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CT Suite

CT Colonography:

A Visual, Noninvasive, and Patient-Friendly Colorectal Cancer Screening Option

A CLINICAL MONOGRAPH

Committed **to Science,**
Committed **to You.**™

Bracco Diagnostics Inc. is committed to helping decrease morbidity and mortality rates in the United States due to colorectal cancer…

Colorectal cancer (CRC) is currently the second leading cause of cancer-related mortality in the United States.[1,2] Early detection and removal of early-stage cancers or precancerous adenomatous polyps has been shown to significantly reduce mortality from CRC.[3,4] The American Cancer Society (ACS) currently recommends that men and women of average risk should begin CRC screening at age 50.[5] Optical colonoscopy (OC) has been the most widely adopted visual screening method for CRC; however, screening rates with OC are hampered by the invasive nature of the exam, the need for extensive bowel prep, and the use of anesthesia.

Computed tomography colonography (CTC), sometimes referred to as virtual colonoscopy, represents a visual, noninvasive, patient-friendly option that healthcare professionals can use for CRC screening in asymptomatic adults of average risk.[6,7] CTC is associated with very high patient satisfaction that may contribute to improved adherence rates, attracting individuals who might otherwise forego screening.[8–11] This clinical monograph is designed to help healthcare professionals learn more about CTC as an option for CRC screening.

Recent recommendations, including those from the U.S. Preventive Services Task Force (USPSTF),[12,13] the Centers for Disease Control and Prevention (CDC),[14,15] the ACS, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology (ACR)[16] all include CTC as an option for CRC screening in asymptomatic patients. In 2013, the U.S. Food and Drug Administration (FDA) convened a joint meeting of the Gastroenterology-Urology Devices Panel and the Radiological Devices Panel, and the members unanimously agreed "CTC should be available as an option for CRC screening of asymptomatic patients."[17] Most recently, the Healthcare Effectiveness Data and Information Set (HEDIS) manuals, published in 2017 by the National Committee for Quality Assurance (NCQA), recognize CTC as a quality measure for CRC screening.[18]

Nevertheless, CRC screening remains underutilized. To address this, the National Colorectal Cancer Roundtable (NCCRT), established by the ACS and the CDC, recently developed a campaign to increase CRC screening rates: "80% screening by 2018."[19] At Bracco we believe that by offering eligible patients the option of a visual, noninvasive, patient-friendly screening method such as CTC, the NCCRT's goal of increasing adherence to CRC can be met, perhaps even exceeded. In February 2017, the CDC launched the *Screen for Life*—National Colorectal Cancer Action Campaign, which provides CRC fact sheets, posters, and reminder postcards for the general public, healthcare providers, campaign partners, and national, state, and local health organizations.[20]

Bracco Diagnostics is committed to the diagnostic imaging community, providing innovative products for x-ray studies including computed tomography, magnetic resonance imaging, nuclear medicine, and ultrasonography. All of our products are developed to help radiologists and other healthcare professionals improve diagnostic efficacy, patient safety, and cost effectiveness, while helping to ensure positive patient outcomes. To assist healthcare professionals in performing CTC, Bracco provides two important products: the PROTOCO$_2$L TOUCH® Colon Insufflator and TAGITOL™ V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent, which have been developed to meet the needs of modern radiology practices that provide CTC.

TAGITOL™ V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent

Indications and Usage:

For use in opacifying residual stool in the colon during CTC. TAGITOL V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent is a low-volume radiopaque marker that blends into stool as it forms. With just a 20mL dose with breakfast, lunch and dinner the day prior to the exam, TAGITOL V Stool Tagging Agent provides immediate, visible identification of retained feces via comparative density analysis, simplifying the distinction between tagged feces and colonic abnormality.

IMPORTANT SAFETY INFORMATION:

This product should not be used in patients with known or suspected gastric and intestinal perforation, or hypersensitivity to barium sulfate or any component of this barium sulfate formulation. Rarely, severe and occasionally fatal allergic reactions have been reported following administration of barium sulfate contrast agents.

Please see full Prescribing Information for TAGITOL V Stool Tagging Agent.
http://imaging.bracco.com/us-en/products/ct-ct-colonography/tagitol-v

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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Impact of Colorectal Cancer: At a Glance

- Colorectal cancer (CRC) is currently the second leading cause of cancer death in the United States[2]
- In 2017, an estimated 135,000 persons will be diagnosed with the disease, and approximately 50,000 will die from it[2]
- Early detection and removal of early-stage cancers or precancerous adenomatous polyps has been shown to reduce mortality from CRC[3,4]
- If CRC is diagnosed while still localized, the 5-year survival rate is 90%; however, this rate drops to 71% for regional disease, and just 14% if distant metastases are present[1]

Evolving CRC Screening Guidelines: At a Glance

- "*Screen for Life*—National Colorectal Cancer Action Campaign" is a major media campaign that was launched in February 2017 by the Centers for Disease Control and Prevention (CDC) that provides CRC fact sheets, posters, and reminder postcards for the general public, healthcare providers, campaign partners, and national, state, and local health organizations[20]
- The American Cancer Society (ACS) recommends that men and women of average risk should be screened starting at age 50[5]
- Individuals at higher risk for CRC may require earlier and/or more frequent screening[5]
- Adherence to screening recommendations is suboptimal: screening in U.S. adults aged ≥50 years varies from 57% to 76%[21]
- Attempts to increase CRC screening rates are ongoing. The National Colorectal Cancer Roundtable (NCCRT) has a new campaign, "80% by 2018," aimed to increase screening rates[19]
- Physicians who offer more CRC screening options are better able to increase screening rates in their patient populations

Which CRC Screening Method Is the Best?

- According to the U.S. Preventive Services Task Force (USPSTF), the best screening test is "*the one that gets done*"[12,13]
- Both the USPSTF and the CDC include computed tomography colonography (CTC) as a CRC screening option[12–15]
- When selecting a screening test, it is often necessary to balance diagnostic performance, procedural risks, patient acceptability, and cost effectiveness
- Due to its ability to remove visualized polyps or take biopsy from the suspicious area, optical colonoscopy (OC) remains the procedure of choice for symptomatic and high-risk patients[5]; however, for the vast majority of adults, CTC screening offers a potentially attractive option[6,7]
- The Cancer Intervention and Surveillance Modeling Network (CISNET), when analyzing risk versus benefit of different screening methods, found that "screening colonoscopy every 10 years generates the highest degree of associated burden or harm"[12,13]
- Currently, the new stool- and blood-based tests are generally considered preferable in patients such as the frail and elderly, who are unable to withstand the prep and/or anesthesia that are generally a necessary part of direct visualization tests

Why Select CTC as a Screening Modality?

- For the average-risk population, CTC offers a potentially attractive, patient-friendly screening option[6,7]
- CTC is noninvasive; with no risk of bleeding or bowel perforation, and no need for sedation and pain management; therefore, patients can miss less work and can also drive themselves to and from the procedure[6,7,9]
- Surveys show that patients demonstrate a high rate of satisfaction with CTC; the ability to offer additional options potentially leads to higher screening adherence rates[8–11]
- CTC requires relatively low-dose radiation exposure (≤6 mSv)[22,23]
- For patients concerned about the invasive nature and anesthesia associated with OC, CTC offers a possible option for CRC screening
- CTC provides a permanent anatomical record of colon health that can be used in subsequent exams to monitor changes[24,25]

Colorectal cancer (CRC) is the 2nd leading cause of cancer death in the United States

