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Computed tomographic (CT)  
colonography for the detection of  
colorectal cancer – a Technical Brief

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## LEVEL OF EVIDENCE CONSIDERED IN TECHNICAL BRIEFS

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Technical Briefs are rapidly produced assessments of the *best available evidence* for a topic of highly limited scope. They are less rigorous than systematic reviews. Best evidence is indicated by research designs which are least susceptible to bias according to the National Health and Medical Research Council's (NHMRC) criteria (2000; 2005). Where methodologically acceptable and applicable, appraised evidence is limited to systematic reviews, meta-analyses, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials (RCTs). Where not available, poorer quality evidence may be considered.

## CONFLICT OF INTEREST

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None.

## EXECUTIVE SUMMARY

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### *Aim and scope*

This Technical Brief aimed to review evidence for the effectiveness and safety of computed tomographic (CT) colonography for the early identification and management of colorectal cancer.

Eligible studies were those reporting on the use of CT colonography (CTC) for the early detection of CRC for primary population screening of asymptomatic patients at average risk of CRC; for secondary screening of asymptomatic patients at high risk of CRC; and/or for diagnostic testing of patients with symptoms of bowel disease (for surveillance and management). Relevant comparators were optical/visual endoscopy colonoscopy and double-contrast barium enema. Studies required a valid reference standard (results from complete optical colonoscopy or surgery, performed independently and in a blinded fashion, following CTC). Outcomes of interest were health outcomes, test accuracy in detection of polyps and CRC; and safety and patient experience outcomes including benefits, harms, preferences and acceptability.

Research papers were excluded if they: were non-systematic reviews; included fewer than 40 participants; reported solely on cost effectiveness analyses, decision analyses, or on data on extracolonic outcomes; compared CTC technologies or techniques with each other; used CTC for diagnosis of non CRC conditions; evaluated capsule endoscopy or MRI colonography; and/or used CTC for pre-operative evaluation or staging, for evaluation of the proximal colon in patients with occlusive colon cancer, or in patients with an incomplete colonoscopy.

High quality secondary research (systematic reviews and meta analyses) were considered best evidence on the topic. These were included where selection criteria overlapped with those established for this review.

### *Methods*

The search strategy considered original articles published from July 2004 in the English language. The search included major bibliographic and review databases and secondary sources, and mostly published and indexed literature. Databases included: Medline, Embase, Current Contents, Cochrane Library Controlled Trials Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluation Database, PubMed, Clinical Evidence, ACP Journal Club, and Health Technology Assessment Database. Search terms and keywords included: computed tomographic colonography, colonoscopy, virtual colonoscopy, virtual colonography. References of retrieved publications were also scanned for eligible reviews.

As sufficiently high quality, relevant and recently published systematic reviews were identified; these alone were included in the Technical Brief. Summaries of appraisal results were presented in Evidence Tables which detailed study design, study setting, sample, methods, results, reported conclusions, and reviewer comments based on the limitations and validity of the review. Results were synthesised and overall conclusions made.

### *Key results and conclusions*

From the search strategy, 775 potentially relevant articles/abstracts were identified, of which 67 were retrieved. Of these, eight secondary research articles/reports were identified as eligible for appraisal and were included in the review. Three were published in 2005, three in 2006, and two in 2007. Appraised papers included three relatively poor quality, largely narrative reviews, and one limited quality and four high quality meta-analyses.

The following findings and conclusions were made:

1. CT colonography is a relatively safe procedure compared to DCBE, and at least as safe as, or safer than, diagnostic colonoscopy. Ionizing radiation exposure is relatively low but a cumulative risk for regular screening. There is a very small risk of colonic perforation.
2. Generally there have been inconsistent findings regarding preferences for and experiences from CTC versus colonography. However one meta-analysis of 11 studies of increased risk or symptomatic patients concluded that CTC may be preferred over colonoscopy, and that the majority of studies have reported results favouring CTC over colonoscopy with respect to pain and discomfort.

3. CT colonography has reasonable test sensitivity and specificity in the detection of large and medium polyps, but is poorly accurate for small lesions. Whilst specificity has been consistently high, test sensitivities have varied and pooled statistics need to be considered with caution. There is some evidence that CTC is highly accurate in the detection of symptomatic cancer.
4. There is some evidence that CTC is more accurate than air-contrast barium enema for detecting polyps and cancers in increased risk or symptomatic populations. However, conventional colonoscopy appears to be more accurate than CTC for large polyps, and particularly for smaller polyps.
5. Limitations of the current evidence base include that there is a lack of evidence about the accuracy of CTC for primary screening in average risk populations. There is also a need for greater investigation of the reasons for such wide variations in test accuracy achieved in different trials with respect to patient and scanner characteristics. Likely sources of variation relate to prevalence of disease, CTC techniques (such as width of collimation, type of detector, and mode of imaging), and radiologist experience. The definition of what constitutes a clinically important polyp in size and morphology also requires evidence-based elucidation. Whilst the methodological quality of studies is improving, comparisons between studies would be facilitated by more consistency in reporting and more appropriate statistical analysis and data synthesis techniques.
6. There have been no studies reporting on overall health outcomes of CTC including efficacy in reducing CRC incidence or mortality.
7. Based on the evidence and conclusions considered in this review CTC is not currently recommended for generalised screening.

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## RESEARCH QUESTION

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Dr John Childs (Principal Advisor, Cancer Control) and Sarah Greensmith (Senior Policy Analyst, Strategic Screening Team, National Screening Unit) from the Ministry of Health, New Zealand Government, requested this Technical Brief. The focus is on the use of computed tomographic (CT) colonography for the identification and management of colorectal cancer in three domains:

- population screening,
- screening of increased risk cohorts, and
- management of symptomatic people.

The National Screening Unit is interested in what are the benefits and risks of this procedure, and whether it has potential to improve morbidity and mortality from CRC.

The full research question is: What is the effectiveness and safety of computed tomographic (CT) colonography for the early identification and management of colorectal cancer (CRC)?

## BACKGROUND

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### *Overview of CT colonography*

Computed tomographic colonography or CTC, also known as virtual colonoscopy, simulates conventional endoscopy colonoscopy (EC). Virtual colonoscopy using computed tomography (CT) scanners is a modality that has been considered as potentially suitable for colorectal cancer screening of average risk and above average risk patients, as well as for diagnosis and management of symptomatic patients. The technique generally involves a similar bowel preparation to conventional endoscopy colonoscopy. Air or carbon dioxide is insufflated into the colon through a rectal tube and then data are acquired by the scanner which generates images of the colon. It provides a complete examination, allowing imaging of the outside and inside of the bowel and neighbouring organs. Depending on the equipment used, data obtained from rapid helical CT scanning of the abdomen are presented as two-dimensional images, with three-dimensional images generated of areas identified as suspicious (Levin et al. 2003). Data can be double read which increases sensitivity without increased risks for the patient. Sedation is not required, although some mild patient discomfort may be experienced from the air insufflation (Walsh and Terdiman 2003). According to the NZ Branch of the Royal Australian and New Zealand College of Radiologists, the procedure has no significant risk of perforation, and does not require a post-procedure recovery period (Colorectal Cancer Screening Advisory Group 2006). After radiologist review of results, patients noted to have suspicious-looking polyps or a colonic mass need to proceed to conventional colonoscopy, to enable biopsy or resection of the lesion. CTC identifies incidental (extracolonic) abnormalities outside the bowel in a significant proportion of cases (e.g., liver and kidney cysts), most of which are benign, and these may require further (sometimes invasive) investigative procedures (Colorectal Cancer Screening Advisory Group 2006).

CTC has several potential advantages over other tests considered for early detection of CRC. It potentially can identify large-bowel malignancies that are often poorly assessed by conventional colonoscopy, such as those located within haustral folds, as well as being able to view the entire colon. For this reason it has also been suggested as the examination of choice for failed or incomplete colonoscopies in many settings (Levin et al. 2003; Medical Services Advisory Committee (MSAC) 2006). CTC may also allow for small (and probably hyperplastic, low-risk) colonic polyps to be left in-situ when detected, and for regular reassessment to be carried out to monitor them (Levin et al. 2003), although patients may prefer it to be removed even if considered to be low risk (Banerjee and Van Dam 2006). Future potential developments for this modality include the 'patient-friendly' possibility of avoiding pre-imaging bowel preparation (Iannaccone et al. 2004), through faecal tagging with oral contrast, electronic cleansing (where the stool density relative to other tissues is calculated and subtracted during image generation), or using noncathartic protocols. Computer-aided detection (CAD) software is also being investigated to improve diagnostic accuracy (Perumpillichira et al. 2005).

High resource costs for equipment and radiologist training are currently well-recognised barriers to widespread use of virtual colonoscopy. By contrast, CTC is less time consuming for the patient and the relevant medical specialists than conventional colonoscopy and is less expensive. Multislice CT scanners are already widely available in New Zealand.

As with any test, virtual colonoscopy also has disadvantages. Patients are exposed to ionizing radiation, although low-radiation dose protocols are under investigation. False positives can occur as a result of retained stool in the bowel, diverticular disease (which can produce poorly distensible areas of the colon), or thickened bowel folds. Virtual colonoscopy may be less sensitive to detecting relatively rare flat adenomas (Levin et al. 2003), which are defined as having a height that is no more than one-half of their width (Nicholson et al. 2005a). As polyps cannot be removed during the procedure, patients with polyps detected at CTC require an additional endoscopic procedure for their removal. Variable factors such as radiologist experience and training may also influence accuracy (Pignone et al. 2002; Walsh and Terdiman 2003), and training specific to CTC interpretation is being advocated.

CTC is already well established as a reliable diagnostic tool in symptomatic patients who are unable to undergo complete colonoscopy. Whilst not yet endorsed as a screening test in the general risk population, there is general consensus that the technology holds promise for the future, and there is burgeoning research into CTC for colorectal cancer screening. Since 2003, there has been an exponential growth in studies investigating test performance of CTC, usually using visual colonoscopy as a reference standard. There is also a growing literature investigating psychological outcomes including patient discomfort and acceptability.

## METHODOLOGY

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### *Study inclusion criteria*

*Secondary studies* were eligible for inclusion where they:

- included a methods section describing how the relevant studies were identified (including bibliographic database/s)
- considered primary studies with selection criteria overlapping with those presented below
- were published from July 2004.

### Population

Studies considering the use of CT colonography for the early detection of CRC in the following modalities:

- For primary population screening of asymptomatic patients at average risk of CRC
- For secondary screening of asymptomatic patients at high risk of CRC. These include those with a personal history of CRC, colorectal adenoma, or inflammatory bowel disease; positive faecal occult blood; family history of CRC; gene carriers of/at risk for hereditary nonpolyposis colorectal cancer (HNPCC); and/or gene carriers of/at risk for familial adenomatous polyposis (FAP)
- For diagnostic testing of patients with symptoms of bowel disease (for surveillance and management).

### Intervention

Studies evaluating computed tomographic colonography (CTC) for the detection of precancerous (adenomatous and benign) polyps and CRC.

### Comparators

Other commonly used examinations including:

- optical/visual endoscopy colonoscopy (EC) (rigid or flexible scope)
- double-contrast barium enema.

