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Updates on Age to Start and Stop Colorectal Cancer Screening: Recommendations From the U.S. Multi-Society Task Force on Colorectal Cancer

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

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The U.S. Multi-Society Task Force on Colorectal Cancer (MSTF), comprised of representatives from the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy, has long supported colorectal cancer (CRC) screening in the general population.[1] The MSTF recommendations on screening of average-risk individuals, defined as those without a personal or family history of colorectal neoplasia (CRC or neoplastic colorectal polyps) and those without clinical features of CRC (eg, gastrointestinal bleeding, iron deficiency anemia, or abnormal imaging) were last updated in 2017.[2] At that time, the MSTF presented recommendations offering average-risk individuals a tiered approach to CRC screening in which tier 1 tests were colonoscopy and fecal immunochemical test (FIT) beginning at age 45 for Black Americans (African Americans) and age 50 for non-Black Americans. The 2017 recommendations also emphasized that the target for CRC screening should be early detection of CRC (ie, curable) *and* early detection and removal of high-risk precancerous lesions—with the goal of decreasing both CRC-associated mortality and CRC incidence. The consensus statement recommended screening until at least age 75 or when life expectancy is less than 10 years, that screening should involve shared decision-making between ages 76 and 85, and that individuals beyond age 85 should not undergo screening.

This Consensus Statement provides updated recommendations on average-risk screening, focused on when to start and

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when to stop CRC screening. A detailed review of approaches to screening, specific screening tests, screening targets, and quality of screening are reviewed in our prior screening recommendations.[2] Similarly, recommendations for colorectal neoplasia surveillance are reviewed in MSTF surveillance guidelines.[3,4]

METHODS

Literature review

A focused literature search was performed by medical librarian consultants to address the principal questions of when to begin and when to stop colorectal screening in average-risk individuals, with the intended targets of screening as early detection of colorectal adenocarcinoma and high-risk precancerous lesions. Our search also aimed to address a secondary question of preferred screening modality.

For when to start screening, Ovid Medline, Embase, and Web of Science were queried in February 2021. This search was limited to human participants, with no limitations on language, country of publication, or publication date. This resulted in 10,123 unique citations; 9,791 were excluded based on title and abstract review, and 332 full text articles were reviewed.

The literature search for when to stop average-risk screening was conducted in March 2021 and queried the same databases. This search was limited to publications from 2017 to 2021 and identified 109 citations from which 37 full-text articles were reviewed. For both questions, a search in the Cochrane Database of Systematic Reviews (2014 to March 5, 2021) and the Database of Abstracts of Reviews and Effects (2014 to March 5, 2021) was updated from the 2017 recommendations.

Systematic reviews, meta-analyses, gastroenterology textbooks, and editorials were searched manually for additional pertinent references. Relevant publications were identified by searching a combination of keywords and database-specific indexing terms for the CRC screening with the following subheadings: fecal occult blood test, a FIT, colonoscopy, sigmoidoscopy, computerized tomography and CT colonoscopy, fecal-DNA, serum testing, and cost-effectiveness. Case reports and studies performed in individuals with inflammatory bowel disease, family history of colorectal neoplasia, prior CRC or polyps, or hereditary CRC syndromes were excluded. All results were exported and de-duplicated in EndNote (Clarivate Analytics, Philadelphia, PA, USA).

Process and levels of evidence

Evidence-based weighted recommendations are provided with supporting discussion to help guide clinicians. The MSTF develops consensus guidance statements through evidence review to develop draft statements that are moved to consensus through a series of joint teleconferences. The completed document was then submitted for review and approval by the governing boards of the American College of Gastroenterology, American Gastroenterological Association, and American Society for Gastrointestinal Endoscopy.

The use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) has been outlined in prior MSTF documents.[4] The GRADE process separates evaluation of the quality of the evidence to support a recommendation from the strength of that recommendation. This is done in recognition of the fact that although the quality of the evidence impacts the strength of the recommendation, other factors can influence a recommendation, such as side effects, individual preferences, values, and cost. The MSTF has adapted the GRADE approach by performing critical review of evidence without traditional meta-analysis. Similar to prior statements, "strong recommendations" are those that would be chosen by most well-informed individuals. "Weak recommendations" are those where individuals' values and preferences may play a larger role than the quality of evidence available. Strong recommendations presented in this article are preceded by "we recommend," whereas weak recommendations are presented as "we suggest."

BURDEN OF CRC IN PERSONS UNDER AGE 50

Over the last several decades, CRC incidence and mortality rates have decreased in the United States.[5] Reasons for this decline include increasing uptake of CRC screening and colonoscopic polypectomy in those over age 50 and changing risk factors (eg, decreased smoking, increased aspirin use).[6,7] Recent data, however, show that CRC incidence rates in individuals ages 50 to 64 have increased by 1% annually between 2011 and 2016.[5,8] Similarly, CRC incidence and mortality rates in persons under age 50, termed early-age onset CRC (EAO-CRC), are also increasing (Figure 1).[9] Detailed reviews of EAO-CRC epidemiology, clinicopathologic features, pathogenesis, and risk factors are presented elsewhere.[10-12] The discussion below is focused on data that inform screening considerations.

Epidemiology of EAO-CRC

Overall incidence and mortality. In the United States, CRC is the second most common cancer and the third leading cause of cancer-related death in men and women under age 50.[13] In 2020, 11% of all colon cancer and 15% of all rectal cancer diagnoses were estimated to occur in individuals under age 50.[5] CRC incidence has been steadily increasing in younger Americans for the last several decades, with the sharpest rise seen in the incidence of rectal cancer (Figure 1). Based on data from the North American Association of Central Cancer Registries, which includes 47 states and the District of Columbia, there has been a 1.1% increase per year (95% confidence interval [CI], .3%-2.0%) from 2006 to 2015 for those under age 50.[14] This includes an increase of .7% per year (95% CI, .5%-.9%) for colon tumors and 1.7% per year (95% CI, 1.4%-2.0%) for rectal tumors.[14] When stratified by tumor histology and age from Surveillance, Epidemiology, and End Result 18 (SEER 18) spanning 2000 to 2016, for those 20 to 29, 30 to 39, and 40 to 49, there was a 5.6% (95% CI, .5%-11.1%), 1.6% (95% CI, 1.2%-2.0%), and .9% (95% CI, .7%-1.2%) annual percentage increase in overall colorectal adenocarcinomas and 1.6% (95% CI, .1%-3.1%), 2.2% (95% CI, 1.7%-2.7%), and 1.2% (95% CI, .7%-1.7%) increase in rectal adenocarcinomas, respectively.[15] Although the steepest increase in adenocarcinoma incidence rates was found in 20- to 29- and 30- to 39-year-olds, a 13% increase in colon adenocarcinoma and 16% increase in rectal adenocarcinoma rates were found in those aged 40 to 49 years from 2000 to 2016.[15]

