Non-invasive colorectal cancer screening modalities: an overview

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Disclosures

The presenters have no conflicts of interest to disclose.

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Objectives

1. Discuss the pros/cons of the most common non-endoscopic forms of colon cancer screening.
2. Understand the evidence behind the most common non-endoscopic forms of colon cancer screening.
3. Increase confidence and equip learners to provide evidence-based options counseling for non-endoscopic colon cancer screening.

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Non-invasive colorectal cancer screening modalities

- **FOBT**
- **FIT**
- **Cologuard**
- CT colonography

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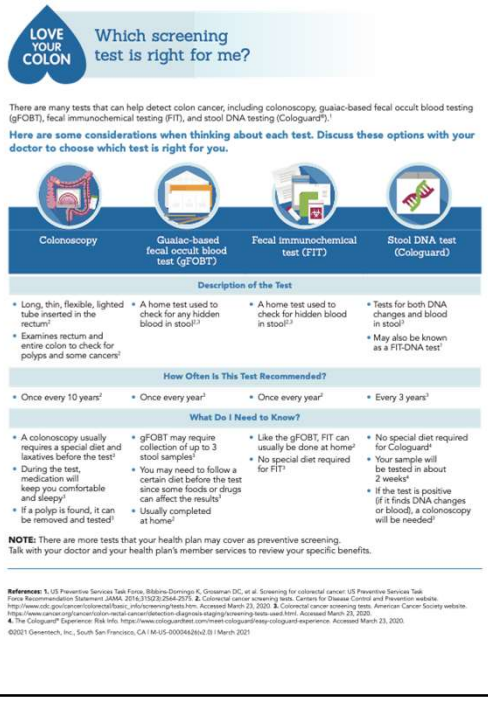


LOVE YOUR COLON

Which screening test is right for me?

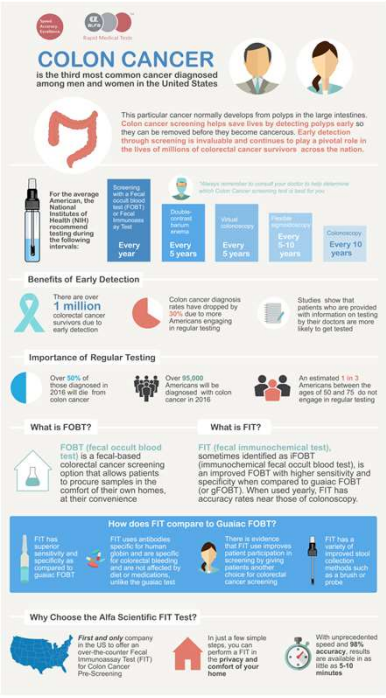
There are many tests that can help detect colon cancer, including colonoscopy, guaiac-based fecal occult blood testing (gFOBT), fecal immunochemical testing (FIT), and stool DNA testing (Cologuard®).[1]

Here are some considerations when thinking about each test. Discuss these options with your doctor to choose which test is right for you.

Colonoscopy	Guaiac-based fecal occult blood test (gFOBT)	Fecal immunochemical test (FIT)	Stool DNA test (Cologuard)
Description of the Test			
• Long, thin, flexible, lighted tube inserted in the rectum[2] • Examines rectum and entire colon to check for polyps and some cancers[2]	• A home test used to check for any hidden blood in stool[2,3]	• A home test used to check for hidden blood in stool[2,3]	• Tests for both DNA changes and blood in stool[3] • May also be known as a FIT-DNA test[4]
How Often Is This Test Recommended?			
• Once every 10 years[2]	• Once every year[2]	• Once every year[2]	• Every 3 years[3]
What Do I Need to Know?			
• A colonoscopy usually requires a special diet and laxatives before the test[2] • During the test, medication will keep you comfortable and sleepy[2] • If a polyp is found, it can be removed and tested[2]	• gFOBT may require collection of up to 3 stool samples[1] • You may need to follow a certain diet before the test since some foods or drugs can affect the results[1] • Usually completed at home[2]	• Like the gFOBT, FIT can usually be done at home[2] • No special diet required for FIT[1]	• No special diet required for Cologuard[4] • Your sample will be tested in about 2 weeks[4] • If the test is positive (if it finds DNA changes or blood), a colonoscopy will be needed[2]

NOTE: There are more tests that your health plan may cover as preventive screening. Talk with your doctor and your health plan's member services to review your specific benefits.

