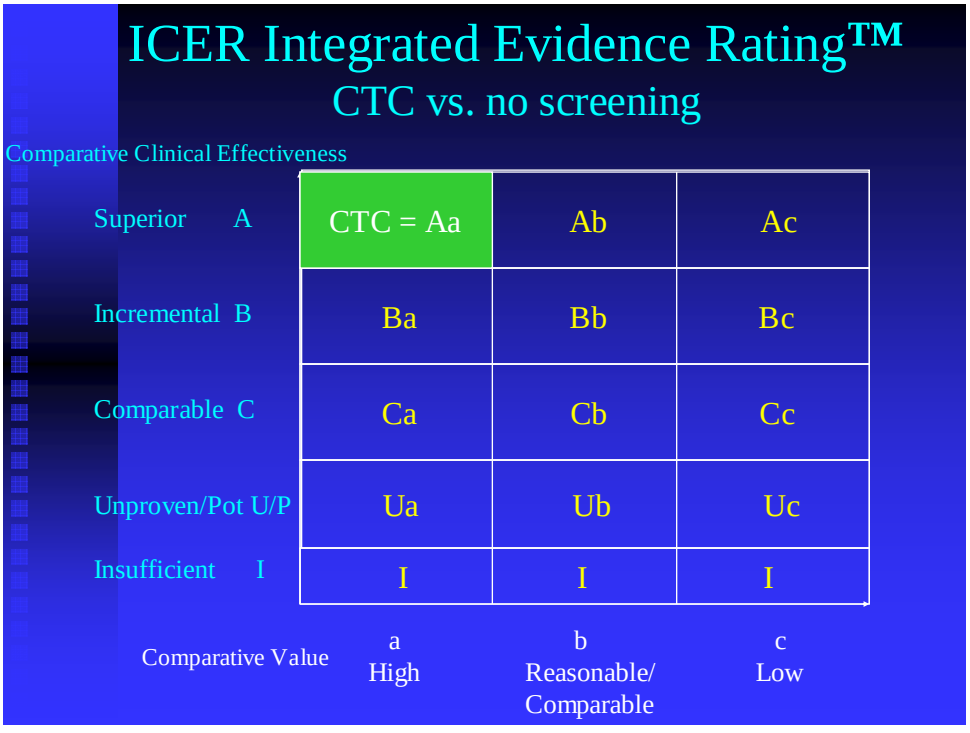
- **A --- Superior.**

The Comparative Value of CT colonography for colorectal cancer screening vs. no screening is rated as:

- **a --- High***

The Integrated Evidence Rating = Aa*

*** Reimbursed price of CTC assumed to = approximately $523**



ICER Integrated Evidence Rating™: CTC vs. OPTICAL COLONOSCOPY

The Comparative Clinical Effectiveness of CT colonography for colorectal cancer screening vs. OPTICAL COLONOSCOPY is rated as:

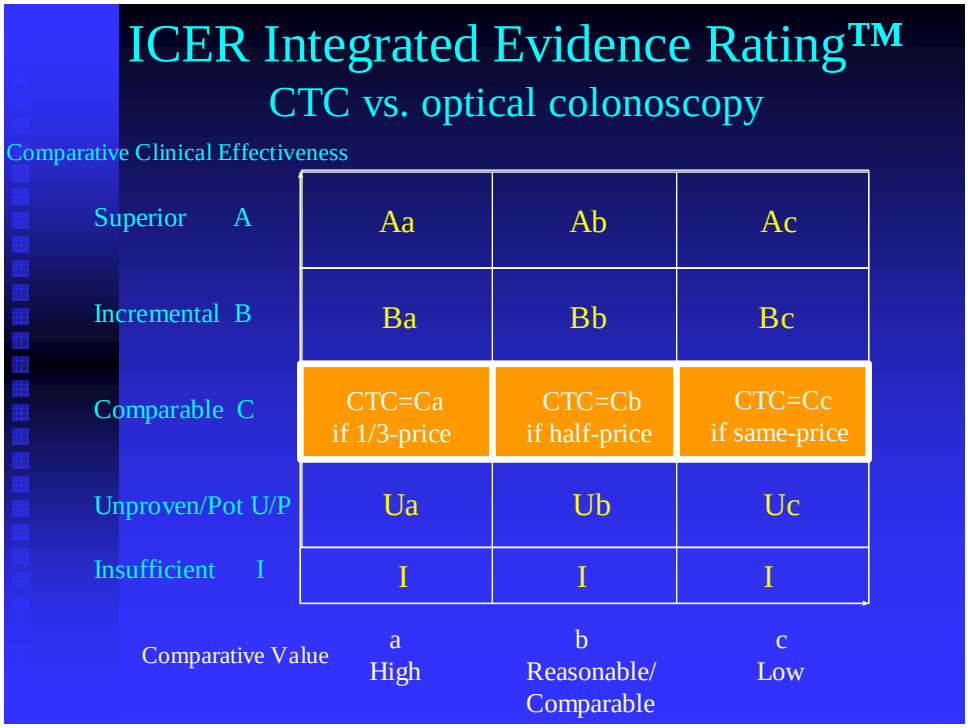
- **C --- Comparable**

The Comparative Value of CT colonography for colorectal cancer screening vs. optical colonoscopy screening is rated as:

- **c, b, or a --- low, comparable, or high, depending on reimbursed price ratio***

The Integrated Evidence Rating = Cc, Cb, or Ca*

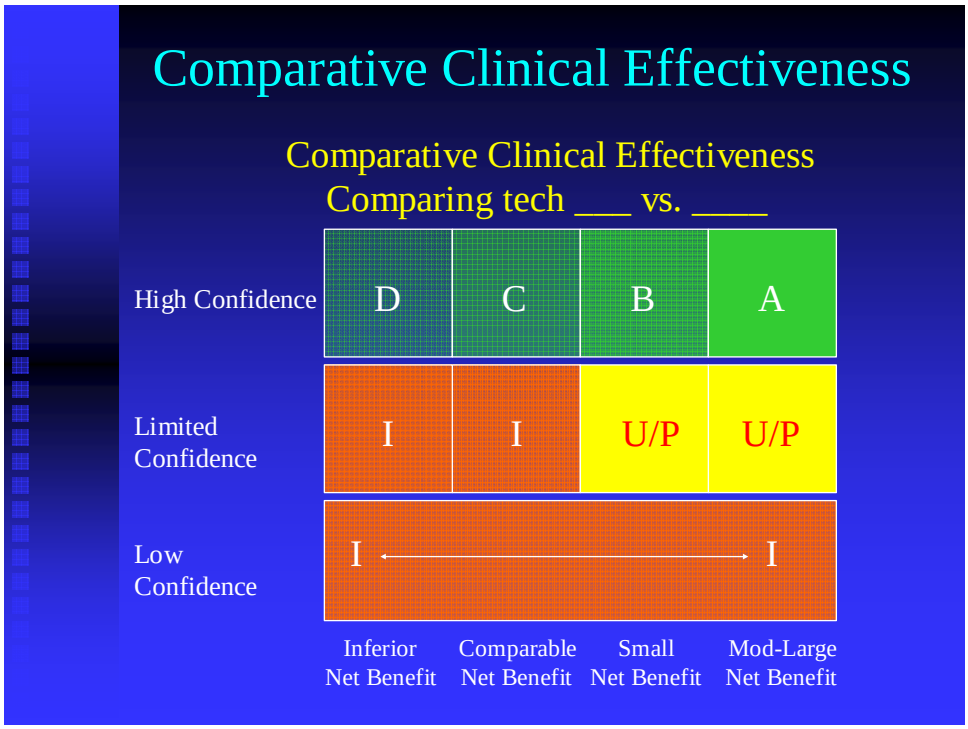
***If reimbursed price of CTC = same price as optical colonoscopy, comparative value = c**
If reimbursed price of CTC = half the price of optical colonoscopy, comparative value = b
If reimbursed price of CTC = one-third that of optical colonoscopy, comparative value = a