### Reference standard

The reference standard used for verification of test accuracy included results from complete optical colonoscopy or surgery, performed independently and in a blinded fashion, following CTC.

Note that whilst colonoscopy is the current gold standard, it has a miss rate of 6% for polyps 1cm or more in diameter, and may be incomplete in 5-15% of examinations (Banerjee and Van Dam 2006; Nicholson et al. 2005b). To adjust for this, some test accuracy studies have employed "segmented unblinding" during colonoscopy as the reference standard. After evaluation by colonoscopy is completed for a segment, the endoscopist is given the CTC results for that segment and the area is re-

examined if a polyp is noted on the CTC. This identifies a false negative rate for colonoscopy and a false positive rate for CTC more accurately (Nicholson et al. 2005b).

Outcomes

Outcome measures including any of the following:

- health outcomes including CRC morbidity or mortality, incidence of CRC, and overall mortality
- test accuracy in detection of polyps (precancerous adenomatous and benign) and CRC, presented per-polyp and per-patient, including sensitivity (Se) and specificity (Sp); true positive, false positive, and false negative results; and positive predictive value, negative predictive value, and likelihood ratios; ideally presented for different polyp size ranges
- other outcomes relating to the procedure, including benefits and harms (including physical or psychological sequelae) and acceptability for the intervention compared with the comparator.

Study design

A range of study designs were relevant, dependent on the outcomes considered:

- for health outcomes (mortality and morbidity), randomised and pseudo-randomised controlled trials
- for test characteristics, prospective studies of test accuracy involving within-subjects, independent, blinded comparison of CT colonography with a valid reference standard (performed after the CTC) in people with a defined clinical presentation
- for benefits and harms relating to patient experience (including acceptability, pain, discomfort and preference), prospective controlled trials with within-subjects comparisons of outcomes following CTC to those following conventional examination comparators in a clinical setting
- for adverse events, data from national database/s of adverse events.

Sample size

Studies with samples of at least 40 participants.

### ***Study exclusion criteria***

Research papers were excluded if they:

- were not published in English,
- were “correspondence”, editorials, comments, book chapters, conference proceedings, abstracts,
- reported animal studies,
- did not clearly describe their methods and results or had significant discrepancies,
- were narrative (non systematic) reviews,
- were case presentations, and/or reported on:
  - participants aged under 18 years of age,
  - cost effectiveness analyses or decision analyses,
  - data on extracolonic outcomes,
  - studies comparing CT colonography technologies or techniques with each other, including use of bowel preparation methods, oral (e.g., faecal tagging) contrast techniques, intravenous contrast techniques, colonic insufflation, smooth-muscle relaxants, image acquisition, bipositional scanning, image processing, or reader training or experience,
  - studies using CT colonography for diagnosis of non CRC conditions, such as colonic diverticulitis or acute appendicitis,
  - studies evaluating capsule endoscopy, or MRI colonography (alone), and/or
  - studies using CT colonography for pre-operative evaluation or staging of CRC tumours in patients with known CRC, or for evaluation of the proximal colon in patients with occlusive colon cancer, or in patients with an incomplete colonoscopy.

### ***Main search terms***

Details of the search strategy are presented in **Appendix 1**.

**MESH headings (Medline subject headings):** colonography-computed-tomographic, exp colonoscopy

**Embase subject headings** (where different from Medline): computed tomographic colonography

**Additional free text** (used in all databases): (virtual adj colonoscopy), (virtual adj colonography), (ct adj colonograph\$), (ct adj colonograph\$)

Search sources

The NZHTA CORE Search was employed. Characteristics of the core search include: essential sources only, major databases and secondary sources, and mostly published and indexed literature.

Principal sources of information

**Bibliographic databases**

- Medline
- PubMed (last 90 days)
- Embase
- Current Contents
- Cochrane Central Register of Controlled Trials

**Review databases**

- Cochrane Database of Systematic Reviews
- Clinical Evidence
- DARE database
- NHS Economic Evaluation Database
- Health Technology Assessment Database
- ACP Journal Club

**Other sources of information**

- National Institute for Clinical Evidence (NICE)
- Institute for Clinical Services Improvement
- Blue Cross Blue Shield Technical Assessment Program
- New Zealand Ministry of Health
- Australian National Health and Medical Research Council
- National Cancer Control Initiative (Australia)

Cited references of retrieved articles were scanned for additional potentially eligible papers.

Extended searching of internet websites, meeting abstracts, hand searching of journals, and contacting of authors for unpublished data was not undertaken.

***Publication date and level of evidence***

Following an initial scoping search, several recently published, well-conducted systematic reviews and meta-analyses were identified on the topic. In recognition that well conducted systematic reviews are considered “best evidence”, literature considered eligible for critical appraisal were restricted to *secondary research* published from July 2004 onwards.

***Selection and appraisal***

The search strategy identified abstracts and titles for published articles. The reviewer (MB) applied the inclusion and exclusion criteria to identify those potentially eligible for selection and appraisal and these were retrieved as full text. The selection criteria were fully applied to the retrieved articles to identify the final set of papers to be appraised and included in the review.

***Data extraction into evidence tables***

Systematic reviews and/or meta-analyses were described and critiqued. Summaries of appraisal results were shown in evidence tables, and included:

- reference (authors, publication date)
- review question or aim
- search method employed by the review (including databases searched, search dates, search terms, other reference identification processes)
- review inclusion and exclusion criteria, data extraction and appraisal methods
- results of analyses comparing intervention and comparator groups on eligible outcomes including statistically-tested comparisons and reporting relevant statistical data
- comments on the review’s limitations

- authors' conclusions
- critical comments (strengths and weaknesses of the review).

For appraisal of the methodology of the included secondary studies, specific criteria assessed whether the review asked a focused question, if the eligibility criteria for included studies were explicit, what search strategy was used, how the validity of included trials was assessed, and whether results of included studies were similar. A summary of these criteria is presented in **Table 1** below.

**Table 1.** Validity criteria for appraisal of secondary studies

Is there a focused research question? i.e. PICO elements: patient, intervention/diagnostic or screening test of interest, comparator, outcomes
Are inclusion and exclusion criteria for selected studies stated?
Is there an explicit and comprehensive search strategy? Did review incorporate a search strategy comprehensive enough that it was unlikely to have missed studies?
Are the included trials appraised for validity? Are validity criteria stated?
Are results consistent from study to study? Is homogeneity assessed?
Summary of main results
Strengths and limitations

Adapted from Evidence Based Medicine Toolkit, University of Alberta (<http://www.med.ualberta.ca/ebm/ebm.htm>)

In addition to evidence tables, the appraised secondary studies were summarised in the report's text. Inter-review consistency was considered, results synthesised and overall conclusions drawn.

## RESULTS

From the search strategy 775 potentially relevant articles/abstracts were identified of which 67 were retrieved (including one paper that was found opportunistically when scanning the contents of a recently published Journal). Retrieved papers included primary research, however once it was determined that there was sufficient high order (level I) secondary evidence according to NHMRC's (2000) hierarchy of evidence, primary studies were excluded. In total, 59 retrieved articles were excluded and these are listed in **Appendix 2**.

Eight publications reporting on systematic reviews/meta analyses were eligible for appraisal and inclusion in the Technical Brief (listed in **Appendix 3**). Evidence tables of included papers are presented in **Table 2** in chronological order of year of publication (and within each year, in alphabetical order of first author).

Halligan et al (2005)

The systematic review and meta-analysis of Halligan et al (2005) employed a rigorous search strategy to identify studies published between 1994 and December 2003. A preliminary search to May 2003 included Medline, Cochrane Controlled Trials Register, EMBASE, Science Citation Index, and hand-searching of Journals. The search was extended to December 2003 using Medline only as the broader initial search had not found any articles that were not in Medline. The authors reported that as this search strategy did not identify any eligible articles not already identified by Medline, the May to December 2003 search only employed Medline. A broad range of search terms with no language restrictions were used, with additional references obtained from the bibliographies of the retrieved articles. Authors were contacted for clarification only.

Inclusion criteria required that the study focused on the detection of colorectal polyps verified with blinded within-subject reference colonoscopy or surgical findings. Required procedures were the inclusion of full bowel preparation, acquisition of prone and supine images, and helical scanners using commercially available software. Studies that used computer-aided detection (CAD) systems were excluded (reportedly to avoid bias as two authors worked for a company that develops such systems), as were studies with intravenous contrast material administered to patients. Included studies were to involve at least 30 patients. Studies where the prevalence of abnormality was broadly known to CT observers were also excluded. Two researchers conducted searches, applied selection criteria and abstracted data independently, resolving discrepancies by consensus or in discussion with other authors where necessary. Explicit quality assessment guidelines were employed.

The reviewers identified 24 eligible studies, including one study which included average risk patients only, and one multi-centre study. For detection of large polyps (1cm or larger) most studies had good per-patient sensitivity (93%, 95% CI 73%-98%) and all had excellent per-patient specificity (97%, 95% CI 95%-99%). For detection of medium and larger polyps (6mm and above), again studies had good per-patient sensitivity (86%, 95% CI 75%-93%) but specificity was variable (86%, 95% CI 76%-93%).

For detection of polyps of all sizes, studies were too heterogenous in sensitivity (range 45%-97%) and specificity (26%-97%) to pool results. The number of cancers per study was too small to allow meta-analysis. However, when treating data as if it were from a single study, sensitivity was 96% (95% CI 91%-99%). There were too few studies to permit sensitivity analyses investigating the effects of either using a modified reference standard (segmental unblinding of colonoscopy), or involving individual observer assessment versus consensus assessment.

Halligan et al (2005) concluded that CTC seems sufficiently sensitive and specific in the detection of large and medium polyps; it is especially sensitive in the detection of symptomatic cancer. They further argued that CTC should be further investigated as a diagnostic tool for cancer. As only one study considered patients at average population risk alone, the authors argue that data may not be applicable to a screening situation. This review provided a detailed discussion of methodological issues in the field and suggested improvements for future research. In addition to a comprehensive assessment of study limitations, a minimum data set was proposed for future researchers to observe in reporting studies of diagnostic accuracy.

Mulhall et al (2005)

Mulhall et al's (2005) systematic review and meta-analysis considered the test performance of CTC compared to endoscopy colonoscopy or surgery. The search strategy considered English language publications between 1975 and February 2005 identified from a range of databases (though without journal hand-searching, citation searching or contact with authors). Explicit selection criteria specified that studies included prospective trials of adults undergoing CTC after full bowel preparation, with colograms interpreted blind to the result of the EC or surgery (as the gold reference standard). Studies needed to have used state-of-the-art technology, including at least a single-detector CT scanner with supine and prone positioning, insufflation of the colon with air or carbon dioxide, collimation smaller than 5mm, and both 2-D and 3-D views used during scan interpretation. Two researchers independently searched the literature, applied selection criteria, abstracted data and coded aspects of methodological quality with disagreements resolved by consensus.

