National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colorectal Cancer Screening

Version 1.2022 — March 4, 2022

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Colorectal Cancer Screening

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NCCN Guidelines Panel Disclosures

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Colorectal Cancer Screening

For High-Risk Colorectal Cancer Syndromes,
see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
For Principles of Cancer Risk Assessment and Counseling,
see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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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.

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Updates in Version 1.2022 of the NCCN Guidelines for Colorectal Cancer Screening from Version 2.2021 include:

Table of contents
- General
  - Removed: Definitions of Common Colorectal Resections (CSCR-B)

CSCR-PREV 1 of 2
- Lifestyle/dietary factors associated with reduced CRC risk/recurrence:
  - Bullet 3 modified: *Dietary supplements*: In general, nutrients should be obtained from natural food sources rather than solely from dietary supplements.
  - Bullet 4 modified: *Smoking cessation:* Smoking cessation counseling is strongly recommended. See NCCN Guidelines for Smoking Cessation.
- Lifestyle/dietary factors associated with increased CRC risk:
  - Bullet 1 modified: Smoking: Long-term cigarette smoking is associated with *increased CRC incidence and mortality* ~~after controlling for screening, multiple risk factors, and mortality~~. Risk reduction is seen with early smoking cessation.

CSCR-1
- Average risk
  - Sub-bullets removed:
    - ◊ ~~The data supporting lowering the age to initiate screening are largely from modeling studies.~~
    - ◊ ~~The incidence of CRC in individuals <50 years has increased 22% between 2003 and 2013.f Between 1992 and 2015 there was a relative increase of 30% in the incidence of CRC in 40 year olds. However, this translates into an absolute difference in incidence of 8.2 cases per 100,000.b~~
    - ◊ ~~We currently lack empirical data to support screening in those <50 years, as screening studies in average-risk individuals have been limited to those aged ≥50 years.~~
  - Sub-bullet 4 modified: ~~Considerations for the age to initiate CRC screening may be dependent on race/ethnicity, patient preference, and resources available.~~ Because there are multiple options for screening, the choice of a particular screening modality should include a conversation with the patient concerning their preference and availability.
  - Bullet 4 added: No personal history of high-risk CRC genetic syndromes
  - Bullet 7 modified: *Negative family history for* confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) or an advanced SSP (≥1 cm, any dysplasia) *in first-degree relatives.*
- Increased risk
  - Sub-bullet 3 modified: IBD (ulcerative colitis, Crohn's ~~disease~~ colitis)
  - Bullet 3 added: Cystic fibrosis
  - Footnote modified: The panel has reviewed existing data for beginning screening of average-risk individuals at age <50 years. 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.*
  - Footnote removed: Stoffel EM, et al. Gastroenterology 2020;158:341-353.
  - Footnote removed: ~~Levine O, et al. Pediatr Blood Cancer 2019;66:e27941. Pearlman R, et al. JAMA Oncol 2017;3:464-471.~~
  - Footnote added: Ochs-Balcom HM, et al. Cancer Epidemiol-2021;73:101973.

CSCR-2
- Average risk
  - Evaluation of alarm symptoms in patients <45 years:
    - ◊ *Half of the patients who present with early-onset CRC are <45 years of age. Many have* signs and symptoms of CRC such as iron deficiency anemia, rectal bleeding, or a change in bowel habits presenting in individuals <45 years warrant prompt evaluation with a colonoscopy ~~or at least with flexible sigmoidoscopy.~~
  - Bullet 1 removed: ~~Half of the patients who present with early-onset CRC are <45 years of age. The incidence of CRC in individuals <50 years has increased 22% between 2003 and 2013.~~
  - Bullet 2 modified: The majority of *early onset* CRC~~s~~ *appears to be sporadic. Nonetheless,* the possibility of an inherited cancer syndrome should be investigated given the higher incidence of inherited CRC syndromes in younger compared to older patients. ~~in these younger individuals appear to be sporadic but an inherited cancer syndrome should be ruled out given the higher incidence of inherited CRC syndromes in younger patients when compared to older patients.~~
  - ~~High-risk syndromes~~ *Hereditary Syndromes with Predisposition to Colorectal Cancer:*
  - Sub-bullet removed: Colonic adenomatous polyposis of unknown etiology
  - Footnote removed*:* ~~Levine O, et al. Pediatr Blood Cancer 2019;66:e27941. Pearlman R, et al. JAMA Oncology 2017;3:464-471.~~
  - Footnote removed: Siegel RL, et al. CA Cancer J Clin 2017;67:177-193.

CSCR-3
- Evaluation of screening findings after positive stool based testing modified: Colonoscopy in *6–12* months

CSCR-3A
- Footnotes modified:
  - Footnote n: When a screening stool-based test is positive, a colonoscopy is recommended for further evaluation. Recommendations for an appropriate time frame for followup 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. ~~Thus, we recommend that follow-up colonoscopy is completed ideally within 6 to 10 months after an abnormal stool-based test.~~ (Corley DA, et al. JAMA 2017;317:1631-1641; *Forbes N, et al. Clin Gastro Hepatol 2020)*
  - Footnote o: If the colonoscopy is negative after a FIT or mt-sDNA and no ~~additional~~ symptoms are present, there is no need for further tests *prior to the next recommended screening interval.*
  - Footnote p: ~~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.~~ *If >20 serrated polyps are found at colonoscopy, consider a diagnosis of serrated polyposis syndrome. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.* ~~*Guideline*~~ *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.*
  - Footnote q: There are limited data to support whether individuals with hyperplastic

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Continued

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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. For this reason, it is reasonable to follow patients with hyperplastic polyps ≥1 cm in size similarly to patients with SSPs, particularly if they have not been reviewed by an expert gastrointestinal pathologist. *Anderson JA, et al. Gastrointest Endosc 2020;92:387-393.*

- Footnote r: 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.*

CSCR-4
- Clinical findings, high risk, bullet 4 modified: Between 3 and ~~10~~ *9* adenomatous polyps and/or SSPs
- Pathways for ≥10 adenomatous polyps and/or SSP in a single colonoscopy, and ≥20 cumulative adenomatous polyps and/or SSP have been significantly revised.

CSCR-5
- Footnote u modified: *Consider testing for 10-19 cumulative adenomas if other factors suggest the possibility of a polyposis/colorectal cancer syndrome such as age of onset, family orpersonal history of colorectal cancer.* Ten or fewer polyps in the setting of a strong family history or younger age (<40 years) may sometimes be associated with aninherited polyposis syndrome.
- Footnote removed:
  - Consider a referral to a center of expertise for large polyp management. For sessile polyps or LSL ≥20 mm size, recommend endoscopic tattoo placement for future lesion identification
- Footnote w modified:
  - Available data suggest that individuals with low-risk adenomas or SSPs 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.*
- Footnote x modified:
  - If genetic testing is negative or ~~if evaluation~~ *it* 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.*

CSCR-6
- Clinical Findings
  - Pathway after high-risk endoscopic features for invasive cancer modified: *Biopsy.*
- Follow-up of clinical findings
  - No invasive cancer after incomplete resection or biopsy: ~~Referral for surgical evaluation OR Referral to center with expertise in management of large colorectal polyps~~ *Referral to center with expertise in management of large colorectal polyps OR referral for surgical evaluation*

CSCR-6A
- Footnotes
  - Footnote cc modified: Paris subtype 0–IIa, 0–IIb, 0–IIc, *0-III* lesions. The Panel recommends consideration of referral to a center of expertise for management of these lesions.
  - Footnote gg added: Consider follow-up <3 y when polyp(s) is >2 cm or confidence of complete en bloc resection is low.

CSCR-7
- Header modified: Diagnosis of colorectal cancer ~~increased risk based on personal history of colorectal cancer risk status testing/surveillance~~

CSCR-8
- Surveillance Modality and Schedule
  - Bullet 2 modified: Chromoendoscopy *(dye spray or high-definition virtual)* with targeted biopsies, including extensive sampling of strictures or masses (high-definition colonoscopy is suggested, if available).
  - Footnotes
    - ◊ Footnote kk modified: If PSC is present, annual surveillance colonoscopies should be started independent of the individual's time since symptom onset or colonoscopic findings and insteadshould 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 maybenefit from earlier initiation of colonoscopic surveillance. Samadder NJ, et al. Clin Gastroenterol Hepatol 2019;17:1807-1813. *Shergill AK, et al. Gastrointest EndoscClin N Am 2014;24:469-481*
    - ◊ Footnote removed: Shergill AK, et al. Gastrointest Endosc Clin N Am 2014;24:469-481.

CSCR-9
- Follow-up of Clinical Findings
  - Incomplete endoscopic resection, bullet 3 modified: ~~Consider surgical consultation, particularly if felt not amenable to complete endoscopic resection at center with expertise in IBD and experience in endoscopic management of large colorectal lesions~~. *Consider referral to a surgeon with expertise in IBD*

CSCR-10
- Evaluation of Surveillance Findings modified: No dysplasia ~~(no invisible dysplasia, polypoid/ nonpolypoid lesion or mass)~~
  - Follow-up of Clinical Findings, no dysplasia pathway modified
    - ◊ Low risk: ~~Left-sided disease~~
    - ◊ High risk: ~~Extensive colitis~~
  - The pathway for colon stricture has been extensively revised.

CSCR-11
- New page: Increased Risk Based on Personal History of Cystic Fibrosis

CSCR-12
- Header modified: 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)*
- Family history criteria:
  - First-degree relative with confirmed advanced adenoma(s) (ie, high-grade dysplasia, ≥1

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cm, villous or tubulovillous histology, TSA), or advanced SSPs *at any age* (≥1 cm, any dysplasia) *at any age.*

- Screening:
  - Second- and third-degree relatives with CRC at any age: Colonoscopy beginning at age 45~~-50~~
- Footnotes:
  - Footnote yy modified: Current risk estimates for a family history of CRC in only second- and third- degree relatives are not sufficiently elevated to recommend increased screening. *There is 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 Epidemiology. 2021;73 101973* ~~Furthermore, some data indicate that the overwhelming majority of all cancers in those with only a second-degree relative are diagnosed after age 50.~~ 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.* ~~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:l803.~~
  - Footnote removed: For individuals not willing to undergo colonoscopy, there are emerging data that FIT may be a reasonable substitute. Quintero E, et al. Gastroenterology 2014;147:1021-1030.

CSCR-A 1 of 5

- Bullet 2 modified: 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 and for repeat screening and surveillance intervals.~~*and 5) follow-up of those with a positive test. The program should also include a systematic method for the arranging of repeat screening and surveillance.*

CSCR-A 2 of 5

- Screening Modality and Schedule table updated.

CSCR-A 4 of 5

- Colonoscopy, sub-bullet 4 modified: Photographic documentation of endoscopic landmarks, including the ileocecal valve, the appendiceal orifice, and *retroflexed view of rectum if intact/ technically feasible*
- Stool-based screening
  - Bullet 2 modified: ~~Any positive test requires further evaluation.~~ I*f a stool-based screening test is positive, colonoscopy should be recommended.* Recommendations for an appropriate time frame for follow-up colonoscopy in this population lack a strong evidence base, but a large observational study 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. Thus, we recommend that follow-up colonoscopy is completed ideally within 6 to 10 months after an abnormal stool-based test (Corley DA, et al. JAMA 2017;317:1631-1641; Forbes N, et al. Clin Gastro Hepatol 2020).
- FIT/mt stool DNA-based testing
  - Bullet 1 added: This modality is only FDA approved for average risk individuals of average risk
  - Bullet 8 modified: If the colonoscopy is negative after a FIT or mt-sDNA and no *additional* symptoms are present, there is no need for further tests.

CSCR-A 5 of 5

- CTC, Follow-up of identified lesions
  - Sub-bullet 1 modified: Data on optimal frequency, polyp size leading to colonoscopy referral, and protocol for evaluation of extracolonic lesions are evolving. The ACR has recommended that reporting of polyps <5 mm in size is not necessary. If polyp(s) of this size are reported, the decision to refer for colonoscopy with polypectomy versus surveillance ~~colonoscopy~~ *CTC* should be individualized.
  - Sub-bullet 2 removed: When identified, lesions ≤5 mm do not need to be reported or referred for colonoscopy.

