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Colonoscopy and Colorectal Cancer Screening

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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06/23/2025
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Definitions

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Scope of Policy

This Clinical Policy Bulletin addresses colonoscopy and colorectal cancer screening.

I. Medical Necessity

A. *Routine Screening*

Aetna considers *any* of the following colorectal cancer screening tests medically necessary preventive services for average-risk members aged 45 years and older when these tests are recommended by their physician:

1. Colonoscopy (considered medically necessary every 10 years for persons at average risk); *or*
2. CT Colonography (virtual colonoscopy) (considered medically necessary every 5 years); *or*
3. Double contrast barium enema (DCBE) (considered medically necessary every 5 years for persons at average risk); *or*
4. Immunohistochemical or guaiac-based fecal occult blood testing (FOBT) (considered medically necessary every year for persons at average risk); *or*
5. Sigmoidoscopy (considered medically necessary every 5 years for persons at average risk); *or*
6. Sigmoidoscopy (every 5 years) with annual immunohistochemical or guaiac-based fecal occult blood testing (FOBT); *or*
7. Stool DNA (FIT-DNA, Cologuard, Cologuard Plus) (considered medically necessary every 1 to 3 years).

Routine colorectal cancer screening for members 85 years of age or older is considered not medically necessary unless life expectancy is greater than or equal to 10 years.

Note: The U.S. Preventive Services Task Force (USPSTF) guidelines apply to routine screening. The USPSTF guidelines have no A or B recommendations for high-risk screening. The USPSTF guidelines explain: “This recommendation applies to asymptomatic adults 50 years and older who are at average risk of colorectal cancer and who do not have a family history of known genetic disorders that predispose them to a high lifetime risk of colorectal cancer (such as Lynch syndrome or familial adenomatous polyposis), a personal history of inflammatory bowel disease, a previous adenomatous polyp, or previous colorectal cancer. When screening results in the diagnosis of colorectal adenomas or cancer, patients are

followed up with a surveillance regimen, and recommendations for screening no longer apply. The USPSTF did not review or consider the evidence on the effectiveness of any particular surveillance regimen after diagnosis and removal of adenomatous polyps or colorectal cancer."

B. *High-Risk Testing*

Aetna considers colorectal cancer testing with sigmoidoscopy, DCBE, or colonoscopy as frequently as every 2 years medically necessary for members with *any* of the following risk factors for colorectal cancer:

1. A first-degree relative (sibling, parent, child) who has had colorectal cancer or adenomatous polyps (screening is considered medically necessary beginning at age 40 years, or 10 years younger than the earliest diagnosis in their family, whichever comes first); *or*
2. Family history of familial adenomatous polyposis (screening is considered medically necessary beginning at puberty); *or*
3. Family history of hereditary non-polyposis colorectal cancer (HNPCC) (screening is considered medically necessary beginning at age 20 years); *or*
4. Family history of MYH-associated polyposis in siblings (screening is considered medically necessary beginning at age 25 years); *or*
5. Diagnosis of Cowden syndrome (screening is considered medically necessary beginning at age 35 years).

Aetna considers annual FOBT, alone or in conjunction with sigmoidoscopy, medically necessary for testing of members with any of the above risk factors for colorectal cancer.

C. *Surveillance*

Aetna considers colorectal cancer surveillance with colonoscopy, flexible sigmoidoscopy or DCBE medically necessary as frequently as every year for members who meet *any* of the following criteria:

1. Member has inflammatory bowel disease (including ulcerative colitis or Crohn's disease) (colorectal cancer surveillance is considered medically necessary as frequently as every year); *or*
2. Personal history of adenomatous polyps (surveillance is considered medically necessary as frequently as every 2 years); *or*
3. Personal history of colorectal cancer (surveillance is considered medically necessary as frequently as every year).

Aetna considers annual FOBT, alone or in conjunction with sigmoidoscopy, medically necessary for surveillance of colorectal cancer.

Note: Providers may be required to submit photographs of mucosal abnormalities seen on colonoscopy.

D. *Diagnostic Testing*

Aetna considers diagnostic testing with fecal occult blood testing (FOBT), colonoscopy, sigmoidoscopy and/or double contrast barium enema (DCBE) medically necessary for evaluation of members with signs or symptoms of colorectal cancer or other gastrointestinal diseases. For diagnostic esophagogastroduodenoscopy (EGD)/upper endoscopy, see CPB 0738 - Upper Gastrointestinal Endoscopy and Gastrointestinal Biopsy (../700_799/0738.html).

E. *Biopsy of the Lower Gastro-Intestinal Tract*

Aetna considers biopsy of the lower gastro-intestinal tract medically necessary for the following indications:

1. Microscopic colitis - 8 or more biopsies are considered medically necessary in persons with symptoms suggestive of microscopic colitis (e.g., diarrhea and/or functional abdominal pain) (2 or more from the ascending, transverse, descending, and sigmoid colon);

2. Inflammatory bowel disease, diagnosis - 2 or more biopsies from 5 different locations, including the ileum and rectum;
3. Inflammatory bowel disease, screening for dysplasia - targeted biopsies, plus:

    a. Pancolitis - biopsies from the 4 quadrants each 10 cm;
    b. Segmental colitis - biopsies from the 4 quadrants each 10 cm limited to involved areas in previous examinations;

4. Pouchitis - multiple biopsies from the pouch and afferent loop;
5. Colonic polyps - biopsies of polyps that cannot be removed;
6. Acute graft-versus-host disease:

    a. Flexible sigmoidoscopy - 4 or more biopsies from the rectum/sigmoid and 4 or more biopsies from the left colon;
    b. Ileocolonoscopy - 4 or more biopsies from the terminal ileum, ascending colon, transverse colon, descending colon, and rectum/sigmoid colon.

II. **Experimental, Investigational, or Unproven**

A. *Colorectal Cancer Screening*

Aetna considers colorectal cancer screening with any of the following experimental, investigational, or unproven because the effectiveness of these approaches has not been established:

- Artificial intelligence-aided colonoscopy (including computer-aided colonoscopy)
- Blood-based protein biomarkers (e.g., BeScreened-CRC, Beacon Biomedical, Inc.)
- Capsule endoscopy
- CD3 immuno-staining
- Chromoendoscopy or narrow-band imaging optical colonoscopy

- Colon AiQ
- Fecal volatile organic compounds
- Full-spectrum endoscopy (FUSE) colonoscopy
- Guardant Shield Test
- Methylated Septin 9 (ColoVantage, Epi proColon)
- MicroRNAs
- Performance of multiple screening strategies simultaneously in the same individual (e.g., virtual colonoscopy screening every 5 years plus stool DNA testing every 3 years)
- Plasma/serum biomarkers (C-reactive protein, complement C3a anaphylatoxin, plasma GATA5 and SFRP2 methylation, serum CD26 (sCD26), serum matrix metalloproteinase-7 (MMP-7), and tissue inhibitor of metalloproteinases (TIMP-1))
- PolypDx (Atlantic DiagnosticLaboratories, LLC, Metabolomic Technologies Inc.)
- Screening beginning at earlier than standard recommended ages for persons at increased risk due to smoking or obesity
- SimpliPro Colon Test
- Stool-based protein biomarkers
- Stool molecular genetic tests other than Cologuard (e.g., ColoCaller Test, ColoSense multi-target stool RNA test, ColoSure, PreGen-Plus)
- Whole-blood DNA methylation markers.

B. *Anal Pap Smear*

Aetna considers screening for anal cytological abnormalities (anal Pap smear) or for anal human papilloma virus (HPV) infection experimental, investigational, or unproven because of the lack of evidence that such screening improves clinical outcomes.

C. *Drug-Coated Balloon*

Aetna considers drug-coated balloon experimental, investigational, or unproven for the treatment of colonic strictures because the effectiveness of this approach has not been established.

III. Related Policies

- CPB 0140 - Genetic Testing (../100_199/0140.html)
- CPB 0352 - Tumor Markers (../300_399/0352.html)
- CPB 0535 - Virtual Gastrointestinal Endoscopy (0535.html)
- CPB 0588 - Capsule Endoscopy (0588.html)
- CPB 0717 - Analysis of Volatile Organic Compounds (../700_799/0717.html)
- CPB 0738 - Upper Gastrointestinal Endoscopy and Gastrointestinal Biopsy (../700-799/0738.html)
- CPB 0783 - In Vivo Analysis of Colorectal Polyps and Crohn's Disease (../700-799/0783.html)

CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
44388 – 44393, 44401 - 44408	Colonoscopy through stoma
45330 - 45350	Sigmoidoscopy, flexible
45378-45393, 45398	Colonoscopy, flexible
74263	Computed tomographic (CT) colonography, screening, including image postprocessing
74270	Radiologic examination, colon; contrast (eg, barium) enema, with or without KUB
74280	air contrast with specific high density barium, with or without glucagon

Code	Code Description
81528	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result
82270	Blood, occult by peroxidase activity (eg, guaiac), qualitative; feces, consecutive collected specimens with single determination, for colorectal neoplasm screening (ie, patient was provided 3 cards or single triple card for consecutive collection)
82272	Blood, occult, by peroxidase activity (eg, guaiac), qualitative, feces, 1 - 3 simultaneous determinations, performed for other than colorectal neoplasm screening
82274	Blood, occult, by fecal hemoglobin determination by immunoassay, qualitative, feces, 1-3 simultaneous determinations
CPT codes not covered for indications listed in the CPB:	
Full-spectrum endoscopy (FUSE) colonoscopy and stool - based protein biomarker, SimpliPro Colon Test and CD3 immuno-staining, analysis of fecal volatile organic compound, ColoCaller Test, Guardant Shield Test - no specific code	
0002U	Oncology (colorectal), quantitative assessment of three urine metabolites (ascorbic acid, succinic acid and carnitine) by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using multiple reaction monitoring acquisition, algorithm reported as likelihood of adenomatous polyps
0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas

Code	Code Description
0261U	Oncology (colorectal cancer), image analysis with artificial intelligence assessment of 4 histologic and immunohistochemical features (CD3 and CD8 within tumor-stroma border and tumor core), tissue, reported as immune response and recurrence-risk score
0421U	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 8 RNA markers (GAPDH, SMAD4, ACY1, AREG, CDH1, KRAS, TNFRSF10B, EGLN2) and fecal hemoglobin, algorithm reported as a positive or negative for colorectal cancer risk
0453U	Oncology (colorectal cancer), cell- free DNA (cfDNA), methylation- based quantitative PCR assay (SEPTIN9, IKZF1, BCAT1, Septin9-2, VAV3, BCAN), plasma, reported as presence or absence of circulating tumor DNA (ctDNA)
0537U	Oncology (colorectal cancer), analysis of cell-free DNA for epigenomic patterns, next-generation sequencing, >2500 differentially methylated regions (DMRs), plasma, algorithm reported as positive or negative
81327	SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis
86140 - 86141	C-reactive protein
87623	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), low-risk types (eg, 6, 11, 42, 43, 44)
87624	Human Papillomavirus (HPV), high-risk types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
87625	Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed
91113	Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy), colon, with interpretation and report
Other CPT codes related to the CPB:	
81201 - 81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis

Code	Code Description
81292 - 81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis
81295 - 81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis
81298 - 81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis
81317 - 81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis
88271 - 88275	Molecular cytogenetics
HCPCS codes covered if selection criteria are met:	
C9901	Endoscopic defect closure within the entire gastrointestinal tract, including upper endoscopy (including diagnostic, if performed) or colonoscopy (including diagnostic, if performed), with all system and tissue anchoring components
G0104	Colorectal cancer screening; flexible sigmoidoscopy
G0105	Colorectal cancer screening; colonoscopy on individual at high risk
G0121	Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk
S0285	Colonoscopy consultation performed prior to a screening colonoscopy procedure
HCPCS codes not covered for indications listed in the CPB:	
G0327	Colorectal cancer screening; blood-based biomarker
G0464	Colorectal cancer screening; stool-based DNA and fecal occult hemoglobin (e.g., KRAS, NDRG4 and BMP3)
G0476	Infectious agent detection by nucleic acid (DNA or RNA); human papillomavirus HPV), high-risk types (e.g., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) for cervical cancer screening, must be performed in addition to pap test

Code	Code Description
Other HCPCS codes related to the CPB:	
C1738	Powered, single-use (i.e. disposable) endoscopic ultrasound-guided biopsy device
S3833	Complete APC gene sequence analysis for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP
S3834	Single-mutation analysis (in individual with a known APC mutation in the family) for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP
ICD-10 codes covered if selection criteria are met:	
C18.0 - C21.8	Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal
C7a.020 - C7a.026	Malignant carcinoid tumors of the appendix, large intestine, and rectum
D12.0 - D12.9	Benign neoplasm of colon, rectum, anus and anal canal
D3a.020 - D3a.029	Benign carcinoid tumors of the appendix, large intestine, and rectum
D50.0	Iron deficiency anemia secondary to blood loss (chronic)
D50.9	Iron deficiency anemia, unspecified
D62	Acute posthemorrhagic anemia
K51.00 - K55.9	Noninfective enteritis and colitis
K57.20 - K57.93	Diverticular disease of intestine
K59.00 - K59.09	Constipation
K62.0 - K62.1	Anal and rectal polyp
K62.5	Hemorrhage of anus and rectum
K63.5	Polyp of colon
K92.1	Melena
Q85.81, Q85.82, Q85.83, Q85.89	Other phakomatoses, not elsewhere classified [Cowden syndrome]
R19.5	Other fecal abnormalities

Code	Code Description
Z15.09	Genetic susceptibility to other malignant neoplasm
Z80.0	Family history of malignant neoplasm of digestive organs
Z83.710 - Z83.719	Family history of colonic polyps
Z85.038, Z85.048	Personal history of other malignant neoplasm of large intestine, rectum, rectosigmoid junction, and anus
Z86.0100 - Z86.0109	Personal history of colonic polyps
ICD-10 codes not covered for indications listed in the CPB:	
B97.7	Papillomavirus as the cause of diseases classified elsewhere
R85.610 - R85.619	Abnormal cytologic smear of anus
R85.81 - R85.82	Other abnormal findings in specimens from anus
Z11.51	Encounter for screening for human papillomavirus (HPV)
Z12.10 - Z12.12	Encounter for screening for malignant neoplasm of intestinal tract, colon and rectum
Cologuard:	
CPT codes covered if selection criteria are met:	
81528	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result
ICD-10 codes covered if selection criteria are met:	
Z00.00	Encounter for general adult medical examination without abnormal findings
Z00.01	Encounter for general adult medical examination with abnormal findings
Z12.10 - Z12.12	Encounter for screening for malignant neoplasm of intestinal tract, colon and rectum

Code	Code Description
Cologuard Plus:	
CPT codes covered if selection criteria are met:	
0464U	Oncology (colorectal) screening, quantitative real-time target and signal amplification, methylated DNA markers, including LASS4, LRRC4 and PPP2R5C, a reference marker ZDHHC1, and a protein marker (fecal hemoglobin), utilizing stool, algorithm reported as a positive or negative result
ICD-10 codes covered if selection criteria are met:	
Z12.10 - Z12.12	Encounter for screening for malignant neoplasm of intestinal tract, colon and rectum
Biopsy of the Lower Gastro-Intestinal Tract :	
CPT codes covered if selection criteria are met:	
44010	Duodenotomy, for exploration, biopsy(s), or foreign body removal
44020	Enterotomy, small intestine, other than duodenum; for exploration, biopsy(s), or foreign body removal
44025	Colotomy, for exploration, biopsy(s), or foreign body removal
44382	Ileoscopy, through stoma; with biopsy, single or multiple
44386	Endoscopic evaluation of small intestinal pouch (eg, Kock pouch, ileal reservoir [S or J]); with biopsy, single or multiple
44389	Colonoscopy through stoma; with biopsy, single or multiple
44361	Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, not including ileum; with biopsy, single or multiple
44377	Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, including ileum; with biopsy, single or multiple
44407	Colonoscopy through stoma; with transendoscopic ultrasound guided intramural or transmural fine needle aspiration/biopsy(s), includes endoscopic ultrasound examination limited to the sigmoid, descending, transverse, or ascending colon and cecum and adjacent structures
45100	Biopsy of anorectal wall, anal approach (eg, congenital megacolon)
45305	Proctosigmoidoscopy, rigid; with biopsy, single or multiple
45331	Sigmoidoscopy, flexible; with biopsy, single or multiple

Code	Code Description
45342	with transendoscopic ultrasound guided intramural or transmural fine needle aspiration/biopsy(ies)
45380	Colonoscopy, flexible; with biopsy, single or multiple
45392	with transendoscopic ultrasound guided intramural or transmural fine needle aspiration/biopsy(s), includes endoscopic ultrasound examination limited to the rectum, sigmoid, descending, transverse, or ascending colon and cecum, and adjacent structures
46606	Anoscopy; with biopsy, single or multiple
46607	with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, with biopsy, single or multiple
ICD-10 codes covered if selection criteria are met:	
D89.810	Acute graft-versus-host disease
K50.00 - K50.919	Crohn's disease [regional enteritis]
K51.00 - K51.919	Ulcerative colitis
K52.831 - K52.839	Microscopic colitis
K52.9	Noninfective gastroenteritis and colitis, unspecified
K59.00 - K59.09	Constipation
K59.1	Functional diarrhea
K59.81 - K59.89	Other specified functional intestinal disorders
K59.9	Functional intestinal disorder, unspecified
K63.5	Polyp of colon
K91.850	Pouchitis
R10.0 - R10.9	Abdominal and pelvic pain
R11.0 - R11.2	Nausea and vomiting
R12	Heartburn

Code	Code Description
R13.0 - R13.19	Aphagia and dysphagia
R14.0 - R14.3	Flatulence and related conditions
R15.0 - R15.9	Fecal incontinence
R19.7	Diarrhea, unspecified
R19.00 - R19.8	Other symptoms and signs involving the digestive system and abdomen
Drug-coated balloon:	
CPT codes not covered for indications listed in the CPB:	
0885T	Colonoscopy, flexible, with initial transendoscopic mechanical dilation (eg, nondrug-coated balloon) followed by therapeutic drug delivery by drug-coated balloon catheter for colonic stricture, including fluoroscopic guidance, when performed
0886T	Sigmoidoscopy, flexible, with initial transendoscopic mechanical dilation (eg, nondrug-coated balloon) followed by therapeutic drug delivery by drug-coated balloon catheter for colonic stricture, including fluoroscopic guidance, when performed
ICD-10 codes not covered if selection criteria are met:	
K56.690 - K56.699	Other intestinal obstruction [Colonic strictures]

Background

Colorectal cancer (CRC) is a term used to describe cancer that develops in the colon or rectum. Colorectal cancer (CRC) is the third most commonly diagnosed cancer among persons in the United States. The 5-year survival rate of CRC detected in early states is 90 %, but the 5-year survival rate is only 8 % for those diagnosed after the cancer has metastasized. Almost 90 % of CRC cases are found in persons age 50 and older.

CRC screening refers to the process of looking for cancer in people who have no symptoms of the disease. Screening tests may identify cancers at an early and potentially more treatable stage. Testing may also detect precancerous abnormal growths (eg, polyps) which can be removed before becoming malignant.