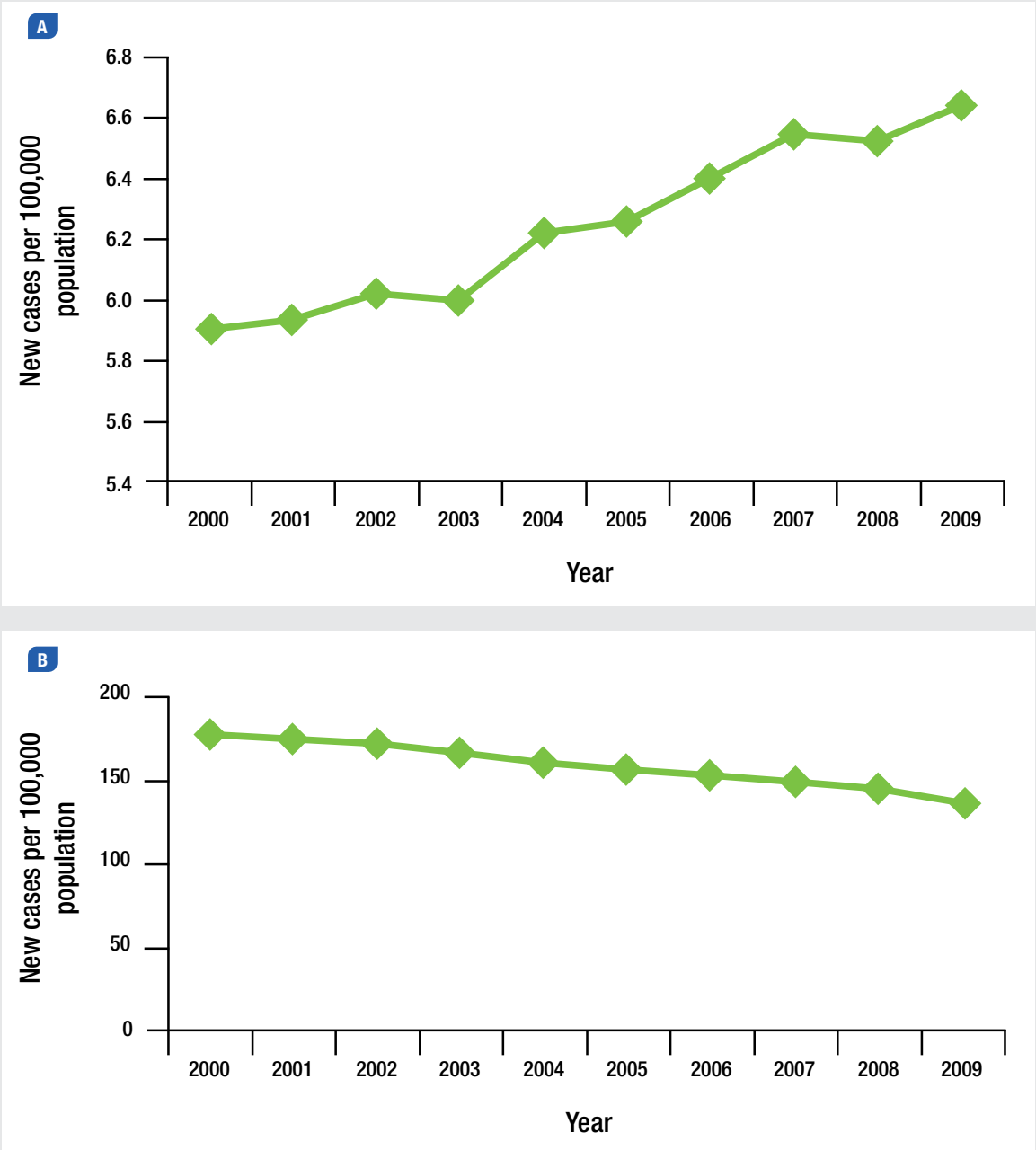
Colorectal Cancer: An Introduction

CRC is currently the second leading cause of cancer death in the United States.[1,2] In 2017, an estimated 135,000 persons will be diagnosed with the disease, and approximately 50,000 will die from it.[2] A main risk factor for CRC is older age: CRC is most frequently diagnosed among adults aged 65 to 74 years, with a median age at death of 73 years.[1] In addition, since the late 1980s, rates of CRC have been consistently higher in African Americans.[21] Both a personal history of polyps or inflammatory bowel disease (IBD) and a family history increase the risk of CRC; 1 in 5 people with CRC have family members with the disease, and patients with a first-degree relative with CRC are at increased risk.[21] Finally, lifestyle-related factors, such as obesity, smoking, and heavy alcohol use, increase the risk of CRC.[21]

CRC rates in younger adults have been increasing

Despite the fact that only about one-quarter of cases occur among patients aged 50 to 64,[1] there is a current trend, particularly in developed nations, toward a decline in older patients developing CRC and a concomitant rise in the incidence of this cancer in younger patients (**Figure 1**).[26,27] Since the mid-1980s, colon cancer incidence rates have increased by 1.0% to 2.4% annually in adults age 20 to 39 years and by 0.5% to 1.3% since the mid-1990s in adults age 40 to 54 years.[28] Yet in younger patients, the use of screening is more limited, and symptoms may go unrecognized.[26] Outcomes in these younger patients tend to be worse, with higher mortality rates, likely because their disease is detected at a later stage.[29] Increasing awareness of this trend could lead healthcare professionals and advocacy groups to focus resources on recognizing and treating CRC in younger populations, particularly individuals at increased risk.[26]

Figure 1. Surveillance, Epidemiology, and End Results age-adjusted colorectal cancer incidence per 100,000 individuals in those aged (**A**) <50 years and (**B**) ≥50 years.[26]



(Adapted from Ahnen 2014 with permission.)

Early detection of CRC reduces mortality

Benefits of Population-based Screening for CRC

Early detection and removal of early-stage cancers or precancerous adenomatous polyps has been shown to reduce mortality from CRC.[3,4] If CRC is diagnosed while still localized (i.e., confined to the bowel wall), the 5-year survival rate is 90%; however, this drops to 71% for regional disease (i.e., disease with lymph node involvement) and just 14% if distant metastases are present.[1] According to the ACS, the death rate from CRC has been dropping for several decades in both men and women, most likely due to a combination of screening and removal of precancerous lesions.[30]

Adherence to screening recommendations is suboptimal: screening in adults aged ≥50 years varies from 57% to 76%

Evolving CRC Screening Guidelines

As of 2016, the ACS recommends that men and women of average risk should be screened starting at age 50.[5] The frequency of screening recommended by the ACS depends on the screening test (**Table 1**).[16] For individuals whose risk is higher than average (i.e., a personal history of CRC, adenomatous polyps, or IBD, or a family history of CRC or polyps, or a hereditary CRC syndrome), earlier and/or more frequent screening may be necessary. Nevertheless, adherence to screening recommendations falls short: statistics show that actual CRC screening in U.S. adults aged 50 years and older varies from 57% to 76% (depending on the state).[21]

Barriers to CRC screening include cost and lack of access to adequate healthcare; lack of awareness regarding need for CRC screening; inadequate communication about the importance of CRC screening; the availability of various testing options; and patient fear and/or embarrassment. The need for bowel preparation, sedation, and transportation are also factors, more so with some test options than others.[21,31]

According to the USPSTF, the best screening test is "the one that gets done"

USPSTF Recommendations

The USPSTF recently assigned an "A" grade to CRC screening exams, including CTC. In the 2016 recommendations for CRC screening, the USPSTF reiterated the benefit of CRC screening in average-risk, asymptomatic adults aged 50 to 75 (with screening beyond the age of 75 indicated as an individual decision, to be based on the patient's overall health and prior screening history), along with the well-established fact that CRC screening is a substantially underused preventive health strategy.[12,13] The recommendations also noted that there is no empirical evidence to demonstrate that any specific CRC screening test is superior; rather, they emphasized that each type of screening test has advantages and disadvantages, and that the best screening test is "*the one that gets done*." This approach is supported by a growing body of evidence that demonstrates that patient outreach including offering patients different test options substantially increases screening rates.[32,33]

Table 1. ACS–U.S. Multi-Society Task Force on Colorectal Cancer–ACR Guidelines for Screening for the Early Detection of Colorectal Cancer and Adenomas for Average-Risk Women and Men Aged ≥50 Years[16]

Test	Interval	Key Issues for Infomed Decisions
Tests that detect adenomatous polyps and cancer		
FSIG with insertion to 40 cm or to splenic flexure	Every 5 years	Complete or partial bowel preparation is required; sedation usually is not used, so there may be some discomfort during the procedure; the protective effect of sigmoidoscopy is primarily limited to the portion of the colon examined; patients should understand that positive findings at sigmoidoscopy usually result in a referral for colonoscopy
Colonoscopy	Every 10 years	Complete bowel preparation is required; conscious sedation is used in most centers; patients will miss a day of work and will need a chaperone for transportation from the facility; risks include perforation and bleeding, which are rare but potentially serious; most of the risk is associated with polypectomy
DCBE	Every 5 years	Complete bowel preparation is required; if patients have ≥1 polyps ≥6 mm, colonoscopy will be recommended, and follow-up colonoscopy will require complete bowel preparation; risks of DCBE are low; rare cases of perforation have been reported
CTC	Every 5 years	Complete bowel preparation is required; if patients have ≥1 polyps ≥6 mm, colonoscopy will be recommended, but if same-day colonoscopy is not available, a second complete bowel preparation will be required before colonoscopy; risks of CTC are low; rare cases of perforation have been reported; extracolonic abnormalities may be identified at CTC that could require further evaluation
Tests that primarily detect cancer		
gFOBT with high sensitivity for cancer and FIT with high sensitivity for cancer	Annually	Depending on manufacturer's recommendations, 2–3 stool samples collected at home are needed to complete testing; a single sample of stool gathered during a digital examination in the clinical setting is not an acceptable stool test and should not be done; positive results are associated with an increased risk of colon cancer and advanced neoplasia; colonoscopy should be recommended if the test results are positive; if the result is negative, the test should be repeated annually; patients should understand that one-time testing is likely to be ineffective
Stool DNA test with high sensitivity for cancer	Interval uncertain	An adequate stool sample must be obtained and packaged with appropriate preservative agents for shipping to the laboratory; the unit cost of the currently available test is significantly higher than other forms of stool testing; if the result is positive, colonoscopy will be recommended; if the result is negative, the appropriate interval for a repeat test is uncertain

Note: The above options are acceptable choices for colorectal cancer screening in average-risk adults beginning at age 50 years. Since each of the tests has inherent characteristics related to prevention potential, accuracy, costs, and potential harms, individuals should have the opportunity to make an informed decision when choosing one of the above options. In the opinion of the guidelines development committee, *colon cancer prevention* should be the primary goal of colorectal cancer screening. Tests that are designed to detect both early cancer and adenomatous polyps should be encouraged if resources are available and patients are willing to undergo an invasive test.

ACR = American College of Radiology; ACS = American Cancer Society; CTC = computed tomography colonography; DCBE = double-contrast barium enema; FIT = fecal immunochemical test; FSIG = flexible sigmoidoscopy; gFOBT = guaiac-based fecal occult blood test.

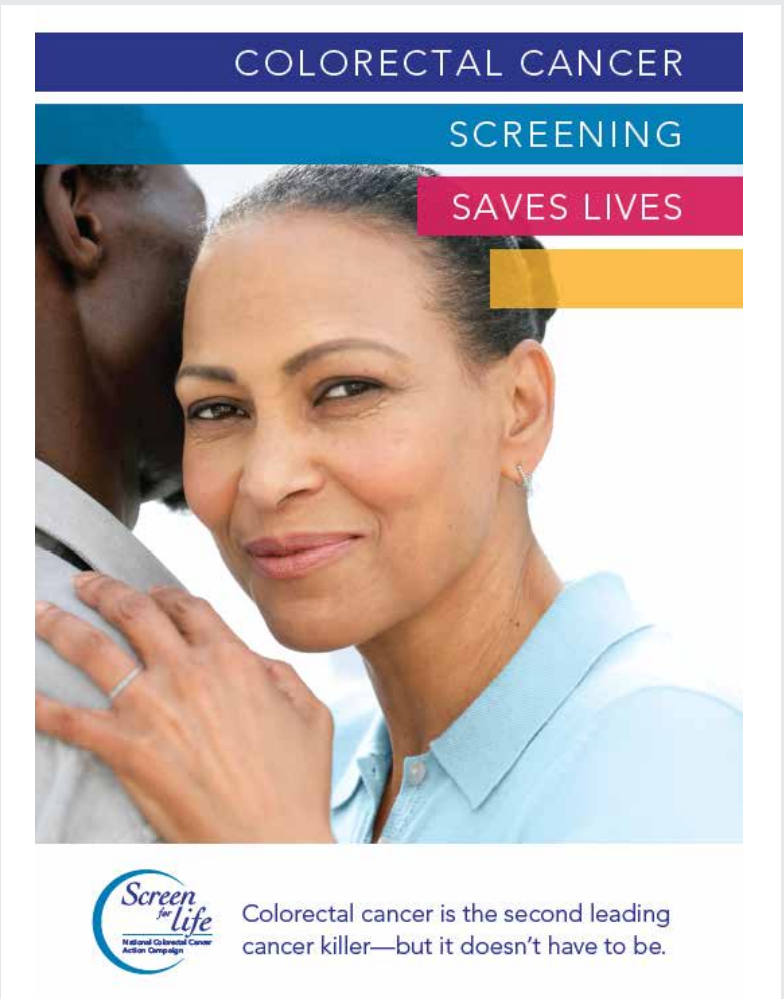
(Reproduced from McFarland EG, et al. *Radiology*. 2008;248:717-720; with permission.)

