Computed tomography colonography for the diagnosis or exclusion of colorectal neoplasia

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The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee that has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Purpose of application

This review addresses the available evidence to support an application requesting MBS funding of computed tomography colonography (CTC) for the diagnosis or exclusion of colorectal neoplasia in patients with a history of incomplete colonoscopy, contraindications to colonoscopy or limited access to colonoscopy. The application was received from the Abdominal Radiology Group of Australia and New Zealand (ARGANZ) by the Department of Health in December 2011.

Currently, CTC is MBS listed under items 56552 and 56554 and is restricted to patients who have had an incomplete colonoscopy in the preceding 3 months (item 56552) or who fit a narrow list of contraindications as specified by item 56554. The application from ARGANZ requested (a) removal of the 3-month restriction rule; (b) removal of specific contraindications such that patients with *any* contraindication to colonoscopy can access CTC through the MBS; and (c) a new item number to provide publicly funded CTC for patients with limited access to colonoscopy.

A team from Adelaide Health Technology Assessment (AHTA), University of Adelaide, was contracted to conduct a systematic review of the literature and an economic evaluation of CTC. A decision analytic protocol (DAP) was developed before commencement of the assessment and was approved by the Protocol Advisory Sub-Committee (PASC) of the Medical Services Advisory Committee (MSAC).

Description of computed tomography colonography

Computed tomography colonography is a minimally invasive investigative procedure that is conducted in radiology rooms, either in a hospital or private practice, using a multi-detector CT scanner with a minimum of eight rows (RANZCR 2012). CTC requires distension of the bowel by insufflation with air or CO_2 that is conducted through a thin rectal catheter. The procedure does not require an endoscope, and the patient is not anaesthetised and does not generally require pain relief. The procedure requires patients to ingest a laxative solution and follow a clear liquid diet in the 24 hours prior to CTC. Alternatively, faecal tagging, an increasingly popular technique, negates the need for laxation. Tagging requires patients to add a barium or iodinated oral contrast medium to their meals for 48 hours prior to the scan (NICE 2005), but also necessitates 'additional interpretive experience … and additional resources' in terms of cost and 'complexity of patient preparation' (Burling 2010). In some circumstances intravenous (IV) contrast and/or anti-spasmodics may be required in the provision of CTC. No in-vitro diagnostic testing is required in addition to the procedure.

Comparators for CTC

For patients who are: (a) clinically unsuitable for colonoscopy, as identified by incomplete or technically difficult colonoscopy, or (b) contraindicated to colonoscopy, the appropriate comparator is 'double contrast barium enema' (DCBE). Barium enema is the diagnostic method currently listed on the MBS for patients with symptoms indicative of, or at high risk of, colorectal cancer (CRC) who are contraindicated to colonoscopy but who do not meet eligibility for CTC under current funding arrangements. DCBE is not a satisfactory technique for visualising the rectum or rectosigmoid region, and consequently sigmoidoscopy or colonoscopy are recommended for these investigations.

For patients with limited access to colonoscopy, the nominated comparators are DCBE and 'delayed colonoscopy', although it is unlikely that these patients would be offered DCBE as access to this procedure is also limited. As this CTC indication relates to access rather than the most clinically appropriate service, delayed colonoscopy is intended to denote 'colonoscopy with date determined by clinician according to urgency'.

Resources typically required to deliver DCBE are a consultation with a specialist radiologist, a radiology facility (public or private) in which to provide work-up including a barium meal, imaging and post-procedural support, and follow-up with a gastroenterologist or other specialist. In Australia there are private radiology providers in addition to radiology facilities located within major hospitals. The relevant specialists provide consultations through both private practice and the publically funded health system.

If polyps or CRCs are identified using either of the DCBE or CTC techniques, management (i.e. removal or biopsy) with colonoscopy or surgery is required (Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005).

Clinical need

CTC is a *replacement* for DCBE in the diagnosis or exclusion of colorectal neoplasia in symptomatic patients or asymptomatic patients with a high risk of colorectal neoplasia. For those in whom access to colonoscopy is difficult, CTC with/without subsequent colonoscopy is a *replacement* for delayed colonoscopy; that is, CTC (and DCBE) may be seen as a triage tool for further investigations/interventions. Where patient access to colonoscopy is difficult, it is expected that a positive finding on CTC would result in patients being given faster access to colonoscopy than they would have without having had the CTC.

Should the application for broadened eligibility for CTC services be successful, it is envisaged that uptake would slowly increase, as not all radiology services are equipped with CT scanners and demand for those available may be high. It is expected that there would be a consequent slow decrease in DCBE services until the procedure becomes obsolete. Unless

recommended by MSAC, there would be no limitation on the number of services provided to each patient, but the frequency would differ according to clinical context. Patients who undergo regular surveillance for CRC would be likely to require CTC every 1–3 years, provided they fulfil the MBS requirements. CTC could be performed as a once-off procedure in some patients, such as the symptomatic elderly, although a repeat procedure within a short interval may be required when the outcome of the first procedure is not definitive. As colonoscopy is considered the gold standard for diagnosis of CRC, CTC is not being considered as a replacement for colonoscopy in patients who are clinically able to tolerate colonoscopy, and who are able to access it within the time recommended by their clinician.

Comparative safety

Two articles reporting on one randomised controlled trial (RCT) (Halligan et al. 2013; von Wagner et al. 2011) compared CTC versus DCBE with respect to primary and secondary safety outcomes.

No safety data were identified comparing CTC with delayed colonoscopy.

Primary safety outcomes

Halligan and colleagues reported that there was no difference in serious adverse events (requiring hospitalisation) between DCBE and CTC. In both groups adverse events were rare: four events versus one event in the DCBE and CTC groups, respectively (RR=1.00, 95%CI 0.99, 1.00). Similarly, any deaths reported were not considered attributable to the imaging received.

Secondary safety outcomes

Von Wagner et al. (2011) reported that DCBE was associated with significantly higher rates of symptoms of abdominal pain/cramp, nausea/vomiting, wind, bottom soreness and soiling than CTC ($p<0.05$).

Radiation exposure

There were no studies identified that measured radiation exposure from CTC in the populations considered for this review. A study that reported on the radiation risk of CTC *screening* estimated that a single CTC screen (64-slice scanner) at age 60 years would result in a lifetime risk of radiation-related cancer of 0.05%, a risk that decreases with decreasing life expectancy (Berrington de Gonzalez, Kim & Yee 2010). Other authors compared radiation doses required for imaging using CTC or DCBE in patients with CRC, and found that the dose required for DCBE was almost double that for CTC (4.12 ± 0.17 mSv vs 2.17 ± 12 mSv, respectively; $p<0.001$) (Neri et al. 2010).

Overall conclusion with respect to comparative safety

Based on the limited available evidence, CTC is at least as safe as DCBE, with equivalent rates of serious adverse events and fewer minor adverse events. Although there is a radiation risk associated with CTC, it is lower than that associated with DCBE.

No evidence on the safety of CTC versus delayed colonoscopy could be made although, as colonoscopy is a more invasive procedure than CTC, it may be assumed that CTC has superior safety outcomes.

Patient acceptability

Five studies investigated preferences (overall and based on quality-of-life domains) among patients randomly assigned to receive either DCBE or CTC (level II interventional evidence), and two studies assessed preferences among patients who underwent these procedures in prospectively followed cohorts (level III-2 interventional evidence) (Bosworth et al. 2006; Gluecker et al. 2003; Kataria 2011; Sofic et al. 2010; Taylor et al. 2005; Taylor et al. 2003; von Wagner et al. 2011).

Self-reported physical discomfort, assessed in all seven studies, favoured CTC over DCBE in all but one study (Kataria 2011), while self-reported worry responses indicated that CTC was favoured over DCBE in two studies (Bosworth et al. 2006; Taylor et al. 2003). Patients were most satisfied with CTC in four studies (Bosworth et al. 2006; Taylor et al. 2005; Taylor et al. 2003; von Wagner et al. 2011). The results suggest that CTC is better tolerated (less physical discomfort and cause for worry) than DCBE. Overall findings indicated that CTC was more acceptable and the procedure most preferred (Bosworth et al. 2006; Gluecker et al. 2003; Taylor et al. 2005; Taylor et al. 2003).

No studies were identified that assessed the comparison between CTC and *delayed* colonoscopy due to limited access to colonoscopy. However, one systematic review of 23 studies (level I interventional evidence) that compared patient acceptability between CTC and colonoscopy without a specified delay period was included (Lin et al. 2012). This review reported that CTC was preferred over colonoscopy in the majority (16/23) of studies (5,616 patients). Only a small number (3/23) of studies reported a statistically significant preference for colonoscopy over CTC, with preference for CTC being more likely in populations with a low risk of requiring a subsequent colonoscopy (i.e. screening populations rather than diagnostic populations).

Comparative effectiveness

Unlike CTC, DCBE cannot provide information about extracolonic pathology, and therefore evidence comparing health outcomes resulting from extracolonic findings between the two methods is not available.

Direct evidence

One RCT (level II intervention evidence) reported that all-cause mortality was the same in the 4 years after patients received either a CTC or a DCBE procedure (RR=1.00, 95%CI 0.97, 1.03, p=0.94); Halligan et al. (2013).

No evidence comparing the effectiveness of CTC with delayed colonoscopy was identified.

Linked evidence

Diagnostic accuracy

There were no studies that assessed the *comparative* accuracy of CTC and DCBE in those who either failed a previous colonoscopy or were contraindicated for colonoscopy. However, when the population was broadened to include patients that were at high risk or symptomatic for CRC (without necessarily having contraindications to colonoscopy), five studies were identified to inform the analysis (Halligan et al. 2013; Johnson et al. 2004; Rockey et al. 2005; Sofic et al. 2010; Thomas, Atchley & Higginson 2009). These studies indicated that CTC was more sensitive and slightly less specific than DCBE.

A further five studies were identified that provided information on the accuracy of CTC alone within the target populations—i.e. cross-classified against a clinical reference standard, but there was no comparison with DCBE—(Duff et al. 2006; Kealey et al. 2004; Ng et al. 2008; Robinson, Burnett & Nicholson 2002; Saunders et al. 2013). The accuracy of CTC at identifying CRC lesions in people who have either failed colonoscopy or are contraindicated for colonoscopy was similar to that observed in the broader populations specified above (i.e. at high risk or symptomatic for CRC but able to have colonoscopy). This suggests that the better sensitivity and similar, or slightly poorer, specificity of CRC relative to DCBE is likely to be the same in patients who have failed or are contraindicated to colonoscopy. The high negative predictive value associated with CTC (96–100%) also suggests that, for the majority of patients undergoing CTC, a negative result will accurately indicate that the presence of any lesions can be ruled out. This means that these patients are able to avoid having a subsequent, more invasive, colonoscopy. It was hypothesised that the higher rate of patients testing false negative from DCBE will not receive treatment as early as if they were detected by CTC. This was investigated when assessing the impact of test results on patient management.

Impact of test results on clinical management

The impact of diagnostic outcomes on patient management was investigated in one study that compared the confidence of radiologists in excluding clinically significant colonic lesions using CTC and DCBE (Taylor et al. 2006; level III-2 intervention evidence). The study found no difference between CTC and DCBE in terms of radiologist confidence in excluding clinically significant polyps in the sigmoid, rectum and transverse colon. However, for the descending and ascending colon and caecum, the confidence regarding exclusions was significantly higher with CTC. Also, radiologists excluded lesions >6 mm in more segments with CTC than with DCBE (382 vs 314 of 444 segments, $p<0.001$).

In this same study there was a comparison of CTC and DCBE results with colonoscopy (Taylor et al. 2006). Consistent with the test accuracy results, there was a tendency for radiologists to report more false positive diagnoses with CTC than with DCBE. However, the trade-off was that, for DCBE, all smaller polyps (1–5 mm) went undetected, compared with CTC. This means that treatment for small polyps would be instituted later with DCBE than with CTC.

No studies were identified that compared CTC and delayed colonoscopy and reported on the impact of these investigations on patient management. It is assumed that patients who receive CTC due to a lack of access to colonoscopy would receive earlier diagnosis and treatment than if they had a delayed colonoscopy. Thus, similar to the findings when comparing CTC and DCBE, the expected impact on patient management is the ability to commence treatment earlier with the use of CTC.

Impact of change in clinical management on patient outcomes

Evidence of the impact on patient outcomes of changes in clinical management was identified in one systematic review of 17 studies (level I intervention evidence), presented in two publications (Ramos et al. 2007; Ramos et al. 2008). The review assessed whether diagnostic and/or therapeutic delay (i.e. early versus late treatment) affected survival rate, or stage of disease at the time of diagnosis/treatment. Of the 17 studies included in the review, the authors included 8 in a meta-analysis, and found that longer delays were associated with *better* survival (n=3,680; RR=0.92, 95%CI 0.87, 0.97). These data were not stratified according to the type or severity of presenting symptoms, but it is hypothesised that if they were, results would favour shorter waiting periods. There was no association between delay and disease stage for patients with CRC. These results suggest that CRC patients are being triaged appropriately, i.e. those with more-severe symptoms receive a diagnosis or treatment more promptly than those with less-severe symptoms.

While evidence of a clinical benefit from reducing waiting times to CRC diagnosis and treatment in the populations relevant to this assessment is lacking, it is known that CRC-

specific survival is stage dependent (National Cancer Institute 2013). Earlier diagnosis is assumed to lead to earlier intervention and better outcomes. Within the general population the benefit of early versus late treatment has been evaluated in the NHMRC clinical practice guidelines for CRC (Australian Cancer Network 2005). Based on evidence from RCTs, the guidelines report that screening for faecal occult blood in asymptomatic patients reduces CRC-specific mortality by 15–33% and the incidence of CRC by 20%. Other trials have shown a survival benefit among individuals at elevated risk of CRC due to a family history of adenomatous polyposis (Australian Cancer Network 2005).

Overall conclusion with respect to comparative effectiveness

The 4-year survival rate for patients receiving CTC is the same as for those receiving DCBE. It is unknown if there is any survival benefit associated with CTC compared with delayed colonoscopy.

CTC is more sensitive than DCBE. Thus, a patient's CRC is more likely to be identified using CTC than DCBE, and when a patient is ruled out by CTC the radiologist has greater confidence that there is truly no lesion than when a patient is ruled out by DCBE. As a consequence, CTC is a more accurate way of ruling out patients who do not need to proceed to further investigations or interventions (e.g. colonoscopy); it results in fewer false negative diagnoses than DCBE. Patients who receive a false negative result from DCBE would have a delayed diagnosis, compared with if they had been investigated with CTC. Results also indicate that CTC can be slightly less specific than DCBE; that is, of those who are truly negative, slightly fewer are ruled out by CTC than DCBE. Therefore, more patients are referred for further unnecessary investigations after CTC than would be the case for DCBE (i.e. more false positive diagnoses).

Survival outcomes for CRC are highly stage dependent. Although this finding may be partially due to lead-time bias, evidence from a *screening* population suggests that earlier diagnosis is associated with improved health outcomes. Findings from a *symptomatic* population suggest the reverse (i.e. better survival with shorter waiting periods), but there is a high likelihood that this result is confounded because of the lack of stratification by disease stage and severity.

Economic evaluation

To address the question of cost-effectiveness, two separate economic evaluations are required: one for symptomatic or high-risk patients who are either clinically unsuitable or have a contraindication to colonoscopy, for whom DCBE is the appropriate comparator; and one for symptomatic or high-risk patients who have limited access to colonoscopy such as may cause delay in diagnosis, for whom delayed colonoscopy is the appropriate comparator.

For the latter target population there was no evidence available to demonstrate or refute whether prompt access to CTC will result in an improvement in the health of patients compared with receiving a delayed colonoscopy. Given the absence of evidence on the effectiveness and safety of CTC compared with delayed colonoscopy, the lack of reliable data on the clinical consequences of a delay in diagnosis in symptomatic patients, and the considerable potential for use of this item outside the requested MBS listing, it was considered that quantifying health outcomes and costs in an economic evaluation would be speculative and potentially misleading. An economic evaluation has not been presented for this target population.

The cost-effectiveness of CTC compared with DCBE has been estimated for those patients who are symptomatic or at high risk of CRC and have: a) had an incomplete or technically difficult colonoscopy, or b) a contraindication for colonoscopy. As data located during the review failed to show a difference between the two testing strategies in terms of 4-year survival rates, it was considered that the use of a modelled evaluation estimating the cost–utility of CTC compared with DCBE, over the lifetime of a cohort, would result in an unacceptable degree of uncertainty in the modelled outcome. However, while there is no apparent difference in terms of survival rate in patients receiving either CTC or DCBE, the evidence suggests that the difference in the accuracy of the two tests is likely to change patient management.

Therefore, a simple decision-analytic model was used to estimate the incremental cost-effectiveness of CTC compared with DCBE for the exclusion or diagnosis of colorectal neoplasia in symptomatic and high-risk patients, in terms of the 'incremental cost per additional CRC diagnosed or large polyp identified'. The model was developed from a study-based evaluation using the outcomes in the RCT reported in Halligan et al. (2013). In both the study-based evaluation and the model, symptomatic patients were assigned to an initial investigation using either the proposed intervention (CTC) or the comparator (DCBE). Unless diagnosed with inoperable CRC, all patients who tested positive for any lesion were referred for further colonic investigation (mainly colonoscopy or surgery) to confirm diagnosis and/or subsequent treatment. At the discretion of the clinician, patients for whom no lesions were detected could also be referred for further colonic investigation.

The economic analysis estimates the costs and diagnostic outcomes associated with CTC and DCBE over the complete diagnostic process, including follow-up confirmatory colonoscopy and polypectomy, if indicated; however, costs of subsequent treatment, and the impact on survival, were not considered in the economic evaluation. In addition, the difference in costs associated with the re-assessment and treatment of people receiving a false negative test result from the initial diagnostic process is not included; this is a conservative approach, favouring DCBE over CTC. Given the pragmatic design of this trial,

the clinical outcomes reflect both the accuracy of the two investigative procedures as well as clinical decision-making over the diagnostic process.

The model was constructed in such a way that the proportions of true positive, false positive, true negative and false negative outcomes for each testing strategy were derived from the sensitivity and specificity of each test and the prevalence of CRC in the relevant population.

In the base-case scenario the majority of parameters determining the comparative effectiveness of the two investigative procedures, including test accuracy data, were sourced from the trial, with adjustment. The prevalence of colorectal neoplasia was assumed to be that reported in Australian National Bowel Cancer Screening Program (NBCSP) patients who had a positive screening faecal occult blood test (FOBT), as reported for 2011–12 in the NBCSP monitoring report (AIHW 2013). Costs were analysed from the perspective of the Australian healthcare sector.

The cost-effectiveness of CTC compared with DCBE improves as the prevalence of colorectal neoplasia increases. In the base-case scenario, in which the prevalence of CRC and large polyps was estimated at 3.1% and 6.7%, respectively, the average cost per patient assigned to CTC was $752, compared with $254 for patients assigned to DCBE. The incremental cost per additional CRC or large polyp diagnosed for CTC compared with DCBE was $19,380. CTC was relatively less cost-effective in patients presenting with more general clinical symptoms. The incremental cost-effectiveness ratio (ICER) increased to $26,260/additional CRC or large polyp diagnosed as a result of the lower prevalence of large polyps in this patient group (3.6%); however, the reported prevalence of colorectal neoplasia in this population is likely to be an underestimate.

The difference in the sensitivity of the two investigative procedures is the key determinant of the comparative effectiveness of the two testing strategies; the considerable variation in the reported sensitivity of both CTC and DCBE is a major source of uncertainty in the economic analysis. The outcome of the evaluation is relatively insensitive to changes in the costs associated with the two procedures.

Key uncertainties

Given the variation in the clinical evidence, the main source of uncertainty in the economic evaluation is the comparative sensitivities of CTC and DCBE. In the base-case scenario the sensitivities of CTC and DCBE for 'all lesions' were 0.97 and 0.66, respectively, while the corresponding sensitivities for CRC were 0.93 and 0.80, respectively. When the 'all lesion' sensitivities were reduced to 0.59 for CTC and 0.48 for DCBE, as reported in Rockey et al. (2005), the ICER increased to $48,230 per additional CRC or large polyp.

A further uncertainty is whether the 4-year follow-up for deaths, as reported in Halligan et al. (2013), was sufficient to accurately capture CRC survival rates and, subsequently, whether there was any true difference in survival between the two investigative procedures. As a result, it is possible that there are survival benefits resulting from the lower rate of false negative outcomes with CTC, compared with DCBE, that are not captured in the economic analysis. This is discussed further in the main section of the report.

Overall conclusion with respect to comparative cost-effectiveness

Due to the introduction of the NBCSP in Australia, patients who have a positive FOBT result are likely to represent an increasing proportion of patients presenting with symptoms suggestive of CRC that requires further investigation. In this population the estimated incremental cost per additional CRC or large polyp diagnosed for CTC compared with DCBE is $19,380. In the population of patients presenting with other clinical symptoms and with some degree of contraindication for colonoscopy, CTC is relatively less cost-effective, with an ICER of $26,258 per additional CRC or large polyp diagnosed; this is mainly due to a lower prevalence of large polyps in this population.

The cost-effectiveness of CTC compared with DCBE improves as the prevalence of CRC in the target population increases. The difference in sensitivity of the two procedures is the key determinant of their comparative effectiveness, and the main source of uncertainty in the economic analysis.

Financial/budgetary impacts

Patients with limited access to colonoscopy

Due to the limitations of the data available for the proposed new MBS item, it is not possible to provide a robust assessment of the potential financial implications. However, the potential cost to the MBS has been estimated using an epidemiological approach, which assumes that the existing population with an inability to access colonoscopy (number of services per 1,000) can be estimated using the difference in the rate of colonoscopy and CTC services in regional and remote areas of Australia compared with the major cities. If the proposed new MBS listing is approved, these patients could potentially be referred for CTC. The results are summarised in Table 1.

Table 1 Summary of the estimated potential number of additional CTC services and cost to the MBS and patients

	2015	2016	2017	2018	2019
Number of additional CTC services [a]	18,316	18,559	18,806	19,055	19,308
Cost in-hospital	$1,318,467	$1,335,957	$1,353,686	$1,371,658	$1,389,876
Cost out-of-hospital	$8,085,534	$8,192,790	$8,301,515	$8,411,728	$8,523,451

	2015	2016	2017	2018	2019
Total cost to MBS [b]	**$9,404,001**	**$9,528,748**	**$9,655,201**	**$9,783,386**	**$9,913,328**
Patient co-payments	$1,585,773	$1,606,809	$1,628,132	$1,649,748	$1,671,660

[a] Difference between regional/remote and metropolitan CTC services

[b] Assumes that 16% of services are performed in-hospital and 84% are out-of-hospital

It is estimated that the cost to the MBS resulting from the increased use of CTC services may be in the order of $10 million per year. Due to the limited data available on the number of patients who would be eligible for this proposed MBS item, these estimates are uncertain and should be interpreted with caution. In addition, due to the failure to clearly define what constitutes a 'limited access to colonoscopy such as to cause delay in diagnosis', there is considerable potential for use of this item outside the intended purpose.

Patients unsuitable/contraindicated to colonoscopy

The financial impact of a CTC item for patients unsuited or contraindicated to colonoscopy has been estimated using a market share approach. As CTC is more sensitive and more acceptable to patients than DCBE, if an extended listing for CTC is approved, it is assumed that CTC will completely replace DCBE for the exclusion or diagnosis of colorectal cancer in patients who are considered unsuitable for colonoscopy. The number of DCBE services has steadily decreased over the past 6 years and in the tabulated analysis it is assumed that this trend would continue. The results are summarised in Table 2.

Table 2 Summary of the estimated financial impacts on the MBS and the patients / private health insurers of the proposed extension of the CTC listing

	2014–15	2015–16	2016–17	2017–18	2018–19
Total number of services per year [a]	4,893	4,351	3,866	3,427	3,026
Cost to MBS					
Excluding safety net impacts:					
Cost of CTC	$2,512,266	$2,233,790	$1,984,685	$1,759,342	$1,553,620
Less cost of substituted DCBE	–$556,643	–$494,941	–$439,747	–$389,818	–$344,236
Net cost to MBS	$1,955,623	$1,738,849	$1,544,938	$1,369,524	$1,209,384
Including safety net impacts:					
Cost of CTC	$2,667,945	$2,372,213	$2,107,671	$1,868,364	$1,649,894
Less cost of substituted DCBE	–$604,324	–$537,337	–$477,415	–$423,209	–$373,722
Net cost to MBS	$2,063,621	$1,834,876	$1,630,256	$1,445,155	$1,276,172
Cost to patients / health insurers					
Cost of CTC	$295,140	$262,425	$233,160	$206,687	$182,519
Less cost of substituted DCBE	–$174,776	–$155,403	–$138,073	–$122,396	–$108,084
Net cost to patients / health insurers	$120,364	$107,022	$95,088	$84,291	$74,435

[a] Projected value based on existing Medicare data reports for DCBE over the past 6 financial years, showing annual decline in use of services

The main source of uncertainty is the number of additional CTC services that are likely to be performed *under the proposed extended eligibility criteria for CTC*. This demand is not able to be captured in existing market data. If it is assumed that CTC replaces all current use of DCBE (which in 2012–13 was approximately 6,000 services per year) and that, conversely to the trend for DCBE, the level of demand for CTC remains constant, the estimated net cost to the MBS, including safety net payments, would be approximately $2,550,000 per year.

Other relevant considerations

Repeat colonoscopy procedures

One of the populations under investigation in this review is that of patients who have undergone an incomplete colonoscopy. In a large proportion of incomplete colonoscopy cases it may be appropriate to repeat the procedure rather than request a radiological investigation. Colonoscopy is considered the gold standard procedure for CRC detection and has the added benefit of incorporating treatment capability, if needed, during the procedure. Potentially, the need for additional investigations could be reduced if colonoscopy was performed more effectively.

Studies reveal that a repeat colonoscopy in those who have undergone a previous incomplete procedure can be successfully completed at least 95% of the time. Reasons reported for not completing a colonoscopy are an extremely redundant colon, large colonic hernia, obstructing malignant mass, obstructing diverticular stricture and poor bowel preparation. In the vast majority of these cases a second colonoscopy can be completed with care and attention to the problems and modifiable factors, and occasionally by using additional tools such as straighteners, paediatric scopes and more varied positioning (Brahmania et al. 2012; Kao et al. 2010; Rex, Chen & Overhiser 2007). The evidence provided by these studies suggests that patients who have undergone an incomplete colonoscopy should have a clear and justifiable medical reason for referral to a CTC rather than a second colonoscopy.

Consumer impact statement

Consumer agreement on the value of the proposed intervention is broadly reflected by Cancer Voices Australia (CVA) in response to public consultation during the development of the final DAP, which was released for public comment on 2 October and closed for comments on 9 November. The reasons provided for supporting CTC for the proposed indications are summarised below:

- CTC may reduce a delay in diagnosis, as it is able to be performed by a specialty other than gastroenterologists and surgeons, who are responsible for performing colonoscopies.

- CTC is a quicker procedure compared with colonoscopy or DCBE, and patients may go home immediately. Unlike colonoscopy, there is no pre-anaesthesia appointment, post-procedural surveillance, or the need for a carer to monitor the patient for the next 12 hours in case of unexpected haemorrhage or collapse.

- CTC is also more acceptable to alternative CRC diagnostics due to the ability to use faecal tagging rather than bowel cleansing. This is an important factor for frail elderly people who may become dehydrated or weak from lack of food; may fall; and may have accidents once bowel cleansing starts, as a result of weak anal sphincters.

- Maintaining anticoagulant therapy reduces the risk of an interval stroke or other issues associated with foregoing anticoagulation medication.

- The majority of patients are found not to have CRC, and therefore triaging with CTC would allow many patients to avoid undergoing an invasive colonoscopy.

CVA also noted potential disadvantages from the use of CTC:

- If the CTC finds a polyp or cancer, patients are required to undergo an additional procedure (compared with if they underwent a colonoscopy initially).

- There is concern that radiologists in more isolated locations may not have the throughput for optimal skill in CTC interpretation.

Glossary and abbreviations

ABS	Australian Bureau of Statistics
AHTA	Adelaide Health Technology Assessment
AIHW	Australian Institute of Health and Welfare
AR-DRG	Australian Refined Diagnosis Related Groups
ARGANZ	Abdominal Radiology Group of Australia and New Zealand
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
ASGC	Australian Standard Geographical Classification
CI	confidence interval
CRC	colorectal cancer
CTC	computed tomography colonography
DAP	decision analytic protocol
DCBE	double contrast barium enema
FOBT	faecal occult blood test
HESP	Health Expert Standing Panel
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
MBS	Medicare Benefits Schedule
MDCT	multi-detector computed tomography
MSAC	Medical Services Advisory Committee
NBCSP	National Bowel Cancer Screening Program
NHMRC	National Health and Medical Research Council
PASC	Protocol Advisory Sub-Committee
RANZCR	Royal Australian and New Zealand College of Radiologists
RCT	randomised controlled trial
SIGGAR	Special Interest Group for Gastrointestinal and Abdominal Radiology

TGA	Therapeutic Goods Administration

Introduction

A rigorous assessment of evidence is the basis for decision-making when funding for medical services is sought under the Medicare Benefits Schedule (MBS).

The Medical Services Advisory Committee (MSAC) evaluates these new and existing health technologies and procedures, in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, informed by reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC is a multi-disciplinary expert body, comprising members drawn from disciplines including diagnostic imaging, pathology, surgery, internal medicine, general practice, clinical epidemiology, health economics, consumer health and health administration.

A team from Adelaide Health Technology Assessment (AHTA), School of Population Health, University of Adelaide, as part of its contract with the Department of Health, was commissioned to conduct a systematic review and economic evaluation of the use of computed tomography colonography (CTC), in order to inform MSAC's decision-making.

A decision analytic protocol (DAP) was developed prior to commencement of the assessment and was approved by the Protocol Advisory Sub-Committee (PASC) of MSAC. The purpose of a DAP is to describe in detail a limited set of decision option(s) associated with the possible public funding of a proposed medical service. A DAP also describes current Australian clinical practice regarding the diagnosis and treatment of the condition being targeted by the proposed medical service, along with likely future practice if the proposed medical service is publicly funded. It also describes all potentially affected healthcare resources. The guiding framework of the DAP was used throughout this assessment. Input and advice from members of a Health Expert Standing Panel (HESP; see Appendix B) was also sought.

Public comment was sought during the development of the final DAP (no. 1269). The DAP was released for public comment on 2 October 2012 and closed for comments on 9 November 2012. This public comment was incorporated into the final DAP subsequent to PASC deliberation at a meeting on 12–13 December 2012.

This report is an assessment of the current evidence available for use of CTC in the diagnosis or exclusion of colorectal cancer (CRC) in people who are symptomatic or at high risk of the disease.

Rationale for assessment

MBS items 56552 and 56554 were added to the schedule on 1 July 2007 following the completion of a previous review on CTC on behalf of MSAC, which was published in 2006. Under current listing arrangements MBS item 56552 stipulates that an incomplete colonoscopy must have occurred not more than 3 months prior to CTC, with the date of the incomplete colonoscopy set out on the scan request. Item 56554 limits contraindications specifically to suspected perforation of the colon, and complete or high-grade obstruction that will not allow passage of the endoscope.

This review is the result of an application by the Abdominal Radiology Group of Australia and New Zealand (ARGANZ) requesting an extension of the indications for the MBS listing of CTC.

The available evidence has been reviewed on CTC for the diagnosis or exclusion of colorectal neoplasia[1] in order to inform MSAC's decision as to whether it is appropriate to make alterations to the current listing of CTC to allow access to the procedure for people who:

- are symptomatic or at high risk of CRC (see Table 3) and have had an incomplete *or technically difficult colonoscopy at any time* (item 56552, see Table 4);
- are symptomatic or at high risk of CRC but have a contraindication to colonoscopy—additional contraindications to those currently under item 56554 (see Table 5) are given in Table 6, although potential contraindications are not necessarily limited to these; or
- are symptomatic for CRC and require exclusion or diagnosis of CRC but have limited access to colonoscopy such as to delay diagnosis[2].

Specifically, the assessment aims to test whether it is warranted to:

1. remove the 3-month restriction rule for item 56552;
2. extend/amend the eligibility criteria for item 56554[3]; and
3. create a new item to provide CTC for patients with limited access to colonoscopy.

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[1] Neoplasia refers to the growth of cells outside of normal physiological control. A neoplasm may or may not be/become cancer. Cancer implies malignancy, whereas neoplasms can be classified as either benign or malignant (see http://library.med.utah.edu/WebPath/NEOHTML/NEOPL102.html). With respect to colorectal neoplasms, methods of detection and removal unequivocally aim to (a) prevent the development of cancer or (b) remove cancers at any early stage before more invasive disease occurs. Accordingly, the term 'colorectal cancer', rather than colorectal neoplasia, has been used in most instances throughout this document.

[2] The determination of a clinically relevant delay in diagnosis is left to the discretion of the relevant clinician(s).

[3] It should be noted that one currently listed contraindication, perforation of the colon, is a contraindication for both colonoscopy and CTC. Despite this, perforation of the colon is listed in the current item descriptor for MBS item 56554 as an indication for CTC. Current understanding of the CTC procedure necessitates that 'perforation of the colon' be deleted as an indication for CTC in the descriptor for item 56554, regardless of the outcome of this application.

Background

Clinical need

Colorectal cancer

Colorectal cancer (CRC) is a type of cancer that develops via a multi-stage process in which a series of cellular mutations occur in the epithelial cells that line the large intestine (i.e. colon and rectum). Most commonly, CRC develops over time from benign adenomas, which can vary in size from tiny nodules to polyps 12 mm across, but can also arise from *de novo* lesions. Given the relatively slow disease progression, the early detection and removal of small cancers, and polyps that may become cancerous, is recognised as an effective strategy to prevent morbidity and mortality due to CRC (AIHW 2009; Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005).

Burden of disease

Epidemiological data indicate that CRC is the second most frequently occurring cancer in Australia and the second most common cause of cancer-related death (10.7% of cancer deaths in 2005) after lung cancer (AIHW 2008). The Australian Institute of Health and Welfare (AIHW) provides online data on CRC incidence for 2009, indicating that there were 7,982 and 6,428 cases among males and females, respectively, for that year[4]. Predicted rates up until 2011 indicate that CRC incidence is gradually increasing in women, with a 30% rise in new cases between 2001 (5,883 cases) and 2011 (7,673 cases; 95%CI 7,034, 8,414)[5]. For men, a 33% increase in new cases was predicted between 2001 (6,961 cases) and 2011 (9,249 cases; 95%CI 7,627, 12,710) (AIHW 2005). However, this was a reflection of Australia's ageing population and more recent data indicate that age-standardised incidence rates of CRC are decreasing for both men and women. For the period 2006 to 2010 the projected age-standardised rate of CRC for males decreased from 74.1 to 72.7 cases per 100,000, and for females from 51.2 to 50.3 cases per 100,000 (AIHW 2008).

Colorectal cancer screening

In 2006 the Australian Government introduced a screening program for 55–65 year olds using a faecal occult blood test (FOBT), with the aim of reducing the incidence of CRC[6].

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[4] http://www.aihw.gov.au/

[5] CI – confidence interval

[6] The 2012–13 Australian Federal Budget announced that the National Bowel Cancer Screening Program will be expanded to include Australians turning 60 years of age from 2013 and those turning 70 years of age from 2015. (http://www.cancerscreening.gov.au/)

Persons with a positive FOBT result are referred to a specialist to undergo further evaluation, usually by colonoscopy.

Existing procedures/tests

Colonoscopy is performed for the exclusion or diagnosis of colorectal neoplasia and is considered the gold standard for detecting polyps and pre-cancerous lesions of the colon, with a 95% sensitivity (Australian Cancer Network 2005) for detecting CRC. An advantage of colonoscopy is that it provides the opportunity for both diagnosis and simultaneous treatment by removal of polyps, as instruments for removal can be passed down the endoscope directly to the polyp site[7]. Alternative methods for detection and diagnosis of polyps or CRC are double contrast barium enema (DCBE) and computed tomography colonography (CTC), also known as virtual colonoscopy.

Historically, DCBE has been the alternative to a colonoscopy when the latter is contraindicated or incomplete. DCBE is not a satisfactory technique for visualising the rectum or rectosigmoid region, and consequently sigmoidoscopy or colonoscopy are recommended for these investigations. If polyps or CRCs are identified using either DCBE or CTC, management (i.e. removal or biopsy) with colonoscopy or surgery is required (Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005).

Computed tomography colonography

Computed tomography colonography is a less invasive investigative procedure than either colonoscopy or DCBE. The procedure is conducted in radiology rooms, either in a hospital or private practice. CTC requires distension of the bowel by insufflation with air or CO_2, which is conducted through a thin rectal catheter. No endoscope is used and the patient generally is not anaesthetised and does not require pain relief. Performing CTC requires a multi-detector CT scanner (minimum 8 rows; RANZCR 2012) and dedicated software for post-processing and interpretation of the data. Not all radiology services are equipped with CT scanners and there can be substantial demand for those that are available. The patient is required to undergo bowel preparation, which usually involves taking a laxative solution and having a clear liquid diet in the 24 hours prior to the scheduled scan. The laxation method is standard in many centres; however, faecal tagging is an increasingly popular technique that negates the need for laxation. The tagging requires patients to add a barium or iodinated contrast medium to their meals for 48 hours prior to the scan (NICE 2005). While faecal tagging is preferred by many clinicians, the method requires 'additional interpretive

[7] Colonoscopy, with or without polypectomy, is the reference standard investigation for this assessment.

experience of validated tagged examinations, and additional resources by adding to cost and complexity of patient preparation' (Burling 2010).

Intended purpose

Computed tomography colonoscopy is undertaken to identify early pre-cancerous lesions or small cancers so that they can be removed through a colonoscopy or surgery before they become malignant and spread. CTC is intended as a triage tool, such that people who are symptomatic or at high risk of CRC (Table 3) who are found *not* to have colorectal lesions do not need to undergo more invasive testing, i.e. colonoscopy.

Table 3 Asymptomatic people considered to be at high risk of colorectal cancer (Australian Cancer Network 2005)

Asymptomatic people fit into the high-risk category if they have:

- three or more first-degree or a combination of first-degree and second-degree relatives on the same side of the family diagnosed with bowel cancer (suspected hereditary non-polyposis colorectal cancer or NPCC)
- two or more first-degree or second-degree relatives on the same side of the family diagnosed with bowel cancer, including any of the following high-risk features:
  - multiple bowel cancers in the one person
  - bowel cancer before the age of 50 years
  - at least one relative with cancer of the endometrium, ovary, stomach, small bowel, ureter, biliary tract or brain
- at least one first-degree relative with a large number of adenomas throughout the large bowel (suspected familial adenomatous polyposis or FAP); or
- somebody in the family in whom the presence of a high-risk mutation in the adenomatous polyposis coli (APC) gene or one of the mismatch repair (MMR) genes has been identified.

Source: NHMRC (2005); in: Explanatory notes for MBS items 56552 and 56554.

The proposed item numbers as described in the DAP are shown in Table 4. However, during the preparation of the protocol for this assessment it was determined that the wording of the item descriptor for 56552 is inappropriate, as the availability of such an item number has the potential to lead to inappropriate referral to CTC. There is literature that indicates that among cases of incomplete or difficult colonoscopy, the reasons underlying the technical failure are only clinical in a proportion of these cases (Brahmania et al. 2012; Copel et al. 2007; Sidhu et al. 2011; Witte & Enns 2007). Reasons for a failed colonoscopy include a number of conditions / patient factors that may be discovered only after the commencement of a colonoscopy (e.g. long and tortuous colons and high-grade obstructions that prevent passage of the endoscope). Other reasons can include inadequate preparation of the colon, problems with intra-procedural patient positioning, and limitations due to the level and type of endoscopist training and/or experience. This leads to the conclusion that not all patients who fail colonoscopy due to 'technical difficulties' are clinically unsuitable for reattempting colonoscopy at a later date. Given this, the following change to the descriptor for item 56552 is proposed:

- replace description at (a) with 'the patient has had an incomplete or technically difficult colonoscopy and is assessed as unsuitable for a repeat colonoscopy'.

The role of CTC in the diagnosis or exclusion of colorectal neoplasia, in symptomatic patients or in asymptomatic patients with a high risk of colorectal neoplasia, places CTC as a possible replacement for DCBE or delayed colonoscopy.

The application proposes that there would be no limitations on the number of services per patient and that the frequency of CTC investigations for each patient would differ according to the clinical context. Under the proposed extended population funding arrangements, patients who undergo regular surveillance for colorectal neoplasm would be likely to require CTC every 1–3 years, provided they fulfil the MBS conditions. CTC could be performed as a once-off procedure in some patients such as the symptomatic elderly, although a repeat procedure within a short interval may be required when the outcome of a first procedure is not definitive.

This assessment will not address the value of CTC as a screening test in patients at general risk of colorectal neoplasia.

Table 4 Proposed MBS item descriptors for 56552 and 56554

Category 5 – Diagnostic Imaging Services
56552 COMPUTED TOMOGRAPHY OF COLON for exclusion or diagnosis of colorectal neoplasia in symptomatic or high risk patients if: (a) the patient has had an incomplete or technically difficult colonoscopy, and is assessed as unsuitable for a repeat colonoscopy; and (b) the service is not a service to which items 56301, 56307, 56401, 56407, 56409, 56412, 56501, 56507, 56801, 56807 or 57001 applies (R) (K) Bulk bill incentive (Anaes.) Fee: $600.00 Benefit: 75% = $450.00 85% = $526.30
56554 COMPUTED TOMOGRAPHY OF COLON for exclusion of colorectal neoplasia in symptomatic or high risk patients if: (a) a contraindication to colonoscopy exists (b) the service must not be a service to which item 56301, 56307, 56401, 56407, 56409, 56412, 56501, 56507, 56801, 56807 or 57001 applies (R) (K) Bulk bill incentive (Anaes.) Fee: $600.00 Benefit: 75% = $450.00 85% = $526.30 (See para DIL, DIQ of explanatory notes to this Category)
[Proposed new item number] COMPUTED TOMOGRAPHY OF COLON for exclusion or diagnosis of colorectal neoplasia in symptomatic or high risk patients if: (a) there is limited access to colonoscopy such as to cause delay in diagnosis (b) the service must not be a service to which item 56301, 56307, 56401, 56407, 56409, 56412, 56501, 56507, 56801, 56807 or 57001 applies (R) (K) Bulk bill incentive (Anaes.) Fee: $600.00 Benefit: 75% = $450.00 85% = $526.30

Marketing status of technology

Under the *Therapeutic Goods Act 1989*, CT scanners are classified as medical devices and are required to be registered as such (TGA 2011). Legislation for medical devices is administered by the Office of Devices Authorisation (ODA) for pre-market regulation and the Office of Product Review for post-market regulation, the aim being to maintain public confidence in the safety, performance, benefits and risks associated with the use of medical devices on the Australian market. The proposed medical service does not involve any changes to the medical device (CT scanner) or associated services used for items 56552 or 56554. There are currently several CT systems registered with the Therapeutic Goods Administration (TGA).

Computed tomography is a form of diagnostic radiology and its usage is overseen by the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA). Regulations governing the practice of nuclear medicine, radiology and radiotherapy are currently the domain of state and territory regulators. In some states the regulatory body forms part of the health or environmental department, and while current regulations are broadly consistent, there are some differences (ARPANSA 2008).

Additionally, the parent body of the applicant, the Royal Australian and New Zealand College of Radiologists (RANZCR), has developed guidelines for the training and practice of CTC (RANZCR 2012) with reference to the International Collaboration for CT Colonography Standards (Burling 2010). The proposed medical service involves the use of a CT scanner, laxative solutions for bowel preparation and, in some circumstances, intravenous (IV) contrast and/or anti-spasmodics. Oral contrast may be used for faecal tagging. In-vitro diagnostic testing is not an additional requirement of the procedure.

Current reimbursement arrangements

In Australia CTC is subsidised for patients who are at high risk or symptomatic for CRC and have undergone an incomplete colonoscopy not more than 3 months previously. Development of breathing difficulties can be a reason for not completing a colonoscopy and subsequent referral for CTC. Further contraindications to colonoscopy can be seen in Table 6. According to the current MBS item descriptor 56554, patients with a perforated colon are also recommended for CTC. However, a perforated colon is a contraindication for both colonoscopy and CTC, and so this item number will be amended accordingly, regardless of the outcome of the assessment of MSAC Application 1269[8]. Also recommended for CTC are patients who are symptomatic or at high risk of CRC and have contraindications for colonoscopy due to a complete or high-grade bowel obstruction. These patient populations are reflected in the current MBS item descriptors for CTC (Table 5).

