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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# Colorectal Cancer Screening

Version 2.2025 — June 24, 2025

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# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

\***Reid M. Ness, MD, MPH**/Chair ☐  
Vanderbilt-Ingram Cancer Center

\***Xavier Llor, MD, PhD**/Vice Chair ☐ ♀  
Yale Cancer Center/  
Smilow Cancer Hospital

**Leonard Baidoo, MD** ☐  
St. Jude Children's Research Hospital/The  
University of Tennessee Health Science Center

**Shrinivas Bishu, MD** ☐  
University of Michigan Rogel Cancer Center

**Gregory Cooper, MD** ☐  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer  
Center and Cleveland Clinic Taussig  
Cancer Institute

**Dayna S. Early, MD** ☐  
Siteman Cancer Center at Barnes-  
Jewish Hospital and Washington  
University School of Medicine

**Mark Friedman, MD** ☐  
Moffitt Cancer Center

**David Fudman, MD** ☐  
UT Southwestern Simmons  
Comprehensive Cancer Center

**Susan Gearhart, MD** ¶  
Johns Hopkins Kimmel Cancer Center

**Kathryn Glaser, PhD, MA** «  
Roswell Park Comprehensive Cancer Center

**Suryakanth Gurudu, MD** ☐  
Mayo Clinic Comprehensive Cancer Center

**Michael Hall, MD, MS** †  
Fox Chase Cancer Center

**Lyen C. Huang, MD, MPH** ¶  
Huntsman Cancer Institute  
at the University of Utah

**Rachel Issaka, MD, MAS** ☐  
Fred Hutchinson Cancer Center

**Bryson Katona, MD, PhD** ☐  
Abramson Cancer Center  
at the University of Pennsylvania

**Trilokesh Kidambi, MD** ☐  
City of Hope National Medical Center

**Audrey J. Lazenby, MD** ≠  
Fred & Pamela Buffett Cancer Center

**Jennifer Maratt, MD, MS** ☐  
Indiana University Melvin and Bren Simon  
Comprehensive Cancer Center

**Arnold J. Markowitz, MD** ☐  
Memorial Sloan Kettering Cancer Center

**Joseph Marsano, MD** ☐  
UC Davis Comprehensive Cancer Center

**Folasade P. May, MD, PhD, MPhil** † ☐  
UCLA Jonsson Comprehensive Cancer Center

**Robert J. Mayer, MD** † ♀  
Dana-Farber/Brigham and Women's  
Cancer Center | Mass General Cancer Center

**Kinga Olortegui, MD, MS** ¶  
The UChicago Medicine  
Comprehensive Cancer Center

**Swati Patel, MD, MS** ☐  
University of Colorado Cancer Center

**Shajan Peter, MD** ☐  
O'Neal Comprehensive  
Cancer Center at UAB

**Laura D. Porter, MD** ¥  
Independent Patient Advocate

**Mehnaz Shafi, MD** ☐  
The University of Texas  
MD Anderson Cancer Center

**Peter P. Stanich, MD** ☐  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Brian Sullivan, MD** ☐  
Duke Cancer Institute

**Jonathan Terdiman, MD** ☐  
UCSF Helen Diller Family  
Comprehensive Cancer Center

**Peter Vu, MD** †  
UC San Diego Moores Cancer Center

**Jennifer M. Weiss, MD, MS** ☐  
University of Wisconsin  
Carbone Cancer Center

**NCCN**  
**Carly J. Cassara, MSc**  
**Vaishnavi Sambandam, PhD**

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# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

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#### For High-Risk Colorectal Cancer Syndromes,

##### [see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric](#)

#### For Principles of Cancer Risk Assessment and Counseling,

##### [see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate](#)

### [Abbreviations \(ABBR-1\)](#)

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**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

[Erratum on CSCR-A 2 of 7 published on July 11, 2025](#), the specificity for mt-sRNA testing was updated from 95% to 86% for advanced adenomas.

Updates in Version 2.2025 of the NCCN Guidelines for Colorectal Cancer Screening from Version 1.2025 include:

- The discussion section has been updated to reflect changes within the algorithm.

Updates in Version 1.2025 of the NCCN Guidelines for Colorectal Cancer Screening from Version 1.2024 include:

### [CSCR-PREV 1 OF 2](#)

- Lifestyle/dietary factors associated with increased CRC risk, bullet 3: *Alcohol*: Moderate to heavy alcohol consumption: This level of consumption is associated with increased CRC risk.

### [CSCR-1](#)

- Footnote c modified: The terms sessile serrated polyp, sessile serrated lesion, SSP/SSL sessile serrated polyp (SSP), sessile serrated lesion (SSL), and sessile serrated adenoma...

### [CSCR-2](#)

- Header modified: Evaluation of alarm *signs and symptoms* in patients <45 years

► Bullet 1: Half of the patients who present with early-onset CRC (<50 years of age) are <45 years of age. All patients, regardless of age, who present with symptoms potentially associated with CRC, including but not limited to rectal bleeding, iron deficiency anemia, abdominal pain, or weight loss should undergo a prompt tailored evaluation for both gastrointestinal (GI) and non-GI causes. In most unexplained cases, an anorectal exam and colonoscopy should be considered. Patients with rectal bleeding initially attributed to hemorrhoids that does not resolve with treatment should also be considered for colonoscopy.

- Hereditary CRC syndromes

► Bullet removed: LS (hereditary nonpolyposis CRC [HNPCC])

► Bullet 1 modified: *Lynch syndrome (LS)* (aka hereditary nonpolyposis CRC [HNPCC])

- Footnote modified: Stoffel EM, et al. *Gastroenterology* 2020;158:341-353. Demb J, et al. *JAMA Netw Open* 2024;7:e2413157

### [CSCR-3](#)

- Page extensively modified

### [CSCR-4](#)

- Flexible sigmoidoscopy, upper pathway: ~~Biopsy or Polypectomy~~

- Flexible sigmoidoscopy, lower pathway, last column: Rescreen with any modality in 5–10 y

### [CSCR-5](#)

- New to Guidelines. (Also for CSCR-6 and CSCR-7)

### [CSCR-7A](#)

- Footnotes removed:

► A blood test that detects circulating methylated SEPT9 DNA has been FDA-approved for CRC screening for those who refuse other screening modalities. Based on current data, the panel concludes that the interval for repeating testing is unknown/unclear. The panel will continue to review this strategy and monitor data as they emerge.

► There are alternative strategies that have been recommended with flexible sigmoidoscopy, including flexible sigmoidoscopy every 10 years with annual FIT or considering longer interval

- Footnotes modified

► k: If colonoscopy is incomplete or the preparation is suboptimal, ~~colonoscopy~~ it should be repeated as soon as possible and no later than 1 year after the index procedure (Johnson DA, et al. *Gastroenterology* 2014;147:903-924).

► l: ~~For patients who have had incomplete colonoscopy, capsule colonoscopy can be considered (Rex DK, et al. *Gastroenterology* 2015;148:948-957). For patients who have had incomplete colonoscopy, consider CTC or balloon-assisted colonoscopy or capsule colonoscopy as alternative exams for completing the screening (Franco~~

**Note:** All recommendations are category 2A unless otherwise indicated.

**Continued**

**UPDATES**

### Updates in Version 1.2025 of the NCCN Guidelines for Colorectal Cancer Screening from Version 1.2024 include:

- DL, et al. Gastroenterol Hepatol 2017;13:476-483; Dzeletovic I, et al. Dig Dis Sci 2012;57:2680-2686; Rex DK, et al. Gastroenterology 2015;148:948-957).*
- q: There are alternative strategies that have been recommended with flexible sigmoidoscopy, including flexible sigmoidoscopy every 10 years *combined with annual FIT or considering longer interval flexible sigmoidoscopy without FIT* (Knudsen AB, et al. JAMA 2016;315:2595-2609).
  - r: Based on recent evidence, FIT has been shown to have superior sensitivity to guaiac-based tests. However, ~~guaiac-based testing has been shown to reduce mortality from CRC and high-sensitivity fecal occult blood test (FOBT) is a reasonable alternative if an immunochemical test cannot be used (Rabeneck L, et al. Can J Gastroenterol 2012;26:131-147; Schollefield JH, et al. Gut 2012;61:1036-1040). guaiac-based fecal occult blood test (FOBT) screening has been shown to reduce mortality from CRC. Both FOBT- and FIT-based stool tests can be considered as alternatives to multitargeted stool DNA (mt-sDNA) based on accessibility.~~ (Rabeneck L, et al. Can J Gastroenterol 2012;26:131-147; Schollefield JH, et al. Gut 2012;61:1036-1040).
  - t: If the colonoscopy is negative after a *positive* FIT or mt-sDNA or *mt-sRNA*, no symptoms are present, and the colonoscopy was a high-quality examination, patients can return to average-risk screening intervals beginning at 10 years after the colonoscopy. This interval could be modified based on the presence of symptoms or signs or additional CRC risk factors such as family history.

#### CSCR-8

- Page extensively modified

#### CSCR-8A

- Footnote w: ...~~Ten~~ Nine or fewer polyps in the setting of a strong family history or younger age (<40 years) may sometimes be associated with an inherited polyposis syndrome.
- Footnote z added: In patients who previously had high-risk adenomas, high-risk SSP/SSLs, TSAs, or hyperplastic polyps ≥1 cm, surveillance interval should not be increased to >5 years.

#### CSCR-9

- Complete resection, pathways modified

#### CSCR-9A

- Footnote removed: Wang R, et al. Surg Endosc 2016;30:1530-1533; Hayashi N, et al. Gastrointest Endosc 2013;78:625-632; Li M, et al. World J Gastroenterol 2014;20:12649-12656; Ishiguro A, et al. Gastrointest Endosc 1999;50:329-333; Belderbos TD, et al. Endoscopy 2014;46:388-402; Tate DJ, et al. Gastrointest Endosc 2017;85:647-656. e6; The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58:S3-S43.

#### CSCR-11

- Surveillance, chromoendoscopy, sub-bullet 2 modified: Non-targeted (random) biopsies as described above should be considered in addition to ~~chromoendoscopy to targeted biopsies..~~
- Footnote nn: Risk factors for dysplasia include Crohn's colitis historically involving more than one third of the colon; ulcerative colitis; extensive colitis; colonic stricture; PSC; family history of CRC, especially age <50 years; personal history of dysplasia; *and* severe long-standing inflammation; *and* dense pseudopolyposis. Confirmation by an expert GI pathologist is desirable. For patients with proctitis, who have little or no increased risk for CRC compared with the population at large, consider 5-year follow-up or average-risk follow-up. *Patients with isolated small bowel Crohn's disease should follow average-risk screening and surveillance recommendations* (Lutgens M, et al. Clin Gastroenterol Hepatol 2015;13:148-154.e1; Beaugerie L, et al. Gastroenterology 2013;145:166-175.e8; Murthy SK, et al. Gastroenterology 2021;161:1043-1051.e4).

#### CSCR-12A

- Footnote added: Gordon H, et al. J Crohns Colitis 2023;17:827-854.

#### CSCR-13

- Lower pathway, non-traversable stricture: Consider referral to an IBD or therapeutic endoscopy expert with expertise in *endoscopic management of IBD-associated colonic strictures and/or a surgeon with expertise in IBD for surgical resection*.~~large/complex polyp resection and/or a surgeon with expertise in IBD for resection at a~~

Note: All recommendations are category 2A unless otherwise indicated.

Continued

UPDATES

### Updates in Version 1.2025 of the NCCN Guidelines for Colorectal Cancer Screening from Version 1.2024 include:

center with expertise in management of IBD-associated colonic strictures.

#### CSCR-15

- Footnote modified: a patient meets the criteria for an inherited colorectal syndrome, see *Assessment for Hereditary CRC Syndrome General Criteria for Testing and Genetic Evaluation for Hereditary Syndromes Associated with Colorectal, Endometrial, and Gastic Cancer (HRS-1)* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.

#### CSCR-16

- Lower pathway, sub-bullet 2: History of systemic therapy and/or radiotherapy for a childhood or young adult cancer, specifically radiotherapy and/or chemotherapy.

#### CSCR-A 2 of 7

- Rows added
  - mt-sRNA test
  - bb-cf DNA test
- Statement removed: A blood test that detects circulating methylated SEPT9 DNA has been FDA-approved for CRC screening for those who refuse other screening modalities. Based on current data, the panel concludes that the interval for repeating testing is unknown/unclear. The panel will continue to review this strategy and monitor data as they emerge.

#### CSCR-A 3 of 7

- References added
  - Barnell EK, Wurtzler EM, La Rocca J, et al. Multitarget stool RNA test for colorectal cancer screening. JAMA 2023;330:1760-1768. Erratum in: JAMA 2024;331:888.
  - Chung DC, Gray DM II, Singh H, et al. A cell-free DNA blood-based test for colorectal cancer screening. N Engl J Med 2024;390:973-983.

#### CSCR-A 4 of 7, 5 of 7, 6 of 7, and 7 of 7

- Pages extensively modified.

#### CSCR-GLOS 1 of 7

- Row added: Cell-free blood-based screening

#### CSCR-GLOS 2 of 7

- Rows added:
  - Multi-target stool RNA
  - Advanced precancerous lesion
  - Advanced neoplasia
- Low-risk adenomas, definition modified: 1–2 nonadvanced polyps/adenomas <10 mm in size
- Traditional serrated adenoma, definition modified: Polyps with complex villous growth pattern; ectopic crypt formation is a unique feature that leads to mucosal protrusions; are associated with high-risk polyp recurrence, and high-risk neoplasia and CRC

#### CSCR-GLOS 3 of 7

- Invisible dysplasia, definition modified: Dysplasia diagnosed on pathology but not described grossly detectable on endoscopy; identified on random/non-targeted biopsies of colon mucosa without a visible lesion

#### CSCR-GLOS 6 of 7

- Reference added: Trivedi M, Godil S, Demb J, et al. Baseline characteristics and longitudinal outcomes of traditional serrated adenomas: A cohort study. Clin Gastroenterol Hepatol 2023;21:1637-1645.

Note: All recommendations are category 2A unless otherwise indicated.

Continued

UPDATES



# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### PRIMARY AND SECONDARY PREVENTION OF COLORECTAL CANCER

Certain lifestyle modifications are associated with a reduced risk of colorectal cancer (CRC) and can be an important adjunct to screening for CRC prevention. For risk assessment of individuals at average risk of disease, see [CSCR-1](#).

Lifestyle/dietary factors associated with reduced CRC risk/recurrence:

- Physical activity: Regular physical activity (ie, occupational, recreational, transportation) has been associated with decreased CRC risk.<sup>1</sup>
- Fruits and vegetables: A diet high in fruits and vegetables has been associated with decreased CRC risk in some studies.<sup>2,3</sup>
- Dietary supplements: In general, nutrients should be obtained from natural food sources rather than solely from dietary supplements.<sup>1</sup>
- Smoking cessation: Smoking cessation counseling is strongly recommended. See [NCCN Guidelines for Smoking Cessation](#).

Lifestyle/dietary factors associated with increased CRC risk:

- Smoking: Long-term cigarette smoking is associated with increased CRC incidence and mortality.<sup>4,5</sup> Risk reduction is seen with early smoking cessation.<sup>5</sup>
- Red meat and processed meat: Long-term consumption is associated with increased CRC risk.<sup>1,6</sup>
- Alcohol: Moderate to heavy alcohol consumption is associated with increased CRC risk.<sup>1,7,8</sup>
- Obesity: Obesity is associated with an increased risk for CRC.<sup>1,9,10,11</sup>
- Vitamin D: Low levels of vitamin D have been associated with increased CRC risk.<sup>12</sup>
- While supplemental calcium, vitamin D, and folate use have all been linked to a decreased risk of conventional adenomas, some evidence suggests that these agents may increase the risk of serrated polyps.<sup>13,14</sup>

Aspirin:

- Evidence is unclear whether aspirin use reduces the risk of CRC incidence or mortality when employed for primary prevention.<sup>15</sup>
- Aspirin use has been associated with improved CRC-specific survival and overall survival when employed for secondary prevention.<sup>16</sup>
- There is evidence supporting the use of aspirin for CRC chemoprevention in patients with Lynch syndrome (LS) (a hereditary CRC syndrome).<sup>17</sup> See [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric](#).

Please also see relevant sections in:

- [NCCN Guidelines for Colon Cancer](#) - Principles of Survivorship
- [NCCN Guidelines for Survivorship](#)

Note: All recommendations are category 2A unless otherwise indicated.

CSCR-PREV  
1 OF 2

## REFERENCES

- <sup>1</sup> World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report. 2018. Available at: <https://www.wcrf.org/dietandcancer>. This comprehensive report analyzed 99 studies comprising greater than 29 million adults with over 247,000 cases of CRC.
- <sup>2</sup> Koushik A, Hunter DJ, Spiegelman D, et al. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst* 2007;99:1471-1483.
- <sup>3</sup> Michels KB, Edward G, Joshipura KJ, et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J Natl Cancer Inst* 2000;92:1740-1752.
- <sup>4</sup> Hannan LM, Jacobs EJ, Thun MJ. The association between cigarette smoking and risk of colorectal cancer in a large prospective cohort from the United States. *Cancer Epidemiol Biomarkers Prev* 2009;18:3362-3367.
- <sup>5</sup> Chao A, Thun MJ, Jacobs EJ, et al. Cigarette smoking and colorectal cancer mortality in the cancer prevention study II. *J Natl Cancer Inst* 2000;92:1888-1896.
- <sup>6</sup> Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol* 2015;16:1599-1600.
- <sup>7</sup> LoConte NK, Brewster AM, Kaur JS, et al. Alcohol and cancer: A statement of the American Society of Clinical Oncology. *J Clin Oncol* 2018;36:83-93.
- <sup>8</sup> Fedirko V, Tramacere I, Bagnardi V, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann Oncol* 2011;22:1958-1972.
- <sup>9</sup> Ligibel JA, Alfano CM, Courneya KS, et al. American Society of Clinical Oncology position statement on obesity and cancer. *J Clin Oncol* 2014;32:3568-3574.
- <sup>10</sup> Karahalios A, English DR, Simpson JA. Weight change and risk of colorectal cancer: a systematic review and meta-analysis. *Am J Epidemiol* 2015;181:832-845.
- <sup>11</sup> Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer--viewpoint of the IARC Working Group. *N Engl J Med* 2016;375:794-798.
- <sup>12</sup> IARC. Vitamin D and Cancer. IARC Working Group Report Volume 5, International Agency for research on Cancer. Lyon: 2008. Available at: <https://publications.iarc.fr/Book-And-Report-Series/larc-Working-Group-Reports/Vitamin-D-And-Cancer-2008>.
- <sup>13</sup> He X, Wu K, Ogino S, et al. Association between risk factors for colorectal cancer and risk of serrated polyps and conventional adenomas. *Gastroenterology* 2018; 155:355-373.e18.
- <sup>14</sup> Crockett SD, Barry EL, Mott LA, et al. Calcium and vitamin D supplementation and increased risk of serrated polyps: results from a randomised clinical trial. *Gut* 2019;68:475-486.
- <sup>15</sup> Guirguis-Blake JM, Evans CV, Perdue LA, et al. Aspirin use to prevent cardiovascular disease and colorectal cancer: Updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2022;327:1585-1597.
- <sup>16</sup> Bains SJ, Mahic M, Myklebust TA, et al. Aspirin as secondary prevention in patients with colorectal cancer: An unselected population-based study. *J Clin Oncol* 2016;34:2501-2508.
- <sup>17</sup> Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. *Lancet* 2020;395:1855-1863.

Note: All recommendations are category 2A unless otherwise indicated.

**CSCR-PREV**  
**2 OF 2**



# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### RISK ASSESSMENT FOR COLORECTAL CANCER

#### Average risk:

- Age 45–75 years<sup>a,b</sup>
- No personal history of adenoma or sessile serrated polyp/sessile serrated lesion (SSP/SSL)<sup>c</sup> or CRC
- No personal history of inflammatory bowel disease (IBD)
- No personal history of high-risk CRC genetic syndromes (list of syndromes on [CSCR-2](#))
- No personal history of cystic fibrosis
- No personal history of childhood cancer
- Negative family history of confirmed advanced adenoma (ie, high-grade dysplasia ≥1 cm, villous or tubulovillous histology) or an advanced SSP/SSL<sup>c,d</sup> (≥1 cm, any dysplasia) in first-degree relatives<sup>e</sup>
- Negative family history for CRC<sup>f</sup>



#### Increased risk:

- Personal history
  - ▶ Adenoma or SSP/SSL<sup>c</sup> → Follow-up of Clinical Findings:  
Polyp Found at Colonoscopy ([CSCR-8](#))
  - ▶ CRC → Diagnosis of Colorectal Cancer ([CSCR-10](#))
  - ▶ IBD (ulcerative colitis, Crohn's colitis) → Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease ([CSCR-11](#))
  - ▶ Cystic fibrosis → Increased Risk Based on Personal History of Cystic Fibrosis ([CSCR-14](#))
- Positive family history → Increased Risk Based on Positive Family History ([CSCR-15](#))
- Personal history of childhood, adolescent, and young adult cancer (including individuals who meet criteria for therapy-associated polyposis) → Increased Risk Based on Personal History of Childhood, Adolescent, and Young Adult Cancer ([CSCR-16](#))

For individuals at average risk, the choice of a particular screening modality should include a conversation with the patient concerning their preference and availability. For individuals at increased risk, colonoscopy is the preferred method.

[Footnotes on CSCR-1A](#)

Note: All recommendations are category 2A unless otherwise indicated.

**FOOTNOTES FOR CSCR-1**

- <sup>a</sup> The Panel has reviewed existing data for beginning screening of individuals at age <50 years who are of average risk. Based on their assessment, the Panel agrees that the data are stronger to support beginning screening at 50 years, but acknowledges that lower-level evidence supports a benefit for screening earlier. When initiating screening for all eligible individuals, the Panel recommends a discussion of potential harms/risks and benefits, and the consideration of all recommended CRC screening options (Ladabaum U, et al. Gastroenterology 2019;157:137-148; Knudsen AB, et al. JAMA 2021;325:1998-2011).
- <sup>b</sup> CRC screening is recommended in adults aged 45–75 years who might have a life expectancy of ≥10 years. The decision to screen between ages 76–85 years should be individualized and include a discussion of 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.
- <sup>c</sup> The terms sessile serrated polyp (SSP), sessile serrated lesion (SSL), and sessile serrated adenoma are synonymous; SSPs/SSLs are a type of serrated polyp that are not dysplastic but they can develop foci of dysplasia and are then termed SSP/SSL with dysplasia (SSP/SSL-d). These guidelines will use “SSP/SSL” for SSPs/SSLs without dysplasia and “SSP/SSL-d” for SSPs/SSLs with dysplasia. In general SSPs/SSLs are managed like tubular adenomas and SSP/SSL-d with any grade dysplasia are managed like high-risk adenomas but may need even more frequent surveillance. Classification systems for serrated lesions are evolving, and a recent proposal by WHO suggests using the term sessile serrated lesion (WHO Classification of Tumours Editorial Board. Digestive System Tumours. Lyon, France: IARC;2019:162-169). See [CSCR-GLOS 3 of 7](#).
- <sup>d</sup> Advanced SSPs/SSLs are generally considered to have a comparable cancer risk and are managed similarly to advanced adenomas, rather than high-risk adenomas, a definition that includes multiplicity.
- <sup>e</sup> Ochs-Balcom HM, et al. Cancer Epidemiol 2021;73:101973.
- <sup>f</sup> While current risk estimates for a family history of CRC in only second- and third-degree relatives may not be sufficiently elevated to recommend increased screening (Taylor DP, et al. Gastroenterology 2010;138:877-885; Taylor DP, et al. Genet Med 2011;13:385-391; Samadder NJ, et al. Gastroenterology 2014;147:814-821; Tian Y, et al. BMJ 2019;364:1803), there are some data showing that having a second- and, to a lesser degree, a third-degree relative with early-onset (<50 years old) CRC increases risk of both CRC and early-onset CRC (Ochs-Balcom HM, et al. Cancer Epidemiol 2021;73:101973). Some combinations of affected first-, second-, and third-degree relatives may increase risk sufficiently to alter screening guidelines. If there are multiple distant relatives affected, consider evaluation for an inherited CRC syndrome in the family.

**Note:** All recommendations are category 2A unless otherwise indicated.



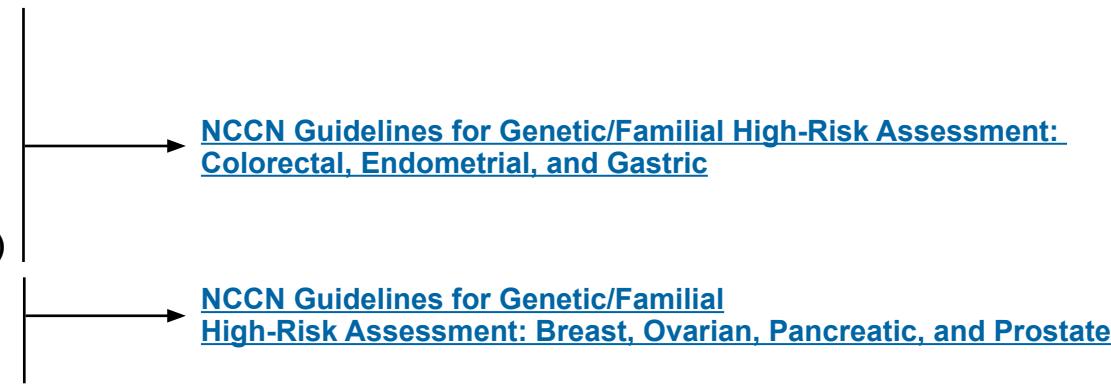
## RISK ASSESSMENT FOR COLORECTAL CANCER (CONT.)<sup>g,h</sup>

### Evaluation of alarm signs and symptoms

- All patients, regardless of age, who present with symptoms potentially associated with CRC, including but not limited to rectal bleeding, iron deficiency anemia, abdominal pain, or weight loss should undergo a prompt tailored evaluation for both gastrointestinal (GI) and non-GI causes. In most unexplained cases, an anorectal exam and colonoscopy should be considered. Patients with rectal bleeding initially attributed to hemorrhoids that does not resolve with treatment should also be considered for colonoscopy.

### Hereditary CRC syndromes:

- Lynch syndrome (LS)
- Polyposis syndromes
  - ▶ Classical familial adenomatous polyposis
  - ▶ Attenuated familial adenomatous polyposis
  - ▶ MUTYH-associated polyposis
  - ▶ Peutz-Jeghers syndrome
  - ▶ Juvenile polyposis syndrome
  - ▶ Serrated polyposis syndrome (rarely inherited)
- Other pathogenic variants
- Cowden syndrome/PTEN hamartoma tumor syndrome
- Li-Fraumeni syndrome



<sup>g</sup> Demb J, et al. JAMA Netw Open 2024;7:e2413157.

<sup>h</sup> Fritz CD, et al. J Natl Cancer Inst 2023;115:909.