References: 1. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(23):2564-2575. 2. Colorectal cancer screening tests. Centers for Disease Control and Prevention website. http://www.cdc.gov/cancer/colorectal/basic_info/screening/tests.htm. Accessed March 23, 2020. 3. Colorectal cancer screening tests. American Cancer Society website. https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/screening-tests-used.html. Accessed March 23, 2020. 4. The Cologuard® Experience: Risk Info. https://www.cologuardtest.com/meet-cologuard/easy-cologuard-experience. Accessed March 23, 2020.



COLON CANCER

is the third most common cancer diagnosed among men and women in the United States

This particular cancer normally develops from polyps in the large intestines. Colon cancer screening helps save lives by detecting polyps early so they can be removed before they become cancerous. Early detection through screening is invaluable and continues to play a pivotal role in the lives of millions of colorectal cancer survivors across the nation.

For the average American, the National Institutes of Health (NIH) recommend testing during the following intervals:

Screening with a Fecal occult blood test (FOBT) or Fecal Immunoassay Test	Double contrast barium enema	Virtual colonoscopy	Flexible sigmoidoscopy	Colonoscopy
Every year	Every 5 years	Every 5 years	Every 5-10 years	Every 10 years

*Always remember to consult your doctor to help determine which Colon Cancer screening test is best for you

Benefits of Early Detection

- There are over 1 million colorectal cancer survivors due to early detection
- Colon cancer diagnosis rates have dropped by 35% due to more Americans engaging in regular testing
- Studies show that patients who are provided with information on testing by their doctors are more likely to get tested

Importance of Regular Testing

- Over 50% of those diagnosed in 2016 will die from colon cancer
- Over 95,600 Americans will be diagnosed with colon cancer in 2016
- An estimated 1 in 3 Americans between the ages of 50 and 75 do not engage in regular testing

What is FOBT?

FOBT (fecal occult blood test) is a fecal-based colorectal cancer screening option that allows patients to procure samples in the comfort of their own homes, at their convenience

What is FIT?

FIT (fecal immunochemical test), sometimes identified as iFOBT (immunochemical fecal occult blood test), is an improved FOBT with higher sensitivity and specificity when compared to guaiac FOBT (or gFOBT). When used yearly, FIT has accuracy rates near those of colonoscopy.

How does FIT compare to Guaiac FOBT?

- FIT has superior sensitivity and specificity as compared to guaiac FOBT
- FIT uses antibodies specific for human globin and are specific for colorectal bleeding and are not affected by diet or medications, unlike the guaiac test
- There is evidence that FIT use improves patient participation in screening by giving patients another choice for colorectal cancer screening
- FIT has a variety of improved stool collection methods such as a brush or probe

Why Choose the Alfa Scientific FIT Test?

- ***First and only*** company in the US to offer an over-the-counter Fecal Immunoassay Test (FIT) for Colon Cancer Pre-Screening
- In just a few simple steps, you can perform a FIT in the **privacy and comfort of your home**
- With unprecedented speed and **98% accuracy**, results are available in as little as **5-10 minutes**

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Who are these for?

Average risk.

- No first degree relative with h/o CRC, advanced adenoma, or polyp requiring surgical excision
- No personal history of lesions precluding their participation
- No hereditary high-risk colorectal cancer syndromes
- No inflammatory bowel disease
- No history of prior radiation treatment to abdomen or pelvic area

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FOBT

- 3 stool samples
- Peroxidase reaction to identify hemoglobin
- Possibility of false positives
- Recommend special diet (red meat, no Vitamin C, some recommend against NSAIDs)
- Collected annually

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Fecal Immunochemical Test (FIT)

- Single sample
- Targets blood in the lower GI tract via specific antibodies
- Less risk of false positives
- Collected annually
- Lower sensitivity for advanced adenomas.
- Doesn't detect serrated lesions.
- Less detection of proximal lesions

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FIT: Qualitative vs Quantitative

- 2 options
- Qualitative answers whether blood in lower GI tract
- Quantitative answers how much blood in lower GI tract
- Quantitative tests are run at certified labs through standardized machines, generally more accurate increasing PPV.