"80% by 2018" is the NCCRT's campaign to increase screening rates

Attempts to increase CRC screening rates are ongoing. For example, the NCCRT, established by the ACS and the CDC, is a national coalition of public, private, and voluntary organizations dedicated to reducing the incidence of and mortality from CRC in the United States, and they have developed an important educational campaign, "80% by 2018," aimed to increase screening rates.[19]

In February 2017, the CDC launched the *Screen for Life*—National Colorectal Cancer Action Campaign, which provides CRC fact sheets, posters, and reminder postcards for the general public, healthcare providers, campaign partners, and national, state, and local health organizations (**Figure 2**).[20]

Figure 2. Centers for Disease Control and Prevention patient brochure from *Screen for Life*—National Colorectal Cancer Action Campaign.[15]



(Reproduced from CDC 2017 by permission.)

When selecting a screening test, it is often necessary to balance diagnostic performance, procedural risks, patient acceptability, and cost effectiveness

Currently Available Screening Methods

CRC screening can be performed using various methods (summarized in **Table 1**). Such methods include stool-based tests and direct visualization tests. Direct visualization tests are able to detect both colorectal polyps and cancer, allowing for removal of potentially cancerous polyps, while stool-based tests, although generally less invasive, mainly detect cancer and are much less likely to detect polyps.[34] Such tests vary in the frequency with which they should be performed (**Table 1**). When selecting a screening test, it is often necessary to balance diagnostic performance, procedural risks, patient acceptability, and cost effectiveness.[7]

Currently the new stool- and blood-based tests are generally considered preferable in patients such as the frail and elderly, who are unable to withstand the prep and/or anesthesia that are generally a necessary part of direct visualization tests

Stool-based Tests

The two most recently approved, noninvasive tests for CRC screening include the multitarget stool DNA test Cologuard® (Exact Sciences) and the blood test Epi proColon® (Epigenomics). With both tests, if the results are positive, additional testing (typically a direct visualization test) is necessary to confirm the presence and determine the location of the lesion(s).

Cologuard is approved for CRC screening in average-risk adults. A stool sample is collected at home and shipped back to the company to obtain the results. Using DNA amplification techniques, the test is designed to detect material that is sloughed off of invasive cancers (and presumably also off of advanced benign neoplasms).[35] Cologuard combines this stool DNA test with a fecal immunochemical test (FIT), evaluating for a number of DNA and immunohistochemical markers. Compared with FIT alone, Cologuard demonstrates better sensitivity (92%) but lower specificity (87%), and is particularly lacking in detection of large, advanced adenomas (detecting 42%). Some controversy exists as to the utility of Cologuard: considering a 0.2% prevalence rate of CRC in an average-risk screening population, this test provides only a 1.4% positive predictive value (PPV), indicating that most "positive" tests, which will be referred to colonoscopy, will ultimately be false-positives. Yet, because the results are considered "genetically positive," concerns may lead to additional—often excessive and invasive—testing, contradicting one of the main benefits of a noninvasive screening test.

The blood-based mSEPT9 Epi proColon assay is also indicated for screening of adults at average risk of CRC. A blood test to detect CRC, such as the Epi proColon assay, represents the ultimate simple, noninvasive screening method; however, the only prospective trial published to date showed a sensitivity of only 48.2% for this test.[36] Therefore, at this time, these new stool- and blood-based tests are generally considered preferable in patients such as the frail and elderly, who are unable to withstand the prep and/or anesthesia that are generally a necessary part of direct visualization tests.

For the average-risk population, CTC offers a visual, noninvasive, patient-friendly screening option

Direct Visual Tests

Due to its ability to remove visualized polyps, OC remains the procedure of choice for symptomatic and high-risk patients[5]; however, for the vast majority of adults (i.e., those in the average-risk population), CTC (also referred to as virtual colonoscopy) screening (with OC reserved for therapeutic intervention, which occurs in <10% of cases) offers a potentially attractive alternative.[6,7]

Selection of CTC does not mean the patient will need two tests

For patients undergoing CTC, OC is reserved for therapeutic intervention; however, only approximately 10% of patients will require removal of polyps. Therefore, the perception that with selection of CTC, "most" patients will have to undergo two tests, is false.[6,7] Also, if the patient should require OC following CTC, many centers ensure that the patient can have the follow-up OC on the same day.

The Cancer Intervention and Surveillance Modeling Network (CISNET), when analyzing risk vs. benefit of different screening methods, found that "screening colonoscopy every 10 years generates the highest degree of associated burden or harm"

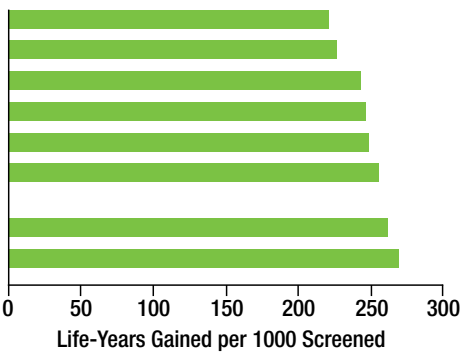
In developing their 2016 CRC screening recommendations, the USPSTF used simulations developed by CISNET. The simulations were developed to analyze risk versus benefit over a lifetime from different CRC screening methods. The CISNET report states, "The harms from a single administration of a screening test must be considered in the context of how often the test will be repeated over a patient's lifetime. In the case of colorectal cancer screening, this means considering how many colonoscopies (the primary source of serious harms) will be required to follow-up abnormal findings. The CISNET models suggest that the available strategies range from an estimated 1,714 to 4,049 total colonoscopies required per 1,000 persons screened over a lifetime."[12,13] **Figure 3** depicts the findings of the modeling. All screening methods analyzed provide benefits, with OC and CTC generally providing the largest benefits (**Figures 3A and B**) in life-years gained and averting CRC deaths. Interestingly, **Figures 3C and D** demonstrate that screening colonoscopy every 10 years generates the highest degree of associated burden or harm.[37]

CTC provides 2D and 3D displays of the colon and rectum reconstructed from computed tomography (CT) scanning data. The advantages of CTC are well demonstrated. In terms of efficacy, evidence shows CTC is effective for screening,[38] with a high PPV (>90% for polyps ≥6 mm) in clinical practice.[39–41] CTC screening is also effective for detection of large adenomas and early cancers.[42] In addition, many studies have demonstrated that CTC is effective for CRC diagnosis in symptomatic patients[43] and for surveillance after resection.[44] Based on the ACR Practice Parameters for the Performance of CTC, however, not all patients are eligible for CTC. **Table 2** summarizes the indications and contraindications for CTC.[45]

Figure 3. Benefits, harms, and burdens of CRC screenings over a lifetime.[12,13] Screening occurs between the ages of 50 and 75 years, with follow-up continuing throughout an individual's remaining lifespan.

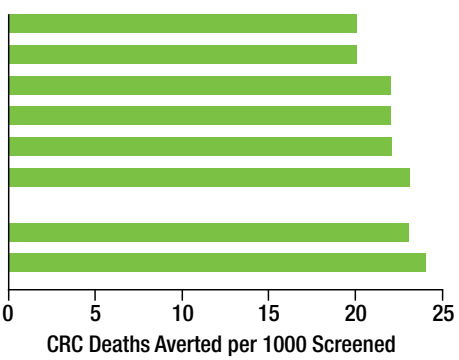
A **Benefit:** Life-years gained per 1000 individuals screened

Screening Method and Frequency	Model Estimates, Life-Years Gained per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	221	181	227
FIT-DNA every 3 y	226	215	250
FIT every year[a]	244	231	260
HSgFOBT every year	247	232	261
CT colonography every 5 y[b]	248	226	265
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	256	246	270
FIT-DNA every year	261	246	271
Colonoscopy every 10 y[a]	270	248	275



B **Benefit:** Colorectal cancer deaths averted per 1000 individuals screened

Screening Method and Frequency	Model Estimates, CRC Deaths Averted per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	20	17	21
FIT-DNA every 3 y	20	19	22
FIT every year[a]	22	20	23
HSgFOBT every year	22	20	23
CT colonography every 5 y[b]	22	20	24
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	23	22	24
FIT-DNA every year	23	22	24
Colonoscopy every 10 y[a]	24	22	24



C **Harms:** Complications (gastrointestinal and cardiovascular events) of colorectal cancer screening and follow-up testing per 1000 individuals screeded[c]

Screening Method and Frequency	Model Estimates, Complications per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	10	9	12
FIT-DNA every 3 y	9	9	10
FIT every year[a]	10	10	11
HSgFOBT every year	11	11	11
CT colonography every 5 y[b]	10	10	11
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	11	11	12
FIT-DNA every year	12	12	13
Colonoscopy every 10 y[a]	15	14	15

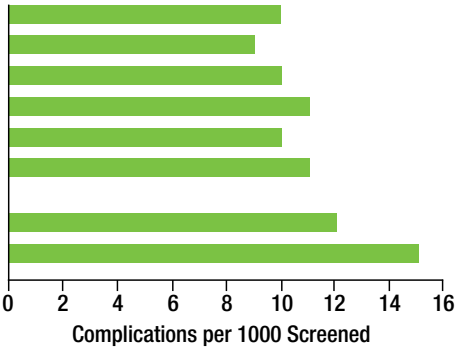
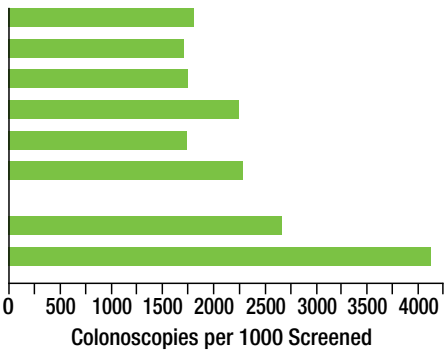


Figure 3, Continued

D **Burden:** Lifetime no. of colonoscopies per 1000 individuals screened

Screening Method and Frequency	Model Estimates, Lifetime Colonoscopies per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	1820	1493	2287
FIT-DNA every 3 y	1714	1701	1827
FIT every year[a]	1757	1739	1899
HSgFOBT every year	2253	2230	2287
CT colonography every 5 y[b]	1743	1654	1927
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	2289	2248	2490
FIT-DNA every year	2662	2601	2729
Colonoscopy every 10 y[a]	4049	4007	4101



CRC = colorectal cancer; FIT = fecal immunochemical test; FIT-DNA = multitargeted stool DNA test; HSgFOBT = high-sensitivity guaiac-based fecal occult blood test.

