Definition of ‘Average Risk’ and ‘High Risk’ According to CRC Guidelines

How is “Average Risk” for CRC Defined?

Asymptomatic Patients Are Generally Considered to Be at Average Risk for CRC if They **Do NOT Have**:[1-5]

A Personal History* of

- **CRC, adenomatous polyps, or IBD** (including Crohn’s disease and ulcerative colitis)
- **A confirmed or suspected hereditary CRC syndrome** (such as familial adenomatous polyposis or Lynch syndrome)

A Family History of

- **First-degree relatives (parents, siblings, children) who had CRC, adenoma or sessile serrated polyp**
- **Familial adenomatous polyposis**
- **Hereditary nonpolyposis CRC syndrome**

The Following Factors May Be Considered When Estimating CRC Risk for Average-risk Individuals But These Alone Do Not Elevate People Beyond the Average-risk Category[5]

- Cigarette smoking
- Diabetes
- Lack of physical activity
- Excess body weight
- Moderate to high consumption of alcohol and/or long-term consumption of red and processed meat
- Low consumption of fiber, calcium, fruits, and vegetables

*ACS guideline excludes patients with radiation to the abdomen/ pelvic area to treat prior cancer from the average-risk category.

CRC: colorectal cancer

1. American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. Atlanta: American Cancer Society; 2020. 2. Davidson KW, et al. *JAMA*. 2021;325(19):1965-1977. doi:10.1001/jama.2021.6238 3. Wolf AMD, et al. *CA Cancer J Clin*. 2018;68(4):250-281. doi:10.3322/caac.21457 4. Rex DK, et al. *Am J Gastroenterol*. 2017;112(7):1016-1030. doi:10.1038/ajg.2017.174 5. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf

How is “Average Risk” for CRC Defined?

- The concept of “average risk” vs “high risk” is key to making decisions about CRC screening; while there are common features, the definition of “average risk” is not uniformly consistent in the scientific literature
- A patient is considered to be in the average-risk category if he or she is not in the high-risk category or has no known risk factors other than age
- High risk is generally defined as having any of the following:
  - A personal history of
    - Colorectal cancer, adenomatous polyps, or inflammatory bowel syndrome
    - A confirmed or suspected hereditary CRC syndrome
    - ACS only has an additional category: ACS excludes patients with radiation to the abdomen/ pelvic area to treat prior cancer from the average-risk category (reflected in the footnote section)
  - And/or a family history of
    - First-degree relative (parents, siblings, children) who has had CRC, adenoma or sessile serrated polyp
    - Familial adenomatous polyposis
    - Hereditary nonpolyposis colorectal cancer

How is “Average Risk” for CRC Defined? (continued)

- Certain factors associated with Western lifestyles are known to increase the risk of developing CRC. While assessment of these factors provides an important opportunity for lifestyle modification advice, their presence is not considered sufficient to elevate individuals beyond the average-risk category, and there is no evidence to support their use in stratifying subgroups of the population within the average-risk category.

- **Additional information on CRC risk factors:**
  - CRC Risk factors according to NCI (the most complete list, no direct evidence available, only associations). NCCN 2021 guideline update also includes low levels of Vitamin D association with increased risk for CRC. https://www.cancer.gov/types/colorectal/patient/colorectal-prevention-pdq
    - The following risk factors **increase** the risk of colorectal cancer:
      - Age
      - Family history of colorectal cancer
      - Personal history
      - Inherited risk
      - Alcohol
      - Cigarette smoking
      - Race
      - Obesity
  - The following *protective* factors **decrease** the risk of colorectal cancer:
    - Physical activity
    - Aspirin [The USPSTF has made a recommendation statement on aspirin use to prevent cardiovascular disease and colorectal cancer. As stated in Figure 1 of JAMA article]
    - Combination hormone replacement therapy
    - Polyp removal
  - It is **not clear** if the following affect the risk of colorectal cancer:
    - Nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin
    - Calcium
    - Diet
  - The following factors **do not affect** the risk of colorectal cancer:
    - Hormone replacement therapy with estrogen only
    - Statins