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Stool DNA Test (Cologuard)

- 1 sample collected every 3 years
- Multiple tests:
  - FIT test for hemoglobin
  - Molecular assays to test for KRAS mutations
  - Gene amplification to test for methylation biomarkers.
- Better sensitivity for advanced adenomas and large serrated lesions.
- Additional directions: diarrhea, menstruating, bleeding hemorrhoids.

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How accurate are they?

Test (for CRC)	Sensitivity	Specificity
gFOBT	12.9-79.4%	86.7-97.7%
FIT	79%	94%
Cologuard	92%	87%

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FOBT vs FIT

FIT is:

- More convenient
  - 1 vs 3 samples
  - No dietary changes
- More sensitive for CRC and advanced adenomas

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FIT vs Cologuard

Cologuard is:

- More sensitive for CRC (92% vs 74%)
- More sensitive for Advanced adenomas (42% vs 24%)
- More sensitive for SSLs > 10mm (42% vs %)
- Less specific for CRC or advanced lesions (87% vs 95%)

2 recent modeling studies:

- Annual FIT or Q10yr colonoscopy more effective and less costly than Q3yr Cologuard.

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Table 1. Sensitivity and Specificity of the Multitarget Stool DNA Test and the Fecal Immunochemical Test (FIT) for the Most Advanced Findings on Colonoscopy.

Most Advanced Finding	Colonoscopy (N=9989)	Multitarget DNA Test (N=9989)		FIT (N=9989)	
		Positive Results	Sensitivity (95% CI)	Positive Results	Sensitivity (95% CI)
	no.	*no.*	%	*no.*	%
Colorectal cancer					
Any	65	60	92.3 (83.0–97.5)	48	73.8 (61.5–84.0)
Stage I to III*	60	56	93.3 (83.8–98.2)	44	73.3 (60.3–83.9)
Colorectal cancer and high-grade dysplasia	104	87	83.7 (75.1–90.2)	66	63.5 (53.5–72.7)
Advanced precancerous lesions†	757	321	42.4 (38.9–46.0)	180	23.8 (20.8–27.0)
Nonadvanced adenoma	2893	498	17.2 (15.9–18.6)	220	7.6 (6.7–8.6)
			Specificity (95% CI)		Specificity (95% CI)
All nonadvanced adenomas, non-neoplastic findings, and negative results on colonoscopy	9167	1231	86.6 (85.9–87.2)	472	94.9 (94.4–95.3)
Negative results on colonoscopy	4457	455	89.8 (88.9–90.7)	162	96.4 (95.8–96.9)

* These stages of colorectal cancer, as defined by the system recommended by the American Joint Committee on Cancer, are associated with an increased rate of cure.
† Advanced precancerous lesions include advanced adenomas and sessile serrated polyps measuring 1 cm or more.

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Table 1. Outcomes of CRC Screening Strategies Over a Lifetime, in Order of Life-Years, Gained

Screening Method and Screening Interval	Life-Years Gained per 1000 Screened	CRC Deaths Averted per 1000 Screened	Complications of Screening and Follow-Up per 1000 Screened	Lifetime No. of Colonoscopies per 1000 Screened
Flexible sigmoidoscopy, 5 y	221	20	10	1820
FIT-DNA, 3 y	226	20	9	1714
FIT, 1 y	244	22	10	1757
FOBT, 1 y	247	22	11	2253
CT colonography, 5 y	248	22	10	1743
Flexible sigmoidoscopy, 10 y +	256	23	11	2289
FIT-DNA, 1 y	261	23	12	2662
Colonoscopy, 10 y	270	24	15	4049

Adapted from Knudsen et al (2016).[15]
CRC: colorectal cancer; CT: computed tomography; FIT: fecal immunochemical testing; FOBT: fecal occult blood testing.

