

Medical Policy



Title: Virtual Colonoscopy / CT Colonography

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are asymptomatic and undergoing colorectal cancer screening 	Interventions of interest are: <ul style="list-style-type: none"> Computed tomography colonography 	Comparators of interest are: <ul style="list-style-type: none"> Optical colonoscopy Sigmoidoscopy Fecal occult blood test 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test accuracy Test validity Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With positive colorectal cancer screening tests or signs or symptoms of colorectal cancer 	Interventions of interest are: <ul style="list-style-type: none"> Computed tomography colonography 	Comparators of interest are: <ul style="list-style-type: none"> Optical colonoscopy Standard care without colonoscopy 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test accuracy Test validity Treatment-related morbidity

DESCRIPTION

Computed tomography colonography (CTC), also known as virtual colonoscopy, is an imaging modality that has been investigated as an alternative to conventional endoscopic ("optical") colonoscopy. It has been most widely studied as an alternative screening technique for colon cancer, and for the diagnosis of colorectal cancer (CRC) in people with related symptoms and for other colorectal conditions.

OBJECTIVE

THE OBJECTIVE OF THIS EVIDENCE REVIEW IS TO DETERMINE WHETHER COMPUTED TOMOGRAPHY COLONOGRAPHY IMPROVES THE NET HEALTH OUTCOME IN INDIVIDUALS WHO ARE ASYMPTOMATIC BEING SCREENED FOR COLORECTAL CANCER OR HAVE POSITIVE SCREENING RESULTS FOR COLORECTAL CANCER.

BACKGROUND

Computed tomography colonography (CTC), also known as virtual colonoscopy, is an imaging modality that uses thin-section helical computed tomography to generate high-resolution, 2-dimensional axial images of the colon. Three-dimensional images, which resemble the endoluminal images obtained with conventional endoscopic colonoscopy, are then reconstructed offline. Computed tomography colonography has been investigated as an alternative to conventional endoscopic ("optical") colonoscopy. While CTC requires a full bowel preparation, similar to conventional colonoscopy, no sedation is required, and the examination is less time-consuming. However, the technique involves gas insufflation of the intestine, which may be uncomfortable to the patient, and training and credentialing of readers may be needed to achieve optimal performance.

REGULATORY STATUS

Multiple computed tomography devices, including multiple CTC devices, have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. FDA product code: JAK.

POLICY

- A. Virtual colonoscopy / CT colonography may be considered **medically necessary** as a screening technique for colorectal cancer in average risk, asymptomatic individuals between the ages of 50 and 75 years when no other colorectal cancer screening has been performed during the recommended screening interval:
1. Guaiac-based fecal occult blood test in the past year, **OR**
 2. Fecal immunochemical test in the past year, **OR**
 3. Multi-targeted stool DNA test in the past 3 years, **OR**
 4. Colonoscopy in the past 10 years, **OR**

5. CT colonography in the past 5 years, **OR**
 6. Flexible sigmoidoscopy in the past 5 years.
 7. In patients who failed to successfully complete a conventional colonoscopy (an inadequate prep does not constitute a failed colonoscopy)
- B. Except for the indications outlined in the policy statements above, virtual colonoscopy / CT colonography is considered **experimental / investigational**.

POLICY GUIDELINES

1. Average risk of developing colorectal cancer include those individuals who have no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn's disease and ulcerative colitis, no family history of colorectal cancers or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer.
2. Asymptomatic individuals include those who have no signs or symptoms of colorectal disease including, but not limited to, lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 26, 2021.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

COLON CANCER SCREENING

Clinical Context and Test Purpose

Diseases of the colon and rectum for which computed tomography colonography (CTC) may be considered as a diagnostic or screening tool include colorectal cancer (CRC) and precancerous conditions, diverticulosis and diverticulitis, and inflammatory bowel disease. The most widely studied use of CTC is as an alternative screening technique for colon cancer.

The purpose of CTC in patients who are asymptomatic and undergoing CRC screening is to prevent morbidity by detecting early colon cancers and detecting and removing cancer precursors such as polyps. The detection of cancer and removal of polyps ultimately requires an optical colonoscopy. Computed tomography colonography is an imaging procedure that can identify cancers or polyps. The effectiveness and efficiency of CTC depend on its ability to identify cancer

or polyps accurately so that all or most patients who have such lesions are appropriately referred for optical colonoscopy for diagnosis and treatment.

The question addressed in this evidence review is: Does the use of CTC improve the net health outcome in patients who are asymptomatic and undergoing CRC screening?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are asymptomatic and eligible for CRC screening.

Interventions

The test being considered is CTC.

Comparators

The following tests are currently being used to make decisions about managing patients who are asymptomatic and undergoing CRC screening: optical colonoscopy, sigmoidoscopy, and fecal occult blood test (FOBT).

Outcomes

The outcomes of interest are disease-specific morbidity and mortality. Beneficial outcomes relate to true-positive testing, which leads to the detection of disease that would be otherwise missed. Harmful outcomes result from false-negative testing, which may delay the diagnosis and management of CRC. Follow-up immediately after test results is of interest for CTC test accuracy and validity and test-related morbidity. Follow-up at 1 to 5 years is of interest for CRC outcomes for disease-specific mortality and morbidity.