Thirty-three studies were identified for inclusion. The pooled per-patient sensitivity of CTC was heterogenous and improved as polyp size increased, being 0.48 for polyps <6mm (95% CI 0.25-0.70), 0.70 for polyps 6-9mm (95% CI 0.55-0.84), and 0.85 for polyps >9mm (95% CI 0.79-0.91). Characteristics of the CTC scanner explained some of the heterogeneity, including width of collimation (thinner led to higher sensitivity), type of detector (multiple scanners more sensitive than single detectors), and mode of imaging ("fly through" being more sensitive, though based on only two studies using this method). Other possible sources of false-negative results were discussed but limited reporting and number of studies limited ability to investigate them systematically. By contrast, specificity was homogenous, being 0.92 for polyps <6mm (95% CI 0.89-0.96), 0.93 for polyps 6-9mm (95% CI 0.91-0.95), and 0.97 for polyps >9mm (95% CI 0.96-0.97).

Detailed tables highlighted common sources of bias. These included: differences in disease severity or prevalence among studies, investigators being aware of baseline risk (clinical review bias), differential verification of findings, and variability in observer experience. The review considered limitations of the evidence base, including that the studies differed widely (with the extractable variables explaining only a small amount of variance), that only a few studies considered the newest CTC technology, that

only three studies were designed to evaluate a true screening population of average risk people, and that there are several limitations of colonoscopy as a gold standard.

Mulhall et al (2005) concluded that whilst CTC is highly specific, the range of reported sensitivities is wide. Patient or scanner characteristics do not fully account for this variability, but collimation, type of scanner, and mode of imaging explain some. This heterogeneity raises concerns about consistency of performance and about technical variability. The authors advised that these issues must be resolved before CTC can be advocated for generalised screening for colorectal cancer and that in the meantime CTC should only be used in research protocols or when other accepted screening methods are not appropriate.

Nicholson et al (2005b)

A systematic review by Nicholson et al (2005b) considered the role of CTC in CRC screening. The review employed a single database search (Medline), although cross-checking of paper references was also performed to identify additional papers. The review presented no details on search dates, search terms, selection criteria, or data extraction or appraisal methods. Appraisal and synthesis was narrative, with no tabular presentation of findings. Despite these limitations, the paper provides a useful critical account of research relating to CTC across the following areas: performance characteristics, flat lesions, extra-colonic findings, indication for CTC, patient preference, ways of improving the technique, and cost effectiveness.

With respect to test accuracy, the authors reported that some studies reported promising sensitivity (of more than 90% for detection of polyps at least 10mm in diameter), whilst other studies reported disappointing results with sensitivity ranging between 55% and 64%. Nicholson et al (2005b) discuss reasons for variation including the following: inclusion of polyp-enriched populations, inclusion of faecal tagging with electronic cleansing, varying radiologist experience (and use of single institution expertise), use of radiologists' consensus interpretation following double-reading, and primary reliance on 3D image review. As expected, the authors found that CTC performs better in detecting polyps greater than 10mm than those around 5mm in diameter. They cited the meta-analysis of Sosna et al's (2003) involving 14 prospective studies published to July 2002. This found a pooled per patient sensitivity of 0.84 for polyps 6-9mm, and of 0.88 (and specificity of 0.95) for polyps 10mm or larger.

Nicholson et al (2005b) argued that the detection of flat polyps has been under-investigated and therefore it is difficult to draw firm conclusions about this issue. They suggest that what 2D and 3D imaging combination formats are optimal is also not established.

With respect to research reporting on patient experience outcomes, Nicholson et al (2005b) noted that there has been conflicting findings, with some studies finding greater preference for CTC, others favouring visual colonoscopy, and some studies finding similar acceptance for both methods. The authors argue that the literature on patient experience is limited by a reliance on unvalidated and subjective questionnaires. Several studies were described suggesting that patients generally find CTC less painful and embarrassing than colonoscopy. The reviewers concluded that CTC may be favored by patients compared with other screening tests due to the ease of performance and comfort, and may become more acceptable once noncathartic preparation methods have been perfected. It is also noted that radiation exposure for CTC is in the realm of that received with barium enema, an accepted screening technique.

Nicholson et al's (2005b) review was supported by industry funding. The reviewers provided a summary of various medical society recommendations and concluded that although not yet endorsed for widespread use by major gastroenterological societies, "CTC shows promise as a screening tool".

Banerjee and Van Dam (2006)

This review considered CTC's efficacy for colorectal screening in a largely narrative review that included a systematic process for ranking quality of a subset of studies on test accuracy. The reviewers considered research published in English between 1960 and March 2005 identified using a Medline search and a comprehensive range of search terms for CTC. There was no hand-searching of Journals, or checking of reference lists performed. Papers which compared CTC with colonoscopy in prospective, blinded trials were examined independently by two investigators and assigned a categorical rating of quality, A, B or C, in decreasing order of study quality. Evidence A studies considered over 500 patients, were multicentre, used multidetector CT scanners, and employed segmental unblinding. Evidence B studies included over 100 patients, were single or multicentre studies, used single row or multidetector CT scanners, and did not employ segmental unblinding. Evidence C studies were those with 100 or fewer subjects, were single centre studies, used single row

CT scanners, and again did not employ segmental unblinding. Results were presented in tables as well as described in the text, although there were some minor discrepancies and the Table results are referred to here.

Six studies were graded as being of the poorest quality (Evidence C). CTC was unequivocally poor at detecting small lesions in these studies, with per-polyp sensitivity for detecting polyps of at least 5mm ranging between 11% and 55%. For medium sized polyps (6-9mm), per-polyp sensitivity ranged from 36% to 82%, and increased to between 50% and 91% for polyps at least 10mm in size. Per-patient sensitivity for 6-9mm sized polyps was 43% to 94% and specificity was between 58% and 92%. The per-patient sensitivity for polyps of at least 10mm in diameter ranged from 37% to 96%, with specificity of between 74% and 96%.

For somewhat higher quality designs (Evidence B), seven studies were identified. Results were still widely variable, with per-polyp sensitivity for detecting 6-9mm sized polyps ranging between 29% and 82%, and between 32% and 93% for polyps of at least 10mm in diameter. Per-patient sensitivity for 6-9mm polyps were 41% to 93%, with specificity of between 71% and 95%. For the larger polyps of at least 10mm, per-patient sensitivity ranged from 35% to 100%, and specificity was between 92% and 98%.

Finally, the highest quality group (Evidence A) included three recently published studies. Pickhardt et al's (2003) study considered asymptomatic patients at average or increased through family history risk for CRC. Unlike the other two evidence A studies, this trial involved careful bowel preparation with solid-stool tagging and electronic cleansing, primary readings using 3D images and 2D images for problem solving, and experienced readers. The study achieved similar per-polyp sensitivity for CTC and EC in detection of polyps of 6mm or greater (86% and 90% for CTC and EC respectively) and those sized 10mm or greater (92% and 88% for CTC and EC respectively). Per-patient sensitivity for polyps at least 6mm for CTC and EC was 88% and 80% respectively, and for polyps at least 10mm was 94% and 96% respectively. Test accuracy was poorer for CTC in a more recent study by Cotton et al (2004) involving symptomatic patients or patients with family history of polyps at nine academic centres. Per-polyp sensitivity for 6-9mm polyps was 23% for CTC compared with 96% for EC, and for polyps of at least 10 mm in size, per-polyp sensitivity was 52% for CTC compared with 96% for EC. The reviewers argued that poor results may relate to inexperienced readers, as the largest centre had sensitivity for polyps greater than 6 mm of 82%. Most recently, in a sample of increased risk subjects Rockey et al (2005) found similarly poor results, despite using superior scanners and more experienced readers than Cotton et al (2004). Sensitivity for polyps 6-9mm was 47% for CTC compared with 99% for EC, and for larger polyps of at least 10mm in diameter, sensitivity was 53% for CTC compared with 99% for EC.

The reviewers also considered evidence for other outcomes, though it was unclear whether these papers were systematically identified and appraised. With respect to patient experience literature, Banerjee and Van Dam (2006) concluded that it is unclear whether CTC is preferred to EC, and mixed results were described. Two larger trials found similar levels of discomfort expressed for each procedure, and no preference for either procedure in a third study. The reviewers described the study by Iannaccone et al (2004) where CTC with faecal tagging and no cathartic preparation was offered, and preferred by 61% of subjects compared with EC following catharsis. Nevertheless, it is emphasised that a significant sub-group of 35% still preferred EC, possibly because it allowed for immediate polyp removal where necessary. With respect to safety, the authors noted that the radiation dose of 0.44 rem from CTC is similar to that received when undergoing two abdominal radiographs. However they argued that this level could still be of concern if CTC was used as a regular screening tool. The reviewers identified only two cases of perforation from CTC arising in patients with diseased colons due to over-inflation with air, and noted that no cases had occurred in average-risk populations to date.

Whilst there were no overall conclusions, the review provided a useful description of results of studies organised in relation to technique, false negative and false positive results on CTC, effects of training, difficulties of detecting flat and small polyps, CTC in special situations, extracolonic findings, cost-effectiveness, and upcoming advances in CTC.

Davila, Rajan and Baron (2006)

This review was conducted to update a guideline of the American Society for Gastrointestinal Endoscopy relating to the use of gastrointestinal endoscopy for colorectal cancer screening and surveillance. Details on the limited search were scant, however a Medline search was undertaken with additional references obtained from the bibliographies of the identified articles and from

recommendations of expert consultants. Search dates, search terms, selection criteria and appraisal methods were not described and results were discussed narratively.

From a number of recent studies, the following test accuracy results were described for comparisons between CTC and colonoscopy. Per-polyp sensitivity for polyps at least 6mm ranged between 39% and 94%, and specificity between 79% and 92%. By comparison, per-polyp sensitivity for polyps of at least 10mm ranged between 55% and 100%, and specificity between 94% and 98%. The prospective trial of Rockey et al (2005) for people at high risk for CRC was reported with sensitivity for at least 10mm diameter lesions being 59% for CTC, compared with 48% for DCBE and 98% for colonoscopy. The authors noted that there were no studies reporting on efficacy of CTC in reducing CRC incidence or mortality. They also commented that EC may detect clinically important extracolonic findings, and that cost effectiveness studies indicate that under most assumptions endoscopy colonoscopy is more cost-effective than CTC. Comparative studies on patient acceptance data were cited as suggesting that there was no consistent preference.

Davila et al (2006) concluded that as studies evaluating virtual colonoscopy (and faecal DNA testing) for CRC screening have yielded conflicting results it therefore cannot be recommended.

MSAC (2006)

This systematic review and meta analysis by the Australian Federal government's Medical Services Advisory Committee (2006) was conducted by a team from the NHMRC Clinical Trials Centre. Clinical and consumer expertise were also involved through the establishment of an advisory panel. The reviewers aimed to assess the safety and effectiveness of CTC for the diagnosis or exclusion of colorectal neoplasia in symptomatic patients or in patients that are asymptomatic but at high risk of colorectal neoplasia due to a personal or family history of colorectal polyps or cancer, versus DCBE and versus endoscopy colonoscopy. Note that studies of average risk asymptomatic patients were not considered. Cost effectiveness evidence and evidence relevant to patients who are ineligible for colonoscopy was also considered but are not reported here as beyond the scope of the current Technical Brief.