**Note:** All recommendations are category 2A unless otherwise indicated.

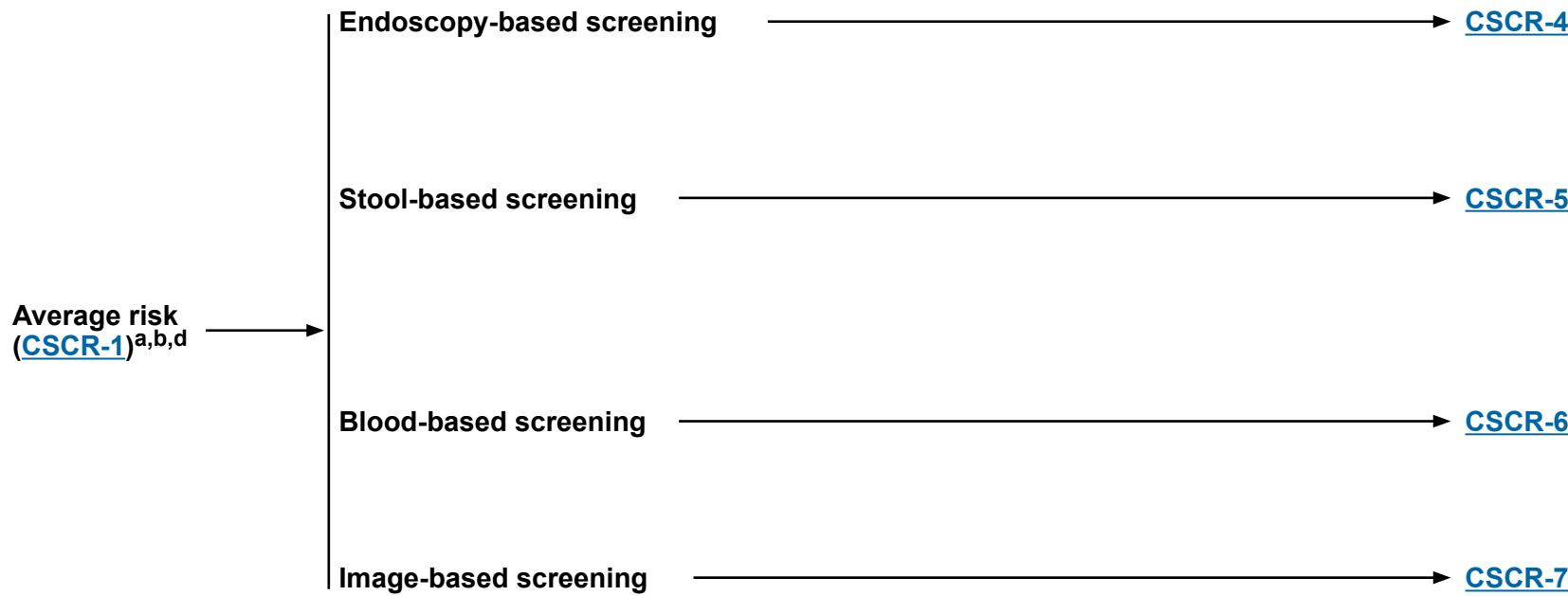


# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### RISK STATUS

### SCREENING MODALITY AND SCHEDULE<sup>i,j</sup>



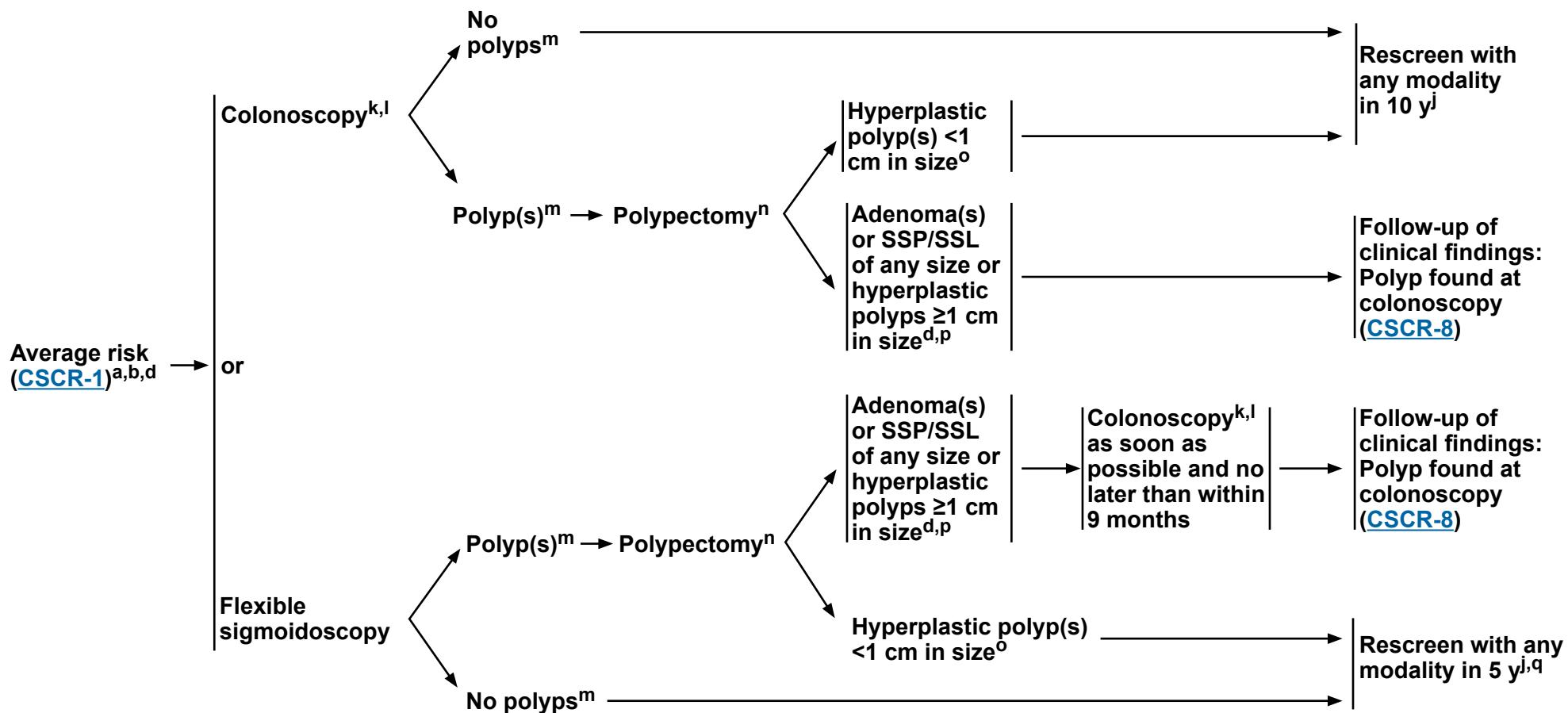
[Footnotes on CSCR-7A](#)

Note: All recommendations are category 2A unless otherwise indicated.

**ENDOSCOPY-BASED SCREENING**

RISK STATUS    SCREENING MODALITY  
AND SCHEDULE<sup>i,j</sup>

EVALUATION OF SCREENING FINDINGS



Footnotes on [CSCR-7A](#)

Note: All recommendations are category 2A unless otherwise indicated.

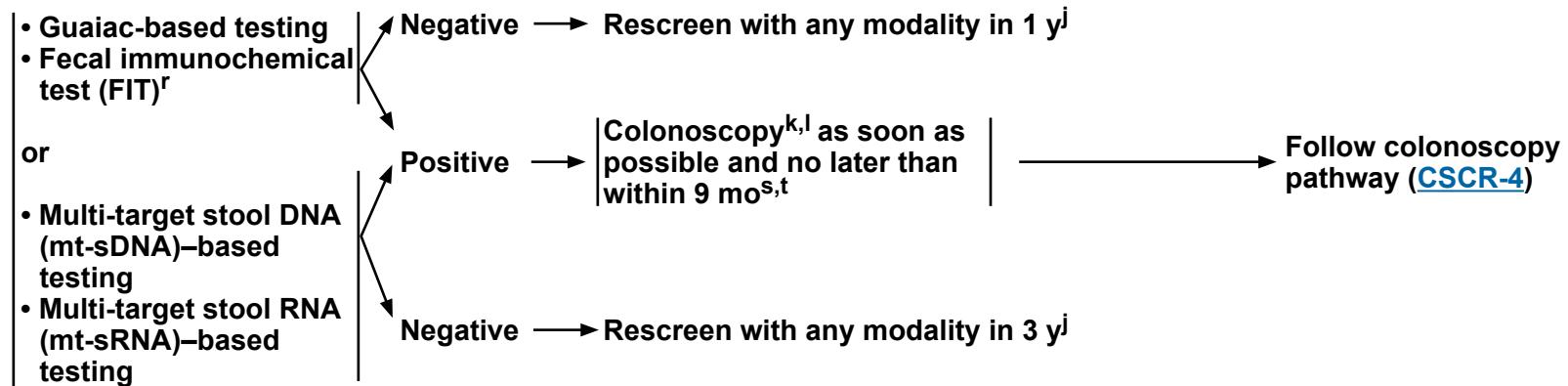
**STOOL-BASED SCREENING**

**RISK STATUS**

**SCREENING MODALITY  
AND SCHEDULE<sup>i,j</sup>**

**EVALUATION OF SCREENING FINDINGS**

Average risk  
([CSCR-1](#))<sup>a,b,d</sup>



Note: All recommendations are category 2A unless otherwise indicated.



# NCCN Guidelines Version 2.2025

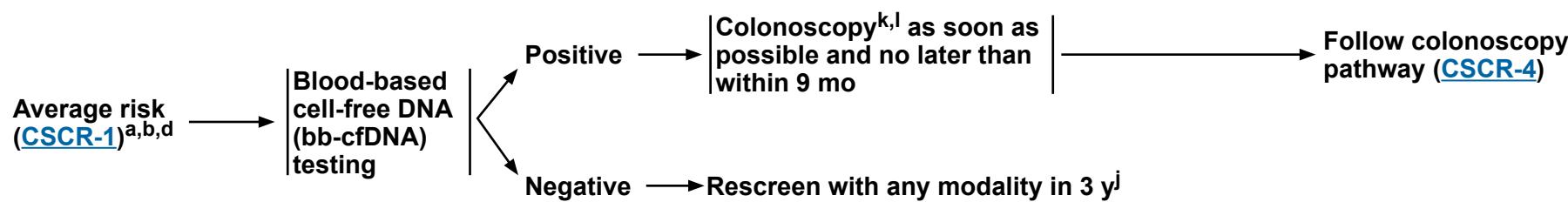
## Colorectal Cancer Screening

### RISK STATUS

### SCREENING MODALITY AND SCHEDULE<sup>i,j</sup>

### BLOOD-BASED SCREENING

### EVALUATION OF SCREENING FINDINGS

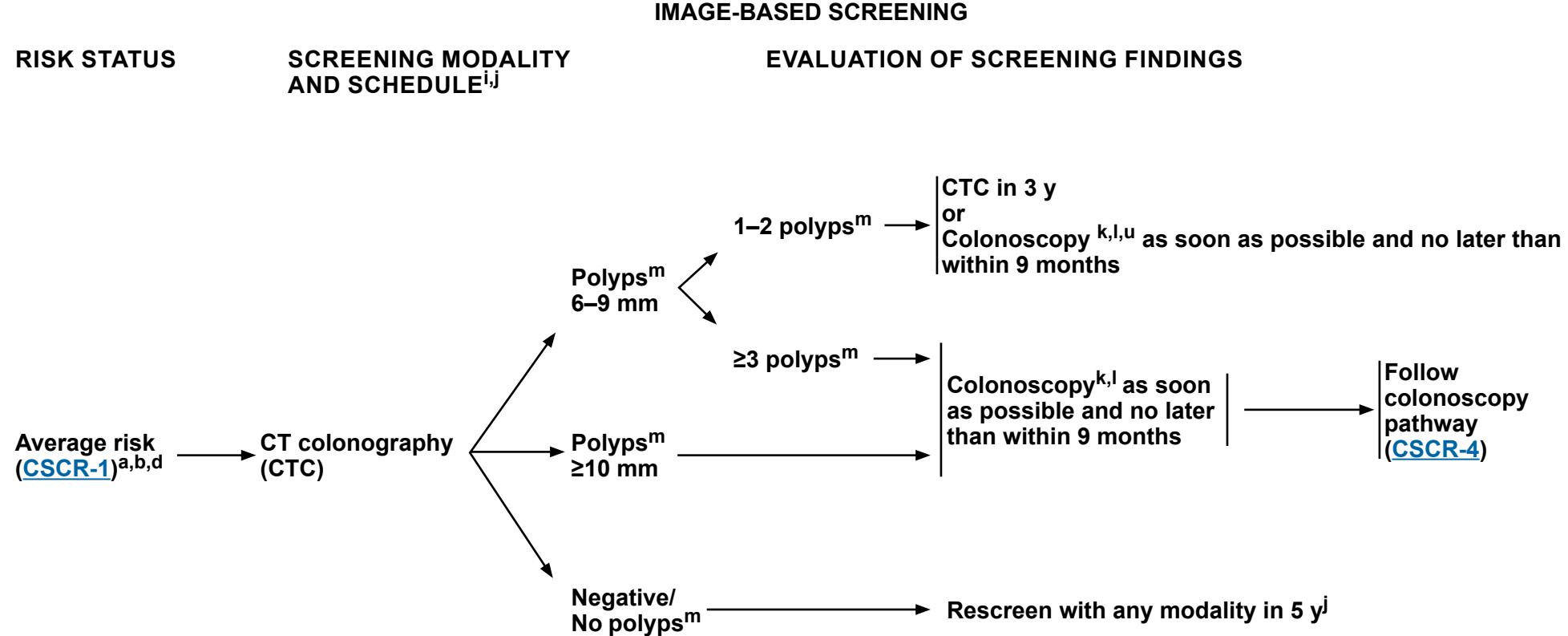


[Footnotes on CSCR-7A](#)

Note: All recommendations are category 2A unless otherwise indicated.

# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening



[Footnotes on CSCR-7A](#)

Note: All recommendations are category 2A unless otherwise indicated.

## FOOTNOTES

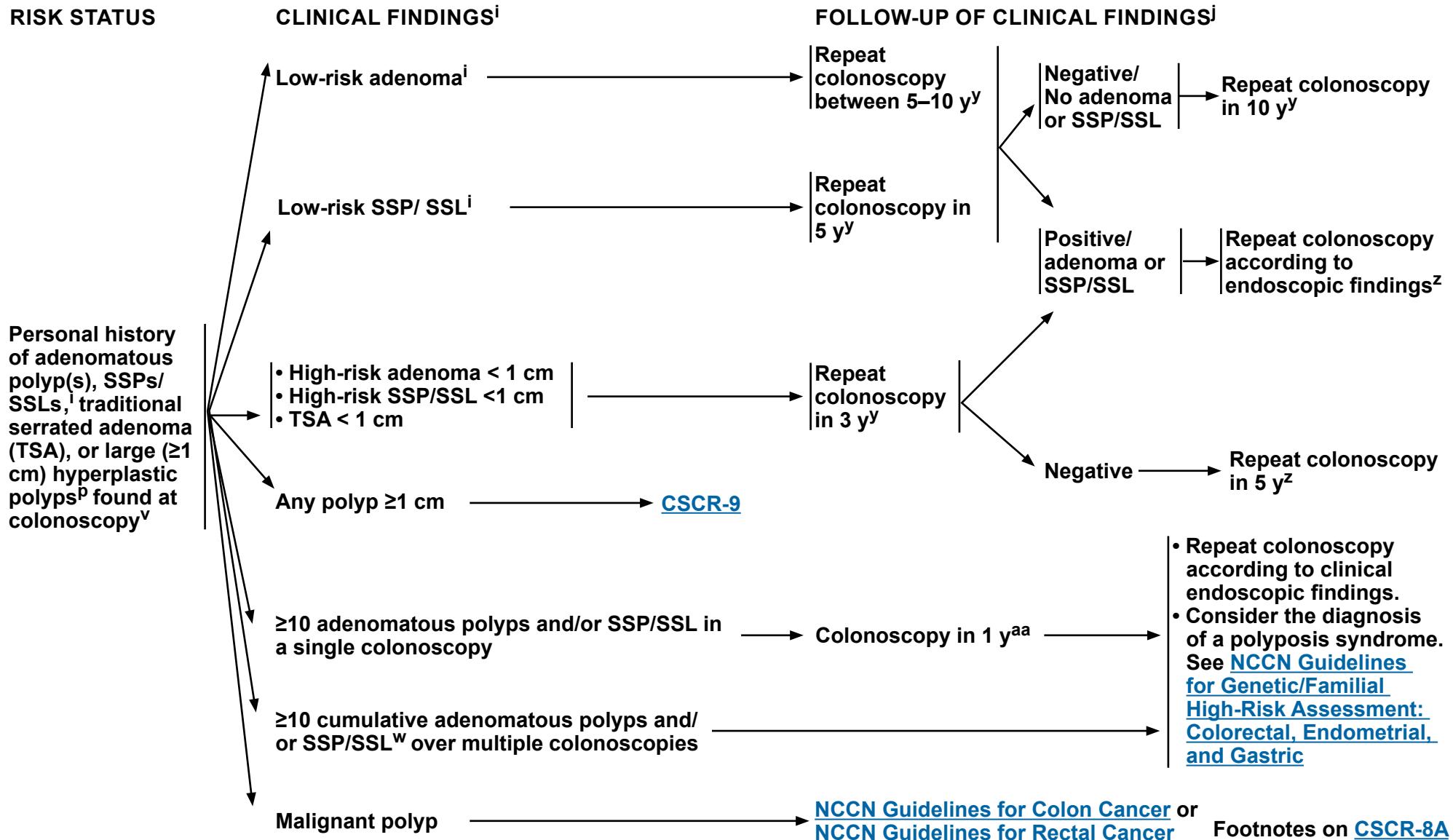
- <sup>a</sup> The Panel has reviewed existing data for beginning screening of individuals at age <50 years who are of average risk. Based on their assessment, the Panel agrees that the data are stronger to support beginning screening at 50 years, but acknowledges that lower-level evidence supports a benefit for screening earlier. When initiating screening for all eligible individuals, the Panel recommends a discussion of potential harms/risks and benefits, and the consideration of all recommended CRC screening options (Ladabaum U, et al. Gastroenterology 2019;157:137-148; Knudsen AB, et al. JAMA 2021;325:1998-2011).
- <sup>b</sup> CRC screening is recommended in adults aged 45–75 years who might have a life expectancy of ≥10 years. The decision to screen between ages 76–85 years should be individualized and include a discussion of 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.
- <sup>d</sup> Advanced SSPs/SSLs are generally considered to have a comparable cancer risk and are managed similarly to advanced adenomas, rather than high-risk adenomas, a definition that includes multiplicity.
- <sup>i</sup> For details on classification, see footnote c on [CSCR-1A](#). For definitions of commonly used terms, see [CSRC-GLOS 1 of 7](#).
- <sup>j</sup> Screening should be individualized and include a discussion of the risks and benefits of each modality. See [Screening Modality and Schedule \(CSCR-A\)](#).
- <sup>k</sup> If colonoscopy is incomplete or the preparation is suboptimal, it should be repeated as soon as possible and no later than 1 year after the index procedure (Johnson DA, et al. Gastroenterology 2014;147:903-924).
- <sup>l</sup> For patients who have had incomplete colonoscopy, consider CTC or balloon-assisted colonoscopy or capsule colonoscopy as alternative exams for completing the screening (Franco DL, et al. Gastroenterol Hepatol 2017;13:476-483; Dzeletovic I, et al. Dig Dis Sci 2012;57:2680-2686; Rex DK, et al. Gastroenterology 2015;148:948-957).
- <sup>m</sup> The term "polyp" refers to both polyps and nonpolypoid (flat) lesions.
- <sup>n</sup> If polypectomy is unable to be performed, the patient should be referred to a provider who can perform endoscopy with polypectomy.
- <sup>o</sup> If >20 serrated polyps are found at colonoscopy, consider a diagnosis of serrated polyposis syndrome ([NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric](#)). There are conflicting data to suggest that hyperplastic polyp(s) (<1 cm) proximal to the sigmoid colon pose an increased risk and whether they should be managed differently (Li D, et al. Gastroenterology 2020;159:502-511; Anderson JA, et al. Gastrointest Endosc 2020;92:387-393).
- <sup>p</sup> There are limited data to support whether individuals with hyperplastic polyps ≥1 cm in size represent an increased risk group. Several analyses suggest that many of the larger polyps classified as hyperplastic in the past were reclassified as SSPs/SSLs when reviewed by experts. For this reason, it is reasonable to follow patients with hyperplastic polyps ≥1 cm in size similarly to patients with SSPs/SSLs, particularly if they have not been reviewed by an expert GI pathologist (Anderson JC, et al. Gastrointest Endosc 2020;92:387-393).
- <sup>q</sup> There are alternative strategies that have been recommended with flexible sigmoidoscopy, including flexible sigmoidoscopy every 10 years combined with annual FIT (Knudsen AB, et al. JAMA 2016;315:2595-2609).
- <sup>r</sup> FIT has been shown to have superior sensitivity to guaiac-based tests. However, guaiac-based fecal occult blood test (FOBT) screening has been shown to reduce mortality from CRC. Both FOBT- and FIT-based stool tests can be considered as alternatives to mt-sDNA-based on accessibility (Rabeneck L, et al. Can J Gastroenterol 2012;26:131-147; Schollefeld JH, et al. Gut 2012;61:1036-1040).
- <sup>s</sup> When a screening stool-based test is positive, a colonoscopy is recommended for further evaluation. Recommendations for an appropriate time frame for follow-up colonoscopy in this population lack a strong evidence base, but a large observational study and a meta-analysis reported significantly higher risks for CRC and advanced-stage disease when follow-up occurred 10 months or later with a trend towards increased cancer risk observed as early as 6 months after an abnormal result (Corley DA, et al. JAMA 2017;317:1631-1641; Forbes N, et al. Clin Gastro Hepatol 2020;19:1344-1354).
- <sup>t</sup> If the colonoscopy is negative after a positive FIT or mt-sDNA or mt-sRNA, no symptoms are present, and the colonoscopy was a high-quality examination, patients can return to average-risk screening intervals beginning at 10 years after the colonoscopy. This interval could be modified based on the presence of symptoms or signs or additional CRC risk factors such as family history.
- <sup>u</sup> Data on optimal frequency, polyp size leading to colonoscopy referral, and protocol for evaluation of extracolonic lesions are evolving. The [American College of Radiology](#) has recommended that reporting of polyps ≤5 mm in size is not necessary. If polyp(s) of this size are reported, a decision to refer for colonoscopy with polypectomy versus surveillance CTC should be individualized (Zalis ME, et al. Radiology 2005;236:3-9; Tutein Nolthenius CJ, et al. Am J Gastroenterol 2015;110:1682-1690; Pickhardt PJ, et al. Lancet Oncol 2013;14:711-720).

Note: All recommendations are category 2A unless otherwise indicated.

# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### PERSONAL HISTORY OF POLYP FOUND AT COLONOSCOPY<sup>x</sup>



Note: All recommendations are category 2A unless otherwise indicated.

## FOOTNOTES FOR CSCR-8

- <sup>i</sup> For definitions of commonly used terms, see [CSCR-GLOS](#). For details on classification, see footnote c on [CSCR-1A](#).
- <sup>j</sup> Screening should be individualized and include a discussion of the risks and benefits of each modality. See [Screening Modality and Schedule \(CSCR-A\)](#).
- <sup>P</sup> There are limited data to support whether individuals with hyperplastic polyps  $\geq 1$  cm in size represent an increased risk group. Several analyses suggest that many of the larger polyps classified as hyperplastic in the past were reclassified as SSPs/SSLs when reviewed by experts. For this reason, it is reasonable to follow patients with hyperplastic polyps  $\geq 1$  cm in size similarly to patients with SSPs/SSLs, particularly if they have not been reviewed by an expert GI pathologist (Anderson JA, et al. Gastrointest Endosc 2020;92:387-393).
- <sup>v</sup> Surveillance colonoscopy is recommended in adults aged 45–75 years with a history of adenomas. Surveillance of individuals between ages 76–85 years should be individualized and include a discussion of risks and benefits of continued colonoscopy based on comorbidity status, estimated life expectancy, and findings on the last or the most recent colonoscopy.
- <sup>w</sup> Consider germline genetic testing for 10–19 cumulative adenomas if other factors suggest the possibility of a polyposis/CRC syndrome such as age of onset or family or personal history of CRC. Nine or fewer polyps in the setting of a strong family history or younger age (<40 years) may sometimes be associated with an inherited polyposis syndrome.
- <sup>x</sup> Surveillance intervals assume complete resection, adequate bowel preparation, and complete examination.
- <sup>y</sup> Available data suggest that individuals with low-risk adenomas or SSPs/SSLs may not have an increased risk of metachronous advanced colorectal neoplasia compared to the general population (Cottet V, et al. Gut 2012;61:1180-1186; He X, et al. Gastroenterol 2019;158:852-861). Any recommendation for a shorter interval should include a discussion with the individual based on an assessment of individual risk, including age, family history, comorbidity, and the results of previous colonoscopies (Dube C, et al. Am J Gastroenterol 2017;112:1790-1801; Click B, et al. JAMA 2018;319:2021-2031; Lieberman D, et al. Gastroenterology 2020;158:862-874; Lee J, et al. Gastroenterology 2020;158:884-894.e5).
- <sup>z</sup> In patients who previously had high-risk adenomas, high-risk SSP/SSLs, TSAs, or hyperplastic polyps  $\geq 1$  cm, surveillance interval should not be increased to >5 years.
- <sup>aa</sup> If genetic testing is negative or if evaluation is not performed, repeat colonoscopy within 1–3 years. Frequency of surveillance may be modified based on factors such as age at which patient met cumulative adenoma threshold or total number of adenomas at most recent colonoscopy, with more frequent surveillance favored for younger age at meeting threshold or higher adenoma burden at last colonoscopy.

**Note:** All recommendations are category 2A unless otherwise indicated.

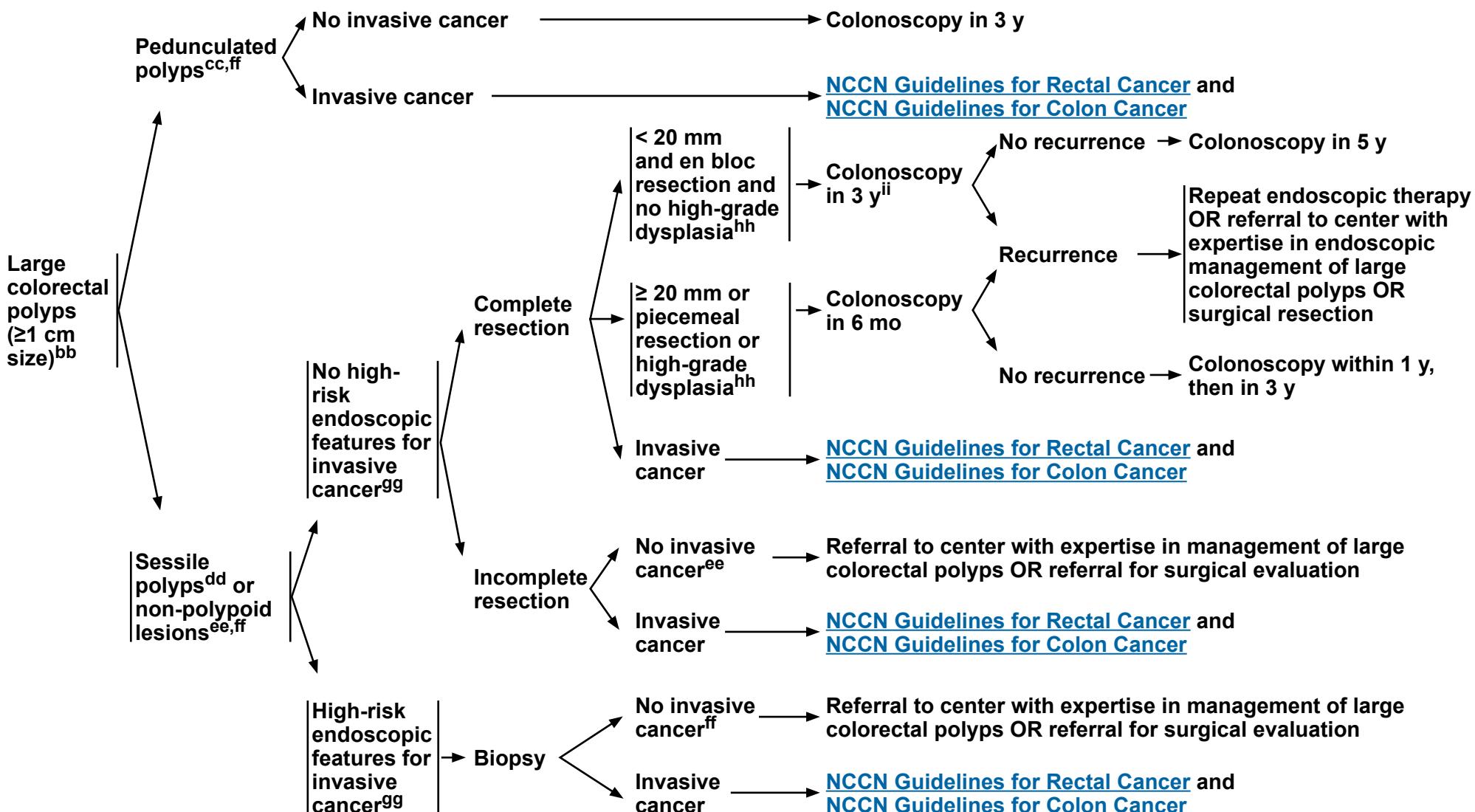


# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### MANAGEMENT OF LARGE COLORECTAL POLYPS<sup>cc</sup>

#### CLINICAL FINDINGS



Note: All recommendations are category 2A unless otherwise indicated.