[8] The minutes from the PASC meeting of 16 August 2012 state, 'The current descriptor for item 56554 needs to be altered to remove reference to perforated colon as an indicator for CTC'.

Table 5 Current MBS item descriptors for 56552 and 56554

Category 5 – Diagnostic Imaging Services
56552 COMPUTED TOMOGRAPHY OF COLON for exclusion of colorectal neoplasia in symptomatic or high risk patients if: a) the patient has had an incomplete colonoscopy in the 3 months before the scan; and b) the date of incomplete colonoscopy is set out on the request for scan; and c) the service is not a service to which items 56301, 56307, 56401, 56407, 56409, 56412, 56501, 56507, 56801, 56807 or 57001 applies (R) (K) Bulk bill incentive (Anaes.) Fee: $600.00 Benefit: 75% = $450.00 85% = $526.30 (See para DIL, DIQ of explanatory notes to this Category)
56554 COMPUTED TOMOGRAPHY OF COLON for exclusion of colorectal neoplasia in symptomatic or high risk patients if: a) the request for scan states that one of the following contraindications to colonoscopy is present: i. suspected perforation of the colon; ii. complete or high-grade obstruction that will not allow passage of the scope; and b) the service must not be a service to which item 56301, 56307, 56401, 56407, 56409, 56412, 56501, 56507, 56801, 56807 or 57001 applies (R) (K) Bulk bill incentive (Anaes.) Fee: $600.00 Benefit: 75% = $450.00 85% = $526.30 (See para DIL, DIQ of explanatory notes to this Category)

Table 6 Additional contraindications to those listed in current MBS item 56554

Contraindications to colonoscopy
• active colitis • large abdominal aortic aneurysms • recent myocardial infarction or pulmonary embolism • coagulopathies, including therapeutic anticoagulation • patients unable to tolerate adequate bowel preparations for colonoscopy • frail patients of advanced age • abdominal large-bowel hernias • splenomegaly

Source: List supplied by ARGANZ

Access to colonoscopy

As one of the proposed indications for CTC is limited access to colonoscopy, this premise was examined. It was expected that access would be limited to a larger degree in rural and remote areas than in metropolitan areas. MBS data showed that the current rate of CTC and colonoscopy *combined* was 16.3 services per 1,000 people in major cities, compared with

9.0 per 1,000 in remote areas (Table 7, with remoteness based on the Australian Standard Geographical Classification (ASGC)).

Table 7 **Number of services per 1,000 by ASGC remoteness for financial year 2012–13 (MBS items 32084, 32087, 32090, 32092, 56552, 56554)**

ASGC Remoteness Area	Number of services	Number of services per 1,000 population
Major cities	260,196	16.3
Inner regional	62,379	15.0
Outer regional	26,378	12.8
Remote	2,539	9.0
Very remote	760	3.7
Australia	356.083	15.7

Source: MBS statistics, received via personal communication, 9 December 2013

Although these data were requested to be separated for colonoscopy items and CTC items, for privacy reasons (due to too few services per category) CTC items cannot be presented separately.

Although this may suggest differential access between major cities and rural and remote areas, data from 2008–09 (Figure 1) show that a higher proportion of colonoscopies in remote and very remote areas are non-Medicare-rebated compared with major cities and regional areas (from the National Admitted Patient Care dataset, cited in the MBS review of colonoscopy (DLA Piper Australia 2011)). The data may not, therefore, reflect the actual rate of colonoscopy in rural and remote areas.

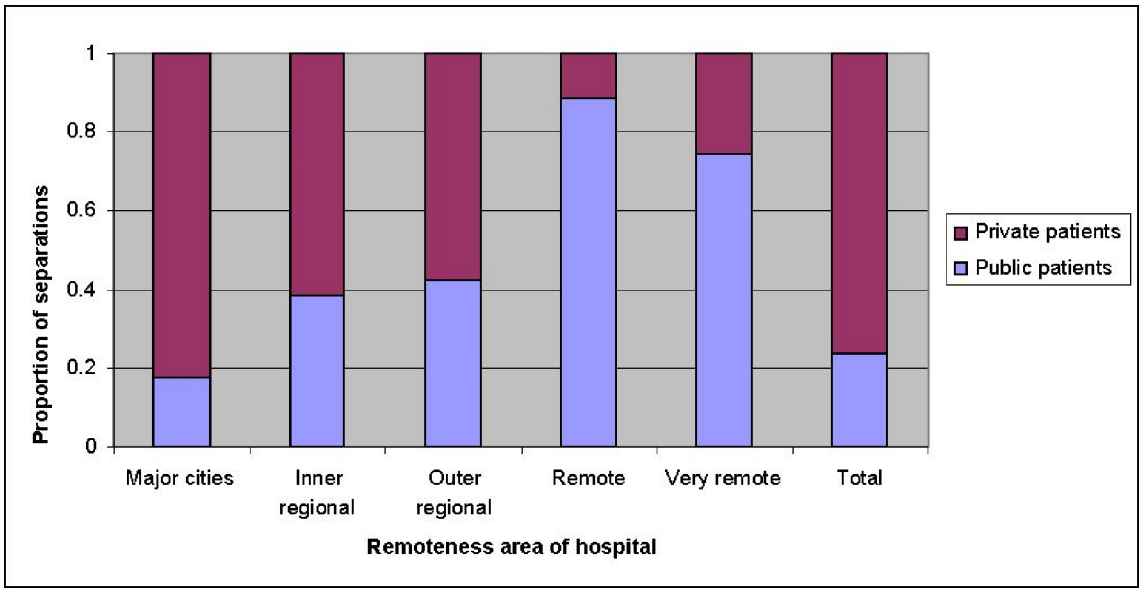


Figure 1 **Rates of MBS-related colonoscopy as a proportion of all public and private hospital colonoscopies, 2008–09**

Thus, access may be difficult due to geographical remoteness through the private system, and patients in remote areas are more likely to go through the public system.

Waiting times in public hospitals for endoscopies are not reportable, as they are considered medical procedures rather than surgical operations (Antill 2013). Data from individual publications have therefore been reported.

Western Australia

Viiala et al. (2007) reported on waiting times for colonoscopies within Fremantle Hospital, in Western Australia, between 1 November 2003 and 31 October 2005. Patients were divided into three categories of clinical urgency: Category I (recommended to have procedure within 30 days), Category II (procedure within 90 days) and Category III (procedure within 180 days) (Viiala et al. 2007; Table 8).

Table 8 Waiting time by triage category and number of patients with colorectal cancer (November 2003 – October 2005)

Outcome by clinical urgency [a]	Category I (n=352)	Category II (n=777)	Category III (n=503)
Mean age (years)	59	59	60
Median waiting time (days)	17	113	258
Colorectal cancer detected (no. (%))	42 (12.2%)	19 (2.4%)	3 (0.6%)
Median waiting time (days) to colorectal cancer diagnosis	7	43	213
Proportion of colonoscopies performed within recommended time	81%	42%	36%

[a] Recommended waiting times are: Category I, <30 days; Category II, <90 days; Category III, <180 days

For patients in Category I (main indications: blood loss in 32%, alteration in bowel function in 20% and strong suspicion of CRC in 17%), the majority of patients had a colonoscopy within the recommended timeframe, with a median waiting time of 17 days. However, for Category II (main indications: blood loss in 27%, alterations in bowel function in 26% and follow-up procedure in 20%) and Category III (main indications: follow-up procedure in 28%, screening because of family history in 22% and alteration in bowel function in 14%), the majority were not able to have a colonoscopy within the recommended timeframe, with median waiting times of 113 days for the group recommended to be seen within 90 days, and 258 days for the group recommended to be seen within 180 days. Therefore, within this particular hospital, urgent cases were seen within the recommended time period but semi-urgent and routine colonoscopies were delayed.

South Australia

Data on the consequences of the National Bowel Cancer Screening Program (NBCSP) in South Australian metropolitan hospitals, between 1 January 2006 and 31 December 2009, showed that for patients who had a positive faecal immunohistochemical test result, the

mean waiting time between GP consultation and a colonoscopy was 52±24.2 days (significantly longer than the recommended 30 days) (Bobridge et al. 2013).

Queensland

Since the start of the NBCSP in August 2006 and June 2011, the mean waiting time for colonoscopies has been 36 days (Mullen 2012). A survey of 563 patients reported that 78% said they were satisfied with the time to colonoscopy.

In summary, if patients wish to seek their healthcare through the private system, access to colonoscopy appears to be limited in remote settings. The majority of patients from a remote setting requiring a colonoscopy would be likely to use the public system, where the length of time they are required to be on a waiting list would depend on the severity of their symptoms. In response to the consultation DAP prepared for this topic, the Colorectal Surgical Society of Australia and New Zealand suggested that access to colonoscopies is difficult within the public hospital setting, and waiting times are unacceptable. They felt that if an indication for CTC was 'limited access to colonoscopy', a large increase in demand for CTC would be seen.

Approach to assessment

Objective

The objectives of this assessment are to assess the capability of CTC in the detection or exclusion of colorectal neoplasia among the relevant populations with regard to:

- **clinical effectiveness**
  - *Direct evidence:*
    - impact on health outcomes—do the people who receive the investigative procedure have better health outcomes?

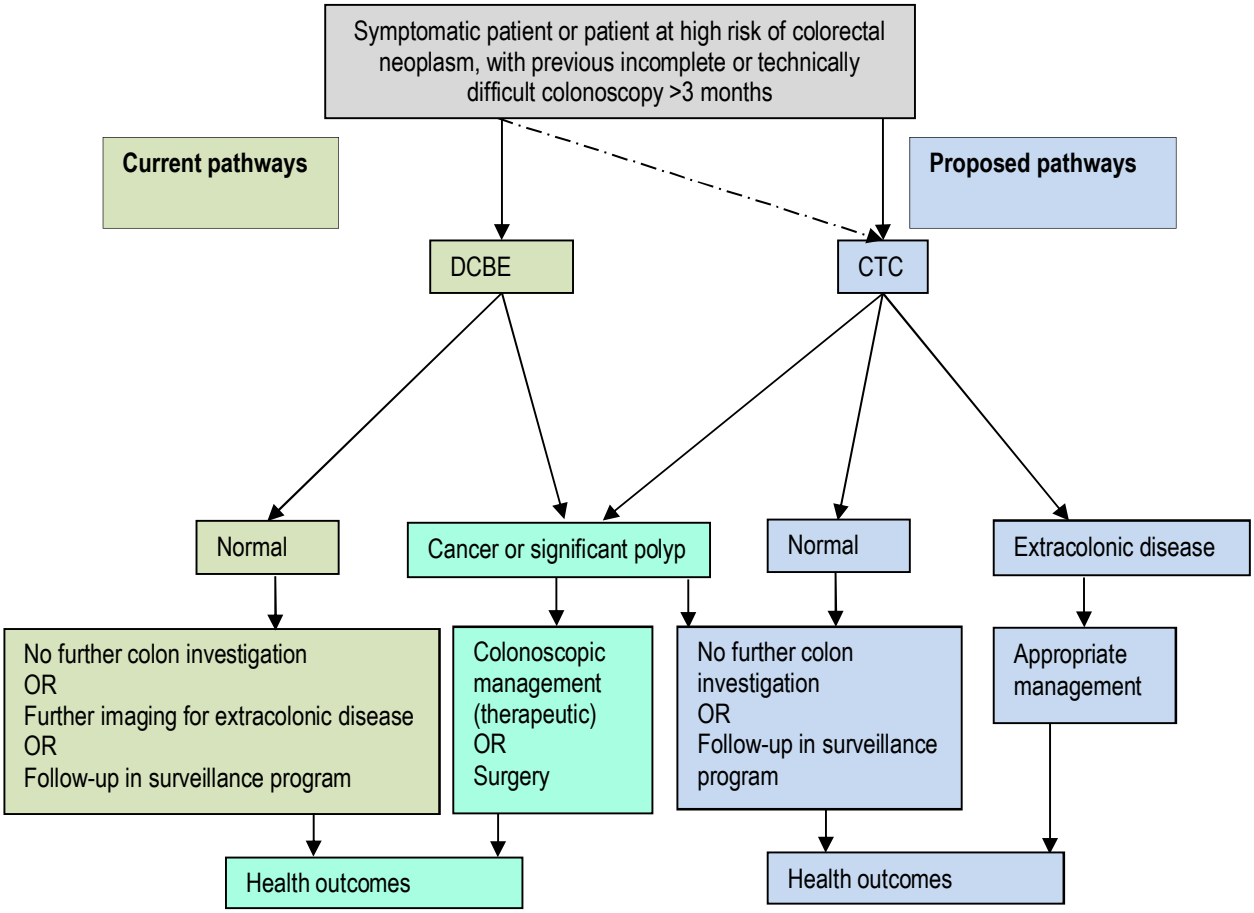
    and/or
  - *Linked evidence:*
    - diagnostic accuracy—this involves comparing CTC diagnostic results against a reference standard ('truth'), which may be determined by colonoscopy or long-term clinical diagnosis
    - impact on clinical decision-making—measured as the change in treatment decision made by clinicians in response to the information provided by the CTC
    - effectiveness of treatment—does treatment of those people with colorectal neoplasia impact on their health status?
- **safety**
- **economic considerations**

Clinical pathway

Three management algorithms are shown in Figure 2, Figure 3 and

. These algorithms contrast the investigational procedures that are available to the three population groups previously defined. Specifically, Figure 2 and Figure 3 both apply to asymptomatic, high-risk patients and symptomatic patients. In Figure 2 patients will have had a previous colonoscopy that has been incomplete/difficult due to clinical factors that obviate colonoscopy as unsuitable for those patients. Figure 3 shows patients who have a pre-existing contraindication to colonoscopy from the outset.

presents pathways for patients who are symptomatic or at high risk of colorectal neoplasia and have limited access to colonoscopy (but no clinical reason that precludes colonoscopy).

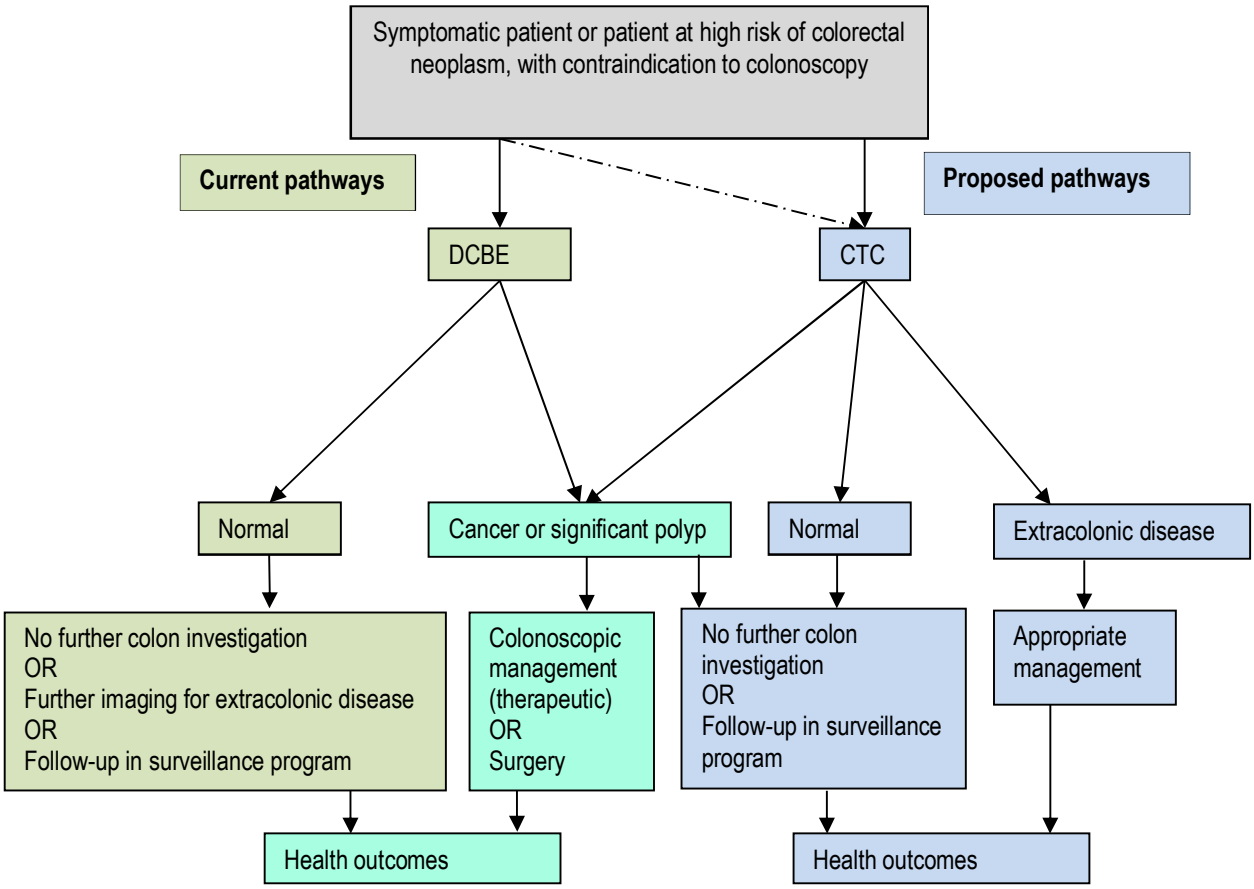


Note: The pathway from incomplete colonoscopy to CTC (dashed line) is at present only possible with documentation that the patient underwent the colonoscopy within the previous 3 months. Patients with contraindications for colonoscopy, other than suspected colon perforation (a contraindication to both OC and DCBE) or high-grade obstruction, cannot currently be reimbursed for CTC (also shown by way of dashed line) but may receive DCBE (solid line).

OC – optical colonoscopy; DCBE – double contrast barium enema; CTC – computed tomography colonography

Figure 2 Clinical management algorithm for patients who have had an incomplete or technically difficult colonoscopy

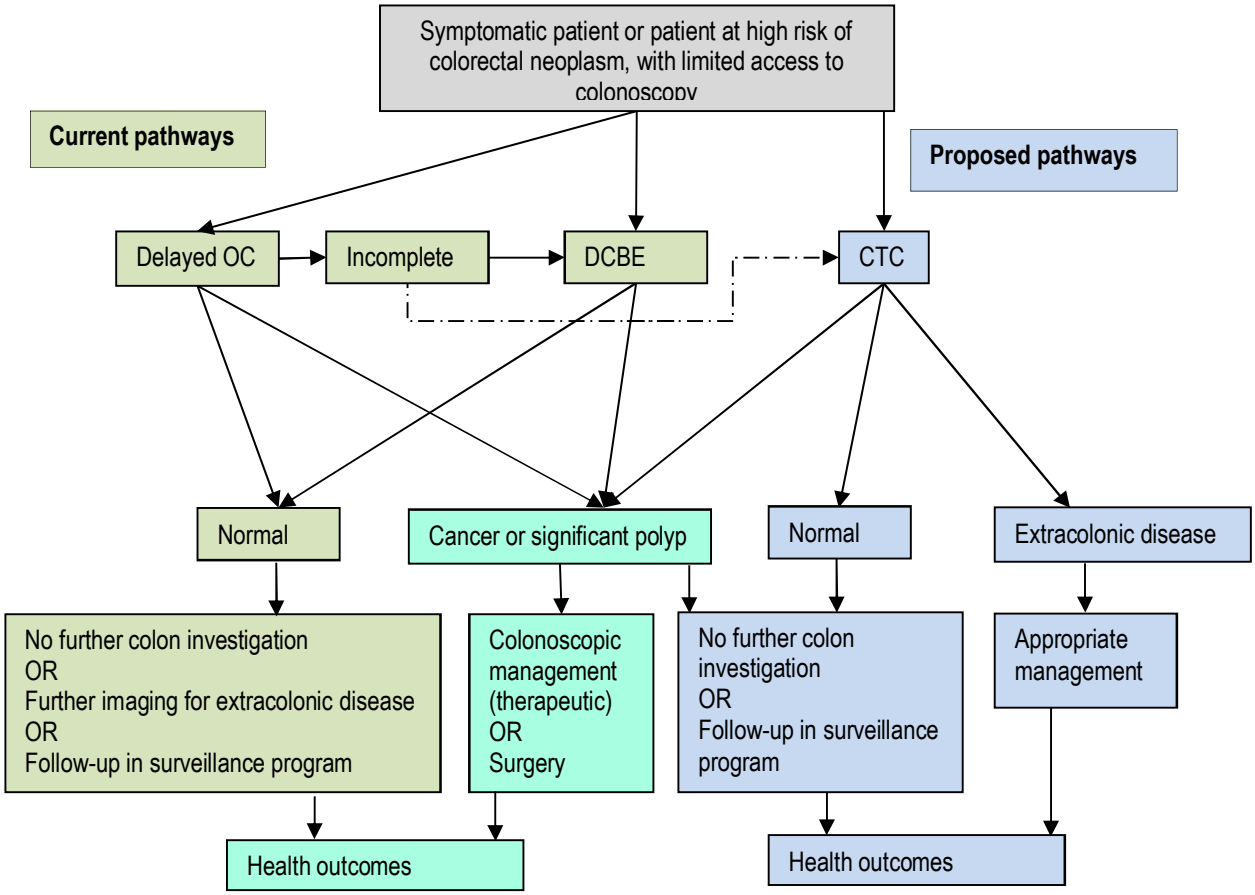
The role of CTC for the diagnosis or exclusion of CRC indicates that CTC is a replacement for DCBE or delayed colonoscopy in the patient groups defined above. Should MSAC recommend changes to the MBS items for CTC that broaden the eligible population in line with the applicant's proposal, it is envisaged that uptake of CTC services would slowly increase, with a consequent downward turn in DCBE services until it becomes obsolete.



Note: Patients with contraindications to colonoscopy, other than suspected colon perforation (a contraindication for both OC and DCBE) or high-grade obstruction, cannot currently be reimbursed for CTC (shown by way of dashed line) but may receive DCBE (solid line).

OC – optical colonoscopy; DCBE – double contrast barium enema; CTC – computed tomography colonography

Figure 3 Clinical management algorithm for patients with contraindications for colonoscopy



Note: The pathway from incomplete colonoscopy to CTC (dashed line) is at present only possible with documentation that the patient underwent the colonoscopy within the previous 3 months. The 'limited access' item is proposed regardless of whether there has been a previous successful or unsuccessful OC.

OC – optical colonoscopy; DCBE – double contrast barium enema; CTC – computed tomography colonography

Figure 4 Clinical management algorithm for patients with limited access to colonoscopy

Comparators

The appropriate comparator among patients who are (a) clinically unsuitable for colonoscopy, as identified by incomplete or technically difficult colonoscopy, or (b) contraindicated to colonoscopy, is DCBE. This procedure was MBS-listed (item 58921) on 1 December 2007 for patients with suspected, or at high risk of, CRC who are contraindicated to colonoscopy but who do not meet eligibility for CTC under current funding arrangements (Table 9).

Table 9 Current MBS item descriptors for double contrast barium enema (58921)

Category 5 – Diagnostic Imaging Services
58921 OPAQUE ENEMA, with or without air contrast study and with or without preliminary plain films – (R) Schedule fee: $135.25 Benefit: 75% = $101.45 85% = $115.00 (See para DIL, DIQ of explanatory notes to this Category)

Barium enema delivers a higher dose of radiation compared with CTC and, unlike CTC, DCBE cannot provide information about extracolonic pathology. DCBE is not a satisfactory technique for visualising the rectum or rectosigmoid region, and consequently sigmoidoscopy or colonoscopy are recommended for these investigations. If polyps or CRC are identified using either the DCBE or CTC technique, management (i.e. removal or biopsy) with colonoscopy or surgery is required (Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005).

The resources typically required to deliver DCBE are a consultation with a specialist radiologist; a radiology facility (public or private) in which to provide work-up including a barium meal, imaging and post-procedural support; and follow-up with a gastroenterologist or other specialist. In Australia there are private radiology providers in addition to radiology facilities located within major hospitals. There are relevant specialists providing consultations through both private practice and the publicly funded health system.

For patients with limited access to colonoscopy, the comparators nominated are DCBE and 'delayed colonoscopy', although it is unlikely that these patients would be offered DCBE. As the concerns in this population are related to access rather than choosing the most clinically appropriate service, delayed colonoscopy is intended to denote 'colonoscopy with date determined by clinician according to urgency'. The relevant item numbers for colonoscopy (all MBS-listed on 1 December 1991) are shown in Table 10.

Table 10 Current MBS item descriptors for colonoscopy (32084, 32087, 32090, 32093)

Category 3 – Therapeutic procedures
32084 FLEXIBLE FIBREOPTIC SIGMOIDOSCOPY or FIBREOPTIC COLONOSCOPY up to the hepatic flexure, WITH or WITHOUT BIOPSY Multiple services rule Schedule fee: $111.35 Benefit: 75% = $83.55 85% = $94.65 (See para T8.17 of explanatory notes to this Category)
32087 Endoscopic examination of the colon up to the hepatic flexure by FLEXIBLE FIBREOPTIC SIGMOIDOSCOPY or FIBREOPTIC COLONOSCOPY for the REMOVAL OF 1 OR MORE POLYPS or the treatment of radiation proctitis, angiodysplasia or post-polypectomy bleeding by ARGON PLASMA COAGULATION, 1 or more of, not being a service to which item 32078 applies Multiple services rule Schedule fee: $204.70 Benefit: 75% = $153.55 85% = $174.00 (See para T8.17 of explanatory notes to this Category)
32090 FIBREOPTIC COLONOSCOPY examination of colon beyond the hepatic flexure WITH or WITHOUT BIOPSY Multiple services rule Schedule fee: $334.35 Benefit: 75% = $250.80 85% = $284.20 (See para T8.17 of explanatory notes to this Category)
32093 Endoscopic examination of the colon beyond the hepatic flexure by FIBREOPTIC COLONOSCOPY for the REMOVAL OF 1 OR MORE POLYPS, or the treatment of radiation proctitis, angiodysplasia or post-polypectomy bleeding by ARGON PLASMA COAGULATION, 1 or more of Multiple services rule Schedule fee: $469.20 Benefit: 75% = $351.90 85% = $398.85 (See para T8.17 of explanatory notes to this Category)

The reference standard

The nominated reference standard is colonoscopy (see

Table 10) and it is considered the gold standard in the diagnosis (or exclusion) of CRC. Colonoscopy, which uses an optical endoscope to visualise the interior wall of the colon, has been found to detect polyps and pre-cancerous lesions with 95% sensitivity (Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005). The ability to simultaneously detect and remove polyps has historically placed colonoscopy as the definitive method of investigation in persons suspected of CRC, provided no true contraindications to the procedure exist. Where colonoscopy cannot be performed due to medical reasons, DCBE has been the singular alternative, prior to the inception of CTC, to detect polyps or CRC in persons contraindicated for colonoscopy.

In addition to the reference standard of colonoscopy, the assessment group considered that studies using a clinical reference standard (such as all available information, including histology) was appropriate, given the scarcity of comparative accuracy evidence that uses colonoscopy as the reference standard.

Research questions

The research questions are outlined below.

1. What is the safety, effectiveness, cost-effectiveness and acceptability of CTC compared with DCBE for:

   a) symptomatic or high-risk patients who have had an incomplete or technically difficult colonoscopy due to clinical factors that make colonoscopy unsuitable; and

   b) patients who have a contraindication to colonoscopy?

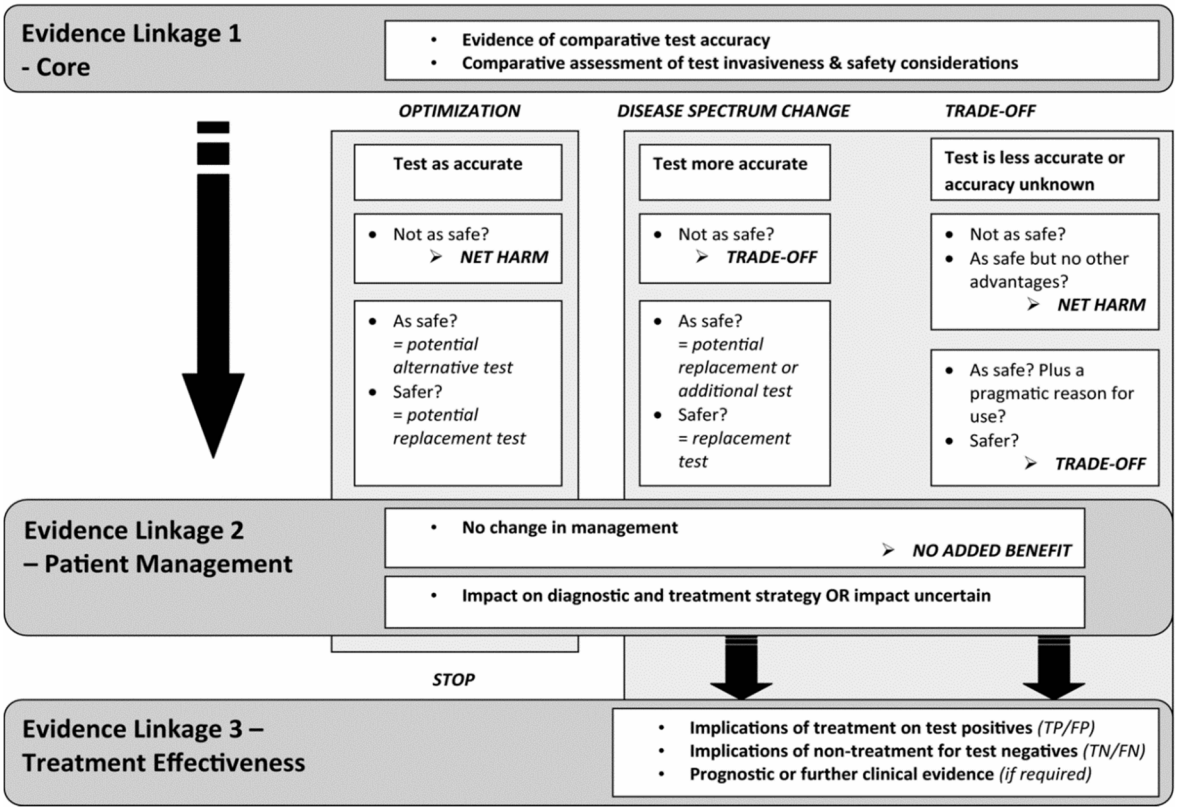
2. What is the safety, effectiveness, cost-effectiveness and acceptability of CTC compared with DCBE, delayed colonoscopy and DCBE following delayed incomplete colonoscopy for patients who have limited access to colonoscopy such as to delay diagnosis.

There was a lack of evidence within the three target populations of interest to this assessment, namely: (1) patients who are symptomatic or at high risk of CRC and have undergone a previous incomplete / technically difficult colonoscopy due to clinical factors that identify the patient as unsuitable for colonoscopy; (2) patients who are symptomatic or at high risk of CRC and are contraindicated for colonoscopy; and (3) patients who are symptomatic or at high risk of CRC with poor access to colonoscopy. Therefore, evidence was canvassed on CTC use within the broader population of those who are symptomatic or at high risk of CRC and require an investigational procedure to exclude/diagnose CRC without further limitations of: contraindications, previous complicated or difficult colonoscopy, or poor access to colonoscopy. The amended research question can be seen in the PICO box (Table 11).

In addition, as there was only very limited direct evidence available addressing the health impact of CTC and DCBE, supplementary evidence was obtained through the use of a linked evidence approach.

Decisions about the type of evidence needed for a linked evidence approach were based on the decision framework illustrated in Figure 5 Decision framework to implement the linked evidence approach when evaluating medical tests (Merlin et al. 2013). The framework incorporates horizontal elements concerning the types of evidence needed, while the vertical

elements indicate the process and decisions that are made regarding the need for the different evidence types.



Source: Merlin et al. (2013)

Figure 5 Decision framework to implement the linked evidence approach when evaluating medical tests

The first step of the decision framework for linked evidence is to assess the diagnostic accuracy of the test.

Research questions—Test accuracy (evidence linkage 1)

1. What is the diagnostic accuracy of CTC compared with DCBE for patients who (a) have undergone a previous complicated / technically difficult colonoscopy due to clinical factors that identify the patient as unsuitable for colonoscopy; or (b) are contraindicated for colonoscopy?

2. What is the diagnostic accuracy of CTC compared with DCBE, delayed colonoscopy or DCBE following delayed incomplete colonoscopy for patients who have poor access to colonoscopy?

The available diagnostic accuracy evidence indicated that CTC is likely to be more accurate than, and at least as safe as, DCBE in the majority of clinical scenarios involving the defined populations, and thus the 'Disease spectrum change' scenario (see Figure 5) was adopted to

determine potential differences in treatment effectiveness between those who are found to have polyps/CRC using CTC versus using DCBE. In order to do this, it was necessary to determine whether: (1) there was any evidence that the test changes patient management and, if so, (2) whether this leads to any observable changes in health outcomes for persons diagnosed with polyps/CRC using the alternative methods.

Research questions—Patient management (evidence linkage 2)

3. Does CTC change clinical management, compared with DCBE, for patients who (a) have undergone a previous complicated / technically difficult colonoscopy due to clinical factors that identify the patient as unsuitable for colonoscopy; or (b) are contraindicated for colonoscopy?

4. Does CTC change clinical management, compared with DCBE, delayed colonoscopy or DCBE following incomplete delayed colonoscopy for patients who have limited access to colonoscopy such as to delay diagnosis?

The changes in management expected, based on the accuracy of the test, are due to CTC having a higher sensitivity and lower specificity than DCBE. When patients undergo DCBE, they are more likely to have false negative results and be ruled out from having a colonoscopy or surgical management. They are therefore likely to either have no treatment or have further investigations for alternative causes of their symptoms. This would lead to a delay in the appropriate treatment. Information regarding early versus delayed treatment was sought to determine if there are benefits associated with the reduction in false negative results as a consequence of using CTC rather than DCBE. Although it appears that CTC may be associated with more false positive outcomes than DCBE, it is not expected that this would have a significant health impact, although it will have a cost impact. This is because, in the scenarios being assessed, those who have false positive results are expected to be referred for a colonoscopy, i.e. the 'gold standard' indication that they were indicated for initially.

Colonoscopy and surgery are well-established treatments for colorectal neoplasia, so there is no need to re-assess the effectiveness of these procedures for people receiving a true positive diagnosis. Similarly, imaging for extracolonic disease and follow-up surveillance are standard procedure for people receiving a true negative diagnosis, so these options do not require re-assessment.

Research question—Treatment effectiveness (evidence linkage 3)

5. Do alterations in clinical management and treatment options have an impact on the health outcomes of patients who were thought to be at high risk of, or symptomatic for, CRC but who received an incorrect diagnosis?

Review of literature

Literature sources and search strategies

A systematic literature review was undertaken for the research questions addressing 'direct evidence' and linkages 1 and 2 of the 'linked evidence approach'. The medical literature was searched to identify relevant studies and reviews for the period January 2005 to August 2013, updating a previous systematic review[9]. See Appendix B for details of databases searched.

Search strategies were developed using the key elements of the research questions defined above. For CTC, search strategies using terms for both population and intervention were found to be only marginally more specific than searches that used intervention search terms alone. It was therefore decided not to restrict the searches by using population terms. The search terms used for this review are also tabulated in Appendix B.

Based on the expected change in management, a separate rapid review of only high-level (level I) evidence in a limited number of databases was performed to address the last question (evidence linkage 3), to assess the benefit of early versus late diagnosis and treatment. Furthermore, in the absence of any information comparing CTC against delayed colonoscopy, a rapid review was performed seeking high-level (level I) evidence on the comparison between CTC and colonoscopy with no specified time delay. This evidence was outside the scope of the PICO criteria specified *a priori* but was included to assist the MSAC to make their decision in the absence of more-relevant information.

Selection criteria

In general, studies were excluded if they:

- did not address the research questions
- did not provide information on the pre-specified target populations
- did not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes

[9] MSAC previously engaged a team from the NHMRC Clinical Trials Centre to conduct a systematic review to assess CTC (published March 2006). The 2006 review conducted literature searches from 1994 to June 2005. As the population in the 2006 report is included in the three research questions listed above, the current review includes the relevant studies identified in the 2006 report as well as identifying relevant literature published after June 2005 (for ease of identifying literature, the search period commenced from January 2005).

- were studies in languages other than English that were of a lower level of evidence (than the studies in English)
- did not have the appropriate study design.

The criteria for including studies that address research questions for this review are outlined in Table 11 to Table 14.

Table 11 PICO criteria to determine the safety, effectiveness, cost-effectiveness and patient acceptability of computed tomography colonography (direct evidence)

Populations	1. Patients with colonic symptoms or asymptomatic patients with high risk of colorectal neoplasia who are unable to receive optimal management with colonoscopy because of previous incomplete or technically difficult colonoscopy due to clinical factors that identify the patient as unsuitable for colonoscopy 2. Patients with colonic symptoms or asymptomatic patients with high risk of colorectal neoplasia who are unable to receive optimal management with colonoscopy due to contraindications to colonoscopy 3. Patients with colonic symptoms or asymptomatic patients with high risk of colorectal neoplasia who are unable to receive optimal management with colonoscopy due to limited access to colonoscopy so as to delay diagnosis *Note: Due to the absence of sufficient evidence within these populations, evidence from the wider population of those with colonic symptoms or at high risk of CRC (without further restriction), requiring an investigational procedure to exclude/diagnose CRC, was used but was restricted to comparative evidence.*
Intervention	CTC
Comparators	Population 1 and Population 2: DCBE Population 3: DCBE; delayed colonoscopy [a]; and DCBE following incomplete delayed colonoscopy
Outcomes	Safety Potential physical and psychological harms from testing, radiation exposure, need for retesting and consequences of delayed colonoscopy Effectiveness Primary: overall survival, quality of life and progression-free survival Other: patient acceptability and tolerance, detection and consequences of extracolonic findings, and need for retesting Cost-effectiveness Cost per gain in QALYs, life years saved Patient acceptability No restrictions
Study design	Randomised or non-randomised controlled trials, cohort studies, case-control studies, comparative studies without concurrent controls, case series or systematic reviews of these study designs
Search period	The previous MSAC assessment of CTC included studies from the same populations between 1994 and June 2005, so the search was updated to include January 2005 – August 2013
Language	Studies in languages other than English would have been translated if they represented a higher level of evidence than that available in the English language evidence-base
Review questions	**1. What is the safety, effectiveness, acceptability and cost-effectiveness of CTC compared with DCBE in (a) patients who have undergone a previous complicated / technically difficult colonoscopy due to clinical factors that identify the patient as unsuitable for colonoscopy compared with DCBE; or (b) patients who are contraindicated for colonoscopy?** **2. What is the safety, effectiveness, acceptability and cost-effectiveness of CTC compared with DCBE, delayed colonoscopy or DCBE following incomplete delayed colonoscopy in symptomatic patients with limited access to colonoscopy such as to delay diagnosis?**

[a] NB: There was no literature identified that compared delayed colonoscopy against the evidentiary standard of colonoscopy (without a delay). MBS data were therefore provided by the Department of Health to answer the question involving this comparator.

CRC – colorectal cancer; CTC – computed tomographic colonography; DCBE – double contrast barium enema; QALY – quality-adjusted life year

Table 12 PICO criteria for the accuracy of computed tomography colonography (evidence linkage 1)

Populations	1. Patients with colonic symptoms or asymptomatic patients with high risk of colorectal neoplasia who are unable to receive optimal management with colonoscopy because of previous incomplete or technically difficult colonoscopy due to clinical factors that identify the patient as unsuitable for colonoscopy 2. Patients with colonic symptoms or asymptomatic patients with high risk of colorectal neoplasia who are unable to receive optimal management with colonoscopy due to contraindications to colonoscopy 3. Patients with colonic symptoms or asymptomatic patients with high risk of colorectal neoplasia who are unable to receive optimal management with colonoscopy due to limited access to colonoscopy so as to delay diagnosis [a] *Note: In the absence of sufficient evidence within these populations, evidence from the wider population of those with colonic symptoms or at high risk of CRC (without further restrictions), requiring an investigational procedure to exclude/diagnose CRC, was included but was restricted to comparative evidence.*
Intervention	CTC
Comparators	Population 1 and Population 2: DCBE Population 3: DCBE, delayed colonoscopy and DCBE following incomplete delayed colonoscopy
Evidentiary standard	Optical colonoscopy or clinical diagnosis [a]
Outcomes	Sensitivity, specificity, NPV, PPV, area under the curve, positive likelihood ratio, negative likelihood ratio and level of agreement, diagnostic yield Summary measures: diagnostic odds ratio, receiver–operator characteristic curve
Study design	All study designs listed in the 'Diagnostic accuracy' column of Table 16Table 16 **Designations of levels of evidence according to type of research question**
Search period	The previous MSAC assessment of CTC included studies from the same populations between 1994 and June 2005, so the search was updated to include January 2005 – August 2013
Language	Studies in languages other than English would only have been translated if they represented a higher level of evidence than that available in the English language evidence-base
Review question	**What is the diagnostic accuracy of CTC compared with DCBE, against the evidentiary standard of colonoscopy, for patients who (a) have undergone a previous complicated / technically difficult colonoscopy due to clinical factors that identify the patient as unsuitable for colonoscopy; (b) are contraindicated for colonoscopy; or (c) have limited access to colonoscopy such as to delay diagnosis?**

[a] Optical colonoscopy was the only reference standard agreed to in the DAP. However, due to the paucity of relevant evidence, studies that used clinical diagnosis as a reference standard were also included.

CRC – colorectal cancer; CTC – computed tomographic colonography; DAP – decision analytic protocol; DCBE – double contrast barium enema; MSAC – Medical Services Advisory Committee; NPV – negative predictive value; PPV – positive predictive value

Table 13 PICO criteria to determine the impact on patient management of computed tomography colonography (evidence linkage 2)

Populations	1. Patients with colonic symptoms or asymptomatic patients with high risk of colorectal neoplasia who are unable to receive optimal management with colonoscopy because of previous incomplete or technically difficult colonoscopy due to clinical factors that identify the patient as unsuitable for colonoscopy 2. Patients with colonic symptoms or asymptomatic patients with high risk of colorectal neoplasia who are unable to receive optimal management with colonoscopy due to contraindications for colonoscopy 3. Patients with colonic symptoms or asymptomatic patients with high risk of colorectal neoplasia who are unable to receive optimal management with colonoscopy due to limited access to colonoscopy so as to delay diagnosis *Note: In the absence of sufficient evidence within these populations, evidence from the wider*

	population of those with colonic symptoms or at high risk of CRC (without further restrictions), requiring an investigational procedure to exclude/diagnose CRC, was included but was restricted to comparative evidence.
Intervention	CTC
Comparators	Population 1 and Population 2: DCBE Population 3: DCBE, colonoscopy and DCBE following incomplete delayed colonoscopy
Outcomes	Change in management % change in management plan including surgeries performed and referral for follow-up colonoscopy with polypectomy Time to diagnosis
Study design	Randomised or non-randomised controlled trials, cohort studies, case-control studies, comparative studies without concurrent controls, case series or systematic reviews of these study designs
Search period	The previous MSAC assessment of CTC included studies from the same populations between 1994 and June 2005, so the search was updated to include January 2005 – August 2013
Language	Studies in languages other than English would have been translated if they represented a higher level of evidence than that available in the English language evidence-base
Review questions	**1. Does CTC change clinical management, compared with DCBE, for patients who (a) have undergone a previous complicated / technically difficult colonoscopy due to clinical factors that identify the patient as unsuitable for colonoscopy; or (b) are contraindicated for colonoscopy?** 2. **Does CTC change clinical management, compared with DCBE, delayed colonoscopy or DCBE following incomplete delayed colonoscopy, for patients who have limited access to colonoscopy such as to delay diagnosis?**

CRC – colorectal cancer; CTC – computed tomographic colonography; DCBE – double contrast barium enema; MSAC – Medical Services Advisory Committee

Following the outcomes of the accuracy data, the inclusion criteria for the last step of linked evidence were revised slightly from the protocol (which allowed for an assessment of the impact of false negative *and false positive results*). The criteria then focused on early versus late treatment, which is expected to occur as a result of false negative diagnoses from DCBE, or due to limited access to colonoscopy—that is, more patients are expected to receive treatment at an earlier stage if imaged by CTC than by DCBE or delayed colonoscopy. A separate rapid review was performed, for evidence-based clinical practice guidelines and systematic reviews (providing level I evidence) addressing the consequences of false negative test results. The PICO criteria are given in Table 14.