The American Cancer Society (ACS) (Levin et al, 2008) recommends the following testing options for the early detection of adenomatous polyps and cancer for asymptomatic adults aged 50 years and older:

Tests that Detect Adenomatous Polyps and Cancer

- Colonoscopy every 10 years; *or*
- Computed tomographic (CT) colonography every 5 years; *or*
- Double-contrast barium enema (DCBE) every 5 years; *or*
- Flexible sigmoidoscopy every 5 years;

Tests that Primarily Detect Cancer

- Annual fecal immunochemical test with high test sensitivity for cancer; *or*
- Annual guaiac-based fecal occult blood test with high sensitivity for cancer; *or*
- Stool DNA test with high sensitivity for cancer, interval uncertain.

The U.S. Preventive Services Task Force (USPSTF, 2016) recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The risks and benefits of different screening methods vary. The USPSTF stated that the decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history. Adults in this age group who have never been screened for colorectal cancer are more likely to benefit. The USPSTF stated that screening would be most appropriate among adults who (1) are healthy enough to undergo treatment if colorectal cancer is detected and (2) do not have comorbid conditions that would significantly limit their life expectancy.

The USPSTF (2016) found convincing evidence that screening for colorectal cancer in adults aged 50 to 75 years reduces colorectal cancer mortality. The USPSTF found no head-to-head studies demonstrating that any of the screening strategies it considered are more effective than others, although the tests have varying levels of evidence supporting their effectiveness, as well as different strengths and limitations:

- Colonoscopy every 10 years
- CT colonography every 5 years
- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years plus fecal immuohistochemical test (FIT) every year
- Guiaic-based fecal occult blood test (gFOBT) every year
- FIT test every year
- Stool DNA (FIT-DNA) every one or three years.

A guidance statement from the American College of Physicians on "Screening for colorectal cancer" (Qaseem et al, 2012) stated that “The screening interval for average-risk adults older than 50 years is 10 years for colonoscopy; 5 years for flexible sigmoidoscopy, double-contrast barium enema (DCBE), and computed tomography colonography (CTC); annually for guaiac-based fecal occult blood test (gFOBT) and immunochemical-based fecal occult blood test (iFOBT); and uncertain for stool DNA (sDNA)”.

More frequent screening has been recommended for persons with a first-degree relative (parent, sibling or child) with a history of CRC. The increased risk of developing cancer at younger ages may justify beginning screening before the age of 50 in persons with a positive family history, especially when affected relatives developed CRC at younger ages. The American Society of Colon and Rectal Surgeons (2010) recommends that people with a first-degree relative with colon cancer or adenomatous polyps diagnosed at age less than 60 years of age or 2 first degree relatives diagnosed at any age should be advised to have screening colonoscopy starting at age 40 years or 10 years younger than the earliest diagnosis in their family, whichever comes first, and repeated every 5 years. The American Society for Gastrointestinal Endoscopy (2006) has a similar position.

Regular colonoscopic screening is part of the routine diagnosis and management of individuals at high-risk of developing CRC, including those with a family history of hereditary syndromes (familial polyposis, hereditary non-polyposis colon cancer (HNPCC)); individuals with long-standing ulcerative colitis or Crohn's disease; or high-risk adenomatous polyps or colon cancer. Referral to specialists is appropriate. It has been recommended that persons with a family history of adenomatous polyposis begin screening at puberty, and persons with a family history of HNPCC begin screening at 20 to 30 years of age.

Fecal occult blood test (FOBT) is a noninvasive test that detects hidden (occult) blood in the stool. Such blood may come from anywhere along the digestive tract and for that reason additional types of tests may be ordered. Blood in the stool may be the only symptom of early cancer. There are two main types of FOBT tests: guaiac and immunochemical. Fecal immunochemical testing (FIT) differs from guaiac based FOBT in that there are no dietary or drug restrictions prior to this form of testing. Colonoscopy will be needed if the test is positive. Randomized controlled trials (RCTs) have proven that the fecal occult blood test can detect CRC significantly lowers the rate of death from the disease.

Guaiac FOBTs have been recognized among various CRC screening methods as having the highest quality supporting evidence. Immunochemical tests (e.g., Flexsure OBT, InSure FOBT) may be used as an alternative to standard guaiac-based tests of fecal occult blood, and have several potential advantages that make them more convenient than guaiac tests: (i) unlike guaiac tests, a fecal smear is not required for immunochemical tests -- samples may be obtained from a brush sample of toilet bowl water; (ii) unlike guaiac tests, immunochemical tests are not affected by diet or medications, so that dietary and medicinal restrictions are not necessary prior to testing.

The USPSTF (2016) found that multiple randomized clinical trials (RCTs) have shown that screening with the guaiac-based fecal occult blood test (gFOBT) reduces colorectal cancer deaths. Fecal immunochemical tests (FITs), which identify intact human hemoglobin in stool, have improved sensitivity compared with gFOBT for detecting colorectal cancer. Among the FITs that are cleared by the US Food and Drug Administration (FDA)

and available for use in the United States, the OC FIT-CHEK family of FITs (Polymedco)--which include the OC-Light and the OC-Auto--have the best test performance characteristics (ie, highest sensitivity and specificity) (USPSTF, 2016).

Flexible sigmoidoscopy enables the physician to look at the inside of the large intestine from the rectum through the last part of the colon, called the sigmoid or descending colon. Using this short, flexible fiberoptic tube that is inserted through the anus, the physician can see abnormal growths, bleeding, inflammation and ulcers in the lower part of the large intestine (colon) and the rectum. If polyps or cancer are found, then a colonoscopy will be necessary to screen for polyps or cancer in the rest of the colon. Although there are no RCTs proving that sigmoidoscopy reduces the mortality rate from CRC, a number of case-control studies have suggested that sigmoidoscopy is effective in reducing CRC mortality. The literature indicates that sigmoidoscopy can detect 70 to 80 % of CRC. However, sigmoidoscopy is unable to detect the substantial number of cancers that arise solely in the proximal colon. The literature indicates that some of the additional neoplasms that it misses can be detected by combining sigmoidoscopy with fecal occult blood testing.

The USPSTF (2016) identified several RCTs that show that flexible sigmoidoscopy alone reduces deaths from colorectal cancer. Flexible sigmoidoscopy combined with FIT has been studied in a single trial and was found to reduce the colorectal cancer-specific mortality rate more than flexible sigmoidoscopy alone (citing Holme, et al, 2014). The USPSTF noted that modeling studies also consistently estimate that combined testing yields more life-years gained and colorectal cancer deaths averted compared with flexible sigmoidoscopy alone (citing Zauber, et al., 2015). Flexible sigmoidoscopy can result in direct harms, such as colonic perforations and bleeding, although the associated event rates are much lower than those observed with colonoscopy. Harms can also occur as a result of follow-up colonoscopy.

Some have advocated whole-bowel screening with colonoscopy or DCBE because it is able to detect proximal colon lesions. One study found that approximately 30 % of cancers detected by colonoscopy would not have been detected by sigmoidoscopy. However, no direct evidence

proves that whole-bowel screening, either by colonoscopy or DCBE, reduces mortality, although clinical trials are now underway to investigate this.

Double contrast barium enema (DCBE), also called a lower gastrointestinal (GI) exam, is an x-ray examination of the large intestine (colon and rectum). In a DCBE study, the colon is filled with barium, which helps to see the outline of the colon on an x-ray. The barium is then removed, leaving only a thin layer on the wall of the colon, which is then filled with air. This helps to provide a detailed view of the inner surface of the colon, making it easier to see colon polyps and/or other abnormalities (eg, inflammation, strictures). If the test is positive, a colonoscopy will be needed for further evaluation. A study comparing the use of colonoscopy to DCBE for patients with previously identified polyps found that colonoscopy detected more polyps than DCBE. Double contrast barium enema found only 20 % of adenomatous polyps found by colonoscopy.

Colonoscopy allows the physician to examine the lining of the entire large intestine by using a flexible, fiberoptic instrument (colonoscope) that is inserted through the anus. This test may reveal inflamed tissue, abnormal growths, ulcers or early signs of cancer in the colon or rectum. Special instruments can be passed through the colonoscope to remove polyps if needed. Although the rate of complications from colonoscopy has been shown to be low, complications from colonoscopy are more common than from other screening procedures. Perforation of the colon and complications from anesthesia have been reported to occur in 0.1 to 0.3 % of colonoscopies performed by gastroenterologists, and death occurs in 0.01 % of colonoscopies.

The USPSTF (2017) found that completed trials of flexible sigmoidoscopy provide indirect evidence that colonoscopy -- a similar endoscopic screening method -- reduces colorectal cancer mortality. A prospective cohort study also found an association between patients who self-reported being screened with colonoscopy and a lower colorectal cancer mortality rate. Colonoscopy has both indirect and direct harms. Harms may be caused by bowel preparation prior to the procedure (eg, dehydration and electrolyte imbalances), the sedation used during the procedure (eg, cardiovascular events), or the procedure itself (eg, infection, colonic perforations, or bleeding).

Genetic testing of stool samples is also a possible way to screen asymptomatic high-risk individuals for CRC. Colorectal cancer cells are shed into the stool, providing a potential means for the early detection of the disease by detecting specific tumor-associated genetic mutations in stool samples. Fecal/stool DNA testing (sDNA) is performed on stool samples that are submitted to a laboratory after being collected by individuals at home. This test detects CRC based on the presence of specific, cancer associated mutations in DNA extracted from the stool sample. Individuals with a positive sDNA test result must then undergo a definitive test for colon cancer, such as a colonoscopy. sDNA testing is intended as a first line screening test for colon cancer in asymptomatic individuals. An example of an sDNA test is Cologuard, which may detect colorectal neoplasia associated with DNA markers and the presence of occult hemoglobin.

The U.S. Preventive Services Task Force (2017) stated that multitargeted stool DNA testing (FIT-DNA) is an emerging screening strategy that combines a FIT with testing for altered DNA biomarkers in cells shed into the stool. The USPSTF found that multitargeted stool DNA testing has increased single-test sensitivity for detecting colorectal cancer compared with FIT alone. The harms of stool-based testing primarily result from adverse events associated with follow-up colonoscopy of positive findings. The specificity of FIT-DNA is lower than that of FIT alone, which means it has a higher number of false-positive results and higher likelihood of follow-up colonoscopy and experiencing an associated adverse event per screening test. The USPSTF found no empirical data on the appropriate longitudinal follow-up for an abnormal FIT-DNA test result followed by a negative colonoscopy; there is potential for overly intensive surveillance due to clinician and patient concerns about the implications of the genetic component of the test.

Computed tomographic colonography (CTC), also known as virtual colonoscopy, was developed as a minimally invasive method to examine the colon. This test has been used in screening and to detect abnormalities in the colon and rectum (eg, colorectal cancer [CRC] and polyps). It involves the use of helical computed tomography (CT) and computer generated images to produce high-resolution two- and three-dimensional (3D) images of the colon and rectum. Prior to virtual colonoscopy, standard bowel cleansing preparations are needed to

evacuate any stool and fluid from the colon. During the procedure, a rectal tube is inserted and the colon is distended using room air or carbon dioxide and images are then taken by a helical CT scanner. The results are interpreted by a radiologist. If suspicious lesions are detected, the individual generally must undergo further testing via conventional colonoscopy.

The USPSTF (2017) found that evidence for assessing the effectiveness of computed tomography (CT) colonography is limited to studies of its test characteristics. The USPSTF stated that computed tomography colonography can result in unnecessary diagnostic testing or treatment of incidental extracolonic findings that are of no importance or would never have threatened the patient's health or become apparent without screening (ie, overdiagnosis and overtreatment). The USPSTF stated that extracolonic findings are common, occurring in about 40% to 70%of screening examinations. Between 5%and 37% of these findings result in diagnostic follow-up, and about 3% require definitive treatment. As with other screening strategies, indirect harms from CT colonography can also occur from follow-up colonoscopy for positive findings.

The American Cancer Society (Wolf et al, 2018) recommends that adults aged 45 years and older with an average risk of CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, the ACS recommends that all positive results on noncolonoscopy screening tests should be followed up with timely colonoscopy. The recommendation to begin screening at age 45 years is a qualified recommendation. The recommendation for regular screening in adults aged 50 years and older is a strong recommendation. The ACS recommends (qualified recommendations) that: (1) average-risk adults in good health with a life expectancy of more than 10 years continue CRC screening through the age of 75 years; (2) clinicians individualize CRC screening decisions for individuals aged 76 through 85 years based on patient preferences, life expectancy, health status, and prior screening history; and (3) clinicians discourage individuals older than 85 years from continuing CRC screening. The options for CRC screening are: fecal immunochemical test annually; high-sensitivity, guaiac-based fecal

occult blood test annually; multitarget stool DNA test every 3 years; colonoscopy every 10 years; computed tomography colonography every 5 years; and flexible sigmoidoscopy every 5 years.

On the basis of the strength of the evidence and on the judgment of an overall preponderance of benefit, the recommendation for regular screening in adults aged 50 years and older has been designated by the ACS as a “strong” recommendation (Wolf, et al., 2018). The recommendation to begin screening at age 45 years is based on disease burden, results from microsimulation modeling, and the reasonable expectation that screening will perform similarly in adults aged 45 to 49 years as in persons for whom screening is currently recommended. However, the long-standing recommendation to initiate CRC screening at age 50 years means that there are limited data on screening outcomes in adults aged 45 to 49 years. Because of differences in the type and quality of evidence for screening in adults younger than 50 years, the recommendation to start screening at age 45 years has been designated by the ACS as “qualified.”

The American College of Surgeons recommends against colorectal cancer screening on asymptomatic patients with a life expectancy of less than 10 years and no family or personal history of colorectal neoplasia (Choosing Wisely, 2018a). The Society of General Internal Medicine recommends against cancer screening in adults with life expectancy of less than 10 years (Choosing Wisely, 2018b). Furthermore, the AMDA, the Society for Post-Acute and Long-Term Care Medicine, recommends against colorectal cancer screening if life expectancy is estimated to be less than 10 years (Choosing Wisely, 2018c).

An assessment of CT colonography prepared for the Washington State Health Care Authority (Scherer et al, 2008) found that, in direct comparison to optical colonoscopy, CT colonography every 10 years is substantially more expensive and marginally less effective in preventing cases of cancer (47 versus 52 in a lifetime cohort of 1,000 individuals) and cancer deaths (24 versus 26). The investigators reported that only one CT colonography screening strategy is as effective as optical colonoscopy every 10 years, and that strategy is to perform CT

colonography every 5 years with colonoscopy referral for polyps greater than 6 mm. For this strategy, the cost per life-year gained for CT colonography versus optical colonoscopy was $630,700.

The American College of Gastroenterology (ACG) (Agrawal et al, 2005) issued recommendations to healthcare providers to begin CRC screening in African Americans at age 45 rather than 50 years. Colonoscopy is the preferred method of screening for CRC and data support the recommendation that African-Americans begin screening at a younger age because of the high incidence of CRC and a greater prevalence of proximal or right-sided polyps and cancerous lesions in this population.

In a meta-analysis of surveillance colonoscopy in individuals at risk for HNPCC, Johnson et al (2006) concluded that the best available evidence supports surveillance with complete colonoscopy to the cecum every 3 years in patients with HNPCC (B recommendation). There is no evidence to support or refute more frequent screening. Further research is needed to examine the potential harms and benefits of more frequent screening. However, given the potential for rapid progression from adenoma to carcinoma and missing lesions at colonoscopy, there is consensus that screening more frequently than every 3 years is required.

The National Comprehensive Cancer Network (NCCN) practice guidelines for "Colorectal cancer screening" (v1.2018) state that colorectal cancer screening is recommended for average risk persons ages 50 to 75; however, the decision to screen between ages 76 to 85 years should be individualized and include a discussion on the risks and benefits based on comorbidity status and estimated life expectancy. Eligible individuals who have not been previously screened are most likely to benefit in this age group.

MUTYH-associated polyposis (MAP) is an autosomal recessive hereditary syndrome that predisposes individuals to colorectal cancer (CRC). MAP is caused by biallelic germline mutations in the MUTYH gene which encodes the A/G-specific adenine DNA glycosylase excision repiar protein (also called hMYH) (NCCN, 2018). MYH is a DNA repair gene that corrects DNA base pair mismatch errors in the genetic code before replication. Mutation of the MYH gene may result in colon cancer.

In this regard, the MYH gene has been found to be significantly involved in colon cancer, both in cases where there is a clear family history of the disease, as well as in cases without any sign of a hereditary cause.

The NCCN practice guidelines on "Genetic/familial high-risk assessment: Colorectal" (v.1.2018) recommends colonoscopy surveillance of asymptomatic individuals with known MYH mutations (MUTYH positive mutation) and colonoscopy screening of siblings of affected patients. Surveillance and screening is recommended beginning at age 25 to 30 years and at every 2 to 3 year intervals if negative. If polyps are found (MUTYH-associated polypsosis (MAP)), colonoscopy and polypectomy are recommended every 1 to 2 years. Those with small adenoma burden are surveilled with colonoscopy and complete polypectomies of all polyps. Those with dense polyposis not manageable by polypectomy are recommended surgery. Per NCCN, there are no specific data available to determine screening recommendations for an individual with MUTYH heterozygous mutation and a second-degree relative affected with CRC.

The NCCN practice guidelines on "Genetic/familial high-risk assessment: Breast and ovarian" (v.2.2019) recommend that persons with Cowden syndrome should consider colonoscopy, starting at age 35 years, unless symptomatic or if close relative with colon cancer before age 40 years, then every 5 to 10 years before the earliest known colon cancer in the family. Colonoscopy should be done every 5 years or more frequently if the person is symptomatic or if polyps are found.

No current guidelines of leading medical professional organizations or Federal public health agencies recommend routine upper endoscopy screening of asymptomatic persons. Although screening upper endoscopy has been performed in conjunction with screening colonoscopy, there is no evidence-based support for this practice.

Currently, no leading medical professional organizations or Federal public health agencies recommend anal dysplasia screening. Recommendations from the Centers for Disease Control and Prevention state (Workowski and Berman, 2006): "Routine testing for anal cytological abnormalities or anal human papilloma virus (HPV) infection is not recommended until more data are available on the reliability of screening methods, the safety of and response to treatment, and programmatic

considerations." The Ontario Health Technology Advisory Committee (OHTAC, 2007) recently systematically reviewed the evidence for anal dysplasia screening. OHTAC "does not recommend screening of high risk individuals at this time based on the low specificity for cytological screening, inadequate evidence of effectiveness for current treatment of precancerous lesions, high recurrence rates, and no evidence that cytological screening reduces the risk of developing anal cancer."

Regarding risk factors (smoking and obesity) under consideration for more intense screening, the 2009 ACG guidelines for CRC screening (Rex et al, 2009) did not recommend that screening be initiated earlier in these groups (smokers and obese patients) at this time. The ACG recommended additional study to characterize the potential benefits, harms, and cost-effectiveness of earlier screening in these groups.

MicroRNAs (miRNAs) are short non-coding RNA sequences that play an important role in the regulation of gene expression. They have significant regulatory functions in basic cellular processes (e.g., cell differentiation, proliferation, and apoptosis). Available evidence suggests that miRNAs may function as both tumor suppressors as well as oncogenes. The main mechanism for changes in the function of miRNAs in cancer cells is due to aberrant gene expression.