Study Selection Criteria

For the evaluation of the clinical validity of the CTC test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the technology
- Included a suitable reference standard
- Patient clinical characteristics were described
- Patient selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Systematic Reviews

The diagnostic characteristics of CTC as a colon cancer screening test have been investigated in many studies in which patients referred for optical colonoscopy agreed first to undergo a CTC. Using a second-look unblinded colonoscopy aided by the results of the CTC as the reference standard, the diagnostic characteristics of CTC and the blinded colonoscopy can be calculated and compared. The sensitivity of CTC is a function of the size of the polyp; sensitivity is poorer for smaller polyps.

Lin et al (2016) published a systematic review and meta-analysis of the literature on CRC screening, conducted for the U.S. Preventive Services Task Force.¹ Reviewers identified 9 prospective diagnostic accuracy studies on CTC (N=6,497 patients). Seven studies involved CTC with bowel preparation, and 2 involved CTC without bowel preparation. Five studies, including both without bowel preparation, were rated by the U.S. Preventive Services Task Force as good quality and the remaining 4 were considered fair quality. In 4 studies of CTC with bowel preparation, the sensitivity to detect adenomas 6 mm or larger ranged from 73% to 98%, and the specificity ranged from 89% to 91%. The sensitivity of CTC to detect adenomas 10 mm or larger (7 studies) ranged from 67% to 94%, and the specificity ranged from 96% to 98%. Four (n=4821) of the 9 studies also provided data on colonoscopy. The sensitivity for adenomas 6 mm or larger ranged from 75% to 93%, and the sensitivity to detect adenomas 10 mm and larger ranged from 89% to 98%.

In addition, the Lin et al (2016) systematic review evaluated evidence on harms and extracolonic findings associated with CTC. Eleven fair or good quality prospective studies (N=10,272 patients) suggested little or no risk of serious adverse events such as perforation. In contrast, reviewers estimated that, with optical colonoscopy, the risk of perforation was 4 in 10,000 procedures (95% confidence interval [CI], 2 to 5 in 10,000) and the risk of major bleeding was 8 in 10,000 procedures (95% CI, 5 to 14 in 10,000). Radiation exposure is a potential harm of CTC, but many of the studies did not report the extent of radiation exposure. Using data from 4 studies, reviewers estimated that the radiation dose of a full-screening CTC examination was 4.5 to 7 mSv. However, in more recent studies (i.e., published between 2004 and 2008), the estimated radiation dose was lower, at 1 to 5 mSv. Among studies reporting this outcome, extracolonic findings occurred in 27% to 69% of CTC examinations. Approximately 1% to 11% underwent diagnostic evaluation, and 3% required treatment. Extracolonic cancers occurred in about 0.5% of individuals undergoing CTC examinations.

Martin-Lopez et al (2014) published a meta-analysis that included 9 studies of CRC screening.² Studies conducted for the diagnosis of CRC or in elderly, high-risk, or symptomatic patients were excluded. The overall per-patient pooled sensitivity and specificity of CTC were 66.8% (95% CI, 62.7% to 70.8%) and 80.3% (95% CI, 77.7% to 82.8%), respectively. For colonoscopy, the pooled sensitivity was 92.5% (95% CI, 89.0% to 95%) and pooled specificity was 73.2% (95% CI, 67.7% to 78.1%). In the subgroup with larger lesions, the diagnostic accuracy of both approaches was less divergent. For lesions 10 mm or larger, CTC had a pooled sensitivity of 91.2% (95% CI, 86.5% to 94.6%) and a specificity of 87.3% (95% CI, 86.2% to 88.3%). The pooled sensitivity of colonoscopy for lesions 10 mm or larger was 92.9% (95% CI, 86.0% to 97.1%), and the specificity was 91.3% (95% CI, 89.9% to 92.5%).

Randomized Controlled Trials

Regge et al (2017) reported on a controlled trial in which 5412 individuals were randomized to CTC (n=2674) or flexible sigmoidoscopy (n=2738).³ The detection rate for advanced adenomas did not differ significantly between groups (p=.52). Detection rates were 133 (5.1%) in the CTC group and 127 (4.7%) in the flexible sigmoidoscopy group. Ten CRCs were identified in the CTC group and 9 in the flexible sigmoidoscopy group. No serious adverse events were reported.

Other large randomized controlled trials (RCTs) have compared the diagnostic accuracy of CTC with a different method of CRC screening. In the IJspeert et al (2016) trial, 8,844 individuals were invited to be screened, and 2,258 (26%) agreed to participate.⁴ This included 982 (34%) of

2920 randomized to CTC and 1276 (22%) of 5924 randomized to standard colonoscopy. The analysis focused on the detection of high-risk sessile serrated polyps. Sessile serrated polyps were detected significantly more often in the colonoscopy examinations (n=55 [4.3%]) than in CTC examinations (n=8 [0.8%]). For the outcome of all sessile serrated polyps (high- and low-risk), significantly more were detected with the colonoscopy (n=83 [6.5%]) than with CTC (n=21 [2.1%]); $p < .001$). Adverse events were not discussed.