[Footnotes on CSCR-9A](#)

## FOOTNOTES

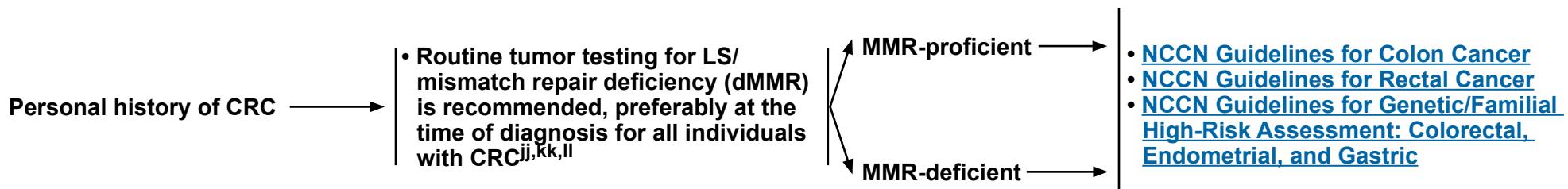
- <sup>bb</sup> Consider a referral to a center of expertise for large polyp management. For sessile polyps or laterally spreading lesions (LSLs)  $\geq 20$  mm size, recommend endoscopic tattoo placement for future lesion identification.
- <sup>cc</sup> Paris subtype 0–1p lesions.
- <sup>dd</sup> Paris subtype 0–1s lesions.
- <sup>ee</sup> Paris subtype 0-IIa, 0-IIb, 0-IIc, and 0-III lesions. The Panel recommends consideration of referral to a center of expertise for management of these lesions.
- <sup>ff</sup> Histology may include adenoma, SSP/SSL, hyperplastic polyp, or TSA.
- <sup>gg</sup> High-risk features suggestive of submucosal invasion include NICE classification type 3, Kudo classification type V (VN and VI), and non-lifting sign.
- <sup>hh</sup> Consider margin ablation using snare tip soft coagulation (STSC) to prevent polyp recurrence. Gauci JL, et al. Gut 2025;74:752–760
- <sup>ii</sup> Consider follow-up in < 3 years when confidence in complete en bloc resection is low.

**Note:** All recommendations are category 2A unless otherwise indicated.

# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### DIAGNOSIS OF COLORECTAL CANCER



<sup>jj</sup> The Panel recommends universal screening of all CRC tumors to maximize sensitivity for MMR deficiency and/or LS, and to inform prognosis and care processes in patients with or without LS. The Panel recommends tumor testing with immunohistochemistry (IHC) for MMR and/or microsatellite instability (MSI) be used as the primary approach for pathology-lab-based universal screening and to guide treatment decisions.

<sup>kk</sup> See pros and cons of screening for LS using colonoscopy-based biopsies versus a surgical resection specimen. See [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric](#).

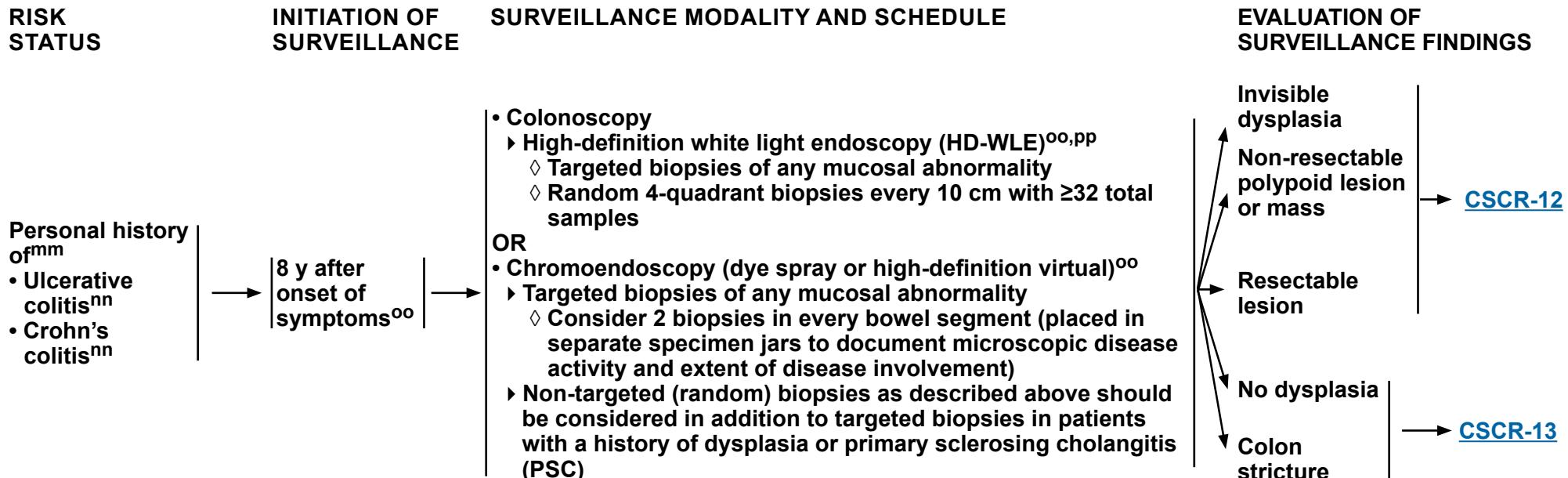
<sup>ll</sup> Germline multigene testing for evaluation of LS and other hereditary cancer syndromes is recommended for individuals with CRC <50 years of age. See [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric](#).

**Note:** All recommendations are category 2A unless otherwise indicated.

# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE<sup>mm</sup>



<sup>mm</sup> If PSC is present, annual surveillance colonoscopies should be started independent of the individual's time since symptom onset or colonoscopic findings and instead should be initiated at time of PSC diagnosis. Family history of CRC is another important risk factor for developing CRC in patients with IBD, and such individuals may benefit from earlier initiation of colonoscopic surveillance (Samadder NJ, et al. Clin Gastroenterol Hepatol 2019;17:1807-1813; Shergill AK, et al. Gastrointest Endosc Clin N Am 2014;24:469-481).

<sup>nn</sup> Risk factors for dysplasia include Crohn's colitis historically involving more than one third of the colon; ulcerative colitis; extensive colitis; colonic stricture; PSC; family history of CRC, especially age <50 years; personal history of dysplasia; severe long-standing inflammation; and dense pseudopolyposis. Confirmation by an expert GI pathologist is desirable. For patients with proctitis, who have little or no increased risk for CRC compared with the population at large, consider 5-year follow-up or average-risk follow-up. Patients with isolated small bowel Crohn's disease should follow average-risk screening and surveillance recommendations. Patients with isolated small bowel Crohn's diseases should follow average-risk screening and surveillance recommendations (Lutgens M, et al. Clin Gastroenterol Hepatol 2015;13:148-154.e1; Beaugerie L, et al. Gastroenterology 2013;145:166-175.e8; Murthy SK, et al. Gastroenterology 2021;161:1043-1051.e4).

<sup>oo</sup> Endoscopy should be performed during quiescent disease. Targeted biopsies improve detection of dysplasia, and should be performed for surveillance colonoscopies in patients with ulcerative colitis. High-definition colonoscopes are suggested. If using standard-definition colonoscopes, non-targeted biopsies in 4 quadrants every 10 cm should be performed and dye spray chromoendoscopy is recommended (Murthy Y, et al. Gastrointest Endosc 2013;77:351-359; Picco MF, et al. Inflamm Bowel Dis 2013;19:1913-1920; Laine L, et al. Gastrointest Endosc 2015;81:489-501).

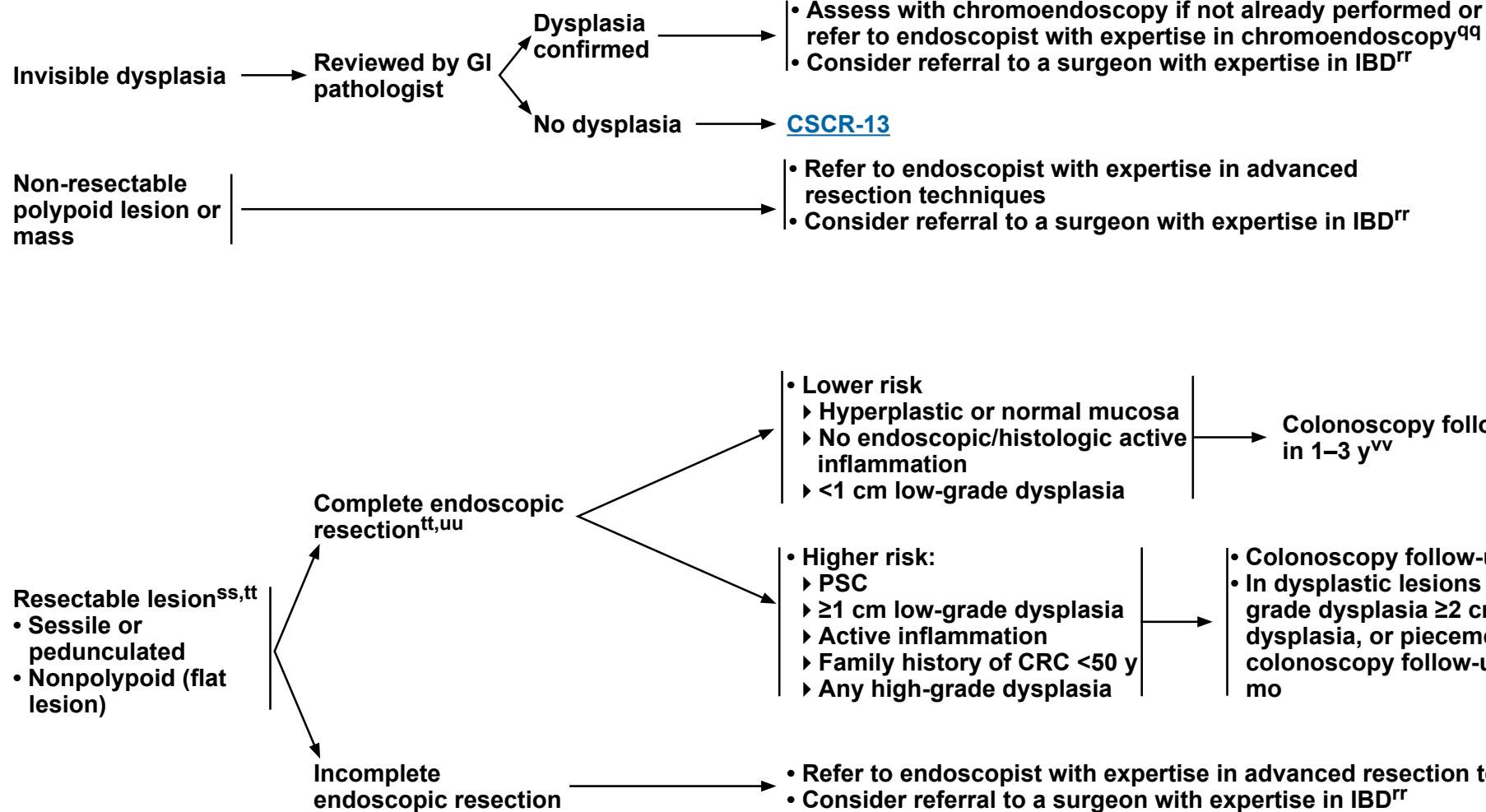
<sup>pp</sup> If HD-WLE or chromoendoscopy is not available, refer to institutions with expertise in these modalities.

Note: All recommendations are category 2A unless otherwise indicated.

## INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE

### EVALUATION OF SURVEILLANCE FINDINGS

### FOLLOW-UP OF CLINICAL FINDINGS



Note: All recommendations are category 2A unless otherwise indicated.

[Footnotes on CSCR-12A](#)

## FOOTNOTES

<sup>qq</sup> In patients with endoscopically invisible dysplasia, the recommendation for referral to an endoscopist with IBD expertise for chromoendoscopy is consensus-based as data to support its use in this setting are limited.

<sup>rr</sup> A surgical consult may include a discussion about surveillance and colectomy based on multiple factors including other visible dysplastic lesions in the same segment, histology, and a discussion with the patient about risks and benefits of each approach (Laine L, et al. Gastroenterology 2015;148:639-651).

<sup>ss</sup> Consider utilizing Paris classification to describe lesion. Lesions should be described as polypoid ( $\geq 2.5$  mm tall), nonpolypoid ( $<2.5$  mm), or invisible. All polypoid and nonpolypoid lesions should be completely resected.

<sup>tt</sup> Patients with ulcerative colitis develop sporadic colorectal adenomas at the same rate as the general population. Lesions that appear endoscopically and histologically similar to a sporadic adenoma or SSP/SSL and without invasive carcinoma in the polyp can be treated safely by polypectomy. Some lesions may require endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) techniques for complete resection. Confirmation of all polyp histology and dysplasia by an expert GI pathologist is desirable.

<sup>uu</sup> Following endoscopic resection of visible lesions, biopsy of surrounding mucosa is not routinely necessary, but should be considered if there is any doubt regarding the completeness of resection (Murthy SK, et al. Gastroenterology 2021;161:1043-1051.e4; Lahiff C, et al. Gastrointest Endosc 2018;88:782-783; Cleveland NK, et al. Gastrointest Endosc 2018;87:1304-1309; Ten Hove JR, et al. Clin Gastroenterol Hepatol 2017;15:222-228.e222).

<sup>vv</sup> Gordon H, et al. J Crohns Colitis 2023;17:827-854.

**Note: All recommendations are category 2A unless otherwise indicated.**



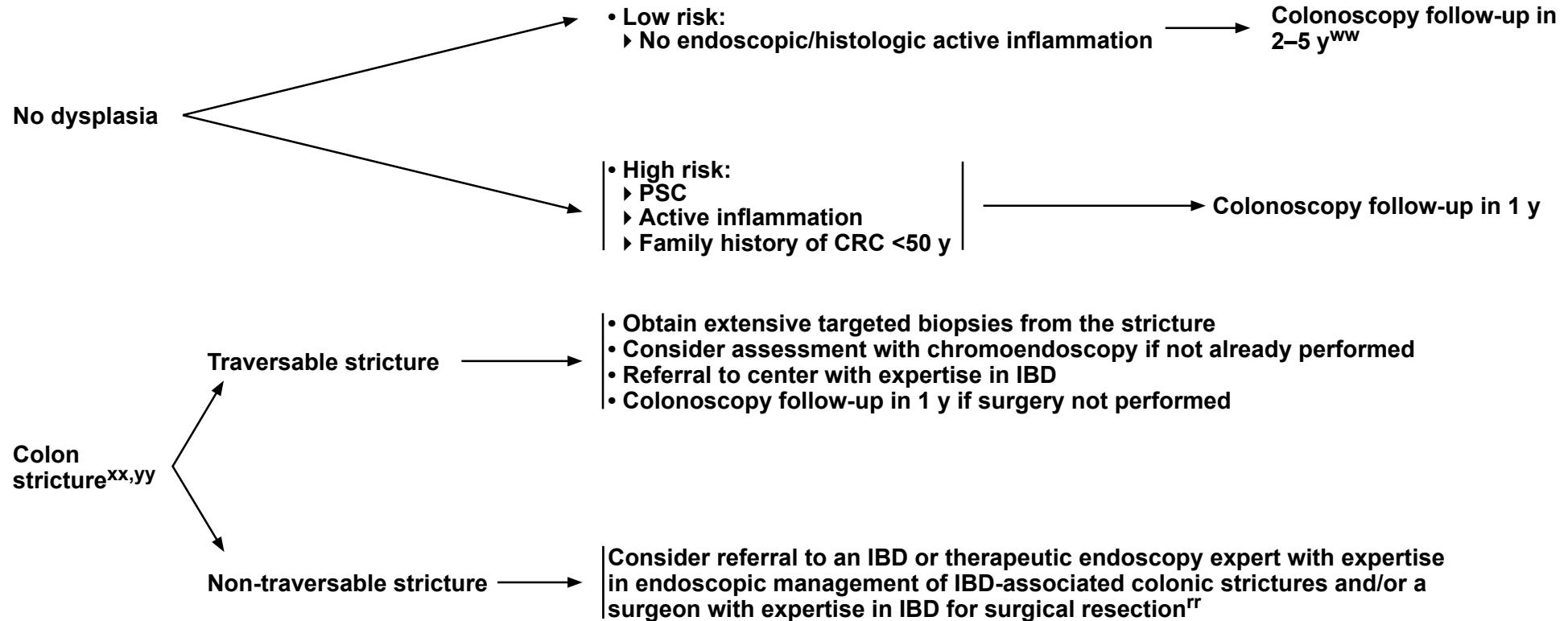
# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE

#### EVALUATION OF SURVEILLANCE FINDINGS

#### FOLLOW-UP OF CLINICAL FINDINGS



<sup>rr</sup> A surgical consult may include a discussion about surveillance and colectomy based on multiple factors including other visible dysplastic lesions in the same segment, histology, and a discussion with the patient about risks and benefits of each approach (Laine L, et al. Gastroenterology 2015;148:639-651).

<sup>ww</sup> UK, Australian, and European GI societies position statements recommend risk-stratified surveillance with increased surveillance interval to 3–5 years in lower risk patients (Shergill AK, et al. Gastrointest Endosc Clin N Am 2014;24:469-481; Gordon H, et al. J Crohns Colitis 2023;17:827-854; Lamb CA, et al. Gut 2019;68:s1-s106).

<sup>xx</sup> Consider surgery in patients with symptomatic or non-traversable strictures as there is risk of underlying cancer, particularly in patients with long-standing IBD.

<sup>yy</sup> The literature describes a wide range of prevalence of dysplasia or cancer in colitis-associated colonic strictures, with rates of up to 7% in Crohn's disease, and reported rates between 2% and 90% in ulcerative colitis. Among strictures with negative surveillance biopsies, reported rates of dysplasia or cancer in follow-up range from 2%–6% in Crohn's disease and 7.5%–27% in ulcerative colitis (Fumery M, et al. J Crohns Colitis 2021;15:1766-1773).

Note: All recommendations are category 2A unless otherwise indicated.

## **INCREASED RISK BASED ON PERSONAL HISTORY OF CYSTIC FIBROSIS<sup>22</sup>**

```

graph LR
    A[History of solid organ transplant] --> B["Age ≥30 y or within 2 y of the transplantation"]
    C[No history of solid organ transplant] --> D["Age ≥40 y"]
    B --> E[Colonoscopyaaa,bbb]
    E --> F[Normal]
    E --> G[Adenomatous or SSPs/SSLs]
    F --> H[Repeat colonoscopy in 5 y]
    G --> I[Repeat colonoscopy in 3 y]
  
```

**RISK STATUS**

**INITIATION OF SURVEILLANCE**

**SURVEILLANCE MODALITY AND SCHEDULE**

**EVALUATION OF SURVEILLANCE FINDINGS**

History of solid organ transplant → Age  $\geq 30$  y or within 2 y of the transplantation → Colonoscopy<sup>aaa,bbb</sup> → Normal → Repeat colonoscopy in 5 y

No history of solid organ transplant → Age  $\geq 40$  y → Colonoscopy<sup>aaa,bbb</sup> → Adenomatous or SSPs/SSLs → Repeat colonoscopy in 3 y

<sup>zz</sup> Hadjiliadis D, et al. Gastroenterology 2018;154:736-745; Matson AG, et al. BMC Gastroenterol 2019;19:89.

**aaa** Patient should undergo cystic fibrosis-specific intensive bowel preparation.

**bbb** Alternative screening tests could be considered but data on their efficacy in cystic fibrosis are limited.

**Note:** All recommendations are category 2A unless otherwise indicated.

# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### INCREASED RISK BASED ON POSITIVE FAMILY HISTORY

(Not meeting criteria for consideration of a hereditary cancer syndrome or appropriate testing for a hereditary cancer syndrome non-diagnostic or not done)<sup>ccc</sup>

#### FAMILY HISTORY CRITERIA

≥1 first-degree relative with CRC at any age

#### SCREENING<sup>ddd</sup>

Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC, whichever is first

Repeat every 5 y<sup>ddd,eee,fff,ggg</sup>  
or if positive, repeat per colonoscopy findings

Second- and third-degree relatives with CRC at any age

Colonoscopy beginning at age 45 y<sup>eee</sup>

Repeat every 10 y  
or if positive, repeat per colonoscopy findings

First-degree relative with confirmed advanced adenoma(s) (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology, TSA), or advanced SSPs/SSLs (≥1 cm, any dysplasia) at any age<sup>hhh,iii,jjj</sup>

Colonoscopy beginning at age 40 y or at age of onset of adenoma in relative, whichever is first

Repeat every 5–10 y<sup>ddd,fff</sup>  
or if positive, repeat per colonoscopy findings

<sup>ccc</sup> If a patient meets the criteria for an inherited colorectal syndrome, see General Criteria for Testing and Genetic Evaluation for Hereditary Syndromes Associated with Colorectal, Endometrial, and Gastic Cancer (HRS-1) in the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric](#).

<sup>ddd</sup> Colonoscopy intervals may be further modified based on personal and family history as well as on individual preferences. Factors that modify age to begin screening and colonoscopy intervals include: age of individual undergoing screening; specifics of the family history, including number and age of onset of all affected relatives, whether relatives had an inciting cause such as IBD; size of family; completeness of the family history; participation in screening; and colonoscopy findings in family members. See [Discussion](#).

<sup>eee</sup> While current risk estimates for a family history of CRC in only second- and third-degree relatives may not be sufficiently elevated to recommend increased screening (Taylor DP, et al. Gastroenterology 2010;138:877-885; Taylor DP, et al. Genet Med 2011;13:385-391; Samadder NJ, et al. Gastroenterology 2014;147:814-821; Tian Y, et al. BMJ 2019;364:1803), there are some data showing that having a second- and, to a lesser degree, a third-degree relative with early-onset (<50 years old) CRC increases risk of both CRC and early-onset CRC (Ochs-Balcom HM. Cancer Epidemiol 2021;73:101973). Some combinations of affected first-, second-, and third-degree relatives may increase risk sufficiently to alter screening guidelines. If there are multiple distant relatives affected, consider evaluation for an inherited colorectal syndrome in the family.

<sup>fff</sup> Multiple (≥ 2) negative colonoscopies may support stepwise lengthening in the colonoscopy interval.

<sup>ggg</sup> Samadder NJ, et al. Am J Gastroenterol 2017;112:1439-1447.

<sup>hhh</sup> It is important for endoscopists to add specific recommendations to endoscopy reports for first-degree relatives (ie, siblings, parents, children) or alternatively generate a letter meant to be shared with first-degree relatives to increase adherence when this applies. Examples of patient letters can be found at: [National Colorectal Cancer Roundtable](#). Cottet V, et al. Gastroenterology 2007;133:1086-1092; Ng SC, et al. Gastroenterology 2016;150:608-616.

<sup>iii</sup> Advanced SSPs/SSLs are generally considered to have a comparable cancer risk and are managed similarly to advanced adenomas. While there are limited data concerning the specific risk of CRC in first-degree relatives of individuals with advanced serrated polyps, it is reasonable to follow the same recommendations used for first-degree relatives of those with advanced adenomas (Cottet V, et al. Gastroenterology 2007;133:1086-1092; Ng SC, et al. Gastroenterology 2016;150:608-616).

<sup>jjj</sup> Cottet V, et al. Gastroenterology 2007;133:1086-1092; Ng SC, et al. Gastroenterology 2016;150:608-616.

Note: All recommendations are category 2A unless otherwise indicated.

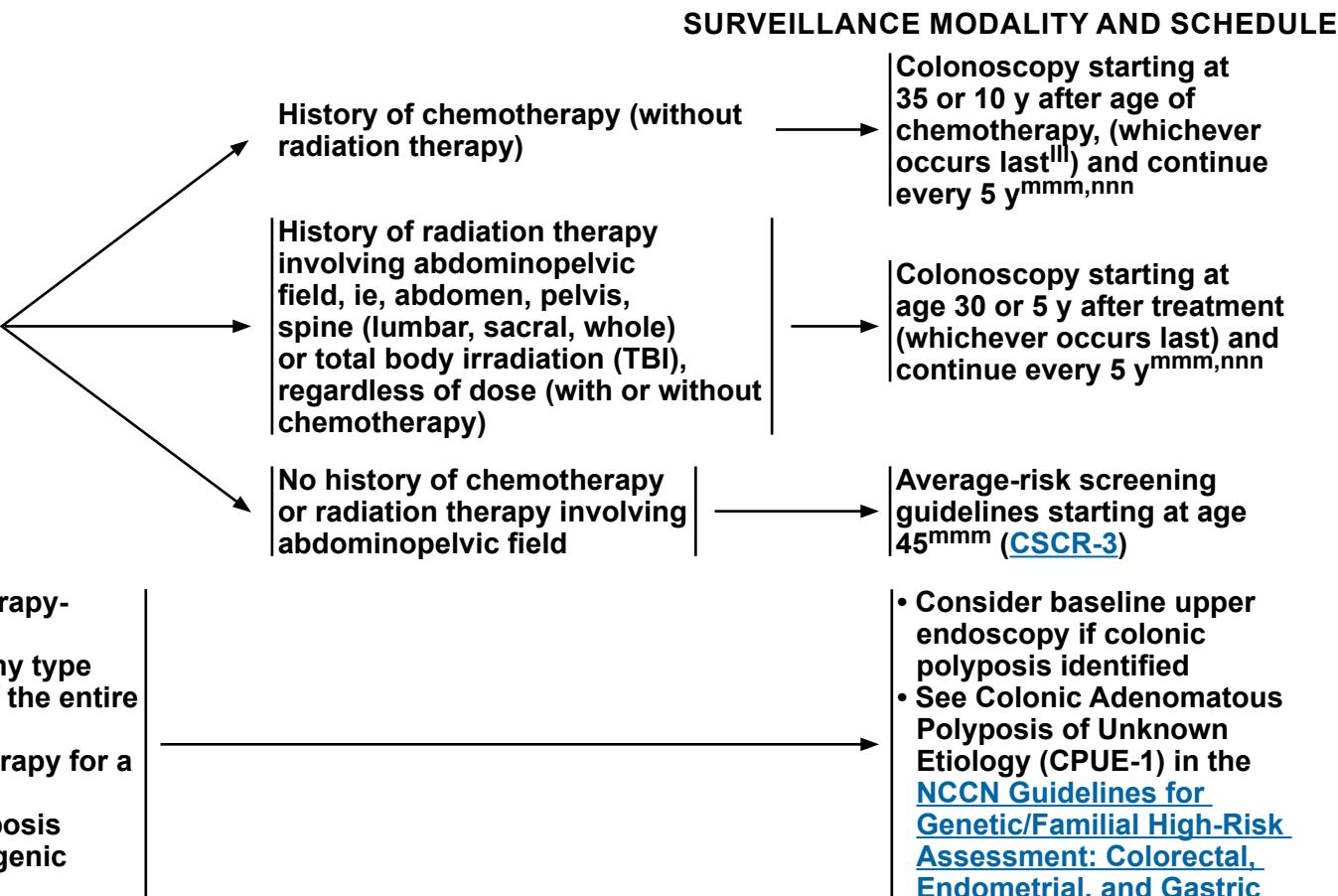
# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### INCREASED RISK BASED ON PERSONAL HISTORY OF CHILDHOOD, ADOLESCENT, AND YOUNG ADULT CANCER

#### RISK STATUS

Personal history of childhood, adolescent, or young adult cancer<sup>kkk</sup>



kkk The adolescent and young adult (AYA) oncology patient is defined as an individual aged 15–39 years of age at the time of initial cancer diagnosis. This definition is based on the National Cancer Institute (NCI) Progress Review Group recommendations for a national agenda to advance AYA oncology. See [NCCN Guidelines for Adolescent and Young Adult \(AYA\) Oncology](#).