The review considered research published between 1994 and June 2005 through a comprehensive search of several databases and websites using a detailed list of search terms. Additional references were obtained from the bibliographies of the retrieved articles. Inclusion criteria were that: studies were to perform multislice CTC (at least 4-slice CT scanning); use colonoscopy or surgical findings as the reference standard; and use double contrast barium enema and/or colonoscopy as a comparator. Studies had to report on at least one of the following: diagnostic accuracy with sufficient data to calculate sensitivity and specificity; changes in clinical management; and patient outcomes (morbidity, mortality, adverse events, quality of life, patient preferences). Exclusion criteria were: not being an appropriate clinical study, studies with average risk asymptomatic patients, studies with fewer than 10 patients undergoing CTC, studies which compared two or more different techniques of CTC without a reference standard, and studies not published in the English language.

A second researcher scanned abstracts for potentially eligible articles, with discrepancies resolved by discussion. Data were extracted using a standardised instrument by one reviewer, and checked by a second, with discrepancies resolved by discussion with a third reviewer. Data on quality was rated against explicit criteria relevant to patient outcomes using the QUADAS tool.

The review found that no studies compared overall health outcomes following the use of CTC, DCBE or endoscopy colonoscopy. The review included four systematic reviews, including two appraised in this Technical Brief (Halligan et al. 2005; Mulhall et al. 2005), 24 clinical studies reported on safety and accuracy, and 11 studies reported on patient preferences or quality of life outcomes.

With respect to CTC accuracy, CTC was found to be generally highly sensitive and specific for the diagnosis or exclusion of cancers and polyps greater or equal to 10mm in size in symptomatic patients and asymptomatic patients at high risk of colorectal neoplasia. This was based on 11 studies of variable quality, with median CTC sensitivity of 84% (range 55-100%), and median CTC specificity of 97% (range 74-100%). Estimates of CTC accuracy were higher for the detection of cancer alone. From a meta-analysis of four studies: CTC sensitivity was 97% (95% CI 89-100%) and CTC specificity was 98% (95% CI 95-99%). These findings were interpreted as being consistent with results from three published systematic reviews. The authors concluded that the results also indicated that CTC is only moderately sensitive for the detection of lesions 6-9 mm in diameter (from six studies, CTC sensitivity range 30-80%, CTC specificity range 93-99%), and is poorly sensitive for lesions less than 6mm in diameter (from four studies, CTC sensitivity range 14-57%, CTC specificity range 83-

97%). Reviewers commented that variation observed between studies demonstrates that CTC is less accurate in some population subgroups or settings. They further argued that the extent to which patient characteristics, prevalence of disease, CTC techniques, the experience of those performing and interpreting the tests or other factors may influence CTC performance has not yet been clearly defined.

Relative accuracy of CTC, DCBE and colonoscopy was investigated in only one eligible study, which was appraised as being of fair quality (Rockey et al. 2005). The study found that CTC and DCBE accuracy was lower than found in noncomparative studies and systematic reviews of CTC accuracy. The study's results suggested that CTC is a more specific test than DCBE, but less sensitive and specific than colonoscopy for the detection of cancers and polyps greater than or equal to 10 mm. The study suggested that CTC may be a more sensitive test than DCBE; this only reached statistically significance for lesions 6-9 mm in size.

With respect to patient preferences, the evidence reviewed suggested that CTC may be preferred over colonoscopy. However, comparison of pain and discomfort experienced by patients undergoing both tests showed mixed results with five of eight studies reporting results in favour of CTC, and three in favour of colonoscopy.

CTC was found to be a relatively safe procedure compared to DCBE and at least as safe as, or safer than, diagnostic colonoscopy. Both CTC and DCBE were said to expose patients to ionizing radiation and to be associated with a very small risk of colonic perforation.

The authors concluded that CTC is a relatively safe test compared to DCBE and colonoscopy. Evidence about CTC accuracy for the detection of cancers and polyps greater than or equal to 10 mm was said to compare favourably with DCBE. The reviewers also argued that there is some evidence to suggest that patients prefer CTC over DCBE, and over colonoscopy. It was concluded that CTC is less accurate than colonoscopy for the detection of cancers and polyps greater than or equal to 10 mm.

MSAC (2006) recommended that public funding for CTC as a substitute investigation for colonoscopy should not be supported. Whilst beyond the scope of the current Technical Brief, based on evidence appraised MSAC also recommended that public funding for CTC should be supported for exclusion of colorectal neoplasia in symptomatic or high risk patients who are either ineligible for colonoscopy due to patient contraindications, or where there is an inability to perform or complete a colonoscopy. The review also reported on additional considerations relating to CTC's success in visualising the entire colon in patients following an incomplete colonoscopy, visualising the proximal colon in patients with a distal obstruction, in detecting extracolonic lesions, and test failure rates.

Purkayastha et al (2007)

The meta-analytic study by Purkayastha et al (2007) aimed to indirectly compare the diagnostic accuracy of CTC with magnetic resonance colonography (MRC) (when compared with conventional colonoscopy) for patients presenting with colorectal cancer (CRC). The literature search was relatively broad considering several databases, and additional references from the bibliographies of the retrieved articles. There were no language restrictions. Articles were considered to end of October 2005. Included studies were prospective, blinded trials comparing CTC (or MRC) to visual colonoscopy and reporting data on CRCs with sufficient information for calculations of sensitivity and specificity. Data were extracted by three reviewers and discrepancy resolved by consensus with comprehensive assessment of study quality undertaken using published guidelines.

Twelve studies were included comparing CTC with EC (data on MRC not reported here as beyond the scope of the current review). Results indicated high sensitivity (0.96, 95% CI 0.92-0.99) and specificity (1.00, 95% CI 0.99-1.00). There was a high area under the summary receiver operating characteristic (SROC) curve (0.99) and high diagnostic odds ratio (DOR) (1461.90, 95% CI 135.00-2448.56). Sensitivity analyses revealed that no factors improved diagnostic accuracy from CTC except studies with more than 100 patients (AUC=1.00, DOR=2938.35, 95% CI 701.84-12,302.91).

In sum, Purkayastha et al's (2007) meta-analysis indicated high diagnostic accuracy for CTC compared with EC for detecting CRC in patients presenting with CRC.

Rosman and Korsten (2007)

A sophisticated meta-analysis of the accuracy of CTC using an sROC approach was recently conducted by Rosman and Korsten (2007). The search was somewhat limited, considering publications to November 2005, identified from one database, Medline. There was no reported citation searching or Journal hand-searching. Inclusion criteria were that all subjects underwent CTC and colonoscopy (as a reference standard), that studies reported per-patient sensitivity and specificity for polyp detection, and

that studies included at least five patients with disease or controls in the sample. Excluded were studies that only reported per-polyp sensitivity (and not per-patient), studies with overlapping patients, or studies with samples with excess colorectal cancers without sub-grouping.

Two researchers applied selection criteria but whether this was performed independently was not reported. Appraisal and data extraction methods were not described. Detailed description of statistical analyses were described. The reviewers suggested that statistical pooling in meta-analyses such as employed by Mulhall et al (2005) may not be adequate, arguing that sensitivity and specificity represent a trade-off and pooling them can give an inaccurate assessment. Rosman and Korsten (2007) recommend that sROC curves be constructed in addition to pooled results.

Thirty studies were identified as eligible for inclusion in the meta-analysis. Results included that the pooled per-patient sensitivity of CTC was higher for polyps greater than 10mm (0.82, 95% CI 0.76-0.88) compared with polyps 6-10mm (0.63, 95% CI 0.52-0.75) and polyps 0-5mm (0.56, 95% CI 0.42-0.70). The sROC curve analyses supported these findings with higher exact areas under the curve for the threshold of over 10mm compared with thresholds of greater than 5 mm, and any size. Endoscopy colonoscopy (EC) had significantly higher sensitivities and specificities than CTC at either a threshold of greater than 5mm or greater than 10mm. At a threshold of greater than 5mm, the exact area under the sROC curve was significantly higher for conventional colonoscopy compared with CTC ( $0.998 \pm 0.006$  vs  $0.884 \pm 0.033$ ,  $P < .005$ ).

Other findings reported include that there were no significant differences in the diagnostic characteristics of 2-dimensional versus 3-dimensional software algorithms (“fly-through”) for initial analysis of the CT images. Further, based on only two studies, the reviewers concluded that CTC seems to be more accurate than air-contrast barium enema for detecting polyps regardless of size.

Limitations were discussed, including that the design of studies comparing CTC and EC have an inherent bias in favour of colonoscopy because EC is used as the “gold standard”. The use of segmental unblinding attempts to address this but is of limited success because some polyps (such as those in mucosal folds) may be difficult to locate even after a second unblended attempt.

Rosman and Korsten (2007) concluded from these results that CTC has reasonable sensitivity and specificity for detecting large polyps but was less accurate than endoscopy colonoscopy for smaller polyps. Given the limitations of CTC for small polyps, the authors argue that CTC may not be a reasonable alternative in situations in which a small polyp may be clinically relevant. Therefore they suggest that CTC should not be considered as a first-line screening test in patients with a strong family history of CRC, where the progression of small polyps to cancer may require only 2-3 years. Further the authors argue that if CTC is used for screening for people without a family history, it should be repeated more frequently than surveillance schedules for conventional colonoscopy.

**Table 2. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
(Halligan et al. 2005)	<p>Aim To assess the methodological quality of available data in published reports of computed tomographic (CT) colonography by performing a systematic review and meta-analysis.</p> <p>Search period: 1994 – December 2003.</p> <p>Databases searched: Medline (but a preliminary search to May 2003 included Cochrane controlled trials register, EMBASE, Science Citation Index), handsearching of Journals (the broader search did not find articles that were found in Medline).</p> <p>Search terms: colonography, colography, computed tomographic colonography, CT pneumocolon, virtual colonoscopy, and virtual endoscopy.</p> <p>No language restrictions. Additional references were obtained from the bibliographies of the retrieved articles. Authors were contacted to determine whether there was patient overlap.</p>	<p>Inclusion criteria: the focus was the detection of colorectal polyps verified with blinded within-subject reference endoscopy colonoscopy (EC) or surgical findings. Methods included full bowel preparation, prone and supine images acquired, and helical scanners used. Software used needed to be (or mimic those) commercially available, and allow 2-dimensional interpretation and luminal 3-dimensional rendering for problem solving, or use primary 3-dimensional interpretation. Full reports from human in vivo studies only considered.</p> <p>Exclusion criteria: studies that used computer-aided detection (CAD) systems (to avoid bias as two authors work for a company that develops such systems). Studies reported only as Abstracts, studies with fewer than 30 patients. Studies where the CT observers could guess that the prevalence of abnormality was excessively high (eg, where EC was incomplete due to an obstructing tumour in more than 50% of patients). Studies with artificially inserted polyps. Studies where intravenous contrast material was routinely administered to patients, or during subsequent CT. Duplicate studies.</p> <p>Appraisal methods: Two researchers conducted searches, applied selection criteria and abstracted data independently, resolving discrepancies by consensus or monthly meetings with other authors where necessary. Only reported results from experienced observers. Data on methodological quality recorded using the QUADAS tool.</p>	<p>24 studies eligible of 1398 studies identified by search strategy. One included average risk patients only, and one was a multi-centre study.</p> <p>For detection of large polyps (1cm or larger): Per-patient Se (compared with EC): 93%, 95% CI 73%-98%. Per-patient Sp (compared with EC): 97%, 95% CI 95%-99%.</p> <p>For detection of medium and larger polyps (6mm and above): Per-patient Se (compared with EC): 86%, 95% CI 75%-93%. Per-patient Sp (compared with EC): 86%, 95% CI 76%-93%.</p> <p>For detection of polyps all sizes, studies were too heterogenous in sensitivity (range 45%-97%) and specificity (26%-97%). The number of cancers per study was too small to allow meta-analysis. When treating data as if from a single study, Se was 96% (95% CI 91%-99%)</p> <p>Author/s Conclusions CT colonography seems sufficiently sensitive and specific in the detection of large and medium polyps; it is especially sensitive in the detection of symptomatic cancer. Authors also concluded that CT colonography should be further investigated as a diagnostic tool for cancer.</p>	<p>Comments</p> <ul style="list-style-type: none"> <li>▪ relatively extensive search strategy, range of databases and list of search terms with citation checking, and hand-searching of Journals</li> <li>▪ very detailed selection criteria provided</li> <li>▪ search strategy and selection criteria applied and quality rated independently by two reviewers</li> <li>▪ brief background section</li> <li>▪ quantitative meta-analysis performed</li> <li>▪ sensitivities and specificities determined</li> <li>▪ several tables presented reasons for exclusion, forest plots and sROC plots, and suggested minimum data set</li> <li>▪ too few studies to permit sensitivity analyses investigating the effects of using a modified reference standard (segmental unblinding of colonoscopy), and individual observer assessment versus consensus assessment</li> <li>▪ makes point that data may not be applicable to a screening situation</li> <li>▪ an extremely detailed and comprehensive assessment of study limitations in conduct, design and reporting and description of minimum data set based on difficulties with data extraction.</li> </ul>