Dong and colleagues (2011) noted that recent researches have shed light on the biological importance of miRNAs in CRC genesis, progression and response to treatments. The potential utility of miRNAs in the pre-clinical stage have been explored and investigated. These researchers explored the literature and reviewed the cutting edge progress in the discovery of non-invasive plasma and fecal miRNAs for CRC early diagnosis, as well as their measurability and predictability. They also discussed the utility of miRNAs as novel prognostic and predictive markers, and their association with CRC clinical phenotypes including recurrence, metastasis and therapeutic outcomes. These investigators summarized miRNA-related single-nucleotide polymorphisms and their potential influence on sporadic CRC susceptibility and therapeutic response. The authors concluded that the use of miRNAs as biomarker for CRC is still in its infancy and need further characterization and evaluation.

Sandhu and Garzon (2011) stated that early studies have established that miRNAs are widely de-regulated in cancer and play a critical role in cancer pathogenesis. Recent research efforts are directed now towards translating these basic discoveries into novel tests or treatments that could improve the diagnosis and outcome of cancer patients. These researchers summarized the potential applications of miRNAs for cancer diagnosis, prognosis, as well as treatment; and discussed current pitfalls and future directions. The authors noted that there are still hurdles to overcome such as the development of reliable and reproducible miRNA expression assays and improvements in oligonucleotide delivery to specific tissues or cell types.

Ma et al (2012) carried out a comprehensive systematic review of published studies that compared the miRNA expression profiles between CRC tissue and paired neighboring non-cancerous colorectal tissue to determine candidate miRNA biomarkers for CRC. A miRNA ranking system that takes the number of comparisons in agreement, total study sizes and direction of differential expression into consideration was devised and used. One of the most up-regulated miRNAs, miRNA-106a, was consistently reported to be differentially expressed in 6 studies and the 5 most down-regulated miRNAs, miR-30a-3p, miR-139, miR-145, miR-125a and miR-133a, were consistently reported to be differentially expressed in 4 studies. Moreover, these investigators further validated 5 miRNAs in a clinical setting using quantitative reverse transcription polymerase chain reaction (qRT-PCR), which demonstrated that miR-106a expression was increased, whereas the expression of miR-30a-3p, miR-145, miR-125a and miR-133a was decreased in the CRC tissues. The authorsconcluded that these miRNAs may be the candidates to develop a panel of biomarkers with sufficient sensitivity and specificity for the diagnosis of CRC in a clinical setting.

Wang et al (2012) stated that the recently identified class of miRNAs provided a new insight in cancer research. As members of miRNAs family, miR-34a, miR-155 and miR-200c abnormalities have been found in various types of cancer. However, the relationship between these 3 miRNAs (miR-34a, miR-155 and miR-200c) and CRC is unclear. These researchers applied stem-loop real-time PCR to quantitatively detect miR-34a, miR-155 and miR-200c expression in 109 pair-matched human CRC and the corresponding normal mucosa. MiR-34a (2.2-fold), miR-155 (2.3-

fold) and miR-200c (3.1-fold) were all expressed at higher levels in CRC (p = 0.001, 0.005 and 0.001, respectively). In the rectum, miR-34a and miR-200c were significantly up-regulated (p = 0.006 and 0.007), while the miR-155 over-expression was not statistically significant (p = 0.083). In the colon, the higher expression of 3 miRNAs was seen, however, without significant difference (p > 0.05). Thee investigators also found that the miR-34a expression was higher in rectal cancer having more advanced TNM stage (III + IV, p = 0.03). Then miR-200c expression was positively correlated with and sera CEA level of rectal cancer patients (p = 0.04). The authors concluded that these findings suggested that the over-expression of miR-34a, miR-155 and miR-200c may be associated with the development of CRC, meanwhile miR-34a may be involved in the development and progression of rectal cancer. They stated that more deeply and larger scale research are required to prove the correlation.

Peacock et al (2012) noted that accurate discrimination of miRNA profiles between tumor and normal mucosa in CRC allows definition of specific expression patterns of miRNAs, giving good potential as diagnostic and therapeutic targets. MicroRNAs expressed in CRC are also abundantly present and stable in stool and plasma samples; their extraction from these sources is feasible and reproducible. The ease and reliability of determining miRNA profiles in plasma or stool makes them potential molecular markers for CRC screening.

Kannan et al (2013) examined the potential use of circulating miRNAs as biomarkers of CR adenomas. These investigators screened for 380 plasma-miRNAs using microfluidic array technology (Applied BioSystems) in a screening cohort of 12 healthy controls, 9 patients with CR adenomas, and 20 patients with CRC. A panel of the most dysregulated miRNAs (p < 0.05, False Discovery Rate: 5 %) was then validated in a blinded cohort of 26 healthy controls, 16 patients with large adenomas, and 45 patients with CRC. A panel of 8 plasma miRNAs (miR-532-3p, miR-331, miR-195, miR-17, miR-142-3p, miR-15b, miR-532, and miR-652) distinguished polyps from controls with high accuracy [area under curve (AUC) = 0.868 (95 % confidence interval [CI]: 0.76 to 0.98)]. In addition, a panel of 3 plasma miRNAs (miR-431, miR-15b, and miR-139-3p) distinguished stage IV CRC from controls with an [AUC = 0.896 (95 % CI: 0.78 to 1.0)]. Receiver-operating-characteristic curves of miRNA panels for all CRC versus controls and polyps versus all CRC

showed AUC values of 0.829 (95 % CI: 0.73 to 0.93) and 0.856 (95 % CI: 0.75 to 0.97), respectively. The authors concluded that plasma miRNAs are reliable, non-invasive, and inexpensive markers for CR adenomas. They stated that this miRNA panel warrants study in larger cohorts to confirm and then increase its sensitivity and specificity. Plasma-based assays could provide better screening compliance compared to fecal occult blood or endoscopic screening.

Furthermore, a guidance statement from the American College of Physicians on "Screening for colorectal cancer" (Qaseem et al, 2012) does not list miRNA as one of the tests for CRC.

In vivo analysis can be described as real time additional imaging that has been suggested for use as an adjunct to endoscopic procedures. The methods include, but may not be limited to, chromoendoscopy, confocal microscopy, fiberoptic analysis and narrow band imaging. These techniques are utilized during the endoscopic procedures and purportedly improve analysis of the lesions in the colon. An example of a confocal microscopy device is the Cellvizio system.

Chung et al (2014) stated that virtual chromoendoscopy (CE) is expected to enhance adenoma yield and reduce variation in performance between colonoscopists. These researchers compared the efficacy of narrow-band imaging (NBI), flexible spectral imaging CE (FICE) and white light (WL) colonoscopy and their impact for less experienced endoscopists. They performed a randomized tandem colonoscopy trial controlling for withdrawal time and bowel preparation. Average-risk adults undergoing screening colonoscopy were enrolled and randomly assigned to first withdrawal with one of the three imaging modalities (NBI (NBI-WL group), FICE (FICE-WL group) and WL (WL-WL group)). Eight colonoscopists were categorized into expert and non-expert subgroups. A total of 1,650 subjects (mean age of 51.4 years, 63.9 % men) were included (550 in each group). Compared with WL, neither NBI nor FICE increased the mean number of adenomas detected per patient (0.37 versus 0.35 and 0.36; p = 0.591) or the percentage of patients with adenoma (25.3 % versus 24.5 % and 23.6 %; p = 0.753). For all 3 modalities, expert subgroups had higher yields of adenomas than non-expert subgroups. Learning curves were observed only for non-expert subgroups with all 3 modalities. The percentage of missed adenomas did not differ between

the 3 groups (20.8 % by WL versus 22.9 % by NBI and 26.0 % by FICE, p = 0.300) and was not affected by endoscopists' expertise. The authors concluded that neither NBI nor FICE improved adenoma detection or miss rates, with no difference in diagnostic efficacy between the 2 systems; virtual CE had no additional benefits over WL for non-experts.

Jang et al (2014) noted that distinguishing deep submucosa (SM) from superficial SM cancer in large sessile and flat colorectal polyps (greater than 2 cm) is crucial in making the most appropriate therapeutic decision. These researchers evaluated the additional role of magnifying NBI and magnifying CE (MCE) in assessing the depth of invasion in large sessile and flat polyps in comparison to morphological evaluation performed by experienced endoscopists. From May 2011 to December 2011, a total of 85 large sessile and flat polyps were analyzed. Endoscopic features of the polyps were independently evaluated by experienced endoscopists. Subsequently, the polyps were observed using magnifying NBI and MCE. A total of 58 intra-mucosal lesions and 27 SM cancers (5 superficial and 22 deep) were identified. The diagnostic accuracy of the experienced endoscopists, NBI, and MCE were 92.9, 90.6, and 89.4 %, respectively, for deep SM cancer. In combination with NBI or MCE, the diagnostic accuracy of the experienced endoscopists did not change significantly for deep SM cancer, with an accuracy of 95.3 % for both NBI and MCE. The authors concluded that conventional colonoscopy can differentiate superficial from deep SM cancers with an accuracy of as high as 92.9 % in large sessile and flat polyps.

In a meta-analysis, Xing and colleagues (2014) identified the value of serum matrix metalloproteinase-7 (MMP-7) levels for the diagnosis of CRC. Through searching the following electronic databases: Cochrane Library (Issue 12, 2014), Web of Science (1945 to 2014), PubMed (1966 to 2014), CINAHL (1982 to 2014), EMBASE (1980 to 2014), and CBM (1982 to 2014), related articles were determined without any language restrictions. Stata statistical software (Version 12.0, Stata Corporation, College Station, TX) was chosen to deal with statistical data. Standard mean difference (SMD) and its corresponding 95 % CI were calculated to clarify the correlation between serum MMP-7 levels and CRC. A total of 7 clinical case-control studies that recruited 430 CRC patients and 357 healthy subjects were selected for statistical analysis. The main findings of the meta-analysis showed that the serum MMP-7 level in CRC patients

was significantly higher than that in control subjects (SMD = 2.15, 95 % CI: 1.46 to 2.84, p < 0.001). Ethnicity-stratified analysis indicated a higher serum MMP-7 level in CRC patients than that of control subjects among the Asians and the Caucasians (Asians: SMD = 2.83, 95 % CI: 1.76 - 3.91, p < 0.001; Caucasians: SMD = 1.06, 95 % CI: 0.46 to 1.66, p = 0.001; respectively). The authors concluded that the present meta-analysis indicated that the increased serum level of MMP-7 may be connected with the development of CRC; thus, serum levels of MMP-7 could be an independent biomarker for CRC patients.

Shah et al (2014) stated that there is growing interest in early detection of CRC as current screening modalities lack compliance and specificity. These researchers reviewed the literature to identify biomarkers for early detection of CRC and polyps. Literature searches were conducted for relevant papers since 2007. Human studies reporting on early detection of CRC and polyps using biomarkers were included. Methodologic quality was evaluated, and sensitivity, specificity, and the positive predictive value (PPV) were reported. The search strategy identified 3,348 abstracts. A total of 44 papers, examining 67 different tumor markers, were included. Overall sensitivities for CRC detection by fecal DNA markers ranged from 53 % to 87 %. Combining fecal DNA markers increased the sensitivity of CRC and adenoma detection. Canine scent detection had a sensitivity of detecting CRC of 99 % and specificity of 97 %. The PPV of iFOBT was 1.26 %, compared with 0.31 % for the current screening method of gFOBT. A panel of serum protein biomarkers provided a sensitivity and specificity above 85 % for all stages of CRC, and a PPV of 0.72 %. Combinations of fecal and serum biomarkers produced higher sensitivities, specificities, and PPVs for early detection of CRC and adenomas. The authors concluded that further research is needed to validate these biomarkers in a well-structured population-based study.

An UpToDate review on “Tests for screening for colorectal cancer: Stool tests, radiologic imaging and endoscopy” (Fletcher, 2015) states that “Serum markers -- Current serum markers are not sufficiently sensitive or specific to be used for screening. The potential to utilize a combination of six serum markers to improve the test has been reported in a feasibility study, but validation studies in screening populations are needed before clinical relevance can be determined.

One blood test that detects Septin 9 hypermethylation in DNA from plasma (ColoVantage™) has been approved in 2011 by the New York State Health Department for colon cancer. In one study of an assay for Septin 9 (SEPT9), the sensitivities for adenomas (1 to 5 cm), for stage I to III CRC, and for stage IV CRC were 14, 50, and 88 %, respectively. The false-positive rate was 27 %. These test characteristics suggest that a serum Septin 9 assay is not sufficiently sensitive for identifying cancer or cancer precursors at a treatable stage, but would lead to many false-positive findings.

Blood-based biomarker panels are tests to assess the expression of genes to purportedly calculate a relative risk of having CRC. An example of this type of test is ColonSentry, which is supposedly believed to increase individual compliance with colonoscopy. The seven genes that are measured in this test include:
ANXA3, CLEC4D, IL2RB, LMNB1, PRRG4. TNFAIP6, and VNN139.

The New York State Department of Health also approved a 7-gene test (ColonSentry) in February 2012 to be used to identify patients at increased risk of colorectal cancer in order to target such patients for monitoring to assure compliance with regular colonoscopy. However, it has not been shown that the test can detect early-stage cancers, for which screening would be most effective, and test sensitivity (61 to 82 %) and specificity (64 to 77 %) were only fair for CRC at any stage when tested in populations that included a substantial proportion of patients with known CRC.

In a study that compared the performance of serum markers (C-reactive protein, serum CD26 [sCD26], complement C3a anaphylatoxin, and tissue inhibitor of metalloproteinases [TIMP-1]) with stool fecal occult blood tests for the detection of colon cancer and advanced adenomas among patients with known and no known colon disease, at a specificity of 97.7 %, the sensitivity of the 4 serum markers was less than 20 % compared with 40 % for gFOBT and 66 % for iFOBT.

Thus, until further evidence is available, we do not recommend serum tests for colorectal cancer screening".

The UpToDate review (Fletcher, 2015) also states that “Several other technologies have been used in various clinical settings, but their value in screening for colorectal cancer has yet to be established.

- Chromoendoscopy involves the application of stains or pigment to improve the identification of abnormal mucosal tissue.
- Magnification endoscopy, with or without staining, allows the endoscopist to better visualize mucosal details with 80- to 100-fold image enhancement.
- Narrow band imaging optical colonoscopy modifies the bandwidth and wavelength of the light used in colonoscopy, allowing better visualization of vascular changes in superficial lesions”.

Retrograde imaging/illumination (e.g., Third Eye Retroscope, Third Eye Panoramic Auxiliary Endoscopy System) are imaging devices that have been suggested to provide illumination and continuous retrograde views of the colon. Examples of these devices include, but may not be limited to, are the Third Eye Retroscope, which involves the use of a J-shaped catheter that contains an imaging device that can be inserted into endoscopic working channel. It is intended for single use and is disposable. Another example of these devices is the Third Eye Panoramic device, which can be attached to the distal end of the colonoscope with a flexible clip and provides continuous left-side and right-side views of the colon and are displayed simultaneously on three monitors.

Anal Pap Smear

In a prospective, cohort study, Schofield and colleagues (2016) sought to establish the feasibility and acceptability of anal screening among men who have sex with men (MSM). Subjects were known HIV-positive and negative MSM who have anoreceptive intercourse. Intervention was anal screening with HPV testing, liquid-based cytology and high-resolution anoscopy (HRA) with biopsy of anoscopic abnormalities. Participants completed questionnaires at baseline and at 6 months. Anal HPV was highly prevalent in MSM (HIV-positive, 88 %; and HIV-negative, 78 %). Despite the high prevalence of cytological abnormality in both HIV-positive (46.2 %) and HIV-negative (35.0 %) MSM, almost 50 % of anal intraepithelial neoplasia (AIN) of all grades were associated with negative cytology. Anoscopically directed biopsies detected AIN3 or worse

(AIN3+) in 14 of 203 (6.9 %) of HIV-positive MSM and 3 of 81 (3.7 %) HIV-negative MSM. The corresponding prevalence of AIN2+ was 26.6 % and 20.9 %, respectively; 1 case of AIN3 was detected at the 2nd visit. Screening was considered to be highly acceptable by participants. The authors concluded that high prevalence of high-risk-HPV and frequency of false negative cytology in this study suggested that HRA would have most clinical utility, as a primary screening tool for anal cancer in a high-risk group. The prevalence of AIN3+ in HIV-positive MSM provided support for a policy of screening this group, but the high prevalence of lower grade lesions that do not warrant immediate treatment and the limitations of treating high-grade lesions requires careful consideration in terms of a screening policy.

In a review on “Anal cancer and intraepithelial neoplasia screening”, Leeds and Fang (2016) focused on the early diagnosis of anal cancer and its precursor lesions through routine screening. A number of risk-stratification strategies as well as screening techniques have been suggested, and currently little consensus exists among national societies. Much of the current clinical rationale for the prevention of anal cancer derives from the similar tumor biology of cervical cancer and the successful use of routine screening to identify cervical cancer and its precursors early in the disease process. It is thought that such a strategy of identifying early anal intraepithelial neoplasia will reduce the incidence of invasive anal cancer. The low prevalence of anal cancer in the general population prevents the use of routine screening. However, routine screening of selected populations has been shown to be a more promising strategy. Potential screening modalities include digital anorectal exam, anal Papanicolaou testing, HPV co-testing, and HRA. The authors concluded that additional research associating high-grade dysplasia treatment with anal cancer prevention as well as direct comparisons of screening regimens is needed to develop further anal cancer screening recommendations.

An UpToDate review on “Anal squamous intraepithelial lesions: Diagnosis, screening, prevention, and treatment” (Palefsky and Cranston, 2017) stated that “Formal guidelines recommending anal screening for precancerous lesions have not been adopted by the United States Public Health Service. For HIV-infected patients, the HIV Medical Association of the Infectious Diseases Society of America makes a weak

recommendation based on moderate quality evidence for screening with anal cytology in MSM, women with a history of receptive anal intercourse or abnormal cervical Pap test results, and those with genital warts".

Analysis of Fecal Volatile Organic Compounds for Colorectal Cancer Screening

Bosch and colleagues (2019) noted that the fecal volatolome, which is composed of fecal volatile organic compounds (VOCs), appeared to hold potential as non-invasive biomarker for the detection of CRC and its precursor lesions advanced adenomas (AA). The potential of the fecal volatolome has been subject of various studies using either chemical analytical or pattern-recognition techniques. These investigators reviewed available literature on the potential of the fecal volatolome as CRC and AA biomarker. They performed a systematic literature search in PubMed, Embase, the Cochrane Library, Google Scholar and ResearchGate using the following keywords: Colorectal cancer, advanced adenoma, volatile organic compound, metabolome, gas chromatrography-mass spectrometry, selected-ion flow-tube mass spectrometry, eNose, and fecal biomarkers. A total of 88 titles or abstracts were identified from the search, of which 11 papers describing the potential of the fecal volatolome for CRC detection were selected. In these studies, different techniques were used for the headspace analyses of fecal VOCs, limiting the possibility to compare outcomes. Increased levels of amino acids and short chain fatty acids, and decreased levels of bile acids and polyol alcohols in the gas phase of feces were observed repeatedly. All selected papers reported high diagnostic value for the detection of both CRC and AA based on fecal VOCs. The authors concluded that based on the included studies, fecal VOC analyses appeared promising for future screening of CRC and AA, with potentially improved test performances allowing for earlier detection of AA and CRC; and consequently earlier initiation of treatment, possibly reducing morbidity and mortality rates next to lower rates of (unnecessary) colonoscopies.