As discussed above, an assessment of the consequences of false positive findings from CTC (or DCBE) would not affect the health outcomes of patients, as all positive test results are expected to result in a colonoscopy in any event. Any additional patient anxiety due to the false positive result was not captured by this review.

Table 14 PICO criteria to determine the clinical impact of early versus late treatment to estimate the impact of a false negative result from CTC or DCBE, or in those whose diagnosis and treatment is delayed due to limited access to colonoscopy (evidence linkage 3)

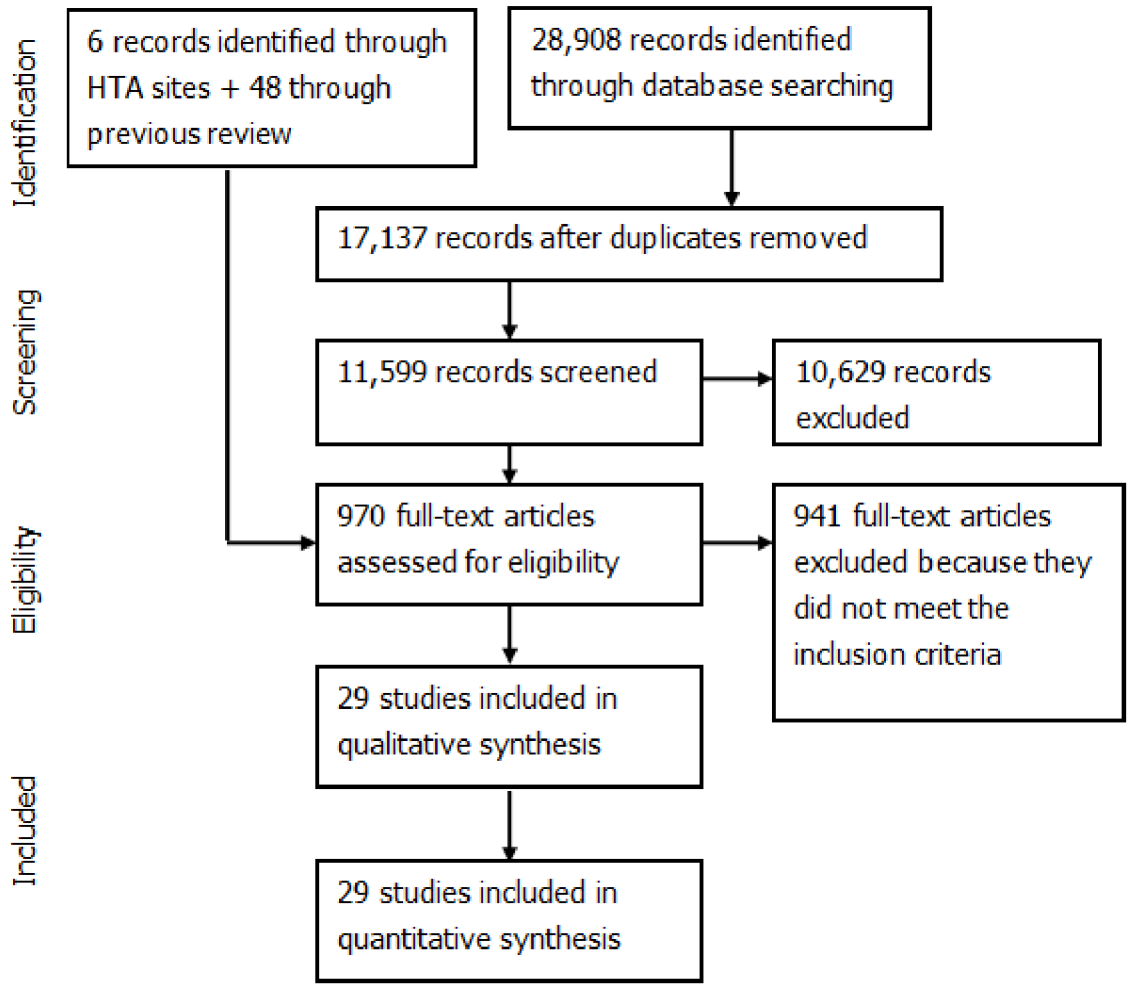
Population	Patients with undiagnosed CRC
Intervention	Delayed treatment

Comparator	Treatment for CRC
Outcomes	Quality of life, progression to advanced bowel cancer and possible metastasis, symptom resolution
Study design	Level I evidence—systematic reviews, if available; otherwise randomised or non-randomised controlled trials and cohort studies, case control studies, case series
Search period	No limits
Language	Studies in languages other than English would have been translated if they represented a higher level of evidence than that available in the English language evidence-base
Review question	**Do alterations in clinical management and treatment options have an impact on the health outcomes of patients who were thought to be at high risk of or symptomatic for CRC but who received a delayed diagnosis?**

CRC – colorectal cancer

Search results

PRISMA flowchart



Source: Adapted from Liberati et al. (2009)

Figure 6 Summary of the process used to identify and select studies for the review

Data extraction and analysis

Data were extracted by three research officers using a standard template. A study profile was developed for each included study (see Appendix C). Studies that were unable to be retrieved or that met the inclusion criteria but contained insufficient or inadequate data are provided in Appendix D. Definitions of all technical terms and abbreviations are provided in the Glossary.

Meta-analyses were not undertaken as there were too few studies providing data on the same outcomes. The results were therefore provided in tables and a qualitative synthesis provided. A statistically significant difference was assumed at $p<0.05$.

Where two (or more) papers reported on different aspects of the same study; for example, the methodology in one and the findings in the other, they were treated as one study. Similarly, if the same data were duplicated in multiple articles, results from the most comprehensive or most recent article were included.

Appraisal of the evidence

Appraisal of the evidence was conducted in three stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review (strength of the evidence).

Stage 2: Appraisal of the precision, size of effect and clinical importance of the results for primary outcomes in individual studies—used to determine the safety and effectiveness of the intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Stage 1: strength of the evidence

Evidence retrieved that met the PICO criteria was assessed according to the NHMRC dimensions of evidence, which are listed in Table 15.

There are three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified for a particular intervention; the last two require expert clinical input as part of their determination.

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The 'level of evidence' reflects the effectiveness of a study

design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results. The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (see Table 16 Designations **of levels of evidence according to type of research question**

Study quality was evaluated and reported using an appropriate instrument for critical appraisal: studies of diagnostic accuracy were assessed by QUADAS-2 (Whiting et al. 2011); case series were assessed using the NHS CRD checklist (Khan 2001); cross-sectional studies were assessed using an adapted version of the NHS CRD checklist; randomised and non-randomised controlled trials and observational studies were appraised using the appraisal tool by Downs and Black (1998); and systematic reviews were critiqued using the PRISMA checklist (Liberati et al. 2009).

Table 15 Evidence dimensions

Type of evidence	Definition
Strength of the evidence:	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect; it reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval (CI)
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

Table 16 Designations of levels of evidence according to type of research question

Level	Intervention [a]	Diagnostic accuracy [b]
I [c]	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard [d], among consecutive persons with a defined clinical presentation [e]
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard [d], among non-consecutive persons with a defined clinical presentation [e]
III-2	A comparative study with concurrent controls: ▪ non-randomised, experimental trial [f] ▪ cohort study ▪ case-control study ▪ interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	A comparative study without concurrent controls: ▪ historical control study ▪ two or more single-arm studies [g] ▪ interrupted time series without a parallel control group	Diagnostic case-control study [h]
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[i]

Source: NHMRC (2009)

Explanatory notes:

[a] Definitions of these study designs are provided in NHMRC (2000; pp. 7–8) and in the Glossary accompanying Merlin et al. (2009).

[b] These levels of evidence apply only to studies assessing the accuracy of diagnostic or screening tests. To assess the overall effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (MSAC 2005; Sackett & Haynes 2002). The evidence hierarchy given in the 'Intervention' column should be used when assessing the impact of a diagnostic test on health outcomes relative to an existing method of diagnosis/comparator test(s). The evidence hierarchy given in the 'Screening' column should be used when assessing the impact of a screening test on health outcomes relative to no screening or alternative screening methods.

[c] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies and study designs might contribute to each different outcome.

[d] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al. 2003)

[e] Well-designed population-based case-control studies (e.g. screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease is compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease, are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin & Miller 2002).

[f]This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilising A vs B and B vs C to determine A vs C, with statistical adjustment for B).

[g] Comparing single-arm studies, i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilising A vs B and B vs C to determine A vs C, but where there is no statistical adjustment for B).

[h] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of smallpox after large-scale vaccination.

[i] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within randomised controlled trials, in which case lower levels of evidence may be the only type of evidence that is practically achievable; both physical and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarms and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question, e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Note C: Each individual study that is attributed a 'level of evidence' should be rigorously appraised using validated or commonly used checklists or appraisal tools to ensure that factors other than study design have not affected the validity of the results.

Sources: Hierarchies adapted and modified from NHMRC (1999a), Lijmer et al. (1999), Phillips et al. (2001), Bandolier (1999)

Stage 2: precision, size of effect and clinical importance

Precision of effect was determined using statistical principles. Small confidence intervals (CIs) and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000). Appraisal of the evidence therefore needed to consider whether the analysis was appropriately powered to ensure that a real difference between groups was detected in the statistical analysis.

For intervention studies it was important to assess whether statistically significant differences between the comparators were also clinically important. The size of the effect needed to be determined, as well as whether the 95%CI included only clinically important effects.

The outcomes being measured in this report were assessed as to whether they were appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000).

Stage 3: assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 1999b). Five components are considered essential by the NHMRC when judging the body of evidence:

1. the evidence-base—which includes the number of studies sorted by their methodological quality and relevance to patients;

2. the consistency of the study results—whether the better quality studies had results of a similar magnitude and in the same direction; that is, homogeneous or heterogeneous findings;

3. the potential clinical impact—appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;

4. the generalisability of the evidence to the target population; and

5. the applicability of the evidence—integration of the evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 17; NHMRC 2009).

Table 17 Body of evidence matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence-base [a]	one or more level I studies with a low risk of bias or several level II studies with a low risk of bias	one or two level II studies with a low risk of bias or an SR or several level III studies with a low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency [b]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population(s) studied in body of evidence are the same as target population	population(s) studied in body of evidence are similar to target population	population(s) studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population [c]	population(s) studied in body of evidence differ from target population and it is hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Source: adapted from NHMRC (2009)

[a] Level of evidence determined from the NHMRC evidence hierarchy (see Table 16 **Designations of levels of evidence according to type of research question**)

[b] If there is only one study, rank this component as 'not applicable'

[c] For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

SR = systematic review; several = more than two studies

Expert advice: Health Expert Standing Panel (HESP)

HESP has been established as a panel of MSAC and is a pool of experts collated from various medical fields who are nominated by their associated professional body or by the applicants. HESP members are engaged to provide practical, professional advice to evaluators that directly relates to each application and the service being proposed for the MBS. HESP members are not members of either MSAC or its subcommittees, ESC and PASC. Their role is limited to providing input and guidance to the assessment groups to ensure that the pathway is clinically relevant and takes into account consumer interests. HESP member advice informs the deliberations that MSAC presents to the Minister for Health.

Results of assessment

Characteristics and quality of included studies

Searches identified 916 articles for possible inclusion; this was in addition to the 48 studies identified in the 2006 CTC Review conducted by NHMRC Clinical Trials Centre (NHMRC CTC 2006). Of these articles, 29 studies were finally included in the current review, 9 of which were published prior to July 2005 and 20 published after that date. Three systematic reviews were identified (in addition to the MSAC 2006 CTC Review) that compared CTC and DCBE; however, none of these met the criteria for inclusion. A separate search was undertaken to identify HTA reports but none were found that were appropriate to the specified research questions. Clinical practice guidelines (evidence-based) were identified that provided recommendations for CRC screening and treatment, and one guideline was identified that provided recommendations for the populations specified in this review (Schmiegel et al. 2010).

Evidence-based guidelines

Of the evidence-based guidelines identified, one from Germany provided recommendations for populations relevant to this review (Schmiegel et al. 2010). However, all relevant studies included in the guideline had been previously identified and included in the current assessment (Johnson et al. 2004; Neri et al. 2002; Rockey et al. 2005), and therefore this guideline was not considered further.

Systematic reviews

There were four systematic reviews identified that considered the comparison of CTC and DCBE. One of these studies was the MSAC review on CTC published in 2006 (NHMRC CTC 2006). This publication provided the evidence-base for the current review up until June 2005. Two other systematic reviews (Banerjee & Van Dam 2006; Rosman & Korsten 2007) were contemporaneous with the MSAC 2006 report and contributed no additional data for the comparison of CTC and DCBE, and so were not considered further.

The fourth review (Sosna et al. 2008) was published in 2008 and included a meta-analysis indirectly comparing CTC and DCBE intervention studies, as well as published relative accuracy data. Studies of DCBE and CTC included in the meta-analysis were published between 1982 and 2005, and between 1997 and 2006, respectively. All studies were prospective in design and used a reference standard of either sigmoidoscopy or colonoscopy. The majority of the CTC and DCBE studies were conducted in high-risk patients. Study findings were meta-analysed to determine the sensitivity and specificity of DCBE and CTC, with a test for appropriateness using Fisher's exact test ($p<0.001$ for all

endpoints except per-patient sensitivity for polyps 6–9 mm, where p=0.268 for DCBE). When pooled accuracy results for CTC and DCBE were compared, CTC was more specific than DCBE for per-patient polyps ≥10 mm. In addition, CTC was more sensitive than DCBE for per-patient and per-polyp of 6–9 mm and ≥10 mm in size. Neither per-polyp nor per-patient specificity data for polyps 6–9 mm were reported. The results of the meta-analysis are given low weight in the current review, as comparators were inconsistent between CTC and DCBE and results were not separated. Individual studies were assessed and included if they met the criteria for this review.

Primary studies

Direct evidence

One RCT of moderate quality was identified (Halligan et al. 2013), in which patients who were initially referred for either DCBE or colonoscopy were randomised to either CTC or DCBE (level II intervention evidence). In a separate concurrent trial patients were randomised to either CTC or colonoscopy; however, the results of that arm were not considered in this assessment, given that colonoscopy (with no specified time delay) was stated *a priori* to be the reference standard but not a comparator. Halligan et al. provided direct evidence on safety and effectiveness, and also provided information on the diagnostic accuracy of CTC (see the section *Evidence on test performance* below). A second article reporting the same trial provided evidence on secondary safety outcomes and patient acceptability (von Wagner et al. 2011).

Patient acceptability outcomes were assessed by questionnaires in seven studies, five of which were cross-over stud comparisons (Bosworth et al. 2006; Gluecker et al. 2003; Sofic et al. 2010; Taylor et al. 2005; von Wagner et al. 2011) where patients underwent both CTC and DCBE (level III-2 evidence). In the remaining two studies of patient acceptability (level III-2 intervention evidence) participants underwent either CTC or DCBE before completing a questionnaire (Kataria 2011; Taylor et al. 2003). The studies were well designed and reported and of moderate (Gluecker et al. 2003; Sofic et al. 2010) or high (Bosworth et al. 2006; Kataria 2011; Taylor et al. 2005; Taylor et al. 2003; von Wagner et al. 2011) quality. The patient acceptability studies comprised extended reporting from trials assessing the performance of CTC and DCBE.

Evidence on test performance

In addition to Halligan et al. (2013), four studies provided diagnostic accuracy data for CTC compared with DCBE. Of these, three studies (level II diagnostic evidence) were within-patient studies (Johnson et al. 2004; Rockey et al. 2005; Sofic et al. 2010); that is, in which participants underwent both the intervention and the comparator procedures, thereby controlling for participant-related bias. The fourth study was an audit of a retrospective cohort (Thomas, Atchley & Higginson 2009; level III-2 diagnostic evidence). Of the five

included studies, the two based in the United Kingdom (Halligan et al. 2013; Thomas, Atchley & Higginson 2009) and one each in the USA (Rockey et al. 2005) and Bosnia and Herzegovina (Sofic et al. 2010) were of moderate quality. One additional USA-based study (Johnson et al. 2004) was of low quality.

Studies reporting CTC yield of CRC and polyps were included if CTC was in a population who had previously undergone an incomplete colonoscopy or were contraindicated for colonoscopy. Similarly, for extracolonic findings, studies were included if they were conducted in these specific target populations. In total, 15 studies (level IV diagnostic evidence) provided yield data in these populations but were not assessed for quality of execution, as the study design alone was an indicator of poor quality. Twelve studies were conducted in those who had previously undergone an incomplete colonoscopy, and 10 of these studies reported on CRC, polyps and extracolonic findings (El-Sharkawy et al. 2013; Iafrate et al. 2008; Luo Mingyue 2002; Morrin et al. 1999; Neerincx et al. 2010; Neri et al. 2002; Pullens et al. 2013; Salamone et al. 2011; Sali et al. 2008; Yucel et al. 2008). Two studies reported only yield of CRC and polyps (Copel et al. 2007; Macari et al. 1999).

Of the studies included for the contraindicated population, three reported CRC and polyp findings (Duff et al. 2006; Ng et al. 2008; Saunders et al. 2013). An additional two studies were identified through pearling the references of a non-systematic review (otherwise excluded), and these provided data to evaluate CTC test performance relative to clinical reference standards (Kealey et al. 2004; Robinson, Burnett & Nicholson 2002).

Included studies from additional non-systematic searches

Three additional systematic reviews and one evidence-based guideline were included in the report to answer questions regarding the clinical impact of an expected change in management, and to address the comparison of CTC versus colonoscopy with no specified time delay (in the absence of data on CTC versus delayed colonoscopy).

One systematic review (in two publications) reporting on the association between diagnostic/therapeutic delay and health outcomes (stage of disease at diagnosis and survival) was rated as moderate quality (Ramos et al. 2007; Ramos et al. 2008). While the review publications fulfilled the majority of criteria on the PRISMA checklist, they did not indicate whether the quality of the included studies was assessed. One systematic review on the accuracy of CTC versus colonoscopy with no specified time delay also fulfilled most criteria on the PRISMA checklist; however, after the authors performed scoping searches (and found no additional articles from searching Embase and Scopus), they limited their formal literature searches to PubMed. This may have affected the comprehensiveness of the evidence-base collated. It was stated that quality appraisal was performed but the results of the quality appraisal were not included in the published article (Pickhardt et al. 2011). One

final systematic review comparing CTC and colonoscopy with no specified time delay with regard to patient preferences fulfilled most criteria on the PRISMA checklist and was considered to be of high quality (Lin et al. 2012).

Direct evidence

A systematic search was conducted to identify evidence regarding the safety, effectiveness, patient acceptability and cost-effectiveness of CTC compared with DCBE or delayed colonoscopy. The inclusion criteria for identification of studies relevant for evidence of effectiveness of CTC are given in Table 11. There was no direct evidence identified for patients who are symptomatic or at high risk of CRC and have undergone an incomplete or technically difficult colonoscopy. Similarly, there was no direct evidence identified for the population contraindicated for colonoscopy. The review therefore included direct evidence (i.e. for safety, effectiveness, cost-effectiveness and patient acceptability) on CTC compared with DCBE for the expanded population of those symptomatic or at high risk of CRC. This will allow MSAC to have some information on the direct impact of CTC, even if the population is not quite appropriate.

Summary of safety and acceptability:

CTC is as safe as, or more safe than, DCBE, with equivalent rates of serious adverse events and fewer minor adverse events. Repeat testing due to clinical uncertainty or inadequate examination was more frequent after DCBE than CTC. However, the risk of an additional investigation due to visualisation of suspected polyps was higher for those undergoing CTC than for DCBE (an indicator of increased sensitivity).

No safety data were identified comparing CTC against delayed colonoscopy.

CTC is more acceptable to patients than DCBE, and is associated with less discomfort and worry, higher satisfaction and a higher proportion of patients who would be willing to undergo the procedure again.

There was no evidence available to determine acceptance by patients of CTC compared with delayed colonoscopy, but one systematic review on CTC versus colonoscopy with no specified time delay reported that the majority of studies found more patients preferred CTC to colonoscopy.

Is CTC safe compared with DCBE?

One study (Halligan et al. 2013) was identified that compared safety outcomes for CTC and DCBE in symptomatic older patients (level II intervention evidence). Halligan et al. reported serious adverse events associated with either CTC or DCBE as part of a Special Interest Group for Gastrointestinal and Abdominal Radiology (SIGGAR) trial commissioned by the UK Health Technology Assessment program in 2002. The study characteristics are shown in Table 18. Minor adverse events from the SIGGAR trial are reported in a separate publication by von Wagner et al. (2011) and are discussed under 'Secondary safety outcomes'.

Table 18 Studies reporting safety outcomes for CTC and DCBE in patients symptomatic or at high risk of CRC

Study	Study design and quality appraisal	Population	Safety outcomes assessed
Halligan et al. (2013)	Level II evidence Multi-centre, two-armed randomised controlled trial Quality: Moderate	N=3,838 55 years of age or older, symptomatic for CRC	Adverse events Need for repeat procedures

CRC – colorectal cancer; CTC – computed tomographic colonography; DCBE – double contrast barium enema

The SIGGAR study randomised a total population of 3,838 (randomised 1:2, i.e. 1,285 to CTC and 2,553 to DCBE) and found that serious adverse events—were measured in terms of either unplanned hospital admissions or death within 30 days of the procedure—were rare. While a total of 39 serious adverse events were reported, only 4 were considered possibly attributable to DCBE and 1 to CTC. Results are shown in Table 19. There were no statistically significant differences in the rates of serious adverse events between the two methods of investigation.

Table 19 Serious adverse events arising from the randomised procedure

Serious adverse event	CTC (n=1,285)	DCBE (n=2,553)	RR (95%CI)
Unplanned hospital admission within 30 days attributed to procedure	1 (suspected perforation)	4 (1 cardiac arrest, 1 abdominal pain, 1 rectal bleeding, 1 collapse)	1.00 (0.99, 1.00)
Death within 30 days of procedure	1 (obstructive pulmonary disease)	3 (1 cardiac failure, 1 liver failure, 1 perforated viscus)	1.00 (0.99, 1.00)

CTC – computed tomographic colonography; DCBE – double contrast barium enema; RR – relative risk

The need for retesting was considered *a priori* to be a safety outcome for this review. Halligan et al. (2013) reported data on the number of additional colonic investigations required due to clinical uncertainty and to inadequate initial examination for those randomised to both CTC and DCBE. A smaller proportion of those who had CTC underwent additional investigation because of an inadequate examination or clinical uncertainty than those who had DCBE (5.2% vs 8.5%; p<0.001). However, the risk of an additional investigation due to visualisation of suspected polyps was higher for those undergoing CTC than for DCBE (a marker of increased sensitivity). The results are summarised in Table 20.

Table 20 Results of additional colonic investigation in patients following randomised procedure

Original procedure	CTC (n=1,206 patients)	DCBE (n=2,300 patients)	Difference
Reason for additional investigation	N patients referred from CTC N patients with CRC or polyps detected in additional procedure	N patients referred from DCBE N patients with CRC or polyps detected in additional procedure	RR [95%CI] p-value [a]
All referred additional investigations	283 (23.5%) 83 (6.9%)	422 (18.3%) 119 (5.2%)	1.28 [1.12,1.46] p = 0.001
CRC or polyp ≥10 mm suspected	133 (11.0%) 74 (6.1%)	173 (7.5%) 107 (4.7%)	1.47 [1.18,1.82] p <0.001
Patients with smaller polyp	87 (7.2%)	54 (2.3%)	3.07 [2.20,4.28]

suspected	9 (0.7%)	4 (0.2%)	p = <0.001
All referrals from clinical uncertainty (no lesions seen)	63 (5.2%) 0	195 (8.5%) 8 (0.3%)	0.62 [0.47,0.81] p <0.001
Clinical uncertainty due to inadequate examination	34 (2.8%) 0	116 (5.0%) 6 (0.3%)	0.62 [0.47,0.81] p <0.001
Clinical uncertainty despite adequate examination	29 (2.4%) 0		0.62 [0.47,0.81] p <0.001

[a] Pearson's chi-square test

CI – confidence interval; CRC – colorectal cancer; CTC – computed tomographic colonography; DCBE – double contrast barium enema; RR – relative risk

Secondary safety outcomes

A single article by von Wagner et al. (2011) reported on complications after CTC and DCBE (Table 21) as part of a patient acceptability study. This article reported outcomes from the SIGGAR trial that randomised 3,838 patients with symptoms of CRC to either CTC or DCBE. The patient acceptability study took place during the last 12 months of recruitment in the SIGGAR trial, after a series of qualitative interviews had been conducted and analysed. Of these participants, 931 received a questionnaire in which they were invited to report their experience of the test within 24 hours of the procedure with regard to eight complaints. The complaints are listed with the survey results in Table 22.

Table 21 Studies reporting secondary safety outcomes for CTC versus DCBE

Study	Study design and quality appraisal	Population	Outcomes
von Wagner et al. (2011)	Level II evidence Randomised controlled trial (with post-examination survey) Quality: High	N=674/3,838 Age ≥55 years Symptoms or signs of CRC	Satisfaction Worry Physical discomfort Post-test complications

CRC – colorectal cancer; CTC – computed tomographic colonography; DCBE – double contrast barium enema

Table 22 Patient experience of complications at all levels (mild, moderate or severe) for CTC versus DCBE

Post-test complication	CTC (n=224)	DCBE (n=450)	Test favoured	p-value [a]
Abdominal pain/cramp	57%	68%	CTC	0.007
Nausea/vomiting	8%	16%	CTC	0.009
Faint feeling or dizziness	26%	24%	DCBE	Not significant
Wind	84%	92%	CTC	0.001
Bottom soreness	37%	57%	CTC	<0.001
Soiling	23%	31%	CTC	0.034
Sleep difficulties	22%	28%	CTC	Not significant
Anxiety	32%	38%	CTC	Not significant

[a] Pearson's chi-square statistic

CRC – colorectal cancer; CTC – computed tomographic colonography; DCBE – double contrast barium enema

Of the 931 questionnaires distributed, there were 674 responses (73.2% response rate). Analysis of the differences between responders and non-responders indicated that responders were more likely to be from a less socioeconomically deprived area, but there were no differences in gender, age or randomised procedure. Not all responders completed all questions. The results were largely in favour of CTC, with a larger proportion of patients experiencing significantly more abdominal pain/cramps, nausea/vomiting, wind, bottom soreness and soiling in the DCBE group. While a greater proportion of patients experienced faintness or dizziness in the CTC group, the difference between the groups was small and not statistically significant. There was no significant difference in the rate of sleep difficulties or anxiety experienced between the groups.

Is CTC safe compared with delayed colonoscopy?

There were no studies identified that assessed the safety of CTC versus delayed colonoscopy. A search was performed to see if there were any systematic reviews on the safety of CTC compared with colonoscopy with no specified time delay, but none were identified.

Is CTC more acceptable to patients than DCBE?

There were seven studies identified that compared the patient acceptability of CTC and DCBE. One RCT (von Wagner et al. 2011) reported evidence from a post-procedure patient survey. In four cross-over studies (Bosworth et al. 2006; Gluecker et al. 2003; Sofic et al. 2010; Taylor et al. 2005) patients undergoing *both* CTC and DCBE were given questionnaires to compare the experience of the two procedures. In two additional studies (Kataria 2011; Taylor et al. 2003) a questionnaire was used to compare patient acceptability outcomes between groups who had *either* undergone CTC or DCBE. Six out of seven of the studies were conducted in populations of patients at high risk and/or symptomatic for CRC. One study did not report the indication for patients undergoing the investigations (Kataria 2011). Three of the studies were identified in the 2006 review of CTC commissioned by MSAC (Gluecker et al. 2003; Taylor et al. 2005; Taylor et al. 2003). The remaining four studies were identified through searches conducted for this review on literature published since January 2005 (Bosworth et al. 2006; Kataria 2011; Sofic et al. 2010; von Wagner et al. 2011).

The study profiles are outlined in Table 23. The studies ranged from moderate to high quality, with well-described populations and interventions. Reasons for not completing the questionnaire were described in Bosworth et al. (2006). Of 161 incomplete questionnaires out of 614 enrolled patients, 60 patients were lost to follow-up (no further reasons given) and 72 withdrew consent before testing. Taylor also reported exclusions (7 out of 78 enrolled patients), 6 of whom did not complete the questionnaire and 1 in whom the DCBE

procedure was not completed. Response rates ranged between 73.2% and 100% for all studies. Sampling bias was assessed using the Index of Multiple Deprivation (IMD) in the study by von Wagner et al. (2011), with the finding that patients from less socioeconomically deprived areas[10] were more likely to return the questionnaire (IMD median=13.9, inter-quartile range (IQR) 7.4—22.6 for responders; vs IMD=16.6, IQR 8.9—26.6 for non-responders, p=0.004).

Table 23 Studies reporting patient acceptability outcomes for CTC compared with DCBE in patients symptomatic or at high risk of CRC

Study	Study design and quality appraisal	Population	Patient acceptability outcomes assessed
Bosworth et al. (2006)	Level II evidence Cross-over study Quality: High	N=614 High risk or symptomatic for CRC	Patient experience: Pain, worry, difficulty with directions, difficulty with preparations, anxiety, comfort, embarrassment, willingness to have test again, respect, tiredness, inconvenience, overall satisfaction
Gluecker et al. (2003)	Level II evidence Cross-over study: patient survey by self-administered questionnaire Quality: Moderate	N=617 (Group 2: CTC and DCBE) 50 years of age or older High risk of CRC	Quality of life (tolerance): Physical discomfort, inconvenience Patient preference Patient satisfaction
Kataria (2011)	Level III-2 evidence Patient questionnaire following DCBE or CTC Quality: High	N=100 Indication not reported; a mix of both female and male patients as a sample representative of both age and gender	Perception of pain Abdominal discomfort
Sofic et al. (2010)	Level II evidence Cross-over study Quality: Moderate	N=617 Symptomatic for CRC	Procedure comfort
Taylor et al. (2005) [a]	Level II evidence Cross-over study: patient self-administered questionnaires, manual device for pain measurement Quality: High	N=78 60 years of age and older Symptomatic for CRC	Quality of life: Perceived pain, satisfaction, worry, physical discomfort, tolerance Patient acceptance/preference
Taylor et al. (2003)	Level III-2 evidence Prospective cohort study: multi-centre, clinician assessment and self-administered questionnaires Quality: High	N=208 Group 1: Symptomatic or high risk of CRC, referred for CTC Group 2: Symptomatic for CRC, referred for DCBE	Quality of fife: Satisfaction, worry, physical discomfort, tolerance Patient preferences
von Wagner et al. (2011) [a]	Level II evidence Randomised controlled trial (with post-examination survey)	N=921 Age ≥55 years Symptoms or signs of CRC	Satisfaction Worry Physical discomfort Post-test complications

[10] The lower the IMD score, the less socioeconomically deprived

	Quality: High		

[a] Studies reported using a validated instrument to measure quality of life outcomes of satisfaction, physical discomfort and worry
CRC – colorectal cancer; CTC – computed tomographic colonography; DCBE – double contrast barium enema

A validated instrument or adapted version of a validated instrument was reported to have been used for the assessment of quality of life in Taylor's two studies (2003, 2005), and also the study by von Wagner et al. (2011). Three studies (Bosworth et al. 2006; Kataria 2011; Gluecker et al. 2003) used instruments that included questions specifically designed for the study aims, and used Likert and/or visual analogue scales for measurement. The study by Sofic et al. (2010) reported diagnostic accuracy results in addition to patient comfort, but did not describe the survey given to patients regarding the latter outcome.

Quality of life—physical discomfort

Seven studies reported on physical discomfort associated with the procedure, although the studies measured this outcome in different ways (Table 24). The three studies that used a version of a validated instrument measured physical discomfort and reported that there was significantly more physical discomfort associated with DCBE than CTC. Of the remaining studies, three had a statistically significant result that also favoured CTC (they reported outcomes of 'discomfort level', the 'most comfortable procedure' and level of 'comfort'), except for the study by Kataria (2011), which measured abdominal discomfort on a 7-point scale and found no difference between CTC and DCBE.

Table 24 Summary of quality of life—*physical discomfort* for patients undergoing CTC and/or DCBE

Study	Physical discomfort CTC	Physical discomfort DCBE	Procedure favoured	Difference
Bosworth et al. (2006) [a] (median)	27.6% [c] (n=581)	11.8% [c] (n=581)	CTC	p=0.0001 [c h]
Gluecker et al. (2003) [a]	12.0% [e] (n=534)	84.0% [e] (n=534)	CTC	p<0.001 [h]
Kataria (2011)	74.0% [f] (n=50 respondents)	79.6% [f] (n=49)	Neither	0.74 [i]
Sofic et al. (2010) [a]	0% [g] (n=231)	100% [g] (n=231)	CTC	NR
Taylor et al. (2005) [a,b]	Less than DCBE	More than CTC	CTC	p=0.03 [j]
Taylor et al. (2003) [b]	Less than DCBE	More than CTC	CTC	p=0.005 [i]
von Wagner et al. (2011) (IQR) [b]	35.5 (25–47)	10.0 (29–52) [d]	CTC	p<0.001 [i]

[a] Cross-over study
[b] Studies reported using a validated instrument to measure quality of life outcomes of satisfaction, physical discomfort and worry
[c] Proportion of patients who found the procedure more comfortable; Chi-square test
[d] N patients experiencing discomfort

[e] Proportion of patients who found the discomfort level moderate or worse
[f] Proportion of patients who rated discomfort at level 4 or higher
[g] Proportion of patients rating the procedure as less comfortable
[h] Chi-square test
[i] Mann-Whitney test
[j] Wilcoxon matched pairs test
CTC – computed tomographic colonography; DCBE – double contrast barium enema; IQR – inter-quartile range

Quality of life—satisfaction

Patient satisfaction with CTC, DCBE and colonoscopy was measured in four studies (Table 25). Bosworth et al. (2006) found that 36.8% compared with 6.0% of patients were least satisfied with DCBE and CTC, respectively, although 47.8% reported no difference and 9.5% were least satisfied with colonoscopy. The difference between patient satisfaction with DCBE and CTC was statistically significant. The two other studies reporting a satisfaction outcome also found a significant difference between groups favouring CTC over DCBE for satisfaction.

Table 25 Comparison of quality of life—*satisfaction* of patients undergoing CTC and DCBE

Study	Satisfaction CTC	Satisfaction DCBE	Procedure favoured	Difference
Bosworth et al. (2006) [a]	9.5% [c] (n=581)	36.8% [c] (n=581)	CTC	p=0.0001 [c,e]
Taylor et al. (2005) [a,b]	More than DCBE	Less than CTC	CTC	p=0.03 [f]
Taylor et al. (2003) [b]	More than DCBE	Less than CTC	CTC	p<0.001 [g]
von Wagner et al. (2011) [b]	64 [d] (56–69)	61 [d] (54–67)	CTC	p=0.003 [g]

[a] Cross-over study
[b] Studies reported using a validated instrument to measure quality of life outcomes of satisfaction, physical discomfort and worry
[c] Proportion of patients least satisfied
[d] Median number of patients satisfied (IQR)
[e] Chi-square test
[f] Wilcoxon matched pairs test
[g] Mann-Whitney test
CTC – computed tomographic colonography; DCBE – double contrast barium enema; IQR – inter-quartile range

Quality of life—worry

Worry was reported in four studies (Table 26), with varied results. Bosworth et al. (2006) and Taylor et al. (2003) recorded the number of patients who 'worried about their procedure' and found that significantly fewer patients worried about CTC than DCBE. The remaining two studies found that the level of 'worry' was similar for patients undergoing CTC and those undergoing DCBE.

Table 26 Comparison of quality of life—*worry* for patients undergoing CTC and DCBE

Study	Worry CTC	Worry DCBE	Procedure favoured	Difference
Bosworth et al. (2006) [a] (median)	4.3% [c] (n=581)	29.0% [c] (n=581)	CTC	p=0.0001 [c,e]
Taylor et al. (2005) [a,b]	NR	NR	Neither	No difference

Taylor et al. (2003) [b]	Less than DCBE	More than CTC	CTC	p<0.001 [f]
von Wagner et al. (2011) (IQR) [b]	4 (1–5) [d]	3 (1–5) [d]	Neither	p=0.984 [f]

[a] Cross-over study
[b] Studies reported using a validated instrument to measure quality of life outcomes of satisfaction, physical discomfort and worry
[c] Proportion of patients worried about the procedure
[d] Median score on 7-point Likert scale (IQR)
[e] Chi-square test
[f] Mann-Whitney test
CTC – computed tomographic colonography; DCBE – double contrast barium enema; IQR – inter-quartile range

Patient acceptability

One study reported on the acceptability of CTC and DCBE to patients. The survey by Taylor et al. (2005) reported that 98% of patients found CTC to be more acceptable, compared with 2% of patients who found that DCBE to be more acceptable (p<0.001). (Table 27).

Table 27 Comparison of acceptability of CTC and DCBE to patients

Study	CTC overall more acceptable	DCBE overall more acceptable	Procedure favoured	Difference
Taylor et al. (2005)[a] [b]	98% [c] (n=45)	2% [c] (n=45)	CTC	<0.001 [d]

[a] Cross-over study
[b] Studies reported using a validated instrument to measure quality of life outcomes of satisfaction, physical discomfort and worry
[c] Proportion of patients who would prefer the test again over the other
[d] One-sample tests of proportions
CTC – computed tomographic colonography; DCBE – double contrast barium enema

Patient preference

Patient preferences are given in Table 28. Three studies reported the proportion of patients who either preferred one test to another, would choose one test over another if it was necessary to have another investigation, or would be willing to have the test again. All studies reported results that strongly favoured CTC, with a large proportion of patients preferring CTC to DCBE. The differences were statistically significant in all studies.

Table 28 Comparison of patient preferences for CTC and DCBE

Study	Prefer CTC	Prefer DCBE	Procedure favoured	Difference
Bosworth et al. (2006) [a]	25.4% [c] (n=581)	3.2% [c] (n=581)	CTC	p=0.0001 [d]
Gluecker et al. (2003) [a]	97.0% (n=534)	0.04% (n=534)	CTC	p<0.0001 [e]
Taylor et al. (2005) [a,b]	83.0% [c] (n=70)	36.0% [c] (N=70)	CTC	p<0.001 [f]

[a] Cross-over studies
[b] Studies reported using a validated instrument to measure quality of life outcomes of satisfaction, physical discomfort and worry
[c] Proportion of patients willing to have the test again
[d] Chi-square test
[e] Wilcoxon rank sum test
[f] One-sample tests of proportions
CTC – computed tomographic colonography; DCBE – double contrast barium enema

As part of the SIGGAR trial, von Wagner et al. (2009) conducted a qualitative study that assessed patient preferences for CTC, DCBE and colonoscopy through semi-structured interviews. The aim of this work was to characterise patient expectations and experiences in depth and to explore interactions that may have resulted in anxiety or embarrassment. Outcomes were reported under the themes of 'physical experience', 'social interaction' and 'information provision'. The authors reported that different physical sensations for each procedure were 'surprisingly well tolerated overall', but that social interaction with staff was affected by feelings of embarrassment in all procedures. Analysis of interview data found that there were specific advantages for both CTC and colonoscopy, but none for DCBE. Patients believed that CTC reduced barriers to bowel screening, and also had the benefit of imaging the abdomen outside of the colon and rectum. Patients found that there was less anxiety after colonoscopy as anaesthesia reduced memories of the procedure. There was more likely to be instantaneous feedback after colonoscopy, which was appreciated by the patients. While DCBE and CTC were both likely to evoke embarrassment, DCBE was considered more likely to do so.

Is CTC acceptable compared with delayed colonoscopy?

No studies were identified that compared CTC with delayed colonoscopy (due to lack of access). However, one systematic review was identified that compared the acceptability of CTC and colonoscopy without a specified delay period (Lin et al. 2012) to patients who had undergone both procedures, for either screening, high-risk screening or diagnostic purposes (Table 29).

Table 29 Systematic review reporting patient acceptability outcomes for CTC compared with colonoscopy in asymptomatic patients, those at high risk of CRC or those symptomatic of CRC

Review	Study design and quality appraisal	Population	Acceptability outcomes assessed
Lin et al. (2012)	Level I evidence Systematic review Quality: High	K=23 studies, N=5,616 patients Patients who underwent CTC and colonoscopy for the purposes of screening or diagnosis Studies published in English between 1995 and February 2012	Patient preference differences

CRC – colorectal cancer; CTC – computed tomographic colonography; DCBE – double contrast barium enema

This high-quality systematic review included a total of 5616 patients in 23 studies. Overall, 16 (69.6%) of the 23 studies reported a statistically significant preference for CTC over colonoscopy, whereas 3 (13.0%) reported a statistically significant preference for colonoscopy, and 4 (17.4%) showed no difference or preference. There was a high degree of heterogeneity in the study outcomes ($Q=125$, $p<0.001$), so the authors of the review did not provide any pooled estimates of patient preference. However, pooled estimates were

provided for results stratified on a number of difference factors. These results are shown in Table 30. Lin et al. (2012) reported that patients were more likely to prefer CTC if they were having the procedure for screening purposes, if they knew they had a low likelihood of requiring a colonoscopy, if they were asked about their preferences in an unmasked manner, and if the article was published was in a radiology journal.

Table 30 Preference for colonoscopy or CTC based on procedure indication

Procedure indication	Number of studies	Preference difference [95%CI]	Procedure favoured	Difference [a]
Diagnostic	14	0.16 [–0.03, 0.35]	Neither	p=0.10
Screening	8	0.53 [0.32, 0.75]	CTC	p<0.001

[a] Der Simonian and Laird method (weighted least squares solution) with stratifying variables as fixed effects, based on a mixed effects model

CI – confidence interval; CTC – computed tomographic colonography,

Table 31 Preference for colonoscopy or CTC based on journal type

Journal type	Number of studies	Preference difference [95%CI]	Procedure favoured	Difference [a]
Gastro-intestinal	10	0.22 [–0.02, 0.45]	Neither (trend towards CTC)	p=0.07
Radiology	9	0.59 [0.49, 0.69]	CTC	p<0.001
Neither	4	–0.16 [–0.39, 0.07]	Neither	p=0.18

[a] Der Simonian and Laird method (weighted least squares solution) with stratifying variables as fixed effects, based on a mixed effects model

CI – confidence interval; CTC – computed tomographic colonography

Table 32 Preference for colonoscopy or CTC based on whether preference ascertainment was masked or not

Preference ascertainment	Number of studies	Preference difference [95%CI]	Procedure favoured	Difference [a]
Masked	11	0.23 [0.00, 0.46]	Neither (trend towards CTC)	p=0.05
Unmasked	9	0.36 [0.11, 0.61]	CTC	p=0.01

[a] Der Simonian and Laird method (weighted least squares solution) with stratifying variables as fixed effects, based on a mixed effects model

CI – confidence interval; CTC – computed tomographic colonography

Table 33 Preference for colonoscopy or CTC based on whether probability of colonoscopy was given

Colonoscopy probability	Number of studies	Preference difference [95%CI]	Procedure favoured	Difference [a]
Given at 20%	3	0.57 [0.50, 0.64]	CTC	p<0.001
Not given	17	0.23 [0.05, 0.42]	CTC	p=0.02

[a] Der Simonian and Laird method (weighted least squares solution) with stratifying variables as fixed effects, based on a mixed effects model

CI – confidence interval; CTC – computed tomographic colonography

Summary of direct effectiveness:

CTC and DCBE are associated with equivalent 4-year survival rates.

There was no evidence identified for a comparison of effectiveness of CTC and delayed colonoscopy.

Is CTC effective compared with DCBE?

One study that reported on direct effectiveness outcomes for the comparison of CTC and DCBE was included (Halligan et al. 2013). The UK-based SIGGAR trial randomised patients to either CTC or DCBE. The study characteristics are shown in Table 34.

Table 34 Studies reporting effectiveness of CTC compared with DCBE in patients symptomatic or at high risk of CRC

Study	Study design and quality appraisal	Population	Effectiveness outcomes assessed
Halligan et al. (2013)	Level II evidence Multi-centre, two-armed randomised controlled trial Quality: Moderate	N=3,838 55 years of age or older, symptomatic for CRC	Death rates at 48-month follow-up Detection rates of cancer and polyps ≥10 mm Patient preference and tolerance

CTC – computed tomography colonography; DCBE – double contrast barium enema; CRC – colorectal cancer

The SIGGAR trial analysed cancer registration data and reported death rates for trial participants at a 48-month follow-up. The results are shown in Table 35. At the time of analysis the death rates for each group were similar—15.7% vs 15.8% for the CTC and DCBE groups, respectively. The cause of death was not reported.