National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf

Definition of Average Risk for CRC by National Organizations

Organization	USPSTF 2021[1]	ACS 2018[2]	NCCN® 2021[a3]	MSTF 2017[4]
Personal History	• No history of CRC or adenomatous polyps • No history of IBD • No personal diagnosis of genetic disorders[ǂ] that predispose to high lifetime risk for CRC	• No history of CRC or adenomatous polyps • No personal history of abdominal or pelvic radiation for previous cancer • No history of IBD	• No history of CRC, adenoma, or sessile serrated polyp • No history of IBD	• No history of CRC or adenomas • No history of IBD
Family History	• No family history of genetic disorders that predispose to high lifetime risk of CRC[†]	• No family history of CRC • No confirmed or suspected hereditary CRC syndrome[†]	• Negative family history for CRC (≥ 1 FDR or SDR/TDRs with CRC at any age) or FDR with confirmed advanced adenoma* or sessile serrated polyps[Δ]	• No high-risk family history of colorectal neoplasia • No high-risk genetic polyp syndrome[§]

*High-grade dysplasia, ≥1 cm, villous or tubulovillous histology. [†]FAP or Lynch syndrome, [Δ]≥1 cm, any dysplasia.
[ǂ]High-risk syndromes: Lynch syndrome, polyposis syndromes (classical FAP, attenuated FAP, *MUTYH*-associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome, serrated polyposis syndrome, colonic adenomatous polyposis of unknown etiology), Cowden syndrome/PTEN hamartoma syndrome, Li-Fraumeni syndrome
[§]Lynch syndrome, family colon cancer syndrome X.

[a]All recommendations are category 2A unless otherwise indicated. NCCN makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way.

ACS: American Cancer Society, **CRC:** colorectal cancer, **IBD:** inflammatory bowel disease; **NCCN®:** National Comprehensive Cancer Network®, **MSTF:** United States Multi-Society Task Force on Colorectal Cancer, which includes the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), and the American Society for Gastrointestinal Endoscopy (ASGE); **USPSTF:** United States Preventive Services Task Force, **FRD:** first degree relative, **SDR:** second degree relative, **TDR:** third degree relative.

1. Davidson KW, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325(19):1965-1977. doi: 10.1001/jama.2021.6238. 2. Wolf AMD, et al. *CA Cancer J Clin*. 2018;68(4):250-281.3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology - colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. 4. Rex DK, et al. *Am J Gastroenterol*. 2017;112(7):1016-1030.

Definition of Average Risk for CRC by National Organizations

- National organizations agree that a person is at average risk for CRC if they have **no personal history** of adenomas or CRC or advanced adenomas.[1-4] According to NCCN Clinical Practice Guidelines in Oncology for colorectal cancer screening (NCCN Guidelines®), a personal history of sessile serrated polyps also confers increased risk for CRC.[3]
- According to NCCN and MSTF guidelines, a **family history** of CRC or advanced adenoma in a first-degree relative (parents, siblings, and offspring) increases the risk of CRC regardless of the relative's age at diagnosis.[3,4] The ACS defines increased risk as having a first-degree relative with onset of CRC younger than age 60 years.[2]
  - Advanced adenoma includes high-grade dysplasia, ≥1 cm, villous or tubulovillous histology
- Guidelines consistently exclude patients with IBD from the 'average risk' category, as inflammatory bowel conditions, including ulcerative colitis and Crohn's disease, are associated with an increased risk of CRC because chronic inflammation can lead to dysplasia and subsequent malignant conversion.[1] In addition, IBD may also cause false positives on stool-based screening tests due to inflammation-related bleeding.

1. Davidson KW, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325(19):1965-1977. doi: 10.1001/jama.2021.6238. 2. Wolf AMD, et al. *CA Cancer J Clin*. 2018;68(4):250-281.3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology - colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. 4. Rex DK, et al. *Am J Gastroenterol*. 2017;112(7):1016-1030.

Exclusion Criteria for mt-sDNA Pivotal Study

Background information on DeeP-C:

- The mt-sDNA pivotal study included individuals aged 50 years and older, but excluded individuals with any of the following:[5]
  - A personal history of CRC neoplasia or digestive cancer
  - A family history of CRC
  - IBD

Full exclusion criteria (Imperiale TF et al. *N Engl J Med*. 2014;370(14):1287-1297):

- Colonoscopy within the previous 9 years
- Any double-contrast barium enema, CT colonoscopy, or flexible sigmoidoscopy within the previous 5 years
- History of CRC, adenoma, or aerodigestive tract cancer
- Positive FOBT or FIT within the previous 6 months
- Prior colorectal resection for any reason other than sigmoid diverticular disease
- Overt rectal bleeding, eg, hematochezia or melena, within the previous 30 days
- Diagnosis or personal history of any condition associated with high risk for CRC, such as
  - Inflammatory Bowel Disease, including chronic ulcerative colitis and Crohn's disease
  - Familial adenomatous polyposis, including attenuated familial adenomatous polyposis
  - Hereditary nonpolyposis CRC syndrome (also referred to as Lynch syndrome)
  - Other hereditary cancer syndromes, including but not limited to Peutz–Jeghers Syndrome, MYH-associated polyposis, Gardner syndrome, Turcot (or Crail) syndrome, Cowden syndrome, juvenile polyposis, Cronkhite-Canada syndrome, neurofibromatosis and familial hyperplastic polyposis
  - ≥2 first-degree relatives (parents, siblings, or offspring) diagnosed with CRC
  - ≥1 first-degree relative diagnosed with CRC before age 60
- Family history of familial adenomatous polyposis or hereditary nonpolyposis CRC syndrome (eg, hereditary nonpolyposis CRC syndrome/Lynch syndrome

