



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Colorectal Cancer Screening and Surveillance

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

Coverage of colorectal cancer screening is generally subject to the terms, conditions and limitations of a preventive services benefit as described in the applicable benefit plan's schedule of copayments. Please refer to the applicable benefit plan document and schedules to determine benefit availability and the terms, conditions and limitations of coverage.

If coverage for colorectal cancer screening is available, the following conditions apply.

For average-risk individuals age 50 years and older, CIGNA covers as medically necessary the following colorectal cancer (CRC) screening testing regimens:

- annual fecal occult blood test (FOBT) or fecal immunochemical test (FIT)
- stool-based deoxyribonucleic acid (DNA) testing
- flexible sigmoidoscopy every five years
- double-contrast barium enema (DCBE) every five years
- colonoscopy every 10 years
- computed tomographic colonography (CTC)/virtual colonoscopy every five years

For increased- or high-risk individuals who fit into any of the categories listed below, CIGNA covers as medically necessary more intensive colorectal cancer screening, surveillance or monitoring as per the

American Cancer Society (ACS) Guidelines or the National Comprehensive Cancer Network (NCCN) Guidelines™ :

- personal history of adenoma or adenomatous polyps found on colonoscopy
- familial history of adenoma or adenomatous polyp found at colonoscopy in a first-degree relative
- personal or family history of colorectal cancer
- personal history of inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease)
- personal or inherited risk of a colorectal cancer (e.g., familial adenomatous polyposis [FAP], attenuated FAP, hereditary nonpolyposis colorectal cancer [HNPCC], MYH polyposis)

CIGNA does not cover in vivo analysis of colorectal polyps (e.g., fiberoptic polyp analysis, narrow band imaging, and confocal fluorescent endomicroscopy) for the screening, diagnosis or surveillance of colorectal cancer, as its use is experimental, investigational, or unproven.

Please refer to the CIGNA Coverage Policy on Computed Tomographic Colonography/Virtual Colonoscopy for specific coverage criteria for non-screening uses of this procedure.

General Background

Colorectal cancer (CRC) is the third most common cancer diagnosed in men and women and the second leading cause of deaths from cancer in the United States. CRC primarily affects men and women aged 50 years or older. For men, CRC is the third most common cancer after prostate and lung cancer. For women, CRC is the third most common cancer after breast and lung cancer. Age-specific incidence and mortality rates show that most cases are diagnosed in individuals over age 50 (National Cancer Institute [NCI], 2010a). Incidence rates for CRC have been decreasing for most of the last two decades: from 66.3 cases per 100,000 in 1985 to 48.2 in 2004. This decline has been greater over the most recent time period which is considered to be partly due to an increase in screening, which can result in the detection and removal of colorectal polyps before they progress to cancer (American Cancer Society [ACS], 2008a).

The etiology of CRC is heterogeneous and may be influenced by both the environment and genetics. There are groups with a higher incidence of CRC. These include those with hereditary CRC conditions, a personal or family history of CRC and/or polyps, or a personal history of chronic inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease). In addition there are several factors that are considered to be modifiable. These include: obesity, physical inactivity, smoking, heavy alcohol consumption, diet high in red or processed meat and inadequate intake of fruits and vegetables (ACS, 2010b). The risk of CRC increases with age with more than 90% of cases diagnosed in individuals aged 50 or older.

Hereditary CRC conditions include the following:

- Familial adenomatous polyposis (FAP) and attenuated FAP (AFAP) which are caused by changes to the APC gene.
- MYH-associated polyposis (MAP), which is caused by biallelic germ line mutations in the MutY human homolog (MYH) gene.
- Hereditary nonpolyposis CRC (HNPCC), also known as Lynch syndrome and is associated with DNA mismatch repair genes, MLH1, MSH2, MSH6, and PMS2

Risk Stratification

The population has been stratified into risk categories for the potential development of CRC. These groups include: average risk, increased risk with a personal history, increased risk with a family history and increased/high risk due to hereditary conditions. Guidelines for CRC screening, surveillance and monitoring have been developed based on these categories. The National Comprehensive Cancer Network® (NCCN®) and ACS definitions of these groups include (NCCN, 2010; ACS, 2010b):

Risk	NCCN	ACS
average risk	those individuals 50 years or older with no history of adenoma and	individual with no first-degree relatives having a history of CRC or adenomatous polyps and has not

	inflammatory bowel disease and negative family history	experienced these problems personally
increased risk	<p>individuals with personal history of adenomas, CRC, or inflammatory bowel disease as well as those with a positive family history of:</p> <ul style="list-style-type: none"> • first-degree relative with CRC or adenoma • two second degree relatives with CRC • multiple cases of CRC or HNPCC/Lynch syndrome in the family 	individuals those who have a personal history of CRC or adenomas, a family history of CRC or adenomas diagnosed in any first-degree relative before age 50, or in two or more first-degree relatives diagnosed at any age (if not a hereditary syndrome). According to the ACS, individuals who have a personal history of CRC or adenomatous polyp require regular surveillance, not screening.
hereditary/ high risk	individuals who have had CRC before the age of 50 years; those with family history of multiple cases of CRC or HNPCC related cancers; personal or family history of polyposis; or individuals with HNPCC/Lynch syndrome	individuals those who have a personal history of CRC or adenomas, a family history of CRC or adenomas diagnosed in any first-degree relative before age 50, or in two or more first-degree relatives diagnosed at any age (if not a hereditary syndrome). According to the ACS, individuals who have a personal history of CRC or adenomatous polyp require regular surveillance, not screening.

Screening is defined by the ACS as the search for disease, such as cancer, in people without symptoms. Surveillance is considered to be the screening of individuals known to be at an increased risk. Monitoring is the follow-up after a diagnosis or treatment.

Tests and Procedures for CRC Screening/Surveillance/Monitoring

The objective of cancer screening is to reduce mortality through a reduction in incidence of advanced disease. It is thought that CRC screening can reach this goal through the detection of early-stage adenocarcinomas and with the detection and removal of adenomatous polyps, which are generally accepted as the nonobligate precursor lesions.

There is a range of options for CRC screening for average-risk individuals. The choices fall into two general categories (Levin, et al., 2008):

- Stool tests: These include tests for occult blood or exfoliated DNA. These tests are appropriate for the detection of cancer, although they may deliver positive findings for some advanced adenomas. Testing options in this group include:
 - Annual guaiac-based fecal occult blood test with high test sensitivity for cancer
 - Annual fecal immunochemical test with high test sensitivity for cancer
 - Stool DNA test with high sensitivity for cancer, interval uncertain
- Structural exams: These exams can reach the dual goals of detecting adenocarcinoma as well as identifying adenomatous polyps. Testing options in this group include:
 - Flexible sigmoidoscopy every five years
 - Colonoscopy every ten years
 - double-contrast barium enema (DCBE) every five years
 - computed tomographic colonography (CTC) every five years

At times tests are used alone or may be used in combination to improve sensitivity or when the initial test cannot be completed. A choice of screening option may be made based on individual risk, personal preference and access. There has been a change in patterns noted in the proportion of adults utilizing various tests, with sigmoidoscopy rates declining, colonoscopy rates increasing, use of stool blood tests remaining fairly constant and the use of DCBE for screening purposes becoming very uncommon (Levin, et al., 2008).

Fecal Occult Blood Testing (FOBT) and Fecal Immunochemical Testing (FIT): The sensitivity and specificity of diagnostic screening with FOBT has been reported to be extremely variable. this may vary due to the brand or variant of the test, specimen collection technique, number of samples collected per test and whether or not the stool specimen is rehydrated and variations in interpretation, screening interval and other factors. Positive

reactions on guaiac-impregnated cards, the most common form of FOBT testing, can signal the presence of bleeding from premalignant adenomas and early-stage CRC. FOBT testing can also report false-positives caused by the ingestion of foods containing peroxidases, gastric irritants such as salicylates and other anti-inflammatory agents (Eskew, 2001). Small adenomas and colorectal malignancies that bleed only intermittently or not at all can be missed. The correct use of stool blood tests requires annual testing that consists of collecting specimens (two or three depending on the product) from consecutive bowel movements. Guidelines from the ACS (Levin, et al., 2008), the U.S. Preventive Services Task Force (USPSTF) and the NCCN strongly recommend the annual screening of patients using the standard take-home multiple sample FOBT. A positive test should be followed up with a colonoscopy. FOBT is the only CRC screening test where there is published evidence of efficacy from prospective, randomized controlled trials (Levin, et al., 2008). The repeated use of FOBT as a screening method in a properly-implemented screening program has proven its effectiveness (Levin, et al., 2008; NCI, 2010a; NCCN, 2010).