[a]These strategies yield comparable life-years gained (life-years gained with the noncolonoscopy strategies were within 90% of those gained with the colonoscopy strategy) and an efficient balance of benefits and harms (no other strategy or combination of strategies within the class of screening tests provides more life-years with the same [or fewer] number of colonoscopies, which represents the primary source of harms from screening).

[b]Computed tomographic (CT) colonography can also be considered efficient, but if cathartic bowel preparation is considered to be a proxy measure for the burden of screening (instead of number of lifetime colonoscopies), its efficiency ratio (i.e., the incremental number of colonoscopies required to achieve an additional year of life gained [ΔCOL/ΔLYG]) exceeds that of colonoscopy.

[c]Gastrointestinal events include perforations, bleeding, transfusions, paralytic ileus, nausea and vomiting, dehydration, and abdominal pain. Cardiovascular events include myocardial infarction, angina, arrhythmia, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, and shock.

(From USPSTF Final recommendation statement 2016 and USPSTF-JAMA-2016, adapted with permission.)

CTC is 15- to 20-minute, noninvasive exam with no need for sedation or pain management and no risk of bleeding or colonic perforation

The safety of CTC is based largely on its lack of invasiveness.[7] With CTC, sedation and pain management are unnecessary, thus providing a "needle-free experience." There is also essentially zero risk of colonic perforation, particularly with the use of a low-pressure automated CO_2 delivery. Other complications seen with OC (e.g., bleeding, cardiovascular events) are also avoided with CTC.

Patients demonstrate a high rate of satisfaction with CTC; offering CRC screening options potentially leads to higher screening adherence rates

Surveys show that CTC is associated with a very high satisfaction rate and is highly preferred over colonoscopy,[9] with CTC preferred in virtually all head-to-head comparisons (**Figures 4 and 5**).[8,9] CTC also compares favorably to OC for patient convenience and acceptability. The lack of sedation means patients can drive to and from their appointment and, due to the short exam duration, they generally do not have to miss work (**Figure 6**).[9] Importantly, the positive attributes of CTC lead to improved adherence rates, thereby attracting individuals who might otherwise have foregone screening.[8–11]

Table 2. American College of Radiology (ACR) Indications and Contraindications for CTC[45]

Indications (including, but not limited to)

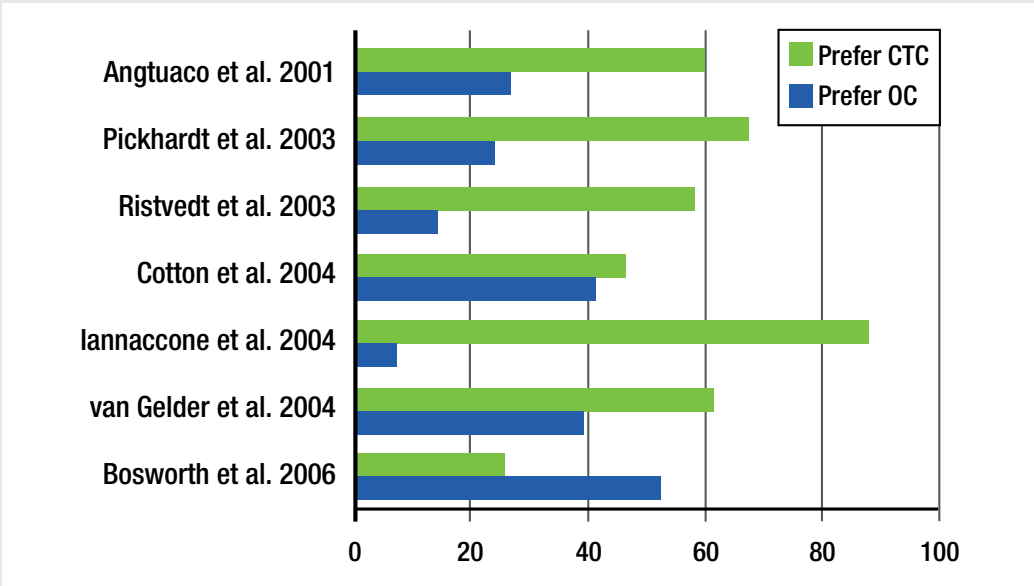
- Screening examination in individuals who are at average or moderate risk for developing CRC. Screening of individuals who are at moderate risk for CRC may be managed individually based on clinical context or local practice patterns
- Surveillance examination in patients with a history of previous colonic neoplasm, depending on the appropriate clinical context
- Diagnostic examination in symptomatic patients, particularly in the setting of incomplete colonoscopy, including, but not limited to, those with the following conditions:
  - Abdominal pain
  - Diarrhea
  - Constipation
  - Gastrointestinal bleeding
  - Anemia
  - Intestinal obstruction
  - Weight loss
- Following incomplete screening, surveillance, or diagnostic colonoscopy and for characterization of colorectal lesions indeterminate on OC
- Patients who may be at increased risk for complications during OC (eg, patients with advanced age, anticoagulant therapy, sedation risk, prior incomplete colonoscopy)
- Follow-up of patients with a colonic stoma or after colectomy. (Intubation of the stoma should be performed with caution to avoid colonic injury or perforation)
- Prior to laparoscopic surgery for CRC in order to accurately localize the tumor or search for synchronous lesions

Contraindications (including, but not limited to)

- Relative contraindications or conditions that require caution:
  - Symptomatic acute colitis
  - Acute diarrhea
  - Recent acute diverticulitis
  - Recent colorectal surgery
  - Symptomatic colon-containing abdominal wall hernia
  - Recent deep endoscopic biopsy or polypectomy/mucosectomy
  - Known or suspected colonic perforation
  - Symptomatic or high-grade small bowel obstruction
- CTC is not indicated for:
  - Routine follow-up of IBD
  - Hereditary polyposis or nonpolyposis cancer syndromes
  - Evaluation of anal canal disease
  - The pregnant or potentially pregnant patient

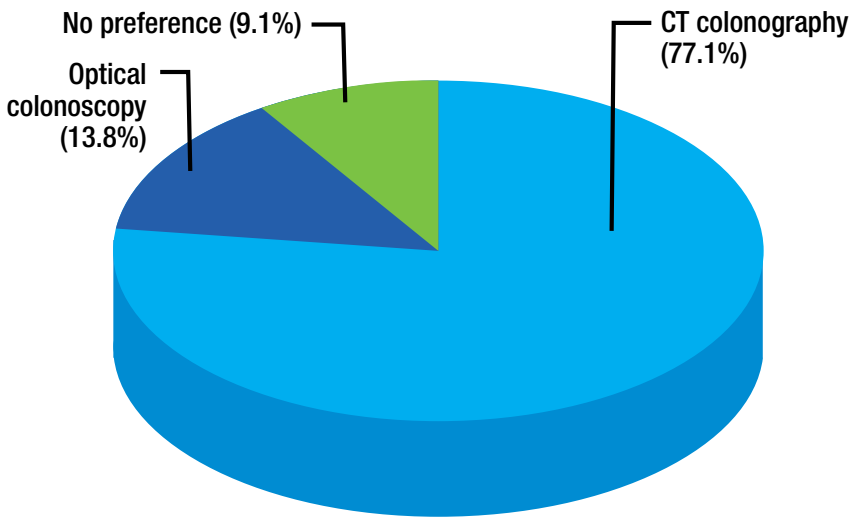
CRC = colorectal cancer; CTC = computed tomography colonography; IBD = inflammatory bowel disease; OC = optical colonoscopy.

Figure 4. Multiple studies have evaluated patient preference between CTC and OC; patients more often prefer CTC.[8]



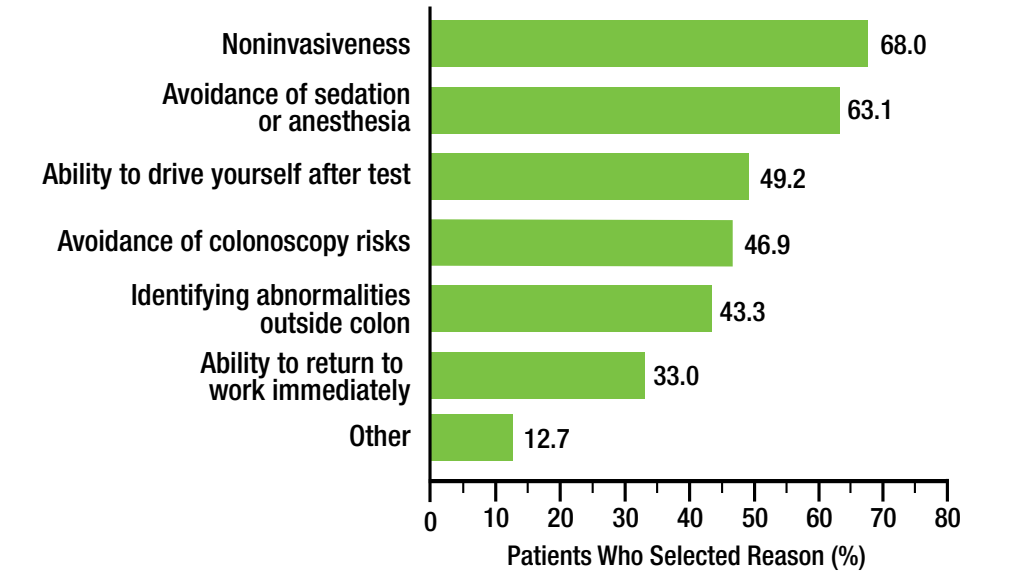
CTC = computed tomography colonography; OC = optical colonoscopy.
(Moawad FJ, et al. *AJR Am J Roentgenol.* 2010;195:1118-1123. Adapted with permission.)