<sup>lll</sup> Biller L, et al. Cancer Prev Res 2020;13:291–298.

<sup>mmm</sup> Children's Oncology Group Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers – Version 6.0–October 2023.

<sup>nnn</sup> Initiate colonoscopy no later than age 45.

<sup>ooo</sup> Therapy-associated polyposis is an acquired phenotype that presents years after exposure to chemotherapy and/or radiotherapy.

<sup>ppp</sup> Germline multigene panel testing should include at minimum the following CRC risk-associated genes: APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11, and TP53. Pathogenic variants associated with adenomatous polyposis include, but are not limited to, monoallelic pathogenic variants in APC, GREM1, POLE, POLD1, and AXIN2, and biallelic pathogenic variants in MUTYH, NTHL1, and MSH3.

**Note:** All recommendations are category 2A unless otherwise indicated.

## SCREENING MODALITY AND SCHEDULE

- Screening of individuals at average risk reduces CRC incidence by detecting and removing precancerous polyps, and reduces CRC mortality by detecting cancer at an early, curable stage.
- CRC screening should be performed as part of a population-based program that includes a systematic method for: 1) identifying those who are eligible for and wish to undergo screening; 2) risk stratification and administration of the screening tests at agreed upon intervals; 3) shared decision-making with patients regarding the choice of screening method; 4) standardized reporting of the results; and 5) follow-up of those with a positive test. Assuring timely colonoscopy completion for individuals with a positive stool-based test or an imaging abnormality on CTC is critical for these screening approaches to be successful. Thus, a robust mechanism to ensure prompt and nearly complete adherence with colonoscopy completion should be established. The program should also include a systematic method for the arranging of repeat screening and surveillance.
- Organized screening programs that provide direct outreach to patients and clinic-focused interventions have been shown to increase CRC screening rates, reduce mortality, and minimize disparities by race/ethnicity.<sup>1</sup> Examples of evidence-based interventions to increase CRC screening rates include mailed stool test outreach, patient navigation, patient education and reminders, and clinician-directed feedback and alerts.<sup>2</sup>
- Screening rates improve when programs offer different screening test options to ensure that testing characteristics are aligned with patient preferences.<sup>3</sup>

<sup>1</sup> Levin TR, et al. Gastroenterology 2018;155:1383-1391; Mehta SJ, et al. J Gen Intern Med 2016;31:1323-1330; Sumit SK, et al. Prev Med 2020;141:106242.

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**Note:** All recommendations are category 2A unless otherwise indicated.

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# NCCN Guidelines Version 2.2025

## Colorectal Cancer Screening

### SCREENING MODALITY AND SCHEDULE

Screening Test	Recommended Testing Interval <sup>a</sup>	Neoplasia			
		Sensitivity <sup>4</sup>		Specificity <sup>4</sup>	
		Colon Cancer		Colon Cancer	
Colonoscopy	Every 10 years	94.7% <sup>5</sup>	89%–95% ( $\geq 10$ mm adenomas) 75%–93% ( $\geq 6$ mm adenomas)	—	89% ( $\geq 10$ mm adenomas) 94% ( $\geq 6$ mm adenomas)
Flexible sigmoidoscopy <sup>b</sup>	Every 5–10 years	58%–75% <sup>6</sup>	72%–86% <sup>6</sup>	—	92% <sup>7</sup>
CT colonography	Every 5 years	86%–100%	89% ( $\geq 10$ mm adenomas) 86% ( $\geq 6$ mm adenomas)	—	94% ( $\geq 10$ mm adenomas) 88% ( $\geq 6$ mm adenomas)
High-sensitivity guaiac-based test	Annually	50%–75%	7%–21% (advanced neoplasia) 6%–17% (advanced adenoma)	96%–98%	96%–99% (advanced neoplasia) 96%–99% (advanced adenoma)
Quantitative FIT <sup>c</sup> (using OC-Sensor)	Annually	74%	25% (advanced neoplasia) 23% (advanced adenoma)	94%	96% (advanced neoplasia) 96% (advanced adenoma)
Quantitative FIT <sup>c</sup> (using OC-Light)	Annually	81%	27% (advanced neoplasia) 28% (advanced adenoma)	93%	95% (advanced neoplasia) 94% (advanced adenoma)
mt-sDNA test	Every 3 years	93%	47% (advanced neoplasia) 43% (advanced adenoma)	85%	89% (advanced neoplasia) 89% (advanced adenoma)
mt-sRNA test <sup>8</sup>	Every 3 years	94%	46% (advanced adenoma)	—	86% (advanced adenoma)
bb-cfDNA test <sup>9</sup>	Every 3 years	83%	13% (advanced pre-cancerous lesions)	90%	90% (advanced pre-cancerous lesions)

<sup>a</sup> Frequency based upon normal (negative) results.

<sup>b</sup> Data for the sensitivity and specificity of flexible sigmoidoscopy are for the entire colon and are based on the completion of colonoscopy for those found to have a distal colon lesion on flexible sigmoidoscopy.

<sup>c</sup> Optimal FIT thresholds will vary across screening programs, taking into consideration available colonoscopy resources to investigate abnormal results, including false-positive tests.

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Note: All recommendations are category 2A unless otherwise indicated.

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- <sup>8</sup> Barnell EK, Wurtzler EM, La Rocca J, et al. Multitarget stool RNA test for colorectal cancer screening. JAMA 2023;330:1760-1768. Erratum in: JAMA 2024;331:888.
- <sup>9</sup> Chung DC, Gray DM II, Singh H, et al. A cell-free DNA blood-based test for colorectal cancer screening. N Engl J Med 2024;390:973-983.

**Note:** All recommendations are category 2A unless otherwise indicated.

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### SCREENING MODALITY AND SCHEDULE

#### Endoscopy-Based Screening Modalities

##### • Colonoscopy

- ▶ This modality can be employed to screen individuals of average and high risk.
- ▶ Recommended every 10 years for average-risk screening.
  - ◊ A 10-year interval is appropriate for those with a complete procedure and adequate bowel prep.
  - ◊ Based on the quality and completeness of the colonoscopy, repeating it within 1 year may be indicated.
  - ◊ Individual risk factors, such as age, medical fitness for colonoscopy/colorectal surgery, family history, and the number and characteristics of previously discovered polyps, should be considered when determining the screening interval and/or decision to continue screening.
- ▶ Colonoscopy bowel preparation<sup>10</sup>
  - ◊ Split-dose prep is superior and should typically be recommended. The preferred timing of the second dose of split-dose preparation should:
    - Start 4–6 hours before colonoscopy
    - End at least 2 hours before colonoscopy
  - ◊ Same-day, morning-only preparation is an acceptable alternative to split-dose preparation, especially in patients scheduled for afternoon procedures.
  - ◊ A preliminary assessment should often be made in the rectosigmoid colon to determine preparation quality. If an inadequate preparation would interfere with the detection of polyps >5 mm, colonoscopy should be repeated within 1 year but preferably as soon as possible. Alternatively, additional bowel cleaning can be attempted so the colonoscopy can proceed that day.
  - ◊ In cases where colonoscopy is complete to the cecum but the preparation is ultimately considered inadequate, it should be repeated within one year, and a more aggressive preparation regimen should be recommended.
  - ◊ An interval shorter than one year is indicated when advanced neoplasia is detected and the prep is inadequate.
- ▶ Accumulating data suggest substantial variability in the quality and, by extension, the clinical effectiveness of colonoscopy. Improving the overall impact of screening colonoscopy requires a programmatic approach that addresses quality issues at several levels. Several quality indicators

have been examined and found to significantly predict procedural fidelity. These colonoscopy quality indicators include the following:<sup>11</sup>

- ◊ Adenoma detection rate
  - The percentage of patients aged ≥45 years who undergo colonoscopy for screening, surveillance, or diagnostic indications other than positive non-colonoscopy screening tests (eg, fecal tests or CTC) with one or more conventional adenomas detected and verified by pathology. Patients with positive non-colonoscopy screening tests, genetic cancer syndromes (eg, polyposis), IBD, or undergoing colonoscopy for therapy of known neoplasms are excluded from the calculation. The stated performance target is >35% (40% in men and 30% in women).
- ◊ SSL detection rate
  - The percentage of patients aged ≥45 years who undergo colonoscopy for screening, surveillance, or diagnostic indications other than positive non-colonoscopy screening tests (eg, fecal tests or CTC) with one or more SSLs detected and verified by pathology. Patients with positive non-colonoscopy screening tests, genetic cancer syndromes (eg, polyposis), IBD, or undergoing colonoscopy for therapy of known neoplasms are excluded from the calculation. The stated performance target is >6%.
- ◊ Appropriate intervals between endoscopic studies based on family and personal history and the number and histologic type of polyps on the last colonoscopy ([CSCR-4](#))
- ◊ Bowel preparation adequacy rate
  - Percentage of patients undergoing colonoscopy with adequate bowel preparation, preferably defined as Boston Bowel Preparation Scale score >2 in each of 3 colon segments or by a description of the preparation as excellent, good, or adequate. The stated performance target is >90%.
- ◊ Cecal intubation rate
  - Percentage of patients undergoing colonoscopy with intact colons who have full intubation of the cecum with photo documentation of cecal landmarks. The stated performance target is >95%.
- ▶ The use of artificial intelligence (AI) in colonoscopy is rapidly evolving. Future studies should help determine the specific uses of AI for CRC screening.

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## SCREENING MODALITY AND SCHEDULE

- **Flexible sigmoidoscopy**
  - ▶ This modality should only be employed to screen individuals of average risk with the commitment to a follow-up colonoscopy for any abnormal result.
  - ▶ Recommended every 5 years for average-risk screening.
    - ◊ A 5 year interval is appropriate for those with a complete procedure and adequate bowel prep.
    - ◊ Based on the quality and completeness of the sigmoidoscopy, repeating it within 1 year may be indicated.
    - ◊ Identifying adenomas, SSP/SSL of any size, or hyperplastic polyps  $\geq 1$  cm should result in a referral for colonoscopy as soon as possible and no later than within 9 months.<sup>19</sup>
    - ◊ Individual risk factors, such as age and medical fitness for colonoscopy or colorectal surgery, should be considered when determining the screening interval and/or decision to continue screening.

### Image-Based Screening Modalities

- These modalities should only be employed to screen individuals of average risk with the commitment to a follow-up colonoscopy for any abnormal result.
- **CTC**
  - ▶ Recommended every 5 years for average-risk screening.
    - ◊ A 5-year interval is appropriate for those with a complete procedure and adequate bowel prep.<sup>12</sup>
    - ◊ Individual risk factors, such as age and medical fitness for colonoscopy or colorectal surgery, should be considered when determining the screening interval and/or decision to continue screening.
    - ◊ Follow-up of identified lesions
      - The American College of Radiology (ACR) has recommended that reporting polyps  $\leq 5$  mm in size is unnecessary. If polyp(s) of this size are reported, the decision to refer for colonoscopy with polypectomy versus surveillance CTC should be individualized.
      - If 1 or 2 lesions that are 6–9 mm are found, then CTC surveillance in 3 years or colonoscopy as soon as possible and no later than within 9 months.<sup>13-15</sup>
      - Colonoscopy within 6 to 10 months is recommended if  $\geq 3$  6–9 mm lesions or any lesion  $\geq 10$  mm are found.
  - ▶ All visualized extracolonic findings should be described, and recommendations for appropriate follow-up (including no follow-up) should be provided.
  - ▶ The future cancer risk related to undergoing a single CTC is unknown but likely very low. No empirical data have shown increased risk below an exposure of 100 mSv.<sup>16</sup>
  - ▶ CTC interpretation should be accomplished only by those trained according to the American Gastroenterological Association<sup>17</sup> or ACR<sup>18</sup> guidelines.

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## SCREENING MODALITY AND SCHEDULE

### Stool-Based Screening Modalities

- These modalities should only be employed to screen individuals of average risk with the commitment to a follow-up colonoscopy for any abnormal result.
- Guaiac-based testing
  - ▶ Recommended annually for average-risk screening.
    - ◊ Requires three successive stool specimens smeared on three non-rehydrated slides<sup>19</sup> (not via digital rectal examination [DRE]), a prescribed diet, and coordination by a health care provider.
    - ◊ Any abnormal result should lead to a referral for a colonoscopy as soon as possible and no later than within 9 months.
    - ◊ Individual risk factors, such as age and medical fitness for colonoscopy or colorectal surgery, should be considered when determining the screening interval and/or decision to continue screening.
- FIT
  - ▶ Recommended annually for average-risk screening.
    - ◊ A single stool specimen must be tested and does not require a prescribed diet.
    - ◊ Optimal FIT thresholds will vary across screening programs, taking into consideration available colonoscopy resources to investigate abnormal results, including false-positive tests.
    - ◊ Any abnormal result should lead to a referral for a colonoscopy as soon as possible and no later than within 9 months.
    - ◊ Individual risk factors, such as age and medical fitness for colonoscopy or colorectal surgery, should be considered when determining the screening interval and/or decision to continue screening.
- mt-sDNA-based testing
  - ▶ Recommended and FDA-approved for every-3-year average-risk screening.
    - ◊ A single stool specimen must be tested and does not require a prescribed diet.
    - ◊ Any abnormal result should lead to a referral for a colonoscopy as soon as possible and no later than within 9 months.
    - ◊ Individual risk factors, such as age and medical fitness for colonoscopy or colorectal surgery, should be considered when determining the screening interval and/or decision to continue screening.
- mt-sRNA-based testing
  - ▶ Recommended and FDA-approved for every-3-year average-risk screening.
    - ◊ A single stool specimen must be tested and does not require a prescribed diet.
    - ◊ Any abnormal result should lead to a referral for a colonoscopy as soon as possible and no later than within 9 months.
    - ◊ Individual risk factors, such as age and medical fitness for colonoscopy or colorectal surgery, should be considered when determining the screening interval and/or decision to continue screening.

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## SCREENING MODALITY AND SCHEDULE

### Blood-Based Screening Modalities

- These modalities should only be employed to screen individuals of average risk with the commitment to a follow-up colonoscopy for any abnormal result.
- bb-cfDNA-based testing
  - Recommended and FDA-approved for every-3-year average-risk screening.
    - ◊ Requires a single blood specimen to be tested.
    - ◊ Any abnormal result should lead to a referral for a colonoscopy as soon as possible and no later than within 9 months.
    - ◊ Individual risk factors, such as age and medical fitness for colonoscopy or colorectal surgery, should be considered when determining the screening interval and/or decision to continue screening.
    - ◊ Given its modest performance, particularly among advanced precancerous lesions, this test is only recommended for individuals who would not be willing to undergo screening through another modality.

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**GLOSSARY OF TERMS COMMONLY USED IN NCCN GUIDELINES FOR COLORECTAL CANCER SCREENING**

Term	Abbreviation (if applicable)	Definition
General Terms		
Colorectal cancer	CRC	Cancer that occurs in the colon or rectum
Crohn's disease	CD	Chronic inflammatory disorder that may affect the entire GI tract <sup>1</sup>
Inflammatory bowel disease	IBD	Comprised of ulcerative colitis or Crohn's disease <sup>2</sup>
Mismatch repair	MMR	Molecular pathway that targets replication errors missed during DNA replication <sup>3</sup>
Mismatch repair deficiency	dMMR	Form of genetic instability in CRC characterized by loss-of-function genetic mutations in the mismatch repair pathway <sup>4</sup>
Primary sclerosing cholangitis	PSC	Chronic cholestatic disease characterized by fibroinflammatory fibrosis of the biliary tree; is a risk factor for CRC <sup>2,5</sup>
Ulcerative colitis	UC	Chronic inflammatory disorder of the colon <sup>6</sup>
Screening/Surveillance Modalities		
Cell-free blood-based screening		Blood-based test that detects colorectal-derived alterations in cell-free DNA (cfDNA), including genomic alterations, aberrant methylation status, and fragmentomic patterns.
Chromoendoscopy		Image-enhanced endoscopic procedure using dye or optical technologies <sup>7</sup>
Colonoscopy		Structural endoscopic examination of the entire colon
Computed tomography colonography	CTC	Also known as virtual colonoscopy; involves helical computed tomographic scanning of the colon after cathartic preparation and colonic distension <sup>8</sup>
Fecal immunochemical test	FIT	Fecal-based CRC screening test that measures amount of human hemoglobin in stool using antibodies against globin moiety of human hemoglobin <sup>9</sup>
Flexible sigmoidoscopy		Structural endoscopic examination of the distal portion of the colon <sup>10</sup>
High-definition white light endoscopy	HD-WLE	Endoscopy procedure that uses high-definition imaging system without optical filters <sup>11</sup>

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## GLOSSARY OF TERMS COMMONLY USED IN NCCN GUIDELINES FOR COLORECTAL CANCER SCREENING

Term	Abbreviation (if applicable)	Definition
Multi-target stool DNA	mt-sDNA	Stool DNA-based CRC screening test, which includes quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and β-actin, plus a hemoglobin immunoassay <sup>12</sup>
Multi-target stool RNA	mt-sRNA	Stool-based test that includes eight RNA molecular biomarkers: ACY1, AREG, CDH1, EGLN2, KRAS, SMAD4, and TNFRSF10B, normalized to the reference housekeeping transcript (GAPDH), as well as an Immunochemical Fecal Occult Blood Test
Polypectomy		Procedure used to remove visually detectable polypoid tissue in the colon <sup>13</sup>
Histology		
Adenoma		Noninvasive neoplastic lesion of the columnar epithelium <sup>14</sup>
Advanced adenoma		Adenoma that is ≥1 cm or has villous/tubulovillous histology or high-grade dysplasia
Advanced precancerous lesion		Advanced adenoma or SSP/SSL ≥1 cm and/or containing dysplasia
Advanced neoplasia		CRC or advanced precancerous lesion
Non-advanced adenoma		Adenoma that is <1 cm and has tubular histology
Tubular adenoma		Tubular adenomas are comprised mostly of tubular glands and have <25% villous features <sup>15</sup>
Villous adenoma		High-risk feature; a polyp/adenoma with >75% villous structures (long finger-like or leaf-like projections on surface) <sup>15</sup>
Tubulovillous adenoma		High-risk feature; a polyp/adenoma with 25%–75% villous histology <sup>15</sup>
Low-risk adenomas		1–2 nonadvanced polyps/adenomas <sup>13</sup>
High-risk adenomas		Advanced adenoma or ≥3 non-advanced adenomas <sup>13</sup>
Traditional serrated adenoma	TSA	Polyps with complex villous growth pattern; ectopic crypt formation is a unique feature that leads to mucosal protrusions, <sup>16,17</sup> are associated with high-risk polyp recurrence, and high-risk neoplasia and CRC <sup>18,19</sup>
Dysplasia		<ul style="list-style-type: none"><li>In sporadic CRC, a dysplastic precursor or preinvasive lesion is an adenomatous polyp, which is a single discrete focus of neoplasia that is managed by polypectomy<sup>20</sup></li><li>In long-standing cases of IBD, dysplasia may be polypoid or flat, localized, diffuse or multifocal, and once detected marks the entire colon as being at increased risk<sup>20</sup></li></ul>

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## Colorectal Cancer Screening

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### GLOSSARY OF TERMS COMMONLY USED IN NCCN GUIDELINES FOR COLORECTAL CANCER SCREENING

Term	Abbreviation (if applicable)	Definition
High-grade dysplasia		High-risk feature; refers to the distribution of nuclei within the cells; in high-grade dysplasia, nuclei are stratified haphazardly between the basal and apical halves of the cells <sup>20</sup>
Invisible dysplasia		Dysplasia diagnosed on pathology but not grossly detectable on endoscopy; <sup>21</sup> identified on random/non-targeted biopsies of colon mucosa without a visible lesion <sup>22</sup>
Hyperplastic polyp	HP	Hyperplastic polyp is a serrated polyp with normal crypt architecture and proliferative characteristics <sup>23,24</sup>
Sessile serrated polyp/sessile serrated lesion	SSP/SSL	Synonymous with sessile serrated adenoma; <sup>25</sup> SSPs/SSLs are a type of serrated polyp that is not dysplastic or does not contain foci of dysplasia; sessile lesions are attached to the mucosa without a stalk
Sessile serrated polyp/sessile serrated lesion with dysplasia	SSP/SSL-d	SSP/SSL with dysplasia
Low-risk SSP/SSL		1–2 SSPs/SSLs <10 mm in size; no dysplasia
High-risk SSP/SSL		SSP/SSL ≥1 cm and/or containing dysplasia and/or ≥3 SSPs/SSLs
Sessile colorectal polyp		Paris subtype 0–1s lesion <sup>14</sup>
Non-pedunculated polyp		Sessile and non-polypoid lesion; <sup>26</sup> lesion not attached to mucosa by stalk, and base and top of lesion have the same diameter <sup>25</sup>
Pedunculated polyp		Paris subtype 0–1p lesion; <sup>14</sup> lesion attached to the mucosa by a stalk and the base of lesion is narrow <sup>22,25</sup>
Polypoid lesion		Lesion protruding from the mucosa into the lumen ≥2.5 mm <sup>22</sup>
Nonpolypoid lesion		Paris subtype 0–IIa, 0–IIb, and 0–IIc lesions; <sup>14</sup> lesion with little (<2.5 mm) or no protrusion above the mucosa; <sup>22</sup> includes superficial elevated, flat, and depressed <sup>25</sup> <ul style="list-style-type: none"><li>• Superficial elevated (0–IIa) lesions: include height &lt;2.5 mm above normal mucosa; sometimes defined as height &lt; one-half of the lesion diameter<sup>25</sup></li><li>• Flat (0–IIb) lesions: those without any protrusion above mucosa<sup>25</sup></li><li>• Depressed (0–IIc) lesions: those with base that is lower than the normal mucosa<sup>25</sup></li></ul>

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**GLOSSARY OF TERMS COMMONLY USED IN NCCN GUIDELINES FOR COLORECTAL CANCER SCREENING**

Term	Abbreviation (if applicable)	Definition
Lateral spreading lesion	LSL	Laterally growing superficial neoplasm (instead of upward or downward growth) ≥10 mm in size; <sup>25</sup> may be used to further classify non-pedunculated lesions <sup>26</sup>
Surgical Procedures		
Endoscopic mucosal resection	EMR	Technique involving injecting solution into submucosal space to separate mucosal lesion from underlying muscularis propria; lesion can then be removed by snare <sup>25</sup>
Endoscopic submucosal dissection	ESD	Technique involving lifting by submucosal injectant and using ESD knife to create incision around lesion's perimeter and to dissect through expanded submucosal layer for en bloc resection <sup>25</sup>
Piecemeal resection		Removal of colorectal lesions or polyps in multiple pieces, which makes it hard to assess for resection margins and may prevent accurate histologic diagnosis <sup>25</sup>
En bloc resection		Removal of colorectal lesions or polyps in one piece <sup>25,27</sup>
Ileocectomy		Removal of the terminal ileum and the appendix and cecum <sup>28</sup>
Right hemicolectomy		Removal of the right colon and proximal transverse colon with ligation of the ileocolic artery and the right branch of the middle colic artery
Extended right hemicolectomy		Removal of the right colon and transverse colon with ligation of the ileocolic artery and the middle colic artery
Transverse colectomy		Removal of the transverse colon with ligation of the middle colic artery <sup>29</sup>
Left hemicolectomy		Removal of the splenic flexure, descending colon, and the sigmoid colon (if indicated) with ligation of the left colic artery or inferior mesenteric artery; may require ligation of the left branch or middle colic artery
Sigmoid colectomy		Removal of the sigmoid colon to the rectosigmoid junction or upper rectum with ligation of the inferior mesenteric artery or the superior rectal branch
Subtotal colectomy		Removal of most but not all of the colon (eg, right colon, transverse colon and descending colon with ligation of the ileocolic, middle colic, and left colic artery) <sup>30</sup>
Total colectomy		Removal of the whole colon down to the upper rectum, with ligation of the ileocolic, middle colic, and inferior mesenteric artery

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**GLOSSARY OF TERMS COMMONLY USED IN NCCN GUIDELINES FOR COLORECTAL CANCER SCREENING**

Term	Abbreviation (if applicable)	Definition
<b>Surgical Procedures</b>		
Low anterior resection	LAR	<b>Removal of the sigmoid colon, some or all of the rectum, and a total or tumor-specific mesorectal excision with ligation of the inferior mesenteric artery or the superior rectal branch<sup>31</sup></b>
Abdominoperineal resection	APR	<b>Removal of the sigmoid colon, rectum, and anus with ligation of the inferior mesenteric artery or the superior rectal branch<sup>32</sup></b>
Total proctocolectomy		<b>Removal of the entire colon and rectum, with or without preservation of the anal canal</b>

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[Continued](#)

Note: All recommendations are category 2A unless otherwise indicated.

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**Note:** All recommendations are category 2A unless otherwise indicated.

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## ABBREVIATIONS

AI	artificial intelligence	SSP/SSL-d	sessile serrated polyp/sessile serrated lesion with dysplasia
AYA	adolescent and young adult	TBI	total body irradiation
bb-cfDNA	blood-based cell-free DNA	TSA	traditional serrated adenoma
CRC	colorectal cancer		
CTC	computed tomography colonography		
dMMR	mismatch repair deficient		
DRE	digital rectal examination		
EMR	endoscopic mucosal resection		
ESD	endoscopic submucosal dissection		
FIT	fecal immunochemical test		
FOBT	fecal occult blood test		
GI	gastrointestinal		
HD-WLE	high-definition white light endoscopy		
IBD	inflammatory bowel disease		
IHC	immunohistochemistry		
LS	Lynch syndrome		
LSL	laterally spreading lesion		
LST	laterally spreading tumor		
MMR	mismatch repair		
MSI	microsatellite instability		
mt-sDNA	multi-target stool DNA		
mt-sRNA	multi-target stool RNA		
PSC	primary sclerosing cholangitis		
SSL	sessile serrated lesion		
SSP	sessile serrated polyp		

**NCCN Categories of Evidence and Consensus**

<b>Category 1</b>	Based upon high-level evidence ( $\geq 1$ randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ( $\geq 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus ( $\geq 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus ( $\geq 50\%$ , but $< 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 3</b>	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.