CSCR-GLOS 1 of 6

- Crohn's disease: *Chronic* ~~Idiopathic~~ inflammatory disorder that may affect the entire GI tract. ~~; begins in late adolescence or young adulthood and continues throughout life~~
- Inflammatory bowel disease: Comprised of ulcerative colitis ~~and~~ *or* ~~CD~~ Crohn's disease
- ~~Proctitis: Inflammation in the lining tissue of the inner rectum.~~
- ~~Proctosigmoiditis: Chronic inflammation of the rectum and sigmoid.~~
- Ulcerative colitis: ~~Idiopathic cC~~ *C*hronic inflammatory ~~bowel disease~~ *disorder of* ~~involving~~ the colon.~~; begins in young adulthood and continues throughout life~~

CSCR-GLOS 2 of 6

- Adenoma: Noninvasive neoplastic ~~and benign~~ lesion of the columnar epithelium.

CSCR-GLOS 3 of 6

- Hyperplastic polyps: ~~Have little or no potential for transformation to neoplastic lesions;15 according to WHO classification of Digestive System Tumors,23 the diagnostic criteria for HPs include:~~
  - ~~Upper (luminal) portion of polyp has funnel-shaped crypts with serrations that give it a "saw-tooth" appearance~~
  - ~~Crypts are typically elongated, straight, and narrow23,24~~
  - ~~Nuclei are small, regular, round, and basally located in luminal half of crypt23~~
  - ~~Proliferative zone of HPs located uniformly in the basal portion of crypts23~~
- *Hyperplastic polyps are serrated polyps with normal crypt architecture andproliferative characteristics*

CSCR-GLOS 5 of 6

- Reference removed: Abdulrazeg O, Li B, Epstein J, Guideline C. Management of ulcerative colitis: summary of updated NICE guidance. BMJ 2019;367:l5897.
- Reference added: Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315-1329; quiz 1314, 1330.

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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 for average-risk individuals, 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.[1]**
- **Fruits and vegetables: A diet high in fruits and vegetables has been associated with decreased CRC risk in some studies.[2,3]**
- **Dietary supplements: In general, nutrients should be obtained from natural food sources rather than solely from dietary supplements.[1]**
- **Smoking cessation: Smoking cessation counseling is strongly recommended. See NCCN Guidelines for Smoking Cessation.**

Aspirin:
- **There is substantial evidence about the protective effect of aspirin for CRC development when taken for at least 5–10 years.[4,5]**
  - ◊ **The U.S. Preventive Services Task Force endorses low-dose aspirin (81 mg) intake for individuals ages 45–59 with a ≥10% 10-year cardiovascular risk for the purposes of lowering both cardiovascular and CRC risk.**
  - ◊ **The decision to offer aspirin should take into consideration risk of bleeding, life expectancy, and long-term compliance.[6] The optimal dose has not been well established.**
  - ◊ **Regarding secondary prevention, aspirin use has been associated with improved CRC-specific survival and overall survival.[7]**

Lifestyle/dietary factors associated with increased CRC risk:
- **Smoking: Long-term cigarette smoking is associated with increased CRC incidence and mortality.[8,9] Risk reduction is seen with early smoking cessation.[9]**
- **Red meat and processed meat: Long-term consumption is associated with increased CRC risk.[1,10]**
- **Moderate to heavy alcohol consumption: This level of consumption is associated with increased CRC risk.[1,11,12]**
- **Obesity: Obesity is associated with an increased risk for CRC.[1,13,14,15]**
- **Vitamin D: Low levels of vitamin D have been associated with increased CRC risk.[16]**

Please also see relevant sections in:
- **NCCN Guidelines for Colon Cancer - Principles of Survivorship**
- **NCCN Guidelines for Survivorship**

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REFERENCES

[1]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 colorectal cancer.
[2]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.
[3]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.
[4]Chubak J, Kamineni A, Buist DS, et al. Aspirin use for the prevention of colorectal cancer: An updated systematic evidence review for the U.S. Preventive Services Task Force. In: Quality AfHRa ed. Vol. Evidence Synthesis No. 133. Rockville, MD; 2015.
[5]Chubak J, Whitlock EP, Williams SB, et al. Aspirin for the prevention of cancer incidence and mortality: Systematic evidence reviews for the U.S. Preventive Services Task Force. Ann Intern Med 2016;164:814-825.
[6]U.S. Preventive Services Task Force. Final Recommendation Statement: Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Preventive Medication. 2017.
Available at: https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer.
[7]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.
[8]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.
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[10]Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. Lancet Oncol 2015;16:1599-1600.
[11]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.
[12]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.
[13]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.
[14]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.
[15]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.
[16]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/Iarc-Working-Group-Reports/Vitamin-D-And-Cancer-2008.

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RISK ASSESSMENT FOR COLORECTAL CANCER

Average risk:

- Age ≥45 years[a]
  - Because there are multiple options for screening, the choice of a particular screening modality should include a conversation with the patient concerning their preference and availability.
- No personal history of adenoma or sessile serrated polyp (SSP)[b] or CRC
- No personal history of inflammatory bowel disease (IBD)
- No personal history of high-risk CRC genetic syndromes
- No personal history of cystic fibrosis
- Negative family history for CRC in first-, second-, or third-degree relatives
- Negative family history for confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) or an advanced SSP[b,c] (≥1 cm, any dysplasia) in first-degree relatives.[d]

→ See Average-Risk Screening and Evaluation (CSCR-3)

Increased risk:

- Personal history
  - Adenoma or SSP[b] → See Follow-up of Clinical Findings: Polyp Found at Colonoscopy (CSCR-5)
  - CRC → Diagnosis of Colorectal Cancer (CSCR-7)
  - IBD (ulcerative colitis, Crohn's colitis) → See Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease (CSCR-8)
  - Cystic fibrosis → See Increased Risk Based on Personal History of Cystic Fibrosis (CSCR-11)
- Positive family history → See Increased Risk Based on Positive Family History (CSCR-12)

[a] The panel has reviewed existing data for beginning screening of average-risk individuals at age <50 years. 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.

[b] The terms sessile serrated polyp (SSP) and sessile serrated adenoma are synonymous; SSPs are a type of serrated polyp that are not dysplastic but they can develop foci of dysplasia and are then termed SSP with dysplasia (SSP-d). These guidelines will use "SSP" for SSPs without dysplasia and "SSP-d" for SSPs with dysplasia. In general SSPs are managed like tubular adenomas and SSP-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: IARC Lyon, France; 2019:162-169). See CRC-GLOS.

[c] Advanced SSPs are generally considered to have a comparable cancer risk and are managed similarly to advanced adenomas, rather than high-risk adenomas, a definition which includes multiplicity.

[d] Ochs-Balcom HM, et al.Cancer Epidemiol 2021;73:101973.

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RISK ASSESSMENT FOR COLORECTAL CANCER (CONT.)

Evaluation of alarm symptoms in patients <45 years:
Half of the patients who present with early-onset CRC (<50 years of age) are <45 years of age[e] and many have signs and symptoms of CRC such as iron deficiency anemia, rectal bleeding, or a change in bowel habits. Individuals with these symptoms warrant prompt evaluation with a colonoscopy regardless of age unless they recently underwent colonoscopy.

- **The majority of early-onset CRCs appears to be sporadic. Nonetheless, the possibility of an inherited cancer syndrome should be investigated given the higher incidence of inherited CRC syndromes in younger compared to older patients.**

High-risk genetic syndromes with predisposition to colorectal cancer:

- **Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC])**
- **Polyposis syndromes**
  - **Classical familial adenomatous polyposis**
  - **Attenuated familial adenomatous polyposis**
  - ***MUTYH*-associated polyposis**
  - **Peutz-Jeghers syndrome**
  - **Juvenile polyposis syndrome**
  - **Serrated polyposis syndrome (rarely inherited)**
- **Cowden syndrome/PTEN hamartoma tumor syndrome**
- **Li-Fraumeni syndrome**

→ **See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal**

→ **See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic**

[e] Stoffel EM, et al. Gastroenterology 2020;158:341-353.

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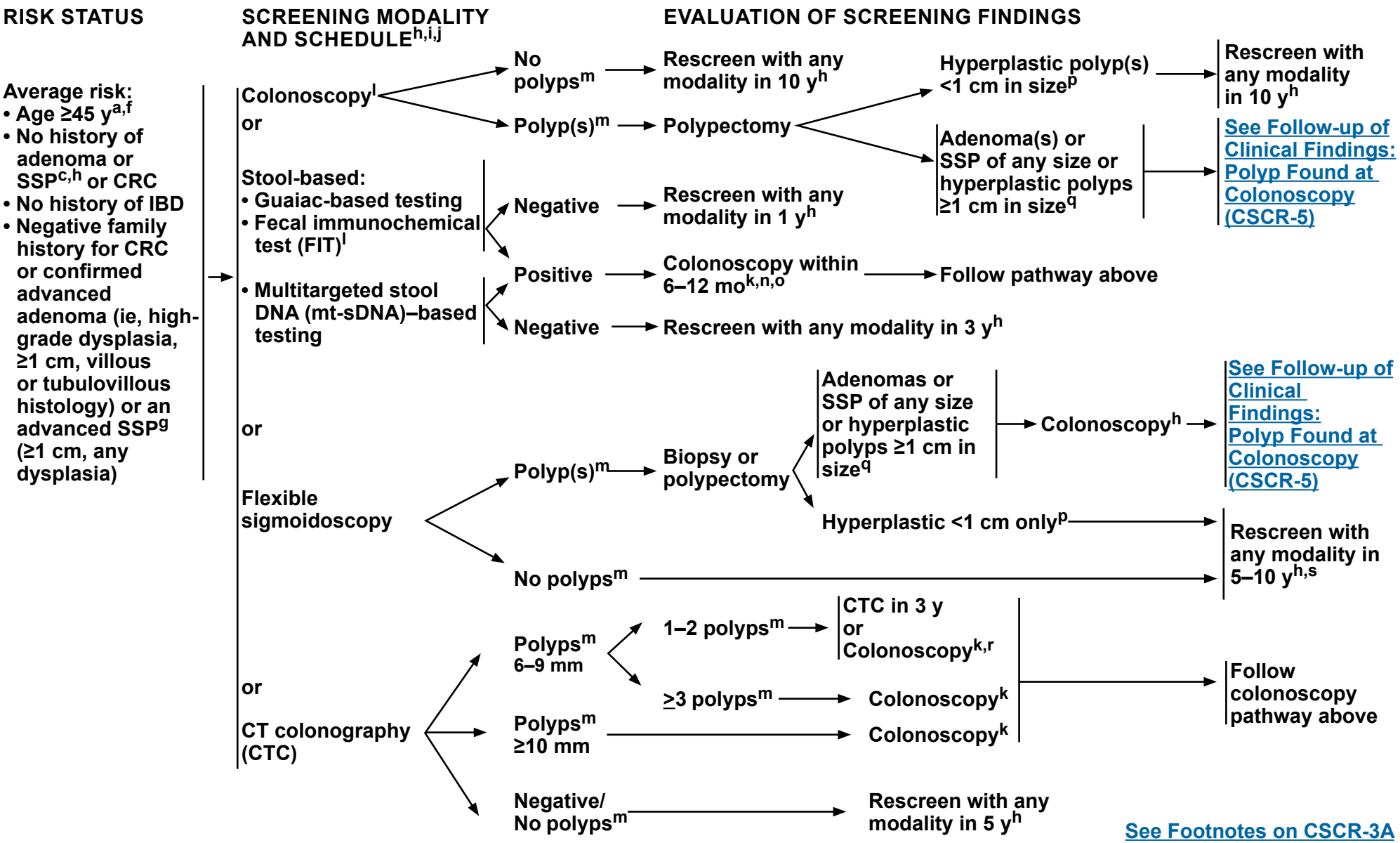

See Footnotes on CSCR-3A

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FOOTNOTES

[a] The panel has reviewed existing data for beginning screening of average-risk individuals at age <50 years. 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.

[c] Advanced SSPs are generally considered to have a comparable cancer risk and are managed similarly to advanced adenomas, rather than high-risk adenomas, a definition which includes multiplicity.

[f] 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.

[g] For details on classification, see footnote b on CSCR-1. For definition of commonly used terms, see CRC-GLOS-1.

[h] See Screening Modality and Schedule (CSCR-A).

[i] 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.

[j] Screening should be individualized and include a discussion of the risks and benefits of each modality.