The current CRC incidence rates in individuals ages 45 to 49 are similar to the incidence rates observed in 50-year-olds in 1992, before widespread CRC screening was performed. From the 2001 to 2010 in the SEER Registry, the CRC incidence among 45- to 49-year-olds was 30.8 and 25.9 per 100,000 for men and women, respectively.[13] CRC incidence in persons aged 50 years in 1992 was 25.6 per 100,000.[16,17] Using historical (1975-2010) population-based SEER data, researchers forecast that for individuals ages 35 to

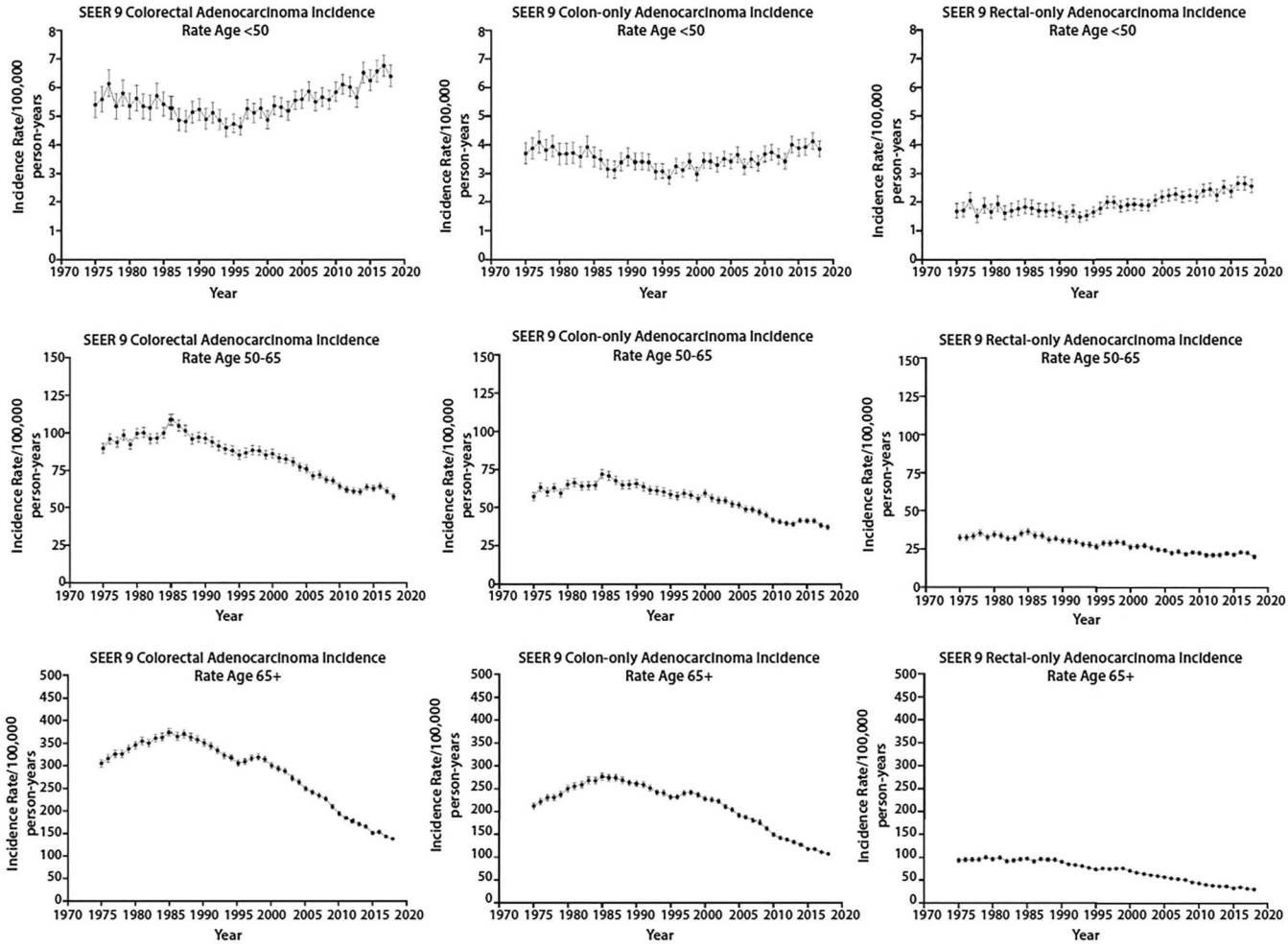

Figure 1. Age-adjusted Surveillance, Epidemiology, and End Results (SEER) incidence rate trends from 1975 to 2018 of colorectal, colon-only site, and rectal-only site adenocarcinoma by age. Incidence rates acquired by E.M., J.K., and M.Z. from SEER 9 Registry (see acknowledgments) using the same methodology as performed in Montminy et al.[15]

49, colon and rectal cancer incidence rates will increase by 27.7% and 46.0%, respectively, by 2030.[18]

Based on data from the National Center for Health Statistics,[19] in 45- to 49-year-olds, mortality from malignant neoplasms of the colon has increased from 6.4 per 100,000 in 1999 to 6.6 per 100,000 in 2019. Mortality from malignant neoplasms of the rectum in this population has increased from 1.3 per 100,000 in 1999 to 1.7 per 100,000 in 2019. Over this same period of time, colon cancer mortality rates have decreased in 50- to 59-year-olds (15.4 to 12.5/100,000), 60- to 69-year-olds (44.1 to 23.9/100,000), and 70- to 79-year-olds (92.7 to 36.1/100,000). Similarly, rectal cancer mortality rates have also decreased in 60- to 69-year-olds (6.5 to 5.1/100,000) and 70- to 79-year-olds (11.9 to 7.5/100,000), although rectal cancer rates have increased in 50- to 59-year-olds (2.6 to 3.1/100,000). This increased mortality from rectal cancer in 50- to 59-year-olds may reflect the cohort effect discussed below.