In a systematic review and meta-analysis, van Liere et al (2023) examined the diagnostic potential of urinary VOCs for CRC/adenomas. By relating VOCs to known pathways, these researchers aimed to gain insight into the pathophysiology of colorectal neoplasia. They carried out

a systematic search in PubMed, Embase and Web of Science. Original studies on urinary VOCs for CRC/adenoma detection with a control group were included. QUADAS-2 tool was used for quality assessment. Meta-analysis was carried out by adopting a bi-variate model for sensitivity/specificity. Fagan's nomogram estimated the performance of combined FIT-VOC. Neoplasm-associated VOCs were linked to pathways using the KEGG database. A total of 16 studies entailing 837 CRC patients and 1,618 controls were included; 11 performed chemical identification and 7 chemical fingerprinting. In all studies, urinary VOCs discriminated CRC from controls. Pooled sensitivity and specificity for CRC based on chemical fingerprinting were 84 % (95 % CI: 73 % to 91 %) and 70 % (95 % CI: 63 % to 77 %), respectively. The most distinctive individual VOC was butanal (AUC 0.98). The estimated probability of having CRC following negative FIT was 0.38 %, whereas 0.09 % following negative FIT-VOC. Combined FIT-VOC would detect 33 % more CRCs. In total, 100 CRC-associated urinary VOCs were identified; particularly hydrocarbons, carboxylic acids, aldehydes/ketones and amino acids, and predominantly involved in TCA-cycle or alanine / aspartate / glutamine / glutamate / phenylalanine / tyrosine / tryptophan metabolism, which was supported by previous research on (colorectal) cancer biology. The potential of urinary VOCs to detect pre-cancerous adenomas or gain insight into their pathophysiology appeared under-studied. The authors concluded that urinary VOCs hold potential for non-invasive CRC screening. These researchers stated that multi-center validation studies are needed, especially focusing on adenoma detection.

Artificial Intelligence-Aided Colonoscopy for Screening of Colorectal Cancer

Brown et al (2022) noted that artificial intelligence (AI)-based computer-aided polyp detection (CADe) systems are intended to address the issue of missed polyps during colonoscopy. The effect of CADe during screening and surveillance colonoscopy has not previously been studied in a U.S. population. In a prospective, single-blind, multi-center, randomized tandem colonoscopy study, these researchers examined the effectiveness of a deep-learning (DL)-based CADe system (EndoScreener, Shanghai Wision AI, China). Participants were enrolled across 4 U.S. academic medical centers from 2019 through 2020. Patients presenting for CRC screening or surveillance were randomized

to CADe colonoscopy first or high-definition white light (HDWL) colonoscopy first, followed immediately by the other procedure in tandem fashion by the same endoscopist. The primary outcome was adenoma miss rate (AMR), and secondary outcomes included sessile serrated lesion (SSL) miss rate and adenomas per colonoscopy (APC). A total of 232 patients entered the study, with 116 patients randomized to undergo CADe colonoscopy first and 116 patients randomized to undergo HDWL colonoscopy first. After the exclusion of 9 patients, the study cohort included 223 patients. AMR was lower in the CADe-first group compared with the HDWL-first group (20.12 % [34/169] versus 31.25 % [45/144]; OR, 1.8048; 95 % CI: 1.0780 to 3.0217; p = 0.0247). SSL miss rate was lower in the CADe-first group (7.14 % [1/14]) versus the HDWL-first group (42.11 % [8/19]; p = 0.0482). First-pass APC was higher in the CADe-first group (1.19 (SD), 2.03 versus 0.90 (SD) 1.55; p = 0.0323). First-pass ADR was 50.44 % in the CADe-first group and 43.64 % in the HDWL-first group (p = 0.3091). The authors concluded that in this multi-center tandem colonoscopy RCT, they showed a decrease in AMR and SSL miss rate and an increase in 1st-pass APC with the use of a CADe-system when compared with HDWL colonoscopy alone. These researchers stated that CADe has the potential to decrease inter-provider variability in colonoscopy quality by reducing AMR, even in experienced providers.

The authors stated that this study had several drawbacks. First, this trial was not powered to detect a difference in ADR. Second, the tandem colonoscopy design used in this trial showed important insights regarding CADe performance; however, was somewhat limited in terms of generalizability to the real-world clinical setting. Endoscopists could not be blinded to a patient's group assignment while conducting each withdrawal. It was possible that endoscopist performance was influenced by being observed or that endoscopists who participated for the length of the study became over-reliant on CADe during withdrawal, leading to an over-estimation or under-estimate of CADe performance. However, these effects should generally have been balanced across both randomization groups. Third, this trial only included experienced endoscopists with a high baseline ADR at U.S. academic medical centers. It was less clear how CADe-assisted colonoscopy would affect endoscopy performance for trainees, for junior endoscopists, and in community settings. Some studies suggested the most benefit for CADe for endoscopists with limited

experience or high procedure volume and for patients who present with a high polyp burden. Fourth, this study employed a 2nd monitor adjacent to the primary endoscopy monitor, similar to other early trials. However, recent studies, including the authors' previous tandem colonoscopy study, had used a single-monitor setup. Although a dual-monitor setup may be less burdensome if latency of the CADe system is above a detectable visible threshold, it may also have negative effects on endoscopist gaze pattern. These investigators suspected a single-monitor setup may be preferred in the long run as it allows for easier integration of the technology.

Mehta et al (2023) stated that as AI-assisted diagnosis gained immense popularity, it is imperative to consider its use and effectiveness in the early diagnosis of CRC, responsible for over 1.8 million cases and 881,000 deaths globally, as reported in 2018. Improved adenoma detection rate, as well as better characterizations of polyps, are significant advantages of AIC. This systematic review examined the effectiveness of AI-assisted colonoscopy (AIC) in the early diagnosis of CRC as compared to conventional colonoscopy. Electronic databases such as PubMed/Medline, SCOPUS, and Web of Science (WOS) were reviewed for original studies (RCTs, observational studies), systematic reviews, and meta-analysis between 2017 and 2022 employing MESH terminology in a broad search strategy. All searches were carried out and analyzed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) methodology and were conducted in November, 2022. A data extraction form based on the Cochrane Consumers and Communication Review group's extraction template for quality assessment and evidence synthesis was used for data extraction. All included studies considered for bias and ethical criteria and provided valuable evidence to answer the research question. The database search identified 218 studies, including 87 from PubMed, 60 from SCOPUS, and 71 from Web of Science databases. The retrieved studies from the databases were imported to Rayyan software and a duplicate article check was performed, all duplicate articles were removed after careful evaluation of the data. The abstract and full-text screening was performed in accordance with the following eligibility criteria: STROBE for observational studies; PRISMA for review articles, ENTREQ for narrative studies; and modified JADAD for RCTs. This yielded 15 studies that met the requirements for the systematic review and were finally included in

the review. The authors concluded that AIC was a safe, highly effective screening tool that can increase the detection rate of adenomas, and polyps resulting in early diagnosis of CRC in adults when compared to conventional colonoscopy. Moreover, these researchers stated that the findings of this systematic review prompted further large-scale research to examine the effectiveness in accordance with gender, race, and socioeconomic status as well as its influence on prognosis and survival rate.

Shah et al (2023) noted that multiple computer-aided techniques utilizing AI have been created to improve the detection of polyps during colonoscopy; thus, reducing the incidence of CRC. While adenoma detection rates (ADR) and polyp detection rates (PDR) are important colonoscopy quality indicators, AMR may better quantify missed lesions, which can ultimately lead to interval CRC. In a systematic review and meta-analysis, these investigators examined the effectiveness of computer-aided colonoscopy (CAC) with respect to AMR, ADR, and PDR in RCTs. These researchers carried out a comprehensive, systematic literature search across multiple databases in September of 2022 to identify RCTs that compared CAC with traditional colonoscopy. Primary outcomes were AMR, ADR, and PDR. A total of 14 studies totaling 10,928 patients were included in the final analysis. There was a 65 % reduction in the adenoma miss rate with CAC (OR, 0.35; 95 % CI: 0.25 to 0.49, $p < 0.001$, $I2 = 50$ %). There was a 78 % reduction in the sessile serrated lesion miss rate with CAC (OR, 0.22; 95 % CI: 0.08 to 0.65, $p < 0.01$, $I2 = 0$ %). There was a 52 % increase in ADR in the CAC group compared with the control group (OR, 1.52; 95 % CI: 1.39 to 1.67, $p = 0.04$, $I2 = 47$ %). There was 93 % increase in the number of adenomas greater than 10 mm detected per colonoscopy with CAC (OR 1.93; 95 % CI: 1.18 to 3.16, $p < 0.01$, $I2 = 0$ %). The authors concluded that findings of the present study showed the promise of CAC in improving AMR, ADR, PDR across a spectrum of size and morphological lesion characteristics.

Spadaccini et al (2023) stated that CRC is the 3rd most common cancer worldwide, with the highest incidence reported in high-income countries. However, because of the slow progression of neoplastic precursors, along with the opportunity for their endoscopic detection and resection, a well-designed endoscopic screening program is expected to strongly decrease CRC incidence and mortality. In this regard, quality of

colonoscopy has been clearly related with the risk of post-colonoscopy CRC. Recently, the development of AI applications in the medical field has been growing in interest. Through machine learning processes, and, more recently, DL, if a very high numbers of learning samples are available, AI systems may automatically extract specific features from endoscopic images/videos without human intervention, helping the endoscopists in different aspects of their daily practice. The aim of this review is to summarize the current knowledge on AI-aided endoscopy, and to outline its potential role in colorectal cancer prevention. These researchers stated that preliminary data on both computer-aided characterization (CADx) systems as well as AI-assisted quality-control systems are promising; however, the lack of high-quality clinical studies prevents any reliable conclusion. Therefore, such studies should be considered as a priority in future research agendas. The steps to be carried out are still many; however, the path does not appear so steep anymore.

Mansur et al (2023) noted that AI is a branch of computer science that employs optimization, probabilistic and statistical approaches to analyze and make predictions based on a vast amount of data. In recent years, AI has revolutionized the field of oncology and spearheaded novel approaches in the management of various cancers, including CRC. Notably, the use of AI to diagnose, prognosticate, and predict response to therapy in CRC, is gaining traction and proving to be promising. There have also been several advancements in AI technologies to help predict metastases in CRC and in CAD Systems to improve miss rates for colorectal neoplasia. These investigators stated that while promising, the use of AI in clinical medicine is still at an early stage. One of the biggest drawbacks with AI is that models tend to be limited by the amount and quality of available labeled data for model development and validation. The generalizability of the models is also based on the type of data used in training. Large datasets that are ethnographically diverse will be needed to ensure that models can be applied for decision-making in diverse patient populations. In addition, there is a need to establish ethical guidelines before models can ever be widely employed to ensure their appropriate use and access. Another issue with the clinical application of AI and machine learning (ML) is the “black box” problem, in which researcher are able to see the inputs and outputs of a model, but not the variables that are used by the model to generate those outputs.

More efforts are needed to make the algorithms, especially DL algorithms, interpretable to clinicians and to allow streamlining of data pre-processing. Furthermore, most of the studies have a retrospective design, and more evidence on the effectiveness of AI is needed from prospective, multi-center studies. Finally, standards need to be established for the required accuracy rates to ensure the safe use and legality of AI technology. Efforts are needed to ensure that sensitive data are kept confidential. Nonetheless, the potential of AI in medicine, and specifically CRC is promising. The authors concluded that while there remains challenges to overcome with regards to the generalizability, validation, and clinical application of these technologies, future developments may eventually result in improved outcomes and to a paradigm shift in how patients with suspected or diagnosed CRC are cared for.

Sekiguchi et al (2025) stated that ensuring the high quality of colonoscopies in CRC screening is crucial in reducing CRC. Recently, computer-aided detection systems (CADe) that employ AI have attracted much attention as potentially useful tools for improving lesion detection in colonoscopy. However, evidence on the effectiveness of CADe in CRC screening is lacking. These investigators have planned a multi-national, multi-center, RCT in the Asia-Pacific region to examine if colonoscopy with CADe (test method) will yield higher lesion detection (primary endpoint: adenoma detection rate) than colonoscopy without CADe (standard method) in CRC screening populations. The study will include 1,400 participants aged 50 to 79 years who are due to undergo colonoscopy for CRC screening, whether as a primary screening colonoscopy or following a positive FIT. If the effectiveness of CADe is proven from this study, the use of CADe in colonoscopy for CRC screening will become standard, resulting in improved CRC screening.

Endo et al (2025) noted that CT colonography is increasingly recognized as a valuable modality for diagnosing colorectal lesions; however, the interpretation work-load remains challenging for physicians. Deep learning (DL)-based AI algorithms have been used for imaging diagnoses. These researchers examined the sensitivity of neoplastic lesions in CT colonography images. Lesion location and size were examined during colonoscopy and a large-scale data-base including a data-set for AI learning and external validation was created. The DICOM

data used as training data and internal validation data (total 453 patients) for this study were CRC screening test data from 2 multi-center joint trial carried out in Japan and data from 2 centers. External validation data (137 patients) were from other 2 centers. Lesions were categorized into ≥ 6 mm, 6 to 10 mm, and ≥ 10 mm. During this study, these investigators adopted a neural network structure that was designed based on the faster R-CNNs to detect colorectal lesion. The sensitivity of detecting colorectal lesions was verified when 1 and 2 positions were integrated. Internal validation yielded sensitivity of 0.815, 0.738, and 0.883 for lesions ≥ 6 mm, 6 to 10 mm, and ≥ 10 mm, respectively, with a false lesion limit of 3. Two external validation produced rates of 0.705 and 0.707, 0.575 and 0.573, and 0.760 and 0.779 for each lesion category. Combining 2 positions for each patient in calculating the sensitivity resulted in significantly improved rates for each lesion category. The authors concluded that the sensitivity of CT colonography images using the AI algorithm was improved by integrating evaluations in 2 positions. These researchers stated that in the future, validation experiments involving radiologists who can interpret images as well as AI to determine the auxiliary diagnosis can reduce the work-load of physicians.

The authors stated that this study had several drawbacks. First, these investigators were unable to assess the specificity due to the absence of negative cases in the external validation dataset. In future research, these researchers believe it is necessary to carry out validation using a large-scale data-set that includes negative cases, and to examine the specificity more accurately along with the sensitivity. Second, this trial did not validate how physicians interpreted the lesions identified by the AI algorithm. The sensitivity of the AI algorithm was evaluated based on its ability to detect lesions that were endoscopically confirmed. In future studies, it will be necessary to carry out evaluations that incorporate physicians' diagnoses to examine the performance of the AI algorithm more accurately. Third, the authors did not examine the threshold value and allowed number of false-positive lesions during the interpretation of the actual images. Fourth, this study did not examine the cost-effectiveness or feasibility of implementing dual-position imaging and diagnosis using AI algorithms in real-world clinical settings. Given the current radiologist shortage, cost and operational considerations are especially important.

Hassan et al (2025) stated that colonoscopy, a crucial procedure for detecting and removing colorectal polyps, has seen transformative advancements via the use of AI, specifically in CADe and CADx. These tools enhance real-time detection and characterization of lesions, potentially reducing human error, and standardizing the quality of colonoscopy across endoscopists. CADe has proven effective in increasing adenoma detection rate, potentially reducing long-term CRC incidence. However, CADe's benefits are accompanied by challenges, such as potentially longer procedure times, increased non-neoplastic polyp resections, and a higher surveillance burden. CADx, while promising in differentiating neoplastic and non-neoplastic diminutive polyps, encounters limitations in accuracy, especially in the proximal colon. Real-world data also showed gaps between trial effectiveness and practical outcomes, emphasizing the need for further research in uncontrolled settings. Moreover, CADx limited specificity and binary output underscore the necessity for explainable AI to gain endoscopists' trust. The authors examined the benefits, harms, and limitations of AI for colon cancer screening, surveillance, and treatment; focusing on CADe and CADx systems for lesion detection and characterization, respectively, while addressing challenges in integrating these technologies into clinical practice.

Blood-Based Protein Biomarkers for Screening of Colon Cancer

Beacon Biomedical, Inc. offers the BeScreened-CRC, an ELISA-based multiplex screening test, that involves testing three blood-based tumor-associated protein biomarkers; an oncoprotein called teratocarcinoma derived growth factor-1 (TDGF-1, Cripto-1); carcinoembryonic antigen (CEA), a well-established biomarker associated with CRC; and an extracellular matrix (ECM) protein involved in early stage tumor stroma changes. These three proteins target immunological activities associated with CRC tumorigenesis; generation, invasion, progression, and migration. This test is designed for those patients over 45 years of age who are at typical average-risk for CRC and who are unwilling or unable to participate in current recommended fecal-based CRC screening tests and colonoscopy procedures. Results are reported as either Negative of Positive for the likely presence of CRC. Patients who receive negative results are recommended to stay compliant with existing, patient specific screening guidance. Patients who receive positive results are

recommended to follow-up with their physician for consult and to schedule a screening colonoscopy. BeScreened-CRC is not a diagnostic test for CRC. It is a screening test that aides in the detection of colorectal cancer and is not intended to replace a colonoscopy. Beacon Biomedical reports 94.6% accuracy at determining the likely presence or absence of CRC. The test kit can be mailed to the patient's home or healthcare providers office. Beacon Biomedical will contact the patient at home to schedule an at-home blood draw if warranted.

Bhardwaj et al. (2020) state that blood-based protein biomarker signatures might be an alternative or supplement to existing methods for early detection of colorectal cancer (CRC) for population-based screening. The authors worked to obtain a protein biomarker signature for early detection of CRC and its precursor advanced adenoma (AA). In a two-stage design, 270 protein markers were measured by liquid chromatography/multiple reaction monitoring/mass spectrometry in plasma samples of discovery and validation sets. In the discovery set consisting of 100 newly diagnosed CRC cases and 100 age- and sex-matched controls free of neoplasm at screening colonoscopy, the algorithms predicting the presence of early- or late-stage CRC were derived by Lasso regression and .632 + bootstrap. The prediction algorithms were then externally validated in an independent validation set consisting of participants of screening colonoscopy including 56 participants with CRC, 99 with AA and 99 controls without any colorectal neoplasms. Three different signatures for all-, early- and late-stage CRC consisting of five-, three- and eight-protein markers were obtained in the discovery set with areas under the curves (AUCs) after .632 + bootstrap adjustment of 0.85, 0.83 and 0.96, respectively. External validation in the representative screening population yielded AUCs of 0.79 (95% CI, 0.70-0.86), 0.79 (95% CI, 0.66-0.89) and 0.80 (95% CI, 0.70-0.89) for all-, early- and late-stage CRCs, respectively. The three-marker early-stage algorithm yielded an AUC of 0.65 (95% CI, 0.56-0.73) for detection of AA in the validation set. Although not yet competitive with available stool-based tests for CRC early detection, the identified proteins may contribute to the development of powerful blood-based tests for early detection of CRC and its precursors AAs.

An UpToDate review on “Tests for screening for colorectal cancer” (Doubeni, 2020) state that “there is no evidence for the effectiveness of screening with plasma or serum markers in reducing the risk of CRC death. Available blood-based markers primarily detect CRC, particularly more advanced CRC, rather than precancerous lesions. Their role in early detection is unclear, and they are not included in major society guidelines for screening. Blood tests for gene expression are in development for patients unwilling to undergo initial colonoscopy. The potential to utilize combinations of serum markers has also been explored, but well-designed studies in unselected screening populations are needed to determine if there is clinical relevance”. Furthermore, carcinoembryonic antigen (CEA) is not useful as a screening test for CRC. It may; however, be used for surveillance of patients with CRC.