Limitations of this test include (Levin, et al., 2008):

- The test is commonly performed in the physician's office as a single-panel test following a digital rectal exam. This method has been noted to have a low accuracy and cannot be recommended as a method of CRC screening.
- The use of FOBT is inadequate for follow-up of a positive test. A survey revealed high rates of repeat office FOBT after a positive FOBT. In addition a substantial number reported referral for sigmoidoscopy after positive FOBT rather than a colonoscopy.

Fecal immunochemical test kits have been developed that can be used as an alternative to the standard guaiac FOBT. Examples of these include, but are not limited to:

- InSure™ (Enterix Inc., Edison, NJ)
- Instant-View™ Fecal Occult Blood Rapid Test (Alpha Scientific Designs, Inc., Poway, CA).

The main advantage of FIT over FOBT is that it detects human globin, a protein that along with heme constitutes human hemoglobin. Unlike the guaiac FOBT tests, these do not require a fecal smear. Samples for testing can be obtained by taking a brush sample of toilet bowl water. The main advantage of FIT over FOBT is that it detects human globin, a protein that along with heme constitutes human hemoglobin. In addition they are more specific for lower intestinal bleeding, which improves the specificity for CRC.

The published peer-reviewed literature indicates that annual screening with FIT can detect a majority of prevalent CRC in an asymptomatic population and that this is an acceptable option for CRC screening in average-risk adults aged 50 or older (Levin, et al., 2008). Similar to FOBT, a positive test should be followed up with a colonoscopy.

A Cochrane review examined whether screening for CRC using fecal occult blood test, guaiac or immunochemical, reduces CRC mortality and to take into account the benefits, harms and potential consequences of screening (Hewitson, et al., 2007). The analysis included four randomized controlled trials. These studies indicated that participants allocated to screening and a 16% reduction in the relative risk (RR) of CRC mortality (RR 0.84, CI: 0.78-0.90). In the review of the three studies that utilized biennial screening there was a 15% relative risk reduction (RR 0.85, CI: 0.78-0.92) in CRC mortality. Adjustment for screening attendance in the individual studies found that there was a 25% relative risk reduction (RR 0.75, CI: 0.66 - 0.84) for those attending at least one round of screening using the fecal occult blood test. The authors concluded that, "Benefits of screening include a modest reduction in CRC mortality, a possible reduction in cancer incidence through the detection and removal of colorectal adenomas, and potentially, the less invasive surgery that earlier treatment of colorectal cancers may involve." **Level of evidence: 1**

Stool-Based DNA Testing: Molecular genetic screening analysis of deoxyribonucleic acid (DNA) in stool has been proposed as an alternate, noninvasive screening tool for CRC (Pignone, et al., 2002; Ahlquist, et al., 2002). Detecting CRC by testing stool for DNA is based on identifying the oncogene mutations characteristic of colorectal neoplasia that are detectable in exfoliated epithelial cells in the stool. While neoplastic bleeding is intermittent, epithelial shedding is continual, potentially making stool-based DNA testing (i.e., also known as fecal DNA [f-DNA] and stool DNA [sDNA]) testing more sensitive than other methods. Early studies of molecular stool screening primarily focused on single mutations (i.e., Kirstan rat sarcoma [K-ras] oncogene). Colorectal neoplasms are varied in nature; however, no single mutation has been identified as being expressed universally.

For this reason, multiple target assay panels currently being studied have the potential to attain higher detection rates than current screening methods. This test requires the entire stool specimen (30g minimum) to ensure an adequate sample of stool for evaluation (Levin, et al., 2008).

PreGen-Plus™ (EXACT Sciences Corporation, Maynard, MA; Laboratory Corporation of America [LabCorp], Burlington, NC), is no longer being marketed. This test has not received FDA premarket (PMA) approval. In Oct 2007, EXACT Science received a warning letter from FDA that states the FDA believes that the commercial PreGen-Plus assay is a medical device requiring pre-market approval or clearance (FDA, 2007).

ColoSure™ (Laboratory Corporation of America [LabCorp], Burlington, NC) is a fecal DNA test that utilizes a methylation-specific PCR and gel electrophoresis technique to detect aberrant methylation in the vimentin gene. Aberrant methylation of exon-1 sequences within the nontranscribed region of the vimentin gene is associated with CRC. According to LabCorp website, ColoSure is not intended to replace a colonoscopy in those patients who are willing or able to undergo the procedure. While it may be used adjunctively or in noncompliant patients, it is not intended as a primary tool for individuals at increased risk for developing disease.

The vendor is recommending a five year interval for routine screening between examinations with normal results. The joint guidelines from the ACS, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology (Levin, et al., 2008) include stool-based DNA testing as an acceptable option for CRC screening in their guidelines; however, it is noted that there is insufficient data to support this interval and further research is needed to determine the interval between negative tests. The appropriate interval for this testing is uncertain at this time.

Literature Review for Stool-Based DNA Testing: Ahlquist et al. (2008) conducted a blinded, multicenter, cross-sectional study to compare stool DNA and fecal blood testing for the detection of screen-relevant neoplasia (curable-stage cancer, high-grade dysplasia, or adenomas >1 cm). The study involved 3784 average-risk adults in communities surrounding 22 participating academic and regional health care systems. Fecal blood cards (Hemoccult and HemoccultSensa, Beckman Coulter, Fullerton, California) were tested on three stools and DNA assays on 1 stool per patient. The study utilized a stool DNA test 1 (SDT-1), which was a precommercial 23-marker assay, and a novel test (SDT-2) that targeted 3 broadly informative markers. The criterion standard was colonoscopy. Sensitivity for screen-relevant neoplasms was 20% by SDT-1, 11% by Hemoccult ($p=0.020$), 21% by HemoccultSensa ($p=0.80$); sensitivity for cancer plus high-grade dysplasia did not differ among tests. Specificity was 96% by SDT-1, compared with 98% by Hemoccult ($p<0.001$) and 97% by HemoccultSensa ($p=0.20$). Stool DNA test 2 detected 46% of screen-relevant neoplasms, compared with 16% by Hemoccult ($p<0.001$) and 24% by HemoccultSensa ($p<0.001$). Stool DNA test 2 detected 46% of adenomas 1 cm or larger, compared with 10% by Hemoccult ($p<0.001$) and 17% by HemoccultSensa ($p<0.001$). Among patients with normal colonoscopies, the positivity rate was 16% with SDT-2, compared with 4% with Hemoccult ($p=0.010$) and 5% with HemoccultSensa ($p=0.030$). The limitations of the study included that the stool DNA test 2 was not performed on all subsets of patients without screen-relevant neoplasms. The stool samples were collected without preservative, which reduced detection of some DNA markers.

Haug et al. (2007) examined the prevalence of mutant K-ras in stool samples of 875 older adults and then assessed the association with colonoscopy findings. The participants were divided into two groups. Group A ($n=535$) consisted of persons who underwent colonoscopy between baseline and two-year follow-up, and the colonoscopy results were available. The group B ($n=340$) selection criteria included only that a large enough sample of stool had been collected. In group A and B, the prevalence of the K-ras mutation was 7% and 10%, respectively. In group A, 441 underwent complete colonoscopy. Advanced colorectal neoplasia was detected in 31 patients, and 25 patients were found to have hyperplastic polyps. None of these patients tested positive for the K-ras mutation. Among those diagnosed with nonadvanced adenomas ($n=50$) and unspecified polyps ($n=35$), K-ras mutations were found in one and three, respectively. The authors reported that none of the individuals diagnosed with advanced adenomas or CRC within two years after stool collection had tested positive for the K-ras mutation. The authors concluded that the results from this study do not support the use of this assay for CRC screening.

Itzkowitz et al. (2007) performed a study to determine the sensitivity and specificity of a newer version of the fecal DNA test. Version 1 analyzed 22 gene mutations and DNA integrity assay (DIA). Sensitivity for this test was reported at 52%, and specificity was reported at 94%. The low sensitivity of the test was due to the low positive rate of the DIA which was a result of DNA degradation during transit of specimens. The improvements

in version 2 included better DNA stabilization, enhanced DNA extraction, and the use of gene-specific methylation. According to the authors, by improving the methods for stabilizing DNA during specimen transport and extracting DNA from stool, the sensitivity of the test increased to 72.5% in version 2—a direct result of an increase in the DIA from 3% in version 1 to 65% in version 2. The addition of gene-specific methylation with vimentin to the new DIA increased the sensitivity of version 2 to 87.5%. Specificity decreased from 94.4% in version 1 to 89.3% in version 2. The authors concluded that at the present time, DNA testing is not a replacement for colonoscopy, but a method to get patients screened who might otherwise avoid an invasive screening test. Further investigation is warranted.