Birth cohort effect. Siegel et al[9] used age-period-cohort modeling to determine the influence of period effects (ie, because of changes in clinical practice) versus birth cohort effects (ie, because of changes in generation-specific risk factors) in the rising incidence of EAO-CRC. SEER incidence data from 1974 to 2013 were analyzed by age group. Interestingly, the incidence curve for those ages 50 to 54 is similar to the older age groups in the 1970s to 1980s but then reflects the younger age group after the mid-1990s. Siegel et al concluded that the younger birth cohorts are carrying the elevated risk with them as they age and that this risk supports a strong cohort effect in the data. The inflection point for the birth cohort effect is for individuals born after 1960. This strong birth cohort effect suggests that exposures increasingly prevalent in early life, or accumulated across the life course, may contribute to the increasing incidence of EAO-CRC.

Racial and ethnic differences in EAO-CRC. Between 2000 and 2013, EAO-CRC incidence increased 2.5% in Native American/Alaskan natives, 2.3% in non-Hispanic Whites, 1.0% in non-Hispanic blacks, and .2% in Asian/Pacific Islanders.[8] In an analysis of SEER data, Murphy et al[20] reported that from 1992 to 1996 to 2010 to 2014, CRC incidence increased from 7.5 to 11.0 per 100,000 in White individuals and from 11.7 to 12.7 per 100,000 in black individuals. The increase in rectal cancer was larger in White (from 2.7 to 4.5 per 100,000) compared with Black (from 3.4 to 4.0 per 100,000) individuals.[20]

The recent increase in mortality rates is limited to White individuals, among whom there has been a 1.4% increase per year from 2004 to 2014 (3.6/100,000 to 4.1/100,000). Among Black

individuals, mortality rates declined by .4% to 1.1% annually[21]; however, Black individuals still had a higher overall risk of cancer-related death (colon cancer: hazard ratio, 1.36; 95% CI, 1.27-1.45; rectal cancer: hazard ratio, 1.52; 95% CI, 1.38-1.68) from 2000 to 2009 when compared with White individuals.[22] Five-year relative survival was 54.9% in Black individuals compared with 68.1% in White individuals.[22]

Clinical and pathologic features

Most CRCs in young patients are identified because of signs and symptoms rather than incidentally or through screening (Table 1). In a series including more than 1,000 patients with EAO-CRCs, the most common presenting symptom was rectal bleeding (50.8%), followed by abdominal pain (32.5%) and change in bowel habits (18.0%).[23] When compared with later-age onset CRC (LAO-CRC) patients, Chen et al[24] reported that EAO-CRC patients were more likely to present with symptoms of hematochezia (28.8% vs 23.2%, $P < .01$) and abdominal pain (41.2% vs 27.2%, $P < .01$). EAO-CRC patients experienced symptoms for longer periods before diagnosis (243 vs 154 days) and had a longer delay to diagnosis (152 vs 87 days) compared with LAO-CRC patients (Table 1).[24]

LAO-CRC patients are more likely to have right-sided cancers (31.1% vs 20.0%, $P < .001$), and EAO-CRC patients are more likely to have rectal cancer (31.2% vs 22.4%, $P < .001$) (Table 1).[25] EAO-CRC also appears to have more aggressive histopathology than LAO-CRC. Overall, mucinous and signet ring histologies were seen in 10.0% to 14.5%[26-29] and 2.0% to 13.0%[26,27,29] of EAO-CRCs, respectively, with up to 27.9% of cancers being poorly differentiated or undifferentiated.24 Data from the National Cancer Database showed that EAO-CRC was modestly, but significantly, more likely to have a mucinous and/or signet-ring histology compared with LAO-CRCs (12.6% vs 10.8%, $P < .01$) and poor or no differentiation (20.4% vs 18%, $P < .01$).[30]

EAO-CRC is diagnosed at a more advanced stage at the time of detection than LAO-CRC (Table 1). Abdelsattar et al[25] reported a relative risk of 1.37 (95% CI, 1.33-1.41) and 1.58 (95% CI, 1.53-1.63) for younger patients to present with regional or distant metastasis, respectively, compared with older patients. Chen et al[24] found that the difference in stage at presentation between EAO-CRC and LAO-CRCs could not be explained simply by a longer time between the onset of symptoms and diagnosis because younger patients with stage III or IV disease had shorter symptom and workup periods compared with those with stage I or II disease. Thus, advanced stage at diagnosis is not likely explained by longer dwell time or time to diagnosis.

Despite seemingly later-stage and more-aggressive histology at presentation, EAO-CRC patients appear to have equivalent, if not improved, survival. In one large report of SEER data, the stage-adjusted, cancer-specific survival was better in younger patients compared with those diagnosed over age 50 (local: 95.1% vs 91.9%, $P < .001$; regional: 76% vs 70.3%, $P < .001$; distant: 21.3% vs 14.1%, $P < .001$).[25]

It is important to note that the literature on EAO-CRC clinical and pathologic features is drawn from retrospective series that have not consistently separated sporadic cancers from those occurring in patients with hereditary cancer syndromes. Two studies characterized the prevalence of germline pathogenic variants in cohorts of EAO-CRC patients with multigene panel testing. Although these were small cohorts, they suggest that left-sided cancers are more common in sporadic EAO-CRC compared hereditary EAO-CRC. Pearlman et al[31] reported pathogenic variants in 16% of 450 unselected CRC cases. Left-sided cancers (including rectal) comprised a larger proportion of sporadic EAO-CRCs (74.9%) compared with those with a germline pathogenic variants (58.3%) in 1 of 25 cancer susceptibility genes