Methodology: ICER Integrated Evidence Rating™

Comparative Clinical Effectiveness

The ICER Integrated Evidence Rating™ combines a rating for comparative clinical effectiveness and a rating for comparative value. The clinical effectiveness rating arises from a joint judgment of the level of confidence provided by the body of evidence and the magnitude of the net health benefit -- the overall balance between benefits and harms. This method for rating the clinical effectiveness is modeled on the "Evidence- Based Medicine (EBM) matrix" developed by a multi-stakeholder group convened by America's Health Insurance Plans. This matrix is depicted below:



A = "Superior" [High confidence of a moderate-large net health benefit]
B = "Incremental" [High confidence of a small net health benefit]
C = "Comparable" [High confidence of a comparable net health benefit]
D = "Inferior" [High confidence of an inferior net health benefit]
U/P = "Unproven with Potential " [Limited confidence of a small or moderate-large net health benefit
This category is meant to reflect technologies whose evidence provides:

1) High confidence of *at least* comparable net health benefit
2) Limited confidence suggesting a small or moderate-large net health benefit

I = "Insufficient" The evidence does not provide high confidence that the net health benefit of the technology is at least comparable to that provided by the comparator(s).

Confidence
The vertical axis of the matrix is labeled as a degree of confidence with which the magnitude of a technology's comparative net health benefit can be determined. This operational definition of confidence thus is linked to but is not synonymous with the overall validity, consistency, and directness of the body of evidence available for the assessment. ICER establishes its rating of level of confidence after deliberation by the Evidence Review Group, and throughout ICER follows closely the considerations of evidentiary strength suggested by the Effective Health Care program of the Agency for Health Research and Quality (AHRQ) (www.effectivehealthcare.org) and the GRADE working group (www.gradeworkinggroup.org).

High Confidence:
An assessment of the evidence provides high confidence in the relative magnitude of the net health benefit of the technology compared to its comparator(s).

Limited Confidence:
There is limited confidence in the assessment the net health benefit of the technology. Limited confidence implies that the evidence is limited in one or more ways so that it is difficult to estimate the net health benefit with precision. ICER's approach considers two qualitatively different types of limited confidence. First, there may be limited confidence in the magnitude of any net health benefit, but there is high confidence that the technology is *at least* as effective as its comparator(s). The second kind of limited confidence applies to those technologies whose evidence may suggest comparable or inferior net health benefit and for which there is not nigh confidence that the technology is at least comparable. These two different situations related to "limited confidence" are reflected in the matrix by the different labels of "Unproven with Potential" and "Insufficient."

Limitations to evidence should be explicitly categorized and discussed. Often the quality and consistency varies between the evidence available on benefits and that on harms. Among the most important types of limitations to evidence we follow the GRADE and AHRQ approaches in highlighting:

1. Type of limitation(s) to confidence
    a. Internal validity
        i. Study design
        ii. Study quality
    b. Generalizability of patients (directness of patients)
    c. Generalizability of intervention (directness of intervention)
    d. Indirect comparisons across trials (directness of comparison)
    e. Surrogate outcomes only (directness of outcomes)
    f. Lack of longer-term outcomes (directness of outcomes)
    g. Conflicting results within body of evidence (consistency)

Low Confidence:
There is low confidence in the assessment of net health benefit and the evidence is insufficient to determine whether the technology provides an inferior, comparable, or better net health benefit.

Net Health Benefit

The horizontal axis of the comparative clinical effectiveness matrix is "net health benefit." This term is defined as the balance between benefits and harms, and can either be judged on the basis of an empiric weighing of harms and benefits through a common metric (e.g. Quality Adjusted Life-Years, or "QALYs"), or through more qualitative, implicit weightings of harms and benefits identified in the ICER appraisal. Either approach should seek to make the weightings as explicit as possible in order to enhance the transparency of the ultimate judgment of the magnitude of net health benefit.