[k] If colonoscopy is incomplete or the preparation is suboptimal, consider either repeating colonoscopy within a year or screening with another modality (Johnson DA, et al. Gastroenterology 2014;147:903-924).

[l] 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; Scholefield JH, et al. Gut 2012;61:1036-1040).

[m] The term “polyp” refers to both polyp and nonpolypoid (flat) lesions.

[n] 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).

[o] If the colonoscopy is negative after a FIT or mt-sDNA and no symptoms are present, there is no need for further tests prior to the next recommended screening interval.

[p] If >20 serrated polyps are found at colonoscopy, consider a diagnosis of serrated polyposis syndrome (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). 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.

[q] 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 re-classified as SSPs 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, particularly if they have not been reviewed by an expert gastrointestinal pathologist. Anderson JA, et al. Gastrointest Endosc 2020;92:387-393.

[r] 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.

[s] There are alternative strategies that have been recommended with flexible sigmoidoscopy, including flexible sigmoidoscopy every 10 years with annual FIT or considering longer interval flexible sigmoidoscopy without FIT (Knudsen AB, et al. AMA 2016;315:2595-2609).

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NCCN Guidelines Version 1.2022
Colorectal Cancer Screening

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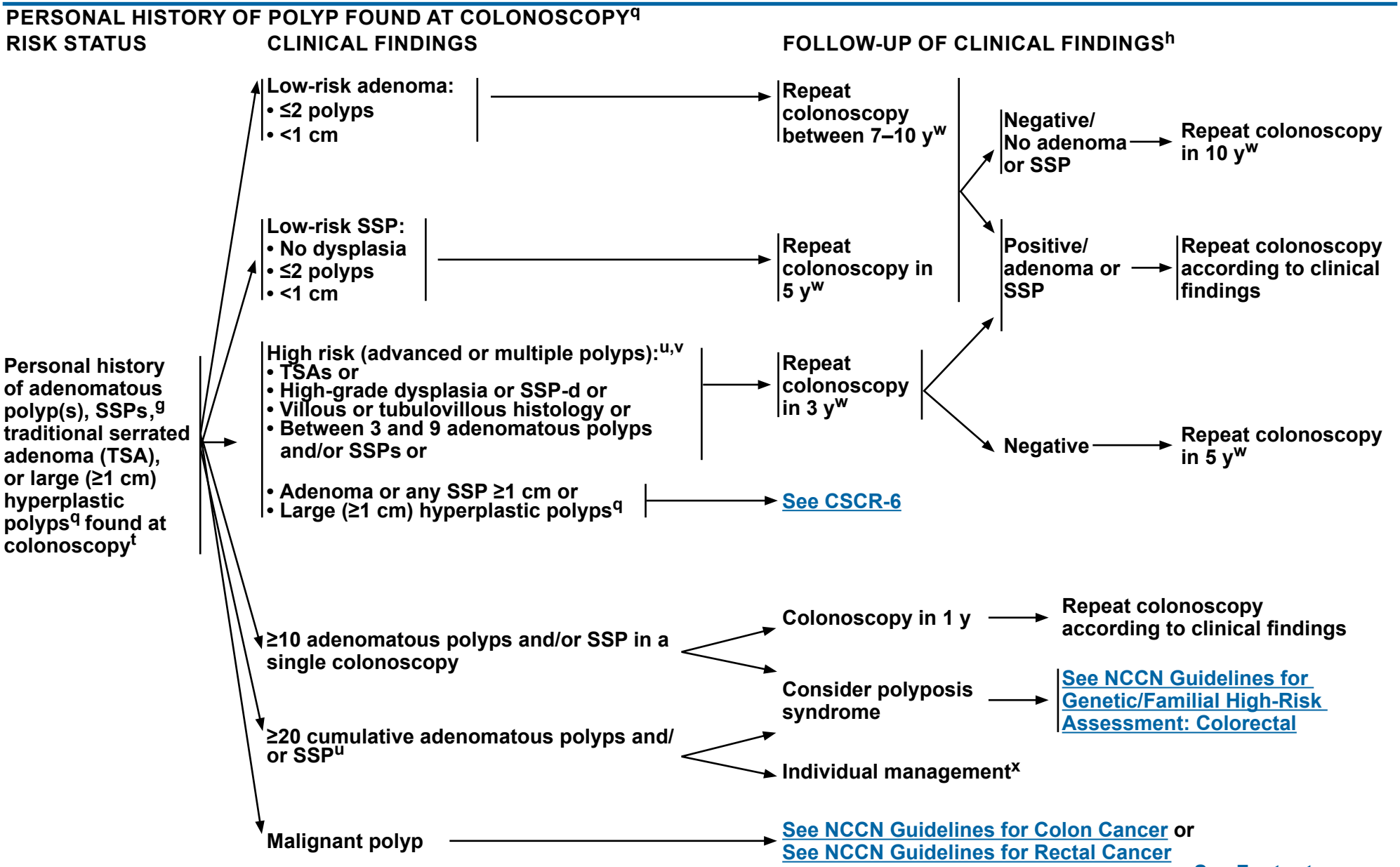
Discussion



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See Footnotes on CSCR-5

FOOTNOTES

[g] For details on classification, see footnote b on CSCR-1. For definition of commonly used terms, see CRC-GLOS-1.

[h] See Screening Modality and Schedule (CSCR-A).

[q] 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 re-classified as SSPs 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, particularly if they have not been reviewed by an expert gastrointestinal pathologist. Anderson JA, et al. Gastrointest Endosc 2020;92:387-393.

[t] 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.

[u] Consider testing for 10–19 cumulative adenomas if other factors suggest the possibility of a polyposis/colorectal cancer syndrome such as age of onset or family or personal history of colorectal cancer. Ten 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.

[v] Surveillance intervals assume complete resection, adequate bowel preparation, and complete examination.

[w] Available data suggest that individuals with low-risk adenomas or SSPs 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.

[x] If genetic testing is negative or if evaluation it 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.

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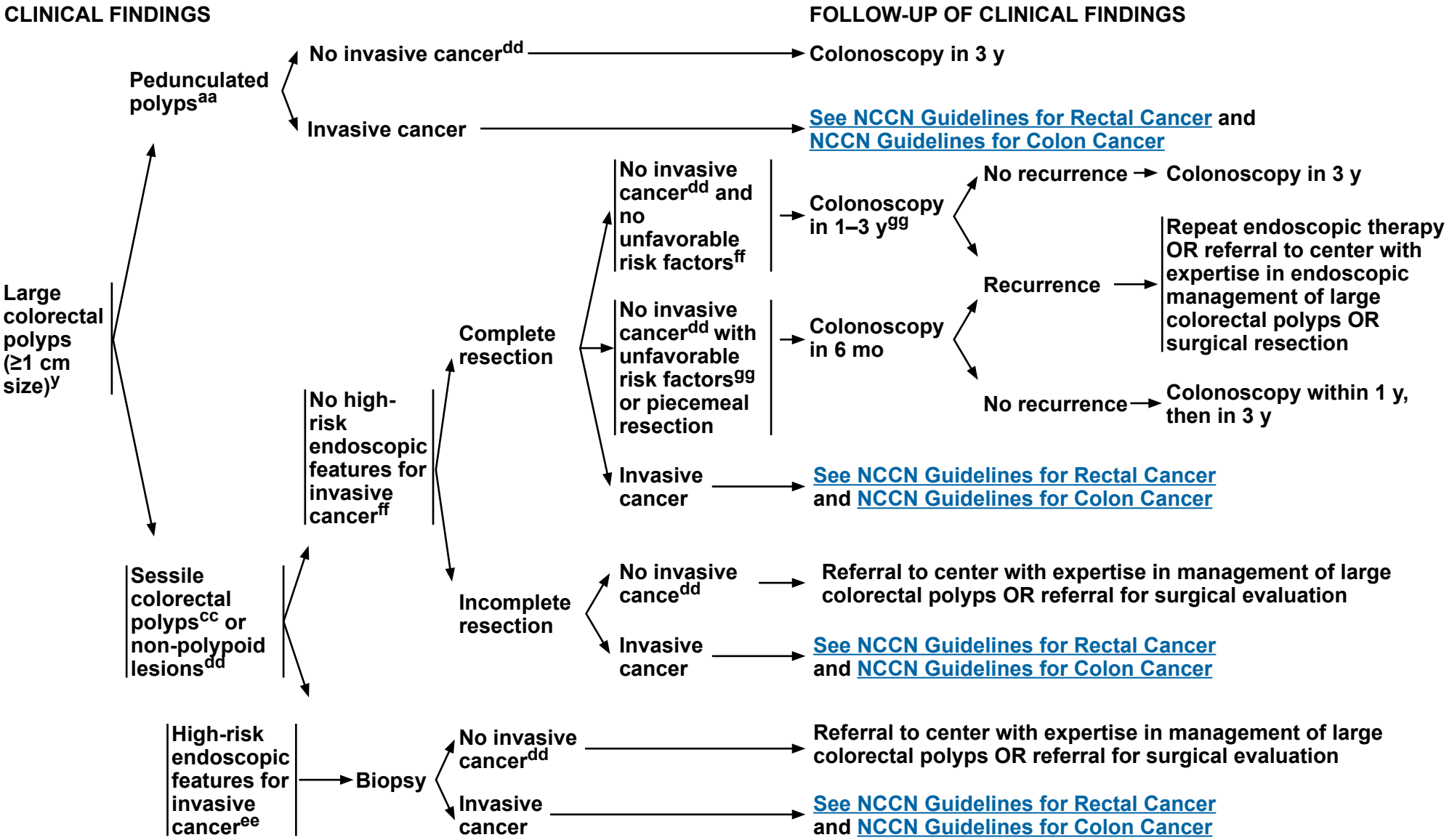
MANAGEMENT OF LARGE COLORECTAL POLYPS[z]



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See Footnotes on CSCR-6A

FOOTNOTES

[y] Consider a referral to a center of expertise for large polyp management. For sessile polyps or LSL ≥20 mm size, recommend endoscopic tattoo placement for future lesion identification.

[z] Wang R, et al. Surg Endosc 2016;30:1530-1533; Hayashi N, et al. Gastrointest Enosc 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.

[aa] Paris subtype 0–1p lesions.

[bb] Paris subtype 0–1s lesions.

[cc] Paris subtype 0–IIa, 0–IIb, 0–IIc, 0-III lesions. The panel recommends consideration of referral to a center of expertise for management of these lesions.

[dd] Histology may include adenoma, SSP, hyperplastic polyp, or TSA.

[ee] High-risk features suggestive of submucosal invasion include NICE classification type 3, Kudo classification type V (VN and VI), and non-lifting sign.

[ff] Unfavorable risk factors for laterally spreading tumor (LST) recurrence include LST size ≥40 mm, intraprocedural bleeding requiring endoscopic control, high-grade dysplasia, and macroscopic tissue ablation performed.

[gg] Consider follow-up <3 y when polyp(s) is >2 cm or confidence of complete en bloc resection is low.

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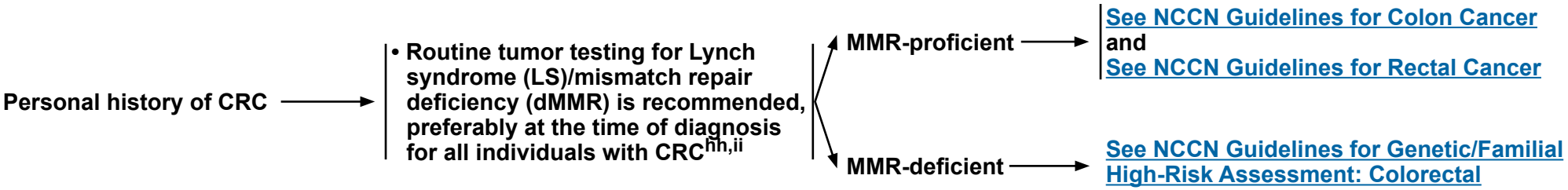
DIAGNOSIS OF COLORECTAL CANCER



[hh] 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 and/or without LS. The panel recommends tumor testing with immunohistochemistry (IHC) and/or microsatellite instability (MSI) be used as the primary approach for pathology-lab–based universal screening and to guide treatment decisions.

[ii] 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.