Table 1. Clinical and pathologic features of CRC diagnosed in patient under and over age 50

Clinical and pathologic features	EAO-CRC (age <50)	LAO-CRC (age ≥50)
Presenting with symptoms, %	86.4[23]-95.6[79,80]	33.9-79.0[80,81]
Incidental or screen detected, %	1.6-5.2[24,80]	3.4-14.6[24,80]
Duration of symptoms, days	243[24]	154[24]
Time to diagnosis, days	152-217[24,82]	29.5-87[24,82]
Family history of CRC, %	13.8-33.5[24,81,83]	8.3-19.3[24,81,83]
Location, %		
Right-sided colon	16.2-35.2[23,24,26,27,35,79-81,83]	28.5-51.5[24,35,81,83]
Left-sided colon	29.1-53.0[23,24,26,27,35,79]	28.9-48.5[24,35,80,83]
Rectal	25.4-49.1[23,24,26,27,79-81]	20.0-35.2[24,35,80,81]
Histology, %		
Mucinous	10.0-15.0[26-28,35,80]	4.7-16.0[28,35,80]
Signet ring	1.0-13.0[26,27,29,35,80]	0.9-4.0[30,35,80,84]
Poor or no differentiation	7.2-27.9[26-28,80]	3.2-18.0[28,30,80]
Stage, %		
Early	11.0-47.0[23,26,27,79,80,83]	37.5-69.7[24,79,80,83]
Late	61.2-89.0[23,24,26,27,79-81,83]	30.3-62.5[24,79-81,83]

EAO-CRC, Early-age onset colorectal cancer; LAO-CRC, later-age onset colorectal cancer; CRC, colorectal cancer.

(which comprised mismatch repair genes and other genes associated with CRC and noncolorectal cancer risk). Similarly, Stoffel et al[32] reported pathogenic variants in 18% of 315 EAO-CRC patients who underwent clinical genetic testing and found that 72.6% of sporadic EAO-CRCs were left-sided versus 38.0% EAO-CRCs in patients with germline pathogenic variants.

Somatic alterations and molecular characteristics of EAO-CRC

The somatic alterations and molecular characteristics of CRCs diagnosed in patients ages 45 to 49 years are similar to CRCs diagnosed in patients age ≥50. In a 2019 a multicenter study, 18,218 CRC cases were subjected to targeted next-generation genomic sequencing of 3,769 exons from 403 cancer-related genes and of 47 introns commonly rearranged in cancer tissues.[33] The patient groups were divided into ages <40 years (n = 1,420), 40 to 49 years (n = 3,248), and >50 years (n = 13,550).[33] Although tumors of patients <40 years of age showed significant differences when compared with tumors in those ages >50, there did not appear to be a significant difference in somatic alterations when comparing tumors from 40 to 49-year-olds compared with >50-year-olds.

Guinney et al[34] described 4 consensus molecular subtypes (CMSs) of CRC: CMS1 (microsatellite instability immune), hypermutated, microsatellite unstable, and strong immune activation; CMS2 (canonical), epithelial, marked WNT and MYC signaling activation; CMS3 (metabolic), epithelial and evident metabolic dysregulation; and CMS4 (mesenchymal), prominent transforming growth factor–β activation, stromal invasion, and angiogenesis. Willauer et al[35] described the molecular features of 36,000 CRCs and demonstrated that CRCs diagnosed in patients under age 50 are not a homogenous group. Patients younger than 40 were predominantly CMS1 or CMS2, whereas patients over age 40 were more likely CMS3 and CMS4. The molecular similarities in patients over age 40 may indicate a birth cohort effect as described above. The similar biology of tumors in 40- to 49-year-olds compared with tumors in those over age 50 suggest they may similarly be appropriate targets for screening.

YIELD OF CRC SCREENING IN PERSONS UNDER AGE 50

Colonoscopy screening

Data are limited on the yield of CRC screening among average-risk individuals <50 years in the United States. Abualkhair et al[36] reported a sharp increase in CRC incidence rates in 50-year-olds compared with 49-year-olds, likely because of screen-detected asymptomatic cancers that were likely present in 45- to 49-year-olds.

A few studies have assessed the yield of CRC screening in average-risk individuals under age 50 in the United States (Table 2). In 2002, Imperiale et al[37] presented results from 906 average-risk adults ages 40 to 49 (61% men) who underwent colonoscopy between 1995 and 2000 as part of an employer-based screening program. They found that 8.7% of their cohort had a nonadvanced adenoma and 3.5% had advanced adenomas. Rundle et al[38] included 553 average-risk individuals ages 40 to 49 who underwent colonoscopy between 2004 and 2006 as part of an employer-sponsored wellness examination and reported nonadvanced adenomas in 12.3% and advanced adenomas in 2% of their cohort. Friedenberg et al[39] reported yield of average-risk screening colonoscopy in 304 black Americans ages 45 to 49 and found nonadvanced adenomas in 12.2% and advanced adenomas in 8.9%. Lieberman et al[40] reported a 4.3% rate of polyps >9 mm in 10,700 individuals younger than age 50 who underwent average-risk colonoscopy screening from 2000 to 2011. Eberth et al[41] found nonadvanced adenomas in 19.1% of Black Americans ages 45 to 49 years undergoing average-risk screening colonoscopy. For each study, advanced adenomas were defined as adenomas ≥1 cm, with villous architecture or with high-grade dysplasia.

There are several limitations to these studies. First, the earlier studies may not reflect the current prevalence of colorectal neoplasia. Second, the generalizability of these studies to the broader U.S. population are limited in that 2 studies included Black Americans only and 2 were part of employer-based programs, disproportionately represented by White individuals and those of higher socioeconomic status. Although the sample size was large for the Lieberman et al[40] study, data on nonadvanced adenomas and CRC were not available, and the retrospective design raises concern that individuals under age 50 undergoing colonoscopy may not have been average risk. The other studies had small sample sizes and no reported CRCs. The studies in non-Black American populations did not stratify results further by age group (40-44 vs 45-49). Finally, these studies were cross-sectional or retrospective in design and thus do not provide data on the efficacy of colonoscopy in decreasing metachronous CRC/advanced colorectal neoplasia incidence or CRC-related mortality.