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## Colorectal Cancer Screening

### Discussion

This discussion corresponds to the NCCN Guidelines for Colorectal Cancer Screening. Last updated on 06/24/2025

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## Colorectal Cancer Screening

### Overview

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second most common cause of cancer death in the United States.<sup>1</sup> It is also the leading cause of cancer deaths in men and second in women <50 years in the United States.<sup>1</sup> In 2025, an estimated 107,320 new cases of colon cancer and 46,950 new cases of rectal cancer will occur in the United States.<sup>1</sup> During the same year, it is estimated that 52,900 people will die from colon and rectal cancer.<sup>1</sup> Screening individuals for CRC can reduce CRC mortality by detecting cancer at an early, curable stage and may decrease CRC incidence by detecting and removing precancerous polyps.<sup>2-4</sup> Depending on the speed of screening recovery after the drop during the COVID-19 pandemic, 4000 to 7000 excess deaths from CRC are estimated by 2040.<sup>5</sup>

Patients with localized CRC have a 91% relative 5-year survival rate, whereas rates for those with regional and distant disease are at 73% and 14%, respectively, demonstrating that earlier diagnosis can have a large impact on survival.<sup>6</sup> The incidence of CRC continued to trend downward from 54.5 to 38.6 per 100,000 people between 2000–2014<sup>7</sup> and to 35.9 from 2015–2019, whereas the 5-year mortality rate from CRC was 13.9% between 2013–2017,<sup>8</sup> and this reduced to 13.1% between 2016–2020 in the United States.<sup>6</sup> Overall, mortality from CRC decreased by almost 35% from 1990 to 2007.<sup>6,8</sup> These improvements in the incidence of and mortality from CRC over past years are thought, at least in part, to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities.<sup>9</sup> According to the Centers for Disease Control and Prevention (CDC), the screening rate among U.S. adults aged 50 to 75 years increased from approximately 42% in 2000 to 72.2% in 2021.<sup>10-12</sup> The CRC death rate has dropped by 55% among males since 1980 and by 60% among females since 1969, with rates decreasing during the most recent decade (2013–2022) by 1.7% per year in both populations.<sup>1</sup> Conversely, the incidence rates of colon and

rectal cancers in adults <50 years of age have been increasing by approximately 2% per year since 2003.<sup>6,9</sup>

In general, CRC incidence rates have doubled in younger adults and most CRC cases in adolescent and young adult (AYA) individuals appear to be sporadic.<sup>13</sup> Causes for this increase in early-onset CRC are unknown and may be attributable to diet, environmental, and lifestyle factors. By 2030, it is estimated that 15% of CRCs will be diagnosed in younger adults and screening strategies need to be updated for appropriate screening and timely diagnosis in this population.<sup>14</sup>

One or a combination of three different mechanisms, namely chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI) can contribute to CRC carcinogenesis. The classical CIN pathway starts with the acquisition of mutations in the APC, followed by the oncogene KRAS activation and TP53 inactivation.<sup>15</sup> Increasing evidence supports that serrated polyps (SPs) represent another precursor lesion of CRC and contribute to about one third of CRC cases through an alternative pathway.<sup>16,17</sup> The serrated pathway plays an important role in the development of “interval cancers,” which occur despite appropriately timed endoscopic surveillance. In contrast to the conventional pathway arising from CIN, the serrated pathway is characterized by the CIMP, BRAF mutation, and often MSI.<sup>18,19</sup>

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Colorectal Cancer Screening describe various colorectal screening modalities as well as recommended screening schedules for patients at an average or increased risk of developing sporadic CRC. They are intended to aid physicians with clinical decision-making regarding CRC screening for patients without defined genetic syndromes. Recommendations regarding the management of inherited syndromes such as Lynch syndrome, familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), Peutz-Jeghers syndrome (PJS),



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juvenile polyposis syndrome (JPS), and serrated polyposis syndrome (SPS) are addressed in the NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (available at [www.NCCN.org](http://www.NCCN.org)).

### Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at [www.NCCN.org](http://www.NCCN.org).

### Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines for Colorectal Cancer Screening, an electronic search of the PubMed database was performed to obtain key literature in the field of CRC screening since the previous Guidelines update using the following search terms: (colorectal cancer screening) or (colon cancer screening) or (rectal cancer screening) or (colorectal cancer prevention) or (colon cancer prevention) or (rectal cancer prevention) or (colonoscopy) or (fecal occult blood) or (fecal immunochemical testing) or (flexible sigmoidoscopy) or (stool DNA) or (CT colonography) or (inflammatory bowel disease cancer) or (ulcerative colitis cancer) or (Crohn's disease cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.<sup>20</sup>

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the Panel have been included in this version of the Discussion section. Recommendations for which high-level

evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

### Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.<sup>21</sup> The NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

### Primary and Secondary Prevention of Colorectal Cancer

Certain lifestyle modifications are associated with a reduced risk of CRC and can be an important adjunct to CRC screening for prevention.<sup>22</sup>

#### Physical Activity and Diet

A report from the Continuous Update Project (CUP) led by the American Institute for Cancer Research and World Cancer Research Fund International recommends maintaining a healthy weight, being physically active (via recreation, occupation, and/or transportation), and eating a



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healthy diet, as these measures are strongly associated with decreased colon and/or rectal cancer risk.<sup>23</sup> Other analyses have shown that adherence to guidelines promoting physical activity and a healthy diet are associated with reductions in the incidence of CRC.<sup>24,25</sup> Initiating physical activity during adolescence also appears to lower the risk of developing colorectal adenomas later in life.<sup>26</sup>

With regard to diet and nutrition, the CUP report recommends obtaining nutrients from natural food sources over solely from dietary supplements.<sup>23</sup> Specifically, low levels of vitamin D have been associated with increased CRC risk.<sup>27</sup> Some studies suggest that a diet high in fruits and vegetables is associated with decreased CRC risk.<sup>28,29</sup> In addition, some data suggest that a high body mass index (BMI) is associated with an increased risk for CRC recurrence and mortality, but the data are not consistent.<sup>30-32</sup>

An international panel of experts formed a working group for the International Agency for Research on Cancer (IARC) and assessed >800 epidemiologic studies that investigated the association of cancer with the consumption of red and processed meats.<sup>33</sup> Based on their review of the data, the IARC working group determined that the consumption of processed meats is carcinogenic to humans based on sufficient evidence for CRC.<sup>33</sup> Due to limited evidence, consumption of red meat was determined to be “probably carcinogenic” to humans.<sup>33</sup> In contrast, the Nutritional Recommendations (NutriRECS) guidelines panel suggests that adults continue current unprocessed red meat consumption (weak recommendation, low-certainty evidence).<sup>34</sup> Similarly, the NutriRECS panel suggests that adults continue current processed meat consumption (weak recommendation, low-certainty evidence).<sup>34</sup>

He et al<sup>17</sup> performed a comprehensive analysis of the risk factor profiles of SPs and conventional adenomas within three large prospective cohort studies, the Nurses’ Health Study (NHS), the NHS2, and the Health Professionals Follow-up Study (HPFS), and assessed several CRC risk

factors with respect to SPs and conventional adenomas. The analysis comprised 141,143 participants who had undergone lower gastrointestinal (GI) endoscopy, provided updated diet and lifestyle data every 2 to 4 years, and were followed until diagnosis of a first polyp. Thirteen risk factors for CRC were assessed in patients with SPs or conventional adenomas, and their associations with histopathology features were also examined.

During the 18- to 20-year follow-up period, 7945 SPs, 9212 conventional adenomas, and 2382 synchronous SPs and conventional adenomas were documented. While lifestyle factors such as smoking and alcohol intake were associated with higher risk of SPs and conventional adenomas, higher intake of vitamin D was associated with lower risk and inversely associated with SPs (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.86–0.98) and conventional adenomas (OR, 0.85; 95% CI, 0.80–0.90). Total folate and calcium intake were also inversely associated with risk of conventional adenomas, with an OR of 0.93 (95% CI, 0.87–0.99) and 0.90 (95% CI, 0.85–0.96), respectively. While this study and others<sup>35-37</sup> favor the association between vitamin D, calcium, and folate and reduced CRC risk, there are several other conflicting studies that highlight the potential harmful effects of these supplements in increasing CRC risk.<sup>38,39</sup>

In a randomized, multicenter, double-blind, placebo-controlled study that aimed at determining the effects of calcium and vitamin D supplementation on the incidence of sessile serrated lesions (SSLs [sessile serrated adenoma (SSA)/sessile serrated polyp (SSP)]), Crockett et al<sup>40</sup> found evidence that calcium and vitamin D supplementation increased the risk of SSLs. This was noted to be a late effect: 6 to 10 years after supplementation began. In this trial, patients between ages 45 and 75 who had a clearing colonoscopy and a scheduled surveillance colonoscopy in 3 or 5 years were invited to participate. Among 2813 eligible participants, 2259 participants were randomized to one of four treatment groups using a partial 2 × 2 factorial



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design: 419 to the calcium carbonate group (1200 mg elemental calcium/day); 420 to the vitamin D3 group (1000 IU/day); 421 to both agents; and 415 to the placebo group. While in the treatment phase, there was no effect of either calcium or vitamin D on incidence of SSLs. During the later observational phase, elevated risks of SSLs were found to be associated with calcium alone and calcium + vitamin D treatment (adjusted relative risk [RR] [95% CI], 2.66 [1.44–4.89] and 3.82 [1.26–11.57] respectively). This study highlighted the risk involved in calcium and vitamin D supplementation regarding the increased risk of SSLs and CRC.

Similarly, the role of folate in carcinogenesis has been best studied for CRC with conflicting conclusions. Collectively, >20 case-control studies have shown equivocal inverse relationships between folate status and the risk of CRC.<sup>41</sup> While several large prospective studies suggest a greater reduction<sup>41,42</sup> in the risk of CRC and adenomas in those with the highest intake of folate, suggesting potential benefits associated with folate supplements in mitigating the risk of CRC, other studies emphasize the potential harmful effect of folate on CRC risk.

In the Aspirin/Folate Polyp Prevention Study<sup>43</sup> that assessed the safety and efficacy of folic acid supplementation for preventing colorectal adenomas, folic acid did not reduce colorectal adenoma risk. The participants were randomly assigned in a 1:1 ratio to receive 1 mg/day of folic acid (n = 516) or placebo (n = 505) and the follow-up consisted of 2 colonoscopy surveillance cycles (the first interval was at 3 years and the second at 3 or 5 years later). During the first 3 years, 987 participants (96.7%) underwent colonoscopy follow-up, and the incidence of at least 1 colorectal adenoma was 44.1% for folic acid (n = 221) and 42.4% for placebo (n = 206) (unadjusted RR, 1.04; 95% CI, 0.90–1.20; P = .58). The incidence of at least 1 advanced lesion was 11.4% for folic acid (n = 57) and 8.6% for placebo (n = 42) (unadjusted RR, 1.32; 95% CI, 0.90–1.92; P = .15). A total of 607 participants (59.5%) underwent a second follow-up, and the incidence of at least 1 colorectal adenoma was 41.9%

for folic acid (n = 127) and 37.2% for placebo (n = 113) (unadjusted RR, 1.13; 95% CI, 0.93–1.37; P = .23); and incidence of at least 1 advanced lesion was 11.6% for folic acid (n = 35) and 6.9% for placebo (n = 21) (unadjusted RR, 1.67; 95% CI, 1.00–2.80; P = .05).

During the additional follow-up after 3 years, among those who extended treatment, any colorectal neoplasia was found in 36% (n = 118) of participants assigned to placebo and 43% (n = 146) assigned to folic acid during the second surveillance interval (RR, 1.21; 95% CI, 0.99–1.47; P = .06). Increased risk of SSL with extended folic acid supplementation was statistically significant during the second surveillance interval (RR, 1.94; 95% CI, 1.02–3.68; P = .04) and the study concluded that folic acid may increase SSL risk.<sup>44</sup> A few prospective, case-controlled studies have also independently demonstrated that low folate status is associated with a reduced CRC risk.<sup>45,46</sup>

Considering these controversies among various epidemiologic studies, the NCCN Panel added a cautionary statement under lifestyle/dietary factors associated with increased CRC risk, which states that while supplemental calcium, vitamin D, and folate use have all been linked to a decreased risk of conventional adenomas, some evidence suggests that these agents may increase the risk of SPs.

### Aspirin

The U.S. Preventive Services Task Force (USPSTF) conducted a systematic evidence review of trials that assessed the benefits and harms of aspirin in primary cardiovascular disease (CVD) and CRC prevention.<sup>47</sup> The 12 trials (including 1 pilot trial) included in this systematic review compared the effects of low-dose aspirin ( $\leq$ 100 mg/day) to placebo or no treatment in adults aged  $\geq$ 40 years. For events occurring within trial periods (4 trials, n = 86,137), low-dose aspirin had no statistically significant association with CRC incidence at 5 to 10



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years of follow-up (OR, 1.07; 95% CI, 0.92–1.24). No statistically significant beneficial association between 10 years of randomized low-dose aspirin and CRC incidence was found in any reported trials.

Based on two trials (Women's Health Study and Thrombosis Prevention Trial), aspirin use for 7 to 10 years was associated with a significantly lower risk of CRC mortality *only* when considering long-term observational follow-up (at 20 years) beyond trial periods (OR, 0.77; 95% CI, 0.61–0.98). The USPSTF recommends that the decision to initiate low-dose aspirin use for the primary prevention of CVD in adults aged 40 to 59 years who have a  $\geq 10\%$  10-year CVD risk should be individualized and recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults aged  $\geq 60$  years

(<https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/aspirin-to-prevent-cardiovascular-disease-preventive-medication>).<sup>48</sup>

However, there is limited trial evidence on benefits for CRC due to differences in duration of aspirin use, timing of outcome measurements, and length of follow-up. Therefore, the USPSTF concluded that the evidence is inadequate that low-dose aspirin use reduces CRC incidence or mortality.<sup>48</sup>

A systematic study of 11 randomized controlled trials (RCTs)<sup>49</sup> found that at 3 years, aspirin statistically reduced the risk of colorectal adenomas (RR, 0.84;  $P < .05$ ) but not advanced lesions (RR, 0.82;  $P = .10$ ). At 5 years, the risk of advanced lesions was significantly reduced (RR, 0.68;  $P < .05$ ), but not in non-advanced adenomas (RR, 0.87;  $P = .22$ ). Beyond 5 years, aspirin had no effect on the risk of advanced lesions (HR, 0.82;  $P = .07$ ) nor adenomas (HR, 0.99;  $P = .82$ ).<sup>49</sup> A similar meta-analysis reported a reduced recurrence of adenomas (RR, 0.83; 95% CI, 0.72–0.99;  $P = .006$ ) and reduced mortality of CRC (RR, 0.79; 95% CI, 0.64–0.97;  $P = .02$ ).<sup>50</sup> The ASPREE trial randomized patients aged  $\geq 70$  years to either aspirin ( $n = 9525$ ) or placebo ( $n = 9589$ ).<sup>51</sup> In contrast to the

other studies, the ASPREE trial reported that aspirin use was associated with a statistically significant increase in CRC mortality at 4.7 years of follow-up (HR, 1.77; 95% CI, 1.02–3.06).<sup>51</sup> Based on the updated USPSTF recommendation, the NCCN Panel revised the Aspirin section to reflect the lack of clarity on aspirin use in reducing the risk of CRC incidence or mortality when employed for primary prevention.

To examine the secondary preventive impact of aspirin, an observational, population-based, retrospective cohort study examined the effect of aspirin on patients diagnosed with CRC from 2004 to 2011 in the Cancer Registry of Norway ( $n = 23,162$ ; 6102) who were exposed to aspirin after CRC diagnosis.<sup>52</sup> After a median follow-up time of 3 years, the mortality rate from all causes was lower in patients who were exposed to aspirin (32.9%) versus patients who were not exposed to aspirin (42.3%). In addition, aspirin exposure after CRC diagnosis was independently associated with improved CRC-specific survival (HR, 0.85; 95% CI, 0.79–0.92) and overall survival (HR, 0.95; 95% CI, 0.90–1.01).<sup>52</sup> A cost-effectiveness analysis also suggested that the risk-benefit profile favored the use of very-low-dose aspirin for secondary prevention in individuals with previous advanced colorectal adenomas.<sup>53</sup> For secondary prevention, the NCCN Panel retains the statement on the association of aspirin with improved CRC-specific survival and overall survival.

In the double-blind, randomized CAPP2 trial,<sup>54</sup> the study reported long-term cancer outcomes for patients with Lynch syndrome enrolled in a randomized trial of daily aspirin (600 mg) use versus placebo. The participants were followed for a mean of 10 years for a longer-term assessment and 40 (9%) of 427 participants who received aspirin developed CRC compared with 58 (13%) of 434 who received placebo (HR, 0.65; 95% CI, 0.43–0.97;  $P = .035$ ). The ongoing CAPP3 trial, which focuses on finding the right dose of aspirin for people with a



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mismatch repair (MMR) gene defect, the underlying cause of Lynch syndrome has completed recruitment, and the results are expected to be published in 2025. This study supported the case for prevention of CRC in patients with Lynch syndrome with aspirin use and the pertinent statement is revised in the NCCN Guidelines for Colorectal Cancer Screening.

### Smoking

Cigarette smoking causes 1 in 5 deaths in the United States every year and is estimated to cause >480,000 deaths every year (including the effects of secondhand smoke).<sup>55</sup> The Cancer Prevention Study II (CPS-II) examined the impact of cigarette smoking in relation to CRC mortality in a prospective cohort study of 1,184,657 adults (aged ≥30 years).<sup>56</sup>

Multivariate-adjusted CRC mortality rates were highest among patients who smoke, intermediate in patients who formerly smoked, and lowest in patients who never smoked.<sup>56</sup> The multivariate-adjusted RR (95% CI) for patients who currently smoke versus patients who do not smoke was 1.32 (1.16–1.49) among men, and 1.41 (1.26–1.58) among women.<sup>56</sup> Increased risk of CRC was observed after ≥20 years of smoking for both men and women, compared to individuals who had never smoked.<sup>56</sup> A subsequent study examined a subgroup of participants from the CPS-II study (n = 184,187).<sup>57</sup> This prospective study assessed the association between cigarette smoking and risk of incident CRC during 13 years of follow-up in which individuals had initiated smoking an average of 44 years before enrollment.<sup>57</sup> The incidence of CRC was significantly higher in patients who currently smoke (HR, 1.27; 95% CI, 1.06–1.52) and those who formerly smoked (HR, 1.23; 95% CI, 1.11–1.36) compared with patients who never smoked.<sup>57</sup> The risk of CRC also decreased with longer time since cessation and earlier age at cessation.<sup>57</sup> Among lifestyle factors, smoking has been differentially strongly associated with SPs more than conventional adenomas.<sup>58,59</sup> For smoking cessation and counseling

interventions, see the NCCN Guidelines for Smoking Cessation (available at [www.NCCN.org](http://www.NCCN.org)).

### Alcohol

Moderate to heavy alcohol consumption is an established risk factor for several malignancies, including CRC, and is a potentially modifiable risk factor for cancer.<sup>60,61</sup> A meta-analysis of 61 independent studies (27 cohort and 34 case-control studies) examined the association of alcohol intake (light, moderate, or high) and CRC risk.<sup>62</sup> Compared to people who do not drink or occasionally drink, moderate drinking (>1–4 drinks/day, equivalent to 12.6–49.9 grams of ethanol/day) and heavy drinking (≥4 drinks/day, equivalent to ≥50 grams of ethanol/day) were associated with increased risk for CRC, at 21% and 52%, respectively.<sup>62</sup>

### Risk Assessment

The NCCN Guidelines for Colorectal Cancer Screening stratify patients into two groups depending on their risk of getting CRC. Colorectal screening is particularly important for African American individuals since they have a higher risk of incidence and mortality (see *Increased Risk*, below). Communication with the patient and referring physician of any updated CRC risk assessment and screening plan based on family history, colonoscopy, and pathology findings is highly encouraged.

### Average Risk

Individuals at average risk of developing CRC are those: aged 45 to 75 years; with no personal history of adenoma or SSP/SSL or CRC; without inflammatory bowel disease (IBD), high-risk CRC genetic syndromes, or cystic fibrosis (CF); or childhood cancer; with a negative family history of CRC or confirmed advanced precancerous lesions in first-degree relatives that includes advanced adenoma (high-grade dysplasia, ≥1 cm in size, villous or tubulovillous histology) and SSP/SSL ≥1 cm and/or containing dysplasia.<sup>63</sup> The terms sessile serrated polyp, sessile serrated lesion,



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SSP/SSL, and SSA are synonymous; SSPs/SSLs are a type of SP that are not dysplastic but they can develop foci of dysplasia and are then termed SSP/SSL with dysplasia (SSP/SSL-d). These guidelines will use “SSP/SSL” for SSPs/SSLs without dysplasia and “SSP/SSL-d” for SSPs/SSLs with dysplasia. In general SSPs/SSLs are managed like tubular adenomas and SSP/SSL-d with any grade dysplasia are managed like high-risk adenomas but may need even more frequent surveillance. Classification systems for serrated lesions are evolving, and a recent proposal by WHO suggests using the term sessile serrated lesion.<sup>64</sup>

Age consideration may be dependent on race/ethnicity, patient preference, and resources available. Epidemiologic reports suggest that CRC incidence is rising in young adults, with nearly half of patients presenting with early-onset CRC being <45 years of age for unknown reasons.<sup>13,65,66</sup> From 2003 to 2013, there has been a 22% increase in CRC in individuals <50 years.<sup>67</sup> The prevalence of pathogenic germline variants in CRC increases with a decreasing age at diagnosis. Thus, while about 10% of those diagnosed at <50 years will have a pathogenic variant causing Lynch syndrome, this percentage reaches 23% among those diagnosed at <35 years. However, most young adults diagnosed with CRC have no hereditary syndrome or germline mutation associated with CRC and many patients lack the classical family history as well.<sup>65</sup> Although age and genetic makeup are linked to CRC, the majority of these patients have no family history of the disease; however, inherited cancer syndrome should be ruled out.<sup>13,66</sup> Based on statistical modeling incorporating these data, which predicted potential increased benefit,<sup>68,69</sup> the American Cancer Society (ACS) recommended—as a qualified recommendation—that individuals at average risk of CRC begin screening at age 45 years.<sup>70</sup>

Different CRC screening Guidelines have been issued by many organizations such as the ACS, USPSTF, U.S. Multi-Society Task Force (MSTF), American College of Gastroenterology (ACG), and American

College of Physicians (ACP). At the most recent annual meeting, the Panel reviewed these Guidelines and other existing data in framing the age recommendation for CRC screening. There is a general consensus among different organizations that adults at average risk aged 50 to 75 years should be screened. The recommendations vary slightly in the recommended age to initiate screening.<sup>71</sup> In 2018, results from modeling analyses<sup>70</sup> identified efficient and model-recommendable strategies that started screening at age 45 years and the ACS recommended that screening begin at age 45 years in all adults (qualified recommendation).<sup>70</sup> In 2021, the microsimulation modeling analysis<sup>72</sup> performed to inform USPSTF on CRC screening strategies suggested that CRC screening starting at age 45 years provided an efficient balance of colonoscopy burden and life-years gained. Based on this analysis, the USPSTF recommended screening for CRC in adults aged 45 to 49 years<sup>4</sup> and the ACG also suggested screening in persons at average risk aged 45 to 49 years as a conditional recommendation.<sup>3</sup>

Regarding the stopping age of CRC screening, generally, these Guidelines agree that screening should either be individualized in adults aged 76 to 85 years (ACS, American Academy of Family Physicians, and MSTF) or stopped altogether (ACP), with clear consensus that screening should stop after age 85 years.<sup>73</sup>

Based on the Panel discussion, the NCCN Panel re-emphasized a footnote that states that CRC screening is recommended in adults aged 45 to 75 years who might have a life expectancy of ≥10 years. The decision to screen between ages 76 to 85 years should be individualized and include a discussion of 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.

Although age consideration may be dependent on race/ethnicity, patient preference, and resources available, prompt evaluation of alarm



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symptoms is of critical importance. Epidemiologic reports suggest that CRC incidence is rising in young adults, with nearly half of patients presenting with early-onset CRC being <45 years of age for unknown reasons.<sup>6,13,65</sup> Many of these young adults have signs and symptoms of CRC such as iron deficiency, anemia, rectal bleeding, or a change in bowel habits.

### Increased Risk

Individuals with a personal history of adenomas or SSP/SSLs, CRC, IBD (ie, ulcerative colitis, Crohn's colitis), or CF, and those with a positive family history of CRC or advanced adenomatous polyps are considered to be at increased risk of developing CRC. Individuals with diabetes mellitus and those who are obese also have a higher risk,<sup>74,75</sup> although these factors are not considered to affect the screening guidelines. Other factors that influence risk include age, sex, and race.<sup>76</sup>

This increased risk has led some to recommend beginning population CRC screening in African American individuals at an earlier age.<sup>77</sup> African American individuals have had a disproportionately higher incidence of CRC in the United States for many years. Using a microsimulation model, one study found that differences in screening accounted for 42% of the disparity in CRC incidence and 19% of the disparity in CRC mortality between African American and white individuals.<sup>78</sup> However, mortality from CRC is multifactorial and is related to host factors, tumor biology, environmental exposures, disparities in access to screening, differences in stage at diagnosis, and treatments received. Nevertheless, mortality from CRC has been decreasing in African American and white individuals since 1999.<sup>79</sup> The incidence rate of CRC in African American individuals aged 40 to 49 years did not change between 2000 and 2017 (annual percent change, -0.03; 95% CI, -0.5– 0.5). However, the absolute incidence rate (all ages) of CRC still remained higher in African American individuals in comparison to individuals of other ethnicities.<sup>80</sup> Therefore, based on the

available data and emerging evidence, methods to further enhance access to screening in African American and other groups with low screening rates should be endorsed. A meta-analysis reported that the most frequently adopted interventions among African American men were educational materials (39%), stool-based screening kits (14%), and patient navigation (11%). Interventions that were most effective at increasing rates of CRC screening completion were stool-based kits (OR, 9.60; 95% CI, 2.89–31.82;  $P = .0002$ ) and patient navigation (OR, 2.84; 95% CI, 1.23–6.49;  $P = .01$ ).<sup>81</sup>

### Evaluation of Alarm Signs and Symptoms

Approximately 1 in 10 new diagnoses of CRC are now made in individuals ≤50 years and 3 of 4 patients with early-onset CRC have no family history of the disease.<sup>65</sup> To date, early-onset CRC patients are prone to experience diagnostic delays and missed diagnostic opportunities,<sup>82,83</sup> due to lack of awareness of red-flag signs and symptoms. Since routine testing is not recommended for patients <45 years of age, symptom recognition remains an important component of early detection and treatment in this patient population. Early recognition of red-flag signs and symptoms (abdominal pain, rectal bleeding, diarrhea, and iron-deficiency anemia) may improve early detection and timely diagnosis of early-onset CRC.<sup>84,85</sup> Numerous studies have suggested that anemia, stomach pain, and constipation are the most common symptoms of the group with missed diagnostic opportunities for CRC.<sup>83,86–88</sup> In a matched, case-control study<sup>89</sup> utilizing longitudinal claims data with 5075 patients with early-onset CRC, 4 red-flag signs and symptoms (abdominal pain, rectal bleeding, diarrhea, and iron deficiency anemia) between 3 months and 2 years prior to the index date were associated with increased risk of early-onset CRC, and the strongest association was found with rectal bleeding. Presence of 1 of these symptoms was associated with 1.9-fold increased risk, 2 of the



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symptoms with 3.6-fold increased risk, and at least 3 of these red-flag signs and symptoms were associated with 6.5-fold increased risk.

The Panel recommends that all patients, regardless of age, who present with symptoms potentially associated with CRC, including but not limited to rectal bleeding, iron deficiency anemia, abdominal pain, or weight loss should undergo a prompt tailored evaluation for both GI and non-GI causes. In most unexplained cases, an anorectal exam and colonoscopy should be considered. Patients with rectal bleeding initially attributed to hemorrhoids that do not resolve with treatment should also be considered for colonoscopy.

### Hereditary CRC Syndromes

Individuals with a family history of Lynch syndrome or with a personal or family history of polyposis syndromes are considered to be in the high-risk category (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial and Gastric, available at [www.NCCN.org](http://www.NCCN.org)).