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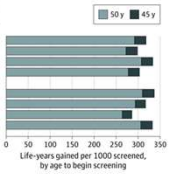
Life years gained:
- FIT = 318 yrs
- Cologuard Q3yrs = 303 yrs

CRC cases averted:
- FIT = 50 cases
- Cologuard Q3yrs = 47 cases

CRC deaths averted:
- FIT = 26 deaths
- Cologuard Q3yrs = 25 deaths

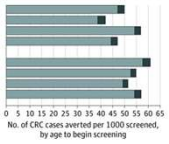
A Benefit: Estimated life-years gained per 1000 individuals screened[a]

Screening modality and frequency	Mean life-years gained if start screening[b] At age 50 y	At age 45 y	Additional life years gained if start screening at age 45 y
Stool tests			
FIT every year	292	318	26
HSgFOBT every year[c,d]	272	298	26
sDNA-FIT every year	307	333	26
sDNA-FIT every 3 y[d]	278	303	25
Direct visualization tests			
COL every 10 y	310	337	27
CT colonography every 5 y	293	317	24
Flexible SIG every 5 y	264	286	22
Flexible SIG every 10 y plus FIT every year	306	332	26



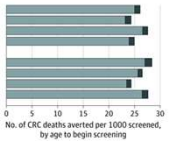
B Benefit: Estimated No. of CRC cases averted per 1000 individuals screened[a]

Screening modality and frequency	Mean CRC cases averted if start screening[b] At age 50 y	At age 45 y	Additional CRC cases averted if start screening at age 45 y
Stool tests			
FIT every year	47	50	3
HSgFOBT every year[c,d]	39	42	3
sDNA-FIT every year	54	57	3
sDNA-FIT every 3 y[d]	44	47	3
Direct visualization tests			
COL every 10 y	58	61	3
CT colonography every 5 y	53	55	2
Flexible SIG every 5 y	49	51	2
Flexible SIG every 10 y plus FIT every year	54	57	3



C Benefit: Estimated No. of CRC deaths averted per 1000 individuals screened[a]

Screening modality and frequency	Mean CRC deaths averted if start screening[b] At age 50 y	At age 45 y	Additional CRC deaths averted if start screening at age 45 y
Stool tests			
FIT every year	25	26	1
HSgFOBT every year[c,d]	23	24	1
sDNA-FIT every year	27	28	1
sDNA-FIT every 3 y[d]	24	25	1
Direct visualization tests			
COL every 10 y	27	28	1
CT colonography every 5 y	26	26	0.9
Flexible SIG every 5 y	23	24	0.9
Flexible SIG every 10 y plus FIT every year	26	28	1



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Expert opinion

- US Preventive Services Task Force
  - Doesn't endorse test preferences

U.S. Preventive Services TASK FORCE

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Expert opinion

- American Cancer Society
  - Doesn't endorse test preferences.

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Expert opinion

- US Multisociety Task Force (ACG, AGA, ASGE)
  - Colonoscopy
  - FIT annually if they don't want colonoscopy
    - Second tier if neither: CT colonography Q5yrs, Cologuard Q3yrs, Flex sig Q5-10yrs.

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Expert opinion

- American Society of Clinical Oncology
  - Base test recommendations on resources available
  - In lower resource settings, favor gFOBT or FIT.
  - In enhanced resource settings, favor noninvasive testing with gFOBT or FIT, but may receive endoscopic screening.

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TABLE 2. Screening/Treatment Capacities by Setting

Intervention	Setting: Basic	Limited	Enhanced	Maximal
Screening	No screening available	No mass screening available; individuals may only access one screening per lifetime	Limited mass screening; primarily opportunistic screening	Invitation, reminder, registration, monitoring, evaluation, recall systems already in place; population likely to access more than one screening per lifetime
Reflex testing/ endoscopy	DRE or barium enema possible	Flex sigmoidoscopy available	Colonoscopy available	Colonoscopy available
Imaging	X-ray and someone to read it	CT	CT/MRI available	CR/MRI/PET widely available
Surgery	General surgery with minor operating room available	General surgery with operating room	OR, ICU, colorectal surgery available, may or may not have access to laprascopic approaches.	Specialist surgery services widely available with minimally invasive surgical options (eg, laprascopic, robotic)
Chemotherapy	Availability of chemotherapy drugs is unpredictable	Some chemotherapy available (maybe not so specific)	More chemotherapy options available; targeted therapy may or may not be available	Chemotherapy available; targeted therapy available
Radiation therapy	No RT available; in some basic settings, radiation may be available but very limited, unpredictable	Limited external RT with no brachytherapy available; services may not always be available/unpredictable	RT including external beam and brachytherapy available; interventional radiology not available	RT including external beam and brachytherapy available; interventional radiology available (eg, IMRT, IORT)
Pathology	If there is a way to send pathology for review when needed, that should occur	Pathology services in development; H&E usually available, IHC and molecular tests usually not available	Pathology services usually available and IHC and molecular tests may be available	Pathology available with specialist pathology templates, genetic/molecular testing available
Palliative care	Palliative care service not available; limited medications for pain may be available	Pain and symptom management available; palliative care service in development	Palliative care specialty service not always available	Specialist palliative care service available

Abbreviations: DRE, digital rectal examination; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; OR, operating room; ICU, intensive care unit; RT, radiation therapy; IMRT, intensity-modulated radiation therapy; IORT, intraoperative; H&E, hematoxylin and eosin; IHC, immunohistochemistry.