Multiple international studies have described the yield of colonoscopy in average-risk individuals under age 50 (Table 2). Studies with available data for individuals ages 45 to 49 reported nonadvanced adenoma rates ranging from 8.2% to 20.2% and advanced adenoma rates of 1.2% to 12.5%.[42-45] Kolb et al[46] conducted a systematic review and meta-analysis of screening colonoscopy performed in 51,811 average-risk individuals under age 50 from 17 international studies published from 2002 to 2020, 5 of which were performed in the United States. Among those ages 45 to 49, this systematic review and meta-analysis reported a pooled rate of any colorectal neoplasia of 17.8% (95% CI, 14.5-21.6) and advanced colorectal neoplasia of 3.6% (95% CI, 1.9-6.7). Based on these pooled rates, 28 average-risk individuals ages 45 to 49 need to undergo screening colonoscopy to detect (and remove) 1 advanced polyp.[46]

Butterly et al[47] recently reported rates of neoplasia in 45- to 49-year-olds using data from the New Hampshire Colonoscopy Registry. Because many adults younger than 50 years have colonoscopies for diagnostic indications as opposed to screening, they excluded symptoms shown to be associated with a high risk for advanced neoplasia, such as rectal bleeding, to better approximate an average-risk screening population. They combined colonoscopy findings in those who underwent colonoscopy for "low-risk" symptoms, such as abdominal pain and constipation, with those who had a screening indication. The low-risk symptoms had no association with advanced neoplasia (odds ratio, 1.00; 95% CI, .81-1.24), suggesting that patients with these symptoms likely represent an average-risk population. In the 45- to 49-year-old average-risk screening equivalent group, 17.5% had any colorectal neoplasia and 3.7% had advanced colorectal neoplasia.[47] This study also found that 5.9% of the New Hampshire Colonoscopy Registry patients ages 45 to 49 had a clinically significant serrated polyp (defined as a sessile serrated polyp/lesion, a traditional serrated adenoma, a hyperplastic polyp ≥1 cm, or a hyperplastic polyp ≥5 mm proximal to the rectosigmoid), which was similar to those ages 50 to 54 years (6.1%).

Despite the limitations noted, these studies show that clinically significant neoplasia rates in 45- to 49-year-olds approaches the rates observed in 50- to 59-year-olds. Kolb et al[46] compared neoplasia rates in 45- to 49-year-olds with rates observed in 50- to

Table 2. Summary of studies reporting yield of colonoscopy screening in average-risk individuals under age 50

Study and location	Study period	No. of individuals included	Design	Reason for colonoscopy	Nonadvanced adenoma n (%)	Advanced adenoma n (%)	Colorectal cancer
Imperiale 2002[37] USA	1995-2000	906	Retrospective, cross-sectional	Employer-sponsored colonoscopy screening	40-49: 79 (8.7%)	40-49: 32 (3.5%)	0
Eisele 2007[85] Germany	1998-2003	285	Prospective cohort	Health assessment program for male military personnel	40-49: 67 (23.5%)	40-49: 9 (3.1%)	0
Rundle 2008[38] USA	2004-2006	553	Prospective cohort	Employer-sponsored wellness exam including colonoscopy screening	40-49: 68 (12.3%)	40-49: 11 (2.0%)	0
Park 2009[86] Korea	2003-2004	1,057	Prospective cohort	Routine screening	40-49: 272 (25.7%)	40-49: 25 (2.4%)	0
Hong 2010[42] Korea	2005-2009	1,049	Cross-sectional	Employer-sponsored wellness program including colonoscopy screening	40-44: 57 (11.9%) 45-49: 98/568 (17.3%)	40-44: 9/481 (1.9%) 45-49: 17/568 (3.0%)	0
Friedenberg 2012[39] USA	2007-2010	304	Cross-sectional	Routine screening for black Americans	45-49: 37 (12.2%)	45-49: 27 (8.9%)	
Lieberman 2014[40] USA	2000-2011	10,700	Retrospective cohort	Routine screening, all polyps >9 mm	Not available	<50: 457 (4.3%)	Not reported
Chang 2014[93] Taiwan	2006-2009	3,855	Prospective cohort	Voluntary health checkup including colonoscopy screening	40-49: 469 (12.2%)	40-49: (1.7%)	Not reported
Wang 2014[87] Taiwan	2009-2011	393	Prospective cohort	Routine screening	<45: 39 (9.9%)	Not reported	Not reported
Jung 2015[92] Korea	2010-2011	12,507	Cross-sectional	Routine screening	40-49: 1.941 (15.5%)	40-49: 300 (2.4%)	40-49: 10 (0.1%)
Hemmasi 2015[88] Iran	2009-2012	333	Prospective cohort	Voluntary health checkup including colonoscopy screening	40-49: 35 (10.5%)	40-49: 4 (1.2%)	0
Ionescu 2015[94] Romania	2007-2008 and 2012-2013	389	Retrospective cohort	Routine screening	<50: 14 (3.6%)	<50: 5 (1.3%)	< 50: 5 (1.3%)
Lee 2016[43] Korea	2012-2014	1,082	Cross-sectional	Routine health checkup including colonoscopy screening	40-44: 83/591 (14.0%) 45-49: 99/491 (20.2%)	40-44: 4/591 (.7%) 45-49: 6/491 (1.2%)	0
Leshno 2016[89] Israel	1995-2014	505	Prospective cohort	Routine screening	40-49: 37 (7.3%)	40-49: 5 (1.0%)	40-49: 1 (.2%)
Eberth 2017[41] USA	2014-2016	47	Retrospective cohort	Routine screening for Black Americans facilitated by statewide programs for patient navigation	45-49: 9 (19.1%)	Not reported	Not reported
Hong 2018[44] China	2013-2014	1,685	Cross-sectional	Routine screening	40-44: 53/857 (6.2%) 45-49: 68/828 (8.2%)	40-44: 13/857 (1.5%) 45-49: 17/828 (2.1%)	Not reported

Table 2. (*continued*)