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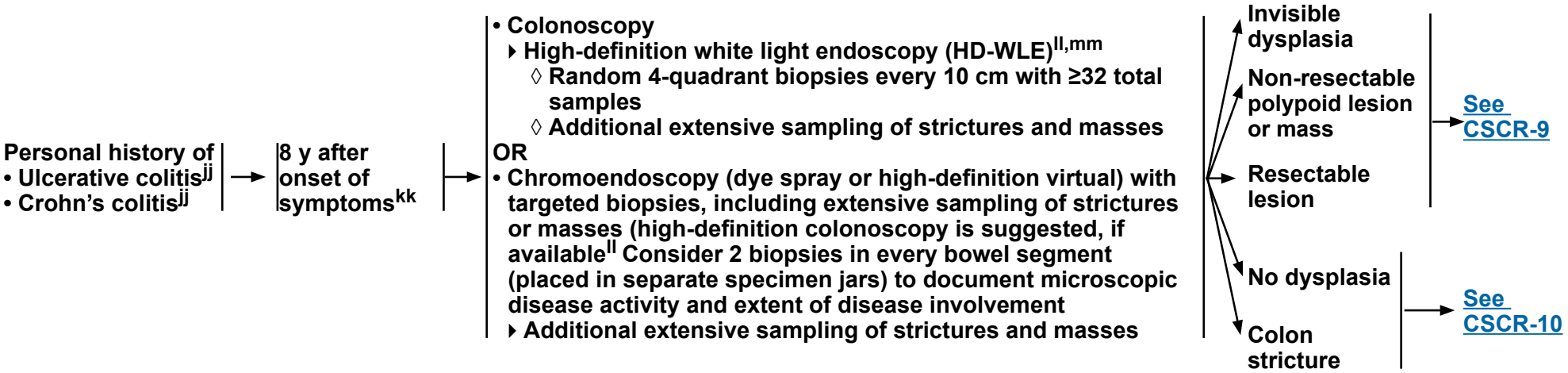
INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE



[jj] Information regarding the value of endoscopic surveillance of long-standing Crohn's disease is limited. Risk factors for dysplasia include ulcerative colitis; extensive colitis; colonic stricture; primary sclerosing cholangitis (PSC); family history of CRC, especially age <50 y; personal history of dysplasia; and severe long-standing inflammation. Confirmation by an expert GI pathologist is desirable. Patients with proctitis, who have little or no increased risk for CRC compared with the population at large, should be managed according to standard CRC screening guidelines. Lutgens M, et al. Clin Gastroenterol Hepatol 2015;13:148-154. Beaugerie L, et al. Gastroenterology 2013;145:166-175.

[kk] 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.

[ll] Endoscopy should be performed during quiescent disease. Targeted biopsies improve detection of dysplasia, and should be considered for surveillance colonoscopies in patients with ulcerative colitis where expertise is available. Murthy Y, et al. Gastointest 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.

[mm] If using standard-definition (SD)-WLE, performing colonoscopy in conjunction with chromoendoscopy is recommended. If HD-WLE or chromoendoscopy is not available, refer to institutions with expertise in these modalities.

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INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE

EVALUATION OF SURVEILLANCE FINDINGS[nn]

Invisible dysplasia → **Confirmed by GI pathologist**
- **Dysplasia confirmed** → • Referral to IBD expert • Assess with chromoendoscopy if not already performed[qq] • Consider referral to a surgeon with expertise in IBD[rr]
- **No dysplasia** → See CSCR-10

Non-resectable polypoid lesion or mass → Consult surgeon with expertise in IBD for resection[rr]

Resectable lesion[oo]
- Sessile or pedunculated polyp
- Nonpolypoid (flat lesion)

→ **Complete endoscopic resection[oo,pp]**
- • Low risk
  - Hyperplastic or normal mucosa
  - No endoscopic/histologic active inflammation
  - Left-sided disease
  → Colonoscopy follow-up in 2–3 y
- • High risk:
  - Primary sclerosing cholangitis
  - Extensive colitis
  - Active inflammation
  - Family history of CRC <50 y
  - Dysplasia
  → • Colonoscopy follow-up in 1 y • In dysplastic lesions with high-grade dysplasia or piecemeal resection, colonoscopy follow-up within 3–6 mo

→ **Incomplete endoscopic resection** → • Referral to center with expertise in IBD management • Consider assessment with chromoendoscopy if not already performed[qq] • Consider referral to a surgeon with expertise in IBD[rr]

[nn] Consider utilizing Paris classification to describe lesion. All polypoid and nonpolypoid lesions should be completely resected.

[oo] 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 and without invasive carcinoma in the polyp can be treated safely by polypectomy. Some lesions may require EMR (endoscopic mucosal resection) or ESD (endoscopic submucosal dissection) techniques for complete resection. Confirmation of all polyp histology and dysplasia by an expert GI pathologist is desirable.

[pp] Following endoscopic resection of visible lesions, may consider biopsy of surrounding mucosa to ensure complete removal. With use of chromoendoscopy, the yield of these biopsies may be negligible.

[qq] 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.

[rr] 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.

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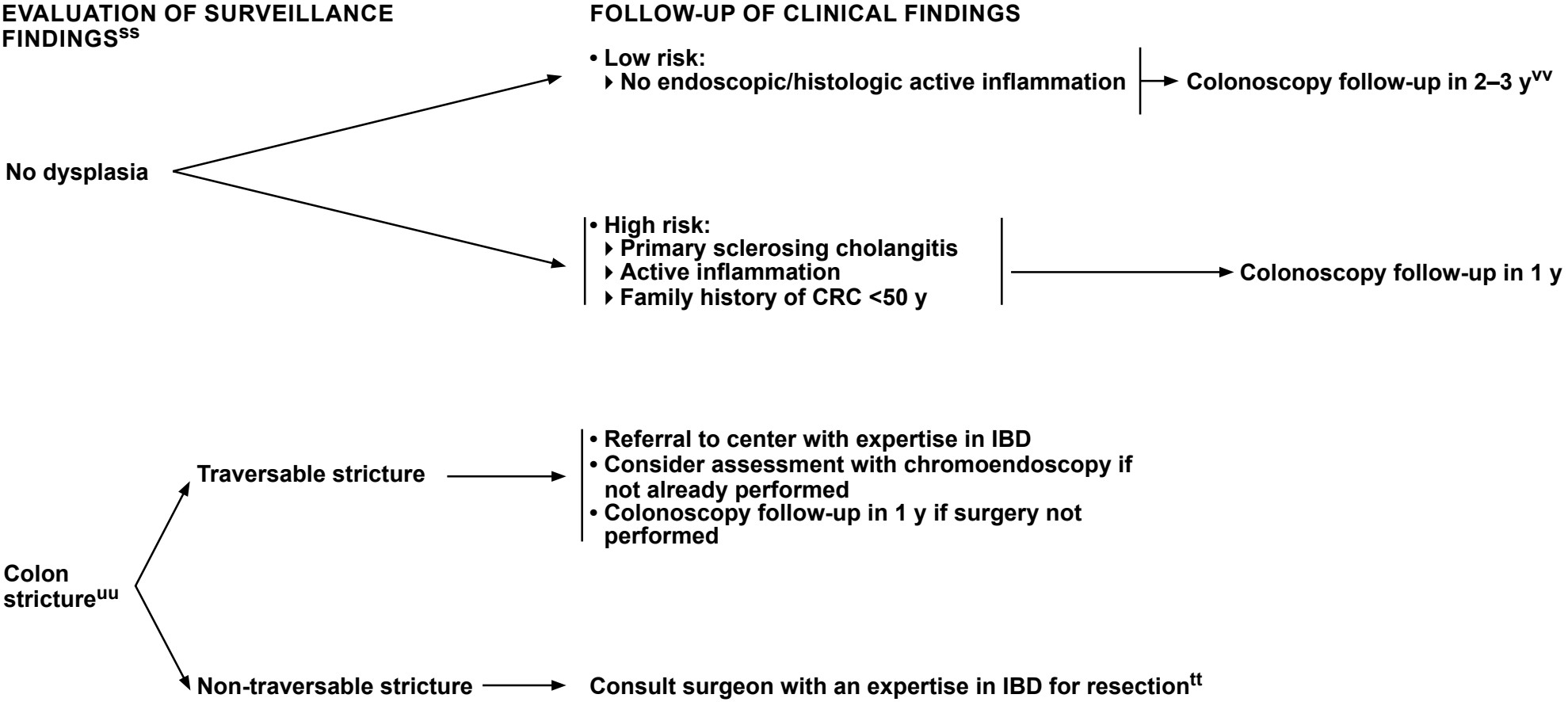
INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE



ss Consider utilizing Paris classification to describe lesion. All polypoid and nonpolypoid lesions should be completely resected.

tt 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.

uu Consider surgery in patients with symptomatic or non-traversable strictures as there is risk of underlying cancer, particularly in patients with long-standing IBD

vv 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. Magro F, et al. J Crohns Colitis 2017;11:649-670; Lamb CA, et al. Gut 2019;68:s1-s106.

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INCREASED RISK BASED ON PERSONAL HISTORY OF CYSTIC FIBROSIS[xx]

RISK STATUS	INITIATION OF SURVEILLANCE	SURVEILLANCE MODALITY AND SCHEDULE	EVALUATION OF SURVEILLANCE FINDINGS
History of solid organ transplant	Age ≥ 30y or within 2 years of the transplantation	Colonoscopy[ww]	Normal → Repeat colonoscopy in 5 years
			Adenomatous polyps → Repeat colonoscopy in 3 years
No history of solid organ transplant	Age ≥40y		

[ww] Patient should undergo cystic fibrosis-specific intensive bowel preparation.
[xx] Hadjiliadis D, et al. Gastroenterology 2018;154:736-745; Matson AG, et al. BMC Gastroenterol 2019;19:89.

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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)[yy]

FAMILY HISTORY CRITERIA	SCREENING[bbb]	
≥1 first-degree relative with CRC at any age	→ Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC	→ Repeat every 5 y[zz,bbb,ccc,ddd] or if positive, repeat per colonoscopy findings
Second- and third-degree relatives with CRC at any age	→ Colonoscopy beginning at age 45 y[zz]	→ 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 (≥1 cm, any dysplasia) at any age [aaa,eee,fff]	→ Colonoscopy beginning at age 40 y or at age of onset of adenoma in relative, whichever is first	→ Repeat every 5–10 y[bbb,ccc] or if positive, repeat per colonoscopy findings

[yy] If a patient meets the criteria for an inherited colorectal syndrome, see Assessment for Hereditary CRC Syndrome (HRS-1) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

[zz] 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.

[aaa] 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 S, et al. Gastroenterology 2016;150:608-616.

[bbb] 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.

[ccc] Multiple (2 or more) negative colonoscopies may support stepwise lengthening in the colonoscopy interval.

[ddd] Samadder NJ, et al. Am J Gastroenterol 2017;112:1439-1447.

[eee] Advanced SSPs 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 S, et al. Gastroenterology 2016;150:608-616.

[fff] Cottet V, et al. Gastroenterology 2007;133:1086-1092. Ng SC, et al. Gastroenterology 2016;150:608-616.

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SCREENING MODALITY AND SCHEDULE

- **Screening of average-risk individuals reduces CRC incidence by detecting and removing pre-cancerous polyps, and 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. 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.[1] 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.[2]**
- **Screening rates improve when programs offer different options of screening tests to ensure that testing characteristics are aligned with patient preference.[3]**

[1] 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.
[2] Sumit SK, et al. Prev Med 2020;141:106242.
[3] Inadomi JM, et al. Arch Intern Med 2012;172:575-582; Mehta SJ, et al. JAMA Netw Open 2019;2:e1910305.