Key: CAD: computer aided detection; CRC: colorectal cancer; CTC: computed tomographic colonography, EC = endoscopy colonoscopy, Se: sensitivity, Sp: specificity, sROC: summary receiver operating characteristic

**Table 2 continued. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
(Mulhall et al. 2005)	<p>Aim To systematically review the test performance of CT colonography compared to colonoscopy or surgery and to assess variables that may affect test performance.</p> <p>Search period: Jan 1975 – February 2005.</p> <p>Databases searched: PubMed, Medline, EMBASE, and the Cochrane Controlled Trials Register.</p> <p>English language only.</p> <p>Search terms: virtual colonoscopy, CT colonography, CT colography, CT pneumocolon.</p>	<p>Selection criteria: Included prospective trial of adults undergoing CTC after full bowel preparation, with cologram interpreted blind to the result of the EC or surgery (as the gold reference standard). Studies needed to have used state-of-the-art technology, including at least a single-detector CT scanner with supine and prone positioning, insufflation of the colon with air or carbon dioxide, collimation smaller than 5mm, and both 2-D and 3-D views during scan interpretation.</p> <p>Appraisal methods: Two researchers independently searched the literature, applied selection criteria, abstracted data and coded aspects of methodological quality (with disagreements resolved by consensus).</p>	<p>33 studies included.</p> <p>The pooled per-patient sensitivity of CTC was heterogenous and improved as polyp size increased: for polyps &lt;6mm (0.48, 95% CI 0.25-0.70), for polyps 6-9mm (0.70 95% CI 0.55-0.84), and for polyps &gt;9mm (0.85 95% CI 0.79-0.91).</p> <p>Characteristics of the CTC scanner, including width of collimation (thinner led to higher sensitivity), type of detector (multiple scanners more sensitive than single detectors), and mode of imaging ("fly through" more sensitive (but based on only 2 studies using this method), explained some of the heterogeneity. Other possible sources of false-negative results are discussed but limited reporting and number of studies limited ability to investigate them.</p> <p>Specificity was homogenous, for polyps &lt;6mm (0.92, 95% CI 0.89-0.96), for polyps 6-9mm (0.93 95% CI 0.91-0.95, and for polyps &gt;9mm (0.97 95% CI 0.96-0.97).</p> <p>Author/s Conclusions Computed tomographic colonography is highly specific, but the range of reported sensitivities is wide. Patient or scanner characteristics do not fully account for this variability, but collimation, type of scanner, and mode of imaging explain some of the discrepancy. This heterogeneity raises concerns about consistency of performance and about technical variability. These issues must be resolved before CT colonography can be advocated for generalised screening for colorectal cancer (from Abstract). CT colonography should be used in research protocols or when other accepted screening methods are not appropriate,</p>	<p>Comments</p> <ul style="list-style-type: none"> <li>▪ moderately broad search strategy, several databases and search terms. No citation checking, hand-searching of Journals, or contact with authors reported</li> <li>▪ detailed selection criteria provided</li> <li>▪ independent quality assessment and data extraction</li> <li>▪ brief introductory section</li> <li>▪ thorough description of statistical analyses and data synthesis</li> <li>▪ quantitative meta-analysis with Se's and Sp's weighted for sample size calculated and heterogeneity explored using stratified analyses and meta-regression techniques</li> <li>▪ performed, pooled per-patient Se and Sp calculated at various polyp size thresholds. No sROC plots or characteristics reported</li> <li>▪ several tables presented, for included relevant studies, study design characteristics; per-patient sensitivities tabulated by polyp threshold size, scanner type (single slice or multidetector), and mode of imaging; per-patient specificities</li> <li>▪ very detailed table of patient characteristics and sources of potential biases</li> <li>▪ the Discussion considered limitations including that the studies differed widely, with the extractable variables explaining only a small amount of variance. Only a few studies considered the newest CTC technology. Discussed limitations of gold standard, and that only 3 studies were designed to evaluate a true screening population of average risk people.</li> </ul>

Key: CAD: computer aided detection, CRC: colorectal cancer, CTC: computed tomographic colonography, EC = endoscopy colonoscopy, Se: sensitivity, Sp: specificity, sROC: summary receiver operating characteristic, 2-D: 2-dimensional, 3-D: 3-dimensional

**Table 2 continued. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
(Nicholson et al. 2005b)	<p>Aim: To review the role of CT colonography in CRC screening (from title).</p> <p>Search period: not provided, (paper submitted March 2005, accepted April 2005).</p> <p>Databases searched: Medline</p> <p>Search terms: not provided.</p> <p>Cross-checking of reference lists of retrieved papers.</p>	<p>Considered original articles and reviews pertaining to CTC.</p> <p>Explicit inclusion criteria not provided.</p> <p>Appraisal methods: not described</p>	<p>Number of articles identified by search strategy not stated.</p> <p>Test accuracy outcomes: Some studies (lists five) reported promising sensitivity, greater than 90% for detection of polyps <math>\geq</math> 10mm in diameter, whilst others reported disappointing results with Se 55-64% range (3 studies). Variation has been attributed to inclusion of polyp-enriched population, inclusion of faecal tagging with electronic cleansing, radiologist experience (and use of single institution expertise), use of double-reading with 2 radiologists' consensus interpretation (unlikely to be available in clinical practice), or primary reliance on 3D image review. CTC performs better in detecting polyps greater than 10mm than those around 5mm. Cites Sosna et al's (2003) meta-analysis of 14 prospective studies using high-quality protocols (published to July 2002) which found a pooled per patient Se for polyps 6-9mm as 0.84 and for polyps 10mm or larger of 0.88 (and specificity of 0.95). Comments that difficult to draw firm conclusions about how well CTC will detect flat polyps as under-investigated in large trials of test accuracy. Also comments that it is not yet clear what 2D and 3D imaging combination formats are optimal. Notes that CAD technology should reduce the number of images that require careful review by a radiologist.</p> <p>Patient experience/safety outcomes: Describes several studies considering patient preference, and notes that there has been conflicting findings, with some finding similar acceptance of CTC and EC, some finding preferences for CTC, and others finding greater preference for EC. Results are limited by reliance on unvalidated subjective questionnaires. Several studies suggest that patients generally find CTC less painful and embarrassing than colonoscopy. Concludes that CTC may be favored by patients compared with other screening tests due to the ease of performance and comfort. Suggested that acceptance for CTC would improve when noncathartic preparation methods perfected. Notes that radiation exposure in the realm of what is offered with the accepted screening technique of barium enema.</p> <p>Author/s Conclusions "Although not yet endorsed for widespread use by major gastroenterological societies, CTC shows promise as a screening tool" (from Abstract).</p>	<p>Comments</p> <ul style="list-style-type: none"> <li>▪ minimal detail of search strategy, or selection criteria</li> <li>▪ no detail of dates of search</li> <li>▪ searched only one database</li> <li>▪ checking of reference lists of retrieved papers</li> <li>▪ no detail of data extraction or appraisal methodology</li> <li>▪ narrative overview of considered evidence under the following headings: performance characteristics, flat lesions, extra-colonic findings, indication for CTC, patient preference, improving the technique, and cost effectiveness</li> <li>▪ some description of study designs, sample characteristics and technology/process variations where relevant, and reasons for variations between findings posed</li> <li>▪ no tabular presentation review findings</li> <li>▪ summary of various medical society recommendations</li> <li>▪ supported by industry funding (unrestricted grant from Medicsight PLC).</li> </ul>

Key: CRC: colorectal cancer, CTC computed tomographic colonography, EC = endoscopy colonoscopy, Se: sensitivity, Sp: specificity