Rennert et al. (2007) evaluated the ability to detect K-ras mutations in stool DNA from FOBT cards and if the presence of the K-ras mutation improved the positive predictive value (PPV) of the screening process. Two hundred and five consecutive positive FOBT cards and an arbitrary sample of 38 negative cards from a population-based screening program were included. DNA was successfully amplified from 180 positive FOBT cards and from 32 of the negative FOBT cards. K-ras mutations were detected in 39 of the positive FOBT cards (21.7%) and in nine of the negative cards (28.1%). Only 130 of the 180 amplified positive FOBT had available follow-up data. Of these 130, 23 malignancies and 25 adenomas were detected on follow-up. K-ras was detected in eight of the malignancies (34.8%) and in eight of the adenomas (32.0%). The PPV of FOBT alone, when four or more of the six test slides on the card were positive, was 60%. The PPV of FOBT with greater than four positive fields plus the detection of the K-ras mutation increased the PPV to 80%. The authors concluded that testing for K-ras is only a partial approach to detecting CRC in stool samples and that testing for other expressions and mutations of other commonly detected genes on the same DNA samples may further improve the detection process.

The Blue Cross Blue Shield Technology Evaluation Center (TEC) (2006) concluded in their “Special report: Fecal DNA analysis for colon cancer screening” that “fecal DNA testing is a noninvasive colorectal cancer screening technology that may eventually offer sensitivity for cancer closer to that of colonoscopy than that of conventional, guaiac-based FOBTs. Although the impact of fecal DNA screening on cancer morbidity and mortality has not yet been studied, it seems reasonable to assume that attaining sensitivities equal to or better than that of FOBT would result in similar or improved outcomes” (Blue Cross Blue Shield [BCBS] TEC, 2006).

Imperiale et al. (2004) conducted an observational clinical trial comparing an approach that identifies abnormal DNA in stool samples to Hemocult® II FOBT in persons of average risk. Asymptomatic persons age ≥ 50 submitted one stool specimen for DNA analysis, underwent standard Hemocult II testing, and then underwent colonoscopy. Of 5486 subjects enrolled, 4404 completed all aspects of the study. A subgroup of 2507 subjects was analyzed, including all those with diagnoses of invasive adenocarcinoma or advanced adenoma, plus randomly chosen subjects with no or minor polyps. The f-DNA panel consisted of 21 mutations. The f-DNA panel detected 16 of 31 invasive cancers; Hemocult II identified four of 31 ($p=0.003$). The f-DNA panel detected 29 of 71 invasive cancers plus adenomas with high-grade dysplasia; Hemocult II identified 10 of 71 ($p<0.001$). Among 418 subjects with advanced neoplasia, the DNA panel was positive in 76 (18.2%), whereas Hemocult II was positive in 45 (10.8%). Specificity in subjects with negative findings on colonoscopy was 94.4% for the f-DNA panel and 95.2% for Hemocult II. Although the majority of neoplastic lesions identified by colonoscopy were not detected by either noninvasive test, the multitarget analysis of f-DNA detected a greater proportion of colorectal neoplasia than did Hemocult II without compromising specificity.

Tagore et al. (2003) conducted an evaluation study to estimate the sensitivity and specificity of a multiple target assay panel of stool DNA changes. The multiple target assay panel/DNA Integrity Assay (DIA) included 21 specific mutations in the APC, p53, K-ras genes, BAT-26 MSI marker and a marker of abnormal apoptosis. Stool samples from patients with colorectal neoplasia ($n=88$) and control subjects ($n=212$) were collected prior to colonoscopy. Patients with hereditary CRC were excluded. The multiple target assay panel detected invasive CRC in 33 of 52 patients, including 26 of 36 with node-negative disease (American Joint Committee on Cancer [AJCC] stage I/II) and seven of 16 with advanced disease (AJCC stage III/IV). Sixteen of 28 patients with advanced adenomas were detected. Specificity was reported to be 96.2% in patients with either no colorectal lesions or diminutive polyps. The authors concluded that the multiple target assay panel has better sensitivity than FOBT with similar specificity, with sensitivity appearing equally high for patients with node-negative disease, advanced disease, and advanced adenomas. The authors acknowledged that the study contained a disproportionately high number of distal cancers and therefore may not represent results in proximal lesions. The researchers concluded that a prospective study in an average-risk population is needed to validate the findings in this study.

Sigmoidoscopy: Flexible sigmoidoscopy is an endoscopic procedure that examines the lower half of the colon lumen. It is generally performed without sedation and with a more limited bowel preparation than standard colonoscopy (Levin, et al., 2008). The use of this test for CRC screening is supported by high-quality case-control and cohort studies. In average-risk individuals, flexible sigmoidoscopy is generally recommended every five years beginning at age 50 (ACS 2009c; NCCN, 2010). A five-year interval between screening examinations is recommended. The interval is shorter than for colonoscopy since the flexible sigmoidoscopy is less sensitive than colonoscopy even in the area examined because of the technique and quality of bowel preparation, the varied experience of the examiners performing the procedure, and the effect patient discomfort and spasm may have on depth of sigmoidoscope insertion and adequacy of mucosal inspection. The test may be combined with the FOBT and FIT performed annually. Positive test findings will need to be followed up with a colonoscopy (Levin, et al., 2008).

Colonoscopy: colonoscopy allows direct mucosal inspection of the entire colon along with same session biopsy sampling or polypectomy in case of pre-cancerous polyps and some early-stage cancers (Levin, et al., 2008). Preparation involves adopting a liquid diet one or more days before the examination, followed by either ingestion of oral lavage solutions or saline laxatives to stimulate bowel movements. Patients generally receive a mild sedative prior to procedure. There are no studies evaluating whether screening colonoscopy alone reduces the incidence or mortality from CRC in people at average risk. However, several lines of evidence support the effectiveness of screening colonoscopy. Colonoscopy was an integral part of the clinical trials of FOBT screening that showed that screening reduced CRC mortality. Visualization of neoplasms by colonoscopy is at least as good as by sigmoidoscopy. There is direct evidence that screening sigmoidoscopy reduces CRC mortality, and colonoscopy allows more of the large bowel to be examined. Colonoscopy has been shown to reduce the incidence of CRC in two cohort studies of people with adenomatous polyps. Colonoscopy permits detection and removal of polyps and biopsy of cancer throughout the colon. However, colonoscopy involves greater risk and inconvenience to the patient than other screening tests, and not all examinations visualize the entire colon. Significant risks include postpolypectomy bleeding and perforation of the colon.

Beginning at age 50, colonoscopy is recommended in average-risk individuals every 10 years (ACS, 2009c; Rex, 2006; NCCN, 2010). Choice of a 10-year interval between screening examinations for average-risk people (if the preceding examination is negative) is based on estimates of the sensitivity of colonoscopy and the rate at which advanced adenomas develop.

Double-Contrast Barium Enema (DCBE): DCBE, also referred to as air-contrast barium enema, examines the colon in its entirety by coating the mucosal surface with high-density barium and distending the colon with air introduced through a flexible catheter that is inserted into the rectum. Multiple radiographs are performed with various patient positions. Colonic preparation is needed, which is usually a 24 hour dietary and laxative regimen. There is no opportunity for biopsy or polypectomy. If there are findings of polyps ≥ 6 mm on DCBE, then a colonoscopy should be performed. There have been no randomized controlled trials evaluating the efficacy of DCBE as a primary screening modality to reduce incidence or mortality from CRC in average-risk adults, and there also are no case-control studies evaluating the performance of DCBE (Levin, et al., 2008). In addition it is noted that the literature describing the test performance of DCBE is limited by study designs that are retrospective and commonly do not report findings from an asymptomatic or average-risk population (Levin, et al., 2008).

Generally it was noted that the majority of the studies that evaluated the cancer-detection capability of DCBE employed a methodology in which all patients in an institution- or population-based database that had been diagnosed with CRC were assessed for a history of a prior DCBE within a defined time frame, the length of which was not consistent between studies but usually ranged from 2 to 5 years. The assumption was that missed cancers on DCBE would subsequently be clinically detected. The majority of these studies showed sensitivity for cancer of 85% to 97% (Levin, et al., 2008).