Continued

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SCREENING MODALITY AND SCHEDULE

Screening Test*	Recommended Testing Interval**	Sensitivity[5]		Specificity[5]	
		Colon Cancer		Colon Cancer	
Colonoscopy	Every 10 years	94.7%[4]	89%–95% (≥10 mm adenomas) 75%–93% (≥6 mm adenomas)	—	89% (≥10 mm adenomas) 94% (≥6 mm adenomas)
Flexible sigmoidoscopy***	Every 5–10 years	58%–75%[6]	72%–86%[6]	—	92%[7]
CT colonography	Every 5 years	86%–100%	89% (≥10 mm adenomas) 86% (≥6 mm adenomas)	—	94% (≥10 mm adenomas) 88% (≥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 (using OC-Sensor)	Annually	74%	25% (advanced neoplasia) 23% (advanced adenoma)	94%	96% (advanced neoplasia) 96% (advanced adenoma)
Quantitative FIT (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)

***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.**
**** Frequency based upon normal (negative) results.**
*****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.**
****** 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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SCREENING MODALITY AND SCHEDULE

Colonoscopy

- In the United States, colonoscopy is the most commonly employed CRC screening test for average- and high-risk populations. There are multiple options; however, the choice of modality should include consideration of patient preference and availability.
- Caveats for the 10-year interval:
  - A 10-year interval is appropriate for those who had a complete procedure with an adequate bowel prep.
  - Repeating within 1 year may be indicated based on the quality and completeness of the colonoscopy. In addition, individual risk factors and physician judgment should be included in the interval determination.
  - The number and characteristics of polyps as well as family history and medical assessment should influence judgment regarding the interval between colonoscopies.
  - Colonoscopy has limitations and may not detect all cancers and polyps.[8]

- Colonoscopy bowel preparation[9]
  - To determine preparation quality, a preliminary assessment should be made in the rectosigmoid colon. 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 for the colonoscopy to proceed that day.
  - In cases where colonoscopy is complete to the cecum but the preparation is ultimately considered inadequate, colonoscopy should be repeated within 1 year. A more aggressive preparation regimen should be recommended in these cases. When advanced neoplasia is detected and prep was inadequate, an interval shorter than 1 year is indicated.
- Accumulating data suggest that there is substantial variability in the quality, and by extension, the clinical effectiveness of colonoscopy. A number of quality indicators have been examined. Quality indicators for colonoscopy are an important part of the fidelity of findings. Improving the overall impact of screening colonoscopy requires a programmatic approach that addresses quality issues at several levels. These colonoscopy quality indicators may include:
  - Cecal intubation rates
  - Withdrawal time
  - Appropriate intervals between endoscopic studies based on family and personal history, and number and histologic type of polyps on last colonoscopy
  - Minor and major complication rates
  - Pre-procedure medical evaluation
  - Appropriate prep instructions[9]
    - ◊ Split-dose prep has been shown to be superior and is recommended.
    - ◊ Preferred timing of the second dose of split-dose preparation:
      – 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.
  - Adenoma detection rate

[8]Singh S, Singh PP, Murad MH, et al. Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. Am J Gastroenterol 2014;109:1375-1389.
[9]Johnson D, Barkun AN, Cohen LB, et. al. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US multi-society task force on colorectal cancer. Gastroenterology 2014;147:903-924.

Continued

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SCREENING MODALITY AND SCHEDULE

Colonoscopy (Continued)

- Standardized colonoscopy reports that contain, at a minimum:[10]
  - Patient demographic, clinical factors including comorbidities, adenoma and cancer history, and GI family history
  - Procedure indications
  - Endoscopic findings, including polyp number, size, location, and method of excision
  - Photographic documentation of endoscopic landmarks, including the ileocecal valve, the appendiceal orifice, and retroflexed view of rectum if intact/technically feasible
  - Estimate of quality of bowel preparation
  - Documentation of follow-up planning, including pathology results
  - Sedation administered
  - Written communication of the findings and plans to the patient and referring physician is encouraged.

Stool-based screening

- If colonoscopy is used as the screening modality in an average-risk patient, then additional, interval stool-based testing is not indicated.
- If a stool-based screening test is positive, colonoscopy should be recommended. Recommendations for an appropriate time frame for follow-up colonoscopy in this population lack a strong evidence base, but a large observational study 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. Thus, we recommend that follow-up colonoscopy is completed ideally within 6 to 10 months after an abnormal stool-based test (Corley DA, et al. JAMA 2017;317:1631-1641; Forbes N, et al. Clin Gastro Hepatol 2020;19:1344-1354).
- High-sensitivity guaiac-based, nonrehydrated[11] requires 3 successive stool specimens annually (not via digital rectal examination [DRE]), prescribed diet, and coordination by health care provider.

FIT/mt stool DNA-based testing

- This modality is only FDA approved for individuals of average risk.
- Non-randomized studies have demonstrated that FIT is more sensitive than guaiac-based testing[12,13,14] and also reduces mortality.[15,16]
- Both detect human globin.
- Prescribed diet is not required.
- Optimal FIT thresholds will vary across screening programs, taking into consideration available colonoscopy resources to investigate abnormal results, including false-positive tests.
- Many brands of FIT require only a single stool annually.
- mt-sDNA is suggested to be performed every 3 years.
- If the colonoscopy is negative after a FIT or mt-sDNA and no additional symptoms are present, there is no need for further tests.

Flexible sigmoidoscopy[11]

- Recommended every 5–10 years for average-risk screening

[10]Lieberman D, Nadel M, Smith R, et al. Standardized colonoscopy reporting and data system: report of the Quality Assurance Task Group of the National Colorectal Cancer Roundtable. Gastrointest Endos2007;65:757-766.
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Continued

SCREENING MODALITY AND SCHEDULE

Radiographic

CTC[17,18]

- **Accuracy**
  - **>10 mm lesions can be identified by CTC with an accuracy similar to colonoscopy.**
  - **Lesions 6–9 mm can be identified with an acceptable accuracy that is less than that identified for colonoscopy.**
  - **Lesions ≤5 mm cannot be identified with acceptable accuracy.**
- **Follow-up of identified lesions**
  - **Data on optimal frequency, polyp size leading to colonoscopy referral, and protocol for evaluation of extracolonic lesions are evolving. The ACR has recommended that reporting of polyps <5 mm in size is not necessary. 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 is recommended.[19,20,21]**
  - **If ≥3 lesions that are 6–9 mm or any lesion ≥10 mm are found, then colonoscopy is recommended.**
- **The recommended performance interval of every 5 years was originally based on barium enema; however, it has been supported with more recent data.[22]**
- **All visualized extracolonic findings should be described and recommendations should be provided as to appropriate follow-up (including no follow-up).**
- **The future cancer risk related to undergoing a single CTC is unknown but likely very low. No empiric data have shown increased risk at levels below an exposure of 100 mSv.[23]**
- **CTC interpretation should be accomplished only by those trained according to American Gastroenterological Association[17] or American College of Radiology (ACR)[18] guidelines.**
- **Procedure quality should be tracked and assured using current ACR practice guidelines for patient preparation, image acquisition, study interpretation, and reporting.**

mSEPT9 blood test

- **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.**

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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.[1]
Inflammatory bowel disease	IBD	Comprised of ulcerative colitis or Crohn's disease[2]
Mismatch repair	MMR	Molecular pathway that targets replication errors missed during DNA replication[3]
Mismatch repair deficiency	dMMR	Form of genetic instability in CRC characterized by loss of function genetic mutations in the mismatch repair pathway[4]
Primary sclerosing cholangitis	PSC	Chronic cholestatic disease characterized by fibroinflammatory fibrosis of the biliary tree; is a risk factor for CRC[2,5]
Ulcerative colitis	UC	Chronic inflammatory disorder of the colon.[6]
Screening/Surveillance Modalities		
Chromoendoscopy		Image-enhanced endoscopic procedure using dye or optical technologies[7]
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[8]
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[9]
Flexible sigmoidoscopy		Structural endoscopic examination of the distal portion of the colon[10]
High-definition white light endoscopy	HD-WLE	Endoscopy procedure that uses high-definition imaging system without optical filters[11]

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Continued

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

Term	Abbreviation (if applicable)	Definition
Multitargeted 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[12]
Polypectomy		Procedure used to remove visually detectable polypoid tissue in the colon[13]
Histology		
Adenoma		Noninvasive neoplastic lesion of the columnar epithelium[14]
Advanced adenoma		Adenoma that is ≥1 cm or has villous/tubulovillous histology or high-grade dysplasia
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[15]
Villous adenoma		High-risk feature; a polyp/adenoma with >75% villous structures (long finger-like or leaf-like projections on surface)[15]
Tubulovillous adenoma		High-risk feature; a polyp/adenoma with 25%–75% villous histology[15]
Low-risk adenomas		1–2 nonadvanced polyps/adenomas <10 mm in size[13]
High-risk adenomas		Advanced adenoma or ≥3 non-advanced adenomas[13]
Traditional serrated adenomas	TSA	Polyps with complex villous growth pattern; ectopic crypt formation is a unique feature that leads to mucosal protrusions;[16,17] are associated with high-risk polyp recurrence[18]
Dysplasia		• 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[19] • 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[19]
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[19]

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

Term	Abbreviation (if applicable)	Definition
Invisible dysplasia		Dysplasia diagnosed on pathology but not described on endoscopy;[20] identified on random/non-targeted biopsies of colon mucosa without a visible lesion[21]
Hyperplastic polyps	HP	Hyperplastic polyps are serrated polyps with normal crypt architecture and proliferative characteristics
Sessile serrated polyp	SSP	Synonymous with sessile serrated adenoma;[24] SSPs 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 with dysplasia	SSP-d	SSP with dysplasia
Low-risk SSP		1–2 SSPs <10 mm in size; no dysplasia
High-risk SSP		SSP ≥1 cm and/or containing dysplasia and/or ≥3 low-risk SSPs
Sessile colorectal polyps		Paris subtype 0–1s lesion[14]
Non-pedunculated polyps		Sessile and non-polypoid lesions;[25] lesion not attached to mucosa by stalk, and base and top of lesion have the same diameter[24]
Pedunculated polyps		Paris subtype 0–1p lesion;[14] lesion attached to the mucosa by a stalk and the base of lesion is narrow[21,24]
Polypoid lesion		Lesion protruding from the mucosa into the lumen ≥2.5 mm[21]
Nonpolypoid lesion		Paris subtype 0–IIa, 0–IIb, and 0–IIc lesions;[14] lesion with little (<2.5 mm) or no protrusion above the mucosa;[21] includes superficial elevated, flat, and depressed[24] • Superficial elevated (0–IIa) lesions: include height <2.5 mm above normal mucosa; sometimes defined as height < one-half of the lesion diameter[24] • Flat (0–IIb) lesions: those without any protrusion above mucosa[24] • Depressed (0–IIc) lesions: those with base that is lower than the normal mucosa[24]
Lateral spreading lesion		Laterally growing superficial neoplasm (instead of upward or downward growth) ≥10 mm in size;[24] may be used to further classify non-pedunculated lesions[25]

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Continued

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

Term	Abbreviation (if applicable)	Definition
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[24]
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[24]
Piecemeal resection		Removal of colorectal lesions or polyps in more than one piece[24]
En bloc resection		Removal of colorectal lesions or polyps in one piece[24,26]
Ileocecectomy		Removal of isolated ileal segment in colon[27]
Right hemicolectomy		Removal of ascending colon
Extended right hemicolectomy		Removal of the ascending colon and transverse colon
Transverse colectomy		Removal of the transverse colon (longest segment of the large intestine)[28]
Left hemicolectomy		Removal of descending colon
Sigmoid colectomy		Removal of the sigmoid/distal colon
Subtotal colectomy		Removal of colon with an ileo-colonic or ileo-rectal anastomosis[29]
Total colectomy		Removal of entire colon
Low anterior resection	LAR	Resection procedure to remove rectal carcinoma with a colorectal anastomosis[30]
Abdominoperineal resection	APR	Removal of anus, rectum, and sigmoid/distal colon[31]
Total proctocolectomy		Surgical removal of the colon and rectum

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Continued

GLOSSARY OF TERMS COMMONLY USED IN NCCN GUIDELINES FOR COLORECTAL CANCER SCREENING
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GLOSSARY OF TERMS COMMONLY USED IN NCCN GUIDELINES FOR COLORECTAL CANCER SCREENING
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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Colorectal Cancer Screening

Discussion

This discussion corresponds to the NCCN Guidelines for Colorectal Cancer Screening. Last updated on 04/13/2021.