**Table 2 continued. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
(Banerjee and Van Dam 2006)	<p>Aim To examine the currently available data on (CTC) efficacy for colorectal screening.</p> <p>Search period: 1960 – March 2005</p> <p>Databases searched: Medline.</p> <p>Search terms: virtual colonoscopy, virtual endoscopy, computed tomographic colonography, computerized tomographic colonography, CT colonography, CT colonography, computed tomographic colography, computerized tomographic colography, CT colography.</p> <p>English language only.</p>	<p>Inclusion criteria: CTC compared with colonoscopy in prospective, blinded trials.</p> <p>Exclusion criteria: abstracts presented at meeting that were not fully published as full articles.</p> <p>Appraisal methods: two investigators examined each article independently, and assigned a categorical rating of quality (differences dealt with by consensus). The three ratings were: Evidence A: over 500 patients, multicentre, multidetector CT scanners used, segmental unblinding used. Evidence B: over 100 patients, single or multicentre, single row or multidetector CT scanners, segmental unblinding not used. Evidence C: 100 patients or fewer, single centre studies, single row CT scanners, segmental unblinding not used.</p>	<p>Test accuracy results comparing CTC and endoscopy colonoscopy (EC) in prospective, blinded trials.</p> <p><i>Evidence C (poorest quality, n= 6 studies, published 1997 – 2002).</i> Per polyp Se for ≤5mm polyp 11%-55%. Per polyp Se for 6-9mm polyp 36%-82%. Per polyp Se for ≥10mm polyp, 50%-91%. Per patient Se for 6-9mm polyp 43%-94%, Sp 58%-92% Per patient Se for ≥10mm polyp 37%-96%, Sp 74%-96%</p> <p><i>Evidence B, 7 studies, published 2000-2004</i> Per polyp Se for 6-9mm polyp 29%-82%. Per polyp Se for ≥10mm polyp, 32%-93%. Per patient Se for 6-9mm polyp 41%-93%, Sp 71%-95% Per patient Se for ≥10mm polyp 35%-100%, Sp 92%-98%</p> <p><i>Evidence A best quality, n=3 studies, published 2003 or later</i> 1) Pickhardt et al (2003) study of asymptomatic patients at average or increased risk for CRC. Involved careful bowel preparation with solid-stool tagging and electronic cleansing, primary readings using 3D images and 2D images for problem solving, and experienced readers. Per polyp Se for CTC and EC in detection of ≥ 6mm polyps (86% and 90% respectively) and ≥10 mm polyps (92% and 88% respectively). Per patient Se for ≥6mm polyps for CTC and EC was 88% and 80% respectively, and for ≥10mm polyps, 94% and 96% respectively. 2) Cotton et al (2004) – symptomatic patients or those with family history of polyps at 9 academic centres. Se for 6-9mm polyps was 23% for CTC cf 96% for EC. Se for ≥10 mm polyps was 52% for CTC cf 96% for EC. Results may relate to inexperienced readers, as largest centre had Se &gt;6 mm polyps of 82%. 3) Rockey et al (2005) – used superior scanners and more experienced reader than Cotton et al, but still poor results for sample of increased risk subjects. Se for 6-9mm polyps was 47% for CTC cf 99% for EC. Se for ≥10 mm polyps was 53% for CTC cf 99% for EC.</p>	<p>Comments</p> <ul style="list-style-type: none"> <li>▪ limited search strategy, with no hand-searching of Journals, or checking of reference lists. English language publications only</li> <li>▪ single data base searched</li> <li>▪ comprehensive list of search terms used</li> <li>▪ selection criteria provided and quality rated using independent ratings by two reviewers</li> <li>▪ brief background section</li> <li>▪ tables present studies included in each evidence level, the sample size, population studied, and per patient Se, per polyp Se and per patient Sp</li> <li>▪ narrative summary in the text of the studies that compare CTC with EC, with some discussion of why results vary due to technical and methodological reasons</li> <li>▪ in addition, there was brief description of results of studies organised in relation to technique, false negatives and false positive on CTC, effects of training, problem with flat and small polyps, CTC in special situations, extracolonic findings, patient preference, cost-effectiveness, and upcoming advances in CTC</li> <li>▪ there was no final discussion or conclusion section.</li> </ul>

**Table 2 continued. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
(Banerjee and Van Dam 2006)  <i>continued</i>			<p>Patient preferences. Concludes that it is unclear whether CTC is preferred to EC, and mixed results described. Two larger trials cited with results including similar levels of discomfort for each procedure, and no preference for either. Bowel preparation was the worst part for both procedures. In a study by Iannaccone et al (2004) where CTC with faecal tagging and no cathartic preparation was offered, 61% preferred "prepless" CTC to EC following catharsis, yet 35% still preferred EC as it allowed for immediate polyp removal where necessary.</p> <p>Safety. Radiation dose of 0.44 rem similar to undergoing 2 abdominal radiographs. Only two cases of perforation from CTC arisen in patients due to over-inflation with air in patients with diseased colons. No cases in average-risk populations to date.</p> <p>Author/s Conclusions No overall conclusions made and no abstract summary.</p>	

Key: CTC computed tomographic colonography, EC = endoscopy colonoscopy, Se: sensitivity, Sp: specificity

**Table 2 continued. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
(Davila et al. 2006)	<p>Aim To replace and supplement a previous guideline of the American Society for Gastrointestinal Endoscopy relating to the use of gastrointestinal endoscopy for colorectal cancer screening and surveillance.</p> <p>Search period: not provided.</p> <p>Databases searched: Medline. Search terms: not described. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants.</p>	<p>Inclusion criteria: not described</p> <p>Exclusion criteria: not described.</p> <p>Appraisal methods: not described.</p>	<p>Synthesises results from a number of studies to provide the following results for CTC compared with endoscopy colonoscopy: Per polyp Se for <math>\geq 6</math>mm polyp 39%-94%, Sp 79%-92% Per polyp Se for <math>\geq 10</math>mm polyp 55%-100%, Sp of 94%-98%</p> <p>Cites Rockey et al's results also for people at high risk for CRC with Se for <math>\geq 10</math>mm lesions being 59% for CTC, compared with 48% for DCBE and 98% for colonoscopy. Notes that there are no studies reporting on efficacy of CTC in reducing CRC incidence or mortality. Comments that EC may detect clinically important extracolonic findings, and that cost effectiveness studies indicate that under most assumptions colonoscopy is more cost-effective than CTC.</p> <p>Also reports on patient acceptance data reporting that comparative studies show no consistent preference.</p> <p>Suggests that whilst CTC cannot be recommended for primary screening, it maybe useful for patients who refuse colonoscopy or who have had an incomplete colonoscopy.</p> <p>Author/s Conclusions "Studies evaluating virtual colonoscopy [and faecal DNA testing] for CRC screening have yielded conflicting results and therefore cannot be recommended."</p>	<p>Comments</p> <ul style="list-style-type: none"> <li>▪ limited search strategy of one database</li> <li>▪ checking of reference lists and experts mentioned</li> <li>▪ search terms and publication date range not described</li> <li>▪ selection criteria not provided</li> <li>▪ brief background section</li> <li>▪ no tabular presentation of results</li> <li>▪ narrative summary in the text</li> <li>▪ notes that an earlier Guideline published in 2003 focuses on CTC explicitly</li> <li>▪ brief summary section.</li> </ul>

Key: CRC: colorectal cancer; CTC: computed tomographic colonography, DCBE: double contrast barium enema, Se: sensitivity, Sp: specificity

**Table 2 continued. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
<p>(Medical Services Advisory Committee (MSAC) 2006)</p>	<p>Aim: To assess the safety, effectiveness (accuracy, patient preferences/quality of life) and cost-effectiveness of CTC for the diagnosis or exclusion of colorectal neoplasia in symptomatic patients or in patients that are asymptomatic but at high risk of colorectal neoplasia due to a personal or family history of colorectal polyps or cancer, versus DCBE and versus colonoscopy.</p> <p>Evidence relevant to patients who are ineligible for colonoscopy was also considered but not reported here as beyond scope of current Technical Brief.</p> <p>Search period: 1994 – June 2005.</p> <p>Databases searched: Medline, preMedline, Current Contents, Cochrane Library, Health Technology Assessment databases, and numerous websites.</p>	<p>Inclusion criteria Studies were to: perform multislice CTC (at least 4-slice CT scanning); use colonoscopy or surgical findings as the reference standard; use double contrast barium enema and/or colonoscopy as a comparator. Studies had to report on at least one of the following: diagnostic accuracy with sufficient data to calculate sensitivity and specificity; changes in clinical management; patient outcomes (morbidity, mortality, adverse events, quality of life, patient preferences).</p> <p>Exclusion criteria: Not an appropriate clinical study. Case series where the use or reporting of a reference standard was based on the CTC result (positive/negative). Case-control studies where patients were selected for inclusion in the study based on their known disease status. Retrospective case referent studies (reporting on subjects all known to have the condition of interest). Studies with average risk asymptomatic patients and studies with &lt; 10 patients undergoing CTC were excluded. Studies which compared two or more different techniques of CTC without performing a reference standard were excluded. Not in English.</p> <p>Appraisal methods: A second researcher scanned abstracts for potentially eligible articles, with discrepancies resolved by discussion. Data extracted using a standardized instrument by one reviewer, and checked by a second, with discrepancies resolved by discussion with a third. Data on quality rated against explicit criteria relevant to patient outcomes using the QUADAS tool.</p>	<p>No studies compared overall health outcomes following the use of CTC, DCBE or colonoscopy. Four systematic reviews and 24 clinical studies reported on safety and accuracy, and 11 studies reported on patient preferences or quality of life outcomes.</p> <p>CTC accuracy: CTC is generally highly sensitive and specific for the diagnosis or exclusion of cancers and polyps <math>\geq 10</math> mm in symptomatic patients and asymptomatic patients at high risk of colorectal neoplasia: 11 studies of variable quality, median CTC sensitivity 84% (range 55-100%); median CTC specificity 97% (range 74-100%). Estimates of CTC accuracy are higher for the detection of cancer alone [meta-analysis of four studies: CTC sensitivity 97% (95% CI 89-100%); CTC specificity 98% (95% CI 95-99%)]. These findings are consistent with results from three published systematic reviews. CTC is only moderately sensitive for the detection of lesions 6-9 mm (lesions 6-9 mm: six studies, CTC sensitivity range 30-80%, CTC specificity range 93-99%). CTC is poorly sensitive for lesions &lt; 6 mm (lesions <math>\leq 5</math> mm: four studies, CTC sensitivity range 14-57%, CTC specificity range 83-97%).</p> <p>Relative accuracy of CTC, DCBE and colonoscopy: Evidence limited to one study of fair quality (Rockey et al. 2005) that found CTC and DCBE accuracy to be lower than noncomparative studies, and systematic reviews of CTC accuracy. The study indicated that CTC is a more specific test than DCBE, but less sensitive and specific than colonoscopy for the detection of cancers and polyps <math>\geq 10</math> mm. The study also suggested that CTC may be a more sensitive test than DCBE; though this only reached statistical significance for lesions 6-9 mm.</p> <p>Patient preferences: The evidence reviewed also suggests that CTC may be preferred over colonoscopy. However, comparison of pain and discomfort experienced by patients undergoing both tests have shown mixed results with five of eight studies reporting results in favour of CTC, and three in favour of colonoscopy.</p> <p>Safety: CTC is a relatively safe procedure compared to DCBE and at least as safe as, or safer than, diagnostic colonoscopy. Both CTC and DCBE expose patients to ionizing radiation and are associated with a very small risk of colonic perforation.</p>	<p>Comments</p> <ul style="list-style-type: none"> <li>▪ an extremely detailed and comprehensive review presented in a 209 page report</li> <li>▪ extensive search strategy, range of databases and list of search terms with citation checking</li> <li>▪ no hand-searching of Journals reported</li> <li>▪ very detailed selection criteria provided</li> <li>▪ search strategy and selection criteria applied and quality rated by one reviewer and checked by a second</li> <li>▪ extensive background section on burden of disease and compared procedures</li> <li>▪ quantitative meta-analysis performed, sensitivities and specificities pooled and sROC plots fitted</li> <li>▪ numerous tables presented results</li> <li>▪ additional considerations were reviewed relating to CTC's success in visualising the entire colon in patients following an incomplete colonoscopy, visualising the proximal colon in patients with a distal obstruction, in detecting extracolonic lesions, and test failure rates.</li> </ul>

Key: CRC: colorectal cancer; CTC: computed tomographic colonography, DCBE: double contrast barium enema; EC = endoscopy colonoscopy; MRC: magnetic resonance imaging; MSAC: Medical Services Advisory Committee, Se: sensitivity, Sp: specificity