Beginning at age 50, DCBE is included in the recommendation from several organizations for screening in average-risk individuals (ACS, 2009c; NCCN, 2010). DCBE is included as a screening option because it offers an alternative means to examine the entire colon. It is widely available, and it detects about half of large polyps, which are most likely to be clinically important. A five-year interval between DCBE examinations is recommended because DCBE is less sensitive than colonoscopy in detecting colonic neoplasm.

Computed Tomographic Colonography (CTC)/Virtual Colonoscopy: Computed tomographic colonography (CTC) uses data from computed tomography (CT) to generate two- and three-dimensional images of the colon and rectum. This procedure is also been referred to as virtual colonoscopy. It is a minimally-invasive procedure that requires no intravenous administration of sedatives or analgesics. The day before the procedure, bowel cleansing is performed, similar to requirements for a colonoscopy. Colonic perforation is extremely low with this test since it is minimally invasive (Levin, et al., 2008).

Use of this procedure has been proposed as an alternative to existing screening tests (e.g., colonoscopy) for CRC, and for surveillance and diagnostic purposes in patients with contraindications for the use of conventional colonoscopy. A traditional colonoscopy is still needed in order to biopsy or remove any lesion/polyp that is found (Torres, 2007; Itzkowitz, 2006). CTC has been included in the 2008 joint guidelines from the ACS, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology. Beginning at age 50, CTC is recommended for average-risk individuals every 5 years (Levin, et al., 2008). Currently, there are no prospective, randomized, controlled clinical trials that are initiated or planned that demonstrate the efficacy of CTC in reducing mortality from CRC, rather studies have focused on the detection of advanced neoplasia (Levin, et al., 2008).

Please refer to the CIGNA HealthCare Coverage Policy on Computed Tomographic Colonography/Virtual Colonoscopy for additional background information and literature review for this procedure.

Literature Review—Screening/Various Screening Methods: Segnan et al. (2005) conducted a multicenter, randomized trial to compare the participation and detection rates achievable through various strategies of CRC screening. This study was conducted from November 1999 to June 2001 and included a population sample of 28,319 individuals who were at average risk of developing CRC. A total of 1637 individuals were excluded from participation due to lack of interest, current CRC, adenomas, inflammatory bowel disease, a family history of CRC, recent fecal occult blood testing or recent colon examination. There were 26,682 patients randomly assigned to one of five screening arms: 1) biennial FOBT received via the mail; 2) biennial FOBT received from the primary care physician or clinic; 3) patient's choice of FOBT or "once-only" sigmoidoscopy; 4) "once-only" sigmoidoscopy; or 5) sigmoidoscopy followed by biennial FOBT beginning two years after the sigmoidoscopy if the results were negative. It was found that of the 2858 subjects screened by FOBT: 122 (4.3%) had a positive test result, 10 (3.5 per 1000) had CRC and 39 (1.4%) had an advanced adenoma. Among the 4466 subjects screened by sigmoidoscopy, it was found that: 341 (7.6%) were referred for colonoscopy, 18 (4 per 1000) had CRC and 229 (5.1%) harbored an advanced adenoma. The researchers concluded that the effect of a single FOBT in protecting against fatal CRC appears to abate after two years or three years for the test. The researchers also noted that the sensitivity rate of the FOBT was twice as high as the findings for adenomas or CRC actually found during colonoscopy. The detection rate for advanced neoplasia was significantly higher following screening by sigmoidoscopy than FOBT.

Cotterchio et al. (2005) conducted a case-control study to evaluate the association between CRC screening and subsequent CRC risk among several thousand participants who were invited to participate in the population-based Ontario Familial Colorectal Cancer Registry (OFCCR). Individuals, ages 20 to 74 with pathology-confirmed CRC that was diagnosed between July 1997 and June 2000, were recruited from this database. A family-history questionnaire was mailed to all participants who agreed to participate in the study. Nine hundred seventy-one cases and 1,944 controls completed questionnaires. Adjusted odds ratios (OR) estimates were determined with multivariate logistic regression analysis. The results included: having had a fecal occult blood screen was associated with reduced CRC risk (OR=0.76; 95% CI: 0.59, 0.97); having had a screening sigmoidoscopy was associated with a halving of CRC risk (OR = 0.52; 95% CI: 0.34, 0.80); having had a screening colonoscopy did not significantly reduce CRC risk (OR = 0.69; 95% CI: 0.44, 1.07). However having had either screening endoscopy was associated with a significant reduction in CRC risk (OR = 0.62; 95% CI: 0.44, 0.87). There was a slight difference noted by anatomic sub-site (e.g., proximal and distal colorectum).

The results of a prospective cohort study of 614 patients was conducted by Rockey and colleagues (2005) that assessed the sensitivity of three imaging tests (i.e., air contrast barium enema [ACBE], CTC, and colonoscopy). The study participants had positive fecal occult blood tests, hematochezia, iron-deficiency anemia, or family history of CRC. All 614 patients completed the three imaging tests (i.e., ACBE, CTC, colonoscopy, respectively), and the outcomes of these tests were then compared. The study participants and the investigators were all blinded to the findings of each imaging study. Analysis on a per-patient basis for lesions 10 mm or larger in size (n=63) were found to be: sensitivity of ACBE was 48% (95% CI 35–61), of CTC 59% (46–71, p=0.1083, for

CTC vs ACBE), and colonoscopy 98% (91–100, $p < 0.0001$ for colonoscopy vs CTC). Analysis for lesions 6–9 mm in size ($n = 116$), the findings were: sensitivity 35% for ACBE (27–45), 51% for CTC (41–60, $p = 0.0080$ for CTC vs ACBE); and 99% for colonoscopy (95–100, $p < 0.0001$ for colonoscopy vs CTC). For lesions of 10 mm or larger in size, the findings were: specificity was greater for colonoscopy (0–996) than for either ACBE (0–90) or CTC (0–96) and decreased for ACBE and CTC when smaller lesions were considered. The researchers concluded that all tests were very specific when large lesions were present. The specificity of ACBE and CTC for lesions of 10 mm or larger was high; for colonoscopy it was greater than that of the other tests. During this study, an older version of software was used to conduct the CTC (i.e., 2-D reads with 3-D problem-solving) and therefore conclusions cannot be drawn whether this enhanced software would provide significant outcome variances.

Systematic reviews/meta-analysis: Sosna, et al. (2008) reported on a meta-analysis that compared the performance of DCBE with CTC for detection of colorectal polyps ≥ 6 mm which used endoscopy as the gold standard. Performance of each procedure was analyzed by separately evaluating each technique's performance along with that of endoscopy and comparing the methods. The study included 11 studies of DCBE (5,995 patients, 1,548 polyps) and 30 studies of CTC (6,573 patients, 2348 polyps). The analysis found that for polyps ≥ 10 mm, a 0.121-per-patient sensitivity difference favored CTC ($p < 0.0001$; DCBE, 0.702 [95% CI, 0.687–0.715]; CTC, 0.823 [0.809–0.836]). Regarding polyps ≥ 10 mm, 0.031-per-polyp sensitivity difference it was found that it favored CTC ($p < 0.0001$; DCBE, 0.715 [0.703–0.726]; CTC, 0.746 [0.735–0.757]). In regards to polyps ≥ 10 mm, a specificity difference of 0.104 favored CTC ($p = 0.001$; DCBE, 0.850 [0.847–0.855]). The analysis also found that DCBE was also less sensitive for 6- to 9-mm polyps ($p < 0.001$). The authors concluded that DCBE has statistically lower sensitivity and specificity than CTC for detecting colorectal polyps ≥ 6 mm.

Rosman and Korsten (2007) conducted a meta-analysis of published studies comparing the accuracies of CTC and colonoscopy for polyp detection. Thirty studies were included in the analysis. Studies were included if all subject undergoing CTC also underwent colonoscopy as a reference standard. In addition the studies were eligible if they reported per-patient sensitivities and specificities for polyp detection. The pooled per-patient sensitivities and specificities were calculated at various thresholds for polyp size and summary receiver operating characteristic (sROC) curves were constructed. The study found the pooled per-patient sensitivity of CTC was higher for polyps greater than 10 mm (0.82, 95% CI, 0.76–0.88) compared with polyps 6–10 mm (0.63, 9% CI, 0.52–0.75) and polyps 0–5 mm (0.56, 95% CI, 0.42–0.70). No difference was found in diagnostic characteristics of two- and three-dimensional CTC. The author concluded that CTC has a reasonable sensitivity and specificity for detecting large polyps but was less accurate than colonoscopy for small polyps.