Capsule Endoscopy for Colorectal Cancer Screening

Kjolhede and colleagues (2021) noted that colon capsule endoscopy (CCE) is a technology that might contribute to CRC screening programs as a filter test between fecal immunochemical testing and standard colonoscopy. These investigators systematically reviewed the literature for studies examining the diagnostic yield of 2nd-generation CCE compared with standard colonoscopy. They carried out a systematic literature search in PubMed, Embase, and Web of Science. Study characteristics including quality of bowel preparation and completeness of CCE transits were extracted. Per-patient sensitivity and specificity were extracted for polyps (any size, greater than or equal to 10 mm, greater than or equal to 6 mm) and lesion characteristics. Meta-analyses of diagnostic yield were performed. The literature search revealed 1,077 unique papers and 12 studies were included. Studies involved a total of 2,199 patients, of whom 1,898 were included in analyses. The rate of patients with adequate bowel preparation varied from 40 % to 100 %. The rates of complete CCE transit varied from 57 % to 100 %. The meta-analyses demonstrated that mean (95 % CI) sensitivity, specificity, and diagnostic odds ratio were: 0.85 (0.73 to 0.92), 0.85 (0.70 to 0.93), and 30.5 (16.2 to 57.2), respectively, for polyps of any size; 0.87 (0.82 to 0.90), 0.95 (0.92 to 0.97), and 136.0 (70.6 to 262.1), respectively, for polyps greater than or equal to 10 mm; and 0.87 (0.83 to 0.90), 0.88 (0.75 to 0.95), and 51.1 (19.8 to 131.8), respectively, for polyps greater than or equal to 6 mm. No serious adverse events (AEs) were reported for CCE.

The authors concluded that CCE had high sensitivity and specificity for per-patient polyps compared with standard colonoscopy; however, the relatively high rate of incomplete investigations limited the application of CCE in a CRC screening setting.

Houwen and Dekker (2021) noted that the European Union recommends FIT as the preferred method for population-based screening programs, followed by colonoscopy in FIT-positive individuals. Such FIT-based programs have high participation rates, and a PPV of approximately 40 %, which makes it not so attractive to follow a positive FIT by another non-invasive test where no therapy nor pathology-based diagnosis is possible. Thus, CCE might only be a sensible option for those FIT-positive individuals who are unwilling to undergo colonoscopy. In other countries, depending on many factors like availability of endoscopy services and finances, the preferred screening methods might be different, and primary screening by colonoscopy may be recommended. In these areas, participation-rates could possibly be increased by offering CCE as an alternative screening method; however, data of prospective studies on aspects like participation rates, accuracy, patient burden, logistics and cost-effectivity are needed first

In addition, European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR)'s guideline on "Imaging alternatives to colonoscopy: CT colonography and colon capsule" (Spada et al, 2021) did not suggest CCE as a 1st-line screening test for CRC (Weak recommendation, low-quality evidence).

Furthermore, an UpToDate review on "Tests for screening for colorectal cancer" (Doubeni, 2021b) states that "Colon capsule endoscopy is approved by the US Food and Drug Administration (FDA) for use only in patients who had an incomplete colonoscopy, not as a screening option by itself. During the test, the patient swallows a capsule containing tiny wireless video cameras that take images as the capsule traverses the colon. Colon capsule endoscopy requires a bowel preparation; however, it does not require sedation or dietary or medication adjustments. This test appears to have a sensitivity and specificity similar to colonoscopy".

CD3 Immuno-Staining for Screening of Colon Cancer

Mima et al (2015) noted that evidence indicates a complex link between gut microbiome, immunity, and intestinal tumorigenesis. To target the microbiota and immunity for colorectal cancer prevention and therapy, a better understanding of the relationship between microorganisms and immune cells in the tumor microenvironment is needed. Experimental evidence suggested that Fusobacterium nucleatum (F nucleatum) may promote colonic neoplasia development by down-regulating antitumor T cell-mediated adaptive immunity. These researchers tested the hypothesis that a greater amount of F nucleatum in colorectal carcinoma tissue is associated with a lower density of T cells in tumor tissue. A cross-sectional analysis was conducted on 598 rectal and colon carcinoma cases in 2 US nationwide prospective cohort studies with follow-up through 2006, the Nurses' Health Study (participants enrolled in 1976) and the Health Professionals Follow-up Study (participants enrolled in 1986). Tissue collection and processing were performed from 2002 through 2008, and immunity assessment, 2008 through 2009. From 2013 through 2014, the amount of F nucleatum in colorectal carcinoma tissue was measured by quantitative polymerase chain reaction assay; these investigators equally dichotomized positive cases (high versus low). Multi-variable ordinal logistic regression analysis was conducted in 2014 to assess associations of the amount of F nucleatum with densities (quartiles) of T cells in tumor tissue, controlling for clinical and tumor molecular features, including microsatellite instability, CpG island methylator phenotype, long interspersed nucleotide element-1 (LINE-1) methylation, and KRAS, BRAF, and PIK3CA mutation status. They adjusted the 2-sided α level to 0.013 for multiple hypothesis testing. Densities of CD3+, CD8+, CD45RO (protein tyrosine phosphatase receptor type C [PTPRC])+, and FOXP3+ T cells in tumor tissue, determined by means of tissue microarray immuno-histochemical analysis and computer-assisted image analysis. F nucleatum was detected in colorectal carcinoma tissue in 76 (13 %) of 598 cases. Compared with F nucleatum-negative cases, F nucleatum-high cases were inversely associated with the density of CD3+ T cells (for a unit increase in quartile categories of CD3+ T cells as an outcome: multi-variable odds ratio, 0.47 [95 % confidence interval [CI]: 0.26 to 0.87]; p for trend = 0.006). The amount of F nucleatum was not significantly associated with the density of CD8+, CD45RO+, or FOXP3+ T cells (P for

trend = 0.24, 0.88, and 0.014, respectively). The authors concluded that the amount of tissue F nucleatum is inversely associated with CD3+ T-cell density in colorectal carcinoma tissue. On validation, their human population data may provide an impetus for further investigations on potential interactive roles of Fusobacterium and host immunity in colon carcinogenesis.

Turksma et al (2016) examined the prognostic and predictive value of tumor-infiltrating lymphocytes (TIL) in colon cancer in a cohort of patients who previously took part in a trial on adjuvant active specific immunotherapy (ASI). These researchers determined the number and location of CD3 and CD8 positive T cells in archival tumor samples of 106 colon cancers. They correlated stromal and epithelial TIL numbers with tumor stage and treatment and determined the effects on disease-specific survival (DSS) and recurrence-free interval (RFI). On the basis of the data presented, these investigators concluded that (i) high numbers of stromal CD3 T cells have positive prognostic value measured as DSS for patients with stage II microsatellite-stable tumors, and (ii) high numbers of epithelial CD8-positive T cells have positive prognostic value measured as RFI for the group of patients with stage II microsatellite-stable tumors as well as for the whole group (so stage II plus stage III together). Furthermore, they concluded that high numbers of pre-existing stromal CD3-positive T cells are of positive predictive value in adjuvant ASI treatment measured as DSS as well as RFI. The authors concluded that ASI therapy may contribute to an improved DSS and RFI in patients with microsatellite-stable colon tumors harboring high numbers of pre-existing stromal CD3(+) TIL; validation in future clinical trials is awaited.

Hagland et al (2017) tested the feasibility of conducting parallel analyses of circulating T-cells in blood and intra-tumoral T-cells in colorectal cancer. A pre-operative “liquid biopsy” to determine immune status would facilitate clinical decision-making. A total of 18 patients with stage I-III colorectal cancer (CRC) were included. Blood was analyzed for T-cell type (CD3+, CD4+ and CD8+) and count using flow cytometry. Intra-tumoral T-cells were stained using immunohistochemistry and quantified by digital pathology. Tumor location was defined as invasive front (IF) or tumor center (TC). The number of CD3+ and CD4+ T-cells in pre-surgical

blood samples correlated with the number of CD3+ T-cells found in the IF (Spearman ϱ = 0.558, p < 0.05 and 0.598, p < 0.01, respectively) and CD3+ in the TC (ϱ = 0.496, p < 0.05, and ϱ = 0.637, p < 0.01, respectively). A strong correlation was found between CD4+ cells in blood and CD8+ T-cells found in the TC and IF (ϱ = 0.602 and ϱ = 0.591, p < 0.01). The authors concluded that there is a correlation between blood CD3+ and CD4+ T-cells and the T-cells found at the TC and IF.

Furthermore, National Comprehensive Cancer Network's clinical practice guideline on "Colon cancer" (Version 2.2017) does not mention CD3 immuno-staining as a management tool.

Cologuard

Redwood and colleagues (2016) evaluated the accuracy of a multi-target stool DNA test (MT-sDNA) compared with FIT for hemoglobin for detection of screening-relevant colorectal neoplasia (SRN) in Alaska Native people, who have among the world's highest rates of CRC and limited access to conventional screening approaches. These researchers performed a prospective, cross-sectional study of asymptomatic Alaska Native adults aged 40 to 85 years and older undergoing screening or surveillance colonoscopy between February 6, 2012, and August 7, 2014. Among 868 enrolled participants, 661 completed the study (403 [61 %] women). Overall, SRN detection by MT-sDNA (49 %) was superior to that by FIT (28 %; p < 0.001); in the screening group, SRN detection rates were 50 % and 31 %, respectively (p = 0.01). Multi-target stool DNA testing detected 62 % of adenomas 2 cm or larger versus 29 % by FIT (p = 0.05). Sensitivity by MT-sDNA increased with adenoma size (to 80 % for lesions greater than or equal to 3 cm; p = 0.01 for trend) and substantially exceeded FIT sensitivity at all adenoma sizes. For sessile serrated polyps larger than 1 cm (n = 9), detection was 67 % by MT-sDNA versus 11 % by FIT (p = 0.07). For CRC (n = 10), detection was 100 % by MT-sDNA versus 80 % by FIT (p = 0.48). Specificities were 93 % and 96 %, respectively (p = 0.03). The authors concluded that the sensitivity of MT-sDNA for cancer and larger polyps was high and significantly greater than that of FIT for polyps of any size, while specificity was slightly higher with FIT. They stated that these findings could translate into high cumulative neoplasm detection rates on serial testing within a screening program; the MT-sDNA represents a potential

strategy to expand CRC screening and reduce CRC incidence and mortality, especially where access to endoscopy is limited. These investigators stated that further consideration and evaluation of the optimal test frequency, physician and patient acceptance, cost-effectiveness, and logistic algorithms for use and distribution within the Alaska Tribal Health System are needed.

Imperiale et al (2014) compared a non-invasive, multi-target stool DNA test with a fecal immunochemical test (FIT) in persons at average risk for CRC. The DNA test includes quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and β-actin, plus a hemoglobin immunoassay. Results were generated with the use of a logistic-regression algorithm, with values of 183 or more considered to be positive. Fecal immunochemical test values of more than 100 ng of hemoglobin per milliliter of buffer were considered to be positive. Tests were processed independently of colonoscopic findings. Of the 9,989 participants who could be evaluated, 65 (0.7 %) had CRC and 757 (7.6 %) had advanced pre-cancerous lesions (advanced adenomas or sessile serrated polyps measuring greater than or equal to 1 cm in the greatest dimension) on colonoscopy. The sensitivity for detecting CRC was 92.3 % with DNA testing and 73.8 % with FIT ($p = 0.002$). The sensitivity for detecting advanced pre-cancerous lesions was 42.4 % with DNA testing and 23.8 % with FIT ($p < 0.001$). The rate of detection of polyps with high-grade dysplasia was 69.2 % with DNA testing and 46.2 % with FIT ($p = 0.004$); the rates of detection of serrated sessile polyps measuring 1 cm or more were 42.4 % and 5.1 %, respectively ($p < 0.001$). Specificities with DNA testing and FIT were 86.6 % and 94.9 %, respectively, among participants with non-advanced or negative findings ($p < 0.001$) and 89.8 % and 96.4 %, respectively, among those with negative results on colonoscopy ($p < 0.001$). The numbers of persons who would need to be screened to detect 1 cancer were 154 with colonoscopy, 166 with DNA testing, and 208 with FIT. The authors concluded that in asymptomatic persons at average risk for CRC, multi-target stool DNA testing detected significantly more cancers than did FIT but had more false-positive results.

In an editorial that accompanied the afore-mentioned study, Robertson and Dominitz (2014) stated that “The new multitarget stool DNA test is clearly an improvement over its predecessors, and the results of this

study will help to inform the current effort of the U.S. Preventive Services Task Force to reevaluate screening tests. Comparative-effectiveness studies are now needed to clarify the role of stool DNA testing with respect to programmatic screening with other test options. Only through a better understanding of other key factors, such as the screening interval, adherence, cost, and diagnostic evaluation of positive results, can we determine the appropriate place for stool DNA testing on the screening menu".

Onieva-Garcia and colleagues (2015) evaluated the available evidence on the validity, diagnostic accuracy and clinical utility of the multi-target DNA test in feces (Cologuard™) for screening for colorectal cancer (CRC). A systematic review was performed by consulting MedLine, EMBASE and Web of Science to July 2014. Studies on diagnostic tests were selected that evaluated the test in asymptomatic adults who underwent CRC screening. The quality and risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies tool. The level of evidence was defined according to the National Institute for Health and Clinical Excellence. A qualitative synthesis was conducted. A total of 299 literature references were identified, including 1 synthesis report and 5 diagnostic test studies; 3 of the 5 studies had a case-control design in Sackett phase II and were of moderate quality, and 2 had a prospective design in Sacket phase III and were of high quality. The sensitivity for detecting CRC was greater than 90 %, but only 40 % for detecting advanced adenomas. The test provided conclusive diagnostic evidence to rule out CRC (negative likelihood ratio, LR-: 0.02 to 0.09), although it was not useful for ruling out advanced adenoma (LR-: 0.5 to 0.7). The authors concluded that Cologuard™ test is a valid screening test for ruling out cancerous lesions but is suboptimal for ruling out precancerous lesions. They stated that there is no evidence in terms of mortality, survival or cost-effectiveness.

An UpToDate review on "Tests for screening for colorectal cancer: Stool tests, radiologic imaging and endoscopy" (Doubeni, 2016) states that "Cologuard has been approved by the US Food and Drug Administration (FDA) in August 2014, as a screening test for colorectal carcinoma to be followed, when abnormal, by diagnostic colonoscopy. The implications of "false positives," abnormal DNA testing in patients who are not found to have colonic lesions on colonoscopy, is uncertain. In a study of

screening with 3 modalities (stool DNA, colonoscopy, and fecal immunochemical tests) in average-risk patients, nearly 10 % of those with an entirely negative colonoscopy had a positive stool DNA test. It is not known whether these positive tests are clinically important, for example, by representing carcinomas elsewhere in the gastrointestinal tract or mucosal predisposition to cancer. The appropriate interval between screening fecal DNA tests is unknown. As of October 2014 the Centers for Medicare and Medicaid Services (CMS) include coverage for this test once every 3 years for asymptomatic Medicare beneficiaries age 50 to 84 years at average risk for CRC. Stool DNA testing is not currently incorporated into screening guidelines from the US Preventive Services Task Force (USPSTF), which were prepared before evidence regarding the current generation fecal test was available".

Cologuard Plus

Liscu, et al. (2024) stated that biomarkers in CRC are of great interest in the current literature due to improvements in techniques such as liquid biopsy and next-generation sequencing (NGS). However, screening methods vary globally, with multi-target stool DNA (mt-sDNA) predominantly used in the U.S. and, more recently, the Cologuard Plus; biomarkers such as the Galectins family and septins show promise in early detection. Gut microbiome assessments, such as Fusobacterium nucleatum, are under intense exploration. Diagnostic tests, such as circulating DNA analysis via NGS, exhibit effectiveness and are being increasingly adopted. Circulating tumor cells emerge as potential alternatives to traditional methods in terms of diagnosis and prognosis.

Imperiale, et al. (2024) evaluated the performance of a next-generation multitarget stool DNA test for colorectal cancer screening. This test includes assessments of DNA molecular markers and hemoglobin levels to enhance specificity and sensitivity compared to previous versions and the fecal immunochemical test (FIT). The study was conducted at 186 sites across the United States, involving 20,176 participants out of 26,758 enrolled. Participants were asymptomatic individuals aged 40 or older scheduled for screening colonoscopy. Exclusions included those with a history of colorectal cancer, advanced precancerous lesions, hereditary cancer syndromes, inflammatory bowel disease, recent positive stool tests, or recent colonoscopy. The primary objective was to determine the

sensitivity of the next-generation test for colorectal cancer and its specificity for advanced neoplasia. Secondary objectives included sensitivity for advanced precancerous lesions and specificity for nonneoplastic findings or negative colonoscopy, and a comparison with FIT. The next-generation test showed a sensitivity of 93.9% for colorectal cancer and 43.4% for advanced precancerous lesions. Specificity for advanced neoplasia was 90.6% and for nonneoplastic findings or negative colonoscopy was 92.7%. In comparison, FIT had a sensitivity of 67.3% for colorectal cancer and 23.3% for advanced precancerous lesions, with specificities of 94.8% for advanced neoplasia and 95.7% for nonneoplastic findings or negative colonoscopy. Sensitivity for colorectal cancer did not vary significantly by disease stage or location. Sensitivity for advanced precancerous lesions was consistent across age groups and lesion subtypes. Specificity for advanced neoplasia was higher in younger participants, with a decrease observed in older age groups. For colorectal cancer, the positive predictive value was 3.4% and the negative predictive value was 99.97%. For advanced neoplasia, the positive predictive value was 37.7% and the negative predictive value was 93.0%. The authors found that the next-generation multitarget stool DNA test demonstrated superior sensitivity for detecting colorectal cancer and advanced precancerous lesions compared to FIT. However, FIT had higher specificity for advanced neoplasia and nonneoplastic findings or negative colonoscopy. Strengths of the study are that it was conducted in a large and diverse participant population, representative of the U.S. screening-eligible population. Another strength was the use of central, blinded adjudication of colorectal cancers ensured diagnostic accuracy. Limitations of the study include: 1) a high proportion of participants whose samples could not be evaluated, possibly due to the COVID-19 pandemic; 2) there was no direct comparison with the current version of the multitarget stool DNA test. The authors concluded that the next-generation multitarget stool DNA test showed high sensitivity for colorectal cancer and advanced precancerous lesions, making it a valuable tool for colorectal cancer screening. However, FIT remains superior in specificity for advanced neoplasia.

The authors stated that a drawback of this trial was the relatively high proportion of individuals who provided informed consent and were enrolled but whose samples could not be examined according to the protocol. A contributing factor may have been conduct of the study during

the coronavirus disease 2019 pandemic, which probably affected enrollment and access to colonoscopy. Multiple imputation analyses that accounted for all the subjects showed results consistent with those from the population of participants with evaluable samples. Another drawback was that these researchers did not directly compare the performance of the next-generation multi-target stool DNA test with the current version of the multi-target stool DNA test. Therefore, the results from this study could not be reliably compared with published findings for the multi-target stool DNA test that is currently available for screening purposes, and valid comparisons would require the assessment of both tests in the same persons and specimens concurrently in the context of screening.