**Table 2 continued. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
(Medical Services Advisory Committee (MSAC) 2006)  <i>continued</i>	Search terms: full search terms for each database were provided, including: colonography, computed tomographic, tomography, X-ray computed, colorectal neoplasms, colonic polyps, cancer, pseudoradiography, virtual colonoscopy, pneumocolon, spiral computer assisted tomography No language restrictions on the search. Additional references were obtained from the bibliographies of the retrieved articles.	An economic analysis was undertaken but results are beyond the scope of this Technical Brief.  Clinical and consumer expertise involved through the establishment of an advisory panel.	<b>Author/s Conclusions</b> CTC is a relatively safe test compared to DCBE and colonoscopy. Evidence about CTC accuracy for the detection of cancers and polyps $\geq$ 10 mm compares favourably with DCBE. There is also some evidence to suggest that patients prefer CTC over DCBE. CTC is less accurate than colonoscopy for the detection of cancers and polyps $\geq$ 10 mm. There is also some evidence to suggest that patients prefer CTC over colonoscopy.  <b>Recommendations</b> Evidence in relation to the comparison of CTC with colonoscopy indicates that CTC is less effective. MSAC recommends that public funding for CTC as a substitute investigation for colonoscopy should not be supported.	<ul style="list-style-type: none"> <li>▪ reviewers commented that variation observed between studies demonstrates that CTC is less accurate in some population subgroups or settings. They further argued that the extent to which patient characteristics, prevalence of disease, CTC techniques, the experience of those performing and interpreting the tests or other factors may influence CTC performance has not yet been clearly defined.</li> </ul>

Key: CRC: colorectal cancer; CTC: computed tomographic colonography, DCBE: double contrast barium enema; EC = endoscopy colonoscopy; MRC: magnetic resonance imaging; MSAC: Medical Services Advisory Committee; Se: sensitivity, Sp: specificity

**Table 2 continued. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
(Purkayastha et al. 2007)	<p>Aim To use meta-regression techniques to indirectly compare the diagnostic accuracy of (i) CTC compared with conventional endoscopy colonoscopy (EC) with that of (ii) magnetic resonance colonography (MRC), compared with conventional colonoscopy, for patients presenting with colorectal cancer (CRC).</p> <p>Search period: to 1 November 2005.</p> <p>Databases searched: Ovid, EMBASE, the Cochrane database, Medline.</p> <p>Search terms: computed tomographic colonography, magnetic resonance colonography, virtual colonoscopy, diagnostic accuracy, colorectal cancer, comparative study. Also used related articles function. No language restrictions. Additional references were obtained from the bibliographies of the retrieved articles. Study authors were not contacted.</p>	<p>Inclusion criteria: all prospective studies comparing CTC or MRC to EC and reporting data on CRCs. CTC compared with colonoscopy in prospective, blinded trials.</p> <p>Exclusion criteria: studies where patients did not undergo EC, studies that did not appear to report the numbers of people diagnosed with CRC, and studies providing insufficient information for calculations of Se and Sp.</p> <p>Appraisal methods: All data were extracted by three reviewers and discrepancy resolved by consensus. Assessment of quality undertaken using the guidelines published by STARD initiative and the QUADAS tool.</p> <p>Note that data per lesion or the accuracy of different sized lesions was not estimated as these data were not available for CRCs in the studies included.</p>	<p>Thirty studies eligible, 12 included studies comparing CTC with EC (data on MRC not reported here as beyond scope of current review).</p> <p>Overall Se for CTC (compared with EC): 0.96 95% CI 0.92-0.99. Overall Sp for CTC (compared with EC): 1.00 95% CI 0.99-1.00.</p> <p>Test showed high area under the summary receiver operating characteristic (sROC) curve = 0.99 and high diagnostic odds ratio (DOR) = 1461.90, 95% CI 135.00-2448.56.</p> <p>Sensitivity analyses revealed that no factors improved diagnostic accuracy from CTC except studies with more than 100 patients (AUC=1.00, DOR=2938.35, 95% CI 701.84-12,302.91).</p> <p>Author/s Conclusions CTC and MRC have similar diagnostic accuracy for detecting CRC. The accuracy, cost, availability and practicality of CTC and MRC have implications for future screening programmes for CRC.</p>	<p>Comments</p> <ul style="list-style-type: none"> <li>▪ relatively extensive search strategy, range of databases and list of search terms with citation checking, but with no hand-searching of Journals or contact of experts</li> <li>▪ selection criteria provided and quality rated using independent ratings by three reviewers</li> <li>▪ brief background section</li> <li>▪ quantitative meta-analysis performed</li> <li>▪ study quality assessed and sensitivities, specificities, DORs calculated</li> <li>▪ sROC curves and sensitivity analyses utilised</li> <li>▪ several Tables presented study characteristics, quality scores, study results, sensitivity analyses, the sROC curve for diagnostic accuracy, and meta-regression analyses</li> <li>▪ discussion of the limitations of indirect comparisons through meta-regression techniques.</li> </ul>

Key: CRC: colorectal cancer; CTC: computed tomographic colonography, EC = endoscopy colonoscopy, MRC: magnetic resonance imaging; Se: sensitivity, Sp: specificity, sROC: summary receiver operating characteristic

**Table 2 continued. Evidence Table of appraised secondary research relating to computed tomographic (CT) colonography for the detection of colorectal cancer.**

Authors, date	Aim and search method	Inclusion and exclusion criteria	Results and authors' conclusions	Comments
(Rosman and Korsten 2007)	<p>Aim To evaluate the accuracy of CT colonography for polyp detection using an sROC approach.</p> <p>Search period: 1996 – November 2005.</p> <p>Databases searched: Medline</p> <p>Search terms: (virtual or CT or computed or CAT) near "colon".</p>	<p>Inclusion criteria: all subjects who underwent CTC also underwent colonoscopy (as a reference standard), studies reported per-patient sensitivity and specificity for polyp detection, and raw data for determining these to allow continuity correction.</p> <p>Exclusion criteria: studies that only reported per-polyp sensitivity (and not per patient), studies with overlapping patients. Studies with fewer than 5 patients with disease or controls or had excess colorectal cancers without sub-grouping.</p> <p>Appraisal methods: Two researchers applied selection criteria.</p>	<p>30 studies included in the meta-analysis of CTC.</p> <p>The pooled per-patient sensitivity of CTC was higher for polyps greater than 10 mm (0.82, 95% CI 0.76-0.88) compared with polyps 6-10mm (0.63, 95% CI 0.52-0.75) and polyps 0-5mm (0.56, 95% CI 0.42-0.70). The sROC curve analyses supported these findings with higher exact areas under the curve for the threshold of over 10mm compared with thresholds of &gt;5 mm and any size.</p> <p>Endoscopy colonoscopy had significantly higher Se's and Sp's than CTC at either a threshold of &gt;5mm or greater than 10mm. At a threshold of &gt;5mm, the exact area under the sROC curve was significantly higher for EC compared with CTC (0.998 ± 0.006 vs 0.884 ± 0.033, P &lt; .005).</p> <p>There were no significant differences in the diagnostic characteristics of 2-dimensional versus 3-dimensional software algorithms ("fly-through") for initial analysis of the CT images.</p> <p>CTC seems to be more accurate than air-contrast barium enema for detecting polyps regardless of size (based on two studies).</p> <p>Author/s Conclusions CT colonography has a reasonable sensitivity and specificity for detecting large polyps but was less accurate than endoscopy (visual) colonoscopy for smaller polyps. Given the limitations of CTC for small polyps, the authors argue that it should not be considered as a first-line screening test in patients with a strong family history of CRC. CT colonography may not be a reasonable alternative in situations in which a small polyp may be clinically relevant.</p>	<p>Comments</p> <ul style="list-style-type: none"> <li>▪ limited search strategy, single database, limited search terms, and citation checking, hand-searching of Journals, or contact with authors</li> <li>▪ detailed selection criteria provided</li> <li>▪ selection criteria applied by two reviewers (not stated whether independent)</li> <li>▪ no description of quality assessment or data extraction methods</li> <li>▪ brief introductory section</li> <li>▪ thorough description of statistical analyses</li> <li>▪ quantitative meta-analysis performed, pooled per-patient Se and Sp calculated at various polyp size thresholds, and sROC curves constructed</li> <li>▪ several tables presented sROC plots, diagnostic characteristics of included studies, 2D CTC, 3D CTC, and endoscopic colonoscopy</li> <li>▪ the Discussion considers limitations of statistical pooling methods in meta-analyses, and biases in favour of colonoscopy in study designs.</li> </ul>

Key: CAD: computer aided detection, CRC: colorectal cancer, CTC: computed tomographic colonography, EC = endoscopy colonoscopy, Se: sensitivity, Sp: specificity, sROC: summary receiver operating characteristic, 2-D: 2-dimensional, 3-D: 3-dimensional

## *Summary of review findings*

### Overview

This Technical Brief identified eight eligible secondary research publications, three published in 2005, three in 2006, and two in 2007. Three were largely narrative reviews involving very limited searching and no quantitative analysis (Banerjee and Van Dam 2006; Davila et al. 2006; Nicholson et al. 2005b). The remaining five were systematic reviews including meta-analysis. Four were of high quality including comprehensive searching and appraisal methods (Halligan et al. 2005; Medical Services Advisory Committee (MSAC) 2006; Mulhall et al. 2005; Purkayastha et al. 2007), and the other reported limited searching but employed sophisticated analysis (Rosman and Korsten 2007). Results will be synthesised according to outcome type.

### Safety

Two of the largely narrative reviews mentioned safety data. Nicholson et al (2005b) noted that radiation exposure for CTC is in the realm of that received with barium enema, an accepted screening technique. Banerjee and Van Dam (2006) observed that the radiation dose of 0.44 rem from CTC is similar to that received when undergoing two abdominal radiographs. However they noted that this level could still be of concern if CTC was used as a regular screening tool. The reviewers identified only two cases of perforation from CTC arising in patients with diseased colons due to over-inflation with air, and noted that no cases had been in average-risk populations (to date). Only one of the meta analyses considered safety rigorously, the high quality systematic review of MSAC (2006). It found CTC to be a relatively safe procedure compared to DCBE, and at least as safe as, or safer than, diagnostic colonoscopy. Supporting the narrative reviews, the MSAC reviewers reported that CTC as well as DCBE were said to expose patients to ionizing radiation and to be associated with a very small risk of colonic perforation.

### Patient experiences

All three of the poorer quality reviews considered patient experience outcomes. Nicholson et al (2005b) summarised studies with conflicting findings, with some finding greater preference for CTC, others favouring visual colonoscopy, and some reporting similar acceptance. However the authors also cited several studies suggesting that patients generally find CTC less painful and embarrassing than endoscopy colonoscopy. The reviewers suggested that CTC may become more acceptable once noncathartic preparation methods have been perfected. The largely narrative review of Banerjee and Van Dam (2006) concluded from mixed results that it was unclear whether CTC is preferred to endoscopy colonoscopy, and cited two trials finding similar levels of discomfort expressed for each procedure. Davila et al (2006) cited comparative studies on patient acceptance data which suggested that there was no consistent preference.

Only one of the high quality systematic reviews and meta analyses reported on patient preferences, the MSAC (2006) review. From 11 studies reporting on patient experience and quality of life outcomes, the reviewers concluded that the evidence suggested that CTC may be preferred over colonoscopy. However, comparison of pain and discomfort experienced by patients undergoing both tests showed mixed results with five of eight studies reporting results in favour of CTC, and three in favour of colonoscopy.