Imperiale TF et al. *N Engl J Med*. 2014;370(14):1287-1297

Risk Factors Associated with Increased Risk for CRC

The Following Factors May Be Considered When Estimating CRC Risk for Average-risk Individuals But These Alone Do Not Elevate People Beyond the Average-risk Category[1-4]:

Cigarette smoking

Lack of physical activity

Diabetes

Moderate to high consumption of alcohol and/or long-term consumption of red and processed meat

Excess body weight

Low consumption of fiber, calcium, fruits, and vegetables

CRC: colorectal cancer..

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology - colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. 2. Wolf AMD, et al. *CA Cancer J Clin*. 2018;68(4):250-281. 3. Rex DK, et al. *Am J Gastroenterol*. 2017;112(7):1016-1030. 4. Davidson KW, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325(19):1965-1977. doi: 10.1001/jama.2021.6238.

Definition of High Risk for CRC by National Organizations

Organization	USPSTF 2021[1]	ACS 2018[2]	NCCN® 2021[a3]	MSTF 2017/2018[4,5]
Personal History	• Adenomatous polyps, CRC, IBD	• Adenomatous polyps, CRC, IBD, abdominal/pelvic radiation for cancer	• Adenoma, SSP, CRC, IBD	• Adenomatous polyps, CRC, IBD
Family History	• Not reviewed	• CRC or adenomatous polyps in relative aged <60 years	• ≥ 1 FDR or SDR/TDRs with CRC at any age) • FDR with confirmed advanced adenoma or SSP	• 1 first-degree relative with • CRC/AA at age • <60 years or 2 first-degree relatives with CRC/AA at any age
Familial Cancer Syndromes	• Genetic disorders that predispose to CRC (e.g., Lynch Syndrome or familial adenomatous polyposis)	• Confirmed or suspected hereditary CRC syndrome	• Lynch syndrome • Polypopsis syndromes* • Cowden syndrome/ PTEN hamartoma tumor syndrome • Li-Fraumeni syndrome	• Lynch syndrome • Family colon cancer syndrome X

*High-grade dysplasia, ≥1 cm, villous or tubulovillous histology, ▵≥1 cm, any dysplasia.

*Classical/attenuated familial adenomatous polyposis, MUTYH-associated polyposis, Peutz-Jeghers syndrome, Juvenile polyposis syndrome, serrated polyposis syndrome, colonic adenomatous polyposis of unknown etiology.

[a]All recommendations are category 2A unless otherwise indicated. NCCN makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way.

AA: adenoma, **ACS:** American Cancer Society, **CRC:** colorectal cancer, **IBD:** inflammatory bowel disease, **NCCN:** National Comprehensive Cancer Network, **SSP:** sessile serrated polyp, **MSTF:** United States Multi-Society Task Force on Colorectal Cancer, which includes the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), and the American Society for Gastrointestinal Endoscopy (ASGE), **USPSTF:** United States Preventive Services Task Force, **FRD:** first degree relative, **SDR:** second degree relative, **TDR:** third degree relative.

1. Davidson KW, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325(19):1965-1977. doi: 10.1001/jama.2021.6238. 2. Wolf AMD, et al. *CA Cancer J Clin*. 2018;68(4):250-281.3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology - colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. 4. Rex DK, et al. *Am J Gastroenterol*. 2017;112(7):1016-1030. 5. Levin B, et al. *Gastroenterology*. 2008;134(5):1570-1595.