In an editorial that accompanied the afore-mentioned study by Imperiale, et al. (2024), Carethers (2024) stated that screening tests for CRC have evolved to include stool-based, endoscopic and image-based, and blood-based methods, with minimal thresholds for sensitivity and specificity for CRC set by the baseline characteristics of FIT. Although multiple tests have been developed over time and vary in cost-effectiveness for CRC screening, the best screening test is the one that gets completed by the patient. Most of the recommended tests, including the 2 newer tests assessed in the studies now published in the Journal, improved on the sensitivity and approached the specificity of FIT, such that these tests appeared to be at least as effective as FIT. Adherence to screening is a key factor, and ease of test use may contribute to increased adherence. Cost-effectiveness and the selection of the testing interval may play roles in adherence, especially in populations that already have lower rates of adherence to CRC screening than the general population. Adherence to screening varies according to age group, including persons in the 45 to 49 years age group who are now eligible for average-risk screening. The editorialist hoped that these newer tests will increase use and adherence and elevate the percentage of the population undergoing screening in order to reduce deaths from CRC.

Colon AiQ

Colon AiQ (Breakthrough Genomics) is a cell-free DNA (cfDNA), methylation-based quantitative PCR assay that evaluates SEPTIN9, IKZF1, BCAT1, VAV3, and BCAN biomarkers in plasma. The test uses DNA methylation technology to find small traces of tumor cfDNA in the

blood. The results are interpreted using an AI-powered computer analysis and reported as presence or absence of circulating tumor DNA (ctDNA). If a patient receives a 'positive' finding that a CRC cancer signal has been detected, then it is recommended that they consult with their healthcare provider and seek further testing including a colonoscopy.

Blood-based colorectal cancer screening tests is an emerging option that has been evaluated by the National Comprehensive Cancer Network (NCCN, 2024). Per NCCN, the methylation status of the SEPTIN9 (SEPT9) gene has been shown to distinguish CRC tissue from normal surrounding tissue, and circulating methylated SEPT9 DNA in plasma is a biomarker for CRC. A multicenter study compared the fecal immunochemical test (FIT) and a SEPT9 DNA methylated blood test for CRC screening of 102 patients with identified CRC, and found that the specificity for CRC detection was higher for FIT (97.4% vs. 81.5%, respectively) but the sensitivity for CRC detection was not significantly different (68% vs. 73.3%, respectively). NCCN does not mention using cell-free DNA (cfDNA), methylation-based quantitative PCR assay that evaluates IKZF1, BCAT1, VAV3, and BCAN biomarkers in plasma for CRC screening.

Colorectal Cancer Screening After Age of 85 Years

The USPSTF (2021) updated its 2016 recommendation on screening for CRC by commissioning a systematic review to examine the benefits and harms of screening for CRC in adults 40 years or older. The review also examined if these findings varied by age, sex, or race/ethnicity. Furthermore, as in 2016, the USPSTF commissioned a report from the Cancer Intervention and Surveillance Modeling Network Colorectal Cancer Working Group to provide information from comparative modeling on how estimated life-years gained, CRC cases averted, and CRC deaths averted vary by different starting and stopping ages for various screening strategies. The USPSTF recommended screening for CRC in all adults aged 50 to 75 years (A recommendation). The USPSTF recommended screening for CRC in adults aged 45 to 49 years (B recommendation). The USPSTF recommended that clinicians selectively offer screening for CRC in adults aged 76 to 85 years. Evidence indicated that the net benefit of screening all persons in this age group is small. In determining

whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences (C recommendation).

Patel et al (2022) presented an update to the 2017 CRC screening recommendations from the U.S. Multi-Society Task Force on Colorectal Cancer, which represents the ACG, the American Gastroenterological Association (AGA), and the American Society for Gastrointestinal Endoscopy (ASGE). This update is restricted to addressing the age to start and stop CRC screening in average-risk individuals and the recommended screening modalities. Although there is no literature demonstrating that CRC screening in individuals under age 50 improves health outcomes such as CRC incidence or CRC-related mortality, sufficient data support the U.S. Multi-Society Task Force to suggest average-risk CRC screening begin at age 45. This recommendation is based on the increasing disease burden among individuals under age 50, emerging data that the prevalence of advanced colorectal neoplasia in individuals ages 45 to 49 approaches rates in individuals 50 to 59, and modeling studies that demonstrate the benefits of screening outweigh the potential harms and costs. For individuals ages 76 to 85, the decision to start or continue screening should be individualized and based on prior screening history, life expectancy, CRC risk, and personal preference. Screening is not recommended after age 85.

Colorectal Cancer Screening in Patients with Cystic Fibrosis

Hadjiliadis and colleagues (2018) noted that improved therapy has substantially increased survival of persons with cystic fibrosis (CF). However, the risk of CRC in adults with CF is 5- to 10-fold greater compared to the general population, and 25 to 30 times greater in CF patients after an organ transplantation. To address this risk, the CF Foundation (CFF) convened a multi-stakeholder task force to develop CRC screening recommendations. The 18-member task force consisted of experts including pulmonologists, gastroenterologists, a social worker, nurse coordinator, surgeon, epidemiologist, statistician, CF adult, and a parent. The committee comprised 3 work groups: Cancer Risk, Transplant, and Procedure and Preparation. A guidelines specialist at the CFF conducted an evidence synthesis February to March 2016 based on PubMed literature searches. Task force members conducted additional

independent searches. A total of 1,159 articles were retrieved. After initial screening, the committee read 198 articles in full and analyzed 123 articles to develop recommendation statements. An independent decision analysis evaluating the benefits of screening relative to harms and resources required was conducted by the Department of Public Health at Erasmus Medical Center, Netherlands using the Microsimulation Screening Analysis model from the Cancer Innervation and Surveillance Modeling Network. The task force included recommendation statements in the final guideline only if they reached an 80 % acceptance threshold. The task force made 10 CRC screening recommendations that emphasize shared, individualized decision-making and familiarity with CF-specific GI challenges. The task force recommended colonoscopy as the preferred screening method, initiation of screening at age 40 years, 5-year re-screening and 3-year surveillance intervals (unless shorter interval is indicated by individual findings), and a CF-specific intensive bowel preparation. Organ transplant recipients with CF should initiate CRC screening at age 30 years within 2 years of the transplantation because of the additional risk for colon cancer associated with immunosuppression. The authors concluded that these recommendations aim to help CF adults, families, primary care physicians, gastroenterologists, and CF and transplantation centers address the issue of CRC screening. They differed from guidelines developed for the general population with respect to the recommended age of screening initiation, screening method, preparation, and the interval for repeat screening and surveillance.

The National Cancer Institute (NCI) partnered with the CFF to examine the cost-effectiveness of CRC screening in the CF population, and to develop screening recommendations from these results. The MISCAN-Colon model was adjusted to the increased risk of CRC in CF patients (with and without organ transplant). Colonoscopy every 5 years starting at age 40 was the optimal strategy for CF patient without an organ transplant, and colonoscopy starting at age 30 to 35 was suggested for CF patients with an organ transplant. Methods and recommendations were described in more detail in the study by Gini and associates (2018). These investigators modeled 76 colonoscopy screening strategies that varied the age range and screening interval. The optimal screening strategy was determined based on a willingness to pay threshold of $100,000 per life-year gained. Sensitivity and supplementary analyses

were performed, including FIT as an alternative test, earlier ages of transplantation, and increased rates of colonoscopy complications, to assess if optimal screening strategies would change. Colonoscopy every 5 years, starting at an age of 40 years, was the optimal colonoscopy strategy for patients with CF who never received an organ transplant; this strategy prevented 79 % of deaths from CRC. Among patients with CF who had received an organ transplant, optimal colonoscopy screening should commence at an age of 30 or 35 years, depending on the patient's age at time of transplantation. Annual FIT screening was predicted to be cost-effective for patients with CF. However, the level of accuracy of the FIT in this population is unclear. The authors concluded that using a Microsimulation Screening Analysis-Colon model, they found screening of patients with CF for CRC to be cost-effective. Because of the higher risk of CRC in these patients, screening should start at an earlier age with a shorter screening interval. The findings of this study (especially those on FIT screening) may be limited by restricted evidence available for patients with CF.

An UpToDate review on “Cystic fibrosis: Overview of gastrointestinal disease” (Sabharwal and Schwarzenberg, 2019) states that “The Cystic Fibrosis Foundation (CFF) has developed Guidelines for Colorectal Cancer Screening for adults with CF. The guideline recommends colonoscopy for screening, beginning at age 40 years, or at 30 years for those who have had an organ transplant. The screening should be repeated every five years. If any adenomatous polyps are identified, the colonoscopy should be repeated in three years or less, depending on characteristics of the individual case. The guideline includes an intensive bowel preparation protocol that should be used for CF patients, because it is very difficult to achieve a satisfactory colonic lavage in these individuals”.

An UpToDate review on “Colorectal cancer: Epidemiology, risk factors, and protective factors” (Macrae, 2019) states that “Patients with cystic fibrosis have an elevated risk of CRC. In a meta-analysis, the pooled standardized incidence ratio was 10.91, 95 % CI 8.42-14.11, and it was two- to five-fold higher following lung transplantation. The Cystic Fibrosis Foundation (CFF) has developed guidelines for CRC screening for adults

with cystic fibrosis. Although risk estimates are provided, the benefits of screening for CRC in these patients, who as a group have substantial comorbidities, are less certain".

Furthermore, in a Medscape review on "Screening for colorectal cancer in cystic fibrosis: New risks require new strategies", Johnson (2019) noted that the recommendations from the CFF were not considered in the CRC screening guidelines produced by the ACS, the U.S. Multi-Society Task Force on Colorectal Cancer, or the ACG. These new guidelines need to be considered and then reviewed since they are not yet weighted in terms of the strength of the recommendations or the grades of evidence. That will need to be carried out by the national societies, because these will otherwise not necessarily get paid for. Most state legislations default to the ACS or the ACG guideline.

ColoSense Multi-Target Stool RNA Test

Yang et al (2010) attempted to specifically quantify transcripts of fecal cytokeratin 19 (CK19) and ribosomal protein L19 (RPL19) RNA expression of CRC and clarified their correlation with clinico-pathological parameters and survival in combination. Solid fecal samples were collected and preserved before any treatment. Levels of fecal CK19 and RPL19 mRNA were measured using quantitative real-time PCR. An expression level higher than median value was defined as positive. Between April 2001 and June 2007, a total of 92 patients were recruited. The levels of both markers increased in a trend as stage. Young patients (less than 67 years) were correlated with higher rate of CK19+ ($p = 0.001$), so were higher stages, but with borderline significance ($p = 0.051$). CK19+ and RPL19+ were highly correlated mutually ($p = 0.001$). Neither CK19+ ($p = 0.12$) nor RPL19+ ($p = 0.14$) alone was a prognostic factor of disease-free survival (DFS); however, CK19+/RPL19+ was shown to be with worse prognosis ($p = 0.037$), but not an independent factor in multi-variate analysis with stage. The authors concluded that both markers were significantly higher in the patients of metastatic disease. The use of 2 markers would recognize the high-risk group better than the single marker usage, although not reaching independent status yet. Multi-target strategy assay was suggested for fecal RNA examination.

Iannone et al (2016) reported an update of current methods for CRC screening based on fecal sample analysis. These investigators carried out a systematic review of the literature in Medline, Embase, and Science Direct electronic databases. Blood in the stools was the 1st and most used strategy; FOBT and FIT are the main methods. Both are economic, easy to perform with high specificity, and low sensitivity. Based on CRC multi-step process with genetic and epigenetic alterations in large bowel cell DNA, single mutations or panels of alterations have been detected. These tests have the advantage of a marked improvement of the sensitivity when compared to fecal blood; however, high costs, poor availability, and correct choice of marker panel represent the major limitations. A specific stool DNA (sDNA) panel including aberrantly methylated BMP3 and NDRG4 promoter regions, mutant k-ras and β-actin (a reference gene for human DNA quantity), and an immunochemical assay for human hemoglobin (Hb) has been recently approved by the FDA. Novel promising biomarkers for CRC screening are represented by microRNAs (miRNAs), a group of 18 to 25 nucleotide non-coding RNA molecules that regulate gene expression. Reports on these fecal biomarkers were case-control studies, and each of them examined single miRNAs or multi-target panels. On the other hand, some fecal proteins have been studied as possible CRC screening markers, even though they showed poor results. Finally, alterations of estrogen receptor-beta (i.e., dramatic reduction in the early stage of CRC) have been demonstrated in tissue samples. The authors concluded that specific investigations are needed in order to add further non-invasive markers to the panel of CRC screening tools.

Barnell et al (2023) stated that non-invasive tests for CRC screening must include sensitive detection of CRC and pre-cancerous lesions. These tests must be validated for the intended-use population, which includes average-risk individuals 45 years or older. In a phase-III clinical trial, these researchers compared the sensitivity and specificity of a non-invasive, multi-target stool RNA (mt-sRNA) test (ColoSense) test with results from a colonoscopy. This study (the CRC-PREVENT Trial) was a prospective, blinded, cross-sectional study to support a pre-market approval (PMA) application for a class-III medical device. A total of 8,920 subjects were identified online using social media platforms and enrolled from June 2021 to June 2022 using a de-centralized nurse call center. All subjects completed the mt-sRNA test, which incorporated a commercially

available FIT, concentration of 8 RNA transcripts, and participant-reported smoking status. Stool samples were collected before subjects completing a colonoscopy at their local endoscopy center. The mt-sRNA test results (positive or negative) were compared with index lesions observed on colonoscopy. Over the course of 12 months, individuals 45 years and older were enrolled in the clinical trial using the de-centralized recruitment strategy. Subjects were enrolled from 49 U.S. states, and obtained colonoscopies at more than 3,800 different endoscopy centers. The primary outcomes included the sensitivity of the mt-sRNA test for detecting CRC and advanced adenomas and the specificity for no lesions on colonoscopy. The mean (range) age of subjects was 55 (45 to 90) years, with 4 % self-identified as Asian, 11 % as Black, and 7 % as Hispanic. Of the 8,920 eligible subjects, 36 (0.40 %) had CRC, and 606 (6.8 %) had advanced adenomas. The mt-sRNA test sensitivity for detecting CRC was 94 %, sensitivity for detecting advanced adenomas was 46 %, and specificity for no lesions on colonoscopy was 88 %. The mt-sRNA test showed significant improvement in sensitivity for CRC (94 % versus 78 %; McNemar $p = 0.01$), and advanced adenomas (46 % versus 29 %; McNemar $p < 0.001$) compared with results of the FIT. The authors concluded that in individuals 45 years and older, the mt-sRNA test showed high sensitivity for colorectal neoplasia (CRC and advanced adenoma) with significant improvement in sensitivity relative to the FIT. Specificity for no lesions on colonoscopy was comparable to existing molecular diagnostic tests.

The authors stated that this study had several drawbacks. First, center-to-center variations in colonoscopy quality metrics (e.g., adenoma detection rate, withdrawal time), which were attributable to a physician's experience, technique, and training might have increased the false-positive and false-negative result rate of the mt-sRNA test. Second, there were differences in participant treatment (e.g., colonoscopy scheduling, and bowel preparation) as well as reporting practices in the colonoscopy and pathology reports (e.g., nomenclature for SSLs, lesion sizing). These factors could have contributed to the variability of results. Third, the decentralized approach likely contributed to the high drop-out rate.

In a review on "Cancer screening: Present recommendations, the development of multi-cancer early development tests, and the prospect of universal cancer screening", Gales et al (2024) noted that the mt-sRNA

ColoSense test demonstrated improvements in sensitivity (94 %), but remains insufficient for advanced adenomas (46 %). However, molecular tumor finger-printing of early cancers using stool samples remains an attractive venue in biomarker research. Furthermore, compared to the standard FOBT, early findings suggested that stool testing can be expanded to include the previously unscreened upper GI tract as well. Moreover, techniques need to be optimized and rigorously tested in the clinic to be adequately evaluated to have a pan-GI screening test. In these researchers' opinion, the diagnostic yield of these tests is dependent on accurately predicting the mutations occurring earliest in tumorigenesis, which may influence the transition between pre-malignant lesions towards neoplasia.

An UpToDate review on "Tests for screening for colorectal cancer" (Doubeni, 2024a) states that "Other stool-based tests may be available in the future. In a phase 3 clinical trial among individuals 45 years and older, a multitarget stool RNA (mt-sRNA) test has been found to have 94 % sensitivity for detecting colorectal cancer, 46 % sensitivity for detecting advanced adenomas, and 88 % specificity for no lesions on colonoscopy".

UpToDate reviews on "Screening for colorectal cancer: Strategies in patients at average risk" (Doubeni, 2024b), and "Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp" (Ramsey and Grady, 2024) do not mention stool RNA as a management option.

Furthermore, National Comprehensive Cancer Network's clinical practice guidelines on "Colon Cancer" (Version 1.2024) and "Rectal Cancer" (Version 1.2024) do not mention stool RNA as a management tool.

Drug-Coated Balloon for the Treatment of Colonic Strictures

Shen and Adorno-Garayo (2024) stated that intestinal strictures are common AEs of chronic bowel conditions such as Crohn's disease (CD), diverticulitis, and ulcerative colitis (UC) or after intestinal surgery. Mechanical endoscopic balloon dilation (EBD) is the standard-of-care (SOC) intervention, whereas multiple, repeat EBD therapy is often needed. A novel drug-coated balloon (DCB) was developed to dilate

strictures while concurrently delivering medication to reduce the rate of recurrence of strictures. These researchers presented the findings of a first-in-human, observational, open-label clinical trial in small- and large-bowel strictures. A total of 10 human adult subjects with chronic single, discrete, and benign intestinal stricture were treated and followed for 2 years. Outcomes included the Endoscopic Obstructive Score (EOS), Obstructive Symptom Score (OSS), and AEs. In this first-in-human trial of benign small- and large-bowel strictures, subjects presented with a mean stricture diameter of 10.3 mm, average EOS of 2.7, and OSS of 25.2. The technical success rate was 90 %, and no subjects had major treatment-related AEs. EOS decreased to 0.2 on average at 6 months. At 2 years, the retreatment-free survival rate was 100 %, and the average OSS was 0.6; and the procedure was well-tolerated. The authors stated that DCB treatment of benign small- and large-bowel strictures appeared to be safe and showed durable results of decreased symptoms and freedom from recurrence through 2 years. Moreover, these researchers stated that these preliminary findings need to be validated in large-scale clinical trials.

The authors stated that the drawbacks of this trial included the small sample size (n = 10) and limited duration of study follow-up (2 years). Other drawbacks may include the lack of a control group and lack of diversity in the population cohort. Malignant strictures were also excluded from this study. However, this was the 1st report of a paclitaxel-coated balloon used to treat intestinal strictures. The POISE Trial was designed as an early phase study to gain initial experience with the device. Pilot studies such as this were usually carried out with a small number of subjects to examine the early safety and effectiveness of the investigational device before evaluating in a larger pivotal trial. Follow-up will continue through the 5-year time-point for subjects enrolled in this study. These researchers stated that a large RCT is planned to examine the ProTractX3 DCB against standard EBD and will provide further insight into the risks and benefits associated with this device.