Study and location	Study period	No. of individuals included	Design	Reason for colonoscopy	Nonadvanced adenoma n (%)	Advanced adenoma n (%)	Colorectal cancer
Panteris 2020[45] Greece	2017	24	Cross-sectional	Individual request on a free access basis	45-49: 4 (16.7%)	45-49: 3 (12.5%)	45-49: 1 (4.2%)

59-year-olds within the same studies. The rate of advanced colorectal neoplasia in 45- to 49-year-olds and 50- to 59-year-olds was 3.6% (95% CI, 1.9-6.7) and 4.2% (95% CI, 3.1-5.7), respectively ($P = .69$). In 50- to 54-year-old average-risk individuals from the New Hampshire Colonoscopy Registry, Butterly et al[47] reported advanced colorectal neoplasia in 3.6% of 50- to 54-year-olds (compared with 3.7% in 45- to 49-year-olds). Brenner et al[48] reported advanced colorectal neoplasia in 6.8% of 50- to 54-year-olds undergoing screening colonoscopy.

Two-Step Screening Modalities

Noncolonoscopic screening approaches (eg, FIT) require a second step (ie, colonoscopy) to complete the screening process when the initial screen is abnormal. Currently, data are limited on the yield of 2-step screening approaches for those under age 50. Levin et al[49] reported that of the 10,232 Black individuals between ages 45 and 50 who were offered a FIT, 33.1% completed testing. Of these individuals, 4.0% had an abnormal (ie, positive) FIT, and 85.3% of the individuals with an abnormal FIT completed a colonoscopy. Of those undergoing colonoscopy, 57.8% had any adenoma, 33.6% had an advanced adenoma, and 2.6% were diagnosed with CRC. In comparison, 22.3% of Black individuals ages 51 to 56 completed a FIT, and 4.6% of these individuals had a positive FIT, of which 81.1% completed a colonoscopy. Adenomas were found in 56.7% of those completing colonoscopy, whereas 20.0% had an advanced adenoma and 3.3% had CRC.[49] Test characteristics (sensitivity, specificity) of the FIT in this population cannot be determined from this study because not all average-risk individuals underwent colonoscopy.

In a cross-sectional study of 816 average-risk individuals ages 45 to 49 who underwent a FIT-fecal DNA testing and colonoscopy, no participants were diagnosed with CRC and 49 (6.0%) had an advanced neoplasm (defined as an advanced adenoma or advanced serrated polyp/lesion, which included lesions ≥1 cm or with cytologic dysplasia).[50] Of the 53 of 816 (6.5%) who had a positive FIT-fecal DNA test, 16 (30.2%) had an advanced neoplasm. Of all 49 participants who had an advanced precancerous lesion on colonoscopy, 16 had an abnormal FIT–fecal DNA; thus, FIT–fecal DNA has a sensitivity of 32.7% for detection of an advanced neoplasm. This study was limited by small sample size, and no CRCs were detected. Currently, no data are available data on the yield of other 2-step screening tests, such as CT colonography, flexible sigmoidoscopy, capsule colonoscopy, or Septin9 assay (Epigenomics, San Diego, CA).

BALANCE OF BENEFITS AND HARMS OF CRC SCREENING IN PERSONS UNDER AGE 50

Although there are no CRC screening safety data for average-risk individuals <50, there are ample data that colonoscopy for other indications (screening based on family history, symptom evaluation, etc) is safer when comparing younger versus older individuals.[51] No controlled studies have assessed the impact of screening on CRC incidence, CRC-related mortality, or the risks and costs of CRC screening versus no screening in individuals under age 50. The Cancer Intervention and Surveillance Modeling Network uses 3 independently developed microsimulation models that incorporate available data to predict life-years gained, CRC incidence and mortality, number of screening tests required, and adverse events of screening for a variety of different screening strategies.[52-54] These models are Microsimulation Screening Analysis (Erasmus University Medical Center and Memorial Sloan Kettering Cancer Center), Simulation Model of Colorectal Cancer (University of Minnesota and Massachusetts General Hospital), and Colorectal Cancer Simulated Population model for Incidence and Natural history (RAND Corporation). Results from these models have informed U.S. Preventative Services Task Force guidelines on CRC screening since 2008.[55,56] Incorporating the changing epidemiology of EAO-CRC reviewed above, an update of the modeling report by the Cancer Intervention and Surveillance Modeling Network drafted in 2020 compared outcomes for different screening tests (colonoscopy, FIT, FIT–fecal DNA, flexible sigmoidoscopy, and CT colonography) at different intervals and at different starting and stopping ages.[57] Although the incidence and mortality rates used in this updated report encompassed all colorectal tumors (adenocarcinoma and neuroendocrine),[15] as pointed out by Fields et al[58] and reviewed above, the 40- to 49-year-old group was largely unaffected by isolating adenocarcinomas from neuroendocrine tumors. This report compared outcomes associated with screening initiated at ages 45, 50, or 55 and found that of the 57 screening strategies that were considered efficient, most (47/57) began average-risk screening at age 45.[57] For every 1,000 individuals screened starting at age 45 versus 50, all 3 models showed a favorable balance of life-years gained compared with adverse events (Table 3). It is important to note that these models assume 100% compliance.

Ladabaum et al[59] demonstrated that starting CRC screening at age 45 would cost $33,900 or $7,700 per quality-adjusted life-year (QALY) for colonoscopy every 10 years and annual FIT screening, respectively. This study also explored hybrid screening options and found that a 1-time flexible sigmoidoscopy at age 45 and then colonoscopy at ages 50 to 75 would cost $55,900 per QALY and an annual FIT from ages 45 to 49 followed by a colonoscopy at ages 50 to 75 would cost $2,500 per QALY. This study did not compare other screening modalities such as CT colonography or FIT–fecal DNA. Azad et al[60] reported cost-effectiveness over a 10-year time horizon of single-episode screening at age 40 versus age 50 and found that all modalities were cost-effective against a $50,000 per QALY willingness to pay threshold but that FIT–fecal DNA had the highest cost per QALY.