### Test accuracy

Considering the three largely narrative reviews first, Nicholson et al's (2005b) industry funded review concluded that CTC performs better in detecting polyps greater than 10mm than those around 5mm in diameter. Banerjee and Van Dam's (2006) review considered evidence graded into quality levels. From the three rated highest, one found high per-patient sensitivity for both CTC and EC, whereas test accuracy for CTC was poorer in the other two trials. The third largely narrative review by Davila et al (2006), which was designed to update a Guideline for the ASGE, described per-polyp sensitivity ranges for polyps of greater to or equal to 6mm ranging 39% - 94%, and specificity ranging 79% - 92%. For larger polyps of greater to or equal to 10mm, per-polyp sensitivity ranging 55% - 100%, and specificity between 94% - 98%. It was noted that there were no studies reporting on efficacy of CTC in reducing CRC incidence or mortality.

Summary statistics were available from five meta-analytic reviews appraised, although the polyp sizes used for reporting varied. Data is summarised in **Table 3**. Note that the reviewers for the MSAC (2006) report warned that as the sensitivities and specificities were statistically different across the

studies considered, pooled results may not provide a valid summary. Median results and/or ranges were therefore described by the MSAC reviewers as the most appropriate summary statistics available.

**Table 3. Summary of per-patient pooled sensitivity and specificity outcomes for CT colonography**

Study	Small polyps		Medium polyps		Large polyps		Cancers	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Halligan et al (2005)			86% (95% CI 75%-93%)#	86% (95% CI 76%-93%)#	93% (95% CI 73%-98%)†	97% (95% CI 95%-99%)†		
Mulhall et al (2005)	0.48 (95% CI 0.25-0.70)*	0.92 (95% CI 0.89-0.96)*	0.70 (95% CI 0.55-0.84)§	0.93 (95% CI 0.91-0.95)§	0.85 (95% CI 0.79-0.91)†	0.97 (95% CI 0.96-0.97)†		
MSAC (2006)*	Range: 14%-57%*	Range: 83%-97%*	Range: 30%-80%§	Range: 93%-99%§	Median 84% Range: 55%-100%†	Median 97% Range: 74%-100%†	97% (95% CI 89-100%)	98% (95% CI 95-99%)
Purkayastha et al (2007)							0.96, 95% CI 0.92-0.99)	1.00 (95% CI 0.99-1.00)
Rosman and Korsten (2007)‡	0.56 (95% CI 0.42-0.70)*	NR	0.63 (95% CI 0.52-0.75)+	NR	0.82, 95% CI 0.76-0.88)Ω	NR		

\* <6mm, § 6-9mm, + 6-10mm, # ≥6mm, † ≥10mm, Ω >10mm, ‡ studies of average risk asymptomatic patients were not considered, NR: not reported

Considering these results and the conclusions of the reviewers, there was general consensus that CTC has reasonable sensitivity and specificity in the detection of large and medium polyps (Halligan et al. 2005; Medical Services Advisory Committee (MSAC) 2006; Rosman and Korsten 2007), but poorly accurate for small lesions (2006). However, whilst specificity has been uniformly high, test sensitivities have varied (based on performance and technical aspects) (Mulhall et al. 2005). The mixed results have also been emphasised by two of the largely narrative reviews (Banerjee and Van Dam 2006; Davila et al. 2006).

In comparisons between CTC and air contrast barium enemas based on two reviews, there appears to be some evidence that CTC is more accurate than air-contrast barium enema for detecting polyps and cancers (Medical Services Advisory Committee (MSAC) 2006; Rosman and Korsten 2007). However conventional colonoscopy appears to be more accurate than CTC for large polyps (Medical Services Advisory Committee (MSAC) 2006; Rosman and Korsten 2007), and particularly for smaller polyps (Rosman and Korsten 2007).

There is a lack of evidence about the accuracy of CTC in average risk populations, and evidence to date may not be applicable to a screening situation (Halligan et al. 2005). There are also concerns about use of CTC for screening in high risk patients such as those with a strong family history given the limitations of CTC in detecting small polyps which may be clinically relevant in such populations (Rosman and Korsten 2007). None of the appraised reviews recommended CTC for generalised screening. It has been suggested that until issues of heterogeneity based on performance and technical variability are resolved, CTC should only be used in research protocols or when other accepted screening methods are not appropriate (Mulhall et al. 2005). More positively, the largely narrative, industry funded review of Nicholson et al (2005b) concluded that CTC shows “promise as a screening tool”.

There appears to be some evidence that CTC is highly accurate in the detection of symptomatic cancer (Halligan et al. 2005; Medical Services Advisory Committee (MSAC) 2006; Purkayastha et al. 2007) and investigation of CTC as a diagnostic tool for cancer has been recommended (Halligan et al. 2005).

#### Factors affecting test accuracy

It is evident from variation observed between studies that CTC is less accurate in some population subgroups or settings (Medical Services Advisory Committee (MSAC) 2006). Various factors have been considered to explain for this heterogeneity. The largely narrative review by Nicholson et al (2005b) noted that what 2D and 3D imaging combination format is optimal, has been under-investigated. The meta-analyses appraised in this Technical Brief considered sensitivity analyses to systematically investigate what factors might improve diagnostic accuracy. There were mixed conclusions from these tests. In considering the detection of cancer in patients presenting with CRC, Purkayastha et al’s (2007) sensitivity analyses revealed that no factors improved diagnostic accuracy from CTC except studies with more than 100 patients. Considering polyp detection more broadly, Halligan et al (2005) suggested that there were too few studies to investigate factors relating to reference standard used or whether individual versus consensus assessment affected results. By contrast, Mulhall et al (2005) reported that whilst patient or scanner characteristics do not fully account for this variability, some factors explain some, including width of collimation (thinner led to higher sensitivity), type of detector (multiple scanners more sensitive than single detectors), and mode of imaging (“fly through” more sensitive, though based on only two studies using this method). More recently, Rosman and Korsten (2007) concluded that there were no significant differences in the diagnostic characteristics of 2-dimensional versus 3-dimensional software algorithms (“fly-through”) for initial analysis of the CT images. In another recent meta analysis, MSAC’s (2006) reviewers concluded that the extent to which patient characteristics, prevalence of disease, CTC techniques, the experience of those performing and interpreting the tests or other factors may influence CTC performance has not yet been clearly defined. However, they suggest that differences in study quality (low to high), prevalence of lesions, the type of techniques used, and radiologist experience may explain some of the variation observed.

### **Conclusions**

Eight reviews were identified as eligible for inclusion in the Technical Brief published since 2005, five of which were published since 2006. Three largely non-systematic reviews (Banerjee and Van Dam 2006; Nicholson et al. 2005b; van Dam et al. 2004) and five meta-analyses were identified as eligible for inclusion and appraisal (Halligan et al. 2005; Medical Services Advisory Committee (MSAC) 2007, Mulhall et al. 2005; Purkayastha et al. 2007; Rosman and Korsten 2007):

Conclusions based on the results from the review are summarised below:

1. CT colonography is a relatively safe procedure compared to DCBE, and at least as safe as, or safer than, diagnostic colonoscopy. Ionizing radiation exposure is relatively low but a cumulative risk for regular screening. There is a very small risk of colonic perforation.
2. Generally there have been inconsistent findings regarding preferences for and experiences from CTC versus colonography. However one meta-analysis of 11 studies of increased risk or symptomatic patients concluded that CTC may be preferred over colonoscopy, and that the majority of studies have reported results favouring CTC over colonoscopy with respect to pain and discomfort.
3. CT colonography has reasonable test sensitivity and specificity in the detection of large and medium polyps, but is poorly accurate for small lesions. Whilst specificity has been consistently high, test sensitivities have varied and pooled statistics need to be considered with caution. There is some evidence that CTC is highly accurate in the detection of symptomatic cancer.
4. There is some evidence that CTC is more accurate than air-contrast barium enema for detecting polyps and cancers in increased risk or symptomatic populations. However, conventional colonoscopy appears to be more accurate than CTC for large polyps, and particularly for smaller polyps.
5. Limitations of the current evidence base include that there is a lack of evidence about the accuracy of CTC for primary screening in average risk populations. There is also a need for greater investigation of the reasons for such wide variations in test accuracy achieved in different trials with respect to patient and scanner characteristics. Likely sources of variation relate to prevalence of disease, CTC techniques (such as width of collimation, type of detector, and mode of imaging), and radiologist experience. The definition of what constitutes a clinically important polyp in size and morphology also requires evidence-based elucidation. Whilst the methodological quality of studies is improving, comparisons between studies would be facilitated by more consistency in reporting and more appropriate statistical analysis and data synthesis techniques.
6. There have been no studies reporting on overall health outcomes of CTC including efficacy in reducing CRC incidence or mortality.
7. Based on the evidence and conclusions considered in this review CTC is not currently recommended for generalised screening.

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## APPENDIX 1: SEARCH STRATEGY

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### *Medline/Medline Pending/Cochrane Central Register of Controlled Trials*

- 1 (virtual adj colonoscopy).mp.
- 2 (virtual adj colonography).mp.
- 3 (ct adj (colonograph\$ or colonoscop\$)).mp.
- 4 Colonography, Computed Tomographic/
- 5 exp Colonoscopy/
- 6 ct.mp.
- 7 5 and 6
- 8 or 1-4,7
- 9 limit 8 to english
- 10 animal/
- 11 animal/ and human/
- 12 10 not 11
- 13 9 not 12
- 14 limit 13 to yr=2005-2007
- 15 200406\$.em.
- 16 200407\$.em.
- 17 200408\$.em.
- 18 200409\$.em.
- 19 200410\$.em.
- 20 200411\$.em.
- 21 200412\$.em.
- 22 or/15-21
- 23 13 and 22
- 24 14 or 23

### *Embase*

- 1 (virtual adj colonoscopy).mp.
- 2 (virtual adj colonography).mp.
- 3 Computed Tomographic Colonography/
- 4 (ct adj (colonograph\$ or colonosc\$)).mp.
- 5 colonoscopy/
- 6 ct.mp.
- 7 5 and 6
- 8 or/1-4,7
- 9 limit 8 to english
- 10 limit 9 to yr=2005-2007
- 11 animal/
- 12 human/ and animal/
- 13 11 not 12
- 14 10 not 13
- 15 letter.pt.
- 16 14 not 15
- 17 200406\$.em.
- 18 200407\$.em.
- 19 200408\$.em.
- 20 200409\$.em.
- 21 200410\$.em.
- 22 200411\$.em.
- 23 200412\$.em.
- 24 or/23-29
- 25 9 and 30
- 26 25 not (13 or 15)

***Current Contents***

1. Virtual SAME colonoscopy
2. Virtual SAME colonography
3. ((colonograph\* OR colonoscop\*) SAME tomograph\* SAME comput\*)
4. CT SAME (colonoscop\* OR colonograph\*)
5. #1 OR #2 OR #3 OR #4

***PubMed (last 60 days)***

1. Virtual colonoscopy
2. Virtual colonography
3. CT colonoscopy
4. CT colonography
5. Colonography, computed tomographic[MESH]
6. #1 OR #2 OR #3 OR #4 OR #5

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*Primary study*

**APPENDIX 3: APPRAISED RETRIEVED PAPERS**

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