Full-Spectrum Endoscopy (FUSE) Colonoscopy for Screening of Colorectal Cancer

In a retrospective, single-center, feasibility study, Song et al (2016) evaluated the full-spectrum endoscopy (FUSE) colonoscopy system in a Korean population. These researchers examined the effectiveness of the FUSE colonoscopy performed between February 1 and July 20, 2015. A total of 262 subjects (age range of 22 to 80 years) underwent the FUSE colonoscopy for colorectal cancer screening, polyp surveillance, or diagnostic evaluation. The cecal intubation success rate, the polyp detection rate (PDR), the adenoma detection rate (ADR), and the diverticulum detection rate (DDR), were calculated. Also, the success rates of therapeutic interventions were evaluated with biopsy confirmation. All patients completed the study and the success rates of cecal and terminal ileal intubation were 100 % with the FUSE colonoscope; these investigators found 313 polyps in 142 patients and 173 adenomas in 95. The overall PDR, ADR and DDR were 54.2 %, 36.3 %, and 25.2 %, respectively, and were higher in males, and increased with age. The endoscopists and nurses involved considered that the full-spectrum colonoscope improved navigation and orientation within the colon. No colonoscopy was aborted because of colonoscope malfunction. The authors concluded that the FUSE colonoscopy yielded a higher PDR, ADR, DDR than did traditional colonoscopy, without therapeutic failure or complications, showing feasible, effective, and safe in this 1st Korean trial.

This study had several drawbacks: (i) as no other Korean center currently employs the FUSE technology, this was a single-center, retrospective, non-comparative and non-randomized study; (ii) these researchers did not use a stop-watch to record time, but they did check the time stamps on the videos taken during each colonoscopy. As these researchers performed many therapeutic interventions, even ESDs, mean total procedure time (18.3 ± 8.6 mins, range of 9 to 48 mins) was thus probably longer than those of other studies. But if they considered only diagnostic interventions, mean total procedure time was shortened to 12.7 ± 1.4 mins (range of 9 to 17 mins), (iii) these investigators reported only the presence of a diverticulum, and not the numbers thereof, because many cases had too many

diverticula to count, and (iv) the authors did not measure the exact polyp size, and thus cannot compare among-study differences in the PDR or ADR by the sizes of polyps or adenomas. Further larger comparative studies are needed.

Leong et al (2017) noted that inflammatory bowel diseases (IBDs) increase the risk of colorectal cancer. Surveillance colonoscopy with chromoendoscopy is recommended, but conventional forward-viewing colonoscopy (FVC) detects dysplasia with low levels of sensitivity. Full-spectrum endoscopy (FUSE) incorporates 2 additional lateral cameras to the forward camera of the colonoscope, allowing endoscopists to view behind folds and in blind spots, which might increase dysplasia detection. In a prospective, randomized, cross-over, tandem colonoscopy study, these researchers compared FUSE versus FVC in the detection of dysplasia in patients with IBDs. These investigators compared FVC versus FUSE in 52 subjects with IBD undergoing surveillance for neoplasia in Australia (23 with Crohn's colitis, 29 with ulcerative colitis; median age of 45.0 years; 60 % men; mean IBD duration of 16.4 years). All subjects met national IBD surveillance inclusion criteria; 27 were assigned randomly to groups that underwent FVC followed by FUSE, and 25 were assigned to groups that underwent FUSE followed by FVC. All procedures were performed from February 2014 through December 2015. Random biopsy specimens were collected and visible lesions were collected; all were analyzed histologically. The primary end-point was dysplasia missed by the 1st colonoscopy detected by the 2nd colonoscopy. Dysplasia was diagnosed by an expert gastro-intestinal (GI) pathologist blinded to the colonoscope allocation in consensus with a 2nd expert pathologist. FVC missed 71.4 % of dysplastic lesions per lesion whereas FUSE missed 25.0 % per lesion ($p = 0.0001$); FVC missed 75.0% of dysplastic lesions per subject and FUSE missed 25.0 % per subject ($p = 0.046$). FUSE identified a mean of 0.37 dysplastic lesions and FVC identified a mean of 0.13 dysplastic lesions ($p = 0.044$). The total colonoscopy times were similar (21.2 mins for FUSE versus 19.1 mins for FVC; $p = 0.32$), but withdrawal time was significantly longer for FUSE (15.8 mins) than for FVC (12.0 mins) ($p = 0.03$). Correcting for per-unit withdrawal time, the mean dysplasia miss rate per subject was significantly lower for FUSE (0.19) than for FVC (0.83; $p < 0.0001$). Targeted tissue acquisition identified significantly more dysplastic lesions

than random biopsies ($p < 0.0001$). The authors concluded that i a prospective cross-over study of IBD patients undergoing surveillance colonoscopy, they found panoramic views obtained by full-spectrum endoscopy increased the number of dysplastic lesions detected, compared with conventional forward-viewing colonoscopy. This was a small study examining surveillance for dysplasia in patients with inflammatory bowel diseases.

Ratone et al (2017) stated that currently, colonoscopy and polypectomy are the gold standard methods for the prevention of incident cases of colorectal cancer. The use of a new colonoscope (Fuse, EndoChoice) with a larger view of up to 330° appears to improve the ADR. In a pilot study, these researchers performed a prospective observational study concerning this scope. The primary end-point was potentially omitted adenomas (POA), i.e., adenomas seen on the side screens that will not appear on the central display during colonoscopy withdrawal without oriented movements. Secondary end-points included ADR, Fuse impact on ADR, time to cecal intubation and withdrawal time. These investigators performed a single-center prospective study in 1 French center. They enrolled patients over 18 years of age between January 2015 and March 2016. This study included 141 patients (78 men and 60 women; sex ratio 1.3); 3 were excluded because their colonoscopies were incomplete. The mean age was 60.4 years. A total of 130 polyps were resected. In all, 88/130 were adenomas (68 %) and 34/88 adenomas (39 %) were POA. The mean time to cecum was 10 mins, and the mean withdrawal time was 12 mins; ADR was 35 % for men and 31 % for women. The estimated ADR without POA was 29 % for men and 19 % for women. The authors concluded that the Fuse system appeared to be safe and efficient; POA represented 39 % of all adenomas. The impact of the panoramic view on the ADR was considered substantial. This study had some limitations. First, was the possible subjectivity of the primary end-point. Indeed, though operators described what they considered to be PPOs during scope withdrawal, a certain diagnosis was difficult. Nevertheless, a non-PPO polyp was also first seen on the side screen and then on the central screen. Of course, the authors did not consider this situation to resemble a PPO, because PPOs required oriented movements to find them on a central screen, but subjectivity remains. Other associated limitations were the lack of randomization or a control group. Moreover, these researchers stated that recently, a high-

quality randomized study questioned the utility of Fuse in the detection of adenomas in a population with a positive fecal immunochemical test: no difference was demonstrated in ADR. This new result called into question the superiority of the Fuse, suggested by the feasibility studies and demonstrated by the tandem study of Gralnek et al. This very interesting study encouraged further clinical research into this scope to examine if it represents a minor or major improvement in CCR screening. Several types of endoscopy center (expert or not) should be involved in future randomized trials for “real-life” studies.

Bevan and Rutter (2018) stated that “Currently, RCT evidence for colonoscopy screening is scarce. Although not yet corroborated by RCTs, it is likely that colonoscopy is the best screening modality for an individual. From a population perspective, organized programs are superior to opportunistic screening. However, no nation can offer organized population-wide colonoscopy screening. Thus, organized programs using cheaper modalities, such as FS/FIT, can be tailored to budget and capacity”.

UpToDate reviews on “Screening for colorectal cancer: Strategies in patients at average risk” (Doubeni, 2018) and “Screening for colorectal cancer in patients with a family history of colorectal cancer” (Ramsey and Grady, 2018) do not mention full spectrum endoscopy as a screening tool.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Colon cancer” (Version 2.2018) and “Rectal cancer” (Version 1.2018) do not mention full spectrum endoscopy as a screening tool.

Guardant Shield Test for Colorectal Cancer

The Guardant Shield Test uses a multi-modal approach, integrating genomics, epigenomics and proteomics, to detect CRC signals in the bloodstream, including DNA that is shed by tumors, called circulating tumor DNA (ctDNA). It demonstrated sensitivity of 91 % in CRC, and 20 % in advanced adenoma detection, with 92 % specificity (true negative rate) in normal cases in validation studies. The Guardant Shield Test is a

laboratory developed test (LDT) that is intended to be complementary to and not a replacement for current recommended CRC screening methods.

Chung et al (2024) noted that CRC is the 3rd most diagnosed cancer in adults in the U.S. Early detection could prevent more than 90 % of CRC-related deaths, yet more than 1/3 of the screening-eligible population is not up-to-date with screening despite multiple available tests. A blood-based test has the potential to improve screening adherence, detect CRC earlier, and reduce CRC-related mortality. These researchers examined the performance characteristics of a cell-free DNA (cfDNA) blood-based test in a population eligible for CRC screening. The co-primary outcomes were sensitivity for CRC and specificity for advanced neoplasia (CRC or advanced pre-cancerous lesions) relative to screening colonoscopy. The secondary outcome was sensitivity to detect advanced pre-cancerous lesions. The clinical validation cohort included 10,258 persons, 7,861 of whom met eligibility criteria and were evaluable. A total of 83.1 % of the participants with CRC detected by colonoscopy had a positive cfDNA test and 16.9 % had a negative test, which indicated a sensitivity of the cfDNA test for detection of CRC of 83.1 % (95 % CI: 72.2 to 90.3). Sensitivity for stage I, II, or III CRC was 87.5 % (95 % CI: 75.3 to 94.1), and sensitivity for advanced pre-cancerous lesions was 13.2 % (95 % CI: 11.3 to 15.3). A total of 89.6 % of the participants without any advanced colorectal neoplasia (CRC or advanced pre-cancerous lesions) identified on colonoscopy had a negative cfDNA blood-based test, whereas 10.4 % had a positive cfDNA blood-based test, which indicated a specificity for any advanced neoplasia of 89.6 % (95 % CI: 88.8 to 90.3). Specificity for negative colonoscopy (no CRC, advanced pre-cancerous lesions, or non-advanced pre-cancerous lesions) was 89.9 % (95 % CI: 89.0 to 90.7). The authors concluded that in an average-risk screening population, this cfDNA blood-based test had 83 % sensitivity for CRC, 90 % specificity for advanced neoplasia, and 13 % sensitivity for advanced pre-cancerous lesions.

These researchers stated that participant adherence varies considerably among the available CRC screening methods, with only 59 % of screening-eligible individuals being up-to-date with screening and more than 49 million un-screened individuals in the U.S. Estimates of adherence to blood-based tests are higher than those reported for stool-

based tests or direct visualization tests. Blood-based testing offers an additional option for CRC screening, in addition to the available stool-based tests, and may improve screening participation and early detection of CRC. These investigators stated that evaluation of participant adherence to this cfDNA blood-based test in various clinical settings is needed and is an area of active investigation, especially given that participant adherence is affected by many factors beyond the test availability. It is also important to highlight that a screening strategy that uses non-invasive testing requires adherence to the screening test and to the diagnostic colonoscopy in those with positive screening tests. Ongoing studies that are examining the screening journey for participants choosing this blood-based test will inform questions on participant follow-up with diagnostic colonoscopy. Furthermore, future investigation that entails health economic and outcomes modeling could inform the effect of this blood-based test on CRC-related outcomes, especially the effect of a test with high adherence and lower sensitivity for advanced pre-cancerous lesions than stool-based testing, and could examine if the 3-year interval of the blood-based test, proposed by the manufacturer for screening, would yield beneficial clinical outcomes. The authors stated that future studies to understand the effect of longitudinal testing on sensitivity for advanced neoplasia warrant consideration. They noted that in this study, the percentage of participants with an invalid cfDNA blood-based test result was 3.7 % (298 of 8,159) and within the target range (less than 5 %) proposed for programmatic FIT offering. Evaluating this percentage in the real-world setting will be important to understand population effect. Given the increasing incidence of CRC among individuals younger than 45 years of age, understanding the potential clinical and health economic effect of a blood-based testing strategy to expand the screening age will be of interest.

Lei et al (2024) stated that CRC and gastric cancer (GC) rank the top 5 common and lethal cancers worldwide. Early detection can significantly reduce the mortality of CRC and GC; however, current clinical screening methods including invasive endoscopic techniques as well as non-invasive fecal occult blood test screening tests/FIT have shown low sensitivity or unsatisfactory patient's compliance. Aberrant DNA methylation occurs frequently in tumorigenesis and cfDNA methylation has shown the potential in multi-cancer detection. These researchers examined the value of cfDNA methylation in the GI cancer detection and

developed a non-invasive method for CRC and GC detection. They applied targeted methylation sequencing on a total of 407 plasma samples from patients diagnosed with CRC, GC, and non-cancerous GI benign diseases (Non-Ca). By analyzing the methylation profiles of 34 CRC, 62 GC and 107 Non-Ca plasma samples in the training set (n = 203), these investigators identified 40,110 GI cancer-specific markers, and 63 tissue of origin (TOO) prediction markers. A new integrated model composed of GI cancer detection and TOO prediction for 3 types of classification of CRC, GC and Non-Ca patients was further developed via logistic regression algorithm and validated in an independent validation set (n = 103). The model achieved overall sensitivities of 83 % and 81.3 % at specificities of 81.5 % and 80 % for identifying GI cancers in the test set and validation set, respectively. The detection sensitivities for GC and CRC were 81.4 % and 83.3 % in the cohort of the test and validation sets, respectively. Among these true positive cancer samples, further TOO prediction showed accuracies of 95.8 and 95.8 % for GC patients, and accuracies of 86.7 % and 93.3 % for CRC patients, in test set and validation set, respectively. The authors concluded that they have carried out comprehensive cfDNA methylation analysis and identified GI cancer-specific methylation signatures and TOO prediction markers for CRC and GC, showing that cfDNA methylation signature is a promising tool for the early detection of GI cancers and non-invasive cancer screening. Moreover, these researchers stated that it was worth noting that the current model was tested in a clinical setting with patients showing discomfort in digestive tract and the test's potential application was primary as an assistant diagnostic tool. For the test to further be applied as a cost-effective screening tool, a future study entailing large-scale validation based on high-risk population is needed.

Henriksen et al (2024) noted that circulating tumor DNA (ctDNA) is proposed as a tool for minimal residual disease (MRD) assessment. Digital PCR (dPCR) offers low analysis costs and turn-around times of less than a day, making it ripe for clinical implementation. In an observational study, these researchers employed tumor-informed dPCR for ctDNA detection in a large CRC cohort to examine the potential for post-operative risk assessment and serial monitoring, and how the metastatic site may impact ctDNA detection. In addition, these investigators examined how altering the ctDNA-calling algorithm could customize performance for different clinical settings. Stage II to III CRC

patients (n = 851) treated with a curative intent were recruited. Based on whole-exome sequencing (WES) on matched tumor and germline DNA, a mutational target was selected for dPCR analysis. Plasma samples (8 ml) were collected within 60 days after operation and, for a patient subset (n = 246), every 3 to 4 months for up to 36 months. Single-target dPCR was used for ctDNA detection. Both post-operative and serial ctDNA detection were prognostic of recurrence (hazard ratio [HR] = 11.3, 95 % CI: 7.8 to 16.4, p < 0.001; HR = 30.7, 95 % CI: 20.2 to 46.7, p < 0.001), with a cumulative ctDNA detection rate of 87 % at the end of sample collection in recurrence patients. The ctDNA growth rate was prognostic of survival (HR = 2.6, 95 % CI: 1.5 to 4.4, p = 0.001). In recurrence patients, post-operative ctDNA detection was challenging for lung metastases (4/21 detected) and peritoneal metastases (2/10 detected). By modifying the cut-off for calling a sample ctDNA positive, these researchers were able to adjust the sensitivity and specificity of the test for different clinical contexts. The authors concluded that these findings from 851 stage II to III CRC patients showed that their personalized dPCR approach effectively detected MRD after operation and revealed promise for serial ctDNA detection for recurrence surveillance. The ability to adjust sensitivity and specificity demonstrated exciting potential to customize the ctDNA caller for specific clinical settings. These investigators stated that while they await clinical utility to be demonstrated in randomized clinical trials, these findings revealed an exciting potential for improvement.

In a randomized study, Coronado et al (2024) examined if individuals who had not completed a FIT for CRC screening would complete a blood-based testing option if offered one during health encounters. Blood-based screening tests for CRC could add to the total number of people screened for CRC by providing another testing alternative. Study participants were patients aged 45 to 75 years at a large, integrated health system who were offered but did not complete an FIT in the previous 3 to 9 months, and were scheduled for a clinical encounter. Participants were randomized (1:1) to be offered a commercially available CRC blood test (Shield, Guardant Health) versus usual care. These investigators compared 3-month CRC screening proportions in the 2 groups. They randomized 2,026 patients; 2,004 remained eligible following post-randomization exclusions (1,003 to usual care and 1,001 to blood draw offer; mean age: of 60 years, 62 % women, 80 % non-

Hispanic white). Of the 1,001 allocated to the blood test group, 924 were recruited following chart-review exclusions; 548 (59.3 %) were reached via phone, of which 280 (51.1 %) scheduled an appointment with the research team. CRC screening proportions were 17.5 percentage points higher in the blood test group versus usual care (30.5 % versus 13.0 %; OR 2.94, 95 % CI: 2.34 to 3.70; $p < 0.001$). The authors concluded that among adults who had declined previous CRC screening, the offer of a blood-based screening test boosted CRC screening by 17.5 percentage points over usual care. Moreover, these researchers stated that further investigation is needed on how to balance the favorable adherence with lower advanced adenoma detection compared with other available tests.

Haynes et al. (2025) evaluated the real-world implementation of blood-based colorectal cancer (CRC) screening in two Appalachian primary care clinics, a region with historically low CRC screening rates and high CRC incidence and mortality. The study used a two-phase design: in Phase 1, only standard-of-care (SOC) screening options (colonoscopy and stool-based tests) were offered; in Phase 2, a blood-based test was added as an option alongside SOC. Screening rates were measured over two consecutive 3-month periods. The introduction of the blood-based test led to a marked increase in overall CRC screening completion: 33 of 74 patients completed screening in Phase 1 (SOC only), compared to 151 of 165 in Phase 2 (SOC plus blood-based test). In Phase 2, the vast majority of patients who completed screening chose the blood-based test (134/151), indicating strong patient preference for this modality over traditional options. The investigators concluded that this study demonstrates that offering a blood-based CRC screening test in primary care settings can substantially improve both screening uptake and completion, particularly in populations with historically low adherence. The study has several important drawbacks. First, the study was conducted in only two primary care clinics in Appalachia, which limits generalizability to other populations and healthcare settings. The sample size was relatively small, and the short duration of each study phase (three months) may not capture longer-term trends in screening behavior or sustainability of increased uptake. Second, the study design did not randomize patients to screening options, introducing potential selection bias and confounding. The observed increase in screening rates may be influenced by unmeasured differences between the two phases or by temporal trends unrelated to the intervention. Third, the study focused on

screening uptake and patient preference, but did not assess clinical outcomes such as detection rates of advanced adenomas or colorectal cancer, nor did it report on follow-up colonoscopy completion after positive blood-based tests. This is a critical limitation, as the effectiveness of any screening program depends not only on initial test uptake but also on the sensitivity for advanced neoplasia and adherence to diagnostic follow-up. Fourth, as highlighted by the American Gastroenterological Association, blood-based tests generally have lower sensitivity for advanced adenomas than FIT or stool DNA tests, which may limit their impact on colorectal cancer prevention even if uptake is higher. Finally, the study did not address cost-effectiveness or health system resource implications, which are important considerations for broader implementation.