Table 3. Life-years gained, additional colonoscopies required, and adverse events of screening per 1,000 individuals screened at ages 45-75 compared with ages 50-75

	Additional life-years gained	CRC prevented	CRC death averted	Additional tests required	Additional adverse events
Colonoscopy every 10 y	16-34	1-4	1-2	Colonoscopy: 756-800	2
Annual FIT	17-33	1-4	1	FIT: 3387-3520 Colonoscopy: 175-205	1
Triennial sDNA–FIT	16-31	1-4	1	sDNA–FIT: 1166-1201 Colonoscopy: 177-196	<1
Flexible sigmoidoscopy every 5 y	13-30	1-3	1	Flexible sigmoidoscopy: 743-801 Colonoscopy: 170-192	<1
CT colonography every 5 y	14-31	1-3	1	CT colonography: 798-806 Colonoscopy: 153-165	1

Results are based on 3 independently developed microsimulation models from the Cancer Intervention and Surveillance Modeling Network: Simulation Model of Colorectal Cancer, Colorectal Cancer Simulated Population model for Incidence and Natural history, and Microsimulation Screening Analysis for Colorectal Cancer.[57]
CRC, Colorectal cancer; CT, computed tomography FIT, fecal immunochemical testing; sDNA, stool DNA.

BALANCE OF BENEFITS AND HARMS OF CRC SCREENING IN PERSONS OVER AGE 75

There are no randomized or observational studies after 2017 that enrolled individuals over age 75 to inform the appropriate time to stop CRC screening. In our search, of 37 relevant article, only 1 presented primary data for when to stop screening.[61] In a 2021 simulation study using the Microsimulation Screening Analysis model and considering only FIT screening, several groups appeared to benefit from screening after age 74.[61] For example, women without a history of screening and no comorbidities benefitted from annual FIT screening until age 90, whereas unscreened men with or without comorbidities benefited from annual FIT screening until age 88. Conversely, screening was not beneficial beyond age 66 in men or women with severe comorbidities (defined as at least 1 of the following: AIDS, chronic obstructive pulmonary disease, cirrhosis, chronic hepatitis, chronic renal failure, dementia, congestive heart failure, or combinations of at least 1 moderate condition [peripheral vascular disease or cerebrovascular disease paralysis] with any mild [myocardial infarction, ulcer, or rheumatologic disease] or moderate condition). The study used Canadian data on CRC incidence and stage distribution and did not evaluate an optimal age to stop screening with colonoscopy.[61]

Given the paucity of new data, the decision to screen a patient between ages 76 and 85 remains individualized based on the balance of benefits and harms and individual patient clinical factors and preferences. The risk of advanced colorectal polyps and CRC increases with age.[62-64] However, prevalence of medical comorbidities and overall mortality also increase with advancing age.[65] Previous guidelines have recommended continuation of screening until at least age 75 when clinically appropriate[52,57,66,67]; however, only limited randomized or modeling data support the continuation of screening beyond age 75 among those who have received previous screening.[57,68] Individuals without a history of prior screening may benefit the most in this setting.[57,69] Thus, the decision to initiate or continue screening after age 75 should involve a shared decision-making process between a patient and provider that considers prior screening history, life expectancy, CRC risk, and patient preferences. Patients emphasize provider trust, perceived health risk, barriers to screening tests, and perceived CRC risk in this decision process.[70]

Individuals ages 86 and older should not be offered CRC screening. Overall mortality risk and risk of adverse events associated with colonoscopy outweigh the life expectancy benefit of polypectomy for this age group.[55,61,71] The primary method for CRC prevention through colonoscopy is the removal of high-risk colorectal polyps, and there is considerable lag time in the progression of a precancerous polyp to malignancy and CRC-related death.[72] Thus, elderly individuals are more likely to die of natural causes than CRC, and screening provides minimal life expectancy gains beyond mean U.S. life expectancy. In addition, unintended harms from screening are higher in elderly populations and include direct adverse events from colonoscopy (eg, GI hemorrhage, perforation) and indirect adverse events related to the procedure (eg, cardiopulmonary events, unnecessary medical evaluation for findings).[73] In the 1 study published since 2017 evaluating screening risk, emergency services utilization and hospitalizations after colonoscopy were found to be significantly higher when age is greater than 75 than when age is 50 to 75.[74]

SUMMARY

Although there are no clinical data on the impact of CRC screening in individuals under age 50 on CRC incidence or CRC-related mortality, *there are sufficient supportive data for the MSTF to suggest average-risk CRC screening begin at age 45.* As outlined in detail above, this recommendation is supported by the following:

- Increasing CRC incidence and mortality, such that incidence rates for 45- to 49-year-olds now matches incidence in populations that are already eligible for average-risk screening. Incidence in 45- to 49-year-olds is similar to the incidence observed in 50-year-olds in 1992 when CRC screening was first recommended for those ages 50 and older. Incidence in all 45- to 49-year-olds is currently similar to incidence in Black Americans ages 45 to 49, for whom the MSTF recommended average-risk screening in 2017.
- Emerging data show that the rate of advanced colorectal neoplasia in average-risk individuals ages 45 to 49 is similar to advanced neoplasia rates observed in screening cohorts of those ages 50 to 59.

- Modeling studies that show benefits of screening outweigh harms in average-risk 45-49 year olds. Although not specific to a screening population, data show that colonoscopy is safe in 45- to 49-year-olds.
- Modeling studies demonstrate acceptable cost-effectiveness of average-risk screening to start at age 45.