Table 35 Death rates for CTC and DCBE in the SIGGAR trial

Effectiveness outcome	CTC (n=1,277)	DCBE (n=2,527)	Procedure favoured	Relative risk [95%CI]
Deaths at 48-month follow-up*, n patients (%)	201 (15.7)	400 (15.8)	Neither	0.99 (0.85, 1.16) p=0.94 [a]

[a] Pearson's Chi-square test

CTC – computed tomographic colonography; DCBE – double contrast barium enema; SIGGAR – Special Interest Group for Gastrointestinal and Abdominal Radiology

Due to the paucity of studies with direct effectiveness outcomes for the comparison of CTC and DCBE, a linked evidence analysis was also conducted.

Is CTC effective compared with delayed colonoscopy?

No evidence was identified to inform the assessment of the effect of patient health outcomes of CTC compared with delayed colonoscopy.

Linked evidence

Summary of test accuracy:

There were no studies that assessed the comparative accuracy of CTC and DCBE in the target populations of those who had failed a previous colonoscopy or were contraindicated for colonoscopy.

In the broader population of those at high risk of, or symptomatic for, CRC, CTC was found to be more sensitive than DCBE and slightly less specific than DCBE, using various reference standards including clinical diagnosis, all subsequent tests or colonoscopy.

CTC accuracy data in the correct populations (but cross-classified against a clinical reference standard) were similar to data found in the broader population. The majority of patients who underwent CTC were ruled out as having any lesions, and would therefore avoid colonoscopy.

Studies providing evidence on the accuracy of CTC in patients for whom there is a delay in accessing colonoscopy were not available.

However, against a histological reference standard, CTC was found to be as sensitive as colonoscopy with no specified time delay. It is therefore reasonable to conclude that CTC would be at least as sensitive as delayed colonoscopy. There were no data on CTC specificity in this population.

Is CTC accurate compared with DCBE?

For the question of CTC accuracy, PICO criteria were designed to target studies that published specificity and sensitivity data for patients who underwent either CTC or DCBE for the diagnosis or exclusion of colorectal neoplasia (see Table 12). As there was no comparative evidence identified (CTC vs DCBE) for patients who underwent an incomplete colonoscopy or who were contraindicated for colonoscopy, the broader populations of symptomatic patients and those asymptomatic and at high risk of CRC were considered. Studies that did not compare CTC with DCBE, but compared CTC results with a clinical reference standard of diagnosis at a long-term follow-up, were included if they were conducted in patients that were contraindicated for colonoscopy or had undergone a previous incomplete colonoscopy.

Relative accuracy of CTC versus DCBE

Five studies were included that compared the accuracy of CTC and DCBE (Halligan et al. 2013; Johnson et al. 2004; Rockey et al. 2005; Sofic et al. 2010; Thomas, Atchley & Higginson 2009). The study characteristics are given in Table 36.

The articles were published between 2004 and 2013 inclusive, with the two earlier studies being conducted in the USA and the latter three in Europe. Four of the five studies were prospectively designed with populations of symptomatic or high-risk patients (Halligan et al. 2013; Johnson et al. 2004; Rockey et al. 2005; Sofic et al. 2010), and the fifth (Thomas,

Atchley & Higginson 2009) was a retrospective analysis of records from a group of UK hospitals where CTC was reportedly used for detection of CRC in symptomatic patients.

CTC was performed in all studies in a similar fashion. All patients underwent full bowel preparation. Supine and prone scanning was used in all five studies. Scanning was performed on four-row detectors in three studies (Halligan et al. 2013; Sofic et al. 2010; Thomas, Atchley & Higginson 2009), four- or eight-row detectors in one study (Rockey et al. 2005), and single or four-row detectors in one study (Johnson et al. 2004). Images were interpreted using a combination of 2D and 3D imaging except in one study (Thomas, Atchley & Higginson 2009), where 2D imaging only was reported.

To undergo DCBE, all patients underwent full bowel preparation. DCBE was generally well described and performed to standard protocols with high-density barium, spot and overhead or additional films, and multi-positioning. Colonoscopy and sigmoidoscopy were generally performed to a standardised procedure.

Table 36 Summary of study profiles reporting comparative diagnostic accuracy for CTC versus DCBE

Study	Study design and quality appraisal	Population	Reference standard	Accuracy outcomes assessed
Halligan et al. (2013)	Level II evidence Multi-centre, two-armed randomised controlled trial Quality: Moderate	N=3,804 55 years of age or older, symptomatic for CRC	Clinical diagnosis at 3 year follow-up	Detection rates of cancer and polyps ≥10 mm
Sofic et al. (2010)	Level II evidence Cross-over study Prospective single-centre comparative study Quality: Moderate	N=227/231 Symptomatic for CRC	Colonoscopy	Diagnostic accuracy
Rockey et al. (2005)	Level III-1 evidence Cross-over study Prospective multi-centre blinded comparison Quality: Moderate	N=614 High risk or symptomatic for CRC	All available information (including colonoscopy)	Diagnostic accuracy
Johnson et al. (2004)	Level III-2 evidence Cross-over study Prospective, blinded single-centre cohort Quality: Low	N=837 50 years of age or older, high risk or symptomatic for CRC	Confirmatory tests (flexible sigmoidoscopy (n=581), colonoscopy (n=116), or rigid proctoscopy (n=89))	Diagnostic accuracy Double-read accuracy
Thomas, Atchley & Higginson (2009)	Level III-3 Retrospective comparative cohort study Quality: Moderate	N=2,520 Patients identified from the picture archiving communication system	Clinical diagnosis through cancer registry	Detection rates of cancer Diagnostic accuracy

CRC – colorectal cancer; CTC – computed tomographic colonography; DCBE – double contrast barium enema

The American multi-centre study by Rockey et al. (2005) was of high quality and enrolled 775 participants. Of these, 614 underwent CTC, DCBE and colonoscopy, and the reasons for

161 non-completions were described. The reference standard was established by reconciliation of all tests (including pathological assessment of histology specimens), which led to the development of a consensus view of the colon. The American study by Johnson et al. (2004) was conducted at a single centre and was of moderate quality. The population consisted of 837 asymptomatic patients at higher than average risk of CRC. Of the enrolled participants, all underwent CTC followed by same-day DCBE. The reference standard was a confirmatory test that was conducted in 691 patients. The majority of confirmatory tests were flexible sigmoidoscopy (n=581), but some patients also underwent colonoscopy (n=116) or rigid proctoscopy (n=89).

The prospective study by Sofic et al. (2010), conducted in Bosnia and Herzegovina, was of moderate quality. Of the 231 enrolled patients, all underwent CTC, DCBE and colonoscopy, but 4 were excluded from the analysis due to undetermined histopathology results. In the retrospective study by Thomas et al. (2009), conducted in the UK, the results of patients undergoing either CTC (n=631) or DCBE (n=2,648) were assessed according to an agreed scale of 'diagnostic', 'indeterminate' or 'negative'. The interpreted results were then assessed for correctness against the cancer registry, which enabled numbers for both true positive and false negative results to be established, and sensitivity and specificity values to be calculated. While the reference standard (clinical diagnosis as per the cancer registry) for this study was not as defined for this review, the study was of high quality and provided a comparison of diagnostic accuracy between CTC and DCBE. The study by Halligan et al. (2013) randomised patients to either CTC or DCBE but they did not undergo a reference standard test. The authors reported CRC diagnosis data of trial participants at a 3-year follow-up, and these results provided a clinical reference standard.

Diagnostic accuracy for polyps or lesions ≥10 mm

The studies by Rockey et al. (2005) and Johnson et al. (2004) reported accuracy results for CTC compared with DCBE (Table 37). Results of both studies indicated that CTC is more sensitive than DCBE; however, statistical significance was not reached. Specificity results were not consistent between the studies—results by Johnson et al. reached statistical significance in favour of DCBE over CTC.

Table 37 Sensitivity and specificity for CTC versus DCBE for detection of polyps or lesions ≥10 mm

Study	Result	CTC	DCBE	Difference
Rockey et al. (2005)	Sensitivity [95%CI]	0.59 [0.45, 0.71]	0.48 [0.35, 0.61]	p=0.1083 [a]
	Specificity [95%CI]	0.96 [0.94, 0.98]	0.90 [0.87, 0.92]	p<0.0001 [a]
Johnson et al. (2004)	Sensitivity—mean of 3 reviewers [95%CI] [b]	0.69 [0.49, 0.85]	0.48 [0.29, 0.68]	p≥0.06 for 3 reviewers [a]
	Specificity—mean of 3 reviewers [95%CI] [b]	0.97 [0.95, 0.98]	0.99 [0.98, 1.00]	p<0.05 for 2 reviewers [a]

[a] McNemar's test

[b] Sensitivity and specificity reported for three reviewers, each reviewing two patients; 95%CIs calculated from reported data
CI – confidence interval; CTC – computed tomographic colonography; DCBE – double contrast barium enema

Diagnostic accuracy for 6–9 mm lesions and 5–9 mm polyps

Accuracy results were reported for polyp sizes of 6–9 mm and 5–9 mm by Rockey et al. (2005) and Johnson et al. (2004), respectively (Table 38). Both studies showed CTC to be more sensitive than DCBE; however, only Rockey et al. reported a statistically significant result. Specificity was greater for DCBE than CTC in the study by Johnson and colleagues, and the result was statistically significant. Rockey et al. did not report specificity for this group.

Table 38 Sensitivity and specificity for CTC versus DCBE for detection of 6–9 mm lesions or 5–9 mm polyps

Study	Result	CTC	DCBE	Difference
Rockey et al. (2005) [a]	Sensitivity [95%CI]	0.51 [0.41, 0.60]	0.35 [0.27, 0.45]	p=0.008 [c]
	Specificity [95%CI]	NR	NR	NR
Johnson et al. (2004) [b]	Sensitivity—mean of 3 reviewers [95%CI] [d]	0.70 [0.51, 0.85]	0.60 (NR)	p≥0.21 for 3 reviewers [c]
	Specificity—mean of 3 reviewers [95%CI] [d]	0.91 [0.89, 0.93]	0.97 (NR)	p<0.0001 for 3 reviewers [c]

[a] Accuracy measured for 6–9 mm lesions
[b] Accuracy measures for 5–9 mm polyps
[c] McNemar's test
[d] Sensitivity and specificity reported for three reviewers, each reviewing two patients; 95%CIs calculated from reported data
CI – confidence interval; CTC – computed tomographic colonography; DCBE – double contrast barium enema; NR = not reported

Diagnostic accuracy for all lesions

The more recent studies by Thomas et al. (2009) and Sofic et al. (2010) reported sensitivity and specificity results for lesions non-stratified for size (Table 39). The sensitivity for CTC was higher than for DCBE in these studies, and the result reported by Thomas et al. was statistically significant. Neither study reported confidence intervals, and Sofic et al. did not report a p-value for test comparison. Specificity results in both studies were also reported without confidence intervals or a value for test comparison.

Table 39 Sensitivity and specificity for CTC versus DCBE for all lesions

Study	Result	CTC	DCBE	Difference
Sofic et al. (2010)	Sensitivity	0.96	0.76	NR
	Specificity	1.00	1.00	NR
Thomas et al. (2009)	Sensitivity	0.97	0.64	p=0.0012 [a]
	Specificity	0.91	0.98	NR

[a] Fisher's exact test
CTC – computed tomographic colonography; DCBE – double contrast barium enema; NR – not reported

Diagnostic accuracy for CRC

The study by Halligan et al. (2013) reported the number of CRC diagnoses for trial participants at a 3-year follow-up (Table 40). This data enabled calculation of sensitivity values for the CTC and DCBE groups based on clinical diagnosis and false negative test numbers. There was no measurement of the difference between groups, but the results favoured CTC.

Table 40 Sensitivity for CTC versus DCBE for CRC

Study	Result	CTC	DCBE	Difference
Halligan et al. (2013)	Sensitivity [a]	0.93	0.81 [b]	NR

[a] Values calculated from reported CRC diagnosis data at a 3-year follow-up
[b] Halligan et al. (2013) states that DCBE missed 12 of 85 CRCs; however, a further 4 CRCs were missed by DCBE but were detected during follow-up colonoscopy
CTC – computed tomographic colonography; DCBE – double contrast barium enema; NR – not reported

Additional investigations after CTC compared with DCBE

Halligan et al. (2013) provided data for the number of additional investigations that patients who initially received CTC or DCBE underwent (see Table 20). A higher proportion of patients randomised to CTC underwent an additional investigation compared with DCBE (23.5% vs 18.3%; p<0.001). In addition, those who underwent CTC had a higher rate of additional investigations for suspected cancers or polyps ≥10 mm (11.0% vs 7.5%; p<0.001) and smaller polyps (7.2% vs 2.3%; p<0.001). The higher additional investigation rate for CTC is likely to have been due to the higher detection rates found in the CTC group compared with the DCBE group.

Diagnostic accuracy of CTC against a clinical reference standard in patients who are contraindicated for colonoscopy

The literature search identified three articles (Duff et al. 2006; Ng et al. 2008; Saunders et al. 2013) that retrospectively assessed the accuracy of CTC in patients contraindicated for colonoscopy, by comparing CTC results with clinical diagnosis at follow-up. Two of these studies were conducted in frail and elderly patients and used a minimal bowel preparation. A third study (Duff et al. 2006) was conducted in symptomatic patients who were unable to undergo colonoscopy (reasons given were hemiplegia, serious comorbidity, frailty, elderly) or having incomplete endoscopic examination (35% of patients). An additional two studies that also used minimal bowel preparation (Kealey et al. 2004; Robinson, Burnett & Nicholson 2002) were identified from the reference list of a non-systematic review (Koo et al. 2006). While this review was excluded from the current assessment due to selectively reporting on four studies with a pooled analysis, the studies by Kealey et al. and Robinson et al. were

considered eligible for inclusion. They had not been identified previously in the NHMRC CTC review (2006), as that review did not specifically address CTC in contraindicated patients.

In the study by Duff et al. (2006) patients who received a negative CTC result and did not present within 12 months' follow-up were assumed to not have CRC (true negatives). The studies by Ng et al. (2008) and Saunders et al. (2013) used patient records to confirm diagnosis by CTC at a minimum of 15 months and 24 months post-procedure, respectively. Two studies reported using colonoscopy or endoscopy to confirm CTC findings (Duff et al. 2006; Saunders et al. 2011), and a third study reported that CTC findings were confirmed by pathology, although how samples for testing were obtained was not reported (Ng et al. 2008). The studies by Kealey et al. (2004) and Robinson et al. (2002) reported 'clinical outcomes' as a reference standard against which CTC accuracy was measured. A summary of the study details is given in Table 41 and diagnostic accuracy results are reported in Table 42.

Table 41 Summary of study profiles for diagnostic accuracy of CTC in patients contraindicated for colonoscopy

Study	Study design and quality appraisal	Population	Reference standard	Accuracy outcomes assessed
Kealey et al. (2004)	Level III-3 evidence Prospective cohort Quality: Moderate	N=72 Frail/elderly patients with clinically significant colonic tumours	Clinical outcome at 1 year: positive end-points—histological confirmation of CRC; clinical presentation consistent with CRC without confirmation if the patient was too unwell for biopsy/surgery; death due to CRC	Yield—CRC findings Diagnostic accuracy for CRC detection Non-cancer findings
Ng et al. (2008)	Level III-3 Retrospective chart review Quality: Poor	N=1,029 Elderly and frail patients with CRC symptoms	Confirmation of CTC diagnosis by pathology, Cancer registry or follow-up at ≥15 months	Diagnostic accuracy Diagnostic accuracy against the specified standards for CRC Yield of extracolonic findings Overall survival
Saunders et al. (2013)	Level III-3 Retrospective chart review Quality: Poor	N=207 Frail and/or elderly patients requiring bowel investigation	Colonoscopy/2nd CTC to confirm CRC Documented diagnosis at 2-year follow-up	Diagnostic accuracy Diagnostic yield for: CRC by location, polyps, bowel disease other than CRC
Robinson, Burnett & Nicholson (2002)	Level III-3 evidence Retrospective review of patient records Quality: Poor	N=195 Elderly and frail patients with CRC symptoms	Clinical outcomes	Diagnostic accuracy for CTC Yield of normal and non-cancer/polyp intracolonic findings Yield extracolonic findings
Duff et al. (2006)	Level III-3 Retrospective chart review Quality: Poor	N=112 Symptomatic for CRC, contraindicated or unable to complete colonoscopy or	Endoscopy to confirm CRC clinical diagnosis at 12-month follow-up	Diagnostic accuracy Diagnostic yield for: CRC, polyps, diverticular disease

		barium enema		Extracolonic findings

CRC – colorectal cancer; CTC – computed tomographic colonography

Table 42 CTC diagnostic accuracy outcomes for CRC

Study [a]	Sensitivity	Specificity	PPV	NPV
Saunders et al. (2013)	91.6%	84.1%	26.2%	99.4%
Ng et al. (2008)	85.7%	91.4%	49.1%	98.5%
Duff et al. (2006)	87.5%	97.1%	70.0%	99.0%
Kealey et al. (2004) [b]	75.0% (95%CI 35, 97)	87,0% (95%CI 75, 94)	43.0%	96.0%
Robinson et al. (2002)	100%	87.0%	46.0%	100%

[a] The Saunders et al. (2013) and Kealey et al. (2004) studies reported accuracy values for the number of CRC findings, whereas the studies by Ng et al. (2008), Robinson et al. (2002) and Duff et al. (2006) reported values for the number of patients with findings

[b] Accuracy for CTC when lesions classified as 'possible' were ignored

CTC – computed tomographic colonography; PPV – positive predictive value; NPV – negative predictive value; CI – confidence interval

When diagnosis by endoscopy/colonoscopy or pathology was used as a reference standard, sensitivity ranged between 85.7% and 91.6% (Duff et al. 2006; Ng et al. 2008; Saunders et al. 2013). Specificity averaged higher and ranged between 84.1% and 97.1%. Saunders et al. (2013) and Kealey et al. (2004) reported accuracy data based on the number of CRC findings, while Ng et al. (2008), Robinson et al. (2002) and Duff et al. (2006) reported accuracy data based on the number of patients found with lesions. As patients may be found to have more than one lesion, this may account for a lower specificity value in Saunders et al. (2013) than the other two studies; however, none of the studies reported multiple CRCs per patient, and Saunders et al. indicated that the 12 CRCs were found in 12 patients. Saunders et al. (2013) reported the lowest positive predictive value (PPV; 26.2%), in which there was a high proportion of false negative results found by CTC (31/42 findings). The study by Ng et al. also reported higher false positive results for CTC (81/159 findings), while Duff et al. reported a higher PPV (70%) and fewer false positive CTC results (3/10 findings). Negative predictive values (NPVs) were consistently high between the studies. The larger study by Ng et al. reported that there was no significant difference in survival rates between those with true positive and false negative CRC findings with CTC, or between those with false positive and true negative CTC CRC findings.

Diagnostic accuracy of CTC against a reference standard of subsequent colonoscopy or surgery in patients who have undergone incomplete colonoscopy

Although there were 12 articles identified that considered diagnostic outcomes for CTC in patients who had undergone an incomplete colonoscopy, only 2 of these produced sufficient data to report diagnostic accuracy for this group (Copel et al. 2007; Neri et al. 2002). The reference standard in Copel et al.'s study was confirmed diagnosis by subsequent

colonoscopy, and in the study by Neri and colleagues CTC results were confirmed by surgical findings (29 of 35 patients) or colonoscopy. These studies confirm that patients with an incomplete colonoscopy are able to have a complete colonoscopy on a subsequent occasion. A summary of the studies reporting CTC accuracy results in patients who had a previous incomplete colonoscopy can be found in Table 43 and the accuracy results can be seen in Table 44 to Table 46.

Table 43 Summary of studies reporting CTC accuracy in patients who underwent an incomplete colonoscopy

Study	Study design and quality appraisal	Population	Reference standard	Accuracy outcomes assessed
Copel et al. (2007)	Level III-3 evidence Non-comparative retrospective chart review Quality: Poor	N=546 Patients who were referred for further examination after incomplete colonoscopy; high risk of CRC (90.1%)	Subsequent colonoscopic findings	Repeat colonoscopy rate Endoluminal findings PPV of CTC
Neri et al. (2002)	Level III-3 evidence Prospective cohort Quality: Poor	N=34 Patients symptomatic for CRC referred for CTC after incomplete colonoscopy	Confirmation of findings with surgery or colonoscopy	Diagnostic accuracy for CTC (polyps and cancer) Yield of polyps, CRC and extracolonic findings

CRC – colorectal cancer; CTC – computed tomography colonography; PPV – positive predictive value

Table 44 CTC diagnostic accuracy for polyps >5 mm to <10 mm in patients who underwent an incomplete colonoscopy—per lesion analysis

Study	Sensitivity	Specificity	PPV	NPV
Copel et al. (2007) [a]	NR	NR	33.3%	NR
Neri et al. (2002) [a]	100%	80.0%	86.0%	100%

[a] Copel categorised polyps as 6–9 mm, Neri categorised polyps as 5–10 mm

PPV – positive predictive value; NPV – negative predictive value; NR – not reported

Table 45 CTC diagnostic accuracy outcomes for polyps ≥10 mm in patients who underwent an incomplete colonoscopy—per lesion analysis

Study	Sensitivity	Specificity	PPV	NPV
Copel et al. (2007)	NR	NR	70%	NR
Neri et al. (2002)	100%	100%	100%	100%

PPV – positive predictive value; NPV – negative predictive value; NR – not reported

Table 46 CTC diagnostic accuracy for CRC in patients who underwent an incomplete colonoscopy—per lesion analysis

Study	Sensitivity	Specificity	PPV	NPV
Copel et al. (2007)	NR	NR	33.3%	NR
Neri et al. (2002)	100%	96%	96%	100%

PPV – positive predictive value; NPV – negative predictive value; NR – not reported

Diagnostic yield for CTC in patients who have undergone an incomplete colonoscopy or who are contraindicated for colonoscopy

A number of studies provided non-comparative data on the yield of polyps in patients receiving CTC. These studies were included if they fitted the target population criteria for this review; that is, those at high risk or symptomatic for CRC *and* also (a) contraindicated for colonoscopy, or (b) had received an incomplete colonoscopy (n=17 studies). Given the low level of evidence for these studies, individual quality assessment of the studies was not performed.

Studies were also identified that assessed or discussed the success rates of repeat colonoscopy in patients who had previously undergone an incomplete colonoscopy. While the results of the repeat colonoscopy procedures do not directly answer the research questions in this review, their outcomes were considered to be relevant as they give some insight to the demand for CTC services that may result from the proposed changes to the MBS item descriptors. A discussion of repeat colonoscopy in those who have undergone an incomplete colonoscopy can be found in the 'Other relevant considerations' section on page 97.

CTC diagnostic yield in patients who have undergone an incomplete colonoscopy

Twelve studies were identified that provided CTC diagnostic yield data for patients who had previously undergone an incomplete colonoscopy. Of these, 4 studies were found in the 2006 CTC Review (Luo Mingyue 2002; Macari et al. 1999; Morrin et al. 1999; Neri et al. 2002) and the remaining studies were published between 2007 and 2013. One study (Yucel et al. 2008) included a group of patients who were contraindicated for colonoscopy, but the results were not separated. These studies are summarised in Table 47.

Table 47 Summary of studies reporting diagnostic yield for CTC in patients who had undergone an incomplete colonoscopy

Study	Study design	Population	Outcomes assessed
Copel et al. (2007)	Level IV evidence Non-comparative retrospective chart review	N=546 Patients who were referred for further examination after incomplete colonoscopy; high risk of CRC (90.1%)	Repeat colonoscopy rate Endoluminal findings PPV of CTC
El-Sharkawy et al. (2013)	Level IV evidence Consecutive case series	N=71 Patients suspected of CRC, and referred for CTC mainly after incomplete colonoscopy (13 patients refused or were contraindicated)	Reasons for incomplete colonoscopy Findings from CTC
Iafrate et al. (2008)	Level IV evidence Non-comparative prospective case series	N=136 Elderly patients (>70 years of age) who were referred for CTC because of a previous incomplete colonoscopy	Colonic CTC findings Extracolonic findings Patient acceptability and compliance
Luo Mingyue (2002)	Level IV evidence Non-comparative	N=60 Patients referred for CTC after incomplete	Yield for CTC Percentage of patients and

	case series	colonoscopy	segments successfully examined Reasons for incomplete colonoscopy and CTC
Macari et al. (1999)	Level IV evidence Single-centre case series	N=20 Patients who underwent CTC and DCBE after incomplete colonoscopy	CTC yield DCBE yield
Morrin et al. (1999)	Level IV evidence Single-centre prospective case series	N=40 Symptomatic or high-risk patients referred for CTC after incomplete colonoscopy	Yield for CTC and DCBE Colonic visualisation Reasons for incomplete colonoscopy Extracolonic findings
Neerincx et al. (2010)	Level IV evidence Multi-centre prospective case series	N=285 Consecutive patients with an incomplete colonoscopy who underwent a secondary investigation (including 2nd colonoscopy, CTC, DCBE, abdominal CT, surgery)	Diagnostic yield Number of malignant lesions missed by incomplete colonoscopy Reasons for incomplete colonoscopy Rates of complete colonic evaluation after a second investigation
Neri et al. (2002)	Level IV evidence Prospective case series	N=34 Patients symptomatic for CRC referred for CTC after incomplete colonoscopy	Diagnostic accuracy for CTC (polyps and cancer) Diagnostic yield (polyps, CRC, extracolonic findings)
Pullens et al. (2013)	Level IV evidence Retrospective chart review	N=136 Patients symptomatic for CRC who underwent an incomplete colonoscopy and were referred for CTC	Reasons for incomplete colonoscopy Yield for incomplete colonoscopy, colonic CTC findings, extracolonic CTC findings
Salamone et al. (2011)	Level IV evidence Non-comparative single-centre case series	N=68 Patients symptomatic for CRC who underwent an incomplete colonoscopy and were referred for CTC	Reasons for incomplete colonoscopy Incomplete colonoscopy, colonic and extracolonic CTC findings
Sali et al. (2008)	Level IV evidence Non-comparative prospective case series	N=42 Patients with a positive FOBT result who underwent an incomplete colonoscopy and were referred for CTC	CTC diagnostic yield PPV for CTC
Yucel et al. (2008)	Level IV evidence Retrospective chart review	N=61 Patients >60 years of age referred for CTC due to contraindication (29%) or incomplete colonoscopy (71%)	Diagnostic yield for colonic and extracolonic CTC findings Reasons for incomplete colonoscopy

CRC – colorectal cancer; CTC – computed tomography colonography; FOBT – faecal occult blood test; DCBE – double contrast barium enema; PPV – positive predictive value

The diagnostic yield from CTC in patients who had previously undergone an incomplete colonoscopy can be seen in Table 48. All 12 studies reported the number of CRCs and polyps found. Polyps were mostly reported in size categories of ≥10 mm and 6–9 mm or 5–10 mm, and in one study a category of ≤5 mm was also reported. For the purposes of this assessment, polyps have been recategorised as either ≥10 mm or <10 mm. In three studies (El-Sharkawy et al. 2013; Neerincx et al. 2010; Salamone et al. 2011) polyps were not given a measurement but were described as 'large', 'medium', 'small' or 'non-advanced adenomas'.

Polyps described as 'large' are categorised here as ≥10 mm, whereas polyps with other descriptors are categorised as <10mm.

Some studies also reported the number of patients diagnosed with CRC or polyps. These results have been included as per-patient yield results due to potential implications for the economic assessment.

Table 48 Diagnostic yield for CTC after incomplete colonoscopy

Study	CTC investigations after incomplete colonoscopies (N patients)	Per-patient yield (CRC and polyps)	Yield—CRCs	Yield—polyps <10 mm	Yield—polyps ≥10 mm
Copel et al. (2007)	546/546	45/546 (8.2%)	12	53	23
El-Sharkawy et al. (2013)	71/71	22/71 (31.0%)	22	9	1[a]
Iafrate et al. (2008)	136/136	17/136 (12.5%)	6	0	9
Luo et al. (2002)	60/60	15/60 (25%)	1	14	2
Macari et al. (1999)	10/20	2/10 (20%)	0	1	1
Morrin et al. (1999)	40/40	7/40 (17.5%)	0	9	0
Neerincx et al. (2010)	14/511	4/14 (28.6%)	1	3[b]	0
Neri et al. (2002)	34	NR	30	36	11
Pullens et al. (2013)	136/136	19/136 (13.9%)	4	19	0
Salamone et al. (2011)	68/68	NR	0	40	20
Sali et al. (2008)	42/65	21/42 (50%)	0	23	6
Yucel et al. (2008)	42/42[c]	22/42 (52%)	0	31	12

[a] Size not given but polyp described as 'large'
[b] Size not given but described as 'non-advanced adenomas'
[c] Group included 12 patients who did not undergo incomplete colonoscopy but were contraindicated for colonoscopy
CTC – computed tomographic colonography; N – number; NR – not reported

While the results in Table 48 do not necessarily reflect an accurate diagnosis, they do indicate that CTC can detect lesions in patients for whom a colonoscopy has been unable to be completed. The number of CRCs and polyps detected per patient varies from study to study, and may reflect random variation in the study populations or indicate the risk level of the study population. The technical level of the scanning or image acquisition equipment, and the skill level of the radiologist performing the service, varied between studies. In some studies not all patients who had undergone an incomplete colonoscopy were given a CTC, as this was dependent on clinical assessment, and in some cases the patients were given investigations other than CTC including a second colonoscopy. Per-patient results for CTC

findings were reported in 10 studies. Table 42 reports the number of patients (and proportion) in each study who underwent CTC and were found to have either polyps or CRC. The proportions range between 8.2% in the largest study (Copel et al. 2007; n=546) to 52% in the study by Yucel et al. (2008; n=42); while varied, these results indicate a trend toward high yield in patients who have undergone an incomplete colonoscopy. This may be a reflection of the higher risk in this population, noting that the population in the study by Copel et al. included 54 (10%) patients at low risk of CRC being screened. The studies are reasonably consistent in that most patients who underwent CTC were ruled out from requiring a colonoscopy, thereby avoiding the need to attempt the invasive procedure again; the exception was the study by Yucel et al., who reported that 52% of patients were detected with a polyp or CRC.

CTC diagnostic yield in patients who are contraindicated for colonoscopy

In addition to the studies that reported diagnostic yield for CTC in patients with an incomplete colonoscopy, five studies were identified that reported similar results for patients who were contraindicated for colonoscopy, including two studies pearled from Koo et al. (2006) (Kealey et al. 2004; Robinson, Burnett & Nicholson 2002). Four of these studies were conducted in frail and elderly patients and used a minimal bowel preparation. A fifth study (Duff et al. 2006) assessed CTC performance for exclusion of CRC at a 1-year clinical follow-up. It was conducted in symptomatic patients who were described as either having an inability to complete, or likely to have an inadequate, barium enema (55% of patients, reasons given were hemiplegia, serious comorbidity, frailty, elderly), or having an incomplete endoscopic examination (35% of patients). A summary of the study characteristics is given in Table 49 and the per-patient yield for CRC and polyps/lesions is shown in Table 50.

Table 49 Summary of studies reporting diagnostic yield for CTC in patients who are contraindicated for colonoscopy

Study	Study design and quality appraisal	Population	Accuracy outcomes assessed
Kealey et al. (2004)	Level III-3 evidence Prospective cohort Quality: Fair	N=72 Frail/elderly patients with clinically significant colonic tumours	Yield—CRC findings Diagnostic accuracy for CRC detection Non-cancer findings
Robinson, Burnett & Nicholson (2002)	Level III-3 evidence Retrospective review of patient records Quality: poor	N=195 Elderly and frail patients with CRC symptoms	Diagnostic accuracy for CTC yield of normal and non-cancer/polyp intracolonic findings Yield—extracolonic findings
Saunders et al. (2013)	Level IV evidence Retrospective chart review	N=207 Frail and/or elderly patients requiring bowel investigation	Diagnostic yield for: CRC by location, polyps, bowel disease other than CRC
Ng et al. (2008)	Level IV evidence Retrospective chart	N=1,029 Elderly and frail patients with CRC	Diagnostic accuracy against the specified standards for CRC

	review	symptoms	Yield of extracolonic findings Overall survival
Duff et al. (2006)	Level IV evidence Retrospective chart review	N=112 Symptomatic for CRC, contraindicated or unable to complete colonoscopy or barium enema	Diagnostic yield for: CRC, polyps, diverticular disease Extracolonic findings

CRC – colorectal cancer; CTC – computed tomography colonography; N – number;

Table 50 Diagnostic yield for CTC in patients who are contraindicated for colonoscopy

Study	CTC investigations (N patients)	Yield—patients with CRC (% of total)	Yield—patients with polyps/lesions (% of total)
Saunders et al. (2013)	207	12/207 (6%)	30/207 (14%)
Ng et al. (2008)	1,029	78/1,029 (8%)	NR
Duff et al. (2006)	112	10/112 (9%)	9/112 (8%)
Kealey et al. (2004)	68	7/68 (10%) [a]	NR
Robinson et al. (2002)	195	12/195 (6%) [b]	NR

[a] Yield for CTC when lesions classified as 'possible' were ignored
[b] 'Definite' CRC ('possible' CRC not shown here)
CRC – colorectal cancer; CTC – computed tomographic colonography; N – number; NR – not reported

The results in Table 50 reflect the ability of CTC to detect CRC and polyps in a population contraindicated for colonoscopy. Furthermore, by using CTC in these populations, the majority of patients were able to avoid the requirement for further invasive investigations, which is considered important in the frail and elderly.

CTC extracolonic findings

In addition to diagnostic yield for CRC and polyps, 10 articles reported extracolonic findings for patients who underwent CTC following an incomplete colonoscopy (El-Sharkawy et al. 2013; Iafrate et al. 2008; Luo Mingyue 2002; Macari et al. 1999; Neerincx et al. 2010; Neri et al. 2002; Pullens et al. 2013; Salamone et al. 2011; Sali et al. 2008; Yucel et al. 2008). One study conducted in patients contraindicated for CTC also reported extracolonic findings (Saunders et al. 2013). Unlike DCBE, CTC has the capacity to diagnose conditions other than those within the bowel, and these findings have the potential to alter patient management in those with and without CRC or polyp diagnoses. The yield of extracolonic findings in the different studies is given in Table 51.

Table 51 Diagnostic yield of extracolonic findings using CTC following incomplete colonoscopy or in patients who are contraindicated to colonoscopy

Study	Incomplete colonoscopies followed by CTC (N patients)	Yield—all findings (N patients)	Yield—all findings (N findings)	Clinically significant findings (N findings)
El-Sharkawy et al. (2013)	71/71	12/71 (16.9%)	NR	Not described
Iafrate et al. (2008)	136/136	92/136 (67%)	204 High clinical importance: 23 (11%) [a] Moderate clinical importance: 60 (29.4%) Low clinical importance: 121 (56.6%)	Lymphadenopathies: 6 Metastasis: 4 Abdominal aortic aneurysm: 5 Pulmonary nodules: 3 Renal solid mass: 1 Mammillary nodule: 1 Gallbladder carcinoma: 1 Adrenal metastasis: 1 Liposarcoma: 1
Luo et al. (2002)	60/60	1/60 (1.7%)	1	Non-Hodgkins lymphoma: 1
Morrin et al. (1999)	40/40	5/40 (12.5%) [b]	5	Mesenteric and pericolic lymphadenopathy: 1 Suprarenal aortic aneurysm: 1 Complex ovarian cyst: 1 Partially obstructing ventral hernia: 1 Large fibroid with bowel compression: 1
Neerincx et al. (2010)	14/511	0/14	0	0
Neri et al. (2002)	34/34	3/34 (8.8%)	4	Hepatic lesions [c]: 4
Pullens et al. (2013)	136/136	15/136 (11%)	23 Potentially important findings: 8 (25%) Likely unimportant findings, incompletely characterised: 15 (65%)	Fistulising diverticulitis: 3 Gastric lymphoma / stromal tumour: 2 Liver abscess: 1 Infected embolisms of the renal arteries: 1 Presacral infiltration due to chronic osteomyelitis: 1
Salamone et al. (2011)	68/68	44/68 (64.7%)	46 Clinically significant findings: 24 (54.5%) Miscellaneous findings: 12 (27.3%) Others: 10 (22.7%)	Focal lesions of kidney: 6 Lythiasis of gallbladder: 3 Fibromatosis of uterus: 3 Hypodense hepatic lesions: 3 Renal cysts: 3 Urolythiasis: 3 Atherosclerosis: 3
Sali et al. (2008)	42/65	7/42 (10.8%)	7	Aneurysm of abdominal aorta: 1 Renal masses: 2 Hepatic focal lesion other than

Study	Incomplete colonoscopies followed by CTC (N patients)	Yield—all findings (N patients)	Yield—all findings (N findings)	Clinically significant findings (N findings)
				cystic: 1 Splenomegaly: 1 Pulmonary nodules: 2
Yucel et al. (2008)	42/42 [c]	High clinical importance [d]: 26/42 (62%) Low clinical importance: 36/42 (86%)	98 High clinical importance: 32 (33%) Low clinical importance: 68 (67%)	Pancreatic mass: 2 Renal mass: 1 Ovarian cyst mass: 1 Renal complex cyst:, 3 Hepatic complex cyst: 1 Adrenal mass: 4 Gallstones: 5 Renal stones: 3 Hydronephrosis: 2 Enlarged lymph nodes: 3 Splenomegaly: 2 Aortic aneurysm: 2 Pleural effusion: 1 Thickened ileal loops due to scleroderma: 1 Chronic calcific pancreatitis: 1

[a] In 14 cases (1 gall-bladder carcinoma, 4 metastases, 3 lymphadenopathies, 3 abdominal aortic aneurysms, 1 adrenal metastasis, 2 pulmonary nodules) diagnosis of extracolonic lesions was known before CTC
[b] Clinically significant findings only
[c] The scanning protocol of this study allowed a three-phase liver study (non-enhanced phase, contrast-enhanced portal and later phases)
[d] The total number of findings is greater than the number of patients because many had more than one finding
CTC – computed tomography colonography; N – number; NR – not reported

Extracolonic findings were varied in nature. The yield for clinically significant extracolonic findings by CTC was lowest in the study by Neerincx et al. (2010; 0 findings) and highest in the study by Yucel and colleagues (2008; 26 findings of high clinical importance; 62% of patients who underwent CTC). Salamone et al. (2011) also reported a high yield per patient and per finding (24 clinically significant findings; 54.5% of patients who underwent CTC). Yield was dependent on the degree and detail of reporting, and four studies (Iafrate et al. 2008; Pullens et al. 2013; Salamone et al. 2011; Yucel et al. 2008) reported findings that were stratified according to clinical importance. Findings of lower clinical importance were more frequent, and in some cases patients had multiple extracolonic findings. An additional two articles (Kealey et al. 2004; Robinson, Burnett & Nicholson 2002) reported extracolonic yield; however, clinically significant findings were not separated and therefore the data are not presented. Kealey et al. (2004) and Robinson et al. (2002), respectively, reported extracolonic findings in 15/68 (22%) and 28/195 (14%) patients who underwent CTC.

Despite the four studies mentioning the clinical importance of the findings, it is unknown to what degree the management of the patients would have been influenced by these findings;

that is, what clinical benefit the extracolonic findings would have had for the patients imaged by CTC.

Is CTC accurate compared with delayed colonoscopy?

No studies were identified that compared CTC and DCBE or delayed colonoscopy—studies providing evidence on the accuracy of CTC in patients for whom there is a delay in accessing colonoscopy. Given that colonoscopy is considered the gold reference standard, CTC could at best be found to be as accurate as colonoscopy. In the absence of directly relevant information, level I evidence was sought to determine the accuracy of CTC against colonoscopy with no specified time delay. The most recent systematic review (Pickhardt et al. 2011), which specified the use of CTC and colonoscopy for diagnostic purposes (rather than only for screening), is described in Table 52. The reference standard was histology—only those who were found to be test positive had their result verified; thus, it was possible to present data on test sensitivity but not specificity.

Table 52 Systematic review reporting on accuracy for CTC compared with colonoscopy for the diagnosis of CRC

Review	Study design and quality appraisal	Population	Reference standard	Accuracy outcomes assessed
Pickhardt et al. (2011)	Level I evidence Systematic review Quality: Moderate	K=49, N=11,151 patients Patients were either asymptomatic (K=6, N=4,883) or symptomatic (K=43, N=6,668)	Histology	Sensitivity

CTC – computed tomographic colonography; CRC – colorectal cancer;

Against a histological reference standard, CTC was found to be as sensitive as colonoscopy with no specified time delay (Table 53). It is therefore reasonable to conclude that it would be at least as sensitive as delayed colonoscopy. No level I evidence could provide data on the specificity of CTC and colonoscopy.

Table 53 Sensitivity for CTC versus colonoscopy

Result	CTC	Colonoscopy	Difference
Overall sensitivity (95%CI)	96.1% (93.8, 97.7)	94.7% (90.4, 97.2)	NR
Screening sensitivity (95%CI)	100% (93, 100)	NR	NR
Diagnostic sensitivity (95%CI)	96% (93, 98)	NR	NR

CTC – computed tomography colonography; NR – not reported

Summary of the change in management:

Radiologists were more confident that patients could be ruled out from requiring further investigations after a negative result on CTC than after a negative result on DCBE.

It is hypothesised that the outcome of the higher rate of false negative results due to DCBE would be delays in diagnosis for those inappropriately ruled out by DCBE. It is expected that CTC would result in earlier diagnosis and treatment in these patients. This may be at the expense of an increase in subsequent, unwarranted investigations, as CTC has a higher false positive rate than DCBE.

In the situation where access to both colonoscopy and DCBE is limited, it is expected that CTC would result in earlier diagnosis and management than delayed colonoscopy.

Does CTC change patient management compared with DCBE?

Following the assessment of the accuracy of CTC compared with DCBE, the next step in the evidence linkage is to determine the impact of the use of CTC on patient management. The published literature was searched for evidence and assessed for inclusion using the PICO criteria illustrated in Table 13. One identified study reported relevant outcomes (Taylor et al. 2006). It assessed the confidence of experienced radiologists to exclude colorectal neoplasia with CTC, compared with DCBE, in a cohort of older patients symptomatic for CRC, who were recruited from a UK radiology department. The study profile summary is provided in Table 54.

Table 54 Summary profile to determine CTC impact on patient management

Study setting	Study design / Quality appraisal	Study participants	Inclusion criteria / Exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed
Taylor et al. (2006) UK 2006	Level III-2 Prospective cohort Quality: Moderate to high	N=78 Females: 56% Median age (range): 70 (61–87) years	Inclusion 60 years of age and older Referred for DCBE with clinical suspicion of CRC Exclusion NR	Diagnostic tests CTC and DCBE Confirmatory tests endoscopy records (22 patients)	Radiologist confidence to exclude colorectal neoplasia

CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema; NR – not reported

Taylor et al. (2006) reported on patients who underwent same-day CTC and DCBE procedures, which were compared with an additional endoscopy examination in a small subgroup (22 out of a total 74 who underwent DCBE and CTC). In all cases where there was a lesion greater than 6 mm, the results underwent radiological review. CTC was performed by one of two experienced radiologists who graded their response for excluding significant findings (defined as a polyp 6 mm or larger) as 'yes', 'probably' or 'no'. For responses of 'probably' or 'no', reasons for non-exclusion were recorded. DCBE was also performed by one of two experienced radiologists, and their responses to findings were similarly rated.

Responses of 'no' and 'probably' were combined and compared with the 'yes' responses, and analysis was performed to determine if there was any difference in confidence levels. Results for radiologist confidence per colonic segment for excluding a significant lesion with CTC and DCBE are shown in Table 55.