Table of Contents

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer in the United States. In 2021, an estimated 104,270 new cases of colon cancer and 43,230 new cases of rectal cancer will occur in the United States.[1] During the same year, it is estimated that 52,980 people will die from colon and rectal cancer.[1] Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early, curable stage and may decrease CRC incidence by detecting and removing polyps.[2-4] Patients with localized CRC have a 90% relative 5-year survival rate, whereas rates for those with regional and distant disease are 71% and 14%, respectively, demonstrating that earlier diagnosis can have a large impact on survival.[5]

Importantly, the incidence of colon and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005.[6] The incidence of CRC continued to trend downward, with an average annual percentage change of -2.7% in men and -2.1% in women from 2004 to 2008.[7] In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[8] and in 2017 was down from peak mortality rates by 53% in men and 57% in women.[9] 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. In fact, modeling suggests that approximately 63% of CRC deaths can be attributed to non-screening.[10] According to the Centers for Disease Control and Prevention (CDC), the screening rate among U.S. adults aged 50 to 75 years has increased from approximately 42% in 2000 to 59% in 2010.[11] The National Colorectal Cancer Roundtable established the goal to increase U.S. CRC screening rates to 80% by 2018, which they estimate could prevent approximately 280,000 new CRC cases and 200,000 CRC deaths through 2030.[12] Conversely, the incidence rates of colon and rectal cancers in adults younger than 50 years of age have been increasing by approximately 2% per year since 2003.[5,13] In general, most CRC cases in adolescent and young adult (AYA) individuals appear to be sporadic.[14] Causes for this increase in early-onset CRC are unknown and may be attributable to diet and other lifestyle factors.[5]

These NCCN Guidelines for Colorectal Cancer Screening describe various colorectal screening modalities as well as recommended screening schedules for patients at 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 (also known as hereditary nonpolyposis colorectal cancer, or HNPCC), familial adenomatous polyposis (FAP), *MutY human homolog* (MUTYH)-associated polyposis (MAP), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and serrated polyposis syndrome (SPS)[15-17] are addressed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

Literature Search Criteria and Guidelines Update Methodology

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.[18]

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 (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Primary and Secondary Prevention of Colorectal Cancer (CSCR-PREV)

Certain lifestyle modifications are associated with a reduced risk of CRC and can be an important adjunct to CRC screening for prevention.[19]

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 healthy diet, as these measures are strongly associated with decreased colon and/or rectal cancer risk.[20] Other analyses have shown that adherence to guidelines promoting physical activity and a healthy diet are associated with reductions in the incidence of CRC.[21,22] Initiating physical activity during adolescence also appears to lower the risk of developing colorectal adenomas later in life.[23]

In regard to diet and nutrition, the CUP report recommends obtaining nutrients from natural food sources over solely from dietary supplements.[20] Specifically, low levels of vitamin D have been associated with increased CRC risk.[24] Some studies suggest that a diet high in fruits and vegetables is associated with decreased CRC risk.[25,26] 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.[27-29]

An international panel of experts formed a working group for the International Agency for Research on Cancer (IARC) and assessed more than 800 epidemiologic studies that investigated the association of cancer with the consumption of red and processed meats.[30] 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.[30] Due to limited evidence, consumption of red meat was determined to be "probably carcinogenic" to humans.[30] In contrast, the Nutritional Recommendations (NutriRECS) guidelines panel suggests that adults continue current unprocessed red meat consumption (weak recommendation, low-certainty evidence).[31] Similarly, the panel suggests that adults continue current processed meat consumption (weak recommendation, low-certainty evidence).[31]

Aspirin

The U.S. Preventive Services Task Force (USPSTF) conducted systematic evidence reviews of trials that assessed the impact of aspirin on: 1) total cancer mortality and incidence in persons eligible for primary prevention of cardiovascular disease (CVD); and 2) CRC mortality and incidence in persons at average CRC risk.[32] The 20 trials included in these systematic reviews compared the effects of oral aspirin to placebo or no treatment in adults aged greater than or equal to 40 years. In CVD primary and secondary prevention trials (4 trials, n = 14,033), 20-year CRC mortality was decreased in persons who received aspirin therapy (relative

risk [RR], 0.67; 95% confidence interval [CI], 0.52–0.86).[32] Based on 3 trials (n = 47,464), aspirin also appeared to reduce CRC incidence beginning 10 to 19 years after initiation (RR, 0.60; 95% CI, 0.47–0.76).[32] Based on these data, the USPSTF recommends low-dose aspirin intake for primary prevention of CVD and CRC in adults aged 45 to 59 years who have greater than or equal to 10% 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.[33] A daily aspirin dose of 81 mg is suggested, although the optimal dose is not well-established.[33]

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; 6,102 were exposed to aspirin after CRC diagnosis).[34] 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%).[34] In addition, aspirin exposure after CRC diagnosis was independently associated with improved CRC-specific survival (hazard ratio [HR], 0.85; 95% CI, 0.79–0.92) and overall survival (OS) (HR, 0.95; 95% CI, 0.90–1.01).[34]

Smoking

Cigarette smoking causes 1 in 5 deaths in the United States every year and is estimated to cause more than 480,000 deaths every year (including the effects of secondhand smoke).[35] 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).[36] Multivariate-adjusted CRC mortality rates were highest among smokers, intermediate in former smokers, and lowest in life-long nonsmokers.[36] The multivariate-adjusted RR (95% CI) for current versus non-smokers was 1.32 (1.16–1.49) among men, and 1.41 (1.26–1.58) among women.[36] Increased risk of CRC was observed after greater than or equal to 20 years of smoking for both men and women, compared to individuals who had never smoked.[36] A subsequent study examined a subgroup of participants from the CPS-II study (n = 184,187).[37] 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.[37] The incidence of CRC was significantly higher in current (HR, 1.27; 95% CI, 1.06–1.52) and former smokers (HR, 1.23; 95% CI, 1.11–1.36) compared with lifelong nonsmokers.[37] The risk of CRC also decreased with longer time since cessation and earlier age at cessation.[37]

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.[38,39] 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.[40] Compared to nondrinkers or occasional drinkers, 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.[40]

Risk Assessment (CSCR-1)

The NCCN Guidelines for Colorectal Cancer Screening stratify patients into three groups depending on their risk of getting CRC. Colorectal screening is particularly important for African Americans 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.

CRC risk assessment in persons without a known family history is advisable by 40 years of age to determine the appropriate age for initiating screening.

Average Risk

Individuals at average risk of developing CRC are those: aged greater than or equal to 45 years; with no history of adenoma or sessile serrated polyps (SSPs) or CRC; with no history of inflammatory bowel disease (IBD); or with a negative family history of CRC or confirmed advanced adenoma (high-grade dysplasia, >1 cm in size, villous or tubulovillous histology, or an advanced SSP). 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 younger than age 45.[14,41,42] From 2003 to 2013, there has been a 22% increase in CRC in individuals younger than 50 years.[43] 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.[14,42] Based on statistical modeling incorporating these data, which predicted potential increased benefit,[44,45] the American Cancer Society (ACS) recommended—as a qualified recommendation—that individuals at average risk of CRC begin screening at age 45 years.[46]

The panel has reviewed these and other existing data for beginning screening of average-risk individuals at younger than 50 years of age. 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. If signs and symptoms of CRC occur in individuals younger than 45 years of age, including iron deficiency anemia, rectal bleeding, or a change in bowel habits,[47] the panel recommends prompt evaluation with a colonoscopy or at least flexible sigmoidoscopy, if symptoms do not promptly respond to medical treatment.

Increased Risk

Individuals with a personal history of adenomas or SSPs, CRC, or IBD (ie, ulcerative colitis, Crohn's disease), and those with a positive family history of CRC or advanced adenomatous polyps, are considered to be at increased risk for developing CRC. Individuals with diabetes mellitus and those who are obese also have a higher risk,[48,49] although these factors are not considered to affect the screening guidelines. Other factors that influence risk include age, sex, and race.[50]

Registry data suggest an increased incidence of CRC in African Americans prior to age 50 years.[51] This increased risk has led some to recommend beginning population CRC screening in African Americans at an earlier age than the rest of the population.[52] Using a microsimulation model, one study found that differences in screening accounted for 42% of disparity in CRC incidence and 19% of disparity in CRC mortality between African Americans and whites.[53] 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. In addition, mortality from CRC has been decreasing in African Americans and whites since 1999.[54] Therefore, based on the available data and emerging evidence, methods to further enhance access to screening in African American and other minority populations should be endorsed.

High-Risk Syndromes

Individuals with a family history of Lynch syndrome (also known as HNPCC) 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).

Colorectal Cancer Screening (CSCR-3)

Current technology falls into two broad categories: structural tests and stool/fecal-based tests.[55] There is direct evidence from randomized controlled trials (discussed in detail below) that fecal occult blood testing (FOBT) and flexible sigmoidoscopy reduce CRC incidence and mortality by detecting and removing pre-cancerous polyps at an early, curable stage. Colonoscopy is supported by case-control and cohort studies and has the potential ability to prevent CRC (with its associated morbidity) and cancer deaths.

In the United States, colonoscopy is the most commonly employed CRC screening test for average- and high-risk populations. 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).[56] Overall, although some techniques are better established than others, panelists 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 were never screened.[57]

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) follow-up of those with a positive test for 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.[58-60] Several randomized studies have provided evidence that offering different screening options to ensure testing characteristics are aligned with patient preferences may improve screening rates.[61,62] These evidence-based interventions may include mailed outreach, patient navigation, patient education and reminders, and clinician-directed feedback and alerts.[60 61,62]

Screening Modalities (CSCR-A)

Structural Screening Tests

Structural screening tests detect adenomatous polyps and cancer using endoscopic or radiologic imaging. 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 the need for 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.[63]

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 average-risk individuals who had a high-quality normal colonoscopy, defined as an exam complete to the cecum with bowel preparation adequate to detect polyps greater than 5 mm in size.[64] Although no randomized controlled trials directly

demonstrate mortality reduction by colonoscopy, findings from case-control and cohort studies show significant impact of colonoscopy and polypectomy on decreasing CRC incidence and mortality.[65-68]

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 odds ratio [OR], 0.33; 95% CI, 0.28–0.39) but not proximal CRC (OR, 0.99; 95% CI, 0.86–1.14).[69] Additional studies have also demonstrated a reduced effectiveness in the right versus the left colon.[70,71] A population-based, case-control study in Germany demonstrated that colonoscopy in the preceding 10 years gave an overall 77% decrease in the risk for CRC.[71] 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.[70,72] 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 (the Nurses' Health Study and the Health Professionals Follow-up Study) followed 88,902 participants for 22 years, comparing long-term outcomes in those who had screening colonoscopies, sigmoidoscopies, or no endoscopy.[68] 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 colonoscopic 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.[73] 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.[73]

Another study estimated CRC mortality in 40,826 patients who underwent polypectomy in Norway.[74] Patients with high-risk adenomas were recommended for repeat colonoscopy in 10 years if they were younger than 75 years of age or in 5 years if 3 or more adenomas were found. No further surveillance was recommended for patients with low-risk adenomas or those older than 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.[74] 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.[74] In addition to cancer prevention, colonoscopic 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.[75] 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; $P < .001$).[75] Furthermore, unscreened patients had higher rates of death and recurrence, shorter survival, and shorter disease-free intervals.

A meta-analysis of 14 randomized controlled trials 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.[76] Interim results of the COLONPREV study, a randomized controlled study comparing one-time colonoscopy with biennial fecal immunochemical testing (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.[77] The data also showed that subjects were more likely to participate in FIT compared to colonoscopy screening (34.2% vs. 24.6%; $P < .001$).[77] Subsequent analyses confirmed these observations.[78]

Colorectal Cancer Screening Programs

An optimal screening program should have an interval during which there is a low likelihood of developing cancer, and it should be cost-effective based on the duration of risk reduction following an initial negative screen. The general consensus is that a 10-year interval is appropriate for most individuals (average risk) who had a complete colonoscopic procedure with an adequate bowel preparation, although a 1-year interval may be indicated depending on the completeness and quality of the colonoscopy.[64] The panel emphasized the importance of family history in the screening scheme. Individual risk factors, the number or characteristics of polyps found, and physician judgment should also be included in the interval determination.