Sali et al (2016) compared reduced cathartic preparation CTC, full cathartic preparation CTC, fecal immunochemical test, and optical colonoscopy as primary screening tests for CRC.⁵ The study invited 16,087 patients for a screening test, and 6,116 patients underwent a test. Patients with a positive fecal immunochemical test and patients with a colonic mass or a polyp larger than 6 mm on CTC underwent optical colonoscopy. The detection rates per participant for advanced neoplasia were 5.2% for the CTC groups (pooled data) versus 1.7% for the fecal immunochemical test (relative risk [RR], 3.08; 95% CI, 2.19 to 4.32; $p < .001$). The detection rates were similar between the 2 CTC groups: 5.5% for the reduced cathartic preparation and 4.9% for the full cathartic preparation (RR, 1.12; 95% CI, 0.67 to 1.88; $p = .65$). The overall detection rates per participant for advanced neoplasia were 1.7% for the fecal immunochemical test, 5.5% for the reduced cathartic preparation CTC, 4.9% for the full cathartic preparation CTC, and 7.2% for optical colonoscopy.

Weinberg et al (2018) compared CTC versus optical colonoscopy in 231 patients undergoing screening at 1 year post curative surgery for CRC.⁶ All patients underwent CTC followed by optical colonoscopy. Compared with optical colonoscopy, CTC had a sensitivity of 44% (95% CI, 30.2% to 57.8%) and specificity of 85.8% (95% CI, 89.7% to 97%) for detecting lesions (all types) 6 mm or larger and a sensitivity of 76.9% (95% CI, 54% to 99.8%) and specificity of 89% (95% CI, 84.8% to 93.1%) for detection lesions (all types) 10 mm or larger. For serrated adenomas, CTC had a sensitivity of 60% (95% CI, 29.6% to 90.4%) and specificity of 76% (95% CI, 70.4% to 81.6%) for sizes 6 mm or larger and a sensitivity of 75% (95% CI, 32.6% to 100%) and specificity of 75.3% (95% CI, 69.7% to 80.9%) for sizes 10 mm or larger. The results with CTC were significantly different from the null hypothesis of 90% for sensitivities to detect all lesions or serrated adenomas 6 mm or larger and for specificities for serrated adenomas of all sizes ($p < .05$ for all comparisons).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs comparing outcomes for patients undergoing CTC screening with patients who did not undergo CTC screening were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence involves evaluating: (1) evidence that CTC is accurate and (2) evidence that CTC identifies appropriate patients with CRC who would not otherwise be screened. The clinical validity of CTC for screening for CRC has been demonstrated in systematic reviews and meta-analysis studies as well as several large RCTs. While modeling studies have reported that optical colonoscopy is likely more beneficial than CTC,^{7,8,9,10,11,12,13} higher participation with CTC may ameliorate otherwise lower improvement in net health outcome compared with optical colonoscopy.

Compliance with recommendations for optical colonoscopy is suboptimal. As reported by Steele et al (2013), the screening rate is about 60% (in the prior 10 years) among people ages 50 to 75.¹⁴ Computed tomography colonography has been proposed as an alternative colon cancer screening technique that may improve patient compliance compared with optical colonoscopy. A literature survey of studies that attempted to determine whether the availability of CTC would improve population screening rates found survey studies, patient satisfaction studies, and focus group studies. It is unclear how such studies provide a sufficient base of evidence to demonstrate that population adherence to colon cancer screening would improve through CTC.

Stoop et al (2012) published an RCT that evaluated the impact of CTC on colon cancer screening rates.¹⁵ This trial was performed in the Netherlands, and members of the general population ages 50 to 75 years were randomized to an invitation for CTC or optical colonoscopy. The CTC protocol included a noncathartic preparation, consisting of an iodinated contrast agent given the day before the exam and 1.5 hours before the exam, in conjunction with a low fiber diet. The participation rate in the CTC group was 34% (982/2920) compared with a rate of 22% (1276/5924) in the optical colonoscopy group ($p < .001$). The diagnostic yield per-patient of advanced polyps was higher in the optical colonoscopy group, at 8.7 of 100 participants compared with 6.1 of 100 participants for CTC ($p = .02$). However, the diagnostic yield of advanced neoplasia per invitee was similar, at 2.1 of 100 invitees for CTC and 1.9 of 100 invitees for optical colonoscopy ($p = .56$). The data would suggest that the increased participation rates with CTC offset the advantages of optical colonoscopy and that overall outcomes would likely be similar between strategies. It is not known whether the different preparation regimens affected participation rates.

Zhu et al (2020) published a meta-analysis of 5 RCTs, including the trial by Stoop et al, exploring participation rates between CTC and colonoscopy.¹⁶ The meta-analysis contained data on 15,974 invitees to participate in a screening test. The participation rate was 28.8% with CTC versus 20.8% with colonoscopy (RR, 1.26; 95% CI, 0.98 to 1.63; $p = .070$). The subgroup analyses revealed a higher participation rate for the reduced or no cathartic preparation CTC compared with colonoscopy (RR, 1.70; 95% CI, 1.40 to 2.07; $p < .001$).

Section Summary: Colon Cancer Screening

There is variability in the diagnostic accuracy of CTC in the literature; this is likely due to improvements in technical reliability over time. Most studies have reported that the diagnostic accuracy for CTC is high and in the same range or slightly below optical colonoscopy for polyps greater than 10 mm.

No long-term comparative studies have directly reported on outcomes of CTC versus optical colonoscopy. The determination of comparative outcomes of CTC and optical colonoscopy is complex, due to the differing patterns of follow-up associated with each strategy.

A recent meta-analysis of 5 key randomized trials revealed similar participation rates with CTC versus colonoscopy but reduced or no cathartic preparation CTC may improve participation rates. The improved screening rate may offset, or even outweigh, any benefit of optical colonoscopy on outcomes. However, similar screening rates may not be achieved with a cathartic preparation.