A systemic review of the literature was conducted by Lindor et al. (2006) to review cancer risks and screening efficacy for individuals with HNPCC. After a review of the available peer-reviewed articles published between January 1996 and February 2006, the authors concluded that evidence supports colonoscopic surveillance, every one to two years beginning at age 20–25, for individuals with HNPCC syndrome, although the optimal age for the initiation of surveillance continues to be studied. Individuals with HNPCC are also at increased risk of developing endometrial cancer and noncolorectal or nonendometrial cancers.

Professional Societies/Organizations

American Cancer Society (ACS)/US Multi-Society Task Force on Colorectal Cancer (USMSTF)/American College of Radiology (ACR): Joint guidelines from these organizations for the screening and surveillance for the early detection of CRC and adenomatous polyps were published in 2008 (Levin, et al., 2008). The USMSTF includes representation from the American College of Gastroenterology (ACG), American Gastroenterological Association (AGA), and American Society for Gastrointestinal Endoscopy (ASGE). The guidelines focus on the needs of screening for average-risk adults. The screening tests for CRC fall into two general categories:

- Stool tests: These tests are appropriate for the detection of cancer, although they may deliver positive findings for some advanced adenomas. Testing options in this group include:
 - Annual guaiac-based FOBT with high test sensitivity for cancer
 - Annual FIT with high test sensitivity for cancer
 - Stool DNA test with high sensitivity for cancer, interval uncertain
- Structural exams: These exams can reach the dual goals of detecting adenocarcinoma as well as identifying adenomatous polyps. Testing options in this group include:
 - Flexible sigmoidoscopy every five years
 - Colonoscopy every ten years
 - DCBE every five years

- CTC every five years

Regarding the noninvasive fecal testing the guidelines make the following comments:

- Collection of fecal samples for blood or DNA testing can be performed at home, without bowel preparation.
- Limitations and requirements of these noninvasive tests include:
 - These tests are less likely to prevent cancer compared with the invasive tests.
 - These tests must be repeated at *regular* intervals to be effective.
 - If the test is abnormal, an invasive test (colonoscopy) will be needed.
- If patients are not willing to have repeated testing or have colonoscopy if the test is abnormal, these programs will not be effective and should not be recommended.

The guidelines note that colon cancer prevention should be the primary goal of CRC screening. The testing that is intended to detect both early cancer and adenomatous polyps should be encouraged if patients are willing to undergo an invasive test. These tests include colonoscopy, sigmoidoscopy, DCBE and CTC. These tests require bowel preparation, an office or hospital visit and involve various levels of risk to patients. In regards to sigmoidoscopy, DCBE, and CTC, if there are significant positive findings a colonoscopy will be required.

American Cancer Society (ACS)/US Multi-Society Task Force on Colorectal Cancer (USMSTF): These two organizations published joint consensus guidelines for colonoscopy surveillance after cancer resection (Rex, et al., 2006; Brooks, et al., 2008). These guidelines include the following:

- Patients with colon and rectal cancer should undergo high quality perioperative clearing. In the case of nonobstructing tumors, this can be done by preoperative colonoscopy. In the case of obstructing colon cancers, CTC with intravenous contrast or double contrast barium enema can be used to detect neoplasms in the proximal colon. In these cases, a colonoscopy to clear the colon of synchronous disease should be considered 3 to 6 months after the resection if no unresectable metastases are found during surgery. Alternatively, colonoscopy can be performed intraoperatively.
- Patients undergoing curative resection for colon or rectal cancer should undergo a colonoscopy 1 year after the resection (or 1 year following the performance of the colonoscopy that was performed to clear the colon of synchronous disease). This colonoscopy at 1 year is in addition to the perioperative colonoscopy for synchronous tumors.
- If the examination performed at 1 year is normal, then the interval before the next subsequent examination should be 3 years. If that colonoscopy is normal, then the interval before the next subsequent examination should be 5 years.
- Following the examination at 1 year, the intervals before subsequent examinations may be shortened if there is evidence of hereditary nonpolyposis CRC or if adenoma findings warrant earlier colonoscopy.
- Periodic examination of the rectum for the purpose of identifying local recurrence usually performed at 3- to 6-month intervals for the first 2 or 3 years, may be considered after low anterior resection of rectal cancer. The techniques utilized are typically rigid proctoscopy, flexible proctoscopy, or rectal endoscopic ultrasound. These examinations are independent of the colonoscopic examinations described above for detection of metachronous disease.

American Cancer Society (ACS)/US Multi-Society Task Force on Colorectal Cancer (USMSTF): These two organizations published joint consensus guidelines for colonoscopy surveillance after polypectomy (Winawer, et al., 2006; Brooks, et al., 2008). These guidelines include the following:

- Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 years. An exception is patients with a hyperplastic polyposis syndrome. They are at increased risk for adenomas and CRC and need to be identified for more intensive follow up.
- Patients with only one or two small (<1 cm) tubular adenomas with only low-grade dysplasia should have their next follow-up colonoscopy in 5 to 10 years. The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician).
- Patients with three to ten adenomas, or any adenoma > 1 cm, or any adenoma with villous features, or high-grade dysplasia should have their next follow-up colonoscopy in three years providing that piecemeal removal has not been done and the adenoma(s) are completely removed. If the follow-up

colonoscopy is normal or shows only one or two small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years.

- Patients who have more than 10 adenomas at one examination should be examined at a shorter (<3 years) interval established by clinical judgment, and the clinician should consider the possibility of an underlying familial syndrome.
- Patients with sessile adenomas that are removed piecemeal should be considered for follow up at short intervals (2 to 6 months) to verify complete removal. Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment. Completeness of removal should be based on both endoscopic and pathologic assessments.
- More intensive surveillance is indicated when the family history may indicate hereditary nonpolyposis CRC.

American Cancer Society (ACS): in addition to the above recommendations for colonoscopy surveillance after polypectomy and colonoscopy surveillance after cancer resection patients, the ACS includes the following screening and surveillance recommendations for increased- and high-risk individuals (ACS, 2009c):

Increased risk—patients with a family history:

- CRC or adenomatous polyps in any first-degree relative before age 60, or in two or more first-degree relatives at any age (if not hereditary syndrome): colonoscopy age at age 40, or 10 years before the youngest case in the immediate family, whichever is earlier
- CRC or adenomatous polyps in any first-degree relative aged 60 or higher, or in at least 2 second-degree relatives at any age: surveillance starting at age 40, with same options and same interval as for those at average risk.

High risk:

- FAP diagnosed by genetic testing or suspected FAP without genetic testing: flexible sigmoidoscopy to look for signs of FAP starting at age 12
- HNPCC, or at increased risk of HNPCC based on family history without genetic testing: start at age 20 to 25 years, or 10 years before the youngest case in immediate family; colonoscopy every one to two years
- Inflammatory bowel disease (i.e., chronic ulcerative colitis, Crohn's disease): colonoscopy every one to two years with biopsies for dysplasia

American College of Gastroenterology (ACG): ACG published guidelines for CRC screening which includes the following recommendations (Rex, et al., 2009):

Preferred CRC screening recommendations:

- Cancer prevention tests should be offered first. The preferred CRC prevention test is colonoscopy every 10 years, beginning at age 50. (Grade 1B*) Screening should begin at age 45 years in African Americans (Grade 2C*)
- Cancer detection test. This test should be offered to patients who decline colonoscopy or another cancer prevention test. The preferred cancer detection test is annual FIT for blood (Grade 1B*)

Alternative CRC prevention tests:

- Flexible sigmoidoscopy every 5–10 years (Grade 2B*)
- CT colonography every 5 years (Grade 1C*)

Alternative cancer detection tests:

- Annual Hemocult Sensa (Grade 1B*)
- Fecal DNA testing every 3 years (Grade 2B*)

Recommendations for screening when family history is positive but evaluation for HNPCC considered not indicated:

- Single first-degree relative with CRC or advanced adenoma diagnosed at age \geq 60 years—recommended screening: same as average risk (Grade 2B*)
- Single first-degree with CRC or advanced adenoma diagnosed at age < 60 years or two first-degree relatives with CRC or advanced adenomas—recommended screening: colonoscopy every 5 years beginning at age 40 years or 10 years younger than age at diagnosis of the youngest affected relative (Grade 2B*)

FAP:

- Patients with known FAP or who are at risk of FAP based on family history (and genetic testing has not been performed) should undergo annual flexible sigmoidoscopy or colonoscopy, as appropriate, until such time as colectomy is deemed by physician and patient as the best treatment (Grade 2B*)
- Patients with retained rectum after subtotal colectomy should undergo flexible sigmoidoscopy every 6–12 months (Grade 2B*)

HNPCC:

- Those with positive genetic testing, or those at risk when genetic testing is unsuccessful in an affected proband, should undergo colonoscopy every 2 years beginning at age 20 – 25 years, until age 40 years, then annually thereafter (Grade 2B*)

*Grading recommendations

1A: Strong recommendation, high-quality evidence

1B: Strong recommendation, moderate quality evidence

1C: Strong recommendation, low-quality or very low-quality evidence

2A: Weak recommendation, high-quality evidence

2B: Weak recommendation, moderate quality evidence

2C: Weak recommendation, low-quality or very low-quality evidence

American Society of Clinical Oncology (ASCO): ASCO recommends additional surveillance for follow-up after primary therapy for stage II and III CRC based on the outcomes of three meta-analyses reviewed from 1999 to 2005 (Desch, et al., 2005). The ASCO panel surveillance guidelines include the following:

- Computed tomography (CT) — annual of the chest and abdomen for three years after primary therapy for patients who are at higher risk of recurrence and who could be candidates for surgery with curative intent.
- Pelvic CT —should be considered for rectal cancer surveillance, especially for patients who have not been treated with radiation.
- Colonoscopy —at three years after operative treatment; if results normal, every five years thereafter
- Flexible proctosigmoidoscopy —every six months for five years for rectal cancer patients who have not been treated with radiation

Institute for Clinical Systems Improvement (ICSI): ICSI (2008a) published updated guidance for the screening of CRC, based on a review of the current literature. CRC screening is recommended for average-risk patients 50 years of age and older, age 45 and older for African Americans, using one of the following methods, based on joint decision-making by patient and provider:

- Stool testing:
 - Guaiac-based fecal occult blood testing (gFOBT) annually
 - Fecal immunochemical testing (FIT) annually
 - Stool DNA testing (sDNA) interval unknown
- 60 cm flexible sigmoidoscopy every five years with or without stool test for occult blood annually
- Double-contrast barium enema every five years
- CT colonography every five years
- Colonoscopy every 10 years

National Comprehensive Cancer Network® (NCCN®): The NCCN Colorectal Cancer Screening Clinical Practice Guidelines™ include recommendations for screening and surveillance (NCCN, 2010). Average-risk individual, age 50 or greater, with no personal history of adenoma or inflammatory bowel disease and a negative family history should have screening with one of these modalities:

- Guaiac-based or immunohistochemical-based testing annually.
- Flexible sigmoidoscopy (60 centimeter scope or longer)—every five years
- Colonoscopy—every 10 years. Available evidence suggests that colonoscopy may be the preferred method.

The guidelines include the following:

- Stool DNA test—it has been shown that there is increasing evidence as a reasonably accurate screening test but there are limited data to determine an interval between screening. At present, this testing is not considered a first line screening test except in specific circumstances.

- Other screening modalities such as DCBE should be reserved for those who are not able to undergo colonoscopy or have incomplete colonoscopy.
- Regarding CTC, it is noted that currently there is not consensus on the use of CTC as a primary screening modality and it is evolving with regards to recommended/programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra-colonic lesions. The available data suggests, that if CTC is negative with no polyps, then CTC should be repeated in five years and if positive/polyps, colonoscopy should be performed.

Increased-risk individual with personal history of adenoma(s)/sessile serrated polyp(s)(SSP) found at colonoscopy:

- Low risk adenoma (≤ 2 polyps, <1 cm, tubular)—repeat colonoscopy within five years. If normal, then repeat every five to ten years. If abnormal, repeat depending on endoscopic and pathologic findings.
- Advanced or multiple adenomas (high-grade dysplasia/carcinoma in situ, larger than 1 cm, villous ($>25\%$ villous), between three and ten polyps—repeat colonoscopy within three years. If normal, then repeat within five years. If abnormal, repeat depending on endoscopic and pathologic findings.

Increased-risk individual with personal history:

- Following curative intent resected CRC: follow-up with a colonoscopy after one year, (within three to six months if there was no or an incomplete preoperative colonoscopy):
 - Normal surgical pathology results: repeat colonoscopy in two to three years, then repeat colonoscopy in every three to five years based on findings
 - Adenoma/SSP findings: repeat colonoscopy in one to three years

Increased-risk Individual with personal history of inflammatory bowel disease (i.e., ulcerative colitis, Crohn's disease)—initiation of screening eight to 10 years after onset of symptoms and then colonoscopy performed every one to two years.

Increased/high-risk screening based on positive family history:

- Positive family history of CRC:
 - For individuals with a first-degree relative (i.e., full sibling, parent, child) age 50-60 years with CRC, or first-degree relative with CRC prior to age 60, or two related second-degree relatives with CRC at any age—colonoscopy should begin at age 40 and repeat colonoscopy every five years.
 - Individuals with a first-degree relative with CRC prior to age 50, or two related first-degree relatives with CRC at any age—colonoscopy should begin at age 40 or 10 years before the earliest diagnosis of CRC and repeat every three to five years.
 - Individuals with one second-degree relative or any third-degree relative(s) with CRC—screen as an average-risk individual beginning at age 50.
 - First-degree relatives with advanced adenoma may present the same risk as first-degree relatives with CRC, and any adenoma under age 40 may present a similar risk to CRC under age 50.
- Personal or inherited risk of polyposis syndromes:
 - Family history of familial adenomatous polyposis (FAP):
 - Individual is a genetic carrier:
 - annual flexible sigmoidoscopy or colonoscopy, beginning at age 10 to 15
 - Genetic status is unknown:
 - annual flexible sigmoidoscopy or colonoscopy, beginning at age 10 to 15, until age 24 then:
 - repeat every two years until age 34
 - repeat every three years until age 44
 - then every three to five years thereafter
 - Individual is not a carrier: average-risk screening should occur
 - Family history of attenuated FAP:
 - Individual is a genetic carrier:
 - annual colonoscopy beginning in late teens, then every two to three years
 - Genetic status is unknown:
 - colonoscopy every two to three years beginning in late teens, if negative and if adenomas are found, annual colonoscopy

- Individual is not a carrier: average-risk screening should occur
- Family history of hereditary nonpolyposis CRC (HNPCC):
 - Individual is a genetic carrier:
 - colonoscopy every one to two years, beginning at age 20 to 25, or 10 years younger than the earliest recorded case in the family, whichever occurs first
 - Genetic status is unknown:
 - colonoscopy every one to two years, beginning at age 20 to 25, or 10 years younger than the earliest recorded case in the family, whichever occurs first. Repeat every one to two years.
 - Individual is not a carrier: average-risk screening should occur
- Family history of sibling with MYH polyposis:
 - Individual is a known genetic carrier of the MYH mutation:
 - colonoscopy and polypectomy every one to two years
 - Individual is asymptomatic and the sibling has known MYH polyposis:
 - colonoscopy every three to five years, beginning at age 25–30, if negative (consider shorter intervals with advancing age).

National Institute for Health and Clinical Excellence (NICE): NICE (2005) conducted a review of the literature and published recommended indications for use of CTC. The authors stated that conventional colonoscopy and double-contrast barium enema are the main methods currently used for examining the colon. They also indicate that CTC may be used:

- for the examination of the colon and rectum to detect abnormalities such as polyps and cancer
- in asymptomatic patients with a high risk of developing CRC.
- as an alternative procedure to barium enema in frail and elderly patients as a diagnostic tool to detect tumors.

U.S. Preventive Services Task Force (USPSTF): The USPSTF published updated evidenced-based recommendations for screening for colorectal cancer (USPTF, 2008, Whitlock, et al., 2008). The recommendations include the following findings:

- For fecal occult blood testing, flexible sigmoidoscopy, and colonoscopy to screen for colorectal cancer, there is high certainty that the net benefit is substantial for adults age 50 to 75 years.
- For adults, age 76 to 85 years, there is moderate certainty that the net benefits of screening are small.
- For adults older than age 85 years, there is moderate certainty that the benefits of screening do not outweigh the harms.
- There is insufficient evidence to assess the sensitivity and specificity of fecal DNA testing for colorectal neoplasia, and that therefore the balance of benefits and harms cannot be determined for this test.
- For CTC, evidence to assess the harms related to extracolonic findings is insufficient, and the balance of benefits and harms cannot be determined.