Whether judged quantitatively or qualitatively, there are two general situations that decision-making groups face in judging the balance of benefits and harms between two alternative interventions. The first situation arises when both interventions have the same types of benefits and harms. For example, two blood pressure medications may both act to control high blood pressure and may have the same profile of side effects such as dizziness, impotence, or edema. In such cases a comparison of benefits and harms is relatively straightforward. However, a second situation in comparative effectiveness is much more common: two interventions present a set of trade-offs between overlapping but different benefits and harms. An example of this second situation is the comparison of net health benefit between medical treatment and angioplasty for chronic stable angina. Possible benefits on which these interventions may vary include improved mortality, improved functional capacity, and less chest pain; in addition, both short and long-term potential harms differ between these interventions. It is possible that one intervention may be superior in certain benefits (e.g. survival) while also presenting greater risks for particular harms (e.g. drug side effects). Thus the judgment of "net" health benefit of one intervention vs. another often requires the qualitative or quantitative comparison of different types of health outcomes.

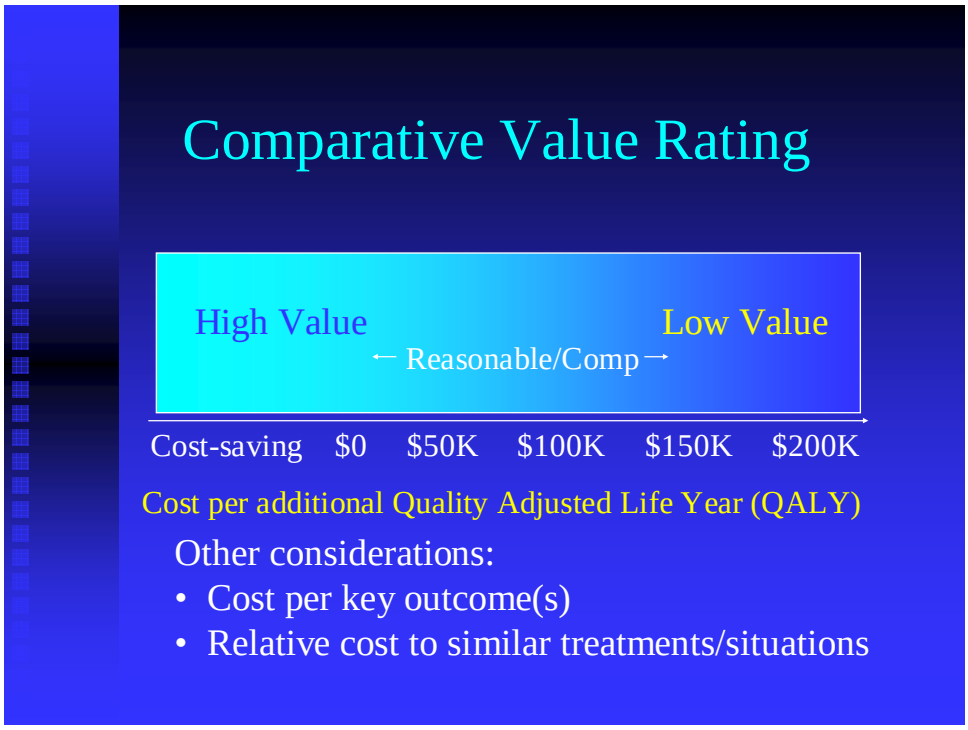
Since net health benefit may be sensitive to individual patient clinical characteristics or preferences there is a natural tension between the clinical decision-making for an individual and an assessment of the evidence for comparative clinical effectiveness at a population level. ICER approaches this problem by seeking, through the guidance of its scoping committee, to identify a priori key patient subpopulations who may have distinctly different net health benefits with alternative interventions. In addition, the ICER appraisal will also seek to use decision analytic modeling to identify patient groups of particular clinical characteristics and/or utilities which would lead them to have a distinctly different rating of comparative clinical effectiveness.

The exact boundary between small and moderate-large net benefit is subjective and ICER does not have a quantitative threshold. The rating judgment between these two categories is guided by the deliberation of the Evidence Review Group.

Comparative Value

The ICER rating for comparative value arises from a judgment largely based on the incremental cost-effectiveness of the technology being appraised. There are three categories of value: high, reasonable or comparable, and low. These categories, as shown in the figure below, are separated by general boundaries established by health care researchers and policy makers. The most commonly used metric for an assessment of comparative value is the quality adjusted life year, or QALY. This measure adjusts any improvement in survival provided by a technology by its corresponding impact on the quality of life as measured by the "utilities" or patients or the public for various health states. Details on the methodology underpinning the design and presentation of cost-effectiveness analyses within ICER appraisals is available on the ICER website at www.icer-review.org.