Lopes et al

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TABLE 3. Screening Recommendations

Recommendation No. (quality of evidence; strength of recommendation)	Basic	Limited	Enhanced	Maximal
1.1. (high; strong)	People should receive highly sensitive gFOBT every 1 (preferred) to 2 years if resources are available (based on resources and patient adherence).	People should receive highly sensitive gFOBT annually.	People should receive highly sensitive gFOBT annually.	People should receive highly sensitive gFOBT annually.
1.2. (intermediate; moderate)	People may receive FIT, if available, every 1 (preferred) to 2 years (based on resources and patient adherence).	People may receive FIT annually.	People may receive FIT annually.	People may receive FIT annually.
1.3. (high; strong)	NA	People should receive flexible sigmoidoscopy every 5 years.	People should receive flexible sigmoidoscopy every 5 years.	People should receive flexible sigmoidoscopy every 5 years.
1.4. (intermediate; strong)	NA	People may receive flexible sigmoidoscopy every 10 years plus FIT (or, if FIT is not available, then FOBT) every year.	People may receive flexible sigmoidoscopy every 10 years plus FIT (or, if FIT is not available, then FOBT) every year.	People may receive flexible sigmoidoscopy every 10 years plus FIT (or, if FIT is not available, then FOBT) every year.
1.5. (low; weak)	NA	NA	People may receive colonoscopy every 10 years.	People may receive colonoscopy every 10 years
1.6. (low; weak)	NA	NA	NA	People may receive CT colonography.
1.7. (low; weak)	NA	NA	NA	People may receive FIT-DNA.

Abbreviations: gFOBT, guaiac fecal occult blood test; FIT, fecal immunochemical testing; NA, not available; CT, computed tomography.

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Expert opinion

- Canadian Task Force on Preventive Health Care
  - FOBT (gFOBT or FIT) Q2yrs
    - OR
  - Flexible sigmoidoscopy Q10yrs

- Doesn't recommend colonoscopy as screening.

CTFPHC

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Colonoscopy: Gold standard?

- Positive screens on other tests require colonoscopy
- Screening and intervention
- Procedure -> risks.
- Less convenient.

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What's next?

- New tests
  - Septin 9 DNA (circulating methylated DNA) FDA approved 2016
    - Concern for lower sensitivity (48%) although one study suggests up to 74.8% sensitivity, 87.4% specificity
  - Circulating tumor cells (CTCs)
    - One study, CellMax, 667 adults, suggesting 95% CRC sensitivity, 86% specificity
  - Urine studies for CRC metabolites
    - Several studies suggesting sensitivity ~80%, specificity ~50%
- Further studies
  - Randomized head-to-head comparing screening methods
  - Factors affecting adherence to screening regimen
  - Additional biomarkers to improve FIT detection of advanced adenomatous polyps

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Clinical Pearls

- There are multiple options available to patients who are average risk and don't want colonoscopy.
- Annual FIT likely optimizes cost and efficacy.
- Colonoscopy is still the gold standard.
- Alternative screening modalities, while promising, have not yet been shown to be more effective than currently available stool studies.