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Based on recent FDA approvals and emerging technology, CRC screening modalities have expanded into four categories: endoscopy-based, stool-based, blood-based, and image-based screening tests.<sup>90</sup> There is direct evidence from RCTs (discussed in detail below) that fecal occult blood testing (FOBT) and flexible sigmoidoscopy reduce CRC incidence and mortality by detecting and removing precancerous polyps at an early, curable stage. Colonoscopy is supported by RCTs, case-control studies, and cohort studies and has the potential to prevent CRC (with its associated morbidity) and cancer deaths.

In the United States, colonoscopy is the most commonly employed CRC screening test for populations at average and high risk. However, multiple

options exist, and the choice of modality should include consideration of patient preference and resource availability. In fact, screening completion rates are higher when FOBT is recommended or when a choice of FOBT or colonoscopy is given than when only colonoscopy is recommended (67% or 69% vs. 38%;  $P < .001$  for both).<sup>91</sup> Overall, although some techniques are better established than others, Panel members agree that any screening is better than none. Results of a large, population-based, prospective study in Australia support this supposition; participants who had received screening by FOBT, sigmoidoscopy, or colonoscopy had a 44% lower risk of developing CRC (HR, 0.56; 95% CI, 0.49–0.63) compared with those who had never been screened.<sup>92</sup> A systematic review for the USPSTF similarly reported statistically significant benefits across many forms of CRC screening (flexible sigmoidoscopy, FOBT, colonoscopy, fecal immunochemical test [FIT], CT colonography) when compared to no screening.<sup>93</sup>

CRC screening should be performed as part of a population-based program that includes a systematic method for: 1) identifying those who are eligible for and desire screening; 2) risk stratification and administration of the screening tests at agreed upon intervals; 3) shared decision-making with patients regarding the choice of screening method; 4) standardized reporting of the results; and 5) timely follow-up of those with a positive test. A CRC screening program should include a systematic method for arranging repeat screening and surveillance at appropriate intervals.

Organized screening programs that provide direct outreach to patients and clinic-focused interventions have been shown to increase CRC screening rates, reduce mortality, and minimize disparities by race/ethnicity.<sup>94–96</sup> Several randomized studies have provided evidence that offering different screening options to ensure testing characteristics are aligned with patient preferences may improve screening rates.<sup>91,97</sup> These evidence-based



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interventions may include mailed outreach, patient navigation, patient education and reminders, and clinician-directed feedback and alerts.<sup>96–99,100</sup> Special attention should be given to certain patient characteristics (particularly to age <60 years, obesity, current smoking, and sedentary behavior) due to the association with non-participation in CRC screening programs as well as omitting doctor visits.<sup>98</sup>

### Screening Modalities

Structural screening tests detect adenomatous polyps and cancer using endoscopic- or imaging-based testing. Endoscopic tests have several limitations, including their relative invasiveness, the need for dietary preparation and bowel cleansing, and the time dedicated to the examination (typically a day). Endoscopic exams require informed consent and usually need sedation and have related risks including perforation and bleeding. A large cohort study of 53,220 Medicare patients between the ages of 66 to 95 years showed that the risks of adverse events after colonoscopy increase with age.<sup>99</sup>

Recent efforts to increase the sensitivity and specificity of noninvasive screening modalities have led to the addition of two new noninvasive tests: a stool-based screening test and a blood-based screening test that have been recently approved by FDA. These new screening modalities have been added to stool-based screening and blood-based screening modalities.

### Endoscopy-Based Screening Tests

#### Colonoscopy

Colonoscopy is the most complete screening procedure and is considered the current gold standard for assessing the sensitivity of detecting neoplasia for other screening modalities. The general consensus is that a 10-year interval is appropriate for most individuals at average risk who had a high-quality normal colonoscopy, defined as an exam complete to the

cecum with bowel preparation adequate to detect polyps >5 mm in size.<sup>100</sup> The NordICC trial showed reduced risk of CRC in the invited group to screen for colonoscopy versus the usual-care group.<sup>101</sup> In this pragmatic, randomized trial, 84,585 participants in Poland, Norway, and Sweden were randomly assigned in a 1:2 ratio either to receive an invitation to undergo a single screening colonoscopy (the invited group, N = 28,220) or to receive no invitation or screening (the usual-care group, N = 56,365). In intention-to-screen analyses, there was a reduced risk of CRC incidence at 10 years (0.98% in the invited group vs. 1.20% in the usual-care group) with a risk reduction of 18% (RR, 0.82; 95% CI, 0.70–0.93). There was also a reduced risk of death from CRC in the colonoscopy invited group (0.28% in the invited group vs. 0.31% in the usual-care group [RR, 0.90; 95% CI, 0.64–1.16]).

In adjusted per-protocol analyses to estimate the effect of screening if all the participants who were randomly assigned to screening had actually undergone screening, the risk of CRC at 10 years was decreased from 1.22% to 0.84%, (RR, 0.69, 95% CI, 0.55–0.83). In the sensitivity analysis, the risk of CRC incidence decreased from 1.3% to 0.86% (RR, 0.66, 95% CI, 0.46–0.86). The corresponding RR was 0.55 (95% CI, 0.38–0.74) in Norway and 0.85 (95% CI, 0.63–1.12) in Poland. The risk of death from CRC was 0.15% in the invited group and 0.30% in the usual-care group (RR, 0.50, 95% CI, 0.27–0.77). In the sensitivity analysis, the risk of death reduced from 0.20% to 0.14% with imprecise estimate (RR, 0.72, 95% CI, 0–3.70).

Interestingly, in a Canadian case-control study that matched each of the 10,292 individuals who died of CRC to five controls, colonoscopy was associated with lower mortality from distal CRC (adjusted conditional OR, 0.33; 95% CI, 0.28–0.39) but not proximal CRC (OR, 0.99; 95% CI, 0.86–1.14).<sup>102</sup> Additional studies have also demonstrated a reduced effectiveness in the right versus the left colon.<sup>103,104</sup> A population-based,



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case-control study in Germany demonstrated that colonoscopy in the preceding 10 years gave an overall 77% decrease in the risk for CRC.<sup>104</sup> However, while risk reduction was strongest for distal cancer, a 56% risk reduction was also seen for proximal disease. A case-control study using the SEER-Medicare database also found that colonoscopies are associated with a decrease in death from CRC, and the association was strongest for distal over proximal CRC.<sup>103,105</sup> Some of these findings of a distal but not proximal risk reduction may be associated with variation in the quality of colonoscopy in alternative settings.

Analysis of two prospective cohorts (NHS and HPFS) followed 88,902 participants for 22 years, comparing long-term outcomes in those who had screening colonoscopies, sigmoidoscopies, or no endoscopy.<sup>106</sup> Death from CRC was reduced after screening sigmoidoscopy (HR, 0.59; 95% CI, 0.45–0.76) and after screening colonoscopy (HR, 0.32; 95% CI, 0.24–0.45). However, mortality from proximal colon cancer was reduced after screening colonoscopy (HR, 0.47; 95% CI, 0.29–0.76) but not after sigmoidoscopy.

The impact of colonoscopy screening on CRC mortality has been investigated in studies that have evaluated the effects of colonoscopies with concurrent polypectomies. In the National Polyp Study, the mortality of 2602 patients with adenomas removed was compared to the incidence-based mortality from CRC in the SEER database.<sup>107</sup> With a median follow-up of 15.8 years, 12 deaths were attributed to CRC in the National Polyp Study group, compared with an expected 25.4 deaths in the general population, suggesting a 53% decrease in mortality.<sup>107</sup>

Another study estimated CRC mortality in 40,826 patients who underwent polypectomy in Norway.<sup>108</sup> Patients with high-risk adenomas were recommended for repeat colonoscopy in 10 years if they were <75 years of age or in 5 years if ≥3 adenomas were found. No further surveillance was recommended for patients with low-risk adenomas or those >74

years. As compared with expected CRC mortality rates in the general population, CRC mortality of patients with low-risk adenomas removed was lower (incidence-based standardized mortality ratio [SMR], 0.75; 95% CI, 0.63–0.88) after a mean follow-up of 7.7 years.<sup>108</sup> On the other hand, CRC mortality was increased in patients with high-risk adenomas removed (SMR, 1.16; 95% CI, 1.02–1.31), likely because these patients were predisposed to CRC and possibly because of the relatively long 5-year screening interval recommended for these patients.<sup>108</sup> In addition to cancer prevention, colonoscopy screening is also expected to lead to earlier diagnosis. Supporting this supposition, a retrospective review of a prospective database compared 217 patients diagnosed with colon cancer through screening colonoscopy with 854 patients with colon cancer not diagnosed through screening.<sup>109</sup> Unscreened patients were at higher risk for more invasive tumors (RR, 1.96;  $P < .001$ ), nodal disease (RR, 1.92;  $P < .001$ ), and metastatic disease on presentation (RR, 3.37;  $P < .001$ ).<sup>109</sup> Furthermore, unscreened patients had higher rates of death and recurrence, shorter survival, and shorter disease-free intervals.

A meta-analysis of 14 RCTs and other controlled studies found that while endoscopic surveillance detected more advanced neoplasms than stool testing, its advantage was offset by a lower participation rate.<sup>110</sup> Interim results of the COLONPREV study, a randomized controlled study comparing one-time colonoscopy with biennial FIT (see discussion of FIT below) in asymptomatic adults aged 50 to 69 years, showed that the two tests identified similar numbers of cancers in initial screening, but colonoscopy identified significantly more advanced and non-advanced adenomas.<sup>111</sup> The data also showed that individuals were more likely to participate in FIT compared to colonoscopy screening (34.2% vs. 24.6%;  $P < .001$ ).<sup>111</sup> Subsequent analyses confirmed these observations.<sup>112</sup>

Colonoscopy has limitations and may not detect all cancers and polyps. In a meta-analysis by Singh et al,<sup>113</sup> pooled prevalence, risk factors, and



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outcomes of CRCs diagnosed within 6 to 36 months of colonoscopy were estimated as compared to CRCs diagnosed at or within 6 months of colonoscopy. Based on this study, 1 in 27 CRCs are interval CRCS, identified within 6 to 36 months and they are likely to arise in the proximal colon.

### *Colonoscopy Quality*

Recommendations made by the Panel are based on the premise of complete, high-quality colonoscopies. The recommended priority quality indicators from the American Society for Gastrointestinal Endoscopy (ASGE)<sup>114</sup> are: 1) adenoma detection rate (ADR); 2) SSL detection rate (SSLDR); 3) rate of using recommended screening and surveillance intervals; 4) bowel preparation adequacy rate; and 5) cecal intubation rate (CIR).

The ADR is the most clinically relevant and best validated quality indicator in colonoscopy. ADR is defined as the fraction of patients aged ≥45 years having ≥1 conventional adenoma in a first-time screening colonoscopy. The minimum acceptable threshold has been increased to 25% (30% in men and 20% in women). The ASGE also recommends inclusion of second and subsequent screening colonoscopies in the ADR calculation without adjustment for the minimum acceptable ADR threshold. Some studies found that ADR is insufficient as a sole detection indicator predicting post-colonoscopy CRC (PCCRC).<sup>115-117</sup> In two different trials, ADR >25% and low serrated lesion detection were found in 13% to 14% of endoscopists,<sup>116,117</sup> whereas another 37% to 45% of endoscopists had ADRs <25% and low serrated detection. In both studies, the correlation between ADR and serrated detection was moderate. The committee considered three serrated detection indicators (clinically significant SP, proximal SP, and SSLDR) because of their association with PCCRC in recent studies,<sup>115,116</sup> and SSLDR is now the quality indicator of choice because it directly measures the precancerous serrated lesion and is not

subjected to endoscopist bias. Literature also shows that the quality measure of ADR is inversely associated with the risk of CRC.<sup>118</sup> It has been demonstrated that higher adenoma detection was associated with lower lifetime CRC incidence and mortality without higher overall costs.<sup>119</sup> These findings demonstrate that variation in colonoscopy quality has meaningful clinical consequences for patients. Frequency with which colonoscopies follow recommended post-polypectomy and post-cancer resection surveillance intervals and frequency of 10-year intervals between screening colonoscopies in patients at average risk who have negative examination results and adequate bowel cleansing is another priority quality indicator. Shorter intervals for screening are appropriate only for inadequate bowel preparation (in cases of inadequate preparation, a repeat colonoscopy with adequate preparation should be performed within 1 year).<sup>120</sup> Rate of bowel preparation adequacy is the percentage of patients undergoing colonoscopy with adequate bowel preparation, preferably defined as Boston Bowel Preparation Scale score ≥2 in each of 3 colon segments or by description of the preparation as excellent, good, or adequate.<sup>121,122</sup> The ASGE/ACG Task Force recommends that at least 90% of outpatient colonoscopies should be accompanied by an adequate bowel preparation. CIR is the percentage of patients undergoing colonoscopy with intact colons who have full intubation of the cecum with photo documentation of cecal landmarks. CIRs >95% are readily achievable by high percentages of independently practicing colonoscopists.<sup>123-125</sup>

A European report on a screening program involving >45,000 individuals confirmed that the endoscopist's rate of adenoma detection is an important predictor of the risk of interval CRC ( $P = .008$ ), highlighting the need for meticulous inspection of the large intestinal tract.<sup>126</sup> The study did not demonstrate statistical significance with CIR, another widely recognized quality indicator. One explanation is that the importance of this factor is restricted to the ascending colon, which gives rise to a small



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number of cancer cases. Data analysis of almost 315,000 colonoscopies from an integrated health care delivery organization showed that higher ADRs were associated with lower rates of interval CRC (HR, 0.52; 95% CI, 0.39–0.69), advanced-stage interval CRC (HR, 0.43; 95% CI, 0.29–0.64), and fatal interval CRC (HR, 0.38; 95% CI, 0.22–0.65).<sup>118</sup> Furthermore, a recent meta-analysis reported that significantly higher colonoscopy volumes were associated with less adverse events and an increase in colonoscopy quality.<sup>127</sup> In an effort to enhance screening quality, the Quality Assurance Task Group of the National Colorectal Cancer Roundtable developed a standardized reporting system for colonoscopy.<sup>128</sup> These NCCN Guidelines list the common quality indicators of colonoscopy and minimum requirements of a colonoscopy report. Quality indicators, including withdrawal time and ADR, are an important part of the fidelity of colonoscopy findings.<sup>118,129–131</sup> It should be noted that purposely seeking out polyps during colonoscopies may not significantly increase the polyp detection rate.<sup>132</sup> Several reports have shown that artificial intelligence assistance, if technologically feasible, may improve polyp rates and ADRs in colonoscopies.<sup>133–135</sup>

### Bowel Preparation for Colonoscopy

Split-dose preparation has been shown to be superior to the traditional regimen administered the day before colonoscopy and is therefore recommended.<sup>136–138</sup> The MSTF on Colorectal Cancer also recommends split preparation.<sup>100</sup>

The NCCN Panel and the MSTF agree that a same-day, morning-only regimen is an acceptable alternative in patients undergoing afternoon procedures.<sup>139–141</sup>

### Incomplete Colonoscopy

If colonoscopy is incomplete or the preparation is suboptimal, colonoscopy should be repeated as soon as possible and no later than 1

year after the index procedure.<sup>100</sup> For patients who have had incomplete colonoscopy, CTC, balloon-assisted colonoscopy, or capsule colonoscopy can be considered as alternative exams for completing the screening.<sup>142–144</sup> In an average-risk screening population, technically adequate capsule colonoscopy identified individuals with ≥1 conventional adenomas ≥6 mm with 88% sensitivity and 82% specificity. Capsule performance seems adequate for patients who cannot undergo colonoscopy or who had incomplete colonoscopies.<sup>143</sup> Colon capsule endoscopy may be an alternative to currently approved modalities. A systematic review of 2485 patients in 13 studies reported that the CRC detection rate was 95% and no complications were described. The polyp detection rate was between 24% and 74%, with a sensitivity rate of 79% to 96% in polyps >6 mm and 84% to 97% in polyps ≥10 mm. Bowel preparation was adequate in 70% to 92% of examinations and completion rates were between 57% and 92%. Accuracy was reported to be comparable to coloscopy and superior to CT colonography.<sup>145</sup>

### Flexible Sigmoidoscopy

Flexible sigmoidoscopy followed by colonoscopic polypectomy in patients with lesions >1 cm significantly reduced mortality risk in early case-control studies.<sup>146,147</sup>

Evidence from RCTs has also demonstrated that flexible sigmoidoscopy reduces the incidence of and mortality from CRC.<sup>106,148–154</sup> The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening group reported CRC mortality rates from its randomized, controlled flexible sigmoidoscopy screening trial, which screened >64,000 participants with flexible sigmoidoscopy and 59% of those participants a second time at 3 or 5 years.<sup>152–154</sup> A 26% reduction in deaths from CRC was seen in the screened group (RR, 0.74; 95% CI, 0.63–0.87;  $P < .001$ ), with a 50% reduction seen in mortality from distal disease and no effect on mortality from proximal disease.<sup>152</sup> This strong effect was seen despite an



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estimated 46% contamination rate of sigmoidoscopy or colonoscopy in the control arm, suggesting that the true benefit of screening is even greater.

The Norwegian Colorectal Cancer Prevention (NORCCAP) Study Group performed an RCT of one-time flexible sigmoidoscopy with or without a concurrent FOBT compared to a non-screened control group in >98,000 participants aged 55 to 64 years.<sup>149</sup> After 7 years of follow-up, the researchers reported no difference in the incidence of or mortality from CRC between screened and unscreened individuals. However, after 11 years of follow-up, the HR for death from CRC was 0.73 (95% CI, 0.56–0.94) in the screened groups.<sup>150</sup> Interestingly, the addition of FOBT did not affect the long-term outcomes of participants screened with sigmoidoscopy in this trial.

The SCORE trial randomized 34,272 participants aged 55 to 64 years to one-time sigmoidoscopy or no screening and reported incidence and mortality results after >10 years of median follow-up.<sup>151</sup> The intention-to-treat analysis demonstrated a 23% reduction in incidence and a 31% reduction in mortality. In addition, a randomized study examined the effect of flexible sigmoidoscopy offered once between ages 55 and 64 years on CRC incidence and mortality.<sup>148</sup> Compared to the population that did not receive any screening, intention-to-treat analysis showed that intervention with flexible sigmoidoscopy decreased CRC incidence by 23% (HR, 0.77; 95% CI, 0.70–0.84) and CRC mortality by 31% (HR, 0.69; 95% CI, 0.59–0.82).<sup>148</sup> The benefit of one-time sigmoidoscopy demonstrating decreased CRC incidence and mortality was sustained after 17 years of follow-up.<sup>155</sup> Although more data are warranted to determine the implications of screening, it is worth noting that some studies suggest the long-term benefit of flexible sigmoidoscopy, in terms of decreased CRC incidence and mortality, may be more apparent in men and lower or undetectable in women.<sup>155,156</sup>

Meta-analyses of RCTs support the conclusion that screening by flexible sigmoidoscopy significantly reduces the incidence and mortality of CRC.<sup>157–160</sup> In addition, analysis of a 5% random Medicare sample of the SEER database found a similar reduction in distal CRC after both colonoscopy and sigmoidoscopy, with a reduction in proximal CRC after colonoscopy but not sigmoidoscopy.<sup>161</sup> A similar result was seen in a nested case-control study of four U.S. health plans in which the reduction of stage IIB or higher CRC was only seen in the distal colon.<sup>162</sup>

Compared to colonoscopy, sigmoidoscopy often requires no sedation and less bowel preparation, but is limited to examination of the distal colon. An analysis of cancers not detected by flexible sigmoidoscopy in the PLCO trial showed that 37% of undetected lesions were beyond the reach of the sigmoidoscope.<sup>163</sup> The authors estimated that an additional 15% to 19% of cancers may have been detected during screening had colonoscopy been used.

Flexible sigmoidoscopy should be performed using a scope ≥60 cm. Polyps identified should be biopsied by trained personnel to determine if they are hyperplastic, adenomatous, or sessile serrated. Patients with lesions ≥1 cm should be referred directly to colonoscopy, since these lesions are almost always adenomatous polyps or SSP/SSLs, which are associated with a risk of proximal colonic neoplasms.

There are alternative strategies that have been recommended with flexible sigmoidoscopy, including flexible sigmoidoscopy every 10 years combined with annual FIT.<sup>164</sup>

### Stool-Based Screening Tests

Stool-based tests are designed to detect signs of CRC in stool samples, specifically occult blood or alterations in exfoliated DNA in combination with occult blood. In contrast to endoscopy-based tests, they are noninvasive and no bowel clearance is necessary. Guaiac-based FOBT



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screening has been shown to reduce mortality from CRC. FIT has been shown to have superior sensitivity for CRC detection compared to guaiac-based tests and multitarget stool DNA (mt-sDNA)/multitarget stool RNA (mt-sRNA) tests have the highest sensitivity, albeit at the expense of somewhat lower specificity.<sup>165,166</sup> FIT and FOBT are less likely to detect advanced precancerous lesions than mt-sDNA/mt-RNA for cancer prevention on single application. Moreover, whereas all mt-sDNA/mt-RNA tests are processed and interpreted by one central laboratory in the United States, sensitivity of FIT and FOBT can be limited by variability in processing and interpretation. These modalities should only be employed to screen individuals of average risk with commitment to a follow-up colonoscopy for any abnormal result.

If a stool-based screening test is positive, colonoscopy is indicated. To ensure adequate follow-up, a health care professional should coordinate testing so that the patient who has a positive result completes colonoscopy evaluation. Recommendations for an appropriate time frame for follow-up colonoscopy in this population lack a strong evidence base, but a large observational study and a meta-analysis reported significantly higher risks for CRC and advanced-stage disease when follow-up occurred  $\geq 10$  months with a trend towards increased cancer risk observed as early as 6 months after an abnormal result.<sup>167,127</sup> The Panel recommends colonoscopy as soon as possible and no later than within 9 months after a positive stool-based test.

If the colonoscopy is negative after a positive FIT or mt-sDNA, no symptoms are present, and the colonoscopy was a high-quality examination, patients can return to average-risk screening intervals beginning at 10 years after the colonoscopy. This interval could be modified based on the presence of symptoms or signs or additional CRC risk factors such as family history.

### **Fecal Occult Blood Test**

Two types of FOBTs are currently available: guaiac-based and FIT. Annual FOBT should not be performed in combination with colonoscopy in a patient at average risk. Any positive result on FOBT, however, should be followed up with colonoscopy. It is important for FOBT alone to be performed annually, because the sensitivity in detecting advanced adenomas in a single test is fairly low.

FOBT of a single specimen obtained at digital rectal examination (DRE) is not recommended due to exceptionally low sensitivity.<sup>168,169</sup> Unfortunately, a survey of >1000 primary care physicians revealed that inappropriate in-office testing is still widely used (25% used in-office testing only and 53% used both in-office and home testing), suggesting the need for strengthened education.<sup>170</sup>

### **Guaiac FOBT**

Based on the pseudoperoxidase activity of heme in human blood, guaiac FOBT is the most common stool test in use for CRC screening. One major disadvantage of guaiac FOBT is that it may miss tumors that bleed in smaller amounts, intermittently, or not at all. Another limitation is the high false-positive rate resulting from reaction with non-human heme in food and blood from the upper GI tract. To compensate for intermittent limitations, guaiac FOBT should be performed on three successive stool specimens obtained while the patient adheres to a prescribed diet.

There is direct evidence from RCTs that low-sensitivity guaiac FOBTs reduce mortality from CRC.<sup>171-173</sup> In the Minnesota Colon Cancer Control Study, >46,000 participants were randomized to receive guaiac FOBT annually, biennially, or not at all. The 13-year cumulative mortality from CRC per 1000 was 5.88 and 8.83 in the annual and unscreened groups, respectively; this 33% difference was statistically significant.<sup>173</sup> After 30-year follow-up, a CRC mortality benefit was seen in both the annual and biennial screening groups (RR for annual FOBT, 0.68; 95% CI, 0.56–



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0.82; RR for biennial FOBT, 0.78; 95% CI, 0.65–0.93).<sup>174</sup> In addition, long-term follow-up of the Nottingham trial showed that individuals randomized to the biennial guaiac FOBT screening arm had a 13% reduction in CRC mortality at a median follow-up of 19.5 years (95% CI, 3%–22%), despite a 57% participation rate. Following adjustment for non-adherence, the reduction in CRC mortality was estimated to be 18%.<sup>166</sup> This reduction in CRC mortality using low-sensitivity guaiac FOBTs has been confirmed by systematic review and meta-analysis of multiple studies.<sup>159,175</sup>

A systematic review of four RCTs involving >320,000 participants showed a 16% reduction in RR for CRC death with guaiac FOBT screening (95% CI, 0.78–0.90).<sup>175</sup> Another meta-analysis came to a similar conclusion, with guaiac FOBT screening reducing CRC mortality by 14% (RR, 0.86; 95% CI, 0.80–0.92).<sup>159</sup> The sensitivity of different guaiac FOBTs for cancer detection ranged from 37% to 79% in a study of about 8000 participants by Allison and colleagues.<sup>176</sup> In the UK National Health Service Bowel Cancer Screening Programme (BCSP), cancer was detected in 11.8% of individuals who had a colonoscopy following an abnormal or weak positive FOBT.<sup>177</sup> Adenomas were found in an additional 49.7% of participants.

The USPSTF defines high-sensitivity guaiac FOBT as a test with a sensitivity for cancer >70% and a specificity >90%.<sup>178</sup> Although high-sensitivity guaiac FOBTs that meet these criteria have not been tested in RCTs, some studies have shown that high-sensitivity guaiac FOBTs have higher CRC detection rates when compared to low-sensitivity guaiac FOBTs.<sup>176,179,180</sup> The NCCN CRC Screening Panel recommends that only high-sensitivity guaiac tests be used.

### Fecal Immunochemical Test

FIT, approved by the FDA in 2001, directly detects human globin within hemoglobin. Unlike guaiac FOBT, FIT does not require dietary restrictions, and a single testing sample is sufficient. In a systematic evidence review

of trials from the USPSTF (14 trials, n = 45,403), the sensitivity and specificity of FIT to detect cancers was 74% and 94%, respectively.<sup>93</sup>

Comparative studies have shown that FIT is more sensitive than guaiac FOBT.<sup>180–185</sup> For example, one study demonstrated a higher sensitivity for cancer by FIT compared to a high-sensitivity guaiac FOBT (82% vs. 64%).<sup>180</sup> A Dutch randomized study also demonstrated higher detection rates of advanced neoplasia by FIT (2.4%) than guaiac FOBT (1.1%), although both were less sensitive for advanced neoplasia than flexible sigmoidoscopy (8.0%).<sup>182</sup> In addition, as seen in other trials, FIT had a significantly higher participation rate than guaiac FOBT in this trial. Following extensive literature analysis, an expert panel in Ontario concluded that FIT is superior to guaiac FOBT in both participation rates and in detection of advanced adenomas and CRC.<sup>165</sup> Non-randomized studies have also shown that FIT screening reduces CRC mortality.<sup>186,187</sup> A large Taiwanese population-based study of 1,160,895 individuals aged 50 to 69 years were screened with 1 to 3 rounds of FIT and compared to an unscreened group. With a maximum follow-up of 6 years, there was a 10% decrease in CRC mortality in the FIT-screened population (RR, 0.90; 95% CI, 0.84–0.95).<sup>186</sup> If the colonoscopy is negative after a positive FIT, no symptoms are present, and the colonoscopy was a high-quality examination, patients can return to average-risk screening intervals beginning 10 years after the colonoscopy.