Table 55 Lesion exclusions for CTC versus DCBE for all lesions

Segment	Lesions excluded using DCBE N patients (%)	Lesions excluded using CTC N patients (%)	Difference [a]
Rectum	64 (86)	69 (93)	p=0.27
Sigmoid	49 (67)	52 (71)	p=0.69
Descending	63 (85)	70 (94)	p=0.02
Transverse	53 (72)	61 (82)	p=0.13
Ascending	44 (59)	65 (87)	p<0.001
Caecum	64 (86)	64 (86)	p<0.001
All segments (444 total segments)	314 segments excluded	382 segments excluded	p<0.001

[a] Separate segments: paired exact test; all segments: logistic regression

DCBE – double contrast barium enema; CTC – computed tomography colonography

Despite the lesion exclusion rate being higher with CTC than DCBE for all but one comparison, there was no statistically significant difference in confidence between CTC and DCBE for exclusion of significant polyps in the sigmoid, rectum and transverse colon. For the descending and ascending colon and caecum, confidence in exclusion was significantly higher with CTC. The study's finding was that, overall, radiologists excluded a lesion >6 mm in significantly more segments with CTC than with DCBE (382 vs 314 of 444 segments, p<0.001). In addition, the study reported the findings of colonoscopy in eight patients who underwent the procedure following CTC or DCBE (Table 56).

Table 56 Findings of colonoscopy following reported abnormal findings with CTC and DCBE

Pathology	Colonoscopy findings	CTC detection (%)	DCBE detection (%)	CTC false positive results	DCBE false positive results
Cancer	1	1 (100)	1 (100)	0	0
Polyp 1–5 mm	10	3 (30)	0 (0)	3	0
Polyp 6–9 mm	0	NA	NA	4	1
Polyp ≥10 mm	2	2 (100)	2 (100)	1	0

CTC – computed tomography colonography; DCBE – double contrast barium enema

While the comparison of results with colonoscopy is reported in only a small number of patients, they show a tendency for radiologists to report more false positive results with CTC than with DCBE. However, for DCBE, all smaller polyps (1–5 mm) went undetected, compared with CTC. The two predominant reasons cited for non-exclusion that occurred with both procedures were residue (DCBE 41%, CTC 35%) and poor distension (DCBE 15%, CTC 45%). Information on false negative findings was not reported in the study. The

author's overall conclusion was that radiologists more confidently excluded significant lesions with CTC than with DCBE. They further commented that confidence in disease exclusion is an important factor in deciding patient outcomes, and could be considered alongside the sensitivity of the diagnostic procedure when determining patient management.

From the accuracy results of CTC versus DCBE, it can be concluded that CTC is more sensitive than DCBE. Thus, when patients have CRC they are more likely to be identified with CTC than DCBE. When a patient *is* ruled out by CTC, the radiologist has greater confidence that there is truly no lesion than when a patient is ruled out by DCBE (as, according to the test accuracy data, there are fewer false negative results from CTC than DCBE). The greater proportion of patients testing false negative from DCBE are therefore hypothesised to not receive treatment as early as would be the case if they received CTC. Consequently, for the linked assessment of the impact of this change, it was decided to compare the results of early versus late treatment.

Specificity was slightly lower for CTC than for DCBE; that is, of those who are truly negative, fewer were ruled out by CTC than DCBE. More patients are therefore referred on for colonoscopy after CTC than after DCBE. In effect, this means that the spectrum of patients referred after CTC is broader than the spectrum referred after DCBE, and the usual methodology for evidence linkage would be to assess the impact of performing colonoscopy in this wider spectrum of patients. However, all patients being considered for either DCBE or CTC in this scenario are those who are already indicated for a colonoscopy. Therefore, despite the change in the spectrum of patients going on to have a colonoscopy after CTC and DCBE, this broader spectrum would already be receiving a colonoscopy if they are able; that is, if they had not already had a failed colonoscopy or a contraindication, or had difficulty accessing colonoscopy. Given that the expected change in patient spectrum when replacing DCBE with CTC would still be captured within the patient group currently recommended to receive colonoscopies, the impact of this spectrum change is likely to be minimal, and therefore has not been formally evaluated.

Does CTC change patient management compared with delayed colonoscopy?

No studies were identified that compared CTC and delayed colonoscopy, and reported the impact on patient management. Australian data were not available on whether CTC is more accessible than colonoscopy, although the assumption in all the public consultation responses to the DAP was that this would be the case. The Applicant expects that accessibility would further improve if MSAC recommends listing for the proposed indications, as the current lack of a rebate is a disincentive to radiologists seeking accreditation in private practice. However, this should be interpreted in the context that CTC is already

available and being rebated for other CRC indications. Accessibility to CTC is also expected to improve as current radiology trainees enter practice. The Applicant has stated that CTC interpretation may be performed remotely—although the reading and interpretation of CTC must be performed by an accredited radiologist, the procedure itself can be performed by a radiographer with/without a nurse at the site of the examination. This may assist with access to CTC for patients in remote locations.

In a setting where access to colonoscopy and, similarly, to DCBE (as it requires similar types of resources) is difficult, it is unknown whether reimbursing CTC would impact the time to treatment—the time from index contact to the time the patient receives intervention. If patients are found to have a lesion visible on CTC, they are likely to be referred for colonoscopy for a biopsy and/or polyp removal. Thus, for those who test positive, access to colonoscopy may still remain a problem. However, it is assumed that these patients would be recommended to travel to a regional centre for further assessment and treatment. Therefore, it is expected that the change in management from accessing CTC would be earlier diagnosis and treatment rather than a scenario in which patients wait for a delayed colonoscopy.

As CTC is expected to rule out some patients not requiring a colonoscopy, it is also expected that CTC would reduce the total number of patients needing a colonoscopy, possibly allowing better access for those who require it.

Those who are found to be negative for signs of CRC on a CTC may receive earlier reassurance, or seek alternative diagnoses, than if they had to wait for a delayed colonoscopy.

Summary of the impact of change in management:

Survival of CRC is highly stage dependent, although this may be partially due to lead-time bias. Within a screening population there is evidence that early intervention improves health outcomes, whereas in a symptomatic population there is an association between early diagnosis or treatment and worse survival. This is likely due to more-severe cases receiving a faster diagnosis and initiation of treatment. While evidence of a clinical benefit from reducing waiting times to CRC diagnosis and treatment in the populations relevant to this assessment is lacking, it is known that CRC-specific survival is stage dependent. Earlier diagnosis is assumed to lead to earlier intervention and better outcomes.

Do changes in management associated with CTC improve patient health outcomes?

The inclusion criteria for the last step of the linked evidence approach are shown in
Table 14. As outlined above, for the comparison of CTC versus DCBE, the main change expected is that patients are more likely to have false negative results from DCBE, which may lead to a delay in diagnosis and treatment of CRC. The increase in false positive results from CTC relative to DCBE will not impact on health outcomes, except in terms of being at risk of adverse events from an unnecessary colonoscopy or further investigation (see safety section). The main impact will be on costs.

In the comparison of CTC versus delayed colonoscopy, it is expected that CTC may result in those with lesions (true positives) receiving earlier diagnosis and treatment than those waiting for a delayed colonoscopy.

Data from the National Cancer Institute in the United States indicates that survival from CRC is stage dependent (National Cancer Institute 2013). Earlier diagnosis is assumed to lead to earlier intervention and better outcomes. However, the difference in survival rates may also be due to lead-time bias, survival being measured from the time of diagnosis until death; thus, with earlier detection of cancer, survival may be seen to be longer without any actual survival difference in the patient (DLA Piper Australia 2011).

Within the general population the benefit of early versus late treatment has been evaluated in the NHMRC clinical practice guidelines for CRC (Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005), reporting on evidence from RCTs that screening in an asymptomatic population for faecal occult blood (on an intention-to-screen basis) reduced mortality by 15–33% and the incidence of CRC by 20%. Further controlled trials have reported benefits within individuals at high risk of CRC due to familial nonpolyposis CRC (Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005).

One systematic review was identified assessing whether diagnostic and/or therapeutic delay impacted survival, or stage of disease at time of diagnosis/treatment (Table 57).

Table 57 Systematic review reporting on the clinical impact of early versus late diagnosis and treatment

Review	Study design and quality appraisal	Population	Health outcomes assessed
Ramos et al. (2007) Ramos et al. (2008)	Level I evidence Systematic review Quality: Moderate	K=17 studies, N=5,209 patients Studies that included patients from hospital-based settings or population-based settings, with colorectal cancer, colon cancer or rectal cancer Published and unpublished studies between 1965 and 2006 in English or Spanish	Survival Stage at time of diagnosis

This systematic review of publications between 1965 and 2006 identified 50 studies, of which only 8 provided sufficient data to meta-analyse (Table 58). According to a random-effects model, longer delays were associated with better survival (K=8, N=3680; RR_p=0.92, 95%CI 0.87, 0.97). It is unlikely that a shorter delay would cause worse survival; rather, it is probable that those with more-severe signs or symptoms would be diagnosed and treated within a shorter time-frame. This suggests that patients may be receiving adequate triage; that is, that patients with more-advanced disease are seen sooner than those with non-specific complaints, or those who are asymptomatic but at high risk of having CRC may experience longer delays until diagnosis or therapy.

Table 58 Review on association between diagnostic or therapeutic delays and stage of disease and survival

Publication	Outcome measure	Site	Number of studies/patients	Results	Significance
Ramos et al. (2007)	Survival	Colorectal	K=8, N=3,680	RR_p=0.92 (95%CI 0.87, 0.97) Favours longer delay	p<0.05
Ramos et al. (2008)	Stage at diagnosis/treatment	Colorectal	K=17, N=5,209	OR_p=0.98 (95%CI 0.76, 1.25)	Not significant
Ramos et al. (2008)	Stage at diagnosis/treatment	Rectal	K=4, N=799	OR_p=1.93 (95%CI 0.89, 4.22)	Not significant
Ramos et al. (2008)	Stage at diagnosis/treatment	Colon	K=4, N=1,001	OR_p=0.86 (95%CI 0.63, 1.19)	Not significant

RR – relative risk; OR – odds ratio

There was no association between delay and disease stage for patients with CRC over the 17 studies reported by Ramos et al. (Table 58). However, when colon cancer and rectal cancer were evaluated separately (in 4 studies), opposite results were found. In rectal cancer there was a non-significant trend towards a shorter delay being associated with less-advanced disease at time of diagnosis, whereas for patients with colon cancer there was a trend towards a shorter delay being associated with more-advanced disease at time of diagnosis. This might be a consequence of symptomatic differences between rectal and colon cancers, and therefore differences in staging at diagnosis, or simply a consequence of other differences in the patient populations included in the two meta-analyses (e.g. patient age). A minority of colon cancer patients present with intestinal obstruction, which can

require emergency treatment; that is, the delay between symptoms and diagnosis/treatment is minimal or non-existent. However, prognosis is worse for these patients than for patients with colon cancers presenting with other index symptoms (Ramos et al. 2008). More research is therefore necessary, stratifying results by symptoms at presentation, to establish whether, for similar patient groups, a delay in the diagnosis of CRC is associated with reduced survival.

These data were not stratified according to the type or severity of presenting symptoms, but it is hypothesised that, if they were, results would favour shorter waiting periods.

Other relevant considerations

Successful colonoscopy after an incomplete colonoscopy

The literature search identified a number of articles that assessed the accuracy or yield of CTC following an incomplete colonoscopy. Several articles also reported the rate of successful repeat colonoscopies in their study populations. A discussion of the information provided in these articles is included here because it is relevant to the decision regarding whether to perform a CTC for those who have undergone an incomplete colonoscopy.

In several studies reporting diagnostic yield for CTC after an incomplete colonoscopy, the number of successful repeat colonoscopies was also reported. Three studies focused on reporting the reasons for incomplete colonoscopy and the rate of successful secondary colonoscopy in retrospective analyses (Brahmania et al. 2012; Kao et al. 2010; Rex, Chen & Overhiser 2007). Common reasons reported for colonoscopy not being completed were similar between studies, and included patient discomfort or pain, inadequate sedation, poor bowel preparation, obstructive mass or stricturing disease (Table 59).

Kao et al. (2010) aimed to investigate whether DCBE was the appropriate procedure after an incomplete colonoscopy. They reported that many patients who underwent an incomplete colonoscopy had modifiable factors that if properly addressed would enable a successful repeat procedure. Increased sedation to improve patient comfort and cooperation, change of bowel preparation or allocating more time to navigate a redundant colon were several factors claimed to lead to successful repeat colonoscopies. For other authors (Brahmania et al. 2012) a standard procedure was successful in 76% of repeat procedures, but more attention was paid to patient positioning or another sized scope was used, and all repeat colonoscopies were performed within the standard allocated time of 30 minutes (±5 minutes). Rex et al. (2007) reported on special manoeuvres or devices used to complete repeat colonoscopies. The most common non-standard device was the paediatric colonoscope, with or without guidewire exchange or external straightener.

The proportion of patients who underwent a successful colonoscopy following an incomplete colonoscopy varied between studies, and was sometimes reported alongside the number of other secondary procedures performed or the diagnostic yield of CRC and/or polyps. In three studies (Brahmania et al. 2012; Kao et al. 2010; Rex, Chen & Overhiser 2007) repeat colonoscopies were successful in a consistently high proportion of patients. The findings of these studies are shown in Table 59.

Table 59 Findings of studies reporting on repeat colonoscopy following incomplete colonoscopy

Study	Reasons for incomplete colonoscopy (% patients)	Proportion successful repeat colonoscopies (%)	CRC yield [a]	Polyp yield [a]
Brahmania et al. (2012)	Poor preparation (11%) Patient discomfort (16%) Tortuous/redundant colon (30%) Diverticular disease (6%) Obstructing mass (6%) Stricturing disease (10%)	87/90 (97%)	Not reported	Not reported
Kao et al. (2010)	Patient discomfort (30.2%); Floppy/redundant colon (29%)	40/42 (95%)	2 (2 patients)	<5 mm: 6 >5 mm: 8 No size given: 2 (10 patients in total)
Rex et al. (2007)	Sigmoid stricture, angulation, diverticulitis or other disease (28%) Looping/redundant colon (45%) Difficulty in sedating (7%)	117/119 (98%)	3 (3 patients)	3 (3 patients)

[a] Findings additional to initial colonoscopy

CRC – colorectal cancer

An important consideration arising from this discussion is that repeat colonoscopic procedures can be successful. When barriers to completing a colonoscopy are technical (e.g. poor bowel preparation or insufficient sedation to enable a comfortable patient experience), a second colonoscopy is likely to be successful if the technical parameters can be corrected. When the barrier to completion is due to bowel disease or obstructing mass, a repeat colonoscopy may not be the recommended procedure; however, in these cases the incomplete colonoscopy has possibly contributed to the diagnosis of the patient. Reasons reported in the three articles listed in Table 59 for incomplete second colonoscopy are extremely redundant colon, large colonic hernia, obstructing malignant mass, obstructing diverticular stricture and poor bowel preparation.

Consumer impact statement

Public comment was sought during the development of the final DAP. The DAP was released for public comment on 2 October 2012 and closed for comments on 9 November 2012. The public comments are summarised below.

In response to the consultation DAP, Cancer Voices Australia (CVA) supported the proposed indications for CTC, for a variety of reasons:

Reduced delay in diagnosis

CTC is performed by staff with different expertise than gastroenterologists and surgeons who do colonoscopies, which allows bottlenecks in colonoscopy services to be avoided. CVA expressed the view that delays in symptomatic patients were associated with overwhelming anxiety and, depending on the symptoms, could be associated with substantial deterioration, regardless of whether patients have cancer or not.

Convenience

CTC is more convenient for patients, as the procedure is shorter and patients may go home straight afterwards. Colonoscopies usually have a pre-anaesthesia appointment as well as post-procedural surveillance. Due to the sedation, a carer is required to drive the patient and monitor the patient for the next 12 hours in case of unexpected haemorrhage or collapse.

Patient acceptability

CTC is more acceptable to patients, with radiologists being able to use faecal tagging rather than the patient having to undergo bowel cleansing. This is an important factor for frail elderly people who may become dehydrated or weak from lack of food; may fall; and may have accidents once bowel cleansing starts, as a result of weak anal sphincters.

Ability to remain on anticoagulants

If a patient is on anticoagulation therapy, they would be required to forego this medication for a period in order to undergo a colonoscopy, which is not a requirement for CTC. This reduces the risk of an interval stroke or other issues associated with going off anticoagulation medication.

Avoidance of invasive procedure

As the majority of patients are found not to have CRC, triaging with CTC would allow many patients to avoid undergoing an invasive colonoscopy.

However, there are also potential disadvantages from the use of CTC:

Additional procedure

If the CTC finds a polyp or cancer, patients are required to undergo an additional procedure (compared with if they underwent a colonoscopy initially).

Skill level

There is also concern that radiologists in more isolated locations may not have the throughput for optimal skill in CTC interpretation.

What are the economic considerations?

Summary of the economic analysis:

Due to the introduction of the NBCSP in Australia, patients who have a positive screening FOBT result are likely to represent an increasing proportion of patients presenting with symptoms suggestive of colorectal neoplasia requiring further investigation. In this population the estimated incremental cost per additional CRC / large polyp diagnosed by CTC compared with DCBE is $19,380. In the more generalised population of patients presenting with other clinical symptoms, CTC is relatively less cost-effective, with an ICER of $26,258 per additional CRC / large polyp diagnosed.

The cost-effectiveness of CTC compared with DCBE improves as the prevalence of colorectal neoplasia in the target population increases. The difference in the sensitivity between the two diagnostic procedures is the key determinant of the comparative effectiveness of the two investigative procedures, and is also the main source of uncertainty in the economic analysis.

Economic analysis

Overview

There are two distinct patient populations, each with a distinct comparator, for which economic evaluations are required:

- Symptomatic or high-risk patients who are either clinically unsuitable for colonoscopy (as identified by incomplete or technically difficult colonoscopy) or have a contraindication for colonoscopy, for whom DCBE is the appropriate comparator; and
- Symptomatic or high-risk patients who have limited access to colonoscopy such as to cause delay in diagnosis, for whom the appropriate comparator is delayed colonoscopy.

Patients with limited access to colonoscopy

For the latter patient population, there is no direct evidence assessing CTC compared with delayed colonoscopy in either the target population or the broader population of patients who are symptomatic or at high risk of CRC. While it may be expected that prompt access to CTC would result in a change in management to earlier diagnosis and treatment compared with patients waiting for access to colonoscopy, no published data were found to support this assumption. Also no evidence that prompt access to CTC resulted in any improvement in clinical outcomes compared with delayed colonoscopy was able to be identified, with the exception that patients could be ruled out from subsequent investigations (and thereby possibly avert any procedure-related adverse events). Due to the subjectivity of the interpretation of what constitutes 'limited access to colonoscopy such as to cause delay in

diagnosis', there would be considerable, but unquantifiable, potential for use of this item outside the proposed MBS listing.

Given the absence of evidence on the relative effectiveness and/or safety of CTC and delayed colonoscopy, the lack of data on the clinical consequences of a delay in diagnosis in symptomatic patients, and the failure to clearly define the target population, it was considered that any economic evaluation for the proposed new listing was likely to be highly speculative and potentially misleading. Therefore, an economic evaluation has not been presented for this target population.

Patients unsuitable/contraindicated for colonoscopy

Due to the paucity of direct evidence for the effectiveness of CTC compared with DCBE, and the heterogeneity in the linked evidence, it was not possible to make robust conclusions regarding the comparative clinical effectiveness and safety of CTC and DCBE. However, both the direct evidence and the linked evidence identified in this report suggested that CTC tends to be more sensitive and possibly less specific than DCBE. As a result of these differences, using CTC rather than DCBE as the initial testing procedure would result in a reduction in the number of false negative diagnoses and an increase in false positive diagnoses, with a corresponding increase in the proportion of patients referred for further investigation.

As CTC is therefore likely to change patient management (see 'Linked evidence' section), an estimate of the cost-effectiveness of CTC compared with DCBE for the diagnosis of colorectal neoplasia in symptomatic or high-risk patients has been performed. See 'Population and setting' below with regard to why the economic evaluation has been conducted for a broader population than the requested MBS listing.

All further economic analyses apply to the population of symptomatic or high-risk patients who are either clinically unsuitable or contraindicated for colonoscopy (MBS items 56552 and 56554).

Population and setting for the economic evaluation

As there was minimal evidence identified in the target patient populations specified in the requested listings for items 56552 and 56554—namely patients who are symptomatic or at high risk of CRC and a) have had an incomplete or technically difficult colonoscopy, or b) have a contraindication for colonoscopy—the population used in the economic analysis for both groups of patients was the wider population of those symptomatic or at high risk of CRC, consistent with the evidence presented in this report.

Due to the introduction of the NBCSP in Australia, patients who have a positive FOBT result, but are mainly otherwise asymptomatic, are likely to represent an increasing proportion of patients presenting with symptoms suggestive of colorectal neoplasia. Therefore, in the base-case of the economic evaluation, the cost-effectiveness of CTC compared with DCBE has been estimated based on the prevalence of colorectal neoplasia in Australian NBCSP patients who had a positive screening FOBT result, as reported for 2011–12 in the NBCSP monitoring report (AIHW 2013).

The prevalence of colorectal neoplasia in this patient subgroup is likely to differ from that in the more general symptomatic population, with lesions being, on average, detected at an earlier stage of development (Ananda et al. 2009). For thoroughness, a secondary scenario has been presented based on the study population in the pragmatic RCT reported by Halligan et al. (2013), which is representative of the more general symptomatic patient population. This RCT was identified in this report as the primary direct clinical evidence of the comparative safety and effectiveness of CTC and DCBE; it is used in the evaluation to inform the diagnostic process for patients symptomatic of colorectal neoplasia in the clinical setting.

In this trial, subjects were recruited from patients referred to one of the participating UK National Health Service hospitals for investigation of symptoms suggestive of colorectal cancer. Patients were eligible for enrolment if they were aged 55 years or older, had no known genetic predisposition to cancer, had not had a whole-colon examination in the last 6 months, and were not in active follow-up for a previous colorectal cancer. In addition, patients were only eligible for randomisation if the consulting clinician had decided, in line with usual practice, to investigate the patient using DCBE rather than colonoscopy; the reasons for the clinicians' decisions were not reported.

The study population was similar to the target population for the proposed MBS listings, in that patients were symptomatic and had some degree of contraindication for diagnostic colonoscopy. While it is not known whether the trial included patients who had previously undergone an incomplete or technologically difficult colonoscopy, the linked evidence presented above indicates that the accuracy of CTC in this patient population is similar to that in the broader symptomatic population. Likewise, the sensitivity and specificity of the two tests are unlikely to differ in high-risk patients, compared with symptomatic patients. It is not clear whether patients with a positive FOBT result were regarded as symptomatic and, therefore, eligible for inclusion in the trial.

Clinical basis of the economic evaluation

Table 60 and Table 61 summarise the direct clinical evidence and the linked evidence forming the basis of the economic evaluation.

Table 60 Direct clinical evidence and linked evidence forming the basis of economic evaluation

Direct evidence	**Study population**	**CTC vs DCBE**
Benefits		
Halligan et al. (2013) Level II evidence	55 years of age or older, symptomatic for CRC [a]	Deaths at 48-month follow-up: CTC 15.7% DCBE 15.8% RR=0.99 (95%CI: 0.85, 1.16)
Harms		
Halligan et al. (2013) Level II evidence	55 years of age or older, symptomatic for CRC [a]	Unplanned hospital admissions within 30 days attributed to procedure: CTC: 1/1285 (0.08%) [b] DCBE: 4/2553 (0.16%) [b] RR=1.00 (95%CI: 0.99, 1.00) Died within 30 days of procedure: CTC: 1/1285 (0.08%) [c] DCBE: 3/2553 (0.12%) [c] RR=1.00 (0.99, 1.00)

[a] The consulting clinician had previously decided, in line with usual practice, to investigate the patient using DCBE rather than colonoscopy

[b] CTC: 1 suspected perforation; DCBE: 1 cardiac arrest, 1 abdominal pain, 1 rectal bleeding, 1 collapse

[C] CTC: 1 obstructive pulmonary disease; DCBE: 1 cardiac failure, 1 liver failure, 1 perforated viscus

CRC – colorectal cancer; CTC – computed tomography colonoscopy; DCBE – double contrast barium enema; RR – relative risk

Table 61 Linked evidence-base for diagnosis of colorectal neoplasia used in economic model

Linked evidence	**Study population**	**CTC**	**DCBE**
Lesions ≥10 mm: Rockey et al. (2005) Johnson et al. (2004)	Rockey et al. (2005): high-risk or symptomatic for CRC Johnson et al. (2004): high-risk or symptomatic for CRC	Sensitivity: 0.59 (0.45, 0.71) 0.69 (0.49, 0.68) Specificity: 0.96 (094, 0.98) 0.97 (0.95, 0.98)	Sensitivity: 0.48 (0.35, 0.61) 0.48 (0.28, 0.68) Specificity: 0.90 (0.87, 0.92) 0.99 (0.98, 1.00)
All lesions: Sofic et al. (2010) Thomas et al. (2009)	Sofic et al. (2010): symptomatic for CRC Thomas et al. (2009): identified from archiving system	Sensitivity: 0.96 0.97 Specificity: 0.93 1.00	Sensitivity: 0.76 0.64 Specificity: 0.98 1.00
CRC: Halligan et al. (2013)	Symptomatic for CRC	Sensitivity: 0.93	Sensitivity: 0.81

CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema

The only direct evidence comparing the clinical effectiveness of CTC and DCBE for diagnosis of colorectal neoplasia found that there was no significant difference in 4-year survival rates between the two testing strategies (Halligan et al. 2013). It is unclear whether this time horizon is of a sufficient duration to capture any survival differences associated with the observed differences in false negative results (which favour CTC over DCBE); however, in the absence of any other data, a trial-based economic evaluation constructed on this premise would be conservative (i.e. would possibly disfavour CTC). There was also no

significant difference reported by Halligan et al. (2013) in the incidence of serious adverse events within 30 days of the procedure. Linked evidence indicated that, in patients who are symptomatic or at high risk of CRC, CTC appears to be more sensitive but slightly less specific than DCBE in detecting colorectal neoplasia, which is likely to result in changes in patient management, as described above.

Selection of the most appropriate economic evaluation to use

While there is no evidence that CTC and DCBE differ in terms of final patient-relevant clinical outcomes such as survival, given that the differences in diagnostic accuracy between CTC and DCBE are likely to change patient management, a cost-effectiveness analysis of CTC compared with DCBE for the diagnosis of colorectal neoplasia in symptomatic or high-risk patients has been performed.

Literature search

A literature search was conducted to identify economic evaluations of CTC and DCBE for the exclusion or diagnosis of colorectal neoplasia in symptomatic and high-risk patients, published subsequent to the 2006 MSAC Assessment report for CTC (NHMRC CTC 2006).

Six economic evaluations comparing the cost-effectiveness of CTC with existing procedures were located (Gomes et al. 2013; Lee et al. 2010; Sweet et al. 2011; Tappenden et al. 2007; Walleser et al. 2007; Whyte et al. 2011). Five of these were based on the Markov model originally described by Tappenden et al. (2007), which simulated the life experience of a cohort of individuals, initially without polyps or cancer, through the development of adenomatous polyps, malignant carcinoma and subsequent death. All but one (Gomes et al. 2013) were evaluations of CTC in screening populations. Whyte et al. (2011) updated the model, using a Bayesian approach to jointly estimate the transition parameters of the CRC natural history state and the test characteristics, but acknowledged that there was considerable uncertainty surrounding several of the parameters, such as adenoma growth rates. None of the economic evaluations provided a comparison of the cost-effectiveness of CTC versus DCBE.

Walleser et al. (2007) presented a decision-analytic model estimating the incremental cost-effectiveness of CTC compared with colonoscopy in individuals with a positive FOBT result. The model structure was the same as that presented in the March 2006 MSAC Assessment report for CTC (NHMRC CTC 2006). The base-case economic analysis found that CTC was less effective and more costly than optical colonoscopy in this population. Model parameters from this study were used to inform the inputs in the present economic evaluation.

Structure of the economic evaluation

The economic evaluation used a simple decision-analytic model to estimate the incremental cost-effectiveness, in terms of dollars per additional diagnosis, of CTC compared with DCBE for the exclusion or diagnosis of colorectal neoplasia in symptomatic and high-risk patients.

There is no clinical evidence to indicate that there is a difference in survival rates between the two testing strategies. There are also no data to indicate the average length of delay in diagnosis following a false negative test result in symptomatic patients, and the consequent risk of disease progression during this period. Further, a recent review of studies of the cost-effectiveness of CTC for screening noted that, due to poor knowledge of the natural history of colorectal neoplasia, there is substantial inter-model variability in transition rates through different types of polyps and CRC stages (Hassan & Pickhardt 2013). This, combined with variations in the CTC accuracy data used in the models, resulted in considerable inter-study heterogeneity in the estimated efficacy of CTC in reducing CRC incidence (40% to 77%) and mortality (58% to 84%).

Due to these issues and the paucity of evidence in the correct populations, it was considered that use of a modelled evaluation attempting to estimate the cost–utility of CTC compared with DCBE over the lifetime of a cohort would result in an unacceptable degree of uncertainty.

The decision-analytic model used in the evaluation was developed from a study-based evaluation using outcomes reported in the multi-centre RCT reported in Halligan et al. (2013). In this trial, symptomatic patients who were considered to be unsuitable for diagnostic colonoscopy by the consulting clinician were randomised to investigation by either CTC or DCBE. Unless diagnosed with inoperable CRC, all patients who tested positive for any lesion were referred for further colonic investigation (mainly colonoscopy or surgery) to confirm diagnosis and/or for treatment. At the discretion of the clinician, patients for whom no lesions were detected could also be referred for further colonic investigation. The reasons for referring test-negative patients were classified as either inadequate examination or other, unspecified, reasons grouped under 'adequate examination'.

The economic analysis estimates the costs and diagnostic outcomes associated with CTC and DCBE over the entire diagnostic process, including follow-up diagnostic procedures. Costs of subsequent treatment and the impact on survival were not considered in the economic evaluation. In addition, the difference in costs associated with the reassessment and treatment of people receiving a false negative test result from the initial diagnostic process are not included; this is a conservative approach, favouring DCBE over CTC. Given the pragmatic design of this trial, the clinical outcomes reflect both the accuracy of the diagnostic tests and the clinical decision-making over the entire diagnostic process. This

approach incorporates the clinicians' awareness of the limitations of each investigative procedure, consistent with normal clinical practice.

The economic evaluation included the following steps:

- An initial study-based evaluation incorporating the results reported in Halligan et al. (2013);
- Construction of a decision-analytic model. The structure of the model was essentially the same as that in the study-based evaluation, but was constructed in such a way that the proportions of true positive, false positive, true negative and false negative outcomes for each testing strategy were derived from the sensitivity and specificity of the test, and the prevalence of colorectal neoplasia in each arm of the trial. The subsequent distribution of patients with each type of lesion along the alternative diagnostic pathways was assumed to be the same as in the trial; and
- Adjustment of the prevalence of colorectal neoplasia in the DCBE arm of the study to match that observed in the CTC arm, based on the assumption that the lower rate of neoplasia diagnosed in the DCBE arm was due to undetected false negative results (see below). The diagnostic accuracy of DCBE was subsequently recalculated based on this adjustment, and the resulting sensitivity and specificity were used in the base-case of the model.

When the prevalence of neoplasia in the DCBE arm was adjusted, the number of colorectal neoplasms detected by DCBE was assumed to be the same as in the trial. As a result, the additional cases of neoplasia were assigned to the 'test negative, no further investigation' arm of the diagnostic pathway (Figure 7), consistent with the supposition that, in the trial, these neoplasms were undetected false negative outcomes. While this alters the relative proportion of false negative and true negative patients in this pathway, the actual proportion of patients following each diagnostic path does not change.

Readjustment of the sensitivity and specificity of DCBE was necessary in order to assess the relative cost-effectiveness of CTC and DCBE in populations in which the prevalence of colorectal neoplasia differs from that in the trial population. The resulting sensitivity and specificity of DCBE for all lesions (66% and 95%, respectively) are reasonably consistent with those reported by Sofic et al. (2010) and Thomas et al. (2009) (Table 61). The impact of the prevalence of neoplasia on the outcome of the economic evaluation has been explored in sensitivity analyses.

The proportions of true positive, false positive, true negative and false positive outcomes for each diagnostic technique were determined from the sensitivity and specificity of each technique and the prevalence of colorectal neoplasia in the population. The subsequent proportion of patients with each type of lesion assigned to each of the alternative diagnostic

pathways was based directly on the distribution of subjects reported in Halligan et al. (2013).

The decision-tree structure of the decision-analytic model is presented in Figure 7.

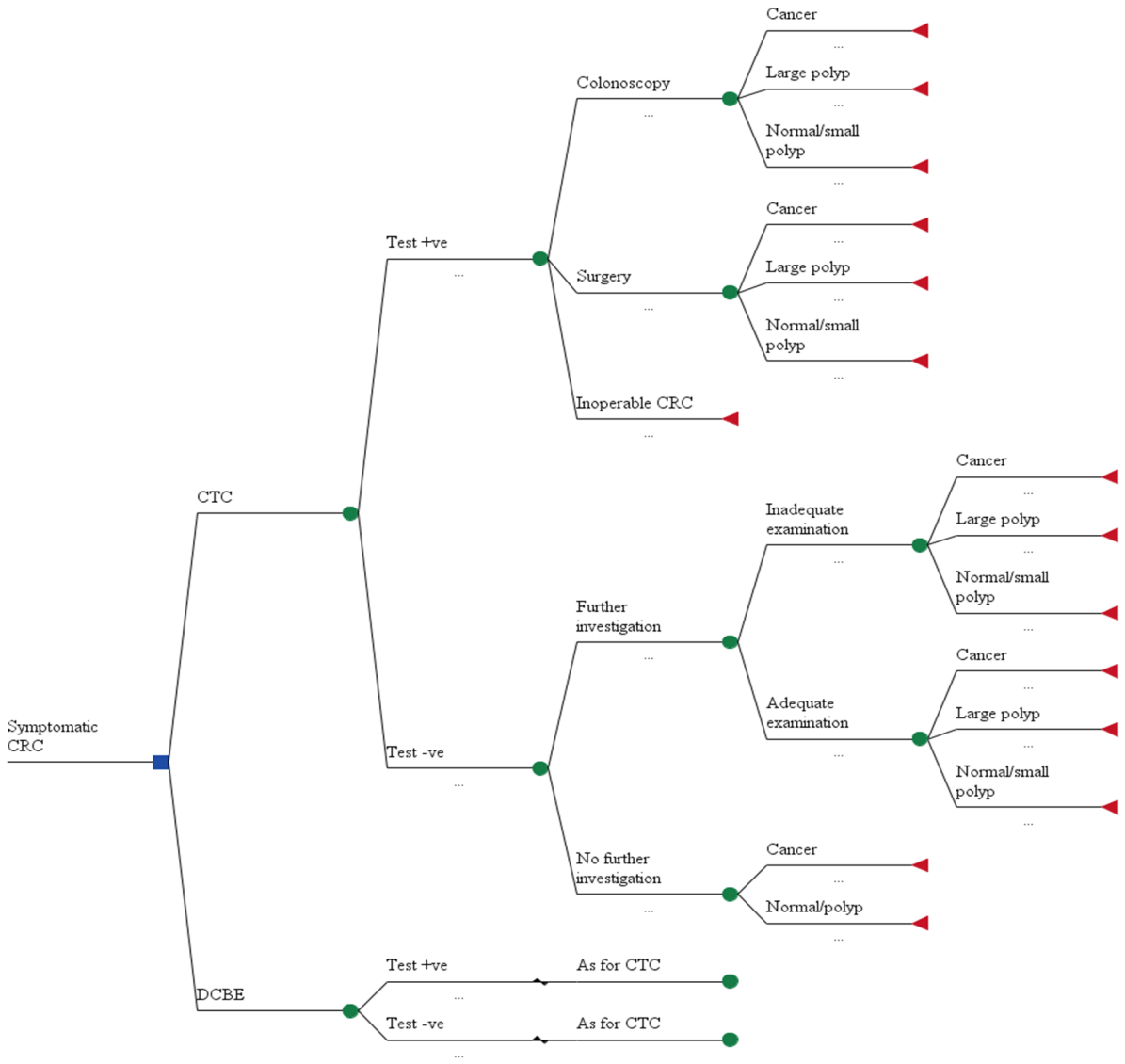


Figure 7 Decision-tree structure of cost-effectiveness model of CTC and DCBE

The measure of clinical effectiveness in the model was the primary outcome of Halligan et al. (2013), namely the number of colorectal cancers and large polyps (≥1 cm) diagnosed. Polyps ≥1 cm are considered to be clinically relevant due to their potential to undergo malignant transformation, whereas adenomas <1 cm, and particularly those measuring 5 mm or less, may remain the same size for years or even regress (Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005). The comparative cost-

effectiveness of the two diagnostic procedures is specified in terms of the incremental cost per additional cancer or large polyp diagnosed.

It is evident from the literature that a relative contraindication for diagnostic colonoscopy does not necessarily preclude the use of colonoscopy for diagnostic confirmation or treatment of lesions detected by other diagnostic procedures. Therefore, as in the trial, colonoscopy was included as a potential line of further colonic investigation.

As the prevalence of neoplasia varies between different patient populations, and as there was considerable variation in the reported estimates of the diagnostic accuracy of CTC and DCBE, the model was constructed in a manner that allowed the impact of variations in key inputs to the clinical and economic performance of CTC compared with DCBE to be assessed. In particular, the following factors were assessed in appropriate sensitivity analyses:

- how the tests compare if the prevalence of colorectal neoplasia in the target population differs from that in the base-case scenario
- how the tests compare assuming different scenarios for the relative accuracy of the two tests, based on the clinical evidence presented in this report.

Additional evidence required to conduct the economic analysis

Prevalence of colorectal neoplasia in the model population

The prevalence of colorectal neoplasia in the base-case of the economic evaluation was assumed to be that reported in Australian NBCSP patients who had a positive screening FOBT result for 2011–12 in the NBCSP monitoring report: July 2011 – June 2112 (AIHW 2013).

As a secondary analysis, representative of the more general symptomatic population, the prevalence was based on the rate of neoplasia observed in the study population of the RCT reported in Halligan et al. (2013). However, the major weakness of this trial was the inability to determine the true prevalence of colorectal neoplasia in the study population. The only information on the true status of patients diagnosed as negative for neoplasia was the incidence of CRC during the 3-year follow-up period of the trial. As a result, it is likely that the prevalence of colorectal neoplasia, especially of less-advanced lesions, is higher than that observed in the trial. In particular, the low proportion of patients diagnosed with large polyps in the DCBE arm of the trial (2.0%) compared with the CTC arm (3.6%) suggests that a considerable proportion of these lesions remained undetected by this testing method. For the economic analysis it was assumed that the prevalence of CRC and large polyps in the study population was that observed in the CTC arm of the trial.

The impact of the prevalence of neoplasia on the outcome of the economic evaluation has been explored in sensitivity analyses.

Assumptions

The following assumptions were made in the model:

- As colonoscopy is considered the gold standard procedure for detection of colorectal neoplasia, it has a diagnostic accuracy of 100%.
- A contraindication for diagnostic colonoscopy does not necessarily preclude confirmatory or therapeutic colonoscopy.
- All patients referred directly to surgery had been diagnosed as having CRC on the basis of their initial test results.
- All colorectal cancers subsequently diagnosed during the 3-year follow-up were present either as CRC or large polyps at the time of initial investigation; that is, they were false negative outcomes.
- All CRCs missed at the time of the initial diagnostic procedure would have been subsequently diagnosed during the 3-year follow-up.

Alternative scenarios (sensitivity analyses)

As in the base-case, in the sensitivity analyses the proportion of true positive, false positive, true negative and false positive outcomes for each diagnostic technique were determined from the assumed sensitivity and specificity of each technique and the prevalence of colorectal neoplasia in the population. Unless otherwise specified, the subsequent distribution of patients with each type of lesion in the alternative diagnostic pathways was assumed to be the same as in the base-case model.

Sensitivity analyses were performed to assess the impact of variations in the following factors on the outcome of the economic evaluation:

- the prevalence of colorectal neoplasia in the target population;
- the sensitivity and specificity of CTC and DCBE;
- the proportion of test-negative patients who undergo further colonic investigation; and
- variations in costs arising from an increase in the risk of serious complications associated with colonoscopy and polypectomy, and the proportion of patients who receive anaesthetist-assisted colonoscopy.

Inputs to the economic evaluation

Epidemiological parameters and test characteristics

In the first two steps of the economic evaluation, an initial study-based evaluation and a decision-analytic model based on the study, the parameters determining the comparative effectiveness of the two investigative procedures were sourced directly from the results of Halligan et al. (2013). Accordingly, the results of the economic analysis for these steps are identical. However, in contrast to the study-based analysis, the outcomes of the decision-analytic model were derived from the sensitivity and specificity of each diagnostic test, as determined from the trial data, and the prevalence of neoplasia in the population.

The inputs in the final base-case model differed only in regard to the readjusted accuracy data for DCBE, to account for undetected false negative results in this arm of the study, and the prevalence of colorectal neoplasia in the population.

The key epidemiological parameters and the test characteristics used in the base-case economic model are presented in Table 62. Table 63 and Table 64 summarise the flow of patients, categorised by lesion type, in the base-case scenario of the modelled evaluation for the CTC arm and DCBE arm, respectively.

Table 62 Epidemiological parameters and test characteristics for CTC and DCBE used in base-case economic evaluation

Variable	Study-based evaluation	Base-case modelled evaluation	Source
Prevalence of neoplasia			
Cancer / large polyp:			Trial-based evaluation: Halligan et al. (2013)
CTC	0.073	**0.098**	Note: In the trial-based evaluation the prevalence is based on the number of neoplasms detected during the trial, including the 3-year follow-up period.
DCBE	0.057	**0.098**	
Cancer:			The prevalence in the base-case model is based on the reported prevalence in Australian NBCSP patients who had a positive screening FOBT result (AIHW 2013).
CTC	0.037	**0.031**	
DCBE	0.037	**0.031**	
Test accuracy [a]			
CTC test accuracy CRC / large polyp:			
Sensitivity CRC / large polyp	0.966	0.966	Trial-based evaluation: (Halligan et al. 2013)
Specificity CRC / large polyp	0.877	0.877	
DCBE test accuracy:			Note: In the trial-based evaluation, the sensitivity and specificity are calculated using the total number of neoplasms of any kind detected during the trial, including the 3-year follow-up period.
Sensitivity CRC / large polyp	0.847	**0.661**	
Specificity CRC / large polyp	0.947	**0.946**	
CTC test accuracy for CRC:			The sensitivity and specificity of DCBE in the base-case model have been recalculated assuming that the prevalence of colorectal neoplasia in the DCBE arm of the trial was the same as that in the CTC arm.
Sensitivity CRC	0.933	0.933	
Specificity CRC	0.845	0.845	
DCBE test accuracy for CRC:			
Sensitivity CRC	0.812	**0.804**	
Specificity CRC	0.929	**0.929**	
Test outcomes			Trial-based evaluation: Halligan et al. (2013)
CTC test positive, any lesion	18.4%	18.4%	Model: derived from test accuracy and prevalence of neoplasia
DCBE test positive, any lesion	9.9%	9.9%	
Probability of further colonic investigation			Halligan et al. (2013)
CTC, test-positive patients:			
No further investigation (inoperable cancer)	0.009	0.009	
Colonoscopy	0.910	0.910	

Surgery	0.081	0.081	
DCBE, test-positive patients:			
No further investigation (inoperable cancer)	0.000	0.000	
Colonoscopy	0.110	0.110	
Surgery	0.890	0.890	
CTC, test-negative patients, total:	0.064	0.064	Halligan et al. (2013)
Inadequate examination (% total)	54.0%	54.0%	
Adequate examination (% total)	46.0%	46.0%	
DCBE, test-negative patients, total:	0.094	0.094	
Inadequate examination (% total)	59.5%	59.5%	
Adequate examination (% total)	40.5%	40.5%	
Probability of serious complications			
Colonoscopy	0.003	0.003	NBCSP monitoring report, July 2011 – June 2012: AIHW (2013)
Polypectomy	0.003	0.003	
% CRC detected during 3-year follow-up			
CTC arm	0.25%	0.25%	Trial-based evaluation: Halligan et al. (2013)
DCBE arm	0.52%	**0.56%**	Model: derived from test accuracy and prevalence of CRC

[a] All patients for whom there is suspicion of a lesion of any kind, regardless of type or size, are referred for further investigation and are regarded as test-positive when calculating test accuracy

CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema

Note: Figures in bold type indicate inputs in the base-case scenario that differ from those in the study-based evaluation; some figures appear the same due to rounding

Table 63 Flow of patients through CTC arm of base-case modelled scenario

	CRC	Large polyp	Normal/SP	Total
Total patients	3.1%	6.7%	90.2%	100%
Test-positive	2.9%	6.6%	11.1%	20.5%
Inoperable cancer	0.1%	0	0	0.1%
Surgery	1.2%	0	0	1.2%
Colonoscopy	1.5%	6.6%	11.1%	19.1%
Test-negative	0.2%	0.1%	79.1%	79.5%
Further examination:	0	0	5.1%	5.1%
Inadequate examination	0	0	2.7%	2.7%
Adequate examination	0	0	2.3%	2.3%
No further examination	0.2%	0.1%	74.1%	74.4%

CRC – colorectal cancer; CTC – computed tomography colonography; SP – small polyp

Table 64 Flow of patients through DCBE arm of base-case modelled scenario

	CRC	Large polyp	Normal/SP	Total
Total patients	3.1%	6.7%	90.2%	100%
Test-positive	2.5%	4.0%	4.9%	11.4%
Inoperable cancer	0	0	0	0
Surgery	0.9%	0	0	0.9%
Colonoscopy	1.6%	4.0%	4.9%	10.5%
Test-negative	0.6%	2.7%	85.3%	88.6%
Further examination:	0.1%	0.3%	7.9%	8.3%
Inadequate examination	0.1%	0.1%	4.7%	4.9%
Adequate examination	0	0.1%	3.3%	3.4%
No further examination	0.5%	2.4%	77.4%	80.3%

DCBE – double contrast barium enema; CRC – colorectal cancer

Costs associated with diagnosis

Costs associated with the initial testing comparing CTC and DCBE, as well as those associated with further colonic investigation to confirm diagnosis, are presented in Table 65, while Table 66 summarises the resources included in the economic evaluation. The costs are analysed from the perspective of the Australian healthcare sector, based on the relevant MBS item number and DRG costs.