Figure 5. Individuals who have experienced both OC and CTC more often prefer CTC.[9]



CTC = computed tomography colonography; OC = optical colonoscopy. (Pooler 2012 adapted with permission.)
(Pooler BD, et al. *AJR Am J Roentgenol.* 2012;198:1361-1366. Adapted with permission.)

Figure 6. The most frequently cited reasons why patients chose CTC.[9]



CTC = computed tomography colonography.
(Pooler BD, et al. *AJR Am J Roentgenol.* 2012;198:1361-1366. Adapted with permission.)

CTC requires relatively low-dose radiation exposure (≤6 mSv)

The potential drawbacks of CTC may actually be due more to misunderstandings or outdated perceptions than to evidence.[7] For example, radiation exposure from CTC has been cited as a potential drawback for this screening method. However, CTC is a relatively low-dose CT exam (≤6 mSv)[22,23] that is made even lower with the use of advanced CT iterative reconstruction algorithms. In addition, CTC is typically performed in older adults in whom radiation presents an overall reduced cancer risk.[7] Also cited is the potential for incidental findings with CTC. In fact, such extracolonic findings can be viewed as an advantage rather than a disadvantage, as long as care is taken to avoid unnecessary follow-up. Use of the CTC Reporting and Data System (C-RADS; see below) allows for systematic categorization and follow-up of relevant extracolonic findings.[24,25]

Use of C-RADS allows for systematic categorization and follow-up of colonic and relevant extracolonic findings

In 2005, the Working Group on Virtual Colonoscopy (experts and key opinion leaders, including members of the ACR Colon Cancer Committee) developed the C-RADS.[25] The purpose of the C-RADS system is to standardize the reporting of colon lesion size, morphology, and location, and provide a framework for interpreting radiologists to classify extracolonic finding. In C-RADS, colonic findings are reported in five categories (**Table 3**).[24,25] Category C0 denotes an inadequate study usually due to technical issues; C1 is a normal exam or one with a benign lesion (<6 mm); C2 is an exam with an intermediate polyp or indeterminate findings; C3 represents an exam with polyps that are possibly advanced adenoma; and C4 is used when a colonic mass, most likely malignant, is detected. Consistent with C-RADS, the ACR recommends that polyps <6 mm in size on CTC do not need to be reported, and polyps 6–9 mm in size can undergo "CTC surveillance" in 3 years (vs. polypectomy). Therefore, only patients with lesions ≥10 mm on CTC require referral to OC.[25] CTC provides a permanent anatomical record of colon health that can be used in subsequent exams to monitor changes.

Table 3. Summary of C-RADS Colorectal and Extracolonic Classification Scores[24]

Score	Description
Colorectal	
C0, inadequate study	Inadequate preparation; inadequate insufflation
C1, normal colon or benign lesion	No polyp ≥6 mm; recommend routine screening with CT colonography or colonoscopy in 5 years
C2, intermediate polyp or indeterminate finding	Polyps 6–9 mm, <3 in number; recommend CT colonography polyp surveillance or colonoscopy with polypectomy
C3, polyp, possibly advanced adenoma	Polyps ≥10 mm; ≥3 polyps, each 6–9 mm; recommend colonoscopy with polypectomy
C4, colorectal mass, likely malignant	Lesion compromises bowel lumen, shows extracolonic invasion; recommend surgical consultation
Extracolonic	
E0, limited examination	Compromised by artifact; evaluation of extracolonic tissues severely limited; not used in practice by our program
E1, normal examination or anatomic variant	No extracolonic abnormalities visible; no workup indicated
E2, clinically unimportant finding	Examples: simple liver or kidney cyst, cholelithiasis without cholecystitis; no workup indicated
E3, likely unimportant, incompletely characterized	Example: minimally complex or homogeneously hyperattenuating kidney cyst; workup may be indicated; dependent on specific clinical scenario
E4, potentially important finding	Examples: solid kidney mass, aortic aneurysm; workup generally indicated, but dependent on specific clinical scenario; communicate to referring physician as per accepted practice guidelines

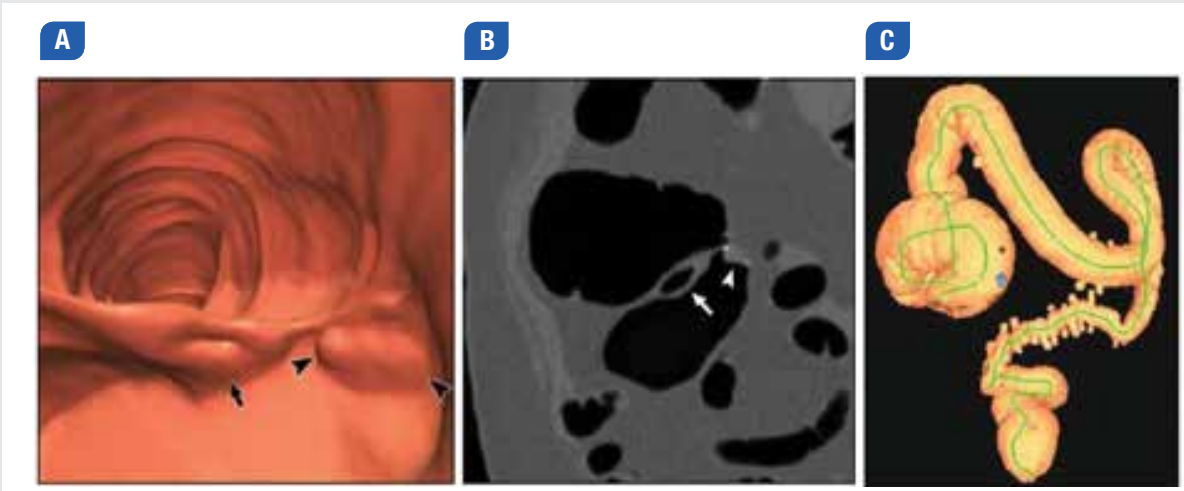
CT = computed tomography.
(Pooler BD, et al. *AJR Am J Roentgenol.* 2014;202:1232-1237. Adapted with permission.)

During CTC, extracolonic structures of the lower thorax, abdomen, and pelvis are visualized, and radiologists interpreting CTCs need to make an overall assessment of the potential clinical significance of extracolonic findings.[25] Category E1 denotes a normal exam; E2 is an exam in which incidental extracolonic abnormalities are found but because of their low clinical importance, these abnormalities do not warrant further diagnostic workup; and E3 is an exam in which indeterminate extracolonic abnormalities are likely to be benign. Of note, E4 is an exam in which the extracolonic findings, if left untreated, have potential to adversely affect the patient's health and most likely require additional diagnostic workup (**Table 3**). C-RADS provides radiologists with a classification system that helps avoid potentially unnecessary additional diagnostic workups when extracolonic findings are detected.[24,25]

Difficulties in detection of flat polyps/carpet lesions are a challenge in CRC screening. Such carpet lesions are a subset of nonpolypoid colorectal lesions that are large, relatively flat, laterally spreading tumors ≥3 cm.[46] In general, such flat lesions are less conspicuous than polypoid lesions of a similar size, but this is true for both OC and CTC. Fortunately, such flat lesions are also typically less histologically aggressive, and usually benign.[46–48] CTC can detect flat lesions with reasonably high sensitivity (80%–90%) when standard techniques of oral contrast tagging and combined 2D/3D interpretation are applied.[49,50]

With respect to tumor location, molecular, clinical, treatment response, and prognostic differences exist between CRC tumors arising in the right versus the left side of the colon.[51] Patients with cancer in the right side of the colon have worse survival outcomes than patients with tumors in the left side.[52] In addition, patients with tumors in the right colon tend to be older, female, and African American.[52–54] Difficulty detecting lesions within the right colon during OC has been well established due to difficulties in advancing an optical colonoscope into the right colon.[55] A recent study that looked at evaluating and characterizing nondiminutive colorectal polyps not detected retrospectively by OC but then detected prospectively by CTC, found that such polyps occurred more frequently in the right colon.[55] In fact, many lesions missed on OC but visualized on CTC have been shown to be OC false-negatives not CTC false-positives, and tended to have clinically significant histopathology and a predilection for the right colon (**Figure 7**), indicating that CTC may be better at detecting cancer in the right side of the colon.[55]

Figure 7. Difficult polyp location for detection and polypectomy with optical colonoscopy (OC) in a 68-year-old woman.[56]



(A) 3D endoluminal computed tomography colonography (CTC) image from perspective of cecal tip shows relatively subtle 1.5-cm sessile polyp (arrowheads) located behind fold and adjacent to ileocecal valve (arrow).

(B) 2D coronal CTC image confirms presence of soft-tissue lesion (arrowhead) next to ileocecal valve (arrow).

(C) 3D colonic map shows anatomic location of cecal polyp (red dot), extensive sigmoid diverticulosis, and automated centerline (green). Blue arrow indicates 3D vantage point shown in A. Polyp was found and removed at OC and proved to be tubulovillous adenoma with high-grade dysplasia. Because of the difficult location of this polyp, the gastroenterologist noted that he would have missed this lesion without detailed knowledge of its existence obtained with CTC.

(Pickhardt PJ. *AJR Am J Roentgenol.* 2007;189:290-298. Adapted with permission.)