In Vivo Analysis of Colorectal Polyps

Several technologies of in vivo analysis of polyps are being researched for the purpose of improving the analysis of lesions and detection of changes in walls of colon. These methods are intended to be used as an adjunct to endoscopic procedures. These methods include fiberoptic analysis, narrow band imaging (NBI) and confocal endomicroscopy. A conventional colonoscopy utilizes white light which has a limited ability to distinguish between benign or neoplastic lesion during the procedure. During a colonoscopy, the standard procedure is to remove all visualized lesions and submit these to histopathology. It is proposed that these technologies may allow for in vivo analysis of the polyps, possibly avoiding unnecessary biopsies and increasing detection of difficult to visualize lesions (e.g., flat lesions). Some of the devices are also utilized during other endoscopic procedures including gastroscopy.

Fiberoptic analysis has been proposed to assist the physician in determining if potential cancerous changes are present within the colon. Positive findings would be suggestive of the need for potential biopsy of the area. The WavSTAT™ Optical Biopsy System (SpectraScience™, Minneapolis, MN) contains a laser, electronic components that collect the emitted fluorescent signals, and a computer that operates the system and analyzes the tissue. The device is intended for the evaluation of polyps that are less than one centimeter that the

physician has not already elected to remove. Use of this device is only to assist in deciding whether such polyps should be removed and submitted for histological examination. It is intended to be used as an adjunct during a sigmoidoscopy or colonoscopy.

Narrow band imaging (NBI) utilizes short wavelength (essentially blue) endoscopic light which penetrates the mucosa only superficially and is mainly absorbed by hemoglobin—this will highlight mucosal surface patterns and microvascular details. It is theorized that this will improve the detection of small and subtle mucosal lesions. It is also thought that there is potential for endoscopic differentiation of lesions with use of NBI, which would enable on-table decisions to be made (van den Brock, et al., 2009). Olympus EVIS EXERA II™ (Olympus, Tokyo, Japan; Center Valley, PA) is NBI device that is used with colonoscope as well as other endoscopy devices.

Confocal fluorescent endomicroscopy, or confocal laser endomicroscopy is based on tissue illumination with a low-power laser with subsequent detection of the fluorescence light reflected from the tissue through a pinhole (ASGE, 2009). Confocal refers to the alignment of both illumination and collections systems in the same focal plane. Confocal endomicroscopy based on tissue fluorescence uses a local and/or intravenous contrast agent and generates a high-quality image that may be comparable with traditional histological examination. Cellvizio® (Mauna Kea Technologies, Newtown, PA) is a probe-based Confocal Laser Endomicroscopy (pCLE) device that is compatible with flexible video-endoscopes. According to the vendor website the device can magnify a polyp by a factor of 1,000 which may assist a physician in detecting cellular-level features that differentiate adenomatous from non-adenomatous colorectal polyps during the colonoscopy procedure in real time.

U.S. Food and Drug Administration (FDA)—In Vivo Analysis of Colorectal Polyps

The Optical Biopsy System received premarket approval (PMA) as a Class III device from the FDA in November 2000. In 2001 the name was changed to WavStat Optical Biopsy System.

The Olympus EVIS EXERA II device received FDA approval as a class II device through the 510 (k) process in 2006.

Confocal Laser Endomicroscopy received FDA approval as a class II device through the 510 (k) approval process in 2006.

Literature review—In Vivo Analysis of Colorectal Polyps:

Fiberoptic Polyp Analysis: A prospective, non-randomized, multicenter study was conducted by SpectraScience regarding the Optical Biopsy System. Results of this study were not published but were available to the FDA for their review. One hundred and one patients underwent a colonoscopy that included the use of this device in comparing polyps that a physician would determine should be removed versus those detected through the use of the “spectral measures.” The physician was blinded to the spectral measures that were taken during this study, and a total of 135 specimens were elevated by two pathologists who were also blinded to the “spectral measures.” The researchers reported the device sensitivity and specificity as 79.0 and 55.6%, respectively. The physician’s visual assessment was measured as having 82.7% sensitivity and 50% specificity. When the results were combined, the sensitivity rose to 96.3% with a specificity of 33.3%. The researchers reported that the outcomes obtained through the combination of colonoscopy and OBS were statistically significant. It is unclear how the use of this device during a colonoscopy would improve patient health outcomes, if a polyp is not removed and submitted for histological analysis, the potential increases for precancerous lesions to go undetected, and an actual increase in CRC to occur.

Confocal fluorescent endomicroscopy: Buchner, et al. (2009) conducted a study with the aim to compare sensitivity and specificity of probe-based confocal laser endomicroscopy (pCLE) to virtual chromoendoscopy for classification of colorectal polyps using histopathology as a gold standard. Colonoscopy was performed with high-resolution colonoscopies, then the surface pit pattern was determined with narrow band imaging (NBI) or Fujinon intelligent color enhancement (FICE) in all patients. The confocal images were recorded and subsequently analyzed offline, while blinded to the endoscopic characteristics and histopathology. Polyps were diagnosed as benign or neoplastic based on confocal features according to modified Mainz criteria. A total of 119 polyps (81 neoplastic, 38 hyperplastic) from 75 patients was considered. The pCLE was found to have higher sensitivity compared to virtual chromoendoscopy when considering histopathology as gold standard (91% vs 77%; p=.010) and modified gold standard (88% vs 76%; p=.037). No statistically significant difference

in specificity was noted between pCLE and virtual chromoendoscopy when considering histopathology or modified gold standard.

Narrow Band Imaging (NBI): There have been several published studies that compare the use of NBI with white light colonoscopy. The studies have reported variable and at times conflicting results regarding detection of adenomas with NBI.

Adler et al. (2009) conducted prospective, randomized, multicenter trial of 1256 patients. The patients were randomized to screening colonoscopy with either NBI or white-light imaging on instrument withdrawal. The primary outcome measurement was the adenoma detection rate. The study found no difference between the two groups in terms of the general adenoma detection rate (0.32 vs 0.34); the total number of adenomas (200 vs 216), or in the detection in subgroups of adenomas. These findings were in light of a minimal, but significantly longer, withdrawal time in the NBI group (8.5 vs 7.9 min; $p < .05$). Hyperplastic polyps were found more frequently in the NBI group ($p = .03$).

Ignjatovic et al. (2009) reported on a prospective, cohort study that aimed to assess whether diagnosis of small polyps with non-magnifying NBI is feasible and safe in routine clinical practice (DISCARD trial). The study included 130 patients referred for surveillance colonoscopy or who had positive fecal occult blood testing. Polyp histology using optical diagnosis with high definition white light was predicted, followed by narrow-band imaging without magnification and chromoendoscopy. The primary outcome was accuracy of polyp characterization using optical diagnosis compared with histopathology, the current gold standard. There were 278 polyps smaller than 10mm that had both optical and histopathological diagnosis. With histology—198 of these polyps were adenomas and 80 were non-neoplastic lesions (62 hyperplastic). Optical diagnosis accurately diagnosed 186 of 198 adenomas (sensitivity 0.94; 95% CI 0.90–0.97) and 55 of 62 hyperplastic polyps (specificity 0.89; 0.78–0.95), with an overall accuracy of 241 of 260 for polyp characterization. Using optical diagnosis alone, 82 of 130 patients could be given a surveillance interval immediately after colonoscopy, and the same interval was found after formal histopathology in 80 patients (98%) using British guidelines and in 78 patients (95%) using US multisociety guidelines.

Adler et al (2008) conducted a prospective study of 401 patients who were randomly assigned to undergo wide-angle colonoscopy using either conventional imaging or NBI during instrument withdrawal. The primary outcome measurement was the difference between adenoma detection rate with the two techniques. The study found more frequent detection of adenomas in the NBI group (23%) than in the control group (17%) with the difference found not to be statistically significant ($p = 0.129$). The two techniques were then compared in consecutive subgroups of 100 study patients—adenoma rates in the NBI group remained fairly stable, whereas these rates steadily increased in the control group (8%, 15%, 17%, and 26.5%, respectively). The significant differences in the first 100 cases (26.5% versus 8%; $p = 0.02$) were not maintained in the last 100 cases (25.5% versus 26.5%, $p = 0.91$). It was theorized by the authors that the increase might be the result of a form of learning effect resulting from the NBI contrast-enhancement technique.