As polypectomy is commonly performed in conjunction with diagnostic colonoscopy, all patients with large polyps confirmed during colonoscopy accrue the additional cost of this procedure, including charges for pathology. Similarly, it was assumed that all CRCs are biopsied during colonoscopy, with subsequent pathology charges. As stated above, the costs associated with treatment of colorectal neoplasia were not included in the analysis; patients referred directly to surgery only accrue the cost of the initial diagnostic procedure (CTC or DCBE). In addition, the difference in costs associated with reassessment and treatment of false negative test outcomes that were not detected in the initial diagnostic process, as

represented in the model, are not included; this will favour DCBE over CTC. The possibility of adverse effects associated with colonoscopy and polypectomy were factored into the costs by calculating a weighted average cost for each procedure (see Appendix E).

Table 65 Costs associated with diagnosis

	Cost	Utilisation	Total cost	Source
CTC				
Bowel preparation	$10.99	1	$10.99	Pharmacy price [a]
Procedure	$600.00	1	$600.00	MBS items 56552, 56554
Total medical costs of CTC			**$610.99**	
DCBE				
Bowel preparation	$10.99	1	$10.99	Pharmacy price [a]
Procedure	$135.25	1	$135.25	MBS item 58921
Total medical costs of DCBE			**$146.24**	
Diagnostic colonoscopy				
Bowel preparation	$10.99	1	$10.99	Pharmacy price [a]
Procedure [b]	$334.35	1	$334.35	MBS item 32090
Anaesthetist-assisted (applied to 14% of cases)				Bobridge et al. (2013)
Anaesthetist (basic units)	$79.20	0.14	$11.09	MBS item 20810
Anaesthetist (time)	$39.60 (26–30 minutes)	0.14	$5.54	MBS item 23023
Bed-day charge	$816 (weighted average)	0.14	$114.19	AR-DRG G43Z, G44B, G44C
Total medical costs of diagnostic colonoscopy			**$476.16**	
Colonoscopy and biopsy [a]				
Cost of colonoscopy (as above)			$476.16	
Pathology				
Examination of complexity level 4 biopsy with 1 or more tissue blocks				
2–4 separately identified specimens	$141.35	1	$141.35	MBS item 72824
Initiation of a patient episode associated with MBS Items 72823 and 72824	$14.65	1	$14.65	MBS item 73924
Total medical costs of diagnostic colonoscopy			**$632.16**	
Therapeutic colonoscopy (polypectomy)				
Bowel preparation	$10.99	1	$10.99	Pharmacy data [a]

Procedure [a]	$469.20		$469.20	MBS item 32093
Anaesthetist-assisted (applied to 14% of cases)				Bobridge et al. (2013)
Anaesthetist (basic units)	$79.20	0.14	$11.09	MBS item 20810
Anaesthetist (time)	$59.40 (30–45 minutes)	0.14	$8.32	MBS items 23031, 23032, 23033
Bed day charge		0.14	$114.19	AR-DRG G43Z, G44B, G44C
Pathology (as for colonoscopy and biopsy)	$816 (weighted average)		$156.00	
Total medical costs of diagnostic colonoscopy			**$769.79**	
Colonoscopy with serious adverse event				DRG G44A
Colonoscopy with serious complication	$5,898			AR-DRG Version 5.1 Round 13 (2008–09), Private Sector
Weighted cost colonoscopy [c]				
Diagnostic colonoscopy			$492.43	
Colonoscopy and biopsy			$647.96	
Therapeutic colonoscopy (polypectomy)			$785.17	

[a] Source: Chemist Warehouse PrepKit C http://www.chemistwarehouse.com.au/product.asp?id=56338&pname=Prepkit%20C%20Glycoprep%20&%20Picoprep, accessed February 2014

[b] For costing, all patients undergoing a colonoscopy are presumed to have an endoscopic examination beyond the hepatic flexure

[c] Assuming a serious adverse event rate of 0.3% in the base-case analysis

AR-DRG – Australian Refined Diagnosis Related Groups; CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema; MBS – Medical Benefits Schedule

Table 66 Summary of resource use in economic evaluation (base-case scenario)

Resource item	Unit cost	Number of units		Total cost		Incremental costs of CTC
		CTC	DCBE	CTC	DCBE	
Initial test						
CTC	$610.99	1	0	$610.99	-	$610.99
DCBE	$146.24	0	1	-	$146.24	–$146.24
Further investigation						
Colonoscopy	$492.43	0.161	0.128	$79.46	$63.12	$16.34
Colonoscopy with biopsy	$647.96	0.015	0.017	$9.82	$11.23	–$1.41
Polypectomy	$785.17	0.066	0.043	$51.61	$33.45	$18.16
Total				**$751.87**	**$254.05**	**$497.83**

CTC – computed tomography colonography; DCBE – double contrast barium enema

Outputs from the economic evaluation

Study-based evaluation

The results of the evaluation based directly on the outcomes of the pragmatic RCT reported in Halligan et al. (2013) were calculated. These results are equivalent to those presented as a secondary scenario in a general, unscreened population in Table 68.

Base-case scenario

The results of the base-case economic analysis are presented for two populations, which differ in respect to the prevalence of colorectal neoplasia:

1. Base-case scenario: the population of patients who have a positive screening FOBT result in which, based on data from the NBCSP, the prevalence of CRC and large polyps was 3.1% and 6.7%, respectively (AIHW 2013); and
2. Secondary scenario: the general symptomatic patient population with some degree of contraindication for colonoscopy, as represented by the trial population in Halligan et al. (2013), in which the adjusted prevalence of CRC and large polyps was 3.7% and 3.6%, respectively.

The results of the economic evaluation are presented in Table 67 and Table 68.

In patients with a positive screening FOBT result the estimated incremental cost per additional CRC / large polyp diagnosed for CTC compared with DCBE is $19,380. Due to the lower prevalence of large polyps in patients presenting with other clinical symptoms of colorectal neoplasia, CTC was relatively less cost-effective, with incremental cost per

additional CTC / large polyp of $26,258; however, as outlined above, the prevalence in this population is likely to be underestimated.

Table 67 Base-case scenario: Incremental cost-effectiveness of CTC vs DCBE in terms of incremental cost per additional diagnosis—patients with positive screening FOBT result [a]

Incremental cost per additional diagnosis	Cost	Incremental cost	Positive diagnoses	Incremental positive diagnoses	ICER ($/additional diagnosis)
Incremental cost per CRC / large polyp diagnosed					
DCBE	$254		0.069		
CTC	$752	$498	0.095	0.026	$19,380
Incremental cost per CRC diagnosed					
DCBE	$254		0.026		
CTC	$752	$498	0.029	0.003	$194,126
Incremental cost per large polyp diagnosed					
DCBE	$254		0.043		
CTC	$752	$498	0.066	0.023	$21,530

[a] Prevalence of CRC 3.1% and large polyps 6.7%

CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema; ICER = incremental cost-effectiveness ratio; FOBT – faecal occult blood test

Note: Numbers may not be exact due to rounding

Table 68 Secondary scenario: Incremental cost-effectiveness of CTC vs DCBE in terms of incremental cost per additional diagnosis—general symptomatic patient population [a]

Incremental cost per additional diagnosis	Cost	Incremental cost	Positive diagnoses	Incremental positive diagnoses	ICER ($/additional diagnosis)
Incremental cost per CRC / large polyp diagnosed					
DCBE	$240		0.052		
CTC	$732	$492	0.070	0.019	$26,258
Incremental cost per CRC diagnosed					
DCBE	$240		0.032		
CTC	$732	$492	0.035	0.003	$159,434
Incremental cost per large polyp diagnosed					
DCBE	$240		0.020		
CTC	$732	$492	0.036	0.016	$31,436

[a] Prevalence of CRC 3.7% and large polyps 3.6%

CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema; ICER = incremental cost-effectiveness ratio

Note: Numbers may not be exact due to rounding

It is evident from the economic analysis that the incremental gain in effectiveness of CTC compared with DCBE is largely driven by the difference in the proportion of large polyps detected by the two tests; the incremental gain in effectiveness in terms of detection of CRC is comparatively small. This results mainly from the fact that the sensitivity of DCBE is considerably higher for CRC than for other, less advanced, neoplasms, while the sensitivity of CTC is consistently high for all lesions. Thus, in the base-case scenario, for every additional $200,000 spent, approximately one additional CRC and nine large polyps will be diagnosed.

Sensitivity analyses—prevalence of lesions

Further alternative scenarios examining the impact of the prevalence of colorectal neoplasia in the target population are presented below. In these analyses the sensitivity and specificity of CTC and DCBE were assumed to be the same as those in the base-case scenario.

The following scenarios reflect different target populations and the variation in the estimated prevalence reported in published studies:

3. A prevalence of CRC of 3.2% and of large polyps of 16.4%, consistent with the data reported in Bobridge et al. (2013), which included 433 NBSCP participants with a positive FOBT result (during 2006–09), of whom 73% had a documented family history of CRC and 85% had relevant bowel symptoms; and
4. A prevalence of CRC of 7.8%, as in the base-case of the model reported in Walleser et al. (2007) in patients screening positive for faecal occult blood, while maintaining the prevalence of large polyps at 16.4%, as reported in Bobridge et al. (2013); that is, a prevalence of CRC / large polyps of 24.2%.

Table 69 summarises the results of these scenarios.

Table 69 Sensitivity analyses on prevalence of lesions

Scenario	Cost	Incremental cost	CRC / large polyps diagnosed	Incremental CRC / large polyp diagnosed	ICER ($/additional CRC / large polyp diagnosed)
Scenario 3					
DCBE	$300		0.137		
CTC	$717	$517	0.189	0.052	$9,902
Scenario 4					
DCBE	$309		0.170		
CTC	$829	$520	0.234	0.063	$8,197

Base-case model assumes that the prevalence of CRC is 3.1% and of CRC / large polyps is 9.8%, and the ICER is $19,380 per additional CRC / large polyp diagnosed
Scenario 3: Prevalence CRC 3.2% and CRC / large polyps 19.6% (Bobridge et al. 2013)

Scenario 4: Prevalence CRC 7.8% (Walleser et al. 2007) and CRC / large polyps 24.2% (Bobridge et al. 2013)
The sensitivity and specificity of CTC and DCBE are assumed to be the same as in the base-case model
CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema; ICER = incremental cost-effectiveness ratio

With increasing prevalence of colorectal neoplasia in the population, both the incremental cost and the incremental effectiveness of CTC compared with DCBE increase. Overall, the incremental cost-effectiveness of CTC compared with DCBE decreases with increasing prevalence of colorectal neoplasia in the patient population. Given that the alternative prevalence scenarios analysed, based on alternative evidence sources, all resulted in lower ICERs, it would suggest that the base-case estimate is, appropriately, conservative. Therefore, remaining uncertainty around the prevalence is primarily in a direction favouring the proposed listing.

Sensitivity analyses—test accuracy

The impact of the sensitivity and specificity of CTC and DCBE on the outcome of the economic evaluation was assessed by varying these parameters based on the linked evidence presented in this report (see Table 61):

5. The sensitivities and specificities of CTC and DCBE for all lesions reported in Sofic et al. (2010);
6. The sensitivities and specificities of CTC and DCBE for all lesions reported in Thomas et al. (2009);
7. The sensitivities and specificities of CTC and DCBE for polyps or lesions ≥10 mm reported in Rockey et al. (2005); and
8. The sensitivities and specificities of CTC and DCBE for polyps or lesions ≥10 mm reported in Johnson et al. (2004).

In Sofic et al. (2010) and Thomas et al. (2009) the sensitivities reported for both CTC and DCBE were considerably higher than those in the earlier publications by Rockey et al. (2005) and Johnson et al. (2004), possibly reflecting improvements in these technologies over the intervening years.

Unless otherwise specified, it was assumed in the sensitivity analyses that none of the patients with CRC or large polyps for whom no lesions were detected by CTC are referred for further investigation, in line with the trial—this is a conservative assumption. Also, when the specificity of CTC is very high, it has minimal effect on the outcome of the economic evaluation, as the number of false negative outcomes is extremely low.

However, the sensitivities for CTC reported in both Rockey et al. (2005) and Thomas et al. (2004) were considerably lower than in the base-case scenario. Given this, in the latter two sensitivity analyses it was assumed that the proportion of patients with false negative CTC results who were referred for further investigation was the same as that in the DCBE arm,

reflecting clinicians' awareness of the potential for false negative results. If this adjustment is not made, the incremental cost per additional CRC or large polyp diagnosed is distorted by the difference between the two investigative procedures in the proportion of false negative results detected by subsequent colonoscopy.

Table 70 Sensitivity analyses on accuracy of diagnostic tests

	Cost	Incremental cost	CRC / large polyps diagnosed	Incremental CRC / large polyp diagnosed	ICER ($/additional CRC / large polyp diagnosed)
Scenario 5					
DCBE	$240		0.078		
CTC	$700	$461	0.094	0.016	$28,389
Scenario 6					
DCBE	$241		0.068		
CTC	$738	$497	0.095	0.027	$18,229
Scenario 7					
DCBE	$264		0.054		
CTC	$710	$445	0.064	0.009	$48,235
Scenario 8					
DCBE	$228		0.054		
CTC	$711	$483	0.072	0.018	$27,396

Base-case model: CRC / large polyps sensitivity CTC 0.97, DCBE 0.66, specificity CTC 0.88, DCBE 0.95; CRC sensitivity CTC 0.93 DCBE 0.80, specificity CTC 0.88 DCBE 0.95; and the ICER is $19,380 per additional CRC / large polyp diagnosed

Scenario 5: Sensitivity CTC 0.96, DCBE 0.76; Specificity CTC 1.0 DCBE 1.0 (Sofic et al. 2010)

Scenario 6: Sensitivity CTC 0.97, DCBE 0.64; Specificity CTC 0.91 DCBE 0.98 (Thomas et al. 2009)

Scenario 7: Sensitivity CTC 0.59, DCBE 0.48; Specificity CTC 0.96 DCBE 0.90 (Rockey et al. 2005)

Scenario 8: Sensitivity CTC 0.69, DCBE 0.48; Specificity CTC 0.97 DCBE 0.99 (Johnson et al. 2004)

The prevalence of CRC / large polyps is assumed to be the same as in the base-case model

CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema; ICER = incremental cost-effectiveness ratio

As the difference in the sensitivity of CTC and DCBE is the main determinant of the comparative effectiveness of the two diagnostic techniques, it has a marked effect on the outcome of the evaluation. As apparent from the linked evidence presented in this report, there is considerable variation in the reported sensitivity for both CTC and DCBE. This is a major source of uncertainty in the economic evaluation, and the sensitivity analyses generally show increased ICERs with the alternative test-accuracy estimates. This would suggest that the direction of uncertainty around test accuracy is associated with a decreased cost-effectiveness of the proposed CTC listing.

Sensitivity analyses—further diagnostic investigation

In accordance with the trial, in the base-case model a proportion of patients for whom no lesion was detected by CTC or DCBE is assumed to undergo further colonic investigation by colonoscopy. Sensitivity analyses have been performed with the following assumptions:

9. Only patients for whom a lesion was detected by CTC or DCBE proceed to further investigation.
10. Test-negative patients are only referred for further investigation if their initial examination with either CTC or DCBE was inadequate.

As in the trial, the base-case assumes that no patients with false negative CTC results are referred for further investigation. Further sensitivity analyses were performed using the following assumptions:

11. In the CTC arm the same proportion of patients with false negative results as in the DCBE arm are referred for further investigation—approximately 25% of false negative patients with CRC and 10% of false negative patients with large polyps.
12. As in point 3, and with a prevalence of CRC of 3.7% and of large adenomas of 3.6%, consistent with the prevalence in the CTC arm of the trial reported in Halligan et al. (2013).

The results are summarised in Table 71.

Table 71 Sensitivity analyses on proportion of patients undergoing further colonic investigation

	Cost	Incremental cost	CRC / large polyps diagnosed	Incremental CRC / large polyp diagnosed	ICER ($/additional CRC / large polyp diagnosed)
Scenario 9					
DCBE	$212		0.065		
CTC	$727	$515	0.095	0.030	$17,251
Scenario 10					
DCBE	$237		0.068		
CTC	$740	$503	0.095	0.027	$18,616
Scenario 11					
DCBE	$254		0.069		
CTC	$763	$509	0.095	0.026	$19,363
Scenario 12					
DCBE	$240		0.052		
CTC	$744	$504	0.071	0.019	$26,066

Base-case ICER is $19,380 per additional CRC / large polyp diagnosed

Scenario 9: Only test-positive patients proceed to further investigation

Scenario 10: Test-negative patients with inadequate examination also proceed to further investigation

Scenario 11: The same proportion of patients with false negative results are referred for further investigation in both arms

Scenario 12: The same proportion of patients with false negative results are referred for further investigation in both arms, and prevalence CRC 3.7% and CRC / large polyps 7.3%

CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema; ICER = incremental cost-effectiveness ratio

Reducing the proportion of test-negative patients who are referred for further investigation results in a small decrease in the ICER for CTC compared with DCBE. When it is assumed that test-negative patients are only referred for further investigation if their initial examination was inadequate, the incremental cost per additional CRC / large polyp diagnosed is $18,616.

The cost-effectiveness of CTC compared with DCBE also improves when it is assumed that a proportion of patients with a false negative CTC result are referred for colonoscopy, as for DCBE, although the effect is relatively small when the sensitivity of CTC is high.

Sensitivity analyses—costs

The two main assumptions made in determining the costs associated with the diagnostic processes were the risk of serious complications with colonoscopy and polypectomy, and the proportion of patients who have an anaesthetist-assisted colonoscopy. The impact of increases in costs arising from these factors has been assessed in the following analyses:

13. Increasing the risk of serious complications with colonoscopy and polypectomy to 0.06 and 0.11, respectively, as in the model presented in the March 2006 MSAC Assessment report for CTC.
14. Increasing the proportion of patients who have anaesthetist-assisted colonoscopy from 14% in the base-case, as reported in Bobridge et al. (2013), to 50%, as in the base-case of the model presented in the 2006 MSAC Assessment report for CTC.

The results are summarised in Table 72.

Table 72 Sensitivity analyses on variations in costs

	Cost	Incremental cost	CRC / large polyps diagnosed	Incremental CRC / large polyp diagnosed	ICER ($/additional CRC / large polyp diagnosed)
Scenario 13					
DCBE	$322		0.069		
CTC	$842	$520	0.095	0.026	$20,248
Scenario 14					
DCBE	$315		0.069		
CTC	$830	$515	0.095	0.026	$20,052

Base-case ICER is $19,380 per additional CRC / large polyp diagnosed

Scenario 13: Increased risk of complications with colonoscopy and polypectomy

Scenario 14: Increased proportion of patients undergoing anaesthetist-assisted colonoscopy

CRC – colorectal cancer; CTC – computed tomography colonography; DCBE – double contrast barium enema; ICER = incremental cost-effectiveness ratio

The outcome of the economic evaluation is relatively insensitive to changes in the costs associated with the diagnostic procedures.

Exploratory analyses—likelihood of progression from polyp to CRC and potential survival impact

While best practice recommends removing all large polyps given their malignant potential, in reality only some polyps would actually progress to carcinomas, and some, if not identified, would not have patient relevance. Using models of disease progression rates, Cafferty et al. (2009) estimated that, in the absence of intervention, between 10% and 37% of patients who have adenomas at baseline will develop cancer by the end of a 5.9-year follow-up. Comparing these estimates with data from a cohort of 1,418 patients who had undergone polypectomy, it was estimated that removal of lesions resulted in a reduction in CRC incidence of between 84% and 86%; follow-up surveillance after polypectomy was estimated to confer an additional reduction of 13% (Cafferty, Sasieni & Duffy 2009).

In the base-case scenario the economic evaluation estimated that, for every additional ~$200,000 spent, approximately one additional CRC and nine large polyps would be diagnosed. An attempt to identify the number of polyps that would impact patient-relevant outcomes—that is, those that would actually progress—can be made, based on the estimates reported in Cafferty et al. (2009). Applying these rates, in the absence of intervention, between 0.9 and 3.4 of the additional polyps diagnosed using CTC, at an additional cost of $200,000, would be likely to progress to CRC within 6 years of the initial examination. Assuming that follow-up examinations would be performed in patients who have undergone polypectomy, resulting in a reduction in CRC incidence of 97%, removal of these additional 9 large polyps could be expected to prevent between 0.9 and 3.3 CRCs from developing.

Therefore, for every additional ~$200,000 spent on CTC, it can be estimated that one additional CRC will be detected and a further 0.9–3.3 will have been prevented through identification (and removal) of large polyps. This equates to an incremental cost per additional CRC detected or prevented of between $45,827 and $103,500. It should be noted, however, that these estimates are not a complete economic analyses, as costs associated with treatment of CRC and follow-up surveillance have not been included.

The 5-year overall survival rate for patients with CRC in Western Australian private hospitals was estimated to be approximately 85% for Stage I, 70% for Stage II, 47% for Stage III and 16.7% for Stage IV (Morris, Iacopetta & Platell 2007). Given this, it is possible that the 4-year follow-up for deaths, as reported in Halligan et al. (2013), was not long enough to accurately capture CRC survival rates and, subsequently, any true difference in survival

between CTC and DCBE. If this is so, there may be survival benefits, resulting from the lower rate of false negative outcomes with CTC, compared with DCBE, that are not captured in the economic analysis.

Despite reporting no survival benefit, Halligan et al. (2013) extrapolated the number of life years saved over 20 years, estimating that CTC yielded 21 additional life years per 1,000 patients compared with DCBE, although details of this extrapolation have not yet been published. Given the limited duration of follow-up in this trial, the lack of any significant difference in 4-year survival rates between the two arms, and the inability to determine the true prevalence of colorectal neoplasia in the trial population, these results should be interpreted with caution. If applied crudely to the modelled analysis presented in this report, it would suggest an ICER of at least $23,700 per life year gained; however, costs associated with treatment of CRC and follow-up surveillance have not been included in this estimate and these would increase the estimated ICER. More importantly, the translation of additional early diagnosis to a survival gain cannot be verified by the available evidence.

The use of CTC in preference to DCBE should lead to a reduction in the proportion of patients for whom diagnosis is delayed due to false negative test results. Theoretically, prompt diagnosis should result in neoplasms being diagnosed, on average, at an earlier stage and, as a consequence, better health outcomes. However, no evidence was located in this report to support this (Halligan et al. 2013). There are also no data on the likely extent of any delay in diagnosis in symptomatic patients and, due to the limited knowledge of the natural history of colorectal neoplasia, the consequent risk of disease progression during this period. Given these issues, any estimation of the comparative cost–utility of CTC compared with DCBE over the lifetime of a cohort would result in an unacceptable degree of uncertainty in the modelled outcome.

Summary of the financial implications:

Patients with limited access to colonoscopy

It was estimated that this new listing could potentially result in an additional 18,000 to 19,000 CTC services per year over the first 5 years of the new listing. On this basis the additional cost to the MBS may be in the order of $10,000,000 per year. These estimates are highly uncertain due to data limitations. There is considerable potential for use outside the intended purpose.

Patients unsuitable/contraindicated for colonoscopy

In the absence of safety net implications, the net cost to the MBS resulting from substitution of CTC for DCBE was estimated to be approximately $1,956,000 in the first year of the revised listings, reducing to $1,209,000 in the fifth year; additional safety net costs increased these figures to $2,064,000 and $1,276,000, respectively. The estimated net increase in cost to the patients / private health insurers, inclusive of safety net payments, was approximately $120,000 in the first year, declining to $74,000 by the fifth year.

The main uncertainty is the number of additional CTC services likely to be performed under the proposed extended eligibility criteria. If it is assumed that CTC replaces all current use of DCBE, and that this level remains constant, the estimated net cost to the MBS, including safety net payments, would be approximately $2,622,000 per year.

Costs associated with changes in the number of colonoscopies performed are relatively small for all sectors of the Australian healthcare system.

Financial implications

Patients with limited access to colonoscopy

Due to the poorly defined patient population for this proposed new MBS item, and the considerable potential for use outside the intended purpose, it is not possible to provide any robust assessment of the potential financial implications of the requested new listing—that is, to extend eligibility for CTC to patients who are symptomatic or at high risk of colorectal neoplasia who have limited access to colonoscopy such as to cause delay in diagnosis. However, an estimate of the potential cost to the MBS resulting from this proposed item, if approved, has been attempted using the limited available data.

As outlined in the background section of this report, it was expected that access would be limited to a larger degree in rural and remote areas than in metropolitan areas. MBS data showed that the current rate of CTC and colonoscopy *combined* was 16.3 services per 1,000 population in major cities, compared with 9.0 per 1,000 in remote areas (see Table 75).

For the financial analysis it was assumed that the difference in the number of services per 1,000 in regional and remote areas, compared with major cities, was due to limited access to colonoscopy services, and that, if the proposed new MBS listing is approved, these patients will be referred for CTC and will be able to access this service.

The data sources and the values used in the estimated financial impact of the proposed new MBS listing for CTC are presented in Table 73 and Table 74, respectively.

Table 73 Data sources used in financial analysis of patients with limited access to colonoscopy

Data source	Purpose
MBS data reports for items 56552, 56554 [a]	Proportion of CTC services in-hospital
MBS data reports for items 32084, 32087, 32090, 32092, 56552, 56554 [a]	To determine the number of services per 1,000 population by remoteness area
MBS [b]	Scheduled fees and benefits for Medicare items 56552, 56554
Australian Bureau of Statistics [c]	• Population by remoteness area • Population change during 2007–12 by remoteness area

[a] Unpublished data requested from the Australian Government Department of Health
[b] MBS online: http://www.health.gov.au/internet/mbsonline/publishing.nsf/Content/Medicare-Benefits-Schedule-MBS-1, accessed February 2014
[c] Source: Australian Bureau of Statistics, http://www.abs.gov.au, accessed March 2014
CRC – colorectal cancer; CTC – computed tomography colonography; MBS – Medicare Benfits Schedule

Table 74 Summary of data used in financial analysis of patients with limited access to colonoscopy

	Value	Data source
Yearly population growth: Inner regional Outer regional Remote Very remote	 1.4% 1.1% 1.0% 2.1%	Derived from ABS data '3218.0—Regional Population Growth, Australia, 2012'
Number of colonoscopies deferred due to limited access in regional/remote areas	2.61 per 1,000 population	Derived from MBS data reports for items 32084, 32087, 32090, 32092, 56552, 56554
% of CTC services out-of-hospital	85%	MBS data reports for items 56552, 56554
Costs of CTC: Scheduled fee Rebate in-hospital Rebate out-of-hospital	 $600.00 $450.00 $525.50	MBS

CTC – computed tomography colonography; MBS – Medicare Benefits Schedule

Table 75 summarises the number of colonoscopy and CTC services per 1,000 population by remoteness area, and the expected number of services in regional and rural areas if the rate was the same as in major cities. The difference between the expected number and the actual number of services is presumed to be due to limited access to colonoscopy in these regions and, subsequently, the number of patients that will potentially be referred for CTC if it is listed for this indication on the MBS.

Table 75 Number of services per 1,000 population by ASGC remoteness for financial year 2012–13 (MBS items 32084, 32087, 32090, 32092, 56552, 56554)

Remoteness area	Number of services [a]	Population [b]	Number of services per 1,000 population	Expected services at rate of 16.3 per 1,000 population	Number of services delayed due to limited access
Major cities	260,196	15,976,750	16.3	260,196	0
Inner regional	62,379	4,161,150	15.0	67,768	5,389
Outer regional	26,378	2,047,432	12.9	33,344	6,966
Remote	2,539	318,969	8.0	5,195	2,656
Very remote	760	206,051	3.7	3,356	2,596
Total	356,083	22,710,352	15.7	369,859	13,776

[a] MBS statistics, received via personal communication, 9 December 2013
[b] Source: Australian Bureau of Statistics, http://www.abs.gov.au, accessed March 2014
ASGC – Australian Standard Geographical Classification; CTC – computed tomography colonography
Note: separate data for colonoscopy and CTC items were not available

Population growth during 2007–12, categorised by remoteness area, was sourced from the Australian Bureau of Statistics (ABS) data. The average yearly growth in population for each area was estimated and used to project the population in remote and regional areas during 2015–19 (Table 76). The assumption that population growth remains constant over the projected period is a conservative approach, as the ABS predicts that population growth rates in remote and regional areas in Australia will decline over time[11].

Table 76 Projected population in ASGC regional and remote areas of Australia

Remoteness area	Yearly growth	2015	2016	2017	2018	2019
Inner regional	1.4%	4,344,643	4,407,588	4,471,445	4,536,227	4,601,947
Outer regional	1.1%	2,112,847	2,135,113	2,157,614	2,180,352	2,203,330
Remote	1.0%	328,234	331,381	334,559	337,767	341,006
Very remote	2.1%	219,190	223,753	228,411	233,166	238,020
Total	-	**7,004,913**	**7,097,835**	**7,192,028**	**7,287,512**	**7,384,303**

AGSC – Australian Standard Geographical Classification

Based on the data presented in Table 75, the total number of colonoscopies deferred due to limited access in regional and remote areas was estimated to be 2.61 per 1,000 population. Conservatively, it was assumed that all these patients could potentially be referred for CTC under the proposed new listing. However, in reality it is likely that some of these patients have decreased accessibility to all medical services, including referral services; therefore, the number of CTCs that could be undertaken subsequent to the proposed listing is a likely overestimate of what would occur in practice. The resulting estimates of the potential

[11] Source: ABS 3222.0—Population projections, Australia, 2012 (base) to 2101; www.abs.gov.au, accessed March 2014.

additional number of CTC services, and the associated costs to the MBS and patients, are summarised in Table 77.

Table 77 Summary of estimated number of additional CTC services in patients with limited access to colonoscopy, and cost to MBS and patients

	2015	2016	2017	2018	2019
Projected population	7,004,913	7,097,835	7,192,028	7,287,512	7,384,303
Number of additional CTC services: [a]	18,316	18,559	18,806	19,055	19,308
Cost in-hospital	$1,318,467	$1,335,957	$1,353,686	$1,371,658	$1,389,876
Cost out-of-hospital	$8,085,534	$8,192,790	$8,301,515	$8,411,728	$8,523,451
Total cost to MBS [b]	**$9,404,001**	**$9,528,748**	**$9,655,201**	**$9,783,386**	**$9,913,328**
Patient co-payments	$1,585,773	$1,606,809	$1,628,132	$1,649,748	$1,671,660
Total cost	**$10,989,774**	**$11,135,556**	**$11,283,334**	**$11,433,134**	**$11,584,987**

[a] Difference between regional/remote and metropolitan CTC services
[b] Assumes that 16% of services are performed in-hospital and 84% are out-of-hospital
CTC – computed tomography colonography; MBS – Medicare Benfits Schedule

Due to the limited data available on the number of patients who meet the eligibility criteria for this proposed item, namely those who are symptomatic or at high risk of colorectal neoplasia who have limited access to colonoscopy such as to cause delay in diagnosis, these estimates are uncertain and should be interpreted with caution. In addition, due to the failure to clearly define what constitutes a 'limited access to colonoscopy such as to cause delay in diagnosis', there is considerable potential for use of this item outside the intended purpose.

Given these limitations, it is estimated that the cost to the MBS resulting from increased use of CTC services may be in the order of $10,000,000 per year.

Patients unsuitable/contraindicated to colonoscopy

As CTC is more specific than DCBE and more acceptable to patients, if the proposed extended eligibility criteria for CTC under MBS items 56552 and 56554 are approved, CTC is likely to fully substitute for DCBE in patients who are considered unsuitable for colonoscopy. The financial impact of this expected change in patient management has been estimated using a market share approach.

Data sources used in the financial analysis

The data sources used in the estimated financial impact of the proposed changes to MBS items 56552 and 56554 are presented in Table 78.

Table 78 Data sources used in financial analysis of patients unsuitable/contraindicated for colonoscopy

Data source	Purpose
MBS statistics for item 58921 [a]	To estimate the number of services for DCBE over the next 5 years that are likely to be performed in the absence of the proposed changes to eligibility for CTC
MBS data reports for items 58921, 56552, 56554 [b]	• Proportion of services in-hospital • Total fees charged • Total benefits paid • Average benefit paid per service • Percentage of services bulk-billed
MBS [c]	Scheduled fees and benefits for Medicare items
Department of Health Round 13 Cost report [d]	Proportion of colonoscopies performed in the public and private sectors Weighted average cost of colonoscopy, including overhead costs (items G43Z, G44A, G44B, G44C)
Bobridge et al. (2013)	Proportion of anaesthetist-assisted colonoscopies
Halligan et al. (2013)	Proportion of patients undergoing colonoscopy following either CTC or DCBE

[a] Medicare Australia Statistics: http://www.medicareaustralia.gov.au/statistics/mbs_item.shtml, accessed February 2014

[b] Unpublished data requested from the Australian Government Department of Health

[c] MBS online: http://www.health.gov.au/internet/mbsonline/publishing.nsf/Content/Medicare-Benefits-Schedule-MBS-1, accessed February 2014

[d] Australian Government Department of Health: http://www.health.gov.au/internet/main/publishing.nsf/Content/Round_13-cost-reports

CTC – computed tomography colonography; DCBE – double contrast barium enema

MBS data reports for items 58921, 56552 and 56554 for the financial years 2007–08 to 2012–13 were provided, on request, by the Australian Government Department of Health, and are tabulated in Appendix E. Table 79 lists the MBS fee and benefits for MBS items included in the financial analysis, while a summary of inputs is provided in Table 80.

Table 79 MBS item fees and patient co-payments for items included in financial analysis of patients unsuitable/contraindicated for colonoscopy

MBS item	Item number(s)	MBS fee	Benefit	
			75%	85%
CTC	56552, 56554	$600.00	$450.00	$525.50
DCBE	58921	$135.25	$101.45	$115.00
MBS items associated with colonoscopy				
Colonoscopy ± biopsy	32090	$334.35	$250.80	$282.20
Colonoscopy with polypectomy	32093	$469.20	$351.90	$398.85
Initiation of management of anaesthesia	20810	$79.20	$59.40	$67.35
Anaesthesia 26–30 minutes	23023	$39.60	$29.70	$33.70
Anaesthesia 31–45 minutes	23031, 23032, 23033	$59.40	$44.55	$50.50
Pathology level 4 material	73924	$141.35	$106.05	$120.15
Initiation of patient episode	73924	$14.65	$11.00	$12.50

CTC – computed tomography colonography; DCBE – double contrast barium enema; MBS – Medicare Benefits Schedule

Table 80 Summary of data used in financial analysis of patients unsuitable/contraindicated for colonoscopy

	CTC	DCBE	Data source
% services out-of-hospital	84%	91%	MBS data report, 2012–13 data [a]
% services bulk-billed	70%	62%	MBS data report, 2012–13 data [a]
Average benefit paid per service	$545.24	$123.50	MBS data report, 2012–13 data [a]
Average fee charged per service	$605.56	$159.22	MBS data report, 2012–13 data [a]
% patients undergoing follow-up colonoscopy:			
Colonoscopy	16.1%	12.8%	Economic evaluation, Table 66
Colonoscopy + biopsy	1.5%	1.7%	
Polypectomy	6.6%	4.3%	
% colonoscopy performed in the private sector	59.1%	59.1%	Round 13 Cost Report [b]
Cost of colonoscopy (MBS items only):			
Scheduled fee:			
Colonoscopy	$350.98	$350.98	See Table 65
Colonoscopy + biopsy	$506.98	$506.98	
Polypectomy	$644.60	$644.60	
MBS rebate:			
Colonoscopy	$291.99	$291.99	See Table 65
Colonoscopy + biopsy	$422.41	$422.41	
Polypectomy	$537.22	$537.22	
Cost of colonoscopy (hospital costs):			Round 13 Cost Report [b]
Public sector	$1,888	$1,888	Weighted average of AR-DRG G43Z, G44A, G44B and G44C
Private sector	$849	$849	

[a] Unpublished data requested from the Australian Government Department of Health

[b] Australian Government Department of Health: http://www.health.gov.au/internet/main/publishing.nsf/Content/Round_13-cost-reports

CTC – computed tomography colonography; DCBE – double contrast barium enema; MBS – Medicare Benefits Schedule

Estimating the change in the utilisation and cost of CTC and DCBE

In the financial estimate it was assumed that all use of DCBE under MBS item 58921 will be replaced by CTC under the extended criteria for MBS items 56552 and 56554.

Table 81 presents the number of services for DCBE over the past 6 financial years. It is evident that the use of DCBE on the MBS has decreased considerably over this period, suggesting that DCBE is already being replaced by alternative diagnostic techniques, possibly including CTC and colonoscopy. Additional costs resulting from this ongoing substitution of DCBE would likely be incurred by the MBS regardless of whether the amendments to the listings for CTC are approved. Therefore, these costs are not included in the main analysis; this issue is explored in a sensitivity analysis.

In the base-case of the financial analysis it is assumed that, in the absence of the proposed changes to the eligibility criteria for CTC, the use of DCBE would continue to fall. The expected use of DCBE was projected using a logarithmic function. Although the regression co-efficient for an exponential function was higher than that for the logarithmic equation, the logarithmic function was selected, as it gave a more conservative rate of decline in the

projected number of services per year (see Appendix E). The resulting projection of the number of DCBE services per year that are likely to be substituted by CTC is presented in Table 82.

Table 81 MBS historical data report for item 58921 (opaque enema), representing DCBE services

58921	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13
Number of services	14,174	11,537	9,804	8,104	6,863	6,039

Source: Medicare Australia Statistics: http://www.medicareaustralia.gov.au/statistics/mbs_item.shtml, accessed February 2014
DCBE – double contrast barium enema

Table 82 Projected number of DCBE services likely to be substituted by CTC, assuming ongoing declining trend in DCBE use in patients unsuitable/contraindicated for colonoscopy

	2013–14	2014–15	2015–16	2016–17	2017–18	2018–19
Number of services	5,508	4,893	4,351	3,866	3,427	3,026

DCBE – double contrast barium enema; CTC – computed tomography colonography

Estimated cost associated with increased use of CTC

Combined 2012–13 MBS data for items 56552 and 56554[12] were used to determine the weighted average proportion of services performed out-of-hospital (84%) and the proportion of services that were bulk-billed (70%).

The cost to the MBS, excluding safety net impacts, was subsequently calculated using the current rebates of $525.50 (85% of fee) for out-of-hospital CTC services and $450.00 (75% of fee) for in-hospital services. The cost to the MBS, including safety net impacts, was derived using the 2012–13 average benefits paid per service for items 56552 and 56554, as provided in the MBS data reports for these items. The 2012–13 figures were used, in preference to the average over the years of data provided, as the benefit paid consistently increased over the past 6 years for which data was available.

Total patient co-payments for MBS items, excluding safety net impacts, were derived assuming that 70% of out-of-hospital services were bulk-billed. The remaining 30% of out-of-hospital services incurred a patient co-payment of $74.50, while the co-payment for in-hospital services was $150.00.

Finally, the total cost to the patient and/or private health insurer was calculated by subtracting the total benefits paid by the MBS from the total fees charged. This inherently incorporates safety net impacts.

[12] Unpublished MBS data report, requested from the Australian Government Department of Health

Table 83 Estimated increase in number of CTC services and cost implications in patients unsuitable/contraindicated for colonoscopy

CTC	2014–15	2015–16	2016–17	2017–18	2018–19
Total number of services per year:	4,893	4,351	3,866	3,427	3,026
Out-of-hospital [a]	4,110	36,55	3,247	2,879	2,542
In-hospital	783	696	618	548	484
Total fees charged	$2,963,085	$2,634,638	$2,340,831	$2,075,051	$1,832,413
Cost to the MBS (benefits payable)					
Excluding safety net impacts:					
Out-of-hospital	$2,160,039	$1,920,606	$1,706,427	$1,512,677	$1,335,798
In-hospital	$352,227	$313,184	$278,258	$246,665	$217,822
Total	**$2,512,266**	**$2,233,790**	**$1,984,685**	**$1,759,342**	**$1,553,620**
Including safety net impacts: [b]	-	-	-	-	-
Average benefits paid per service	$545.24	$545.24	$545.24	$545.24	$545.24
Total	**$2,667,945**	**$2,372,213**	**$2,107,671**	**$1,868,364**	**$1,649,894**
Safety net payments	$155,679	$138,423	$122,986	$109,022	$96,274
Cost to the patients / health insurers					
Patient co-payments (excluding safety net impacts): [c]					
Out-of-hospital	$91,296	$81,176	$72,124	$63,935	$56,459
In-hospital	$117,409	$104,395	$92,753	$82,222	$72,607
Total	**$208,705**	**$185,571**	**$164,876**	**$146,156**	**$129,066**
Total cost to patients / health insurers (including safety net impacts):					
Total fees charged	$2,963,085	$2,634,638	$2,340,831	$2,075,051	$1,832,413
Total benefits paid by MBS	$2,667,945	$2,372,213	$2,107,671	$1,868,364	$1,649,894
Total cost to patients / health insurers	**$295,140**	**$262,425**	**$233,160**	**$206,687**	**$182,519**

[a] Assumes that 84% of services are out-of-hospital

[b] Calculated as: number of services × average benefits paid, sourced from MBS data reports for items 56552 and 56554

[c] Assumes that 70% of out-of-hospital patients are bulk-billed

CTC – computed tomography colonography; MBS – Medicare Benefits Schedule

As the number of DCBE services per year for which CTC will substitute decreases over the 5 years, the yearly cost associated with the substituted CTC services also decreases correspondingly. The yearly cost to the MBS, inclusive of safety net impacts, is estimated to fall from approximately $2,668,000 in 2014–15 to $1,650,000 in 2018–19. Similarly, the yearly cost to the patients and/or private health insurers reduces from $295,000 to $182,000 over the same period. Due to the large proportion of services that are bulk-billed, the average co-payment for patients treated out-of-hospital is only $22.21 per service, prior to safety net adjustments.

Estimated savings associated with reduction in the use of DCBE

The estimation of the savings resulting from substitution of DCBE was performed in a similar manner to the derivation of costs associated with increased use of CTC. Based on MBS data for item 58921, the proportion of services out-of-hospital was assumed to be 91%, and the proportion of out-of-hospital services bulk-billed was 62%.