A 1996 study reported that 27% of individuals had adenomatous polyps identified on repeat colonoscopy a mean of 66 months after an initial negative colonoscopy, but none had colon cancer and only one of 154 individuals had a polyp greater than or equal to 1 cm.[79] These results suggest that an interval of repeat colonoscopy after an initial negative colonoscopy beyond 5 years is safe. Imperiale et al reported on 2436 individuals with no adenomatous polyps at baseline colonoscopy.[80] No cancers were found at rescreening at a mean of 5.3 years later. Adenomatous polyps were identified in 16% of individuals and only 1.3% had advanced adenomatous polyps. The authors recommended a rescreening interval of 5 years or longer. Lieberman and colleagues reported that advanced adenomatous polyps were found in only 2.4% of individuals on repeat colonoscopy within 5.5 years after a baseline normal colonoscopy.[81] In this study, individuals with 1 or 2 adenomatous polyps less than 1 cm at baseline also had a low rate of developing advanced neoplasia.

Singh et al also assessed the time that risk reduction persists after colonoscopy.[82] This study was a population-based retrospective analysis utilizing a physician billing claims database of individuals who had a negative screening colonoscopy. Patients in the surveillance cohort were compared to the general population regarding incidence of CRC. A negative colonoscopy was associated with a standardized incidence ratio (SIR) of 0.28 (95% CI, 0.09–0.65) at 10 years. A similar study calculated the adjusted RR for CRC among subjects with a previous negative colonoscopy.[83] The adjusted OR was 0.26 (95% CI, 0.16–0.40). The low risk was seen even if the colonoscopy had been performed up to 20 or more years previously. The risk reduction seen following negative colonoscopy holds even for patients with a family history of CRC, but not for current smokers.[84]

Colonoscopy Quality

Recommendations made by the panel are based on the premise of complete, high-quality colonoscopies. The recommended priority quality indicators are: 1) the adenoma detection rate in asymptomatic individuals undergoing screening; 2) the frequency at which surveillance colonoscopies follow recommended post-polypectomy and post-cancer resection intervals; 3) the frequency with which 10-year intervals between screening colonoscopies are followed in average-risk patients with negative screens and adequate bowel preparation; and 4) the frequency with which visualization of the cecum is documented using notation and

photodocumentation of landmarks.[85] Other suggested indicators include: 1) incidence of perforation; 2) management of post-polypectomy bleeding without surgery; 3) documentation of withdrawal time; 4) frequency of obtaining biopsies in individuals with diarrhea; 5) frequency of documentation of appropriate recommendation for interval colonoscopy; and 6) notification of the patient of this recommendation after review of histologic findings.[85] A European report on a screening program involving more than 45,000 subjects 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.[86] The study did not demonstrate statistical significance with cecal intubation rate, 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 number of cancer cases. Data analysis of almost 315,000 colonoscopies from an integrated health care delivery organization showed that higher adenoma detection rates 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).[87] Furthermore, a recent meta-analysis reported that significantly higher colonoscopy volumes were associated with less adverse events and an increase in colonoscopy quality.[88]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.[89] These NCCN Guidelines list the common quality indicators of colonoscopy and minimum requirements of a colonoscopy report. Quality indicators, including withdrawal time and adenoma detection rate, are an important part of the fidelity of colonoscopy findings.[87,90-92]

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.[93-95] The U.S. Multi-Society Task Force on Colorectal Cancer also recommends split preparation.[64]

The NCCN Panel and the U.S. Multi-Society Task Force agree that a same-day, morning-only regimen is an acceptable alternative, especially in patients undergoing afternoon procedures.[96-98]

Flexible Sigmoidoscopy

Flexible sigmoidoscopy followed by colonoscopic polypectomy in patients with lesions greater than 1 cm significantly reduced mortality risk in early case-control studies.[99,100]

Evidence from randomized controlled trials has also demonstrated that flexible sigmoidoscopy reduces the incidence of and mortality from CRC.[68,101-107] The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening group reported CRC mortality rates from their randomized, controlled flexible sigmoidoscopy screening trial, which screened more than 64,000 participants with flexible sigmoidoscopy and 59% of those participants a second time at 3 or 5 years.[105-107] 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.[105] This strong effect was seen despite an 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 a randomized controlled trial of one-time flexible sigmoidoscopy with or without a concurrent FOBT compared to a non-screened control group in more than 98,000 participants aged 55 to 64 years.[102] 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.[103] 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 subjects aged 55 to 64 years to one-time sigmoidoscopy or no screening and reported incidence and mortality results after greater than 10 years of median follow-up.[104] 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 age 55 and 64 years on CRC incidence and mortality.[101] 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).[101] The benefit of one-time sigmoidoscopy demonstrating decreased CRC incidence and mortality was sustained after 17 years of follow-up.[108] 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.[108,109]

Meta-analyses of randomized controlled trials support the conclusion that screening by flexible sigmoidoscopy significantly reduces the incidence and mortality of CRC.[110-113] 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.[114] 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.[115]

Compared to colonoscopy, sigmoidoscopy 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.[116] 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 or longer. Polyps identified should be biopsied by trained personnel to determine if they are hyperplastic, adenomatous, or sessile serrated. Patients with lesions larger than 1 cm should be referred directly to colonoscopy, since these lesions are almost always adenomatous polyps, which are associated with a risk of proximal colonic neoplasms.

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.[117] However, a positive finding requires a colonoscopy, and extracolonic findings—which are present in up to 16% of patients—pose a dilemma.[118,119] 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 or more was assessed in the National CT Colonography Trial (ACRIN 6664) organized by the American College of Radiology (ACR) Imaging Network.[120] 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 or larger 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[121,122] and similar to what was reported by Pickhardt and colleagues in a prospective study with a design similar to the ACRIN trial.[123]

Kim et al also compared CT colonography with colonoscopy for the detection of advanced neoplasia.[124] Although this study was not randomized, the detection rates were comparable between the two groups of greater than 3,100 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 as sensitive as colonoscopy for detecting tumors with significant lateral spread.[125]

In 2005, two meta-analyses reviewed the performance of CT colonography in the detection of colorectal polyps.[126,127] In one of these studies, CT colonography showed high average sensitivity (93%) and specificity (97%) for polyps greater than or equal to 1 cm, both of which decreased to 86% when medium polyps (6–9 mm) were included in the analysis.[126] 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.[127] Other studies have assessed growth rates of colorectal polyps (6–9 mm) using CT colonographic surveillance.[128,129] 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.[129] Participants who had lesions greater than or equal to 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.[129] The study suggests that polyps that are 6 to 9 mm in size are unlikely to progress to advanced neoplasia within 3 years.[129] In a longitudinal study screening of 22,006 asymptomatic individuals, 243 adults (mean age, 57.4 years) had 306 colorectal polyps (6–9 mm).[128] 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.[128] 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.[128]

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 confidence intervals.[130] Another analysis focused only on studies of average-risk participants and found the sensitivity and specificity of CT colonography for the detection of adenomas greater than or equal to 1 cm to be 87.9% and 97.6%, respectively.[131]

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.[132] 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 greater than or equal to 1 cm.[133] 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.[134,135] 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.[136] Using the screening 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.[137] 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.[138] 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 colonographic surveillance at year 3 or colonoscopy is recommended. If more than three polyps that are 6 to 9 mm in size or lesions greater than or equal to 10 cm are detected, colonoscopic surveillance is recommended. The ACR has recommended that reporting of polyps less than or equal to 5 mm in size is not necessary.[138] However, if polyps of this size are reported, the decision to refer for colonoscopy with polypectomy versus surveillance CT colonography should be individualized.

Fecal-Based Screening Tests

Fecal-based tests are designed to detect signs of CRC in stool samples, specifically occult blood or, more recently, alterations in exfoliated DNA in combination with occult blood. In contrast to structural tests, they are noninvasive and no bowel clearance is necessary. However, stool tests are less likely to detect polyps for cancer prevention on single application. Also, sensitivity can be limited by inadequate specimen collection or suboptimal processing and interpretation.

Any positive stool test needs to be followed by colonoscopy. To ensure adequate follow-up, a health care professional should coordinate testing so that the patient who has a positive result enters the health care system in a responsible way.

Fecal Occult Blood Test

Two types of FOBTs are currently available: guaiac-based and immunochemical. These tests are recommended annually when used alone, or once at 3 years when used in combination with flexible sigmoidoscopy. Annual FOBT should not be performed in combination with colonoscopy in an average-risk patient. 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.[139,140] Unfortunately, a survey of over 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.[141]

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 gastrointestinal (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 randomized controlled trials that low-sensitivity guaiac FOBTs reduce mortality from CRC.[142-144] In the Minnesota Colon Cancer Control Study, greater than 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.[144] 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, 0.56–0.82; RR for biennial FOBT, 0.78; 95% CI, 0.65–0.93).[145] 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-compliance, the reduction in CRC mortality was estimated to be 18%.[146] This reduction in CRC mortality using low-sensitivity guaiac FOBTs has been confirmed by systematic review and meta-analysis of multiple studies.[112,147]

A systematic review of four randomized controlled trials involving more than 320,000 participants showed a 16% reduction in RR for CRC death with guaiac FOBT screening (95% CI, 0.78–0.90).[147] 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).[112] 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.[148] 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.[149] 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 greater than 70% and a specificity greater than 90%.[4] Although high-sensitivity guaiac FOBTs that meet these criteria have not been tested in randomized controlled trials, some studies have shown that high-sensitivity guaiac FOBTs have higher CRC detection rates when compared to low-sensitivity guaiac FOBTs.[148,150,151] 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. A meta-analysis of studies that evaluated the diagnostic accuracy of FIT for CRC in average-risk patients found the sensitivity to be 79% (95% CI, 0.69–0.86) and the specificity to be 94% (95% CI, 0.92–0.95).[152]

Comparative studies have shown that FIT is more sensitive than guaiac FOBT.[151,153-157] For example, one study demonstrated a higher sensitivity for cancer by FIT compared to a high-sensitivity guaiac FOBT (82% vs. 64%).[151] 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%).[154] 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.[158] Non-randomized studies have also shown that FIT screening reduces CRC mortality.[159,160] 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).[159]

FIT-DNA–Based or Multitarget Stool DNA Test

A combined multitarget stool DNA and occult blood test (mt-sDNA) has emerged as an option for CRC screening [Cologuard® (Exact Sciences)]. It 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 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 SSPs greater than 1 cm (42.4% vs. 5.1%; $P < .001$).[161] 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; $P < .001$), and many more participants were excluded because of problems with mt-sDNA testing (689) than because of problems with FIT (34).

The NCCN CRC Screening Panel recommends the inclusion of mt-sDNA–based testing as a potential screening modality in average-risk individuals, 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. A rescreening interval of every 3 years has been suggested and is approved by the FDA.[3] 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%).[162] At 3-year intervals, such testing was predicted to reduce CRC incidence and mortality by 57% and 67%, respectively. In addition, there are no or limited data in high-risk individuals who refuse colonoscopy or have limited access to conventional screening strategies;[163] therefore, the use of mt-sDNA–based testing should be individualized in these cases.

Emerging Options: Blood-Based Screening Test

The methylation status of the septin9 (*SEPT9*) gene has been shown to distinguish CRC tissue from normal surrounding tissue, and circulating methylated *SEPT9* DNA in plasma is a biomarker for CRC.[164-167] A multicenter study compared the FIT test and a *SEPT9* DNA methylated blood test for CRC screening of 102 patients with identified CRC, and found that the specificity for CRC detection was higher for FIT (97.4% vs. 81.5%, respectively) but the sensitivity for CRC detection was not significantly different (68% vs. 73.3%, respectively).[168] Another clinical trial comparing the uptake of the methylated *SEPT9 DNA* blood-based test to FIT for CRC screening in 413 average-risk adults found that more participants took the blood test (99.5% vs. 88.1%; $P < .001$).[169]

In 2016, a blood test that detects circulating methylated *SEPT9* DNA was approved by the FDA and may provide an alternative for individuals who refuse other screening modalities. The sensitivity of the *SEPT9* DNA test for the detection of CRC has been reported to be 68% with a specificity of 80%.[170] Factors that may potentially negatively impact the performance of the *SEPT9* DNA test have been suggested, including early-stage disease, age greater than 65 years, diabetes,

arteriosclerosis, and arthritis.[171] Based on current data, the panel concludes that the interval for repeating testing is unclear; however, they will continue to review this strategy and monitor new, emerging data.