COLON CANCER DIAGNOSIS

Clinical Context and Test Purpose

The purpose of CTC in patients who have positive CRC screening or signs, and symptoms of CRC is to identify disease.

Computed tomography colonography has not generally been employed as a test to identify disease in persons with positive cancer screening tests or symptoms because, compared with screening settings, the expected probability of disease is much higher. Findings on CTC require confirmation with colonoscopy; thus, it would be inappropriate to use a noninvasive test if the probability of needing a confirmatory invasive test is high.

The question addressed in this evidence review is: Does the use of CTC improve the net health outcome in patients who have positive CRC screening tests or signs or symptoms of CRC?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with positive CRC screening tests or signs or symptoms of CRC.

Interventions

The test being considered is CTC.

Comparators

The following tests are currently being used to make decisions about patients who have positive CRC screening or signs and symptoms of CRC: optical colonoscopy and standard care without a colonoscopy.

Outcomes

The outcomes of interest are disease-specific morbidity and mortality. Beneficial outcomes relate to true-positive testing, which leads to the detection of disease that would be otherwise missed. Harmful outcomes result from false-negative testing, which may delay the diagnosis and management of CRC. Follow-up immediately after test results is of interest for CTC test accuracy and validity, as well as treatment-related morbidity; follow-up at 1 to 5 years is of interest for CTC outcomes for disease-specific morbidity or mortality.

Study Selection Criteria

For the evaluation of the clinical validity of the CTC test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the technology
- Included a suitable reference standard
- Patient clinical characteristics were described

- Patient selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Systematic Reviews

Several studies have evaluated the role of CTC in the diagnosis of CRC in patients with symptoms or positive findings on other screening modalities (e.g., FOBT). Plumb et al (2014) published a systematic review and meta-analysis of studies evaluating the performance of CTC for the diagnosis of colon cancer among subjects with positive FOBT.¹⁷ Fecal occult blood testing is a recommended screening technique for CRC; positive tests are typically followed by a colonoscopy. In this meta-analysis, reviewers included only studies that used CTC in the evaluation of patients who had had a positive FOBT and compared colonography results with a reference test, conventional colonoscopy, segmental unblinded colonoscopy, or surgery with subsequent histopathology. Five articles were analyzed, representing 4 studies with 622 patients. Pooled per-patient sensitivity and specificity for adenomas 6 mm or larger or CRC were 88.8% (95% CI, 83.6% to 92.5%) and 75.4% (95% CI, 58.6% to 86.8%), respectively. Reviewers commented that data were limited on CTC for patients with a positive FOBT (only 4 studies) and based on the available evidence, CTC has a reasonably high sensitivity for detecting adenomas 6 mm or larger (88.8%; 95% CI, 83.6% to 92.5%) but a relatively low specificity (75.4%; 95% CI, 58.6% to 86.8%).

Bai et al (2020) performed a meta-analysis comparing diagnostic accuracy of CTC versus colonoscopy in patients at high risk for CRC.¹⁸ The meta-analysis included 14 published articles with 3578 patients, who had symptoms suggestive of CRC or a family history of CRC, positive findings on FOBT, and CTC followed by colonoscopy. The reference standard for the lesion size was colonoscopy that utilized open biopsy forceps or histological evaluation. For detecting polyps 6 mm or larger with CTC, the results revealed a pooled sensitivity of 87% (95% CI, 83% to 90%) and specificity of 90% (95% CI, 86% to 93%). For detecting polyps 10 mm or larger with CTC, the results showed a pooled sensitivity of 91% (95% CI, 86% to 94%) and specificity of 98% (95% CI, 95% to 99%).

Retrospective Studies

Simons et al (2013) evaluated the false-negative rate and sensitivity of CTC for CRC among patients who presented with symptoms of CRC.¹⁹ The authors included 1855 consecutive patients who underwent CTC at a single-center. These data were linked to a comprehensive population-based cancer registry to determine if patients were diagnosed with CRC in the 2 years after their CTC. Fifty-three patients were diagnosed with CRC, of whom 40 patients had suspected CRC, 5 were diagnosed with large polyps that appeared malignant on histology, and 5 were diagnosed with an indeterminate mass on CTC. Two patients who developed cancer had not been diagnosed on CTC, and 1 patient who developed cancer had an incomplete colonography. The overall sensitivity of CTC was 94.3% (95% CI, 88% to 100%).

Plumb et al (2014) published findings of a retrospective study comparing results from CTC with optical colonoscopy in patients evaluated at a single-center who were indicated for CRC diagnostic assessment because of a positive FOBT.²⁰ This study was not included in the Plumb et al (2014) review (described above). Based on the institutional protocol, optical colonoscopy was

preferred for individuals with a positive FOBT; however, CTC was substituted if the subject was unable to complete colonoscopy bowel preparation safely, was too frail or immobile to undergo colonoscopy (although potentially fit for necessary treatment), had another contraindication to colonoscopy, or had an incomplete colonoscopy. The study analyzed 2731 FOBT-positive patients screened with CTC as their first screening test. Of these, 1027 (37.6%) had CRC or polyps suspected (95% CI, 33.8% to 41.4%), and 911 underwent confirmatory testing. One hundred twenty-four (4.5%) were found to have CRC and 533 (19.5%) were found to have polyps, for an overall CRC- or polyp-detection rate of 24.1% (95% CI, 21.5% to 24.1%). The positive predictive value for CRC or polyps was 72.1% (95% CI, 66.6% to 77.6%). Colonoscopy data were available for 72,817 FOBT-positive patients who underwent colonoscopy as an initial screening test, among whom 9.0% had CRC, and 50.6% had polyps. The authors attributed the difference in CRC and polyp rates between the groups to underlying differences in risk between those referred for CTC and potential biases in the interpretation of screening guidelines.