Rex et al (2007) reported on a randomized controlled trial comparing colonoscopy withdrawal in white light with NBI in 434 patients. It was found that there was no difference in the percent of patients with ≥ 1 adenoma for the entire cohort in white light (67%) versus NBI (65%) ($p = .61$) or in the subset of 257 patients with indication screening (58% vs 57%; $p = .91$). The authors report that the prevalence of adenomas and the numbers of adenomas per colonoscopy are the highest ever reported in colonoscopy studies—the high prevalence rates of adenomas were accounted for by detection of large numbers of adenomas, including flat adenomas, which were ≤ 5 mm.

Professional Societies/Organizations—In Vivo Analysis of Colorectal Polyps

In joint consensus guidelines for colonoscopy surveillance after polypectomy, the American Cancer Society (ACS)/US Multi-Society Task Force on Colorectal Cancer (USMSTF) note that the application of evolving technologies such as chromoendoscopy, magnification endoscopy, narrow-band imaging are not yet established for postpolypectomy surveillance (Winawer, et al., 2006; Brooks, et al., 2008).

American Society for Gastrointestinal Endoscopy (ASGE) published a technology status evaluation report regarding narrow band imaging (NBI). In the report, it is noted that NBI may enhance the diagnosis and characterization of mucosal lesions in the GI tract, in particular as an adjunct to magnification endoscopy; however, standardization of image characterization, further image pathology correlation and validation, and the

impact of these technologies on patient outcomes are necessary before endorsing the use of NBI in the routine practice of gastrointestinal endoscopic procedures (ASGE, 2008).

The ASGE published a report on emerging technology regarding confocal laser endomicroscopy (ASGE, 2009). The report notes that this method is an examiner-dependent technology and the interobserver and intraobserver variability of the technique has not been adequately studied. The review notes that, "In recent years, confocal laser endomicroscopy rapidly moved from the bench to the bedside. It is being analyzed as a potentially valuable addition to conventional endoscopy as a means of in vivo optical biopsy enabling real-time histological examination of the superficial layer of the GI tract. How this will affect the practice of screening, surveillance, and early diagnosis of benign, premalignant, and malignant lesions of the GI tract requires further study."

Summary for In Vivo Analysis of Colorectal Polyps: Due to insufficient published studies involving these technologies within the peer-reviewed published literature, the use as an adjunct to colonoscopy remains unproven. Due to the lack of supporting evidence within the published, peer-reviewed literature, use of these technologies as an adjunct to colonoscopy remains unproven.

Summary

Detection and removal of polyps through colorectal cancer (CRC) screening provides an opportunity to reduce the occurrence of CRC. In addition, early detection of CRC can provide an opportunity for reducing the case fatality rate of those individuals with previously undetected CRC. The American Cancer Society (ACS), American College of Gastroenterology (ACG), American Society of Colorectal Surgeons (ASCR), American Society for Gastrointestinal Endoscopy (ASGE), National Cancer Institute (NCI), National Comprehensive Cancer Network (NCCN) and the U.S. Preventative Services Task Force (USPSTF), and the US Multi-Society Task Force on Colorectal Cancer all support age- and risk-appropriate population screening for the early detection of CRC. The literature and patient morbidity and mortality measures support the ongoing use of preventative screening, early diagnosis and close surveillance of individuals for CRC.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®*	Description
45330	Sigmoidoscopy, flexible; diagnostic, with or without collection of specimen(s) by brushing or washing
45331	Sigmoidoscopy, flexible with biopsy, single or multiple
45338	Sigmoidoscopy, flexible with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
45339	Sigmoidoscopy, flexible with ablation of tumor(s), polyp(s), or other lesions(s) not amenable to removal by hot forceps, bipolar cautery or snare technique
45378	Colonoscopy, flexible, proximal to splenic flexure; diagnostic, with or without collection of specimen(s) by brushing or washing, with or without colon decompression (separate procedure)
45380	Colonoscopy, flexible, proximal to splenic flexure; with biopsy, single or multiple
45383	Colonoscopy, flexible, proximal to splenic flexure; with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
45384	Colonoscopy, flexible, proximal to splenic flexure; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps or bipolar cautery
45385	Colonoscopy, flexible, proximal to splenic flexure; with removal of tumor(s), polyp(s), or other lesion(s) by snare technique
74263	Computed tomographic (CT) colonography, screening including image postprocessing
74270	Radiologic examination, colon; barium enema, with or without KUB

74280	Radiologic examination, colon; air contrast with specific high density barium, with or without glucagon
82270	Blood, occult, by peroxidase activity (eg, guaiac), qualitative; feces 1-3 simultaneous determinations
82274	Blood, occult, by fecal hemoglobin determination by immunoassay. Qualitative, feces, 1-3 simultaneous determinations
83890	Molecular diagnostics; molecular isolation or extraction
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid
83892	Molecular diagnostics; enzymatic digestion
83893	Molecular diagnostics; dot/slot blot production
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide)
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (eg: Southern, Northern)
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first two nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (list separately in addition to code for primary procedure)
83902	Molecular diagnostics; reverse transcription
83903	Molecular diagnostics; mutation scanning, by physical properties (e.g.; single strand conformational polymorphisms (SSCP), heteroduplex, denaturing gradient gel electrophoresis (DGGE), RNA's ase A), single segment, each
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83905	Molecular diagnostics; mutation identification by allele specific transcription single segment, each segment
83906	Molecular diagnostics; mutation identification by allele specific translation, single segment, each segment
83907	Molecular diagnostics; lysis of cells, prior to nucleic acid extraction (e.g.; stool specimens), paraffin embedded tissue)
83908	Molecular diagnostics; amplification, signal, each nucleic acid sequence
83909	Molecular diagnostics; separation and identification by high resolution technique (e.g.; capillary electrophoresis)
83912	Molecular diagnostics; interpretation and report
0066T	CT colonography (i.e., virtual colonoscopy); screening (code deleted 12/31/2009)

HCPCS Codes	Description
G0104	Colorectal cancer screening; flexible sigmoidoscopy
G0105	Colorectal cancer screening; colonoscopy on individual at high risk
G0106	Colorectal cancer screening; alternative to G0104, screening sigmoidoscopy, barium enema
G0120	Colorectal cancer screening; alternative to G0105, screening colonoscopy, barium enema
G0121	Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk
G0122	Colorectal cancer screening; barium enema
G0328	Colorectal cancer screening; fecal-occult blood test, immunoassay, 1-3 simultaneous determinations
S3890	DNA analysis, fecal, for colorectal cancer screening

ICD-9-CM Diagnosis Codes	Description

153.0	Malignant neoplasm of the colon, hepatic flexure
153.1	Malignant neoplasm of the colon, transverse
153.2	Malignant neoplasm of the colon, descending left
153.3	Malignant neoplasm of the sigmoid colon
153.4	Malignant neoplasm of the cecum
153.6	Malignant neoplasm of the ascending colon, right
153.7	Malignant neoplasm of the splenic flexure
153.8	Other specified sites of large intestine, contiguous or overlapping-point of origin unknown
153.9	Primary neoplasm of the colon
154.0	Malignant neoplasm of the rectosigmoid junction, primary
154.1	Malignant neoplasm of the rectum,
154.2	Malignant neoplasm of the anal canal
154.3	Malignant neoplasm of the anus, unspecified
154.8	Malignant neoplasm of rectum, contiguous or overlapping-point of origin unknown
197.5	Malignant neoplasm of the large intestine and rectum, secondary
198.6	Secondary malignant neoplasm of ovary
211.3	Benign neoplasm of colon
211.4	Benign neoplasm of rectum and anal canal
230.3	Carcinoma in situ of colon
555.1	Regional enteritis of large intestine
555.9	Regional enteritis of unspecified site
556.0 – 556.9	Ulcerative colitis
569.0	Anal and rectal polyp
V10.0	Personal history of malignant neoplasm of unspecified site in gastrointestinal tract
V10.05	Personal history of malignant neoplasm of large intestine
V10.06	Personal history of malignant neoplasm of rectum, rectosigmoid junction, and anus
V12.72	Personal history of colonic polyps
V16.0	Family history of malignant neoplasm of gastrointestinal tract
V18.51	Family history, Colonic polyps
V76.41	Screening for malignant neoplasm of the rectum
V76.50	Special screening for malignant neoplasms, intestine, unspecified
V76.51	Special screening for malignant neoplasm, colon

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	6/15/2008	0148	Colorectal Cancer Screening and Surveillance
Great-West Healthcare	1/23/2007 1/23/2008	05.276.03 04.211.03	Preventive Care Guidelines Fecal DNA Testing (PreGen-Plus™) for Colorectal Cancer Screening

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.