Screening of Individuals at Average Risk (CSCR-3,4)

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; annual high-sensitivity guaiac-based testing or FIT, or mt-sDNA–based testing (every 3 years); flexible sigmoidoscopy every 5 to 10 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.[64] 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 annual fecal tests, provides approximately the same benefit with lower risks and costs than colonoscopy.[172]

Following a positive stool-based test, a colonoscopy 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.[173] 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 greater than 12 months.[173] A non-significant increase in any CRC risk and advanced-stage disease was observed beginning at 7 to 9 months.[173] Based on the results of these studies, the panel recommends that after a positive/abnormal stool-based test, the follow-up colonoscopy should ideally be completed within 6 to 10 months afterwards. A negative colonoscopy after a FIT or mt-sDNA with no additional symptoms present warrants no further testing.

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.[174] 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.[175] A survival meta-analysis of four randomized trials[101,103-105] comparing screening with flexible sigmoidoscopy to no screening found that it takes up to 10 years after flexible sigmoidoscopy to attain an absolute reduction in mortality related to CRC.[176] 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.[174]

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), 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 polyps located in the ascending colon, as these tend to be associated with microsatellite instability (MSI) 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.

Flat Adenoma

Flat adenomatous polyps are unusual and can be easily missed during colonoscopy because they are not protruding from the colon wall.[177] More prospective studies are required to clarify their role in CRC risk. In the meantime, all flat adenomatous polyps should be removed upon identification with routine post-adenoma follow-up.

Sessile Serrated Polyps

According to the World Health Organization (WHO) criteria, there are three main subtypes of serrated polyps: SSPs, traditional serrated adenomas (TSAs), and hyperplastic polyps.[178,179] 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).[180] SSPs, also known as sessile serrated adenomatous polyps, are a form of serrated polyps that have been associated with adenocarcinoma.[181] 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.[179,182] Thus, SSPs are managed like tubular adenomas, whereas SSP-ds are managed like high-risk adenomas.[179,183-185]

Traditional Serrated Adenomas

An overall protuberant exophytic configuration, complex villous or tubulovillous growth pattern, and peculiar columnar cells with abundant eosinophilic cytoplasm characterize TSAs.[179,186,187] They are not as prevalent as SSPs in clinical studies,[188-190] and tend to be bulkier than SSPs.[191] Similar to SSPs, TSAs are associated with precancerous lesions.[179] Conventional adenoma-like and serrated dysplasia are observed in TSAs, and it is thought that TSAs increasingly acquire cytologic atypia before the development of CRC.[179] TSAs are managed like SSP-ds.

Hyperplastic Polyps

Hyperplastic polyps are another type of serrated polyp. 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. However, some studies suggest that a small subset of persons 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).[192-194] The majority of these persons had concomitant adenomatous polyps or SSP.[195] SPS is rarely reported to be inherited, and the CRC risk for individuals with affected relatives remains unclear. Furthermore, evidence suggests that some cancers with extensive DNA methylation and MSI might derive from hyperplastic polyps.[196]

Hyperplastic polyps that are less than 1 cm without SSP features indicate average risk for follow-up screening when they occur in the sigmoid colon.

An expert panel concluded that hyperplastic polyps greater than 5 mm occurring proximal to the sigmoid colon warrant a colonoscopic screening interval of 5 years.[179] In addition, when four or more hyperplastic polyps of any size are found proximal to the sigmoid colon, a 5-year colonoscopic screening interval is recommended.[179] Data to support these approaches are limited. There are conflicting data to suggest whether individuals with hyperplastic polyps greater than 1 cm in size represent an increased risk group are limited. Several analyses suggest that many of the larger polyps classified as hyperplastic in the past were re-classified as SSPs when reviewed by experts.[197-200] Therefore, it is reasonable to follow patients with hyperplastic polyps greater than or equal to 1 cm in size similarly to SSPs, especially if an expert GI pathologist has not reviewed them.

Screening of Individuals at Increased Risk (CSCR-5)

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.[184] 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 or more 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.[201,202] Patients are considered to have low-risk adenomas when they have less than or equal to 2 tubular adenomas that are less than 1 cm. In this group, colonoscopy should be repeated between 7 to 10 years. Furthermore, patients are considered to have low-risk SSPs when they have less than or equal to 2 SSPs that are less than 1 cm without 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.[184] 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. If adenomas or SSPs are detected, a colonoscopy should be repeated according to clinical findings. Robertson et al reported on a study of 564 participants who had their first adenoma identified by colonoscopy and underwent two additional colonoscopies.[203] 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 SSP-d, an adenoma/SSP greater than or equal to 1 cm, a polyp with villous or tubulovillous histology, or multiple (3–10) adenomatous polyps and/or SSPs or large (≥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.[204] 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.[205] 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 polyps (advanced or multiple polyps) should have a repeat colonoscopy in 3 years, although some data suggest that intervals of 5 years may be appropriate. 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.[179,206] 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.

In individuals with greater than 10 cumulative adenomatous polyps and/or SSPs, a polyposis syndrome should be considered (see *Assessment for Hereditary Syndrome* in the Discussion section of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal), although only a small fraction of those with no family history and low adenoma burden will have a defined hereditary syndrome. Genetic testing should be considered depending on patient age, the number of polyps, and family history. The cumulative presence of 10 polyps or fewer may occasionally be associated with an inherited polyposis syndrome, especially in patients younger than 40 years of age or with a strong family history. Hence, a detailed family history is crucial in patients with multiple adenomatous polyps. Individual management is emphasized. 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.

The NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer provide recommendations for management if a malignant polyp is found at colonoscopy.

***Management of Large Colorectal Polyps* (CSCR-6)**

The management of large polyps is challenging and often requires surgical resection. For this reason, referral to a center with expertise in large polyp management 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.[184,207] 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.[184,208] 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.[184,209-211] Also, because of this risk of recurrence and the not uncommon necessity of surgical resection, sessile polyps or LSL greater than or equal to 20 mm in size should have endoscopic tattoo placement next to the lesion.

For individuals with non-polypoid lesions or sessile colorectal polyps, evaluation for high-risk features of invasive cancer is necessary. For those with high-risk endoscopic features, but 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.

For patients with no high-risk features receiving complete resection, a follow-up colonoscopy is recommended in 1 to 3 years if no invasive cancer and no unfavorable risk factors for recurrence were found. Surveillance should be maintained in 3 years if no recurrence is found at the first surveillance colonoscopy. If risk factors (LSL size ≥40 mm, intraprocedural bleeding requiring endoscopic control, high-risk dysplasia, or macroscopic tissue ablation performed[210] for recurrence are associated with complete resection or a piecemeal resection is performed, 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 NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer.

Personal History of Colorectal Cancer **(CSCR-7)**

Individuals with a personal history of CRC should be followed according to the surveillance recommendations in the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer. 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.[212-215] In patients with rectal cancer, local recurrence at the rectal anastomosis has been reported to occur in 5% to 36% of patients.[216-218] 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.[219] 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 greater than 30% risk for synchronous and metachronous cancers.

The NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer 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[213,220,221] and in three meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[222-224] 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.[214] 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 5-FU to bolus 5-FU/LV in patients with surgically resectable rectal cancer, local recurrence rates continued to rise after 5 years.[225] 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.[226] Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative CRC surgery.[227,228]

The NCCN Guidelines for Colorectal Cancer Screening recommend that patients with a personal history of CRC should routinely be tested for Lynch syndrome or mismatch repair (MMR) deficieny 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 versus a surgical resection specimen, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). 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 tumor testing with immunohistochemical (IHC) and/or MSI be used as the primary approach for pathology-lab–based universal screening and to guide treatment decisions. Testing for Lynch syndrome is discussed in more detail in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

Evidence is emerging that aspirin can reduce the risk of CRC incidence and mortality in high-risk groups.[229-232] Presently, the USPSTF recommends initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have greater than or equal to 10% CVD risk and are at average risk for CRC.[233] However, the preventive benefit on CRC is not apparent until 10 years after aspirin therapy.[32,233] As additional data emerge, consideration for recommending aspirin use will need to be individualized with consideration for life expectancy, comorbidities, and risk.

Personal History of Inflammatory Bowel Disease **(CSCR-8)**

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.[234-236] 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.[237] 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).[238] 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.[234,239] 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 managed as average risk.[234,239]

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.[240,241] 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.[240,241] A 2001 meta-analysis showed that patients with pancolitis have a higher risk of developing CRC than those with less extensive disease.[242]

Colonoscopic surveillance in patients with IBD should be performed during quiescent disease. Colonoscopic surveillance may be performed by chromoendoscopy with targeted biopsy.[243-245] Targeted biopsies have been found to improve detection of dysplasia and should be considered during surveillance chromoendoscopy where expertise is available.[241,243-246] With chromoendoscopy, consider taking two biopsies in every bowel segment, placed in separate specimen jars, to document microscopic disease activity and extent of disease involvement.[247,248] Additional extensive sampling of strictures and masses is also recommended. Colonoscopic surveillance in IBD may also be performed with high-definition white light endoscopy (HD-WLE). Random four-quadrant biopsies every 10 cm with 32 or more samples should be taken for histologic examination. Additional extensive sampling of strictures and masses is also recommended. If using standard-definition white light endoscopy (SD-WLE), performing the colonoscopy in conjunction with chromoendoscopy is recommended. If HD-WLE or chromoendoscopy is not available, the panel recommends referral to institutions with expertise in these modalities.

Evaluation of Surveillance Findings **(CSCR-9, 10)**

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.[249] Targeted biopsies should be performed of strictures and mass lesions. Lesions may be categorized using the Paris classification.[243,250] Dysplasia is classified as endoscopically visible and identified by resection or targeted biopsies or endoscopically invisible and detected by random biopsies.[247]

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,[251,252] 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.[243,247] 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, left-sided disease, hyperplastic or normal mucosa, no

endoscopic or histologic active inflammation), surveillance colonoscopy should be performed in 2 to 3 years. During surveillance, if the patient has any high-risk factors (ie, PSC, extensive colitis, active inflammation, family history of CRC at <50 years of age, dysplasia), he or she should receive follow-up with colonoscopy 1 year after endoscopic resection. Furthermore, if dysplastic lesions with high-grade dysplasia are detected or if piecemeal resection was performed, follow-up with colonoscopy should be done within 3 to 6 months. If endoscopic resection is incomplete, the patient should be referred to a center with expertise in IBD management. Surgical consultation may be considered if not amenable to complete resection. 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 (CSCR-10), and patients present with left-sided disease and 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 3 years.[253,254] Several GI societies' position statements recommend risk-stratified surveillance with an increased surveillance interval of 3 to 5 years in lowest risk patients.[241] However, if patients present with any of the following high-risk factors—PSC, extensive colitis, active inflammation, or family history of CRC at younger than 50 years of age—they may have increased risk for CRC and follow-up surveillance colonoscopy should be performed in 1 year.

Patients with traversable strictures and low-risk factors (ie, left-sided disease, hyperplastic or normal mucosa, no endoscopic or histologic active inflammation) may undergo follow-up surveillance colonoscopy in 1 year. If patients present with high-risk factors (ie, PSC, extensive colitis, active inflammation, dysplasia, family history of CRC <50 years of age), they should undergo follow-up surveillance colonoscopy in 1 year. In addition, referral to a center with expertise in IBD, and chromoendoscopy assessment are recommended. Due to the risk of underlying CRC,[255] 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 Positive Family History **(CSCR-11)**

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). Sometimes a great deal of information can be obtained by looking at first cousins. 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.[256] For further details and guidance, also see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

Positive Family History

If a patient meets the criteria for an inherited colorectal syndrome (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal), further risk evaluation and counseling, as outlined in the guidelines, is required. When any one of the revised Bethesda criteria[257] are met (listed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal), 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.[258-260] If multiple distant relatives are affected, an evaluation for an inherited colorectal syndrome should be considered.[261] 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 at the latest.[262] 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. 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) should undergo colonoscopy at the relative's age of onset of adenoma or by age 40 years at the latest, 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.[263,264] Colonoscopy intervals may be further modified based on personal and family history as well as on individual preferences. A population-based study analyzed more than 2 million individuals to determine RRs for the development of CRC depending on family history of CRC.[258] 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. For individuals not willing to undergo colonoscopy, there are emerging data that FIT may be a reasonable substitute.[265]

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).[266] However, familial risk for CRC was increased in first-degree relatives regardless of the age of diagnosis of the index patient.[266] 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 subjects with 1 first-degree relative had a modest increase in risk for CRC incidence and mortality.[267] Individuals with greater than or equal to two first-degree relatives with CRC had continued increased risk in older age.[267]

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

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