Sha et al (2020) compared the diagnostic performance of CTC versus colonoscopy for CRC at 2 hospitals in China.²¹ The study enrolled 318 patients presenting with symptoms suggestive of CRC - abdominal pain, rectal bleeding, and/or change in bowel habits- and undergoing both CTC and colonoscopy. From the screened patients, 77 patients with polyps 10 mm and larger, or smaller than 10 mm but suspicious, underwent surgery and surgical pathology. Based on the surgical pathology, sensitivities were 96.1% for CTC and 83.1% for colonoscopy. The accuracies were 92.6% for CTC versus 92% for colonoscopy for polyps 10 mm or larger, and 95.9% for CTC versus 83.7% for colonoscopy for polyps smaller than 10 mm.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Several studies have evaluated the role of CTC for patients with symptoms suggestive of CRC. Atkin et al (2013) reported on the results of an unblinded RCT comparing colonoscopy with CTC in the evaluation of patients who had symptoms suggestive of CRC.²² Given the challenges of conducting a trial that would be adequately powered to detect small differences between CTC and colonoscopy in CRC and large polyp detection, the authors used rates of the need for additional evaluation after CTC as a primary outcome, on the assumption that such rates would strongly affect the evaluation of the benefits of the procedure. The trial randomized patients ages 55 or older with symptoms suggestive of CRC in a 2:1 fashion to colonoscopy or CTC. Both colonoscopy and CTC procedures were conducted with full bowel preparation. The trial's primary outcome was the proportion of patients who had an additional colonic investigation, defined as any subsequent examination of the colon until diagnosis (usually histologic confirmation of cancer or polyp) or until a patient was referred back to his or her physician. Additional diagnostic evaluation of the colon was required in 160 (30.0%) of 533 of those assigned to CTC compared with 86 (8.2%) of 1047 of those assigned to colonoscopy ($p < .001$). The overall detection rate for CRC or large polyps did not differ between the groups (RR, 0.95; 95% CI, 0.70 to 1.27; $p = .69$).

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of CTC for colon cancer diagnosis has not been established, a chain of evidence supporting the clinical utility of CTC for this population cannot be constructed.

Section Summary: Computed Tomography Colonography for Colon Cancer Diagnosis

There is a relatively small number of studies of CTC for diagnosing CRC in patients with a positive screening test or with symptoms of CRC. A systematic review of CTC studies in patients with a positive FOBT identified only 4 studies and found a reasonably high sensitivity for detecting adenomas 6 mm or larger but relatively low specificity. Another meta-analysis of 14 articles found high sensitivity and specificity with CTC for detecting polyps, when confirmed by colonoscopy with open biopsy forceps or histological evaluation, especially for polyps 10 mm or larger. An RCT comparing CTC with colonoscopy in symptomatic patients found a significantly greater need for additional evaluation after CTC compared with colonoscopy. Because the prevalence of the disease is much higher in patients with positive screening tests or symptoms of CRC, going directly to colonoscopy is usually the preferred clinical strategy. Additional studies are needed to determine with certainty the diagnostic accuracy of CTC for diagnosis of CRC; however, for patients unable to undergo a colonoscopy, based on the available evidence, CTC may be a reasonable option.

Summary of Evidence

For individuals who are asymptomatic and undergoing CRC screening who receive CTC, the evidence includes systematic reviews with meta-analysis, randomized and nonrandomized controlled trials, and modeling studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. The available evidence supports the conclusion that the diagnostic accuracy of CTC is in the same range or slightly below optical colonoscopy, with a moderate-to-high sensitivity and a high specificity for the detection of larger polyps and CRC. As a result, screening with CTC may provide similar diagnostic results to screening using conventional optical colonoscopy. Most modeling studies have reported that the overall benefits of a strategy that uses optical colonoscopy likely exceed the benefits of a strategy using CTC. However, these analyses assume equal participation rates in screening between the strategies. Participation in screening may be higher with CTC that has reduced or no cathartic preparation than with optical colonoscopy, and this may ameliorate or offset some improved outcomes associated with optical colonoscopy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have positive CRC screening tests or signs or symptoms of CRC who receive CTC, the evidence includes systematic reviews with meta-analysis, an RCT, and cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. Using CTC on patients with the suspected disease might be an inefficient testing strategy because CTC findings need to be confirmed with conventional colonoscopy. There are a small number of studies on CTC for diagnosis of CRC in patients with a positive screening test or with symptoms of CRC, and thus the diagnostic accuracy cannot be determined with certainty. Studies of patients with a positive FOBT have suggested a reasonably high sensitivity for detection of adenomas 6 mm or larger but a relatively low specificity. There are fewer studies of patients with CRC symptoms; the RCT found that significantly more patients required additional evaluation after CTC than after conventional colonoscopy. The evidence is

insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Physicians

In 2019, the American College of Physicians updated its guidelines for colorectal cancer (CRC) screening.²³ The American College of Physicians recommends 1 of the following 3 strategies for adults aged 50 to 75 years:

- High-sensitivity guaiac-based fecal occult blood test or fecal immunochemical test every 2 years.
- Fecal immunochemical test every 2 years plus flexible sigmoidoscopy every 10 years.
- Colonoscopy every 10 years.