Table 84 Estimated decrease in number of DCBE services and cost implications in patients unsuitable/contraindicated for colonoscopy

DCBE	2014–15	2015–16	2016–17	2017–18	2018–19
Total number of services per year:	4,893	4,351	3,866	3,427	3,026
Out-of-hospital [a]	4,445	3,952	3,512	3,113	2,749
In-hospital	448	398	354	314	277
Cost to the MBS (benefits payable)					
Excluding safety net impacts:					
Out-of-hospital	$511,186	$454,523	$403,836	$357,984	$316,125
In-hospital	$45,457	$40,418	$35,911	$31,834	$28,111
Total	**$556,643**	**$494,941**	**$439,747**	**$389,818**	**$344,236**
Including safety net impacts: [b]					
Average benefits paid per service	$123.50	$123.50	$123.50	$123.50	$123.50
Total	**$604,324**	**$537,337**	**$477,415**	**$423,209**	**$373,722**
Safety net payments	$47,681	$42,396	$37,668	$33,391	$29,486
Cost to the patient					
Patient co-payments (excluding safety net impacts): [c]					
Out-of-hospital	$33,935	$30,173	$26,809	$23,765	$20,986
In-hospital	$15,145	$13,466	$11,964	$10,606	$9,366
Total	**$49,080**	**$43,640**	**$38,773**	**$34,371**	**$30,352**
Total cost to patients / health insurers (including safety net impacts):					
Total fees charged	$779,100	$692,740	$615,487	$545,604	$481,806
Total benefits paid by MBS	$604,324	$537,337	$477,415	$423,209	$373,722
Total cost to patients / health insurers	**$174,776**	**$155,403**	**$138,073**	**$122,396**	**$108,084**

[a] Assumes that 91% of services are out-of-hospital

[b] Calculated as number of services × average benefits paid, sourced from the MBS data report for item 58921

[c] Assumes that 62% of out-of-hospital patients are bulk-billed

DCBE – double contrast barium enema; MBS – Medicare Benefits Schedule

The high rate of bulk-billing for this item reduces the average co-payment for patients treated out-of-hospital to $7.63 per service, prior to safety net adjustments.

Financial implications to the MBS

The financial implications to the MBS, resulting directly from the proposed extended eligibility criteria for CTC and the subsequent substitution of CTC for DCBE, are summarised in Table 85.

Table 85 Net change in costs to MBS associated with changes in use of CTC and DCBE in patients unsuitable/contraindicated for colonoscopy

	2014–15	2015–16	2016–17	2017–18	2018–19
Total number of services per year	4,893	4,351	3,866	3,427	3,026
Cost (excluding safety net impacts):					
Cost of CTC	$2,512,266	$2,233,790	$1,984,685	$1,759,342	$1,553,620
Cost offset from DCBE	$556,643	$494,941	$439,747	$389,818	$344,236
Net cost	**$1,955,623**	**$1,738,849**	**$1,544,938**	**$1,369,524**	**$1,209,384**
Cost (including safety net impacts):					
Cost of CTC	$2,667,945	$2,372,213	$2,107,671	$1,868,364	$1,649,894
Cost offset from DCBE	$604,324	$537,337	$477,415	$423,209	$373,722
Safety net payments	$107,998	$96,027	$85,318	$75,631	$66,788
Net cost	**$2,063,621**	**$1,834,876**	**$1,630,256**	**$1,445,155**	**$1,276,172**

CTC – computed tomography colonography; DCBE – double contrast barium enema

If the proposed extensions of the eligibility criteria for CTC are approved, the highest yearly net increase in cost to the MBS, of approximately $2,064,000 and inclusive of safety net impacts, would occur in the first year of the revised listing. Assuming the trend of decreasing DCBE continues and also applies to substitutable CTC, expenditure on this would subsequently decline to approximately $1,276,000 by the fifth year.

Sensitivity analyses

The majority of inputs in the financial analysis relating to the use of CTC in place of DCBE are sourced directly from MBS data reports for DCBE and the relevant CTC items, and there is limited potential for variation in these factors. However, the main uncertainty is the number of additional CTC services that are likely to be performed under the proposed extended eligibility criteria for MBS items 56552 and 56554.

The base-case assumes that CTC completely replaces DCBE where used. While this is a conservative assumption, there is some uncertainty in the projected future use of DCBE in the absence of the proposed amendments to the CTC listings.

The other variables that are likely to impact on the net cost to the MBS are the proportion of services performed out-of-hospital and the proportion of patients qualifying for both the original and the extended MBS safety net.

The following analyses have been performed to allow assessment of the possible impact of these factors on the financial implications to the MBS:

1. Assuming that the number of DCBE services likely to be substituted by CTC remains at the 2012–13 level of 6,039 services per year; and
2. Increasing the proportion of CTC services that are assumed to be performed out-of-hospital from 84% to 91%, in line with the proportion reported for DCBE.

As no data are available regarding the proportion of patients that qualify for the MBS safety net, it is not possible to assess the impact of variations in this factor on the cost to the MBS; nor is it possible to incorporate safety net impacts into the second sensitivity analysis. Therefore, the estimated net cost to the MBS, excluding safety net implications, is reported.

The results of these analyses are presented in Table 86.

Table 86 Sensitivity analyses for net change in costs to MBS in patients unsuitable/contraindicated for colonoscopy

	2014–15	2015–16	2016–17	2017–18	2018–19
Base-case					
Total number of services per year	4,893	4,351	3,866	3,427	3,026
Net cost to MBS (excluding safety net) [a]	$1,955,623	$1,738,849	$1,544,938	$1,369,524	$1,209,384
Scenario 1					
Net cost (excluding safety net impacts):					
Cost of CTC	$3,100,560	$3,100,560	$3,100,560	$3,100,560	$3,100,560
Cost offset from DCBE	$686,992	$686,992	$686,992	$686,992	$686,992
Net cost to MBS	$2,413,568	$2,413,568	$2,413,568	$2,413,568	$2,413,568
Net cost (including safety net impacts):					
Cost of CTC	$3.292,695	$3.292,695	$3.292,695	$3.292,695	$3.292,695
Cost offset from DCBE	$745,838	$745,838	$745,838	$745,838	$745,838
Net cost to MBS	$2,546,857	$2,546,857	$2,546,857	$2,546,857	$2,546,857
Scenario 2					
Cost of CTC	$2,537,532	$2,256,256	$2,004,645	$1,777,036	$1,569,245
Cost offset from DCBE	$556,643	$494,941	$439,747	$389,818	$344,236
Net cost to MBS	$1,980,889	$1,761,314	$1,564,898	$1,387,218	$1,225,009

[a] Not including safety net impacts

Scenario 1: Assuming the number of DCBE services substituted by CTC remains at the 2012–13 level (6,039 services per year)

Scenario 2: Assuming the proportion of CTC services performed out-of-hospital is the same as for DCBE (91%); base-case 84%

CTC – computed tomography colonography; DCBE – double contrast barium enema; MBS – Medicare Benefits Schedule

Even if it is assumed that, in the absence of the extended listings for CTC, the number of DCBE services per year would remain at current levels, the net cost to the MBS if the listings are approved would be approximately $2,547,000 per year, including safety net impacts.

As the proportion of CTC procedures performed out-of-hospital is already high, there is limited potential for it to increase. The sensitivity analysis demonstrates that this factor has minimal impact on the financial implications to the MBS.

Estimated changes in utilisation and costs of other MBS items

It is evident from the literature that a relative contraindication for diagnostic colonoscopy does not necessarily preclude the use of colonoscopy for diagnostic confirmation or treatment of lesions detected by other diagnostic procedures. In the trial reported in Halligan et al. (2013) 89% of patients who were referred for further colonic investigation underwent confirmatory/therapeutic colonoscopy despite initially being considered to be unsuitable for diagnostic colonoscopy by the consulting clinician (Halligan et al. 2013).

Substitution of CTC for DCBE will lead to changes in management of patients. Due to the higher sensitivity and lower specificity of CTC compared with DCBE, the number of patients referred for further colonic investigation by colonoscopy is likely to increase.

The proportion of patients undergoing colonoscopy subsequent to either CTC or DCBE was assumed to be the same as in the base-case of the economic evaluation (Table 66). MBS items associated with colonoscopy are listed in Table 79, along with the scheduled fee and benefits, while the average total cost of MBS items per colonoscopy, based on the scheduled fee, and the cost to the MBS for these items are provided in Table 80. As in the base-case scenario of the economic evaluation, it is assumed that 14% of colonoscopies are anaesthetist-assisted.

The estimated change in the number of colonoscopies, and the corresponding changes in the MBS item component of the associated costs, are summarised in Table 87. More details of these calculations, including the estimated change in utilisation and cost for each MBS item, are provided in Appendix E.

Table 87 Costs to MBS associated with changes in number of confirmatory/therapeutic colonoscopy services in patients unsuitable/contraindicated for diagnostic colonoscopy

	2014–15	2015–16	2016–17	2017–18	2018–19
Colonoscopies following CTC					
Number of procedures: [a]					
Colonoscopy	467	415	369	327	289
Colonoscopy with biopsy	44	39	35	31	27
Polypectomy	190	169	150	133	118
Total	701	623	553	491	433
Costs:					
Total cost (based on scheduled fee) [b]	$308,519	$274,320	$243,729	$216,056	$190,792
Cost to MBS [b]	$256,874	$228,401	$202,930	$179,889	$158,855
Colonoscopies following DCBE					

	2014–15	2015–16	2016–17	2017–18	2018–19
Number of procedures:					
Colonoscopy	371	330	293	260	229
Colonoscopy with biopsy	50	45	40	35	31
Polypectomy	123	110	97	86	76
Total	544	484	430	381	336
Costs:					
Total cost (based on scheduled fee) [b]	$234,940	$208,898	$185,602	$164,529	$145,290
Cost to MBS [c]	$195,603	$173,921	$154,526	$136,981	$120,963
Net change in colonoscopies					
Number of procedures	157	139	124	110	97
Total cost	$73,578	$65,422	$58,127	$51,527	$45,502
Cost to MBS	**$61,272**	**$54,480**	**$48,404**	**$42,909**	**$37,891**

[a] Assuming that 59.1% performed in the private sector

[b] Includes changes in MBS items 32090, 32093, 20810, 23023, 23031, 72824, 73924 (see Appendix E)

[c] Assumes that 14% of procedures are anaesthetist-assisted

CTC – computed tomography colonography; DCBE – double contrast barium enema; MBS – Medicare Benefits Schedule

It is evident that the additional cost to the MBS, attributable to changes in the number of patients undergoing colonoscopy, is reasonably small compared with the additional costs associated with substitution of CTC for DCBE, with predicted costs to the MBS consistently under $65,000 per year.

Cost to state and territory healthcare systems

The state and territory healthcare systems will incur costs associated with additional colonoscopies performed in the public sector.

The cost of additional colonoscopies was estimated assuming that 41% of the procedures are performed in the public sector. The average cost for colonoscopy was assumed to be $1,888, based on the weighted average total cost of the relevant Australian Refined Diagnosis Related Groups (AR-DRGs) in the public sector[13]. The results of the analysis are presented in Table 88.

Table 88 Estimated cost to state and territory healthcare systems in patients unsuitable/contraindicated for colonoscopy

	2014–15	2015–16	2016–17	2017–18	2018–19
Net change in colonoscopies [a]	108	96	86	76	67
Total net change in cost	$204,442	$181,780	$161,508	$143,171	$126,429

[a] Assuming that 41% of colonoscopies are performed in the public sector

[13] Australian Government Department of Health: http://www.health.gov.au/internet/main/publishing.nsf/Content/Round_13-cost-reports

Costs to private health insurers and/or patients

As discussed above, due to the high proportion of services that are bulk-billed, the average co-payment for a patient undergoing CTC or DCBE out-of-hospital is only $22.21 and $7.63, respectively. In addition, the majority of services are provided out-of-hospital. Therefore, the total cost to patients and/or private health insurers is relatively low for both diagnostic techniques.

Table 89 Net change in costs to patients and/or private health insurers associated with predicted changes in use of CTC and DCBE in patients unsuitable/contraindicated for colonoscopy

	2014–15	2015–16	2016–17	2017–18	2018–19
Total number of services per year	4,893	4,351	3,866	3,427	3,026
Patient MBS co-payments (excluding safety net impacts): [a]					
Cost of CTC	$208,705	$185,571	$164,876	$146,156	$129,066
Cost offset from DCBE	$49,080	$43,640	$38,773	$34,371	$30,352
Net increase in cost	$159,625	$141,931	$126,103	$111,785	$98,714
Total cost to patients / health insurers (including safety net impacts): [b]					
Cost of CTC	$295,140	$262,425	$233,160	$206,687	$182,519
Cost offset from DCBE	$174,776	$155,403	$138,073	$122,396	$108,084
Net increase in cost	**$120,364**	**$107,022**	**$95,088**	**$84,291**	**$74,435**

[a] Assuming that 70% of out-of-hospital CTC services and 62% of out-of-hospital DCBE service are bulk-billed

[b] Includes both MBS co-payments and gap payments on fees above the MBS scheduled fee

CTC – computed tomography colonography; DCBE – double contrast barium enema; MBS – Medicare Benefits Schedule

The average cost per service to the patient / health insurer, inclusive of safety net impacts, would increase by $24.60 if CTC substitutes for DCBE. The net increase in yearly cost to patients / private health insurers ranges from approximately $120,400 in the first year of the revised listing to $74,400 in the fifth year.

In addition, there will be costs associated with colonoscopies for further colonic investigation following CTC. The average hospital cost for a colonoscopy was assumed to be $849, based on the weighted average total cost of the relevant AR-DRGs in the private sector. The patient / private health insurer would also be responsible for paying the co-payments for MBS items associated with colonoscopy.

Table 90 summarises the additional costs to the patients / private health insurers resulting from the increase in the number of colonoscopies, and the total increase in costs from changes in all three diagnostic procedures.

Table 90 Summary of costs to patients and/or private health insurers in patients unsuitable/contraindicated for colonoscopy

	2014–15	2015–16	2016–17	2017–18	2018–19

	2014–15	2015–16	2016–17	2017–18	2018–19
Net change in colonoscopies [a]	157	139	124	110	97
Total net change in cost	$132,855	$ 118,129	$104,955	$93,039	$82,160
MBS item co-payments	$12,307	$10,942	$9,722	$8,618	$7,611
Net cost of colonoscopies	$145,162	$129,071	$114,678	$101,657	$89,770
Net cost of substitution of CTC for DCBE	$120,364	$107,022	$95,088	$84,291	$74,435
Total cost to patients / health insurers	**$265,526**	**$236,094**	**$209,765**	**$185,948**	**$164,205**

[a] Assuming that 59% of colonoscopies are performed in the public sector

CTC – computed tomography colonography; DCBE – double contrast barium enema; MBS – Medicare Benefits Schedule

Total Australian healthcare system costs

The component costs and the total cost across all sectors of the Australian healthcare system are provided in Table 91. It is evident that the majority of the cost associated with the proposed changes in the listings for CTC will be borne by the MBS.

Table 91 Total Australian healthcare system costs in patients unsuitable/contraindicated for colonoscopy

	2014–15	2015–16	2016–17	2017–18	2018–19
Cost to the MBS					
Changes in CTC/DCBE [a]	$2,063,621	$1,834,876	$1,630,256	$1,445,155	$1,276,172
Colonoscopy	$61,272	$54,480	$48,404	$42,909	$37,891
Total cost	$2,124,892	$1,889,356	$1,678,661	$1,488,064	$1,314,063
Cost to state/territory governments					
Colonoscopy	$204,442	$181,780	$161,508	$143,171	$126,429
Cost to patients / health insurers					
Changes in CTC/DCBE	$120,364	$107,022	$95,088	$84,291	$74,435
Colonoscopy	$145,162	$129,071	$114,678	$101,657	$89,770
Total cost	$265,526	$236,094	$209,765	$185,948	$164,205
Total Australian healthcare costs	**$2,594,860**	**$2,307,229**	**$2,049,934**	**$1,817,183**	**$1,604,697**

[a] Including safety net impacts

CTC – computed tomography colonography; DCBE – double contrast barium enema; MBS – Medicare Benefits Schedule

Discussion

Is it safe?

The comparison of safety between CTC with DCBE was limited to data from two articles describing the same RCT that met the inclusion criteria for this review (Halligan et al. 2013; von Wagner et al. 2011). No studies comparing the safety of CTC and delayed colonoscopy were identified.

The article by Halligan et al. (2013) reported post-procedural serious adverse events but commented that, out of a total of 14 and 25 serious events, respectively, only one could be potentially attributed to CTC, while four could be potentially attributed to DCBE (no significant difference). None of the deaths that occurred within 30 days of the investigative procedures were considered attributable to DCBE (3 deaths) or CTC (1 death). Such small numbers preclude any definitive statement regarding the comparative safety of CTC and DCBE; however, it would appear that serious adverse events are rare for both these procedures and that deaths occurring after both CTC and DCBE would rarely be as a consequence of either procedure. Halligan et al. also reported that the results suggest that the risk of needing additional colonic investigation is significantly increased for CTC compared with DCBE, which is likely to be a reflection of the higher rate of polyp detection observed for CTC. Based on the available data, any differences in risk of adverse events from undergoing additional procedures post-CTC and post-DCBE cannot be quantified.

The article by von Wagner and colleagues (2011) suggested a reduced number of minor adverse events for CTC compared with DCBE. Based on self-reported symptoms, patients who underwent CTC reported significantly less abdominal pain, nausea/vomiting, wind, bottom soreness and soiling compared with patients randomised to DCBE. Symptoms of feeling faint/dizzy, difficulty sleeping and anxiety were similar, without statistically significant differences in these outcomes between imaging methods. These results could be interpreted to mean that patients may favour CTC over DCBE, but the findings were not conclusive for all symptoms. While satisfaction with the procedure was higher for patients randomised to CTC than DCBE, levels of worry about the procedure were not statistically different.

Seven studies reported patient acceptability/preference outcomes and/or self-reported physical discomfort/satisfaction/worry (Bosworth et al. 2006; Gluecker et al. 2003; Kataria 2011; Sofic et al. 2010; Taylor et al. 2005; Taylor et al. 2003; von Wagner et al. 2011). Across these studies CTC was found to be more acceptable and the first-preference procedure among patients, where assessed (Bosworth et al. 2006; Gluecker et al. 2003; Taylor et al. 2005; Taylor et al. 2003). Self-reported physical discomfort, assessed in all

seven studies, favoured CTC over DCBE in all but one study (Kataria 2011; no significant difference found), while self-reported worry indicated that CTC was favoured over DCBE in two of the four studies that assessed this outcome (Bosworth et al. 2006; Taylor et al. 2003). Neither von Wagner et al. (2011) nor Taylor et al. (2005) found any differences in patient worry when the two procedures were compared. Patients were most satisfied with CTC across all studies that included satisfaction as an outcome (Bosworth et al. 2006; Taylor et al. 2005; Taylor et al. 2003; von Wagner et al. 2011). These results taken together indicate that the majority of patients are most satisfied with CTC and find it to be a more tolerable procedure (with generally less physical discomfort and cause for worry) than DCBE.

No studies were identified that compared patient acceptability of CTC compared with delayed colonoscopy due to limited access to colonoscopy. However, one systematic review that compared the acceptability of CTC with colonoscopy with no specified time delay was identified (Lin et al. 2012). The majority of studies (16/23; total 5,616 patients) found that CTC was preferred over colonoscopy, and that this was more likely if they knew they had a low likelihood of requiring a colonoscopy or if the article was published in a radiology journal. The authors noted that unquantifiable biases may have influenced the results; for example, response bias[14] and biases resulting from the wording of questionnaires and ascertainment methods.

There were no studies assessing the impact of radiation in the populations identified as eligible for inclusion in this review (based on PICO criteria). However, a US study was identified that provided estimates of potential radiation risks associated with CTC as a bowel cancer *screening* intervention (Berrington de Gonzalez, Kim & Yee 2010). The authors estimated exposure for low-dose radiation using a modified model based on the most recent Japanese bomb survivor BEIR VII studies[15], extrapolating data to project risk of radiation-related cancer in the long term. It was estimated that a single CTC screen (64-slice scanner) at age 60 years would result in a lifetime risk of radiation-related cancer of 0.05% (5 cancers per 10,000 individuals screened) in both males and females. At age 50 years the risk was slightly higher (0.06%) and at age 70 years slightly lower (0.03%), due to longer or shorter life expectancies, respectively. Using the unmodified BEIR VII model, a higher risk of 0.14% for a screen at age 50 years is estimated, a risk purported by Berrington de Gonzalez et al. to approximately coincide with the upper range. They also give projections for patients in whom there are extracolonic findings by CTC, estimating that there will be increased risk resulting from additional radiological examinations. The additional radiation dose associated with an abdominal or pelvic CT scan is predicted to result in a radiation risk that is twice that

[14] Patients may give a different response from the one they actually believe to be true because they feel it is a more socially acceptable response, or because of a desire to respond in a way that ingratiates themselves with their providers.

[15] The US-based National Academy of Science BEIR (Biological Effects of Ionizing Radiation) VII committee developed models to assess risks of exposure to low-level radiation (published in 2006).

of CTC. Berrington de Gonzalez et al. conclude that radiation risks are likely to be similar from DCBE and CTC, but this is not an opinion shared by all authors. Neri et al. (2010) found that the effective dose for diagnostic quality images (64-row multi-detector computed tomography (MDCT) scanner) in patients with CRC was 2.17 ± 12 mSv[16] and effective DCBE images required an average entrance dose of 4.12 ± 0.17 mSv, which was 1.9 times greater than CTC ($p<0.001$).

From a clinician's point of view, the risk associated with not prioritising an appropriate mode of bowel investigation in the populations relevant to this review (i.e. those at increased risk of CRC and those with symptoms or signs suggestive of CRC) may be considered to outweigh any potential risk of cancer due to additional radiation exposure in those *truly* contraindicated for colonoscopy, and hence referred for CTC.

Is it effective?

Direct evidence

Direct evidence for the effectiveness of CTC compared with DCBE was limited to one study that reported on the number of deaths after 48 months among patients randomised to CTC or DCBE (Halligan et al. 2013). Causes of death were not reported and no statistical differences in the number of deaths were observed between the groups (RR=1.00, 95%CI 0.97, 1.03).

No direct evidence comparing CTC and delayed colonoscopy was identified for inclusion in this assessment.

The available evidence for the direct effectiveness comparison of CTC versus DCBE is summarised in the evidence matrix shown below (Table 92).

Table 92 Body of evidence matrix—direct evidence

Component	A Excellent	B Good	C Satisfactory	D Poor	Not applicable
Evidence-base [a]		one level II study with a low risk of bias			
Consistency [b]					one study only
Clinical impact				slight or restricted	
Generalisability		population studied in body of evidence			

[16] A millisievert (mSv) is defined as 'the average accumulated background radiation dose to an individual for 1 year, exclusive of radon, in the United States'; 1 mSv is the dose produced by exposure to 1 milligray (mG) of radiation. Sourced from www.mun.ca/biology/scarr/Radiation_definitions.html

		is similar to target population			
Applicability			probably applicable to Australian healthcare context with some caveats		

Source: adapted from NHMRC (2009)
[a] Level of evidence determined from the NHMRC evidence hierarchy
[b] If there is only one study, rank this component as 'not applicable'

Given the paucity of direct evidence, a linked evidence analysis was performed based on change in management and how this influences downstream patient health outcomes. The key findings are discussed below, with interpretation and main sources of potential biases/confounding noted where relevant.

Linked evidence

Relative accuracy of CTC versus DCBE, and CTC versus clinical reference standards

Five studies that compared the relative accuracy of CTC and DCBE were identified that reported outcomes in patients who were at high risk or symptomatic for CRC (Halligan et al. 2013; Johnson et al. 2004; Rockey et al. 2005; Sofic et al. 2010; Thomas, Atchley & Higginson 2009). They were found to have low to moderate risk of bias, were mostly consistent and were satisfactory in regards to generalisability and applicability. Results for diagnostic accuracy for lesions or polyps ≥10 mm, lesions 6–9 mm, polyps 5–9 mm, lesions of all sizes and CRC tended to show greater sensitivity for CTC and greater specificity for DCBE. However, there was variability between the studies and not all results reached statistical significance. The number of additional investigations required was reported in one study and was higher for those who underwent CTC, likely reflecting the greater sensitivity of CTC.

An additional five studies provided diagnostic accuracy data for CTC against a clinical reference standard in a population of patients who were contraindicated for colonoscopy (Duff et al. 2006; Kealey et al. 2004; Ng et al. 2008; Robinson, Burnett & Nicholson 2002; Saunders et al. 2013). The sensitivity of CTC was found to be variable between studies, but CTC was consistently accurate for excluding CRC in this population, based on the absence of CRC at clinical follow-up. As most of the studies were of poor quality, these results should be interpreted with caution.

Diagnostic accuracy results were reported in two further studies for patients who underwent CTC following a previous incomplete colonoscopy, with colonoscopy or surgery as the

reference standard (Copel et al. 2007; Neri et al. 2002). While the results favoured CTC, they could not be considered reliable due to the poor quality and reporting.

There were no studies identified that compared accuracy between CTC and delayed colonoscopy. One study was identified that compared accuracy between CTC and colonoscopy with no specified time delay (Pickhardt et al. 2011); it found that, against a histological standard, CTC was as sensitive as colonoscopy with no specified time delay. It could therefore be reasonably assumed that CTC would be at least as sensitive when compared with delayed colonoscopy.

Overall findings from the body of available evidence on the relative accuracy of CTC and DCBE, and CTC accuracy against clinical reference standards considered acceptable for the purposes of this assessment, are summarised in the matrix below (Table 93).

Table 93 Body of evidence matrix—relative accuracy of CTC and DCBE, and CTC accuracy against clinical reference standards

Component	A Excellent	B Good	C Satisfactory	D Poor	Not applicable
Evidence-base [a]			one level II study with low risk of bias, and three level II studies and eight level III-3 studies with moderate risk of bias		
Consistency [b]		most studies consistent and inconsistency may be explained			
Clinical impact				slight or restricted	
Generalisability			two study populations in body of evidence are same as target population; populations in remaining studies differ to target population but it is clinically sensible to apply this evidence to target population		
Applicability			probably applicable to Australian healthcare context with some caveats		

Source: adapted from NHMRC (2009)

[a] Level of evidence determined from the NHMRC evidence hierarchy
[b] If there is only one study, rank this component as 'not applicable'

Is CTC accurate compared with delayed colonoscopy?

There were no diagnostic accuracy studies identified comparing CTC and DCBE or delayed colonoscopy in patients for whom there is poor access to colonoscopy. Given that colonoscopy is considered the gold standard and reference standard, CTC would at best be found to be as accurate as colonoscopy, but could not be considered more accurate, when compared against the reference standard as specified in the DAP. In the absence of data on the accuracy of CTC versus delayed colonoscopy, one systematic review (level I evidence) comparing accuracy of CTC and colonoscopy with no specified time delay with a histological reference standard suggested that the sensitivity of CTC does not differ between general screening populations and populations at higher risk or symptomatic for CRC (Pickhardt et al. 2011). While the sensitivity of CTC was presented for general screening populations, and higher risk or symptomatic populations, the sensitivity of colonoscopy was reported only for these groups combined; therefore, no conclusion can be made regarding the relative accuracy of CTC and colonoscopy in the populations relevant to this review. Given that the reference standard was histology, only those who were found to have positive results had their test results verified; thus, specificity was not reported. The evidence is summarised in Table 94.

Table 94 Body of evidence matrix—CTC accuracy compared with colonoscopy with no specified time delay

Component	A Excellent	B Good	C Satisfactory	D Poor	Not applicable
Evidence-base [a]	one level I study low risk of bias				
Consistency [b]					one study only
Clinical impact				slight or restricted	
Generalisability				population studied in body of evidence is similar to target population, but no data reported provided a relevant comparison	
Applicability			probably applicable to Australian healthcare context with some caveats		

Source: adapted from NHMRC (2009)
[a] Level of evidence determined from the NHMRC evidence hierarchy
[b] If there is only one study, rank this component as 'not applicable'

Does CTC change patient management compared with DCBE?

Evidence of whether the accuracy of CTC compared with DCBE changes patient management was limited to one prospective cohort study (Taylor et al. 2006; level III-2 diagnostic evidence). It assessed the confidence of experienced radiologists to exclude colorectal neoplasia with CTC compared with DCBE in a cohort of older patients symptomatic for CRC. The study findings ultimately lead to the conclusion that a broader spectrum of patients will be referred on for colonoscopy following CTC than DCBE. However, the relevant population are those already indicated for colonoscopy and, as such, the broader spectrum would already have had a colonoscopy if it were clinically possible; that is, if they had not already had a failed colonoscopy for medical reasons, been otherwise contraindicated or had difficulty accessing colonoscopy. Therefore, the impact of this spectrum change was not evaluated.

The findings of Taylor et al. (2006) also indicated that a higher rate of false negative outcomes result from DCBE compared with CTC, and it was therefore considered that false negative patients would not be expected to receive treatment as early as if they were detected by CTC. Hence, it was decided that the evidence linkage for the impact on patient health outcomes due to change in management would be more appropriately captured by an analysis of early versus late treatment. This is discussed below (see 'Does change in management improve patient outcomes for CTC versus DCBE, and CTC versus delayed colonoscopy?'). The evidence for the change in patient spectrum is summarised in Table 95.

Table 95 Body of evidence matrix—does CTC change patient management compared with DCBE?

Component	A	B	C	D	
	Excellent	**Good**	**Satisfactory**	**Poor**	**Not applicable**
Evidence-base [a]			one level III-2 study with moderate risk of bias		
Consistency [b]					one study only
Clinical impact				slight or restricted	
Generalisability	population studied in body of evidence is same as target population				
Applicability		applicable to Australian healthcare context with few caveats			

Source: adapted from NHMRC (2009)

[a] Level of evidence determined from the NHMRC evidence hierarchy

[b] If there is only one study, rank this component as 'not applicable'

Does CTC change patient management compared with delayed colonoscopy?

No literature was found to suggest that CTC leads to a change in patient management compared with delayed colonoscopy. In contexts where access to colonoscopy is poor (such as in rural or remote areas), it is uncertain whether publicly funding CTC would decrease the time to receiving treatment. For patients who are found to have lesions on CTC, referral to colonoscopy for a biopsy and/or polyp removal is probable. Therefore, access to colonoscopy may still be a problem for patients with positive CTC findings. However, it has been assumed that these patients would be encouraged to access further investigations and treatment in regional centres. Thus, it is expected that a change in management resulting from accessing CTC would be earlier diagnosis and treatment, compared with if patients waited for delayed colonoscopy.

As CTC is expected to rule out some patients otherwise requiring a colonoscopy, it is also expected that it would reduce the total number of patients needing a colonoscopy, which may lead to better access for those who require it.

Those who are found to be negative for signs of CRC on CTC may receive earlier reassurance, or seek alternative diagnoses, as opposed to having to wait for delayed colonoscopy.

Does change in management improve patient outcomes for CTC versus DCBE, and CTC versus delayed colonoscopy?

As described previously, evidence of improvement in patient outcomes due to change in management is most likely to be captured by an analysis of early versus late treatment. For the comparison of CTC versus DCBE, the main change expected is that patients are more likely to have false negative results from DCBE, which may lead to a delay in diagnosis and treatment of CRC. In the comparison of CTC versus delayed colonoscopy, it is expected that CTC may result in those with lesions (true positives) receiving earlier diagnosis and treatment than those waiting for a delayed colonoscopy.

The one systematic review (in two publications) identified that assessed whether diagnostic and/or therapeutic delay impacted on patient survival, or stage of disease at time of diagnosis/treatment, did not indicate that there is a clinical benefit in avoiding a diagnostic or therapeutic delay in CRC (Ramos et al. 2007; Ramos et al. 2008). This evidence is summarised in Table 96.

Table 96 Body of evidence matrix—does change in management improve patient outcomes?

Component	A	B	C	D	
	Excellent	**Good**	**Satisfactory**	**Poor**	**Not applicable**
Evidence-base [a]	one level I study with low risk of bias				

Consistency [b]					one study only
Clinical impact				slight or restricted	
Generalisability	population studied in body of evidence is same as target population				
Applicability			probably applicable to Australian healthcare context with some caveats		

Source: adapted from NHMRC (2009)
[a] Level of evidence determined from the NHMRC evidence hierarchy
[b] If there is only one study, rank this component as 'not applicable'

While evidence of clinical benefit associated with reduced waiting times to CRC diagnosis and treatment is lacking in the populations considered relevant to this assessment, current knowledge is that CRC-specific survival is stage dependent (National Cancer Institute 2013). Earlier diagnosis is assumed to lead to earlier intervention and better outcomes. However, observed differences in survival may be driven by lead-time bias. In other words, because survival is measured from the time of diagnosis until death, it may be seen to be longer when earlier detection occurs, without a true survival benefit to the patient (DLA Piper Australia 2011).

Within the general population the benefit of early versus late treatment has been evaluated in the NHMRC clinical practice guidelines for CRC (Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005). Based on RCTs, the guidelines report that screening for faecal occult blood in asymptomatic patients (on an intention-to-screen basis) reduces CRC-specific mortality by 15–33% and the incidence of CRC by 20%. Other controlled trials have reported benefits among individuals at elevated risk of CRC due to a family history of adenomatous polyposis (Australian Cancer Network Colorectal Cancer Guidelines Review Committee 2005).

What are the other relevant considerations?

Repeat colonoscopy procedures

A number of authors report on the importance of investigation of those patients in whom colonoscopy was not completed satisfactorily, and on the choice of follow-up treatment appropriate for those individuals. Three retrospective studies (Brahmania et al. 2012; Kao et al. 2010; Rex, Chen & Overhiser 2007) were identified that reported the reasons for incomplete colonoscopy and the rate of successful repeat colonoscopies in a cohort of patients. The studies found that with simple resources such as sufficient allocation of time,

better bowel preparation, well-informed planning and, in some cases, the use of non-standard (but readily available) equipment such as straighteners and paediatric scopes, 95–98% of repeat colonoscopies could be completed successfully.

Other good reasons to perform a repeat colonoscopy in this group of patients, according to one author (Brahmania et al. 2012), were because 13% of procedures were suboptimal in patients who underwent DCBE rather than a second colonoscopy; and in half of those who underwent a second colonoscopy after DCBE, the findings were non-concordant and raised doubts about the reliability of DCBE. The increase in availability and expertise in CTC may provide a better option than DCBE in the future; however, CTC still does not provide the benefit of colonoscopy to immediately intervene with removal of a polyp or tissue for biopsy.

An interesting factor reported by Brahmania et al. was that a Canadian study (Shah et al. 2007) found that repeat colonoscopies performed in tertiary care centres by an experienced gastroenterologist had a lower failure rate than those performed elsewhere. In addition, a finding in an Ohio-based study (Sanaka et al. 2006) found that incomplete colonoscopies in that state were significantly more frequent as afternoon-scheduled procedures than morning procedures, indicating that operator fatigue may play a role in failure rates.

In the context of this review, these findings indicate that caution may be warranted in referring patients who have undergone incomplete colonoscopies for CTC. While the studies discussed in the previous paragraphs were conducted in a mix of screening, surveillance and symptomatic populations, a second colonoscopy provided satisfactory results in the vast majority of cases, thus avoiding the need for CTC. It should be noted that more-difficult procedures are likely to be performed successfully when more care and preparation are taken. Patients for whom there is clear clinical reason (not technical or modifiable factors) may be the best candidates for consideration for CTC following incomplete colonoscopy.

What are the economic considerations?

Direct evidence comparing the clinical effectiveness of CTC and DCBE for diagnosis of colorectal neoplasia found no significant difference in 4-year survival rates between the two testing strategies (Halligan et al. 2013). In the absence of any evidence of a difference in final clinical outcomes, the results of the modelled economic evaluation are largely dependent on the difference in the diagnostic accuracy of the two tests. Given the high degree of variability in the reported sensitivity and specificity for both CTC and DCBE in the published literature, this is a major source of uncertainty in the results of the economic analysis.

As there is no evidence to support any difference in survival rates between the two testing strategies, and due to the poor evidence-base, the cost-effectiveness of CTC compared with DCBE was estimated in terms of incremental cost per additional positive diagnosis (CRC or

large polyp). In the base-case scenario the prevalence of colorectal neoplasia was assumed to be that reported in Australian NBCSP patients who had a positive screening FOBT result, namely 3.1% and 6.7% for CRC and large polyps, respectively (AIHW 2013); the estimated incremental cost per additional CRC or large polyp diagnosed for CTC compared with DCBE was $19,380. The incremental gain in effectiveness of CTC compared with DCBE is largely driven by the difference in the proportion of large polyps detected, with a relatively small difference in the proportion of CRCs detected. Thus, for every additional $200,000 spent, approximately one additional CRC and nine large polyps will be diagnosed.

The results of the economic evaluation were reasonably sensitive to the difference in the relative accuracy of the two tests, especially in the sensitivity. Based on the linked evidence comparing the accuracy of CTC and DCBE, the ICER ranged from $18,200 per additional CRC or large polyp diagnosed when the sensitivities of CTC and DCBE were 0.97 and 0.64, respectively (Thomas, Atchley & Higginson 2009), to $48,200 per additional CRC or large polyp diagnosed when the sensitivities of CTC and DCBE were assumed to be 0.59 and 0.48, respectively, as reported by Rockey et al. (2005). However, the sensitivity reported for both CTC and DCBE in this latter publication and in another published in 2004 (Johnson et al. 2004) were considerably lower than those in more-recent publications (Sofic et al. 2010; Thomas, Atchley & Higginson 2009), possibly indicating that both technologies have improved since this study was performed.

CTC becomes less cost-effective compared with DCBE as the prevalence of colorectal neoplasia in the target population decreases. In patients presenting with clinical symptoms other than a positive FOBT result, in which the estimated prevalence of CRC or large polyps was 7.3%, the incremental cost per additional CRC or large polyp diagnosed increased to $26,258; however, the reported prevalence of neoplasia in these patients is likely to be an underestimate.

There is some uncertainty as to whether the 4-year follow-up for deaths, as reported in Halligan et al. (2013), was long enough to accurately capture CRC survival rates and, subsequently, whether there was any true difference in survival between the two investigative procedures. As a result, it is possible that there are survival benefits resulting from the lower rate of false negative outcomes with CTC, compared with DCBE, that are not captured in the economic analysis.

Financial implications

Patients with limited access to colonoscopy

An epidemiological approach was used to estimate the potential cost to the MBS arising from the increase in the use of CTC if eligibility is extended to patients with limited access to

colonoscopy. For the analysis it was assumed that the difference in the number of colonoscopy services per 1,000 population in regional and remote areas, compared with major cities, was due to limited access to colonoscopy services, and that these patients could potentially be referred for CTC under the proposed new listing.

It was estimated that this new listing could potentially result in an additional 18,000 to 19,000 CTC services per year over the first 5 years of the new listing. On this basis the additional cost to the MBS may be in the order of $10,000,000 per year.

Due to the limited data available on the number of patients who would meet the eligibility criteria for this proposed item, these estimates are uncertain and should be interpreted with caution. In addition, there is considerable potential for use of this item outside the intended purpose.

Patients unsuitable/contraindicated for colonoscopy

MBS data indicate that the use of DCBE has decreased considerably over the past 6 years. This suggests that DCBE is already being replaced by alternative diagnostic techniques, probably including CTC. Any additional costs resulting from this ongoing substitution of DCBE would have been incurred by the MBS regardless of whether the amendments to the listings for CTC are approved or not, and therefore are not included in the main analysis.

A market share approach was used to assess the financial implications to the MBS arising directly from the proposed extended eligibility criteria for CTC and the subsequent substitution of CTC for DCBE. It was assumed that CTC would completely replace DCBE if the changes in the eligibility criteria are approved.

The resulting estimated net costs to the MBS were reasonably modest, decreasing from approximately $2,063,000 in the first year of the new listings to $1,276,000 by the fifth year, inclusive of safety net payments. There are also likely to be some additional costs to the MBS due to an increase in the number of colonoscopies performed for confirmation of diagnosis, but these costs are likely to be relatively small. The net increase in the cost to patients and private health insurers was estimated to decline from $120,000 per year to $74,000 per year over the first 5 years of the new listings.

As the majority of the inputs in the financial analysis are sourced directly from MBS data reports for the relevant items for DCBE and CTC, the results are reasonably robust. The main source of uncertainty is the number of additional CTC services likely to be performed under the proposed extended eligibility criteria. However, if it is conservatively assumed that CTC replaces all current use of DCBE (estimated at approximately 6,000 services per year in 2012–13), and that this level remains constant, the estimated net cost the MBS, including safety net payments, would be approximately $2,622,000 per year.

Conclusions

Safety

The evidence indicated that CTC is a relatively safe procedure and only rarely results in a serious adverse event in patients at high risk or symptomatic of CRC. Rates of serious adverse events were similar between CTC and DCBE. Minor adverse events such as abdominal pain/cramps, nausea/vomiting, wind, bottom soreness and soiling were more likely to occur after DCBE than CTC.

There was no evidence identified, and therefore no conclusions can be drawn, regarding the safety of CTC compared with delayed colonoscopy.

Patient acceptability

CTC was favoured over DCBE for quality of life (physical discomfort, satisfaction and worry) in the majority of studies reporting those outcomes. DCBE was not favoured for any quality of life outcomes. For the outcomes of patient acceptability (two studies) and patient preference (three studies), CTC was consistently favoured over DCBE. Overall, the seven studies indicate that patients find CTC more tolerable and acceptable than DCBE.

There was no evidence on patient acceptability of CTC compared with delayed colonoscopy, but one systematic review on CTC versus colonoscopy with no specified time delay reported that the majority of studies found that more patients preferred CTC to colonoscopy.

Effectiveness

Studies that reported the comparative effectiveness of CTC and DCBE in the specified review populations were scarce. That there are only a few studies reporting on DCBE from 2006 onwards possibly reflects the decreasing favour of DCBE as an investigative procedure. Only one study was identified that reported direct evidence fitting the inclusion criteria of this review, that of 4-year mortality following CTC and DCBE (Halligan et al. 2013; level II diagnostic evidence). This study, which was appraised as having a low risk of bias and is applicable to the Australian setting with few caveats, found that rates of mortality are the same for CTC and DCBE (15.7% vs 15.8%, 48 months post-procedure). Deaths were determined through the cancer registry but, since the causes of death were not reported in the study, the clinical meaning of these results is unclear. Therefore, the hypothesis that CTC leads to better survival than DCBE remains unsubstantiated on the basis of available evidence.

The direct evidence comparing CTC and DCBE was supplemented by a linked evidence analysis. This found that in the broader population of those at high risk or symptomatic of CRC, CTC was found to be more sensitive and less specific than DCBE. More patients are therefore referred for further investigations after CTC than after DCBE, and there would be a lower risk of having a false negative result after CTC. Patients whose lesions are missed by DCBE would be likely to have a delay in diagnosis, which would result in delayed treatment. The impact of this delay is uncertain, however, as systematic review evidence was identified that early diagnosis or treatment is associated with worse health outcomes than late diagnosis or treatment. This suggests that patients are usually triaged appropriately. Therefore, the linked evidence was inconclusive regarding the clinical impact of triaging patients at high risk or symptomatic of CRC with CTC, compared with DCBE.

No evidence was identified comparing CTC and delayed colonoscopy for either direct evidence or test accuracy. It is assumed that patients who have limited access to colonoscopy, who undergo a CTC and are found to have lesions suggestive of CRC, would receive a subsequent colonoscopy earlier than they would have otherwise. The clinical impact of early versus late diagnosis/treatment within a symptomatic population is unclear.

Other relevant considerations

A number of studies reported the proportion of successful colonoscopies performed after a previous incomplete colonoscopy, along with changes to procedure where required. Studies consistently showed that the large majority of patients were able to undergo a complete colonoscopy on a second attempt. Reasons for initial incomplete procedures such as patient discomfort, poor bowel preparation and redundant colon could be considered 'modifiable factors' that can be managed simply with available techniques. Colonoscopy is likely to be performed successfully when more care and preparation are taken. Patients for whom there is clear clinical reason (not technical or modifiable factors) may be the best candidates for consideration for CTC following incomplete colonoscopy.

Economic considerations

The economic analysis used a simple decision-analytic model, developed from a study-based evaluation, to estimate the incremental cost-effectiveness of CTC compared with DCBE for the exclusion or diagnosis of colorectal neoplasia in symptomatic and high-risk patients over the entire diagnostic process, including follow-up diagnostic procedures. When the prevalence of colorectal neoplasia in the target population was assumed to be that reported in Australian NBCSP patients who had a positive screening FOBT result (prevalence of CRC and large polyps of 3.1% and 6.7%, respectively), the estimated incremental cost per additional CRC or large polyp diagnosed for CTC compared with DCBE was $19,380.

The cost-effectiveness of CTC compared with DCBE improves as the prevalence of colorectal neoplasia in the target population increases. The difference in the sensitivity between the two diagnostic procedures is the key determinant of the comparative effectiveness of the two testing strategies, and is also the main source of uncertainty in the economic analysis.