Although the cost per QALY is the most common way to judge the cost-effectiveness and comparative value of alternative medical interventions, ICER also presents the sub-component parts of the QALY, including the cost per key clinical benefits. Sensitivity analyses examining the robustness of results is also performed and presented in detail to the Evidence Review Group for deliberation.



Integrated Ratings

The ICER Integrated Evidence Rating™ combines the individual ratings given for comparative clinical effectiveness and comparative value. The overall purpose of the integrated ratings is to highlight the separate considerations that go into each element but to combine them for the purposes of conveying that clinical benefits provided by technologies come at varying relative values based on their cost and their impact on the outcomes of care and the health care system.

Evidence Review Group members

The Evidence Review Group (ERG) is an independent group brought together by ICER and composed of academic experts, patients, clinicians, epidemiologists, ethicists, and medical policy representatives of stakeholder groups including health plans and manufacturers.

The purpose of the ERG is to guide and help interpret the entire appraisal process. Members of the ERG are first convened to function as a "scoping committee" for the appraisal. During this phase the key questions for the appraisal are outlined, including elements such as the appropriate comparator technologies, patient outcomes of interest, patient subpopulations for which clinical and cost-effectiveness may vary systematically, time horizon for outcomes, and key aspects of the existing data that must be taken into account during the appraisal. The ERG may be divided into sub-committees that advise the ICER appraisal team at the mid-point of the appraisal on the early findings and challenges encountered.

At the final ERG meeting, members are asked to declare any interests in the technology or its comparator(s). The ERG meeting allows for in-depth deliberation on the findings of the ICER appraisal document and provides an opportunity for comment on the determination of the ICER integrated evidence rating. Although the ERG helps guide the final determination of the ICER Integrated Evidence Rating™, the final rating is ultimately a judgment made by ICER, and individual members of the ERG should not be viewed in any way as having endorsed this appraisal.

ERG Participant Name	**Conflict of interest**
John Ayanian, MD Professor of Medicine Harvard Medical School Brigham & Women's Hospital	None declared
Marc Berger, MD Vice President, Global Health Outcomes Eli Lilly and Company	None declared
William Corwin, MD Medical Director, Medical Management & Policy Harvard Pilgrim Health Care	None declared
Wendy Everett, ScD President, New England Healthcare Institute	Philips Medical is a member of her organization, New England Healthcare Institute
Robert Fletcher, MD, MSc Prof. of Ambulatory Care & Prevention Harvard Medical School	Scientific Advisory Board, Exact Sciences (developed DNA stool test for colorectal cancer screening)

G. Scott Gazelle Director, Institute for Technology Assessment, Massachusetts General Hospital and Prof. of Radiology, Harvard Medical School	None declared
Robert McDonough, MD Senior Medical Director, Clinical Research and Policy Development Aetna, Inc.	None declared
Peter J. Neumann, ScD Director, Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research & Health Policy Studies Tufts-New England Medical Center	None declared
Lisa Prosser, Ph.D. Assistant Prof., Dept of Ambulatory Care & Prevention Harvard Medical School	None declared
Paul C. Schroy, MD, MPH Prof. of Medicine, Boston University School of Medicine & gastroenterologist, Boston Medical Center	Exact Sciences, Inc. grant support and speaker's bureau; AmberGen, Inc. scientific advisory board and grant support
William C. Taylor, MD Associate Prof. of Medicine Harvard Medical School	Expert witness in medico-legal cases
Sunny Virmani Research Scientist Philips Medical Systems, Cleveland	Employee of manufacturer of CTC systems
Jed Weissberg, MD Associate Executive Director, Quality and Performance Improvement The Permanente Federation	Involved with purchasing of capital equipment at Kaiser Permanente
Michael Zalis, MD Radiologist, Massachusetts General Hospital	Investigator of CT colonography in academic setting