The guideline stated that computed tomography colonography (CTC) may result in incidental extracolonic findings in 40% to 70% of screening examinations that may lead to additional evaluations and overtreatment. Screening intervals are more frequent for CTC, and positive findings on CTC require follow-up with colonoscopy.

American Cancer Society

In 2018, the American Cancer Society (ACS) updated its guidelines on CRC screening (Table 1).²⁴ The ACS made the following recommendations on colon cancer screening:

"The ACS recommends that adults aged 45 years and older with an average risk of colorectal cancer undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability....The recommendation to begin screening at age 45 years is a qualified recommendation. The recommendation for regular screening in adults aged 50 years and older is a strong recommendation."

Computed tomography colonography was listed as an option for CRC screening (Table 1) and was acknowledged to have comparable sensitivity and specificity to a colonoscopy. Stated limitations associated with CTC included exposure to low-dose radiation as well as complications of full bowel preparation, including rare cases of bowel perforation. It remains unclear whether incidental detection of extracolonic findings during CTC provides net benefit or harm to patients.

Table 1. Guidelines on Colorectal Cancer Screening Options

Colorectal Cancer Screening Guidelines
Stool-based test
Fecal immunochemical test every 1 y
High-sensitivity, guaiac-based fecal occult blood test every 1 y
Multitarget stool DNA test every 3 y
Structural test
Colonoscopy every 10 y
Computer tomography colonography every 5 y

American College of Gastroenterology

In 2017, the American College of Gastroenterology published recommendations of the U.S. Multi-Society Task Force of Colorectal Cancer made up of expert gastroenterologists from the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy.²⁵ The panel recommended CRC screening beginning at age 50 with adjustments based on race and family history using a ranked-tiered CRC screening approach in Table 2. Considerations for recommending the tiered system of current CRC screening tests included performance, cost, patient acceptance, and the lack of randomized trial results that directly compare the effects of different tests on CRC incidence or mortality.

Table 2. Colorectal Cancer Screening Tier Strategy

Tier	Recommendation
Tier 1	<ul style="list-style-type: none"> • Colonoscopy every 10 y • Annual fecal immunochemical test
Tier 2	<ul style="list-style-type: none"> • Computed tomography colonography every 5 y • Fecal immunochemical test-fecal DNA every 3 y • Flexible sigmoidoscopy every 10 y (or every 5 y)
Tier 3	<ul style="list-style-type: none"> • Capsule colonoscopy every 5 y
Available tests not currently recommended	<ul style="list-style-type: none"> • Septin 9

In 2021, the American College of Gastroenterology released updated CRC screening guidelines.²⁶ The guidelines recommend CRC screening in average risk individuals between 50 to 75 years of age (strong recommendation; moderate quality of evidence) and suggest CRC screening in average risk individuals between 45 to 49 years of age (conditional recommendation; very low quality of evidence) to reduce the incidence of advanced adenoma, CRC, and mortality from CRC. The guideline recommends "colonoscopy and fecal immunochemical testing as the primary screening modalities for CRC screening" (strong recommendation; low quality of evidence). Flexible sigmoidoscopy, multitarget stool DNA testing, CTC, or colon capsule are suggested for consideration for individuals unable or unwilling to undergo a colonoscopy or fecal immunochemical testing (conditional recommendation; very low quality of evidence). The guidelines recommend that fecal immunochemical testing should be performed every year and colonoscopy every 10 years (strong recommendation; low quality of evidence) and suggest that a multitarget stool DNA test be performed every 3 years, flexible sigmoidoscopy every 5 to 10 years, CTC every 5 years, and colon capsule every 5 years (conditional recommendation; very low quality of evidence).

American College of Radiology

In 2018, the American College of Radiology updated its 2014 appropriateness criteria on imaging tests for CRC screening.^{27,28} While CTC was not recommended for screening of patients at high-risk for CRC, it was appropriate for screening in the following populations:

- Average-risk individual, >50 years old
- Moderate-risk individual with a first-degree family history of cancer or adenoma
- Average-, moderate-, or high-risk individual with incomplete colonoscopy.

Computed tomography colonography was also appropriate for CRC detection in moderate-risk individuals, and in average-risk individuals after positive fecal screening tests (fecal occult blood test or fecal immunochemical test).

National Comprehensive Cancer Network

Per the National Comprehensive Cancer Network (NCCN), colonoscopy is "the most complete screening procedure and is considered the current gold standard for assessing the severity of detecting neoplasia for other screening modalities. The general consensus is that a 10-year interval is appropriate for most average risk individuals who had a high-quality normal colonoscopy..."²⁹. Regarding CTC, the NCCN guideline states that CTC "is evolving as a promising technique for CRC screening. CT colonography has the advantages of being noninvasive and not requiring sedation. The risk of test-related complications is also very low....CT colonography may be cost-effective when compared to colonoscopy. However, a positive finding requires a colonoscopy, and extracolonic findings - which are present in up to 16% of patients - pose a dilemma."