For patients deterred by OC, CTC represents a noninvasive, pain- and sedation-free alternative screening option

In light of the recent USPSTF recommendations that the best CRC screening test is "*the one that gets done*," it is important to consider the benefits of the visual, noninvasive, patient-friendly CTC exam, including high accuracy with full evaluation of the colon in virtually all patients, as well as improved safety and enhanced patient comfort.[57,58]

How Is CTC Perfomed?

The goals of CTC are to maximize accuracy and productivity while minimizing patient discomfort. The various steps include prepping, fecal and fluid tagging, controlled insufflation, scanning, and image reconstruction for data interpretation. The scan itself takes approximately 20 minutes and does not require sedation.

Patient Prepping

Two categories of bowel preparation exist: "wet preparation," which consists of ingestion of large volumes of polyethylene glycol, and the generally better tolerated "dry preparation," which includes ingestion of saline cathartic laxatives such as magnesium citrate and sodium phosphate.[59] Wet preparations are preferred for OC, while dry preparations are preferred for CTC because their use is associated with less residual fluid in the colon lumen.

Fecal and Fluid Tagging

Consumption of fecal and fluid tagging agents with meals before the examination effectively tags any remaining stool and fluid, an important consideration in the evaluation of CT images. Barium- and iodine-based tagging agents make it easier to interpret image data sets,[60,61] thus contributing to high-quality exam results by simplifying the distinction between tagged feces and colonic abnormalities, improving specificity, and reducing false-positive results.[60–62] According to the American College of Radiology (ACR), barium is better at tagging solid stool without tagging liquids, resulting in more homogeneous tagging, while the stool-softening qualities of iodinated contrast media may improve ease of CTC interpretation.[58] However, minimizing doses of high-osmolality iodinated agents is important, because they may cause diarrhea.

Colonic Insufflation

Optimal colonic distention is a critical requirement for obtaining high-quality CTC exam results.[58] An insufficiently distended colon may either conceal lesions or even mimic them, thereby reducing diagnostic confidence and increase interpretation time.[63] Both room air and CO_2 can be used for colon insufflation. Automated insufflation with CO_2 provides the advantages of consistent distention and decreased demand on staff time, thereby enhancing productivity.[64,65] CO_2 is more rapidly resorbed than room air (up to 150 times faster) and thus can provide improved patient comfort after the examination.[64,66]

CTC Scanning

Once the patient's colon is fully distended, two CT scans of the abdomen and pelvis are taken, one in the supine position and one in the prone position. Low-dose scanning protocols allow for the radiation dose to the patient to be minimized, while preserving the quality of the CT scan. The advent of multidetector CT (MDCT) scanners has resulted in a scanning time of <30 seconds; therefore, the exam can be easily accomplished within one patient breath-hold in each position. Once the scanning is complete, the patient's part is done.

Data Interpretation

After scanning, data from the CT scanner are sent to the CTC workstation, where they are converted into 2D and 3D images for interpretation. The radiologist reviews the images of the colon, as well as the other abdominal and pelvic organs that are included in the data set. Generally, depending on the quality of the study and the complexity of the patient anatomy, the interpretation may take as few as 10 minutes for a normal exam. Patients with significant colonic findings are referred for OC. As mentioned above, the C-RADS system was developed to standardize the reporting of colon lesion size, morphology, and location, and to specify which findings are clinically significant.[25]

BRACCO provides two products to help improve diagnostic performance and patient comfort during CTC

Bracco is very proud to offer two important products for the CTC suite. The PROTOCO$_2$L TOUCH® Colon Insufflator is used during CTC exams to provide optimal colonic distension with automated insufflation via CO_2, which is more rapidly absorbed than room air, resulting in less postprocedural discomfort for patients. TAGITOL™ V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent is a low-volume radiopaque agent used to improve differentiation of soft-tissue intraluminal lesions and retained stool.

TAGITOL™ V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent

Indications and Usage:

For use in opacifying residual stool in the colon during CTC. TAGITOL V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent is a low-volume radiopaque marker that blends into stool as it forms. With just a 20mL dose with breakfast, lunch and dinner the day prior to the exam, TAGITOL V Stool Tagging Agent provides immediate, visible identification of retained feces via comparative density analysis, simplifying the distinction between tagged feces and colonic abnormality.

IMPORTANT SAFETY INFORMATION:

This product should not be used in patients with known or suspected gastric and intestinal perforation, or hypersensitivity to barium sulfate or any component of this barium sulfate formulation. Rarely, severe and occasionally fatal allergic reactions have been reported following administration of barium sulfate contrast agents.

Please see full Prescribing Information for TAGITOL V Stool Tagging Agent.
http://imaging.bracco.com/us-en/products/ct-ct-colonography/tagitol-v

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

PROTOCO$_2$L TOUCH® Colon Insufflator

Product Description

The PROTOCO$_2$L TOUCH Colon Insufflator provides a software-controlled insufflation of CO_2 during CTC (**Figure 8**).[67] As mentioned earlier, automated insufflation helps ensure adequate and consistent distension in a patient- and operator-independent manner. The PROTOCO$_2$L TOUCH Colon Insufflator is an important component for successful CTC, as evidenced by its use as an ACRIN CTC Trial Standard.[68] The PROTOCO$_2$L TOUCH Colon Insufflator uses CO_2, which is more rapidly resorbed than room air, and thus may provide improved patient comfort after CTC examinations.[64,66]

Figure 8. **(A)** PROTOCO$_2$L TOUCH® Colon Insufflator. **(B)** PROTOCO$_2$L TOUCH display. **(C)** Distended colon. **(D)** Patient administration set.[67]

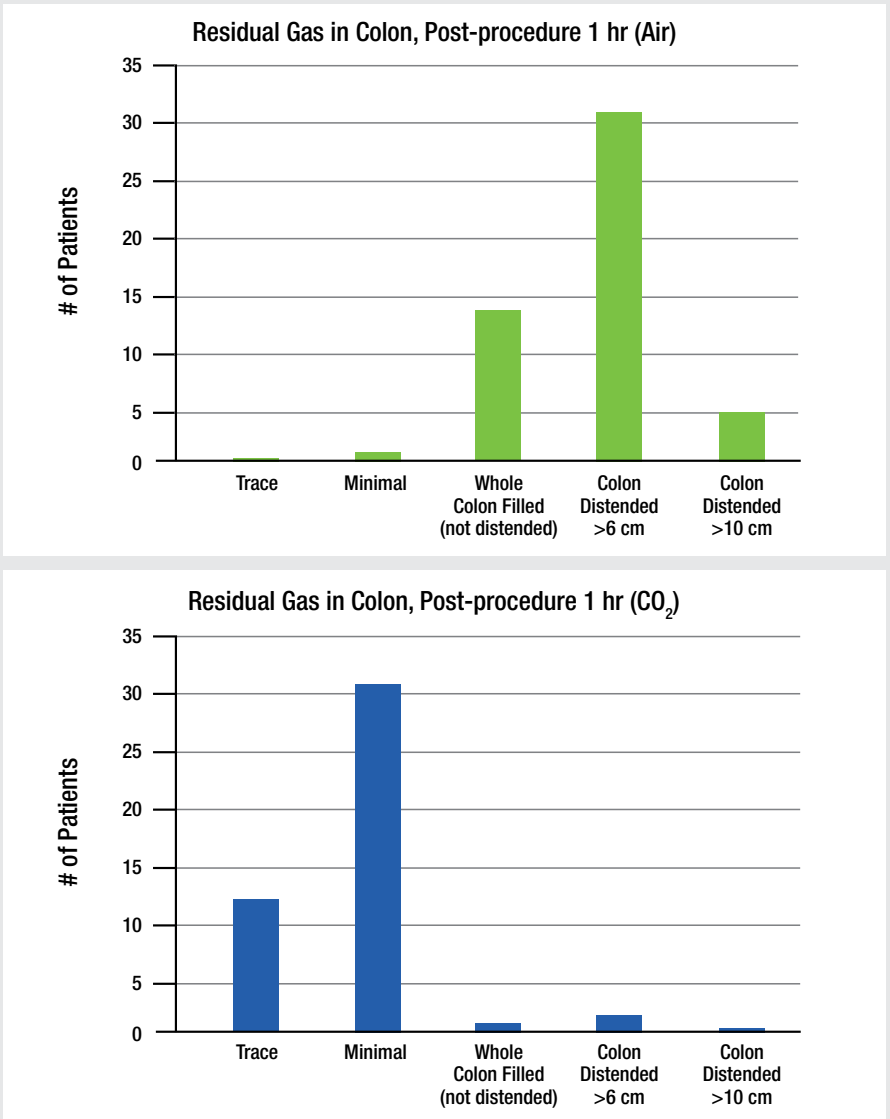
Staff Productivity

Automated operation helps reduce staff time during the insufflation process.[64] The system automatically replaces gas lost during the procedure. A visual display allows for quick reference of CO_2 pressure and volume, and alerts the operator when the CO_2 cylinder is low. Adjustable pressure up to 25 mmHg allows for user control, when desired.

Patient Comfort and Safety

Rapid absorption of CO_2 results in improved comfort after CTC compared with room air insufflation.[56,63,64] A study on minimizing post-colonoscopy abdominal pain showed that 1 hour after colonoscopy, most patients insufflated with room air had substantial residual gas in the colon, whereas 94% of patients insufflated with CO_2 had only trace to minimal residual gas (**Figure 9**).[69] Automated low-pressure insufflation may reduce colonic spasm relative to manual methods, particularly in patients with advanced diverticular disease.[56] Use of this system helps ensure patient safety through redundant pressure-relief valves and automatic flow-stop features, which protect against over-insufflation. A choice of tips for rectal administration allows the practitioner to select the most comfortable tip for the patient.

Figure 9. Results of a study on minimizing post-colonoscopy abdominal pain showing that 1 hour after colonoscopy, most patients insufflated with room air had significant residual gas in the colon (above), whereas 94% of patients insufflated with CO_2 had only trace to minimal residual gas (below).[67,69]



(Data from Sumanac K, et al. *Gastrointest Endosc.* 2002;56:190-194.)