### Multitarget Stool DNA Test

One combined mt-sDNA and occult blood test has emerged as an option for CRC screening. This test screens for the presence of known DNA alterations (KRAS mutations, aberrant NDRG4 and BMP3 methylation) during colorectal carcinogenesis in tumor cells sloughed into stool, as well as occult blood as measured by immunoassay. A study that included 9989 participants at average risk for CRC, each of whom underwent FIT, mt-sDNA testing, and a colonoscopy, found that the mt-sDNA test was

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more sensitive than FIT in the detection of CRC (92.3% vs. 73.8%;  $P = .002$ ), advanced precancerous lesions (42.4% vs. 23.8%;  $P < .001$ ), polyps with high-grade dysplasia (69.2% vs. 46.2%;  $P = .004$ ), and SSP/SSLs  $>1$  cm (42.4% vs. 5.1%;  $P < .001$ ).<sup>188</sup> However, FIT had significantly higher specificity than the mt-sDNA test (94.9% vs. 86.6%, respectively, among participants with non-advanced or negative findings;  $P < .001$ ).

In another prospective study, Imperiale et al<sup>189</sup> evaluated a next-generation mt-sDNA test in asymptomatic adults  $\geq 40$  years of age who were undergoing screening colonoscopy. Out of 20,176 participants in this study, 98 had CRC, 2144 had advanced precancerous lesions, 6973 had nonadvanced adenomas, and 10,961 had nonneoplastic findings or negative colonoscopy. With the next-generation mt-sDNA test, sensitivity for CRC was 93.9% (95% CI, 87.1–97.7) whereas with the FIT, sensitivity was 67.3% (95% CI, 57.1–76.5). With the next-generation mt-sDNA test, sensitivity for advanced precancerous lesions was 43.4% (95% CI, 41.3–45.6) whereas with the FIT, sensitivity was 23.3% (95% CI, 21.5–25.2). However, specificity for advanced precancerous lesions with next generation mt-sDNA was 43.4% (95% CI, 41.3–45.6) and with the FIT, specificity for advanced neoplasia was 94.8% (95% CI, 94.4–95.1). Also, the specificity for nonneoplastic findings with next-generation mt-sDNA was 92.7% (95% CI, 92.2–93.1), while specificity was 95.7% (95% CI, 95.3–96.1) with FIT. When compared to FIT, the next-generation test had superior sensitivity for CRC ( $P < .001$ ) and for advanced precancerous lesions ( $P < .001$ ) but had lower specificity for advanced neoplasia ( $P < .001$ ).<sup>189</sup> The use of mt-sDNA testing is FDA approved for individuals of average risk only.

The NCCN CRC Screening Panel recommends the inclusion of mt-sDNA-based testing as a potential screening modality in individuals at average risk. A rescreening interval of every 1 to 3 years has been recommended

by USPSTF.<sup>190 191</sup> Using a clinical effectiveness model, one study showed that compared with a 10-year colonoscopy interval, annual mt-sDNA testing resulted in similar decreases in CRC incidence (65% vs. 63%) and mortality (73% vs. 72%).<sup>192</sup> At 3-year intervals, such testing was predicted to reduce CRC incidence and mortality by 57% and 67%, respectively. Modeling also shows that at real-world adherence rates, mt-sDNA screening resulted in an 8.4% to 19.1% increase in the number of life-years gained compared with FIT for screening ages 50 to 75 years, with similar results for ages 45 to 75 years.<sup>193</sup>

Additionally, a recent modeling study revealed that among stool-based screening modalities, mt-sDNA provides the most clinical benefit in a Commercial and Medicare population compared to FIT and annual fecal-occult blood test (FOBT).<sup>193</sup> In addition, there are no or limited data in individuals at high risk who refuse colonoscopy or have limited access to conventional screening strategies;<sup>194</sup> therefore, the use of mt-sDNA-based testing should be individualized in these cases. If the colonoscopy is negative after a positive mt-sDNA, no symptoms are present, and the colonoscopy was a high-quality examination, patients can return to average-risk screening intervals beginning 10 years after the colonoscopy.

### Multitarget Stool RNA Test

Another emerging option for CRC screening is mt-sRNA screening that combines a commercially available FIT, concentration of 8 RNA transcripts, and participant-reported smoking status to provide a consistent sensitivity profile for all patients at average risk ( $\geq 45$  years).

In a phase 3 clinical trial (CRC-PREVENT),<sup>195</sup> the sensitivity and specificity of a noninvasive, mt-sRNA test was evaluated compared with colonoscopy in a total of 8920 participants. All participants completed the mt-sRNA test using stool samples that were collected prior to participants completing a colonoscopy at their local endoscopy center and the mt-sRNA test results were compared with index lesions observed on colonoscopy. Of the 8920



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eligible participants, 36 (0.40%) had CRC and 606 (6.8%) had advanced adenomas. While the sensitivity of the mt-sRNA test 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% vs. 78%; McNemar  $P = .01$ ) and advanced adenomas (46% vs. 29%; McNemar  $P < .001$ ) compared with results of the FIT. The specificity of the mt-sRNA is reduced relative to FIT but shows increased sensitivity for colorectal neoplasia, with a comparable level of false-positive results compared with existing molecular screening tests.

The NCCN CRC Screening Panel recommends the inclusion of mt-sRNA-based testing as another potential screening modality in individuals at average risk, but data to help determine adherence to/participation rates of screening and how mt-sDNA testing may fit into an overall screening program are limited. Similar to mt-sDNA testing, a rescreening interval of every 3 years has been suggested and is approved by the FDA. Screening should be individualized and include a discussion with patients of the risks and benefits of each modality. If the colonoscopy is negative after a positive mt-sRNA, no symptoms are present, and the colonoscopy was a high-quality examination, patients can return to average-risk screening intervals beginning 10 years after the colonoscopy.

### Blood-Based Screening Tests

Another modality that was recently FDA approved is the blood test to use as primary screening for people at average risk for CRC and should only be employed to screen individuals of average risk with commitment to a follow-up colonoscopy for any abnormal result. The sensitivity and specificity of a cell-free DNA (cfDNA) blood-based test were assessed in a prospective, observational multi-site study (ECLIPSE).<sup>196</sup> In 7861 evaluable participants, 83.1% with CRC detected by colonoscopy had a positive cfDNA test and 16.9% had a negative test, which indicates a

sensitivity of the cfDNA test for detection of CRC of 83.1% (95% CI, 72.2–90.3). Sensitivity for stage I, II, or III CRC was 87.5% (95% CI, 75.3–94.1), and sensitivity for advanced precancerous lesions was 13.2% (95% CI, 11.3–15.3). A total of 89.6% of the participants without any advanced colorectal neoplasia (CRC or advanced precancerous lesions) identified on colonoscopy had a negative cfDNA blood-based test, whereas 10.4% had a positive cfDNA blood-based test, which indicates a specificity for any advanced neoplasia of 89.6% (95% CI, 88.8–90.3).

With multiple tests being developed over time that vary in cost-effectiveness for CRC screening, the best screening test is the one that gets completed by the patient.<sup>197</sup> 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. These newer tests may increase use and adherence, and thus increase the screening population to reduce deaths from CRC.<sup>197</sup> The NCCN Panel has also included blood-based cfDNA testing as one of the screening modalities with a re-screening interval of 3 years. The cost effectiveness of CRC screening with a blood test was analyzed using three microsimulation models for CRC (MISCAN-Colon, CRC-SPIN, and SimCRC)<sup>198</sup> to estimate the effectiveness and cost-effectiveness of triennial blood-based screening in individuals at average risk compared to no screening, annual FIT, triennial stool DNA testing combined with an FIT assay, and colonoscopy screening every 10 years. Without screening, these models predicted 77–88 CRC cases and 32–36 CRC deaths per 1000 individuals, costing \$5.3–\$5.8 million. While blood-based screening was cost-effective compared to no screening, it was not cost-effective compared to FIT, triennial stool DNA testing combined with FIT, or colonoscopy, and showed a decrease in QALYG and an increase in costs. Due to limited information on the stage-specific sensitivity of a blood test for CRC, it was assumed to have the same sensitivities as for



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FIT. Although uptake of blood-based screening was 20 percentage points higher than uptake of FIT, FIT remained more effective (+5–24 QALYG) and less costly (−\$3.2 to −\$3.5 million) than blood-based screening.<sup>198</sup> Even with increased screening uptake, triennial blood-based screening, with the Centers for Medicare and Medicaid Services (CMS)-specified minimum performance sensitivity of 74% and specificity of 90%, was not projected to be cost-effective compared with established strategies for CRC screening.

The clinical and economic impacts of novel CRC screening tests were also assessed by Ladabaum et al<sup>199</sup> with cost-effectiveness analysis using MOSAIC (Model of Screening and Surveillance for Colorectal Cancer). For colonoscopy every 10 years, annual FIT, and triennial next-generation mt-sDNA, FIT-RNA, cell-free blood DNA (cf-bDNA), the RRs for CRC incidence versus no screening were 0.21, 0.29, 0.33, 0.32, 0.58, and 0.58, respectively; the RRs for CRC death were 0.19, 0.25, 0.28, 0.28, 0.44, and 0.46, respectively. The cf-bDNA test cost \$89,600 (\$74,800–\$102,300) per QALY gained versus no screening; alternatives were less costly and more effective. Although the cf-bDNA test matched FIT's impact on CRC mortality at 1.35-fold FIT's uptake rate, incremental costs exceeded incremental benefits when novel test intervals were shortened to 1 or 2 years. If persons who accept colonoscopy or stool tests shifted to cf-bDNA, CRC deaths increased. If every 3 such patient substitutions were counterbalanced by cf-bDNA uptake by ≥2 people refusing alternatives, this adverse effect was overcome, assuming equal colonoscopy follow-up.<sup>199</sup>

### Image-Based Screening Tests

#### **Computed Tomographic Colonography**

CT colonography, also known as virtual colonoscopy or CTC, is evolving as a promising technique for CRC screening. CT colonography has the advantages of being noninvasive and not requiring sedation. The risk of

test-related complications is also very low, and results of a systematic review suggest that CT colonography may be cost-effective when compared to colonoscopy.<sup>200</sup> However, a positive finding requires a colonoscopy, and extracolonic findings—which are present in up to 16% of patients—pose a dilemma.<sup>201,202</sup> These findings require further investigations and have a potential for both benefit and harm. At the present time, data to determine the clinical impact of these incidental findings are insufficient.

The accuracy of CT colonography in detecting polyps or cancers measuring ≥10 mm was assessed in the National CT Colonography Trial (ACRIN 6664) organized by the American College of Radiology (ACR) Imaging Network.<sup>203</sup> In this study, 2531 participants underwent CT colonography followed by traditional optical colonoscopy. Colonoscopy identified 128 large adenomatous polyps or carcinomas in 109 patients. CT colonography detected 90% of patients who had lesions measuring ≥10 mm found by colonoscopy. There were also 30 lesions found on CT colonography, but not colonoscopy, for which 15 of 27 participants underwent a subsequent colonoscopy. Five of 18 lesions were confirmed: 4 adenomatous polyps and 1 inflammatory polyp. The CT colonography performance in this study (sensitivity of 90% and specificity of 86%) was better than that reported from some earlier studies<sup>204,205</sup> and similar to what was reported by Pickhardt and colleagues in a prospective study with a design similar to the ACRIN trial.<sup>206</sup>

Kim et al also compared CT colonography with colonoscopy for the detection of advanced neoplasia.<sup>207</sup> Although this study was not randomized, the detection rates were comparable between the two groups of >3100 patients each (3.2% for CT colonography and 3.4% for colonoscopy).

Furthermore, a small prospective study of 47 patients with pathologically proven lateral spreading tumors found that CT colonography may not be



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as sensitive as colonoscopy for detecting tumors with significant lateral spread.<sup>208</sup>

In 2005, two meta-analyses reviewed the performance of CT colonography in the detection of colorectal polyps.<sup>209,210</sup> In one of these studies, CT colonography showed high average sensitivity (93%) and specificity (97%) for polyps  $\geq 1$  cm, both of which decreased to 86% when medium polyps (6–9 mm) were included in the analysis.<sup>209</sup> In the other meta-analysis, the sensitivity of CT colonography, although heterogeneous, improved as the polyp size increased (48% for polyps <6 mm, 70% for polyps 6–9 mm, and 85% for polyps >9 mm). The specificity was 92% to 97% for the detection of all the polyps.<sup>210</sup> Other studies have assessed growth rates of colorectal polyps (6–9 mm) using CT colonographic surveillance.<sup>211,212</sup> In a population-based CT colonography screening study, 93 individuals diagnosed with one or two polyps (6–9 mm) were examined with 3-year surveillance CT colonography to determine which polyps would progress to advanced adenomas.<sup>212</sup> Participants who had lesions  $\geq 6$  mm were offered colonoscopy. With a mean surveillance interval of 3.3 years (standard deviation [SD], 0.3; range, 3.0–4.6 years), 35% of the polyps progressed, 38% remained stable, and 27% regressed.<sup>212</sup> The study suggests that polyps that are 6 to 9 mm in size are unlikely to progress to advanced neoplasia within 3 years.<sup>212</sup> In a longitudinal study screening of 22,006 asymptomatic individuals, 243 adults (mean age, 57.4 years) had 306 colorectal polyps (6–9 mm).<sup>211</sup> With a mean surveillance interval of 2.3 years (SD, 1.4; range, 1–7 years), 22% of the polyps progressed, 50% remained stable, and 28% regressed.<sup>211</sup> Volumetric assessment determined that histology-established advanced adenomas grew faster than non-advanced adenomas, and only 6% of the 6- to 9-mm polyps exceeded 10 mm at follow-up.<sup>211</sup>

Two additional meta-analyses were published in 2011. An analysis of 49 studies found the sensitivities for detection of CRC by colonography and colonoscopy to be 96.1% and 94.7%, respectively, with overlapping CIs.<sup>213</sup> Another analysis focused only on studies of participants at average risk and found the sensitivity and specificity of CT colonography for the detection of adenomas  $\geq 1$  cm to be 87.9% and 97.6%, respectively.<sup>214</sup> In a systematic evidence review of trials from the USPSTF in 2021 (7 trials, n = 5328), the sensitivity and specificity to detect adenomas  $\geq 10$  mm were 89% (95% CI, 0.83–0.96) and 94% (95% CI, 0.89–1.0), respectively.<sup>93</sup> Similarly, the sensitivity and specificity to detect adenomas  $\geq 6$  mm were 86% (95% CI, 0.78–0.95) and 88% (95% CI, 0.83–0.95), respectively.<sup>93</sup>

Importantly, CT colonography may be a more acceptable option to many individuals. A randomized study compared participation rates when members of the general population were offered CRC screening by either colonoscopy or CT colonography.<sup>215</sup> Significantly more people accepted the invitation for CT colonography (34% vs. 22%). While colonoscopy had a greater diagnostic yield in screened participants, the yields were similar when determined per the invited population. A prospective study has shown good sensitivity and specificity of laxative-free CT colonography for detecting lesions  $\geq 1$  cm.<sup>216</sup> This technique could present an alternative screening option to patients.

The technical aspects of CT colonography differ from study to study and have not been standardized. These details include the imaging, pre-procedure preparation, use of stool tagging, and expertise of the interpreter.<sup>217,218</sup> Long-term follow-up studies of patients who were screened by CT colonography are not yet available.

The issue of radiation exposure also requires consideration. The future risk related to undergoing a single CT colonography screening procedure is unknown but likely very low, and no empiric data have shown increased risk at levels below an exposure of 100 mSv.<sup>219</sup> Using the screening



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protocol for the ACRIN trial, Berrington de Gonzalez et al estimated the effective dose of low-dose CT colonography to be 9 mSv for women and 8 mSv for men, corresponding to 5 radiation-related cancer cases per 10,000 individuals undergoing one scan at 60 years of age.<sup>220</sup> Risks increase with repeated scanning. The 2014 ACR practice guidelines for the performance of CT colonography in adults recommend the use of a low-dose, non-enhanced CT technique on a multi-detector CT scanner to minimize radiation exposure to the patient.<sup>221</sup> Absorbed doses should not exceed 12.5 mGy total per scan.

Overall, available data indicate that CT colonography may be useful for the detection of larger polyps. Data on optimal frequency, polyp size leading to colonoscopy referral, and protocol for the evaluation of extracolonic lesions are evolving. If one or two lesions that are 6 to 9 mm are detected, CT colonography surveillance at year 3 or colonoscopy is recommended.<sup>211,212,222</sup> If >3 polyps that are 6 to 9 mm in size or lesions ≥10 cm are detected, colonoscopy surveillance is recommended. The ACR has recommended that reporting of polyps ≤5 mm in size is not necessary.<sup>221</sup> However, if polyps of this size are reported, the decision to refer for colonoscopy with polypectomy versus surveillance CT colonography should be individualized.

### Screening of Individuals at Average Risk

It is recommended that screening for persons at average risk begin at 45 years of age after available options have been discussed. Currently, recommended options include: colonoscopy every 10 years; flexible sigmoidoscopy every 5 to 10 years; annual high-sensitivity guaiac-based testing or FIT, or mt-sDNA-based testing or mt-sRNA-based testing or blood-based cfDNA testing (every 3 years); or CT colonography every 5 years.

If a colonoscopy is incomplete or preparation is suboptimal, consider either repeating colonoscopy within a year or screening with another modality.<sup>100</sup> Following a negative test, rescreening at the appropriate interval can be done with any accepted modality. Some data suggest that after one negative colonoscopy, following up with less invasive tests, such as triennial mt-sDNA or annual fecal tests, provides approximately the same benefit with lower risks and costs than colonoscopy.<sup>223</sup>

Following a positive non-colonoscopy test, a colonoscopy as soon as possible and no later than within 9 months is recommended for additional evaluation. Although the data regarding an appropriate time frame for follow-up colonoscopy are limited, a large observational study evaluated whether time to colonoscopy after a positive FIT was associated with increased CRC risk.<sup>167</sup> The participants in this study included 70,124 CRC screening-eligible FIT-positive patients, aged 50 to 75 years, who had a follow-up colonoscopy. Compared to follow-up colonoscopy performed within 8 to 30 days, significantly higher risks for any CRC and advanced-stage disease were observed for examinations performed at 10 to 12 months and >12 months.<sup>167</sup> A non-significant increase in any CRC risk and advanced-stage disease was observed beginning at 7 to 9 months.<sup>167</sup> The Panel recommends that a negative colonoscopy after a FIT or mt-sDNA or mt-sRNA with no symptoms present warrants no further testing prior to the next recommended screening interval.

Alternative proposed strategies with flexible sigmoidoscopy include its use at an interval of every 10 years with an annual FIT, or flexible sigmoidoscopy at longer intervals without FIT.<sup>164</sup> Microsimulation modeling has found that flexible sigmoidoscopy every 5 years with an interval FOBT likely results in similar life-years gained as colonoscopy every 10 years.<sup>224</sup> A survival meta-analysis of four randomized trials<sup>148,150-152</sup> comparing screening with flexible sigmoidoscopy to no screening found that it takes up to 10 years after flexible sigmoidoscopy to attain an absolute reduction



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in mortality related to CRC.<sup>225</sup> Another microsimulation modeling study of a previously unscreened population undergoing CRC screening found that flexible sigmoidoscopy every 10 years with annual FIT offered similar life-years gained and comparable benefit as observed with colonoscopy every 10 years.<sup>164</sup>

The decision to screen between ages 76 to 85 years should be individualized and include a discussion of 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.

### Interpretation of Findings

Colonoscopy is indicated as follow-up of abnormal findings from other screening modalities—stool-based tests, flexible sigmoidoscopy (biopsy-proven adenoma), blood-based testing, or CT colonography. During colonoscopy, any polyps found should be removed and follow-up strategies should be based on the endoscopic and pathologic findings. Special attention should be paid to SPs located in the ascending colon, as these tend to be associated with an increased rate of sporadic CRC with MSI<sup>226</sup> and hence greater cancer risk that warrants additional surveillance. Ideally, all detected polyps should be removed, but this is not always possible. Removed polyps should be examined for degree of dysplasia, as well as for histologic features of SSPs.

### Adenoma/Adenomatous Polyps

Adenomas or adenomatous polyps (most often found to be tubular), the most common form of polyps, are associated with an increased risk for CRC, and patients with these polyps should be followed as described below (see *Screening of Individuals at Increased Risk*). Villous adenomatous polyps have a greater risk of harboring cancer and finding additional adenomatous polyps or cancer on follow-up.

### Sessile Serrated Polyps

According to the World Health Organization (WHO) criteria, there are three main subtypes of SPs: SSP/SSLs, traditional serrated adenomas (TSAs), and hyperplastic polyps.<sup>227,228</sup> It is worth noting that the classification systems for serrated lesions are evolving, and a proposal by WHO suggests using the term sessile serrated lesions (SSLs).<sup>64</sup> SSPs, also known as SSA polyps, are a form of SPs that have been associated with adenocarcinoma.<sup>229</sup> SSPs are not dysplastic; however, they can develop foci of dysplasia and are then termed SSP with dysplasia (SSP-d). SSP-ds are thought to be the immediate precursors of high-frequency MSI sporadic CRC, and any dysplasia in an SSP is thought to be comparable to or more concerning than high-grade dysplasia in a conventional adenoma.<sup>228,230</sup> Thus, SSPs are managed like tubular adenomas, whereas SSP-ds are managed like high-risk adenomas.<sup>228,231-233</sup> The terms sessile serrated polyp, sessile serrated lesion, SSP/SSL, sessile serrated polyp (SSP), sessile serrated lesion (SSL), and SSA are synonymous; SSPs/SSLs are a type of SP that are not dysplastic but they can develop foci of dysplasia and are then termed SSP/SSL with dysplasia (SSP/SSL-d). These guidelines will use “SSP/SSL” for SSPs/SSLs without dysplasia and “SSP/SSL-d” for SSPs/SSLs with dysplasia. In general, SSPs/SSLs are managed like tubular adenomas and SSP/SSL-d with any grade dysplasia are managed like high-risk adenomas but may need even more frequent surveillance.

### Traditional Serrated Adenomas

An overall protuberant exophytic configuration, complex villous or tubulovillous growth pattern, and peculiar columnar cells with abundant eosinophilic cytoplasm characterize TSAs.<sup>228,234,235</sup> They are not as prevalent as SSPs in clinical studies,<sup>16,236,237</sup> and tend to be bulkier than SSPs.<sup>238</sup> Similar to SSPs, TSAs are associated with precancerous lesions.<sup>228</sup> Conventional adenoma-like and serrated dysplasia are observed in TSAs, and it is thought that TSAs increasingly acquire

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cytologic atypia before the development of CRC.<sup>228</sup> TSAs are managed like SSP-ds.

### **Hyperplastic Polyps**

Hyperplastic polyps are SPs with normal crypt architecture and proliferative characteristics. A large body of literature indicates that hyperplastic polyps are not associated with a significantly increased risk for CRC, and supports the recommendation that persons with hyperplastic polyps be screened as average risk. Nevertheless, evidence suggests that some cancers with extensive DNA methylation and MSI might derive from hyperplastic polyps.<sup>239</sup> Furthermore, some studies suggest that a small subset of patients with multiple or large hyperplastic polyps have SPS, with a 26% to 70% risk for CRC (see *Serrated Polyposis Syndrome* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric [available at [www.NCCN.org](http://www.NCCN.org)]).<sup>240-242</sup> The majority of these patients had concomitant adenomatous polyps or SSP.<sup>243</sup> SPS is rarely reported to be inherited, and the CRC risk for individuals with affected relatives remains unclear. Clinical criteria for serrated polyposis include: 1) 5 serrated lesions/polyps proximal to the rectum, all being 5 mm in size, with 2 being 10 mm in size; or 2) >20 serrated lesions/polyps of any size distributed throughout the large bowel, with 5 being proximal to the rectum.<sup>64</sup>

There are conflicting data to suggest that hyperplastic polyp(s) (<1 cm) proximal to the sigmoid colon pose an increased risk and whether they should be managed differently.<sup>244,245</sup> An expert panel concluded that hyperplastic polyps >5 mm occurring proximal to the sigmoid colon warrant a colonoscopy screening interval of 5 years.<sup>228</sup> In addition, when ≥4 hyperplastic polyps of any size are found proximal to the sigmoid colon, a 5-year colonoscopic screening interval is recommended.<sup>228</sup> Data to support these approaches are limited. There are conflicting and limited data to suggest whether individuals with hyperplastic polyps >1 cm in size

represent an increased risk group. Several analyses suggest that many of the larger polyps classified as hyperplastic in the past were re-classified as SSPs when reviewed by experts.<sup>245-249</sup> Therefore, it is reasonable to follow patients with hyperplastic polyps ≥1 cm in size similarly to SSPs, especially if an expert GI pathologist has not reviewed them.

### **Screening of Individuals at Increased Risk**

#### **Personal History of Polyps Found at Colonoscopy**

Individuals with adenomatous polyps, SSPs, TSAs, or large hyperplastic polyps (≥1 cm) are at increased risk for recurrent polyps and CRC. To minimize the risk of developing CRC, a surveillance program is recommended for these patients following colonoscopy and complete polypectomy.<sup>232</sup> The Panel recommends surveillance colonoscopy in adults with a history of adenomas aged 45 to 75 years, who may have a life expectancy of ≥10 years. Surveillance of individuals between ages 76 and 85 years should be individualized and include a discussion of risks and benefits of continued colonoscopy based on comorbidity status, estimated life expectancy, and finding on the last or most recent colonoscopy. For patients with completely resected adenomatous polyps, the surveillance schedule depends on the risk of recurrence, which in turn is related to the number, size, and histology of adenomatous polyps. Furthermore, when there is uncertainty about the completeness of removal in large and/or sessile polyps and when the colonic preparation was suboptimal, shorter surveillance intervals may be necessary.

Large cohort studies suggest that after removal of non-advanced adenomas and low-risk SSPs, there is not a significant increase in CRC risk and these patients may not require intensive surveillance.<sup>250,251</sup> Patients are considered to have low-risk adenomas when they have ≤2 tubular adenomas that are <1 cm. In this group, colonoscopy should be repeated between 5 to 10 years. Furthermore, patients are considered to have low-risk SSPs when they have ≤2 SSPs that are <1 cm without



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dysplasia. In this group, colonoscopy should be repeated in 5 years. In both cases, if this surveillance examination is normal, colonoscopy should be repeated every 10 years.<sup>232</sup> Any recommendations for a shorter interval should include a discussion with the individual based on an assessment of individual risk, including age, family history, comorbidities, and the results of previous colonoscopies.<sup>252-255</sup> If adenomas or SSPs are detected, a colonoscopy should be repeated according to endoscopic findings. Robertson et al reported on a study of 564 participants who had their first adenoma identified by colonoscopy and underwent two additional colonoscopies.<sup>256</sup> The study found that combining results of two prior colonoscopies can help predict the likelihood of high-risk findings (advanced adenomatous polyps or cancers) on the third screen. If no adenomas were found on the second exam, results of the first screening predicted results of the third. In this case, if the first colonoscopy showed only low-risk findings, then the chance of high-risk findings on the third colonoscopy was 4.9%, whereas high-risk findings on the first colonoscopy gave a 12.3% risk of high-risk findings on the third colonoscopy ( $P = .015$ ).

The presence of a TSA, an adenoma with high-grade dysplasia or an adenoma/SSP/SSL  $\geq 1$  cm, a polyp with villous or tubulovillous histology, or multiple (3–9) adenomatous polyps and/or SSPs or large ( $\geq 1$  cm) hyperplastic polyps have been associated with increased risk for CRC. High-grade dysplasia is defined as features of severe dysplasia (marked reduction of interglandular stromas with complex irregularity of glands, papillary infolding, and cytogenetic abnormalities) or severe architectural disturbance of glands along with cytologic features of dysplasia.<sup>257</sup> Carcinoma *in situ* is a term previously used by pathologists to describe colon polyps and cancer that has been replaced by the term *high-grade dysplasia*. A study by Golembeski and colleagues has shown that the identification of villous architecture and high-grade dysplasia is poorly reproducible among pathologists.<sup>258</sup> Studies reporting the association

between polyp size and cancer risk have used 1 cm as the standard measure; data are lacking on the relative significance of intermediate-size adenomatous polyps (size 5–10 mm).