U.S. Preventive Services Task Force Recommendations

In 2021, the U.S. Preventive Services Task Force (USPSTF) updated its recommendations on CRC screening.³⁰ The recommendations included the following:

Adults 50 to 75 years old:

"The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years." (Grade A)

Adults 45 to 49 years old:

"The USPSTF recommends screening for CRC in adults aged 45 to 49 years." (Grade B)

Adults 76 to 85 years old:

"The USPSTF recommends that clinicians selectively offer screening for CRC in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences."
"The

- (Grade C)

Regarding evidence of efficacy for CT colonography, the USPSTF stated:

- "Evidence available that CT colonography has reasonable accuracy to detect CRC and adenomas;
- No direct evidence evaluating effect of CT colonography on CRC mortality;
- Limited evidence about the potential benefits or harms of possible evaluation and treatment of incidental extracolonic findings, which are common. Extracolonic findings

detected in 1.3% to 11.4% of examinations; <3% required medical or surgical treatment."

The USPSTF also noted that "more studies evaluating the direct effectiveness of screening with CT colonography on CRC mortality are needed, as well as more studies that report on long-term consequences of identifying extracolonic findings on CRC screening."

Ongoing and Unpublished Clinical Trials

No ongoing clinical trials were identified.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- | | |
|-------|---|
| 74261 | Computed tomographic (CT) colonography, diagnostic, including image postprocessing; without contrast material |
| 74262 | Computed tomographic (CT) colonography, diagnostic, including image postprocessing; with contrast material(s) including non-contrast images, if performed |
| 74263 | Computed tomographic (CT) colonography, screening, including image postprocessing |

ICD-10 Diagnoses

- | | |
|--------|---|
| C18.0 | Malignant neoplasm of cecum |
| C18.1 | Malignant neoplasm of appendix |
| C18.2 | Malignant neoplasm of ascending colon |
| C18.3 | Malignant neoplasm of hepatic flexure |
| C18.4 | Malignant neoplasm of transverse colon |
| C18.5 | Malignant neoplasm of splenic flexure |
| C18.6 | Malignant neoplasm of descending colon |
| C18.7 | Malignant neoplasm of sigmoid colon |
| C18.8 | Malignant neoplasm of overlapping sites of colon |
| C19 | Malignant neoplasm of rectosigmoid junction |
| Z12.10 | Encounter for screening for malignant neoplasm of intestinal tract, unspecified |
| Z12.11 | Encounter for screening for malignant neoplasm of colon |
| Z12.12 | Encounter for screening for malignant neoplasm of rectum |
| Z12.13 | Encounter for screening for malignant neoplasm of rectum |
| Z80.0 | Family history of malignant neoplasm of digestive organs |

REVISIONS

12-31-2009	Updated Description section. In Policy section: <ul style="list-style-type: none"> ▪ Removed "Virtual colonoscopy/CT colonography as a screening test for colorectal polyps is considered experimental/investigational."
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	<p>Virtual colonoscopy/CT colonography screening for colorectal cancer is considered medically necessary as an alternative to colonoscopy when the patient has failed a colonoscopy AND the patient is at higher than average risk for colorectal cancer based on one or more of the following:</p> <ul style="list-style-type: none"> ▪ Personal history of resected colorectal cancer; OR ▪ Prior history of adenomatous polyps; OR ▪ Older unscreened relatives of an individual with newly diagnosed Familial Adenomatous Polyposis (FAP) but who do not have specific genetic evidence or clinical manifestations of the disease; OR ▪ Patients with a genetic or clinical diagnosis of Hereditary Non Polyposis Colorectal Cancer (HNPCC), OR ▪ Inflammatory bowel disease OR ▪ Family history of colorectal cancer or adenomas as evidenced by ANY ONE of the following: <ul style="list-style-type: none"> ➢ One first degree relative with colorectal cancer or adenoma diagnosed < age 60; OR ➢ Multiple (2 or more) first degree relatives with colorectal cancer or adenomas at any age; OR ➢ One or more first degree relatives with colorectal cancer or adenoma diagnosed > age 60, or two second degree relatives." ▪ Added the policy liberalization of, "Virtual colonoscopy / CT colonography as a test for colorectal cancer is considered not medically necessary, except when the patient failed to successfully complete a colonoscopy." <p>Added Rationale section.</p> <p>In Coding Section (effective 01/01/2010):</p> <ul style="list-style-type: none"> ▪ Added CPT Codes: 74261, 74262, 74263 ▪ Removed CPT Codes: 0066T, 0067T
10-08-2010	<p>Updated Policy Language</p> <p>In the policy language:</p> <ul style="list-style-type: none"> ▪ Removed "screening" to read "Virtual colonoscopy / CT Colonography as a test for colorectal cancer is considered not medically necessary, except when the patient: ..." ▪ Inserted "A. Failed to successfully complete a colonoscopy (an inadequate prep does not constitute a failed colonoscopy)."; "B. when a patient is not an appropriate candidate to safely perform a colonoscopy." ▪ Inserted "Examples of conditions where the patient might not be an appropriate candidate to safely perform a colonoscopy are as follows, but not limited to: <ul style="list-style-type: none"> --Known colonic obstruction or stenosing lesions --Inability to perform colonoscopy because anticoagulant therapy cannot be discontinued --High anesthesia risk for the patient"
09-17-2013	<p>Updated Description section.</p> <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added ICD-10 Diagnosis codes (<i>Effective October 1, 2014</i>) <p>Updated Reference section.</p>
02-16-2015	<p>Updated Description section.</p> <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Changed ICD-10 Diagnoses Effective date to October 1, 2015. <p>Updated References section.</p>
07-21-2015	<p>Updated Description section.</p> <p>Updated Rationale section.</p> <p>Updated References section.</p>