Insufflation Consistency

Regulated pressure gradually distends the colon, and that pressure can then be maintained for the duration of the study (**Figure 8**). Such automated CO_2 insufflation results in more consistent distention and less variability from technologist to technologist.[66] Compared with manual room air insufflation, CO_2 insufflation has demonstrated improved distention in two clinical trials.[63,66] In addition, unlike room air insufflation in which the amount of air introduced is not evident, the volume display on the PROTOCO$_2$L TOUCH Colon Insufflator allows the CO_2 volume and pressure to be monitored and recorded.

Patient Administration Set

The patient administration set (**Figure 8D**) allows for simple connection to and removal from the PROTOCO$_2$L TOUCH Colon Insufflator. An in-line fluid trap captures colon effluent and removes it from the "path" of the CO_2 for proper insufflation. A hydrophobic filter helps protect the PROTOCO$_2$L TOUCH Colon Insufflator from cross-contamination.[67]

TAGITOL™ V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent

Indications and Usage:

For use in opacifying residual stool in the colon during CTC. TAGITOL V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent is a low-volume radiopaque marker that blends into stool as it forms. With just a 20mL dose with breakfast, lunch and dinner the day prior to the exam, TAGITOL V Stool Tagging Agent provides immediate, visible identification of retained feces via comparative density analysis, simplifying the distinction between tagged feces and colonic abnormality.

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Please see full Prescribing Information for TAGITOL V Stool Tagging Agent.
http://imaging.bracco.com/us-en/products/ct-ct-colonography/tagitol-v

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Figure 10. TAGITOL™ V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent.[70]

Cost Effectiveness and Reimbursement Landscape for CTC

In a comparison of the costs of CRC screening of average-risk individuals with CTC versus OC, including the costs of OC referrals for a subset of CTC patients, CTC was found to be 29% less expensive than OC in a Medicare population.[71] It is estimated that for commercially insured patients, the cost differential could be even greater, as anesthesia costs tend to be more costly in non-Medicare patients.

Currently, 37 states and the District of Columbia mandate CRC screening coverage, which includes CTC coverage from private insurance companies. Visit www.myctcolonography.com for more details. Even prior to the June 2016 USPSTF recommendation of CTC as one of the Grade A CRC screening modalities, many private payers were already covering CTC screening, and as of April 2017, the top five national insurers and many state-specific insurers cover CTC as a screening test. We expect to see more companies expand their coverage policies in 2017. Visit www.myctccolonography.com for up-to-date information on coverage by commercial insurers.

Lastly, regarding Medicare coverage for screening, the Colon Cancer Alliance (CCA), Colon Cancer Coalition (CCC), Prevent Cancer Foundation (PCF), Society of Abdominal Radiology (SAR), Society of Computed Body Tomography & Magnetic Resonance (SCBT-MR), ACR, Medical Imaging Technology Alliance (MITA), Bracco Diagnostics, and iCAD Inc. are actively working together to request the opening of the Medicare National Coverage Reconsideration for Screening Computed Tomography Colonography (CTC) for colorectal cancer (CAG-00396N) in 2017. Medicare currently covers CTC as a diagnostic procedure via the respective LCDs (local coverage decisions) in all the MAC (Medicare Administrative contractor) regions of the country. Visit www.myctcolonography.com for more details.

CPT codes for screening and diagnostic CT colonography:

- 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

Diagnosis codes for screening and diagnostic CT colonography:

- Screening Exam
  - Z12.11: Encounter for screening for malignant neoplasm of colon
  - Z12.10: Screening for malignant neoplasm of intestinal tract, unspecified
  - Z12.12: Screening for malignant neoplasm of rectum
  - Z12.13: Screening for malignant neoplasm of small intestine
- Diagnostic Exam
  - Z86.010: Personal history of colonic polyps
  - R93.3: Abnormal findings on diagnostic imaging of other parts of digestive tract
  - K92.2: Gastrointestinal hemorrhage, unspecified

Conclusions

A number of tests are available for screening adults for CRC, including direct visual exams and stool-based exams. Visual CRC screening exams have the advantage of detecting precancerous lesions, while stool-based methods are less invasive. CTC provides a permanent anatomical record of colon health that can be used in subsequent exams to monitor changes. CTC (or virtual colonoscopy) is both highly accurate and noninvasive, and surveys show CTC is associated with a high rate of patient satisfaction. Recent guidelines indicate that no empirical evidence exists for the preference of one screening test over another, and that the best test option is "*the one that gets done.*"

References

1. Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review (CSR), 1975-2013. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. Accessed January 11, 2017.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7-30.
3. Lin JS, Piper MA, Perdue LA, et al. Screening for Colorectal Cancer: A Systematic Review for the U.S. Preventive Services Task Force. Evidence Syntheses, No. 135. Rockville, MD: Agency for Healthcare Research and Quality; June 2016. AHRQ publication 14-05203-EF-1. Available at: https://www.ncbi.nlm.nih.gov/books/NBK373584/. Accessed January 11, 2017.
4. Baxter NN, Warren JL, Barrett MJ, Stukel TA, Doria-Rose VP. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. *J Clin Oncol*. 2012;30:2664-2669.
5. American Cancer Society. American Cancer Society recommendations for colorectal cancer early detection. Available at: http://www.cancer.org/cancer/colonandrectumcancer/moreinformation/colonandrectumcancerearlydetection/colorectal-cancer-early-detection-acs-recommendations. Last revised June 24, 2016. Accessed January 10, 2017.
6. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med*. 2003;349:2191-2200.
7. Pickhardt PJ. CT colonography for population screening: ready for prime time? *Dig Dis Sci*. 2015;60:647-659.
8. Moawad FJ, Maydonovitch CL, Cullen PA, et al. CT colonography may improve colorectal cancer screening compliance. *AJR Am J Roentgenol*. 2010;195:1118-1123.
9. Pooler BD, Baumel MJ, Cash BD, et al. Screening CT colonography: multicenter survey of patient experience, preference, and potential impact on adherence. *AJR Am J Roentgenol*. 2012;198:1361-1366.
10. Pickhardt PJ. Randomized controlled trial evaluating participation and yield of colonoscopy versus CT colonography screening. *Expert Rev Med Devices*. 2012;9:107-110.
11. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncology*. 2012;13:55-64.
12. US Preventive Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;315:2564-2575.
13. US Preventive Services Task Force. Final recommendation statement: colorectal cancer: screening. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/colorectal-cancer-screening. Published November 2016. Accessed January 13, 2017.
14. Centers for Disease Control and Prevention (CDC). Colorectal cancer screening tests. Available at: https://www.cdc.gov/cancer/colorectal/basic_info/screening/tests.htm. Last updated August 8, 2016. Accessed March 21, 2017.
15. Centers for Disease Control and Prevention (CDC). Colorectal cancer screening saves lives. CDC publication 22-1381. Available at: https://www.cdc.gov/cancer/colorectal/pdf/no_pocket_brochure.pdf. Revised February 2017. Accessed March 21, 2017.
16. McFarland EG, Levin B, Lieberman DA, et al. Revised colorectal screening guidelines: joint effort of the American Cancer Society, U.S. Multisociety Task Force on Colorectal Cancer, and American College of Radiology. *Radiology*. 2008;248:717-720.
17. US Food and Drug Administration. 24-Hour Summary: Office of the Commissioner Joint Meeting of the Gastroenterology-Urology Devices Panel and the Radiological Devices Panel. Available at: https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm367975.htm. Updated September 11, 2013. Accessed February 23, 2017.
18. NCQA HEDIS® 2017 Volume 2: Technical Update. Available at: http://www.ncqa.org/Portals/0/HEDISQM/HEDIS2017/HEDIS%202017%20Volume%202%20Technical%20Update.pdf?ver = 2016-10-03-114902-317. Accessed February 23, 2017.
19. National Colorectal Cancer Roundtable. 80% by 2018. Available at: http://nccrt.org/tools/80-percent-by-2018/. Accessed January 10, 2017.
20. Centers for Disease Control and Prevention (CDC). Screen for life campaign print materials. Available at: https://www.cdc.gov/cancer/colorectal/sfl/print_materials.htm. Last updated February 22, 2017. Accessed March 16, 2017.

21. American Cancer Society. Colorectal cancer facts & figures 2014-2016. Atlanta, GA: American Cancer Society; 2014. Available at: http://www.cancer.org/acs/groups/content/documents/document/acspc-042280.pdf. Accessed January 10, 2017.
22. Liedenbaum MH, Venema HW, Stoker J. Radiation dose in CT colonography—trends in time and differences between daily practice and screening protocols. *Eur Radiol*. 2008;18:2222-2230.
23. Graser A, Wintersperger BJ, Suess C, Reiser MF, Becker CR. Dose reduction and image quality in MDCT colonography using tube current modulation. *AJR Am J Roentgenol*. 2006;187:695-701.
24. Pooler BD, Kim DH, Lam VP, Burnside ES, Pickhardt PJ. CT Colonography Reporting and Data System (C-RADS): benchmark values from a clinical screening program. *AJR Am J Roentgenol*. 2014;202:1232-1237.
25. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: a consensus proposal. *Radiology*. 2005;236:3-9.
26. Ahnen DJ, Wade SW, Jones WF, et al. The increasing incidence of young-onset colorectal cancer: a call to action. *Mayo Clin Proc*. 2014;89:216-224.
27. Deen KI, Silva H, Deen R, Chandrasinghe PC. Colorectal cancer in the young, many questions, few answers. *World J Gastrointest Oncol*. 2016;8:481-488.
28. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974–2013. *J Natl Cancer Inst*. 2017;109:djw322.
29. Dozois EJ, Boardman LA, Suwanthanma W, et al. Young-onset colorectal cancer in patients with no known genetic predisposition: can we increase early recognition and improve outcome? *Medicine (Baltimore)*. 2008;87:259-263.
30. American Cancer Society. Key statistics for colorectal cancer. Available at: http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-key-statistics. Last revised January 20, 2016. Accessed January 10, 2017.
31. Levin B, Lieberman DA, McFarland B, et al; American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American College of Radiology Colon Cancer Committee. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin*. 2008;58:130-160.
32. Inadomi JM, Vijan S, Janz NK, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. *Arch Intern Med*. 2012;172:575-582.
33. Gupta S, Halm EA, Rockey DC, et al. Comparative effectiveness of fecal immunochemical test outreach, colonoscopy outreach, and usual care for boosting colorectal cancer screening among the underserved: a randomized clinical trial. *JAMA Intern Med*. 2013;173:1725-1732.
34. American Cancer Society. Colorectal cancer screening tests. Available at: http://www.cancer.org/cancer/colonandrectumcancer/moreinformation/colonandrectumcancerearlydetection/colorectal-cancer-early-detection-screening-tests-used. Last revised June 24, 2016. Accessed January 10, 2017.
35. Pickhardt PJ. Emerging stool-based and blood-based non-invasive DNA tests for colorectal cancer screening: the importance of cancer prevention in addition to cancer detection. *Abdom Radiol (NY)*. 2016;41:1441-1444.
36. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. *Gut*. 2014;63:317-325.
37. Zauber A, Knudsen A, Rutter CM, Lansdorp-Vogelaar I, Kuntz KM. Evaluating the Benefits and Harms of Colorectal Cancer Screening Strategies: A Collaborative Modeling Approach. Rockville, MD: Agency for Healthcare Research and Quality; 2015. AHRQ publication 14-05203-EF-2.
38. Kim DH, Pooler BD, Weiss JM, Pickhardt PJ. Five year colorectal cancer outcomes in a large negative CT colonography screening cohort. *Eur Radiol*. 2012;22:1488-1494.
39. Pickhardt PJ, Wise SM, Kim DH. Positive predictive value for polyps detected at screening CT colonography. *Eur Radiol*. 2010;20:1651-1656.
40. Zueco Zueco C, Sobrido Sampedro C, Corroto JD, et al. CT colonography without cathartic preparation: positive predictive value and patient experience in clinical practice. *Eur Radiol*. 2012;22:1195-1204.