Individuals with high-risk adenomas <1 cm, high-risk SSP/SSL <1 cm, and TSA <1 cm should have a repeat colonoscopy in 3 years, although some data suggest that intervals of 5 years may be appropriate. A recently published systematic review and meta-analysis<sup>259</sup> shows that CRC risk is significantly higher in patients with baseline advanced SPs after 4.9 years of follow-up supporting the current recommendation for 3-year surveillance in patients with advanced SPs. If the examination is normal, subsequent surveillance colonoscopies are recommended in 5 years. These intervals may be individualized based on the colonic preparation and completeness of polypectomy based on endoscopy, histology, and pathology reports.<sup>228,260</sup> It is appropriate to reassess risk, including contributing medical and personal factors, number and characteristics of adenomatous polyps, and family history at each interval prior to and following procedures. While individuals with low-risk adenoma colonoscopy should have a repeat colonoscopy between 5 to 10 years, individuals with low risk SSP/SSL should have repeat colonoscopy in 5 years.

In individuals with  $\geq 10$  adenomatous polyps and/or SSP/SSLs in a single colonoscopy, colonoscopy in 1 year should be considered. Based on clinical endoscopic findings, colonoscopy can be repeated and a diagnosis of polyposis syndrome should be considered (see *Adenomatous Polyposis Testing Criteria* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric, available at [www.NCCN.org](http://www.NCCN.org)). Genetic testing should be considered depending on patient age, the number of polyps, and family history. The cumulative presence of  $\leq 9$  polyps may occasionally be associated with an inherited polyposis syndrome, especially in patients <40 years of age or with a



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strong family history. Hence, a detailed family history is crucial in patients with multiple adenomatous polyps. Individual management is emphasized.

In patients with  $\geq 10$  cumulative adenomatous polyps and/or SSP/SSLs over multiple colonoscopies, individual management is emphasized and genetic testing should be considered for an inherited polyposis syndrome (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric, available at [www.NCCN.org](http://www.NCCN.org)).

Consider testing if 10 to 19 cumulative adenomas if other factors suggest the possibility of a polyposis/CRC syndrome such as age of onset or family or personal history of CRC. If the genetic testing result is negative or genetic testing is not done, the NCCN Panel recommends a repeat colonoscopy within 1 to 3 years. Frequency of surveillance may be modified based on factors such as age at which patient met cumulative adenoma threshold or total number of adenomas at most recent colonoscopy, with more frequent surveillance favored for younger age at meeting threshold or higher adenoma burden at last colonoscopy.

The NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer (available at [www.NCCN.org](http://www.NCCN.org)) provide recommendations for management if a malignant polyp is found at colonoscopy.

### Management of Large Colorectal Polyps

The management of large polyps is challenging and may require surgical resection. For this reason, referral to a center with expertise in large polyp management or referral for surgical evaluation should be considered. Endoscopic resection, including polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD), is the preferred mode of intervention for large polyps.<sup>232,261</sup> However, one major limitation of endoscopic resection is its association with a high rate of recurrence, attributed to the presence of residual adenoma tissue at the time of resection.<sup>232,262</sup> Hence, frequent surveillance with colonoscopy is

appropriate in this setting, particularly when the resection is suspected to be incomplete or was done in piecemeal fashion.<sup>232,263-265</sup> Also, because of this risk of recurrence and the not uncommon necessity of surgical resection, sessile polyps or large sessile lesions (LSLs)  $\geq 20$  mm in size should have endoscopic tattoo placement next to the lesion.

For individuals with sessile polyps or non-polypoid lesions, evaluation for high-risk features of invasive cancer is necessary. For those with high-risk endoscopic features for invasive cancer, a biopsy is recommended to determine if the cancer is invasive. If there is no invasive cancer, referral to a center of expertise for large polyp management or surgical evaluation should be considered. Those with invasive cancer should be followed according to the recommendations in the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer (available at [www.NCCN.org](http://www.NCCN.org)).

For patients with no high-risk features receiving complete resection, a follow-up colonoscopy is recommended in 3 years if the polyp size is  $<20$  mm and there is en bloc resection and no high-grade dysplasia. Surveillance should be maintained in 5 years if no recurrence is found at the first surveillance colonoscopy. If the size of the polyp is  $>20$  mm or there is piecemeal resection or high-risk dysplasia,<sup>264</sup> follow-up with colonoscopy within 6 months is recommended. After complete resection and appropriate follow-up, if there is no disease recurrence, surveillance with colonoscopy within 1 year and subsequently in 3 years is appropriate. If the disease recurs, endoscopic therapy may be repeated. However, alternatively, and in the case of an incomplete resection, referral to a center with experience in endoscopic management of large colorectal polyps is recommended.

For individuals with pedunculated polyps, follow-up with colonoscopy in 3 years is recommended if there is no disease recurrence. If there is invasive cancer present, refer to the NCCN Guidelines for Colon Cancer

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and the NCCN Guidelines for Rectal Cancer (available at [www.NCCN.org](http://www.NCCN.org)).

### Diagnosis of CRC

Individuals with a personal history of CRC should be followed according to the surveillance recommendations in the NCCN Guidelines for Colon Cancer, NCCN Guidelines for Rectal Cancer, and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (available at [www.NCCN.org](http://www.NCCN.org)). These patients are at increased risk for recurrent adenomatous polyps and cancer. Studies have found a high recurrence rate in the 4 to 5 years following CRC resections.<sup>266-269</sup> In patients with rectal cancer, local recurrence at the rectal anastomosis has been reported to occur in 5% to 36% of patients.<sup>270-272</sup> Furthermore, an analysis of 3278 patients with resected stage II and III CRC in the Intergroup 0089 study found that the rate of second primary CRC is especially high in the immediate 5 years following surgery and adjuvant chemotherapy.<sup>273</sup> These results suggest that intense surveillance should be considered during that period, even though this analysis did not exclude patients with Lynch syndrome, who are at >30% risk for synchronous and metachronous cancers.

The NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer (available at [www.NCCN.org](http://www.NCCN.org)) recommend a complete colonoscopy preoperatively as well as at 1 year following surgery. If this examination is normal, colonoscopy should be repeated in 3 years, then every 5 years. Shorter intervals (1 year) are recommended if adenomatous polyps or SSPs are found. Subsequent colonoscopic intervals are individualized and generally should not exceed 5 years.

Advantages of more intensive follow-up of patients with stage II and/or stage III rectal cancer have been demonstrated prospectively in several studies<sup>267,274,275</sup> and in three meta-analyses of RCTs designed to compare

low-intensity and high-intensity programs of surveillance.<sup>276-278</sup> Other studies impacting the issue of post-treatment CRC surveillance include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials.<sup>268</sup> The meta-analysis demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor. However, in the final analysis of Intergroup trial 0114, which compared bolus fluorouracil (5-FU) to bolus 5-FU/leucovorin (LV) in patients with surgically resectable rectal cancer, local recurrence rates continued to rise after 5 years.<sup>279</sup> Furthermore, a population-based report indicated that long-term survival is possible in patients treated for local recurrence of rectal cancer (overall 5-year relative survival rate of 15.6%), thereby providing support for more intensive post-treatment follow-up in these patients.<sup>280</sup> Nevertheless, controversies remain regarding selection of optimal strategies for following up with patients after potentially curative CRC surgery.<sup>281,282</sup>

The NCCN Guidelines for Colorectal Cancer Screening recommend that patients with a personal history of CRC should routinely be tested for Lynch syndrome or MMR deficiency, preferably at the time of diagnosis for all individuals with CRC (for the pros and cons of screening for Lynch syndrome using colonoscopy-based biopsies vs. a surgical resection specimen, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric, available at [www.NCCN.org](http://www.NCCN.org)). The Panel recommends universal screening of all CRC tumors to maximize sensitivity for identifying individuals with MMR deficiency and/or Lynch syndrome, and to inform prognosis and care processes in patients with and/or without Lynch syndrome. The Panel recommends germline multigene testing for evaluation of LS and other hereditary cancer syndromes for individuals with CRC <50 years of age. Testing for Lynch syndrome is discussed in more detail in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (available at [www.NCCN.org](http://www.NCCN.org)).



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### Increased Risk Based on Personal History of Inflammatory Bowel Disease

It is well-recognized that individuals with a personal history of IBD (ie, ulcerative colitis, Crohn's colitis) are at an increased risk for CRC, because chronic inflammation can lead to dysplasia and subsequent malignant conversion.<sup>283-285</sup> Evidence shows that endoscopic surveillance can detect CRC at earlier stages in patients with extensive colitis, and that it may reduce the risk of death from CRC in these patients.<sup>286</sup> A retrospective review of 6823 patients with IBD found that the incidence of CRC in patients without a colonoscopy in the past 3 years was significantly higher than in those with a recent colonoscopy (2.7% vs. 1.6%; OR, 0.56; 95% CI, 0.39–0.80).<sup>287</sup> In addition, a colonoscopy within 6 to 36 months before CRC diagnosis was associated with reduced mortality (OR, 0.34; 95% CI, 0.12–0.95). Information regarding the value of endoscopic surveillance of long-standing Crohn's disease, on the other hand, is limited.

Risk factors for dysplasia in patients with IBD include ulcerative colitis, extensive colitis, colonic stricture, primary sclerosing cholangitis (PSC), family history of CRC (especially with diagnosis <50 years of age), personal history of dysplasia, and severe longstanding inflammation.<sup>283,288,289</sup> Confirmation of dysplasia by an expert GI pathologist is desirable. Patients with proctitis and proctosigmoiditis are likely at little or no increased risk of CRC compared with the general population and should be treated as having average risk.<sup>283,288</sup>

The NCCN Panel recommends colorectal surveillance by colonoscopy, initiated 8 years after the onset of symptoms in patients with a personal history of IBD involving the colon.<sup>290,291</sup> If PSC is present, annual surveillance colonoscopies should be started independent of the individual's time since symptom onset or colonoscopic findings and instead should be initiated at the time of PSC diagnosis. Family history of

CRC is another important risk factor for developing CRC in patients with IBD, and such individuals may benefit from earlier initiation of colonoscopic surveillance.<sup>290,291</sup> A 2001 meta-analysis showed that patients with pancolitis have a higher risk of developing CRC than those with less extensive disease.<sup>292</sup>

Colonoscopic surveillance in patients with IBD should be performed during quiescent disease. Colonoscopic surveillance in IBD is generally performed with high-definition white light endoscopy (HD-WLE). Both targeted biopsy of any mucosal abnormality and random biopsy are recommended. For random biopsy, random 4-quadrant biopsies every 10 cm with ≥32 total samples can be considered. Colonoscopic surveillance may also be performed by chromoendoscopy with targeted biopsy.<sup>293-295</sup> Targeted biopsies have been found to improve detection of dysplasia and should be considered during surveillance chromoendoscopy where expertise is available.<sup>291,293-296</sup> With chromoendoscopy (dye spray or high-definition virtual) with targeted biopsies, consider taking two biopsies in every bowel segment, placed in separate specimen jars, to document microscopic disease activity and extent of disease involvement.<sup>297,298</sup> Non-targeted (random) biopsies as described above should be considered in addition to chromoendoscopy in patients with a history of dysplasia or PSC.<sup>299</sup> If HD-WLE or chromoendoscopy is not available, the Panel recommends referral to institutions with expertise in these modalities.

### Evaluation of Surveillance Findings in Inflammatory Bowel Disease

Biopsies can be better targeted to abnormal-appearing mucosa using chromoendoscopy or confocal endomicroscopy, and several studies indicate increased sensitivity of chromoendoscopy in detecting dysplastic lesions; however, the natural history of these lesions is unclear.<sup>300</sup> Targeted biopsies should be performed of strictures and mass lesions. Lesions may be categorized using the Paris classification.<sup>293,301</sup> Dysplasia is classified as endoscopically visible and identified by resection or



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targeted biopsies or endoscopically invisible and detected by random biopsies.<sup>297</sup>

Patients with ulcerative colitis may develop sporadic colorectal adenomas at the same rate as the general population, and the appropriate management of adenomatous polyps in the setting of ulcerative colitis is dependent on various factors and should be based on individual risk factors such as duration of colitis, presence of dysplasia, and the number and size of adenomas. Lesions that appear endoscopically and histologically similar to a sporadic adenoma or SSP and without invasive carcinoma in the polyp may be managed by polypectomy. Some lesions may require ESD or EMR techniques for complete resection. The confirmation of all polyp histology and dysplasia by an expert GI pathologist is desirable.

If invisible dysplasia (low- or high-grade) is detected or there are polypoid lesions or masses that are non-resectable, the patient should be referred to a surgeon with expertise in IBD to discuss potential surgical options. A surgical consultation may include a discussion about surveillance and colectomy based on multiple factors, including other visible dysplastic lesions in the same colon segment, histology, and a discussion with the patient about the risks and benefits of each approach. The presence of invisible dysplasia may be confirmed with chromoendoscopy, if this procedure has not already been performed. Given that invisible dysplasia is associated with increased risk for CRC,<sup>302,303</sup> if confirmed by an expert GI pathologist, a colectomy may be considered over intensified surveillance. When a single focus of low-grade dysplasia is found in patients with IBD, colectomy versus close colonoscopic surveillance may be discussed.

If dysplasia is detected, all endoscopically resectable lesions (eg, sessile/pedunculated polyp, nonpolypoid/flat lesion) should be removed.<sup>293,297</sup> Following endoscopic resection of visible lesions, consider

taking a biopsy of surrounding mucosa to ensure complete removal. If chromoendoscopy is used, the yield of biopsies may be negligible. If complete endoscopic resection is feasible and patients present with low risk factors (ie, hyperplastic or normal mucosa, no endoscopic or histologic active inflammation, <1 cm low-grade dysplasia), surveillance colonoscopy should be performed in 1 to 3 years.<sup>304</sup> During surveillance, if the patient has any high-risk factors (ie, PSC, ≥1 cm low-grade dysplasia, active inflammation, family history of CRC at <50 years of age, any high grade dysplasia), individuals should receive follow-up with colonoscopy 1 year after endoscopic resection. Furthermore, if dysplastic lesions with high-grade dysplasia ≥2 cm are detected or if piecemeal resection was performed, follow-up with colonoscopy should be done within 3 to 6 months. Following endoscopic resection of visible lesions, biopsy of surrounding mucosa is not routinely necessary, but should be considered if there is any doubt regarding the completeness of resection.<sup>289,305-307</sup> If endoscopic resection is incomplete, the patient should be referred to either a center with expertise in IBD management or a surgeon with expertise in IBD. In addition, the patient may be further evaluated with chromoendoscopy assessment, if this procedure has not already been performed.

If no dysplasia is detected during surveillance, and patients present with no endoscopic or histologic active inflammation, they can be considered to have low risk for CRC and undergo follow-up surveillance colonoscopy in 2 to 5 years.<sup>308,309</sup> Several GI societies' position statements recommend risk-stratified surveillance with an increased surveillance interval of 3 to 5 years in lowest risk patients.<sup>291,304,310</sup> However, if patients present with any of the following high-risk factors—PSC, active inflammation, or family history of CRC at <50 years of age—they may have increased risk for CRC and follow-up surveillance colonoscopy should be performed in 1 year.



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The literature describes a wide range of prevalence of dysplasia or cancer in colitis-associated colonic strictures, with rates up to 7% in Crohn's disease, and reported rates between 2% and 90% in ulcerative colitis. Among strictures with negative surveillance biopsies, reported rates of dysplasia or cancer in follow-up range from 2%–6% in Crohn's disease and 7.5%–27% in ulcerative colitis.<sup>311</sup> Patients with traversable strictures should undergo follow-up surveillance colonoscopy in 1 year if surgery is not performed. In addition, referral to a center with expertise in IBD and consideration of chromoendoscopy assessment are recommended. Due to the risk of underlying CRC,<sup>312</sup> for patients with non-traversable or symptomatic strictures, especially in cases with long-standing IBD, the Panel recommends referral to a surgeon with expertise in IBD to discuss potential surgical options.

### Increased Risk Based on Personal History of Cystic Fibrosis

Numerous reports show an increased risk of CRC in patients with CF,<sup>313–316</sup> and the increasing life expectancy of patients with CF is expected to increase the incidence of CRC in this population. The average age of onset of CRC in patients with CF is approximately 40 years, and the incidence of CRC in patients with CF aged 40 to 49 years is similar to that of the general population aged 65 to 69 years.<sup>313,317</sup> The CRC risk stratification of a patient with CF is dependent on a history of solid organ transplant. A large population-based study involving the Cystic Fibrosis Foundation patient registry from 1990 to 1999 found that patients with CF who underwent transplant had a higher incidence of digestive tract tumors (standardized incidence ratio [SIR], 6.3; 95% CI, 3.4–10.8).

The NCCN Panel recommends that, in patients with a history of solid organ transplant, surveillance should be initiated at  $\geq$ 30 years of age or within 2 years of the transplantation. In patients with no history of solid organ transplant, initiation of surveillance should begin at  $\geq$ 40 years of age. Surveillance methodology involves colonoscopies with intensive

bowel preparation specific for patients with CF, because standard colonoscopy bowel preparation is often inadequate.<sup>318</sup> If the colonoscopy returns no findings, a colonoscopy should be repeated every 5 years. If the colonoscopy reports adenomatous polyps or SSPs/SSLs, a colonoscopy should be repeated every 3 years.

### Increased Risk Based on Positive Family History

Patients not meeting criteria for consideration of a hereditary cancer syndrome or if appropriate testing for a hereditary cancer syndrome rules it out or is not done should have their individualized risk based on family history. It is recommended that risk assessment be individualized and include a careful family history to determine whether a familial clustering of cancers is present in the extended family. Family history is one of the most important risk factors for CRC. It is essential to obtain a detailed family history including first-degree relatives (parents, siblings, and offspring), second-degree relatives (aunts, uncles, grandparents, and half-siblings), and additional relatives (cousins, great-grandparents, nieces, and nephews). Grandchildren are often not old enough to manifest any of the clinical phenotypes of cancer syndromes.

For each of the relatives, current age and age at diagnosis of any cancer as well as a date, age, cause of death, and availability of a tumor sample are very important for discerning whether relatives were at risk for developing cancer, how long they were at risk, and what type of cancer they had. It is particularly important to note the occurrence of multiple primary tumors. Other inherited conditions and birth defects should be included in this family history. Ethnicity and country of origin are also important. The ASCO Cancer Genetics Subcommittee has provided guidance for taking and interpreting a family history that discusses barriers to accuracy in the process.<sup>319</sup> For further details and guidance, also see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (available at [www.NCCN.org](http://www.NCCN.org)).

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### **Family History Criteria**

If a patient meets the criteria for an inherited colorectal syndrome (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric, available at [www.NCCN.org](http://www.NCCN.org)), further risk evaluation and counseling, as outlined in the guidelines, is required. When any one of the revised Bethesda criteria<sup>320</sup> are met (listed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric, available at [www.NCCN.org](http://www.NCCN.org)), the possibility of Lynch syndrome is suggested, and IHC staining of the four MMR proteins and/or MSI testing of the colon tumor of the youngest affected family member is warranted.

Other individuals with a family history of CRC have an increased risk for the disease themselves and should therefore undergo earlier and/or more frequent screenings.<sup>321–323</sup> If multiple distant relatives are affected, an evaluation for an inherited colorectal syndrome should be considered.<sup>324</sup> In cases in which testing for a hereditary syndrome is non-diagnostic or may not have been done, the Panel's recommendations are as follows:

For patients with at least one affected first-degree relative with CRC at any age, colonoscopy is recommended every 5 years, beginning 10 years prior to the earliest diagnosis in the family, or by age 40 years, whichever is first.<sup>325</sup> If colonoscopy is positive, follow-up colonoscopy should be based on findings.

Individuals with second- or third-degree relatives with CRC at any age are recommended to undergo colonoscopy every 10 years, beginning by age 45.<sup>63</sup> If colonoscopy is positive, follow-up should be based on colonoscopy findings.

Individuals with a first-degree relative with a confirmed history of advanced adenoma(s) (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology, TSA) or advanced SSPs (ie, ≥1 cm, any dysplasia) at any age

should undergo colonoscopy at the relative's age of onset of adenoma or by age 40 years (whichever is earliest) with repeat colonoscopy every 5 to 10 years or based on findings. Endoscopists should add specific recommendations to reports for sharing of information with first-degree relatives when applicable.

Multiple (≥2) negative colonoscopies may support stepwise lengthening of the colonoscopy interval in these individuals. Data suggesting an increased risk for CRC in this population are limited.<sup>326,327</sup> Colonoscopy intervals may be further modified based on personal and family history as well as on individual preferences. A population-based study analyzed >2 million individuals to determine RRs for the development of CRC depending on family history of CRC.<sup>321</sup> Results showed that some combinations of affected first-, second-, and third-degree relatives may increase risk sufficiently to alter screening guidelines from the recommendations listed above.

Factors that modify age to begin screening and colonoscopy intervals include: 1) age of individual undergoing screening; and 2) specifics of the family history, including number and age of onset of all affected relatives and/or whether relatives had an inciting cause such as IBD. A retrospective, population-based, case-control study showed that of 18,208 index patients diagnosed with CRC, the highest familial risk was found in first-degree relatives of index patients with CRC who were diagnosed prior to age 40 years (HR, 2.53; 95% CI, 1.7–3.79).<sup>328</sup> However, familial risk for CRC was increased in first-degree relatives regardless of the age of diagnosis of the index patient.<sup>328</sup> The PLCO trial evaluated the effect of family history on CRC risk after 55 years of age, when risk of early-onset cancer has passed, and found that individuals with 1 first-degree relative had a modest increase in risk for CRC incidence and mortality.<sup>329</sup> Individuals with ≥2 first-degree relatives with CRC had continued increased risk in older age.<sup>329</sup>

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Other factors that modify colonoscopy intervals include the size of the family, completeness of the family history, participation of family members in screening, and colonoscopy findings in family members.

### Increased Risk Based on Personal History of Childhood, Adolescent, and Young Adult Cancer

Therapy-associated polyposis (TAP) is an acquired phenotype that presents years after exposure to chemotherapy and/or RT. If an individual has a cumulative incidence of  $\geq 10$  GI polyps of any type (including adenoma, SSLs, or hamartomas) in the entire GI tract, has a history of systemic therapy and/or RT for a childhood or young adult cancer (specifically abdominopelvic RT and/or alkylating chemotherapy), and has completed multi-gene testing without an identified pathogenic variant, then a baseline upper endoscopy is indicated if polyposis is identified. Multi-gene testing should include all hereditary polyposis and CRC genes.<sup>330</sup> Pathogenic variants associated with adenomatous polyposis include, but are not limited to monoallelic pathogenic variants in *APC*, *GREM1*, *POLE*, *POLD1*, and *AXIN2*, and biallelic pathogenic variants in *MUTYH*, *NTHL1*, and *MSH3*. Additional surveillance recommendations on colonic adenomatous polyposis of unknown etiology can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (available at [www.NCCN.org](http://www.NCCN.org)) on CPUE-1.

Individuals who received chemotherapy, RT (particularly to the abdominopelvic field [ie, abdomen, pelvis, spine]), or total body irradiation (regardless of dose, with or without chemotherapy) are at an increased risk for CRC. For patients with a history of chemotherapy only, a colonoscopy starting at 35 years of age or 10 years after chemotherapy (whichever occurs first) is recommended.<sup>331</sup> For patients who have a history of RT that included the abdominopelvic field or total body irradiation with or without chemotherapy, a colonoscopy starting at

30 years of age or 5 years after treatment (whichever occurs last) and repeating every 5 years is recommended.<sup>332</sup> For patients who have no history of chemotherapy or RT that included the abdominopelvic field, it is recommended to follow the average-risk screening guidelines, which entail receiving a colonoscopy starting at age 45 years and repeating every 10 years.<sup>332</sup>

TAP is an acquired phenotype in childhood cancer survivors that presents years after exposure to chemotherapy and/or radiation therapy.<sup>333</sup> If an individual has a cumulative incidence of  $\geq 10$  GI polyps of any type (including adenoma, SSLs, or hamartomas) in the entire GI tract, has a history of systemic therapy and/or RT for a childhood or young adult cancer (specifically abdominopelvic RT and/or alkylating chemotherapy), and has completed multi-gene testing without an identified pathogenic variant, then a baseline upper endoscopy is indicated if colonic polyposis is identified. Multi-gene testing should include all hereditary polyposis and CRC genes.<sup>330</sup> Germline multigene panel testing has been updated to include at minimum the following CRC risk-associated genes: *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMPR1A*, *SMAD4*, *PTEN*, *STK11*, and *TP53*. Pathogenic variants associated with adenomatous polyposis include, but are not limited to, monoallelic pathogenic variants in *APC*, *GREM1*, *POLE*, *POLD1*, and *AXIN2*, and biallelic pathogenic variants in *MUTYH*, *NTHL1*, and *MSH3*. The TAP patients have phenotypic features that resemble numerous hereditary CRC syndromes, suggesting multiple concurrent biologic mechanisms. Recognition of TAP diagnosis is important for cancer risk assessment and screening for childhood and young adulthood cancer (CYAC).

In 2022, a new algorithm page with surveillance modality and schedule for individuals at increased risk based on personal history of childhood, adolescent, and young adult cancer was added. Individuals with CYAC



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who have received prior radiation therapy (particularly to the abdominopelvic field) or total body irradiation (regardless of dose, with or without chemotherapy) are at an increased risk for CRC. For these individuals, the Children's Oncology Group (COG) long-term follow-up Guidelines<sup>332</sup> recommend colonoscopy starting at 30 years of age or 5 years after treatment (whichever occurs last) and repeating every 5 years; the NCCN Panel added this to the recommendation. For CYAC patients with a history of chemotherapy only (without radiation), based on a multi-institutional TAP cohort in CYAC by Biller et al,<sup>331</sup> the previous recommendation was to initiate colonoscopy screening at 35 years or 10 years after chemotherapy treatment (whichever occurs first) and repeat every 5 years.

In this TAP cohort study, 34 individuals with TAP were included; 29/34 (85%) received chemotherapy for their initial CYAC and 28/34 (82%) had radiation therapy. The median age for individuals with CYAC at the time of original diagnosis was 18 years. GI polyposis was first detected at a median of 27 years after CYAC treatment. Among 34 individuals with TAP, 12/34 (35%) had ≥50 colorectal polyps, 32/34 (94%) had >1 histologic polyp type, and 25/34 (74%) had clinical features suggestive of ≥1 CRC predisposition syndrome including 8/34 (24%) with features of multiple such syndromes. In this cohort, almost 20% had polyps first detected at an age prior to the COG-recommended colonoscopy screening start time (at 30 years of age or 5 years after radiation [whichever comes last]), and patients with and without prior radiation therapy fell outside of the COG screening Guidelines.

Based on this TAP cohort,<sup>331</sup> Biller et al proposed that COG Guidelines be expanded to include individuals with CYAC who received chemotherapy (without radiation), and that screening initiation begin at age 35 or 10 years after age of chemotherapy, whichever occurs first. On a closer look at the TAP cohort, the median age of individuals with CYAC

who received only chemotherapy was 22 years and the recommendation to initiate screening at whichever age recommendation comes first was applicable only to this cohort. In order to expand the applicability of this guideline to younger individuals with CYAC, multiple NCCN participating cancer institutes requested to review the screening recommendation in patients with CYAC with a history of chemotherapy at the annual meeting.

The NCCN Panel discussed extensively the surveillance modality and schedule for individuals with CYAC with a personal history of chemotherapy (without radiation therapy), and updated the recommendation to start colonoscopy screening starting at 35 years or 10 years after chemotherapy treatment (whichever occurs **last**) and repeating every 5 years.

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