10-01-2016	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added ICD-10 codes effective 10-01-2016: K52.21, K52.22, K52.29, K52.3, K52.83, K52.831, K52.832, K52.838, K52.839, K58.1, K58.2, K58.8, K59.31, K59.39 ▪ Termed ICD-10 codes effective 09-30-2016: K52.2, K59.3
10-26-2016	<p>Updated Description section.</p> <p>Updated Rationale section.</p> <p>Updated References section.</p>
10-25-2017	<p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ Previous policy language was removed: A. Virtual colonoscopy / CT colonography as a test for colorectal cancer is considered not medically necessary, except when the patient: 1. Failed to successfully complete a colonoscopy (an inadequate prep does not constitute a failed colonoscopy); OR 2. When a patient is not an appropriate candidate to safely perform a colonoscopy. B. Examples of conditions where the patient might not be an appropriate candidate to safely perform a colonoscopy are as follows, but not limited to: 1. Known colonic obstruction or stenosing lesions 2. Inability to perform colonoscopy because anticoagulant therapy cannot be discontinued 3. High anesthesia risk for the patient ▪ The following language was added: A. Virtual colonoscopy / CT colonography may be considered medically necessary as a screening technique for colorectal cancer in average risk, asymptomatic individuals between the ages of 50 and 75 years when no other colorectal cancer screening has been performed during the recommended screening interval: 1. Guaiac-based fecal occult blood test in the past year, OR 2. Fecal immunochemical test in the past year, OR 3. Multitargeted stool DNA test in the past 3 years, OR 4. Colonoscopy in the past 10 years, OR 5. CT colonography in the past 5 years, OR 6. Flexible sigmoidoscopy in the past 5 years. ▪ Added Policy Guidelines. <p>Updated Rationale section.</p> <p>Updated References section.</p>
12-20-2018	<p>Policy published to the bcbsks.com website on 11-20-2018 with an effective date of 12-20-2018.</p> <p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ Added new Item B, "Virtual colonoscopy / CT colonography as a test for colorectal cancer is considered medically necessary in the following clinical situations: 1. In patients who failed to successfully complete a conventional colonoscopy (an inadequate prep does not constitute a failed colonoscopy); OR 2. In patients who are not an appropriate candidate to safely perform a conventional colonoscopy, including, but not limited to, a. those with a known colonic obstruction or stenosing lesions, b. inability to perform colonoscopy because anticoagulant therapy cannot be discontinued, c. high anesthesia risk." ▪ Added new Item C, "Except for the indications outlined in the policy statements above, virtual colonoscopy / CT colonography is considered experimental / investigational." <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Removed ICD-9 codes. ▪ Added ICD-10 codes: Z12.10, Z12.12, Z80.0. ▪ Removed ICD-10 codes: D12.0, D12.1, D12.2, D12.3, D12.4, D12.5, D12.7, D12.8, D12.9, D37.1, D37.2, D37.3, K50.10, K50.111, K50.112, K50.113, K50.114, K50.118, K51.00, K51.011, K51.012, K51.013, K51.014, K51.018, K51.20, K51.211, K51.212, K51.213, K51.214, K51.218, K51.30, K51.311, K51.312, K51.313, K51.314, K51.318, K51.40, K51.411, K51.412, K51.413, K51.414, K51.418, K51.50, K51.511, K51.512, K51.513, K51.514, K51.518, K51.80, K51.811, K51.812, K51.813, K51.814, K51.818,

	K51.90, K51.911, K51.912, K51.913, K51.914, K51.918, K52.0, K52.1, K52.21, K52.22, K52.29, K52.3, K52.83, K52.831, K52.832, K52.838, K52.839, K52.89, K57.20, K57.21, K57.30, K57.31, K57.32, K57.33, K57.40, K57.41, K57.50, K57.51, K57.52, K57.53, K57.80, K52.92, K58.0, K58.1, K58.2, K58.8, K58.9, K59.31, K59.39, K62.0, K62.1, K62.2, K62.3, K62.5, K63.5, Z86.010.
	Updated References section.
05-22-2020	Updated Description section. In Policy section: <ul style="list-style-type: none"> ▪ Removed B, B2, B2a, B2b, B2c. "B. Virtual colonoscopy / CT colonography as a test for colorectal cancer is considered medically necessary in the following clinical situations: 2. In patients who are not an appropriate candidate to safely perform a conventional colonoscopy, including, but not limited to, <ul style="list-style-type: none"> a. those with a known colonic obstruction or stenosing lesions, b. inability to perform colonoscopy because anticoagulant therapy cannot be discontinued, c. high anesthesia risk." ▪ Moved B1 under A7 "In patients who failed to successfully complete a conventional colonoscopy (an inadequate prep does not constitute a failed colonoscopy)"
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Removed ICD-10 Codes:C18.9, C78.5, D01.0, D01.2, D37.4, D37.5
	Updated Reference section.
11-5-2021	Updated Description section Updated Rationale section Updated References section

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