There is some uncertainty regarding whether the 4-year follow-up for deaths, as reported in Halligan et al. (2013), was sufficient to accurately capture CRC survival rates. As a result, it is possible that there are survival benefits resulting from the lower rate of false negative outcomes with CTC, compared with DCBE, that are not captured in the economic analysis.

Costing

Patients with limited access to colonoscopy

The potential for the use of additional CTC in patients without access to colonoscopy is highly uncertain; however, it was estimated that this new listing could potentially result in an additional 18,000 to 19,000 CTC services per year. On this basis the additional cost to the MBS may be in the order of $10,000,000 per year.

Due to the limited data available on the number of patients who would meet the eligibility criteria for this proposed item, these estimates should be interpreted with caution. In addition, there is considerable potential for use of this item outside the intended purpose.

Patients unsuitable/contraindicated for colonoscopy

If it is assumed that CTC completely replaces DCBE for diagnosis of colorectal neoplasia, it is estimated that there would be an additional 4,900 CTC services in the first year of the revised listings, reducing to an additional 3,000 services in the fifth year.

The total cost to the MBS for the predicted increase in the number of CTC services associated with substitution of DCBE with CTC is estimated to be $2,668,000 in the first year of the proposed revised listings for CTC, decreasing to $1,650,000 in the fifth year. When cost offsets from the reduction in DCBE are considered, the net cost to the MBS is approximately $2,064,000 in the first year, reducing to $1,276,000 over the first 5 years.

The total cost to the Australian healthcare system including the MBS resulting from the expected change in patient management, if the revised listings are approved, ranges from $2,595,000 to $1,605,000 over the first 5 years. The majority of the increase in the cost will be incurred by the MBS.

Appendix A Health Expert Standing Panel and Assessment Group

Application 1269, CTC for the diagnosis or exclusion of colorectal neoplasia

Health Expert Standing Panel (HESP)

Member	Expertise or affiliation
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Noted conflicts of interest

There were no conflicts of interest.

Appendix B Search strategies

Suggested search terms for the assessment of CTC

Intervention terms
'colonography' OR 'colography' OR 'pneumocolon' OR 'virtual colonoscopy'/exp OR 'virtual colonoscopy' OR 'virtual colonoscopy'/syn OR 'ct colonography'/exp OR 'ct colonography' OR 'ct colonography'/syn OR 'computed tomographic colonography'/exp OR 'computed tomographic colonography' OR 'computed tomographic colonography'/syn OR 'colonography, computed tomographic'/exp OR 'colonography, computed tomographic' OR 'colonography, computed tomographic'/syn OR (tomograph* OR pneumoradiograph*) NEAR/3 ('colon' OR colon* OR 'rectum' OR 'rectal' OR rect* OR 'bowel' OR 'colorectal' OR colorect*)
Limits Publication date: January 2005 to August 2013** Study model: exclude non-human

* Above terms used for Embase and Medline literature searches. Terms were adapted to perform literature searches in other databases.

** MSAC previously engaged a team from the NHMRC Clinical Trials Centre to conduct a systematic review to assess CTC (published March 2006). The 2006 review conducted literature searches from 1994 to June 2005. As the population in the 2006 report includes that being assessed in the three research questions of the current review, the current review will include the studies identified in the 2006 report, and in addition will identify relevant literature published after June 2005; for ease of identifying literature the search period will be conducted from January 2005.

Searches for evidence on the impact of change of management

For the comparison of CTC against DCBE, the evidence regarding the accuracy of the two tests suggested that there would be more false negative results from DCBE than from CTC, leading to a delay in diagnosis in those inappropriately ruled out from DCBE. The expected change in management for CTC versus delayed colonoscopy is that patients would be diagnosed and treated earlier if imaged by CTC than if examined by delayed colonoscopy. The last steps of linked evidence in each of the comparisons against DCBE and delayed colonoscopy were therefore combined, to be an assessment of early versus late diagnosis and treatment.

A rapid review was therefore performed in PubMed, Embase and Google to identify level I evidence on the efficacy of early versus late diagnosis and treatment for CRC. The search terms used were '(delay* OR wait*) AND (colonoscopy OR colorectal cancer) AND (review

OR meta-analysis)'. Where multiple systematic reviews were identified, the most relevant and recent systematic reviews were chosen.

Searches for evidence on the comparison of CTC versus colonoscopy with no specified time delay

As there were no studies identified in the systematic review comparing CTC versus delayed colonoscopy, and it was beyond the restraints of this assessment to perform a systematic review on the comparison of CTC versus colonoscopy with no specified time delay, a rapid review was performed to identify level I evidence on CTC versus colonoscopy with no specified time delay. Searches were performed in PubMed, Embase, the Cochrane Collaboration and Google, and terms used were '(CTC OR CT colonography) AND colonoscopy AND (review or meta-analysis)'. The most relevant systematic reviews were chosen, and where multiple reviews appeared relevant, the most recent of these was chosen.

HTA websites

AUSTRALIA	
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
Centre for Clinical Effectiveness	http://www.southernhealth.org.au/cce
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/
AUSTRIA	
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita
CANADA	
Institute nationale d'excellance en santé et en services sociaux	http://www.inesss.qc.ca/
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/publications.html
Alberta Institute of Health Economics	http://www.ihe.ca/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database	http://www.mycabot.ca
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca

Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
DENMARK	
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.sst.dk/english/dacehta.aspx?sc_lang=en
Danish Institute for Health Services Research (DSI)	http://dsi.dk/english/
FINLAND	
Finnish Office for Health Technology Assessment (FINOHTA)	http://finohta.stakes.fi/EN/index.htm
FRANCE	
The Haute Autorité de santé (HAS) - or French National Authority for Health	http://www.has-sante.fr/portail/jcms/c_5443/english?cid=c_5443
GERMANY	
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en/index.html
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
THE NETHERLANDS	
Health Council of the Netherlands Gezondheidsraad	http://www.gezondheidsraad.nl/en/
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
NORWAY	
Norwegian Knowledge Centre for the Health Services	http://www.kunnskapssenteret.no
SPAIN	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud “Carlos III”I/Health Technology Assessment Agency (AETS)	http://www.isciii.es/
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat
SWEDEN	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
SWITZERLAND	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
UNITED KINGDOM	
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health	http://www.hta.ac.uk/

Technology Assessment (NCCHTA)	
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
The European Information Network on New and Changing Health Technologies	http://www.euroscan.bham.ac.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
Office of Health Technology Assessment Archive (US)	http://fas.org/ota
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/blueresources/tec/
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm

Bibliographic databases

Electronic bibliographic databases were searched to find relevant studies (those meeting the inclusion criteria) addressing each of the research questions. These databases are described in the box below. The previous MSAC review of CTC included studies of the same populations up until June 2005. To ensure that no papers from the first half of 2005 would be missed, the search period extended from January 2005 (or if inception of the database was later, from that date) until August 2013.

Electronic database	Time period
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	January 2005 – August 2013
Web of Science – Science Citation Index Expanded	
Current Contents	
Embase.com (including Embase and Medline)	
PubMed	
CINAHL	
EconLit	
PsycINFO (for literature on patient preferences)	

Additional literature—peer-reviewed or grey literature—was sought from the sources outlined in the box immediately below and from the health technology assessment agency websites provided listed in this appendix. Websites of specialty organisations were also searched for any potentially relevant information.

Additional sources of literature

Source	Location
Internet	
NHMRC - National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
Clinicaltrials.gov (US National Institutes of Health)	http://www.clinicaltrials.gov/
WHO International Clinical Trials Registry Platform	http://www.who.int/ictrp/en/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	http://www.update-software.com/National/
Google Scholar	http://scholar.google.com/
Hand searching (journals in past 2 years)	
Studies other than those found in regular searches	Library or electronic access
Expert clinicians	MSAC Health Expert Standing Panel (HESP)
Pearling	
All included articles had their reference lists searched for additional relevant source material	

Specialty websites

Abdominal Radiology Group of Australia and New Zealand	http://www.arganz.org/
Royal Australian and New Zealand College of Radiologists	http://www.ranzcr.edu.au/
American College or Radiology	http://www.acr.org/
American Society for Radiation Oncology	https://www.astro.org/
American College of Radiation Oncology	http://www.acro.org/
Colorectal Surgical Society of Australia and New Zealand	http://www.cssanz.org/
American Society of Colon and Rectal Surgeons	http://www.fascrs.org/
Gastroenterological Society of Australia	http://www.gesa.org.au/
American Gastroenterological Association	http://www.gastro.org/join-or-renew/join-aga/physician-scientists/international-physician-

	scientists
American College of Gastroenterology	http://gi.org/
Cancer Council Australia	http://www.cancer.org.au/
Cancer Australia	http://canceraustralia.gov.au/

Appendix C Study profiles of included studies

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
Bosworth et al. (2006) USA 2006	Design: Within-patient study Level: II Quality: High (10/12)	N = 614 30% females Mean age: 57 (+/- 10) years Ethnicity: 430 white (70%), 145 black (24%), 39 other (6%)	Inclusion: One of the following: One or more positive FOBTs; One or more episodes of bright red blood per rectum in previous 3 months; Iron-deficiency anaemia (defined as haemoglobin <130 g/L for men and <120 g/L for women on at least one measurement and abnormally low ferritin, iron-binding saturation or absent bone marrow stores); History of colon cancer or adenoma in a first-degree relative diagnosed before age 60 years, or any two first-degree relatives with colon cancer or adenoma diagnosed at any age Exclusion: Active gastrointestinal haemorrhage (reported or witnessed haematemesis, melaenic stools, repeated haematochezia); Serious medical illness within the previous 6 weeks; Pregnancy, or woman of childbearing age not using birth control; Previous colon surgery; Normal colonoscopy within the previous 2 years;	Air contrast barium enema: according to standard guidelines, bisacodyl, analysis in prone, 35-degree angled, supine, left and right lateral decubitus and left lateral positions CTC: air or CO_2 for insufflation, supine and prone acquisitions, four-slice (n=384) or eight-slice (n=240) scan, nominal slice thickness was 2.5 mm with 1 mm reconstruction intervals Colonoscopy: performed in usual manner. Sedative and pain drugs intravenously	Pain Worry Difficulty in following directions Difficulties with preparations Anxiety of obtaining tests Comfort with procedures Level of embarrassment Willingness to have test again Level of respect Tiredness Level of inconvenience Overall satisfaction	

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
			Known inflammatory bowel disease; Prisoners; Age younger than 18 years; Current participation in research involving drugs, medical devices or biological interventions; Need for special precautions in undertaking endoscopic procedures (e.g. antibiotic prophylaxis); Weight >135 kg			
Copel et al. (2007) Departments of Radiology and Gastro-enterology, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, USA	Design: Retrospective chart review Level: III-3 Quality: Poor	N=546 (90.1% were at high risk of developing CRC; 9.9% low-risk screening population) Female: 401 (73.4%) Mean age (range): 64.1 years (39–88) Indication for CTC: Redundant / tortuous loops, 218 (39.9); Excessive bowel spasm, 143 (26.2); Severe diverticulosis, 76 (13.9); Obstructive tumours, 41 (7.5); Colonic configuration considered to be due to previous surgery, 39 (7.1); Diverticulitis / ischemic colitis, 17 (3.1); External compression from masses, 6 (1.1); Partial bowel obstruction due to ventral hernia, 3 (0.5); Malrotation, 3 (0.5)	Inclusion: Referred for further examination after incomplete colonoscopy	CTC / colonoscopic and post-colonoscopy surgical findings of 45 patients were used to determine if polyps 6–7 mm and 8–9 mm were true or false positives	Repeat colonoscopy rate Endoluminal findings PPV of CTC	45 (i.e. <10%) patients had their diagnosis confirmed by follow-up with colonoscopy as CTC used as test to triage only positive findings to colonoscopy
Duff et al. (2006) Departments of	Design: Retrospective chart review	112 patients (69 female) contraindicated or unable to	Unable to tolerate DCBE (e.g. hemiplegia, serious comorbidity,	4-slice multi-slice CT using low radiation dose	Diagnostic accuracy against specified	Only 11 patients had their diagnosis

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
Surgery and Radiology, Royal Oldham Hospital, United Kingdom	Level: III-3 Quality: Poor	complete colonoscopy or barium enema Median age 78 years (range 39—95)	frailty, elderly) Incomplete DCBE due to severe musculoskeletal deformity/trauma Psychiatric illness / learning disability	12 month follow-up (i.e. no presentation of CRC during the following year was considered as confirmation that diagnosis as negative for CRC at time of CRC was true)	reference standards Diagnostic yield for: CRC, polyps, diverticular disease Extracolonic findings	confirmed by f/ follow-up with colonoscopy as CTC used as test to triage only positive findings to colonoscopy (remainder underwent clinical follow-up only)
El-Sharkawy et al. (2013) Departments of Radiology and Medical Imaging, King Khalid University Hospital, Riyadh, Saudi Arabia	Design: Single institute prospective cohort Level: Quality: NA	N=71 Female: 46% Mean age (range): 53 years (36–83) Indications for bowel investigation: Mass (palpation or colonoscopy) 28.2%; Abdominal pain: 16.9%; Screening: 15.5%; PR bleeding alone: 8.5%; Irritable bowel syndrome: 8.5%; Constipation: 5.6%; Melena and weight loss: 4.2%; Repeated malignant mass (follow-up): 2.8%; Crohn's disease: 2.8%; Abdominal pain and rectal bleeding: 2.8%; Ischemic colitis: 1.4%; Incontinence/pain: 1.4%; Family history of CRC: 1.4%	Inclusion: Referred for CTC due to: Incomplete colonoscopy (58); Contraindication or refusal (13)	CTC	Diagnostic yield for CTC (polyps, CRC) Extracolonic findings	Poor reporting
Gluecker et al. (2003) USA	Design: Within-patient study: single centre, patient survey by self-administered questionnaire	Group 1 (CTC and colonoscopy): N=696, 74% response rate Group 2 (CTC and DCBE): N=617, 87% response rate Males:	Inclusion: Referred to colonoscopy or DCBE; 50 years of age; First-degree relative or prior personal history of colorectal neoplasia, or new	CTC: Single- (14%) or multi-slice (86%) Dual positioning Spasmolytic (glucagon)	Quality of life (tolerance): • physical discomfort • inconvenience	

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
	Level: II Quality: Moderate	Group 1: 63% Group 2: 49% Median age (range) Group 1: 65 (41–84) years Group 2: 64 (50–82) years	onset of asymptomatic anaemia Exclusion: Gastrointestinal symptoms or diagnosis; Recent treatment or surgery	DCBE: Standard procedure Glucagon for pain Colonoscopy: Standard procedure (as per undescribed practice guidelines)	Patient preference Patient satisfaction	
Halligan et al. (2013) UK	Design: SIGGAR study, multi-centre, 2-armed RCT Level: II Quality: Moderate to high	N=3,804 (one arm of a trial of CTC vs colonoscopy and CTC vs DCBE) Female 61% Age (years): 55–64, 33%; 65–74, 39%; 75–84, 25%; ≥85, 3% Withdrawals: CTC, n=8 DCBE, n=26	Inclusion: Age ≥55 years; Able to give informed consent; Symptoms or signs suggestive of CRC by referring physician Exclusion: Known genetic predisposition to cancer; IBF; Patients being followed up for CRC; 'Whole-colon' investigation within previous 6 months	Intervention: CTC Comparator: DCBE Reference standard: Not performed	Primary outcomes: Detection rates of cancer and large polyps (≥10 mm) Secondary outcomes: Time to diagnosis or exclusion; adverse events; technical adequacy; need for repeat procedures; patient preference and tolerance	
Iafrate et al. (2008) Department of Radiological Services, University of Rome, Italy	Design: Retrospective Level: IV Quality: NA	N=136 elderly patients referred for CTC due to incomplete colonoscopy Indications for bowel investigation: Abdominal pain: 81 (59.5%); Rectal bleeding: 28 (20.5%); Weight loss: 17 (12.5%); Anaemia: 10 (7.5%)	Inclusion: Consent; >70 years of age Exclusion: History of familial adenomatous polyposis or hereditary non-polyposis cancer syndromes; Prior colorectal surgery; Suspected diagnosis of inflammatory bowel disease; Bowel obstruction; Acute diverticulitis;	CRC / polyps found on CTC confirmed by subsequent colonoscopy	Diagnostic yield for CTC (polyps, CRC, diverticular disease) Side effects Number of surgeries for CRC following CTC Extracolonic findings	

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
			Contraindications to ingestion of iodine-containing contrast agents			
Johnson et al. (2004) USA	Design: Within-patient prospective single centre blinded comparative study Level: II Quality: Low	N=691 Male: 51% Mean age (SD/range): 63.4 (7.2/50–86) years	Inclusion: 50 years of age or older; Prior history of colorectal neoplasia (33%); First-degree family member with a history of colorectal cancer (64%); New onset of asymptomatic iron-deficiency anaemia Exclusion: Melena; Haematochezia; IBD; Familial polyposis	CTC: Multi-slice 88% Single-slice 12% Dual positioning DCBE: Performed according to Standard of American College of Radiologya High-density barium (80% w/v) Multi-positioning Reference standard: Endoscopy (colonoscopy, sigmoidoscopy or proctoscopy) or surgery	Sensitivity per lesion per patient for lesions: 5–9 mm ≥10 mm Specificity per patient for lesions: 5–9 mm ≥10 mm Double-read CTC of lesions ≥5 mm	
Kataria (2011) Sweden	Design: Patient questionnaire following DCBE or CTC Level: III-2 Quality: High (9/12)	N=100 (50 DCBE and 50 CTC) 60% female Mean age (range) 65.5 (29–89) years	Inclusion: Patients older than 18 years of age (mix of both female and male patients as a sample representative of both age and gender was required) Exclusion: NR	DCBE: manual colon distension with air; images taken in prone, supine and erect positions; butylscopolamin when necessary CTC: Butylscopolamin; insufflation with CO_2; supine and prone scanning; contrast injected during supine series	Perception of pain Abdominal discomfort	As the patients only had 1 of the 2 tests, a direct comparison of the tests cannot be made
Kealey et al. (2004) Department of Radiology, St Vincent's University Hospital, Dublin, Ireland	Design: Prospective cohort Level: III-3 Quality: Fair	N=72 consecutive patients, frail/elderly, (4 lost to follow-up) with clinically significant colonic tumours Male/female proportions NR Mean age, years (range), 81 (62–93)	Exclusion: Age >60 years; Symptoms suggestive of colonic pathology (anaemia, altered bowel habit, weight loss, per rectal bleeding, abdominal mass); Too frail for DCBE or colonoscopy; Previous failed DCBE or colonoscopy	62 patients had 8-mm slice thickness CTC with an incremental scanner; 10 patients had spiral CTC using a non-helical scanner / Clinical outcome at 1 year with positive end-points defined as: histological confirmation of CRC; clinical presentation consistent with CRC without histological confirmation if the patient was too unwell for biopsy/surgery; death directly attributable to CRC	Yield CRC findings Diagnostic accuracy for CRC detection relative to nominated reference standard All-cause mortality Mortality from CRC diagnosed on CTC Non-cancer findings (intra- and extracolonic) Inter-observer	

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
					agreement	
Luo Mingyue (2002) Departments of Radiology, Third University Hospital, Sun Yat-Sen University of Medical Sciences, Guangzhou and Zhongshan Hospital, Shanghai Medical University, China	Design: Retrospective chart review Level: IV Quality: NA	N=60 (25 female) Mean age, 58.2 years (range 20–78)	No details other than patients had incomplete colonoscopy	CTC / biopsy histology from colonoscopy or surgery	Yield of intracolonic findings	Poor reporting
Macari et al. (1999) Departments of Radiology and Gastro-enterology, Tisch Hospital, New York, USA	Design: Retrospective chart review Level: IV Quality: NA	N=20 incomplete colonoscopy patients, of whom 10 went on to receive CTC Mean age, 65 years (range 50–80)	Patients with incomplete colonoscopy performed between September 1997 and December 1998	CTC and DCBE / colonoscopy performed in 1 patient	Yield of intracolonic findings	Very small sample of patients underwent CTC
Morrin et al. (1999) Departments of Radiology and Gastro-enterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA	Design: Retrospective Level: IV Quality: NA	N=40 patients who underwent incomplete colonoscopy over a 10-month period Mean age (range): 62 years (22–97) Female: 28 (70%) Indications for bowel investigation: Passage of blood via rectum, 17; Family history of colon cancer, 7; FOBT, 7; History of colonic polyps, 5; Altered bowel habits, 4	No details other than patients had incomplete colonoscopy	In 26 patients DCBE was carried out within 2 hours of CTC to correlate the findings of colonoscopy and CTC	Yield of intracolonic and extracolonic findings	
Neerincx et al. (2010) Netherlands	Design: Multi-centre retrospective cohort study Level: IV	N=511 (subgroup of total cohort of 5,278) Female: 62% Mean age (±SD): 62.5 ±	Patients who have undergone an incomplete colonoscopy Subgroup: (n=285) those who underwent a secondary investigation	A total of 278 patients underwent follow-up examination, of whom 66 underwent two or more examinations and 12 underwent three or more	Diagnostic yield Diagnostic yield per reason for incomplete colonoscopy	Majority of patients did not undergo CTC

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
	Quality: NA	16.5 years Indications for bowel investigation (numbers NR): Surveillance for CRC and polyps; Surveillance among hereditary polyposis syndromes population; Inflammatory bowel disease surveillance; Gastrointestinal bleeding; Anaemia; CRC suspected; Inflammatory bowel disease suspected; Family history of CRC; Irritable bowel syndrome; Polypectomy; Other		Colonoscopy: 83 DCBE: 151 Abdominal CT scan: 83 Surgery: 25 CTC: 14		
Neri et al. (2002) Diagnostic and interventional Radiology, Department of Oncology, Transplants, and Advanced Technologies in Medicine, University of Pisa, Italy	Design: Retrospective chart review Level: III-3 Quality: Poor	N=34 (16 female) patients clinically suspected of CRC (bright red blood per rectum, positive FOBT, altered bowel habit, anaemia, right lower quadrant pain) Mean age, 63 years (range 35–76)	Incomplete colonoscopy between September 1996 and January 2001	CTC / surgical findings were used as reference standard for patients with positive findings	Diagnostic accuracy for CRC detection Diagnostic yield and accuracy for polyps	
Ng et al. (2008)	Design: Retrospective chart review Level: III-3 Quality: Poor	1,029 elderly and frail patients (685 female) with CRC symptoms Median age 79 (range 72–85) years	Considered too frail/limited by mental disability to undergo DCBE or colonoscopy	MPCT involving helical acquisition (slice data NR) / pathology, cancer registry or ≥15 months follow-up	Diagnostic accuracy against the specified standards for CRC Yield of extracolonic findings Overall survival (Cox proportional hazard model; univariate,	91 patients were diagnosed by either pathology, registry or follow-up (triage from CTC) Survival data were for CTC only, without comparison

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
					multi-variate Survival by CRC status (Kaplan-Meier)	with DCBE, and are not reported in the results of this assessment
Pullens et al. (2013) Departments of Gastro-enterology and Hepatology, and Radiology, University Medical Center, Utrecht, The Netherlands	Design: Retrospective chart review Level: IV Quality: NA	N=136 (76 [55.9%] female) Mean age: 63.9 years Indications for bowel investigation: Anaemia, 35 (25.7%); Haematochezia, 28 (20.6%); Change in bowel habits, 25 (18.4%); Constipation, 9 (6.6%); Abdominal pain, 8 (5.9%); Familial predisposition for CRC, 8 (5.9%); Diarrhoea, 7 (5.1%); Polyp surveillance, 6 (4.4%); Weight loss, 2 (1.5%); Screening of asymptomatic patients, 1 (0.7%); Suspicions of CRC on abdominal ultrasound, 2 (2.2%); Other, 5 (3.7%)	Patients who underwent CTC after incomplete colonoscopy during January 2007 to April 2011	CTC / subsequent colonoscopy for patients found to have CRC or polyps	Yield of intra- and extracolonic findings	Confirmation of intracolonic CTC findings in a subset of patients only (n=19)
Robinson et al. (2002) Department of Diagnostic Radiology, Hope Hospital, Manchester, UK	Design: Retrospective review of patient records Level: III-3 Quality: Poor	N=195 (137 female) consecutive patients recruited by clinical referral with symptoms suspicious of CRC Median age, years (range): 76 (47–96) Indications for bowel investigation (n value NR): Weight loss; Change in bowel habit; Abdominal pain; Bleeding per rectum; Anaemia	Patients were referred by five consultant gastroenterologists/ geriatricians for CTC due to age or frailty	Non-helical CTC, 10 mm slice thickness / Reference standard was clinical outcomes	Diagnostic accuracy for CTC (compared with reference standard) Yield of normal and non-cancer/polyp intracolonic findings Yield extracolonic findings Deaths from colon cancer All-cause mortality	

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
		Prior incomplete investigations n patients: Colonoscopy, 79; DCBE, 11; Colonoscopy and DCBE, 11;				
Rockey et al. (2005) USA	Design: Within-patient prospective Multi-centre blinded comparative study Level: II Quality: Moderate	N=614 Male: 70% Mean age (SD): 57 (10) years	Inclusion *: ≥1 positive FOBT (38%); ≥1 episodes of rectal bleeding (42%); Iron-deficiency anaemia (8%); Family history of colon cancer or adenoma (32%) * Subjects could meet more than 1 inclusion criterion Exclusion: Active gastrointestinal haemorrhage; Previous colon surgery; Normal colonoscopy within the previous 2 years; Known IBD; Test contraindications	CTC: Multi-slice Dual positioning DCBE: Performed according to standard guidelines High-density barium (100% w/v) Multi-positioning Reference standard: Colonoscopy	Sensitivity per lesion, patient and histology for lesions: ≥10 mm 6–9 mm ≥6 mm Specificity per patient for lesions: ≥10 mm ≥6 mm	
Salamone et al. (2011) Department of Radiological Sciences, University of Messina, Italy	Design: Retrospective chart review Level: IV Quality: NA	N=68 patients referred to CTC because of an incomplete colonoscopy Mean age: 60.4 years Female: 48 (70.6%) Indications for bowel investigation: Dolichocolon, 9.7%; Severe diverticulosis, 25.2%; Patient discomfort, 15.5%; Angulations and adherences due to previous abdominal surgery, 46.9%	Incomplete colonoscopy between January 2007 and December 2009	CTC / NA	Diagnostic yield of intracolonic and extracolonic findings	
Sallam et al. (2007) Poland	Design: Retrospective single-centre cohort study	N=77 Females: 57% Average age: 62 years	Inclusion : Clinical suspicion of large bowel disease	Intervention: CTC Comparators: DCBE (35%), colonoscopy (39%) or both (26%)	Diagnostic accuracy Polyp morphology Bowel disease	

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
	Level: III-3 Quality: Low		Exclusion: Incomplete CTC; Lack of patient consent		diagnosis Extracolonic pathology	
Sali et al. (2008) Radio-diagnostic Section, Department of Clinical Physio-pathology, University of Florence, Italy	Design: Prospective Level: III-3 Quality: NA	42/65 patients with positive FOBT results undergoing CTC due to incomplete colonoscopy at screening Mean age (range): 60.7 years (51–70) Females: 25 (59.5%) 65/903 (7.2%) incomplete colonoscopies Indications for CTC: Dolichocolon: 9.7%; Severe diverticulosis: 25.2%; Patient discomfort: 15.5%; Angulations and adherences due to previous abdominal surgery: 46.9%	Incomplete colonoscopy between April 2006 and April 2007	CTC / repeat colonoscopy was performed in 21 (50%) of patients who were found to have polyps or masses on CTC	For polyp findings: true positives, false positives, false negatives and PPV per lesion	
Saunders et al. (2013) Sherwood Forest Hospitals NHS Trust, Sutton in Ashfield, United Kingdom	Design: Retrospective chart review Level: III-3 Quality: Poor	207 frail and/or elderly patients (135 female) requiring bowel investigation Median age 81 years (range 43–95)	Physical fragility Impaired mobility Psychological issues Previous stroke Poor tolerance of bowel preparation Incomplete colonoscopy	MPCT using 8-slice minimum scanner / 2-year follow-up of patient outcomes	Diagnostic accuracy against specified reference standards Diagnostic yield for: CRC by location, polyps, diverticular disease, rectal prolapse, diverticular abscess, chronic pseudo-obstruction, Crohn's disease	Colonoscopy was used to confirm the MPCT diagnosis in 34 patients (CTC used as test to triage only positive findings to colonoscopy) 3 patients were confirmed using a second CTC
Sofic et al. (2010) Bosnia and Herzegovina	Design: Within-patient unblinded prospective comparative study Level: II Quality: Moderate	N=231 Females: 53% Average age (± SD): 57.9 (± 11.3) years	Inclusion: Suspected symptoms of CRC (history of blood in stools, anaemia, constipation, changes in stool, positive FOBT test)	Intervention: CTC Comparators: DCBE and colonoscopy ± histological confirmation	Diagnostic accuracy Patient comfort	

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
			Exclusion: NR			
Taylor et al. (2003) UK	Design: Prospective cohort study: multi-centre, clinician assessment and self-administered questionnaires Level: III-2 Quality: high	Group 1: N=168, 86% response rate Group 2: N=140, 90% response rate Males: Group 1: 50% Group 2: 55% Median age: Group 1: 65 years Group 2: 62 years	Inclusion: High-risk (family history, follow-up of polyps or IBD); Symptoms (rectal bleeding, change in bowel habit, iron deficiency anaemia, palpable abdominal mass, polyps seen on DCBE) Exclusion: NR	CTC: Multi-slice scanner Dual positioning Buscopan (74%) Colonoscopy: Standard procedure IV sedation, analgesia and spasmolytic administered FS: Standard procedure No sedation or spasmolytic DCBE: Standard procedure	QoL: satisfaction, worry, physical discomfort, tolerance (follow-up) Patient preferences	
Taylor et al. (2005) UK	Design: Within patient study: patient self-administered questionnaires, manual device for pain measurement Level: II Quality: High	N=78, response rate 93% Male: 44% Median age (range): 70 (61–87) years	Inclusion: Referred to DCBE due to symptoms of colorectal cancer (change in bowel habit, iron deficiency anaemia, palpable abdominal mass) Exclusion: NR	CTC: Multi-slice scanner Dual positioning Spasmolytic DCBE: Standard procedure Spasmolytic	QoL: perceived pain; satisfaction, worry, physical discomfort, tolerance (f/u) Patient acceptance/ preference	
Taylor et al. (2006) UK	Design: Prospective cohort Level: III-3 Quality: Moderate to high	N=78 Females: 56% Median age (range): 70 (61–87) years	Inclusion: 60 years of age and older; Referred for DCBE with clinical suspicion of CRC; Exclusion: NR	Diagnostic tests: CTC DCBE Confirmatory tests: CTC: Consensus with 2nd reader DCBE: endoscopy records	Radiologist confidence	
Thomas, Atchley & Higginson (2009) UK	Design: Retrospective comparative cohort study Level: III-3 Quality: Moderate	N=2,520 (DCBE); 604 (CTC)	Inclusion: Patients identified from the picture archiving communication system between 1 January 2003 and 31 December 2005	Index tests: CTC or DCBE Reference standard: clinical diagnosis of CRC	Primary outcomes Detection rates of cancer Secondary outcomes Diagnostic accuracy	

Study setting	Study design / Quality appraisal	Study participants	Inclusion / exclusion criteria	Diagnostic tests / Reference standard	Outcomes assessed	Comments
			Exclusion: Incomplete procedures; Procedures for staging or follow-up of cancer			
von Wagner et al. (2011) UK	Design: Randomised controlled trial (with post-examination survey) Level: II Quality: High (10/12)	921/1,018 (90.5%) of randomised patients in final sample 674/921 (73.2%) responded to survey (450 DCBE and 224 CTC) 60.8% female Median age 68 years	Inclusion: >54 years of age; Able to give informed consent; Symptoms suggestive of colorectal cancer needing investigation by a whole colon examination according to the clinician in charge of care Exclusion: Inability to undergo full bowel preparation; Known genetic predisposition to cancer; Having previously received a diagnosis of inflammatory bowel disease or colorectal cancer; Having had a whole-colon examination within the preceding 6 months	DCBE: Spasmolytic unless contraindicated; CO_2 (11 centres) or air (9 centres) insufflation; CTC: Intravenous spasmolytic unless contraindicated; CO_2 or air (or both) insufflation; Prone and supine acquisitions; Multi-detector row CT with maximum 2.5 mm collimation	Satisfaction Worry Physical discomfort Post-test complications	
Yucel et al. (2008) USA Department of Radiology, Thomas Jefferson University Hospital, Philadelphia, USA	Design: Single-centre retrospective chart review Level: IV Quality: NA	61 patients (42 female) referred to CTC because colonoscopy was contraindicated or incomplete Mean age 71 years, range 60–87 years	Age >60 years Incomplete colonoscopy due to sigmoid diverticular disease, colonic redundancy, adhesions, residual colonic content, sigmoid stricture, ventral hernia or other cause Contraindication to colonoscopy due to anticoagulant therapy, increased anaesthesia risk, poor tolerance of colonoscopy preparation	16-slice MDCT / NR	Diagnostic yield for: diverticular disease, polyps, polypoid masses, lipoma, inflammatory stricture Extracolonic findings separated by high and low clinical importance	Findings could only be confirmed in 5/61 patients who went on to have a colonoscopy

Appendix D Excluded studies

Not of a higher evidence level than available in English

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Appendix E Additional economic information

Calculation of average bed-day charge for colonoscopy

DRG	Description	No. of separations	% of separations	Average total cost per DRG	Average weighted cost per DRG
G43Z	Complex colonoscopy	592	0.6%	$1,140	$816
G44B	Other colonoscopy – CSCC	6,541	6.4%	$2,273	
G44C	Other colonoscopy, same day	94,733	93.0%	$713	
Total separations		101,866			
Complications					
G44A	Other colonoscopy + CSCC			$5,898	

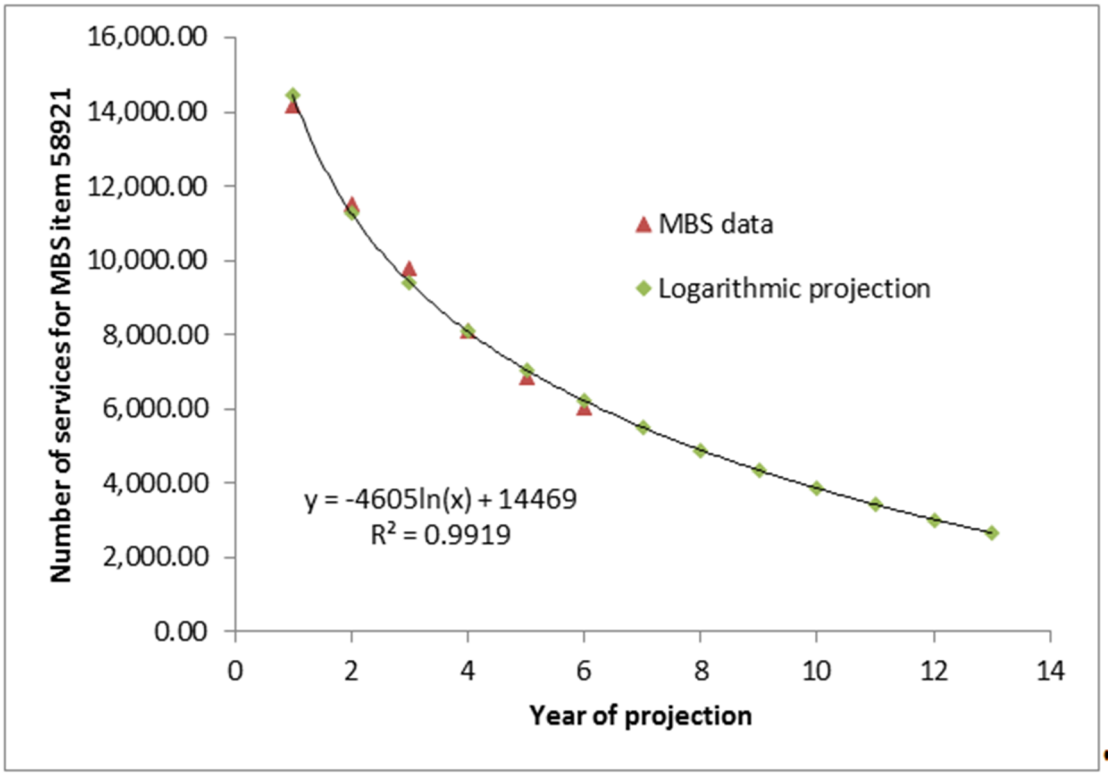
Source: AR-DRG Version 5.1 round 13 (2008–09) – Private sector

MBS data report item 58921, opaque enema (DCBE)

58921	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13
Number of services:	14,174	11,537	9,804	8,104	6,863	6,039
In-hospital	1,059	935	788	653	616	553
Out-of-hospital	13,115	10,602	9,016	7,451	6,247	5,486
Fee charged:	$2,081,932	$1,738,790	$1,517,769	$1,295,111	$1,092,959	$961,541
Average per service	$147	$151	$155	$160	$159	$159
Benefits paid:	$1,636,155	$1,338,737	$1,183,770	$1,007,298	$848,837	$745,838
Average per service	$115	$116	$121	$124	$124	$124
% of services bulk billed	56.0%	54.9%	58.9%	60.9%	61.6%	62.3%

DCBE – double contrast barium enema

Projected number of services for MBS item 58921 from financial year 2007–08 to 2019–20



Projected use of DCBE over the next 5 financial years

58921	2011–12	2012–13	2013–14	2014–15	2015–16	2016–17	2017–18	2018–19
MBS data	6,863	6,039						
Projected:								
Logarithmic	7,058	6,218	5,508	4,893	4,351	3,866	3,427	3,026
Exponential	6,965	5,864	4,938	4,157	3,500	2,947	2,482	2,089

DCBE – double contrast barium enema

MBS data report item 56552, CTC, incomplete colonoscopy

56552	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13
Number of services:	2,525	3,183	3,760	4,150	4,308	7,338
In-hospital	462	580	741	833	762	753
Out-of-hospital	2,063	2,603	3,019	3,317	3,546	3,585
Fee charged:	$1,497,570	$1,881,915	$2,265,402	$2,541,626	$2,628,671	$2,636,549
Average per service	$593	$591	$603	$612	$610	$608
Benefits paid:	$1,313,346	$1,655,192	$1,998,093	$2,239,538	$2,336,960	$2,357,723
Average per service	$520	$520	$531	$540	$542	$544
% of services bulk billed	54.1%	56.0%	58.5%	60.2%	65.3%	68.6%

CTC – computed tomography colonography

MBS data report item 56554, CTC, contraindication for colonoscopy

56554	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13
Number of services:	578	907	949	1,062	1,194	1,057
In-hospital	70	99	113	131	127	110
Out-of-hospital	508	808	836	931	1067	947
Fee charged:	$331,138	$519,910	$557,562	$636,358	$714,335	$630,421
Average per service	$573	$573	$588	$599	$598	$596
Benefits paid:	$302,878	$476,254	$511,655	$583,187	$656,789	$583,838
Average per service	$524	$525	$539	$549	$550	$552
% of services bulk billed	63.7%	66.5%	71.0%	72.1%	73.1%	76.7%

CTC – computed tomography colonography

Combined MBS data for items 56552 and 56554, CTC

56554	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13
Number of services:	3,103	4,090	4,709	5,212	5,502	5,395
In-hospital	532	679	854	964	889	863
Out-of-hospital	2,571	3,411	3,855	4,248	4,613	4,532
Fee charged:	$1,828,708	$2,401,825	$2,822,964	$3,177,984	$3,343,006	$3,266,970
Average per service	$589	$587	$599	$610	$608	$606
Benefits paid:	$1,616,224	$2,131,446	$2,509,748	$2,822,725	$2,993,749	$2,941,561
Average per service	$521	$521	$533	$542	$544	$545
% of services bulk billed	55.9%	58.3%	61.0%	62.6 %	67.0%	70.2%

CTC – computed tomography colonography; MBS – Medicare Benefits Schedule

Costs associated with changes in number of colonoscopy services

	2014–15	2015–16	2016–17	2017–18	2018–19
Colonoscopies following CTC					
Number of procedures: [a]					
Colonoscopy	467	415	369	327	289
Colonoscopy with biopsy	44	39	35	31	27
Polypectomy	190	169	150	133	118
Total	701	623	553	491	433
Costs					
Total cost (based on scheduled fee): [b]					
Colonoscopy	$163,779	$145,624	$129,385	$114,694	$101,283
Colonoscopy with biopsy	$22,220	$19,757	$17,554	$15,561	$13,741
Polypectomy	$122,520	$108,939	$96,790	$85,801	$75,768
Total	$308,519	$274,320	$243,729	$216,056	$190,792
Cost to MBS: [c]					
Colonoscopy	$136,252	$121,149	$107,638	$95,417	$84,260
Colonoscopy with biopsy	$18,513	$16,461	$14,625	$12,965	$11,449
Polypectomy	$102,109	$90,791	$80,666	$71,507	$63,146

	2014–15	2015–16	2016–17	2017–18	2018–19
Total	$256,874	$228,401	$202,930	$179,889	$158,855
Colonoscopies following DCBE					
Number of procedures:					
Colonoscopy	371	330	293	260	229
Colonoscopy with biopsy	50	45	40	35	31
Polypectomy	123	110	97	86	76
Total	544	484	430	381	336
Costs					
Total cost (based on scheduled fee): [b]					
Colonoscopy	$130,104	$115,682	$102,782	$91,112	$80,458
Colonoscopy with biopsy	$25,420	$22,603	$20,082	$17,802	$15,720
Polypectomy	$79,416	$70,613	$62,739	$55,615	$49,112
Total	$234,940	$208,898	$185,602	$164,529	$145,290
Cost to MBS: [c]					
Colonoscopy	$108,236	$96,239	$85,507	$75,798	$66,935
Colonoscopy with biopsy	$21,180	$18,832	$16,732	$14,832	$13,098
Polypectomy	$66,186	$58,850	$52,287	$46,350	$40,931
Total	$195,603	$173,921	$154,526	$136,981	$120,963
Net change in colonoscopies					
Number of procedures	157	139	124	110	97
Total cost	$73,578	$65,422	$58,127	$51,527	$45,502
Cost to MBS	**$61,272**	**$54,480**	**$48,404**	**$42,909**	**$37,891**

[a] Assuming that 59.1% of procedures are performed in private sector

[b] Includes changes in MBS items 32090, 32093, 20810, 23023, 23031, 72824, 73924

[c] Assumes that 14% of procedures are performed in-hospital

CTC – computed tomography colonography; DCBE – double contrast barium enema; MBS – Medicare Benefits Schedule

Change in costs of MBS items associated with expected increase in number of colonoscopy services

MBS item	4–15	5–16	6–17	7–18	8–19
Net cost based on MBS scheduled fee [a]					
32090 (colonoscopy +/- biopsy)	$29,969	$26,647	$23,675	$20,987	$18,533
32093 (polypectomy)	$31,375	$27,897	$24,786	$21,972	$19,403
20810 (anaesth. unit)	$1,735	$1,543	$1,371	$1,215	$1,073
23023 (anaesth. 26–30 minutes)	$497	$442	$393	$348	$307
23031 (anaesth. 30–45 minutes)	$556	$494	$439	$389	$344
72824 (pathology)	$8,560	$7,611	$6,762	$5,994	$5,293
73924 (initiation patient episode)	$887	$789	$701	$621	$549
Total	**$73,578**	**$65,422**	**$58,127**	**$51,527**	**$45,502**
Net cost to MBS [a,b]					
32090 (colonoscopy +/- biopsy)	$25,054	$22,277	$19,792	$17,545	$15,494
32093 (polypectomy)	$26,229	$23,322	$20,721	$18,368	$16,220
20810 (anaesth. unit)	$1,301	$1,157	$1,028	$911	$805

MBS item	4–15	5–16	6–17	7–18	8–19
23023 (anaesth. 26–30 minutes)	$373	$331	$294	$261	$230
23031 (anaesth. 30-45 minutes)	$417	$371	$329	$292	$258
72824 (pathology)	$7,156	$6,363	$5,653	$5,011	$4,425
73924 (initiation patient episode)	$742	$659	$586	$519	$459
Total	**$61,272**	**$54,480**	**$48,404**	**$42,909**	**$37,891**

[a] Assuming that 59.1% of procedures are performed in the private sector

[b] Assuming that 14% of procedures are performed in-hospital

MBS – Medicare Benefits Schedule

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