Measurements of Plasma GATA5 and SFRP2 Methylation as Biomarkers for Colorectal Cancer

Zhang and colleagues (2015) examined GATA5, SFRP2, and ITGA4 methylation in plasma DNA as non-invasive biomarkers for CRC or adenomas. There were 57 CRC patients, 30 adenomas patients, and 47 control patients enrolled in this study. Methylation-specific PCR was used to determine the promoter methylation status of GATA5, SFRP2, and ITGA4 genes in plasma DNA, and their association with clinical outcome in CRC. The predictive ability of GATA5, SFRP2, and ITGA4 methylation, individually or in combination, to detect CRC or adenomas was further analyzed. Hyper-methylated GATA5 was detected in plasma in 61.4 % (35/57) of CRC cases, 43.33 % (13/30) of adenoma cases, and 21.28 % (10/47) of control cases. The hyper-methylation of SFRP2 was detected in 54.39 % (31/57), 40.00 % (12/30), and 27.66 % (13/47) in plasma samples from CRC, adenomas, and controls, respectively. ITGA4 methylation was detected in 36.84 % (21/57) of plasma samples of CRC patients and in 30.00 % (9/30) of plasma samples from patients with colorectal adenomas, and the specificity of this individual biomarker was 80.85 % (9/47). Moreover, GATA5 methylation in the plasma was significantly correlated with larger tumor size ($p = 0.019$), differentiation status ($p = 0.038$), TNM stage ($p = 0.008$), and lymph node metastasis ($p = 0.008$). SFRP2 and ITGA4 methylation in plasma significantly correlated with differentiation status (SFRP2, $p = 0.012$; ITGA4, $p = 0.007$), TNM stage (SFRP2, $p = 0.034$; ITGA4, $p = 0.021$), and lymph

node metastasis (SFRP2, p = 0.034; ITGA4, p = 0.021). From the perspective of predictive power and cost-performance, using GATA5 and SFRP2 together as methylation markers seemed the most favorable predictor for CRC (OR = 8.06; 95 % CI: 2.54 to 25.5; p < 0.01) and adenomas (OR = 3.35; 95 % CI: 1.29 to 8.71; p = 0.012). The authors concluded that a combination of GATA5 and SFRP2 methylation could be promising as a marker for the detection and diagnosis of CRC and adenomas.

Septin9

Septin9 (Sept9) DNA methylated assay for the early detection of colorectal cancer (eg, Epi proColon, ColoVantage) is a plasma based test that detects methylated Septin9 DNA, which is purportedly a marker of the presence of colorectal cancer. It is designed for those who have avoided established CRC screening methods such as colonoscopy, FOBT or fecal immunochemical test (FIT). This test is not intended to replace established CRC tests.

ColoVantage is a plasma-based test that detects circulating methylated DNA from the SEPT9 gene which is involved in cytokinesis and cell cycle control. According to the manufacturer, case-control studies show that presence of methylated SEPT9 DNA in plasma is 58 % to 69 % sensitive for CRC detection at a specificity of 86 % to 90 % (citing Lofton-Day et al, 2008; Grützmann et al, 2008; de Vos et al, 2009). The test is non-invasive and requires no patient preparation. The manufacturer suggests that a physician may order the test for screen-eligible patients who have previously avoided established CRC screening methods such as colonoscopy, FOBT, and fecal immunochemical tests. A patient whose ColoVantage test result is positive may be at increased risk for CRC and further evaluation should be considered. The manufacturer notes, however, that the ColoVantage test has yet to be clinically validated as a screening test. There are no evidence-based guidelines from leading medical professional organizations or public health agencies that recommend measurement of methylated Septin 9 in plasma for CRC screening.

Molnar and colleagues (2015) noted that many countries have implemented various CRC screening programs, but have not achieved the desired compliance. Colonoscopy -- considered the gold standard for CRC screening -- has its limitations as well as the other techniques used, such as irrigoscopy, sigmoidoscopy, fecal blood and hemoglobin tests. The biomarker septin 9 has been found to be hyper-methylated in nearly 100 % of tissue neoplasia specimens and detected in circulating DNA fractions of CRC patients. A commercially available assay for septin 9 has been developed with moderate sensitivity (approximately 70 %) and specificity (approximately 90 %) and a 2nd generation assay, Epi proColon 2.0 (Epigenomics AG), shows increased sensitivity (approximately 92 %). The performance of the assay proved to be independent of tumor site and reaches a high sensitivity of 77 %, even in early cancer stages (I and II). Furthermore, septin 9 was recently used in follow-up studies for detection of early recurrence of CRC. The authors evaluated the opportunities, known limitations and future perspectives of the recently introduced Epi proColon(®) 2.0 test, which is based on the detection of aberrantly methylated DNA of the v2 region of the septin 9 gene in plasma.

Jin and associates (2015) evaluated the performance of the Epi proColon 2.0 test for the detection of CRC, and compared it with FIT. A total of 135 patients with CRC, 169 with adenomatous polyps, 81 with hyperplastic polyps, and 91 healthy controls were included. In all patients, peripheral blood samples were taken for SEPT9 testing using Epi proColon 2.0 test. For 177 patients, both SEPT9 and FIT were performed. The sensitivity and specificity of SEPT9 for CRC were 74.8 % (95 % CI: 67.0 to 81.6 %) and 87.4 % (versus non-CRC, 95 % CI: 83.5 to 90.6 %), respectively. SEPT9 was positive in 66.7 % of stage I, 82.6 % of stage II, 84.1 % of stage III, and 100 % of stage IV CRCs. The sensitivity of SEPT9 for advanced adenomas was 27.4 % (95 % CI: 18.7 to 37.6%). The sensitivity and specificity of FIT for CRC was 58.0 % (95 % CI: 46.1 to 69.2 %) and 82.4 % (95 % CI: 74.4 to 88.7 %), respectively. SEPT9 showed better performance in CRC detection than FIT, but similar among advanced adenomas. The authors concluded that with improved performance characteristics in detecting CRC, the 2nd-generation SEPT9 assay could play an important role in CRC screening and early detection.

Orntoft et al (2015) stated that the Sept9 DNA-methylation assay is among the most well-studied blood-based screening markers. However, earlier reported performances may be misleading: The Sept9 test was recently examined in 2 screening based cohorts and yielded performances lower than expected. These investigators hypothesized that co-morbidities and/or demographic characteristics affect the results of the Sept9 test. Using a retrospective nested case-control study design, these researchers studied plasma from 150 cancer and 150 controls selected from a well-characterized cohort of 4,698 subjects referred for diagnostic colonoscopy due to CRC-related symptoms. The cases and controls were matched on age and gender. Moreover, cases were stratified on tumor-site and tumor-stage. The selected cohort included a wide range of co-morbidities. Plasma Sept9 levels were assessed using a commercially available PCR-based assay (Epi-proColon). Clinical sensitivity for CRC stages I-IV was 37 %, 91 %, 77 %, and 89 %, and the overall sensitivity 73 % (95 % CI: 64 to 80 %) and specificity 82 % (95 % CI: 75 to 88 %), respectively. Age greater than 65 was associated with both increased false positive and false negative results ($p < 0.05$). Arthritis was associated with a higher false negative rate ($p = 0.005$) whereas arterio-sclerosis was associated with a higher false positive rate ($p = 0.007$). Diabetes was associated with Sept9 positivity with an odds ratio (OR) of 5.2 (95 % CI: 1.4 to 19.1). When the performance of Sept9 was adjusted for these parameters in a final multivariate regression model, the OR for a positive Sept9 test to be associated with CRC increased from 8.25 (95 % CI: 4.83 to 14.09) to 29.46 (95 % CI: 12.58 to 69.02). The authors concluded that the findings of this study indicated that the performance of the Sept9 assay is negatively affected by several factors commonly associated with CRC screening populations: early-stage disease, age greater than 65 years, diabetes, arthritis, and arterio-sclerosis. This should be taken into account if the Sept9 assay is used as a single marker for CRC screening, but may also have a wider impact, as it is likely that such factors may affect other blood based DNA markers as well.

On April 14, 2016, the FDA cleared Epi proColon (Epigenomics AG) as the first blood-based screening test for CRC in average-risk patients who choose not to be screened by colonoscopy or a stool-based FIT.

An UpToDate review on “Tests for screening for colorectal cancer: Stool tests, radiologic imaging and endoscopy” (Doubeni, 2016) lists “Septin 9 hypermethylation in DNA from plasma (ColoVantage)” as an investigational test. It states that “Current serum markers are not sufficiently sensitive or specific to be used for screening. The potential to utilize a combination of 6 serum markers to improve the test has been reported in a feasibility study, but validation studies in screening populations are needed before clinical relevance can be determined”.

The USPSTF (2016) stated that the FDA approved a blood test, Epi proColon (Epigenomics) to detect circulating methylated SEPT9 DNA in April 2016.A single test characteristic study met the inclusion criteria for the systematic evidence review supporting this recommendation statement; it found the SEPT9 DNA test to have low sensitivity (48%) for detecting colorectal cancer.

The ACS guidelines (Wolf et al, 2018) do not recommend the SEPT9 DNA test, based upon concerns about poor specificity compared with recommended screening options and the limited base of evidence in asymptomatic, screening populations. In addition, the ACS noted that there has been no microsimulation modeling of the current version of the test to estimate its benefit, a benefit-harm ratio, or a screening interval for regular testing, which also has not been established by the manufacturer. In addition, methylated Sept9 is a novel blood test for CRC early detection with no comparable screening tests from which to infer a benefit in terms of critical outcomes (CRC mortality or incidence reduction), as there are for the included screening test options. The ACS guidelines note that the test has not been cleared by the FDA for unrestricted use in general routine screening.

SimpliPro Colon Test

The SimpliPro Colon Test (Applied Proteomics, Inc., San Diego, CA) is a blood test that uses proprietary mass spectrometry platform and test algorithm designed by Applied Proteomics to measure and analyze 11 protein markers in the blood that are associated with CRC and advanced adenomas. This laboratory-based service is designed to enable better compliance for diagnostic colonoscopy in patients presenting with symptoms associated with CRC. It supposedly is the only blood test that

assesses risk for advanced adenoma in elevated-risk patients; however, the SimpliPro Colon test has not been validated in an asymptomatic screening population for CRC. Applied Proteomics Inc (https://www.appliedproteomics.com/).

The American Cancer Society (2017) does not mention the SimpliPro Colon Test as an option for screening of CRC. Colon Cancer and Rectal Cancer Screening (https://www.cancer.org/latest-news/understanding-tests-that-screen-for-colon-cancer.html).

Currently, there is a lack of evidence reading the clinical benefit of the SimpliPro Colon Test.

Stool-Based Protein Biomarkers

Bosch and colleagues (2017) stated that the FIT for detecting hemoglobin is used widely for non-invasive CRC screening, but its sensitivity leaves room for improvement. In a case-control study, these researchers identified novel protein biomarkers in stool that out-perform or complement hemoglobin in detecting CRC and advanced adenomas. A total of 315 stool samples from one series of 12 patients with CRC and 10 persons without colorectal neoplasia (control samples) and a second series of 81 patients with CRC, 40 with advanced adenomas, and 43 with non-advanced adenomas, as well as 129 persons without colorectal neoplasia (control samples); 72 FIT samples from a third independent series of 14 patients with CRC, 16 with advanced adenomas, and 18 with non-advanced adenomas, as well as 24 persons without colorectal neoplasia (control samples) were included in this analysis. Stool samples were analyzed by mass spectrometry. Classification and regression tree (CART) analysis and logistic regression analyses were performed to identify protein combinations that differentiated CRC or advanced adenoma from control samples. Antibody-based assays for 4 selected proteins were carried out on FIT samples. In total, 834 human proteins were identified, 29 of which were statistically significantly enriched in CRC versus control stool samples in both series. Combinations of 4 proteins reached sensitivities of 80 % and 45 % for detecting CRC and advanced adenomas, respectively, at 95 % specificity, which was higher than that of hemoglobin alone ($p < 0.001$ and $p = 0.003$, respectively). Selected proteins could be measured in small sample volumes used in

FIT-based screening programs and discriminated between CRC and control samples ($p < 0.001$). The authors concluded that mass spectrometry of stool samples identified novel candidate protein biomarkers for CRC screening. Several protein combinations out-performed hemoglobin in discriminating CRC or advanced adenoma from control samples. They stated that this proof of concept study that such proteins can be detected with antibody-based assays in small sample volumes indicated the potential of these biomarkers to be applied in population screening. A main limitation of this study was the lack of availability of antibodies prohibited validation of the top protein combinations in FIT samples.

The ColoCaller Test

Ma et al (2022) noted that because of poor compliance or low sensitivity, existing diagnostic approaches are unable to provide an efficient diagnosis of patients with CRC and gastric cancer. These researchers developed the ColoCaller Test, which simultaneously detects the methylation status of the SDC2, TFPI2, WIF1, and NDRG4 genes in stool DNA, to optimize the screening of CRC and gastric cancer in high-risk populations. A total of 217 stool samples from patients with GI cancer and from patients with negative endoscopy were prospectively collected, complete with pre-operative and post-operative clinical data from patients. The methylation of these samples was detected using ColoCaller, which was designed by selecting CpGs with a 2-step screening strategy; and was interpreted using a prediction model built using libSVM to examine its clinical value for CRC and gastric cancer screening. Compared to pathological diagnosis, the sensitivity and specificity of the ColoCaller test in 217 stool DNA samples were 95.56 % and 91.86 %, respectively, for CRC, and 67.5 % and 97.81 %, respectively, for gastric cancer. The detection limit was as low as 1 % in 8 ng of DNA. The authors developed and established a new test, ColoCaller, which can be used as a screening tool or as an auxiliary diagnostic approach in high-risk populations with CRC and gastric cancer to promote timely diagnosis and treatment.

The authors stated that this is the 1st report on the use of methylated SDC2, TFPI2, WIF1, and NDRG4 genes for early detection of gastric and colorectal cancer (GCC), which not only retains the advantages of simple

and non-invasive characteristics similar to FOBT, but also higher sensitivity and specificity to the screening or auxiliary diagnosis of a high-risk population with GCC. At the same time, due to the convenient sampling (home collection) and cheap costs ($100 to 300 per test), it can be tested repeatedly in clinical application, which is conducive to continuous monitoring. In the future, a screening method with stool examination as the primary screening and endoscopy as confirmation will be conducive to popularization and optimization of GCC screening to further improve the detection rate of early gastric cancer and CRC. In addition to being able to directly detect GCC, the ColoCaller test can further stratify a high-risk population to improve endoscopy compliance; and promote timely diagnosis and treatment. However, the sample size used in this study to verify the performance of the ColoCaller test was limited, and further investigation is still needed, especially due to the lack of patients with advanced adenomas (AAs), furthermore, long-term follow-up data are needed to support these findings. Furthermore, the detailed clinicopathological characteristics of patients with GCC was not included in this study, whether different disease sites or different molecular subtypes, which may under-estimate the diagnostic performance.

In a systematic review, Dolatkhah et al (2022) summarized test data and carried out a meta-analysis, with respect to the multi-target stool DNA (Mt-sDNA) test sensitivity and specificity, compared to colonoscopy. All manuscripts were screened for eligibility according to inclusion criteria. Participants were a normal population at an average risk of developing CRC. Intervention was stool-based, and DNA panel tests compared with colonoscopy, and outcome was detection of CRC and any pre-cancerous lesions. Inter-study and inconsistency (using the I-squared test) were assessed. Meta-analyses of the Mt-sDNA test showed a combined sensitivity of 89 %, 51 %, and 76 % for the detection of CRC, AA, and combined CRC and AA, respectively. The overall specificity was 91 %, 89 %, and 90 % for the detection of CRC, AA, and combined CRC and AA, respectively. Mt-sDNA had significantly acceptable diagnostic accuracy for CRC and AA diagnosis, but still has lower sensitivity and specificity than colonoscopy.

Whole-Blood DNA Methylation Markers for Risk Stratification in Colorectal Cancer Screening

Raut and colleagues (2019) stated that DNA methylation profiles within whole-blood samples have been reported to be associated with CRC occurrence and might enable risk stratification for CRC. These investigators systematically reviewed and summarized studies addressing the association of whole-blood DNA methylation markers and risk of developing CRC or its precursors. They searched PubMed and ISI Web of Knowledge to identify relevant studies published until November 12, 2018. Two reviewers independently extracted data on study population characteristics, candidate genes, methylation measurement methods, methylation levels of patients in comparison to healthy controls, p-values, and ORs of the markers. A total of 19 studies reporting 102 methylation markers for risk assessment of colorectal neoplasms met the inclusion criteria. The studies mostly used methylation specific polymerase chain reaction (MS-PCR) for assessing the methylation status of a defined set of genes . Only 2 studies applied array-based genome-wide assays to evaluate the methylation levels; 5 studies incorporated panels consisting of 2 to 10 individual methylation markers to examine their potential for stratifying the risk of developing colorectal neoplasms. However, none of these associations was confirmed in an independent cohort. The authors concluded that whole-blood DNA methylation markers may be useful as biomarkers for risk stratification in CRC screening, but reproducible risk prediction algorithms are yet to be established by large scale epigenome-wide studies with thorough validation of results in prospective study cohorts including large screening populations. The possibilities of enhancing predictive power by combining methylation data with polygenetic risk scores and environmental risk factors need to be examined. The authors concluded that there is considerable interest in the use of whole-blood DNA methylation biomarkers to examine the likelihood of developing colorectal neoplasms. However, current risk assessment studies are inconclusive as to which methylation markers are promising for CRC risk stratification. This is due to several limitations in methodology outlined in this study. The variation in methodology and incomplete reporting among the studies also limited the analyses of this review. It is, therefore strongly recommended that future risk assessment studies apply more standardized methods, particularly in quantifying methylation data.

Although time-consuming and expensive, diagnostic and risk stratification performance should preferably be evaluated in screening cohorts or large-scale population-based cohort studies rather than case-control studies in which methylation patterns among cases may have been altered through the course of the disease, after diagnosis or even initial treatment. Integrating epigenetic and genetic markers may represent a promising approach for future CRC risk stratification schemes. Thus, further research should aim for assessment and validation of the combined performance of genetic and epigenetic markers for CRC risk prediction in order to best define the use of such signatures for research and clinical practice.

The authors stated that this study had several drawbacks. First, these researchers presented only a structured synthesis of multiple study results. Due to the heterogeneity across the reviewed studies, they did not perform a meta-analysis combining the results of independent studies. Second, selection of studies may have affected the conclusions; even after developing the inclusion/exclusion criteria to ensure that all relevant studies were included, some articles could have been missed. Finally, publication bias with a tendency to publish more promising results may have led to over-estimated associations in this review.

Furthermore, UpToDate reviews on "Screening for colorectal cancer: Strategies in patients at average risk" (Doubeni, 2021a), "Tests for screening for colorectal cancer"(Doubeni, 2021b), and “Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp” (Ramsey and Grady, 2021) do not mention the use of whole-blood DNA methylation markers as a management tool.

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