Definition of High Risk for CRC by National Organizations

- Guidelines consistently define individuals who have a personal history of adenoma, CRC, or IBD as being at high risk of developing future CRC.[1-5]
- In general, national organizations agree that a family history of CRC or advanced adenoma in a first-degree relative places an individual in the high-risk category, particularly if that relative was diagnosed younger than age 60 years.[1-3]
- ACS guidelines state that any confirmed or suspected hereditary CRC syndrome places an individual at high risk,[2] while guidelines from other organizations list particular syndromes, such as Lynch syndrome or polypopsis syndromes.[1,3,5]

1. Davidson KW, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325(19):1965-1977. doi: 10.1001/jama.2021.6238. 2. Wolf AMD, et al. *CA Cancer J Clin*. 2018;68(4):250-281.3. National Comprehensive Cancer Network. Clinical practice guidelines in oncology - colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. 4. Rex DK, et al. *Am J Gastroenterol*. 2017;112(7):1016-1030. 5. Levin B, et al. *Gastroenterology*. 2008;134(5):1570-1595.

CRC Screening Recommendations for Average- vs High-Risk

Based on current recommendations from national organizations[1-4]:

Average Risk	High Risk
• No personal history of CRC, adenomas, sessile serrated polyps or IBD • No family history of CRC or advanced adenomas • No hereditary CRC syndromes	• Personal history of CRC, adenomas, sessile serrated polyps or IBD • First-degree relative with CRC or advanced adenomas or sessile serrated polyps at any age • Confirmed or suspected CRC syndromes
Begin screening at age 45–50 years using methods and frequencies detailed in screening guidelines[1-4]	Screen following schedules recommended in guidelines for each specific high-risk condition[1,5-6]

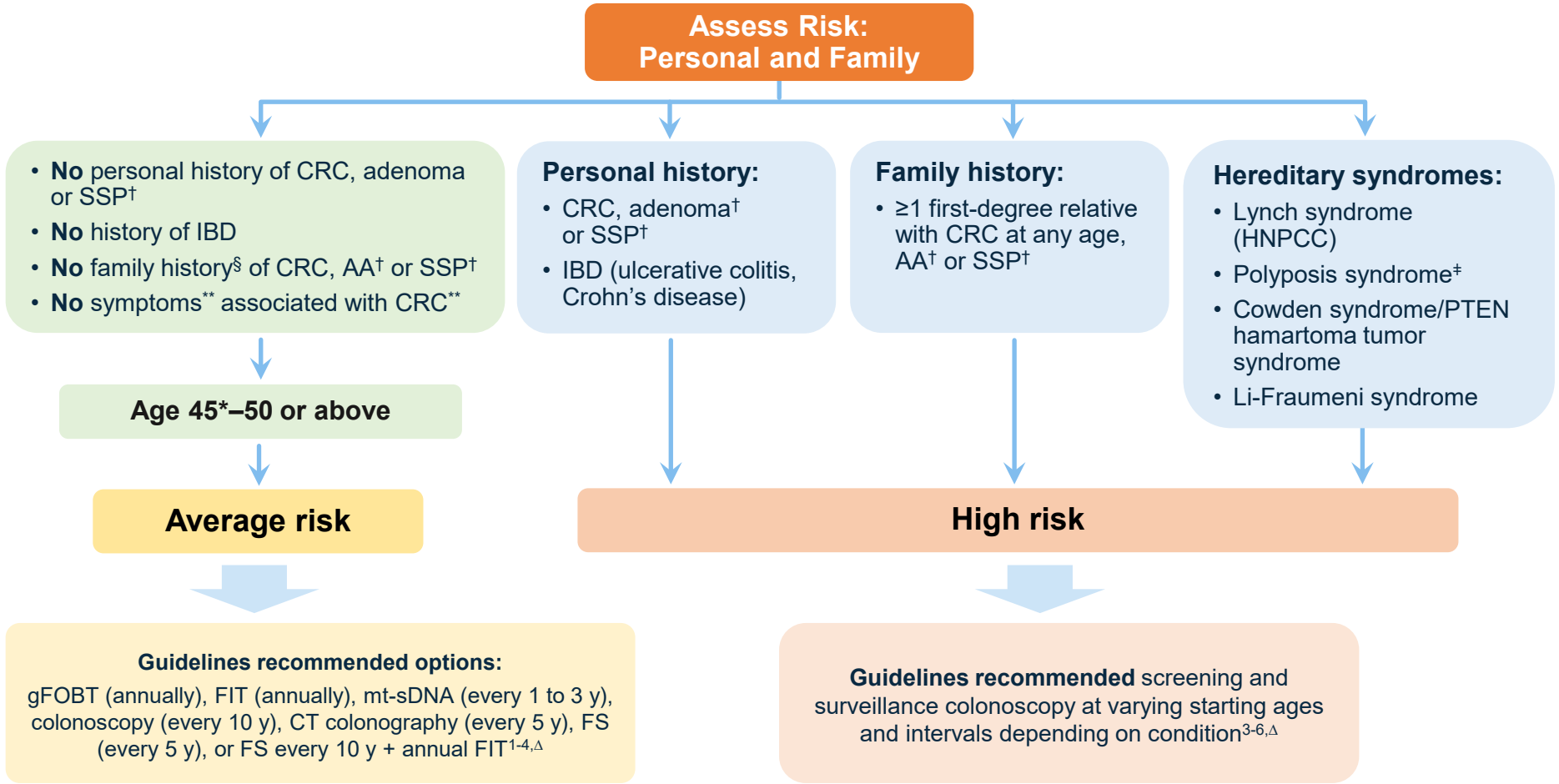
CRC: colorectal cancer, **IBD:** inflammatory bowel disease.