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Table 1. Characteristics of Recommended Colorectal Cancer Screening Strategies

Screening method[a]	Frequency[b]	Evidence of efficacy	Other considerations
Stool-based tests			
High-sensitivity gFOBT	Every year	• Evidence from RCTs that gFOBT reduces colorectal cancer mortality • High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II), although there is still uncertainty about the precision of test sensitivity estimates. Given this uncertainty, it is unclear whether high-sensitivity gFOBT can detect as many cases of advanced adenomas and colorectal cancer as other stool-based tests	• Harms from screening with gFOBT arise from colonoscopy to follow up abnormal gFOBT results • Requires dietary restrictions and 3 stool samples • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)
FIT	Every year	• Evidence from 1 large cohort study that screening with FIT reduces colorectal cancer mortality • Certain types of FIT have improved accuracy compared to gFOBT and HSgFOBT (20 µg hemoglobin per gram of feces threshold was used in the CISNET modeling)	• Harms from screening with FIT arise from colonoscopy to follow up abnormal FIT results • Can be done with a single stool sample • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)
sDNA-FIT	Every 1 to 3[c] y	• Improved sensitivity compared with FIT per 1-time application of screening test • Specificity is lower than that of FIT, resulting in more false-positive results, more follow-up colonoscopies, and more associated adverse events per sDNA-FIT screening test compared with per FIT test • Modeling suggests that screening every 3 y does not provide a favorable (ie, efficient) balance of benefits and harms compared with other stool-based screening options (ie, annual FIT or sDNA-FIT every 1 or 2 y) • Insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative follow-up colonoscopy • No direct evidence evaluating the effect of sDNA-FIT on colorectal cancer mortality	• Harms from screening with sDNA-FIT arise from colonoscopy to follow up abnormal sDNA-FIT results • Can be done with a single stool sample but involves collecting an entire bowel movement • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)
Direct visualization tests			
Colonoscopy	Every 10 y	• Evidence from cohort studies that colonoscopy reduces colorectal cancer mortality • Harms from colonoscopy include bleeding and perforation, which both increase with age	• Screening and follow-up of positive results can be performed during the same examination • Requires less frequent screening • Requires bowel preparation, anesthesia or sedation, and transportation to and from the screening examination
CT colonography	Every 5 y	• Evidence available that CT colonography has reasonable accuracy to detect colorectal cancer and adenomas • No direct evidence evaluating effect of CT colonography on colorectal cancer mortality • Limited evidence about the potential benefits or harms of possible evaluation and treatment of incidental extracolonic findings, which are common. Extracolonic findings detected in 1.3% to 11.4% of examinations; <3% required medical or surgical treatment	• Additional harms from screening with CT colonography arise from colonoscopy to follow up abnormal CT colonography results • Requires bowel preparation • Does not require anesthesia or sedation or transportation to and from the screening examination
Flexible sigmoidoscopy	Every 5 y	• Evidence from RCTs that flexible sigmoidoscopy reduces colorectal cancer mortality • Risk of bleeding and perforation but less than risk with colonoscopy • Modeling suggests that it provides fewer life-years gained alone than when combined with FIT or in comparison to other strategies	• Additional harms may arise from colonoscopy to follow up abnormal flexible sigmoidoscopy results • Test availability has declined in the US but may be available in some communities where colonoscopy is less available
Flexible sigmoidoscopy with FIT	Flexible sigmoidoscopy every 10 y plus FIT every year	• Evidence from RCTs that flexible sigmoidoscopy + FIT reduces colorectal cancer mortality • Modeling suggests combination testing provides benefits similar to those of colonoscopy, with fewer complications • Risk of bleeding and perforation from flexible sigmoidoscopy but less than risk with colonoscopy	• Additional potential harms from colonoscopy to follow up abnormal flexible sigmoidoscopy or FIT results • Flexible sigmoidoscopy availability has declined in the US but may be available in some communities where colonoscopy is less available • Screening with FIT requires good adherence over multiple rounds of testing

Abbreviations: CISNET, Cancer Intervention and Surveillance Modeling Network; CT, computed tomography; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; RCT, randomized clinical trial; sDNA-FIT, stool DNA test with fecal immunochemical test.

[a] To achieve the benefits of screening, abnormal results from stool-based tests, CT colonography, and flexible sigmoidoscopy should be followed up with colonoscopy.

[b] Applies to persons with negative findings (including hyperplastic polyps) and is not intended for persons in surveillance programs. Evidence of efficacy is not informative of screening frequency, with the exception of gFOBT and flexible sigmoidoscopy alone.

[c] As stated by the manufacturer.

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Links

1. https://journals.lww.com/ajg/fulltext/2021/03000/acg_clinical_guidelines__colorectal_cancer.14.aspx
2. https://www.gastrojournal.org/article/S0016-5085(08)00232-1/fulltext#secd13418169e950
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