41. Iafrate F, Hassan C, Ciolina M, et al. High positive predictive value of CT colonography in a referral centre. *Eur J Radiol*. 2011;80:E289-E292.

42. Pickhardt PJ. Recent developments in colorectal imaging. *Curr Opin Gastroenterol*. 2015;31:76-80.

43. Halligan S. CT colonography for investigation of patients with symptoms potentially suggestive of colorectal cancer: a review of the UK SIGGAR trials. *Br J Radiol*. 2013;86:20130137.

44. Kim HJ, Park SH, Pickhardt PJ, et al. CT colonography for combined colonic and extracolonic surveillance after curative resection of colorectal cancer. *Radiology*. 2010;257:697-704.

45. ACR–SAR–SCBT-MR practice parameter for the performance of computed tomography (CT) colonography in adults. Available at: https://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/CT_Colonography.pdf. Revised 2014. Accessed February 23, 2017.

46. Pickhardt PJ, Lam VP, Weiss JM, Kennedy GD, Kim DH. Carpet lesions detected at CT colonography: clinical, imaging, and pathologic features. *Radiology*. 2014;270:435-443.

47. Pickhardt PJ, Kim DH, Robbins JB. Flat (nonpolypoid) colorectal lesions identified at CT colonography in a US screening population. *Acad Radiol*. 2010;17:784-790.

48. O'Brien MJ, Winawer SJ, Zauber AG, et al. Flat adenomas in the National Polyp Study: is there increased risk for high-grade dysplasia initially or during surveillance? *Clin Gastroenterol Hepatol*. 2004;2:905-911.

49. Park SH, Kim SY, Lee SS, et al. Sensitivity of CT colonography for nonpolypoid colorectal lesions interpreted by human readers and with computer-aided detection. *AJR Am J Roentgenol*. 2009;193:70-78.

50. Pickhardt PJ, Nugent PA, Choi JR, Schindler WR. Flat colorectal lesions in asymptomatic adults: implications for screening with CT virtual colonoscopy. *AJR Am J Roentgenol*. 2004;183:1343-1347.

51. Shen H, Yang J, Huang Q, et al. Different treatment strategies and molecular features between right-sided and left-sided colon cancers. *World J Gastroenterol*. 2015;21:6470-6478.

52. Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst*. 2015;107.

53. American Society for Gastrointestinal Endoscopy. Media backgrounder: colorectal cancer screening. Available at: http://www.asge.org/press/press.aspx?id = 552. Reviewed August 2014. Accessed January 10, 2017.

54. Warschkow R, Sulz MC, Marti L, et al. Better survival in right-sided versus left-sided stage I-III colon cancer patients. *BMC Cancer*. 2016;16:554.

55. Pooler BD, Kim DH, Weiss JM, Matkowskyj KA, Pickhardt PJ. Colorectal polyps missed with optical colonoscopy despite previous detection and localization with CT colonography. *Radiology*. 2016;278:422-429.

56. Pickhardt PJ. Screening CT colonography: how I do it. *AJR Am J Roentgenol*. 2007;189:290-298.

57. Laghi A, Iafrate F, Rengo M, Hassan C. Colorectal cancer screening: the role of CT colonography. *World J Gastroenterol*. 2010; 16:3987-3994.

58. American College of Radiology (ACR) Committee on Drugs and Contrast Media. ACR Manual on Contrast Media, Version 10.2. 2016. Available at: https://www.acr.org/Quality-Safety/Resources/Contrast-Manual. Accessed January 10, 2017.

59. Yee J, Weinstein S, Morgan T, Alore P, Aslam R. Advances in CT colonography for colorectal cancer screening and diagnosis. *J Cancer.* 2013;4:200-209.

60. Lefere PA, Gryspeerdt S, Marrannes J, et al. CT colonography after fecal tagging with a reduced cathartic cleansing and a reduced volume of barium. *AJR Am J Roentgenol.* 2005;184:1836-1842.

61. Mang T, Graser A, Schima W, Maier A. CT colonography: techniques, indications, findings. *Eur J Radiol*. 2007;61:388-399.

62. Lefere PA, Gryspeerdt SS, Dewyspelaere J, et al. Dietary fecal tagging as a cleansing method before CT colonography: initial results—polyp detection and patient compliance. *Radiology*. 2002;224:393-403.

63. Burling D, Taylor SA, Halligan S, et al. Automated insufflation of carbon dioxide for MDCT colonography: distension and patient experience compared with manual insufflation. *AJR Am J Roentgenol*. 2006;186:96-103.

64. Dachman AH. Advice for optimizing colonic distention and minimizing risk of perforation during CT colonography. *Radiology*. 2006;239:317-321.

65. Pickhardt PJ. Incidence of colonic perforation at CT colonography: review of existing data and implications for screening of asymptomatic adults. *Radiology*. 2006;239:313-316.

66. Shinners TJ, Pickhardt PJ, Taylor AJ, Jones DA, Olsen CH. Patient-controlled room air insufflation versus automated carbon dioxide delivery for CT colonography. *AJR Am J Roentgenol*. 2006;186:1491-1496.

67. PROTOCO$_2$L TOUCH® insufflation system [product profile]. Available at: http://imaging.bracco.com/us-en/products-and-solutions/ct-colonography/protoco2l-touch/product-profile. Accessed January 11, 2017.

68. Johnson CD, Chen M, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med.* 2008;359:1207-1217.

69. Sumanac K, Zealley I, Fox BM, et al. Minimizing postcolonoscopy abdominal pain by using CO(2) insufflation: a prospective, randomized, double blind, controlled trial evaluating a new commercially available CO(2) delivery system. *Gastrointest Endosc*. 2002;56:190-194.

70. TAGITOL™ V (barium sulfate suspension) [package insert]. Monroe Township, NJ: E-Z-EM, Inc. a subsidiary of Bracco Diagnostics Inc.; revised June 2014.

71. Pyenson B, Pickhardt PJ, Sawhney TG, Berrios M. Medicare cost of colorectal cancer screening: CT colonography vs. optical colonoscopy. *Abdom Imaging*. 2015;40:2966-2976.

PROTOCO$_2$L TOUCH® Colon Insufflator

Indications and Usage:

The PROTOCO$_2$L TOUCH Colon Insufflator administers and regulates carbon dioxide as a distention media to the colon during CTC or Virtual Colonoscopy.

The PROTOCO$_2$L TOUCH Colon Insufflator provides a software controlled insufflation of carbon dioxide during CT Colonoscopy (CTC). Carbon dioxide is more rapidly absorbed than room air and helps minimize the patient's post-procedure bloating and cramping. The PROTOCO$_2$L TOUCH Colon Insufflator helps reduce staff time during the colon insufflation process and enhances productivity. Automated insufflation helps ensure adequate and consistent distension in a patient- and operator-independent manner. It also features a specially designed small tip for patient comfort, as well as safety features to help protect against over-insufflation.

IMPORTANT SAFETY INFORMATION:

The PROTOCO$_2$L TOUCH Colon Insufflator should be used only when colon insufflation is indicated, and should therefore not be used for any other treatment. It should only be used under the direct guidance of a physician experienced in colon insufflation.

PROTOCO$_2$L TOUCH Instructions for Use may be obtained by contacting Bracco Diagnostics Professional Services Department at 800-257-5181, Option 2.

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TAGITOL™ V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent

Indications and Usage:

For use in opacifying residual stool in the colon during CTC. TAGITOL V (Barium Sulfate Suspension 40% w/v, 30% w/w) Stool Tagging Agent is a low-volume radiopaque marker that blends into stool as it forms. With just a 20mL dose with breakfast, lunch and dinner the day prior to the exam, TAGITOL V Stool Tagging Agent provides immediate, visible identification of retained feces via comparative density analysis, simplifying the distinction between tagged feces and colonic abnormality.

IMPORTANT SAFETY INFORMATION:

This product should not be used in patients with known or suspected gastric and intestinal perforation, or hypersensitivity to barium sulfate or any component of this barium sulfate formulation. Rarely, severe and occasionally fatal allergic reactions have been reported following administration of barium sulfate contrast agents.

Please see full Prescribing Information for TAGITOL V Stool Tagging Agent.
http://imaging.bracco.com/us-en/products/ct-ct-colonography/tagitol-v

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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