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology - colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. 2. Wolf AMD, et al. *CA Cancer J Clin*. 2018;68(4):250-281.
3. Rex DK, et al. *Am J Gastroenterol*. 2017;112(7):1016-1030. 4. Davidson KW, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325(19):1965-1977. doi: 10.1001/jama.2021.6238. 5. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2020). Accessed April 2, 2021. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
6. Gupta et al. *Gastroenterology*. 2020; DOI:10.1053/j.gastro.2019.10.026.

CRC Screening Recommendations for Average- vs High-Risk

- To summarize, the definition of ‘average risk’ for CRC used by National Organizations generally encompasses individuals with no personal history of CRC, adenomas, or IBD, no family history of CRC or advanced adenomas, and no evidence of hereditary CRC syndromes.[1-4]
  - Individuals meeting the criteria for ‘average risk’ should begin CRC screening at age 45-50 years according to the recommended methods and schedules detailed in the previous section ‘CRC Screening Guideline Recommendations’.
- Individuals deemed at high risk of CRC should be offered screening and surveillance according to recommendations given in specific guidelines.

1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology - colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. 2. Wolf AMD, et al. *CA Cancer J Clin*. 2018;68(4):250-281.
3. Rex DK, et al. *Am J Gastroenterol*. 2017;112(7):1016-1030. 4. Davidson KW, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325(19):1965-1977. doi: 10.1001/jama.2021.6238. 5. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2020). Accessed April 2, 2021. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
6. Gupta et al. *Gastroenterology*. 2020; DOI:10.1053/j.gastro.2019.10.026.



CRC: Colorectal Cancer, **IBD:** Inflammatory Bowel Disease, **SSP:** Sessile Serrated Polyp, **FAP:** Familial Adenomatous Polyposis, **AA:** Advanced Adenoma, **HNPCC:** hereditary nonpolyposis CRC

§**First Degree Relative** (parents, siblings, and children)

†**Advanced adenoma** (high-grade dysplasia ≥ 10mm, villous or tubulovillous histology) or advanced SSP (≥ 10mm, any dysplasia)

Sx/sx of CRC: iron deficiency anemia, rectal bleeding, abdominal pain, or change in bowel habits

‡**Polyposis Syndromes:** Classical familial adenomatous polyposis (FAP), Attenuated FAP (AFAP), MUTYH-associated polyposis (MAP), Peutz-Jeghers syndrome (PJS), Juvenile polyposis syndrome (JPS), Serrated polyposis syndrome (SPS), Rare genetic causes of multiple adenomatous polyps

*ACS: CRC screening starting at age 45 is a qualified recommendation. Individualized decision for screening at ages 76–85 years, consideration based on patient preference, life expectancy, overall health, and prior screening history (*qualified* recommendation). USPSTF: The USPSTF concludes with moderate certainty that there is a moderate net benefit of starting screening for colorectal cancer in adults aged 45 to 49 years (Grade B recommendation)

ΔAll recommendations are category 2A unless otherwise indicated. The National Comprehensive Cancer Network (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way

1. Davidson KW, et al. *JAMA.* 2021;325(19):1965-1977. doi:10.1001/jama.2021.6238 2. Wolf AMD, et al. *CA Cancer J Clin*. 2018;68(4):250-281. doi:10.3322/caac.21457 3. NCCN Clinical Practice Guidelines in Oncology. Colorectal cancer screening. Version 2.2021. Updated April 13, 2021. Accessed April 19, 2021. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf 4. Rex DK, et al. *Am J Gastroenterol*. 2017;112(7):1016-1030. doi:10.1038/ajg.2017.174 5. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2021). Updated May 11, 2021. Accessed August 17, 2021. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf 6. Gupta S, et al. *Gastroenterol*. 2020;158(4):1131-1153.e5. doi:10.1053/j.gastro.2019.10.026