The MSTF weighed additional factors when issuing this recommendation. As was outlined in the 2017 screening document, the MSTF emphasizes that in addition to early detection of CRC, detection and removal of advanced precancerous polyps is an important target in screening, with the goal of cancer prevention. The similar rates of advanced neoplasia and somatic/molecular features of CRC in 45- to 49-year-olds compared with ≥50-year-olds suggests that the screening target is the same. Although data quantifying the impact of screening under age 50 are currently lacking, a potential advantage is reduction in CRC incidence for those 50 and older via colonoscopic polypectomy. This may be of particular benefit in the context of the observed birth cohort effect, where CRC risk appears to accumulate across the life course. CRC is diagnosed at later stages in individuals under age 50 compared with those over 50 and results in substantial life-years lost. As reviewed by Siegel et al,[75] young CRC patients face unique issues, such as financial toxicity (including material [eg, trouble paying bills], psychological [eg, worrying about paying bills], and behavioral [eg, skipping medications] financial hardships) for those who are in their prime of earning potential, sexual health and fertility concerns, and long-term survivorship. Our recommendation to consider screening in those ages 45 to 49 does not detract from the critical importance of continued efforts to improve screening in those over age 50, where the reported prevalence of screening in individuals ages 50 to 54 years, 55 to 54 years, and ≥65 years is only 48%, 68%, and 71%,[76] respectively, and even lower among those of lower socioeconomic status.[77]

Our recommendation is in congruence with emerging recommendations from other professional societies who are also supporting average-risk CRC screening starting at age 45 on a qualified basis (Table 4). Currently, data are insufficient to guide whether a specific modality of screening is preferred for this age cohort, whether a hybrid approach should be used, or whether screening intervals should be customized.

MSTF recommendations on when to stop screening remain unchanged given a lack of new evidence to alter current practice. For individuals ages 76 to 85, the decision to start or continue screening should be individualized. Important considerations include prior screening history, life expectancy, CRC risk, and personal preference, prompting the need for shared decision-making with providers to weigh the risks and benefits of screening. CRC screening is not recommended after age 85.

CONSIDERATION FOR FUTURE WORK

Although there are many unanswered questions about the etiology, risk factors, and treatment approaches for EAO-CRC, key areas where data are needed to further refine screening guidelines are outlined in Table 5. At present, it is unclear whether all individuals ages 45 and older should undergo CRC screening or whether a precision-screening approach, using a combination of polygenic factors, environmental and lifestyle exposures, and prior screening, is preferred. Data are needed to inform the best screening tools that can optimize yield, efficacy, cost, access, individual, and provider preferences. Data are needed to assess the efficacy and acceptability of a hybrid screening approach, for instance where noninvasive screening is offered at younger ages and colonoscopy is offered as age-related risk increases. As screening expands to younger individuals, it will be critically important to establish systems that track and ensure equitable access to under-represented populations. Although data shows that the United States has sufficient colonoscopy capacity to support expanding screening to 45- to 49-year-olds with colonoscopy either as a primary or follow-up test,[78] it is unclear whether colonoscopy access is equitable. It is also unclear whether the established screening and neoplasia surveillance intervals should be the same in younger individuals as they are in older individuals. Finally, data on whether primary prevention interventions in early adulthood, such as chemoprevention or dietary/lifestyle changes, are needed to assess impact on long-term cancer risk.

When to stop screening also warrants further research. Currently, patients and providers rely on few data elements to determine when there are no longer benefits of screening. Longitudinal trials that follow CRC and other health outcomes for screened participants until the time of death will better inform strategies. However, such studies require decades and are less feasible than microsimulation

Recommendations	
Updated	We suggest that clinicians offer CRC screening to all average-risk individuals ages 45 to 49 (weak recommendation; low-quality evidence). For average-risk individuals who have not initiated screening before age 50, we recommend that clinicians offer CRC screening to all average-risk individuals beginning at age 50 (strong recommendation, high-quality evidence).
Unchanged	We recommend high-quality* colonoscopy every 10 years or an annual FIT as first-tier options for screening of colorectal neoplasia (strong recommendation; moderate-quality evidence). We recommend flexible sigmoidoscopy every 5 to 10 years (strong recommendation; high-quality evidence), CT colonography every 5 years (strong recommendation, low-quality evidence), or FIT–fecal DNA every 3 years (strong recommendation, low-quality evidence) in individuals who decline colonoscopy and a FIT. We suggest that capsule colonoscopy (if available) is an appropriate screening test every 5 years when individuals decline colonoscopy, FIT, FIT–fecal DNA, CT colonography, and flexible sigmoidoscopy (weak recommendation, low-quality evidence). We suggest that individuals who are up to date with screening and have negative prior screening tests, particularly high-quality* colonoscopy, consider stopping screening at age 75 years or when life expectancy is less than 10 years (weak recommendation, low-quality evidence). We suggest that persons without prior screening should be considered for screening up to age 85, depending on consideration of their age and comorbidities (weak recommendation, low-quality evidence).

*Colonoscopy complete to cecum (photo-documentation of the appendiceal orifice, ileocecal valve, or terminal ileum), adequate bowel preparation, performed by a colonoscopist with a ≥25% overall adenoma detection rate.[2]

Table 4. Summary of professional society recommendations on when to start and when to stop CRC screening

	CRC screening start age	CRC screening stop age
MSTF, 2021	"We suggest that clinicians offer CRC screening to all average-risk individuals age 45-49 (weak recommendation; low-quality evidence)."	"We suggest that individuals who are up to date with screening and have negative prior screening tests, particularly high-quality* colonoscopy, consider stopping screening at age 75 years or when life expectancy is less than 10 years (weak recommendation, low-quality evidence)."
	"For average-risk individuals who have not initiated screening before age 50, we recommend that clinicians offer CRC screening to all average-risk individuals beginning at age 50 (strong recommendation, high-quality evidence)."	"We suggest that persons without prior screening should be considered for screening up to age 85, depending on consideration of their age and comorbidities (weak recommendation, low-quality evidence)."
NCCN, 2021 (66)	"Average risk: age ≥45. 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."	Not provided
American College of Gastroenterology, 2021 (67)	"We recommend CRC screening in average-risk individuals between ages 50 and 75 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC." Strong recommendation; moderate-quality evidence "We suggest CRC screening in average-risk individuals between ages 45 and 49 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC." Conditional recommendation; very low-quality evidence	"We suggest that a decision to continue screening beyond age 75 years be individualized (conditional recommendation strength, very low-GRADE quality of evidence)."
USPSTF, 2021 (90)	Grade A: "The USPSTF recommends screening for colorectal cancer in all adults ages 50 to 75 years." Grade B: "The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years."	Grade C: "The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences."
ACP, 2019 (91)	"Clinicians should screen for colorectal cancer in average-risk adults between the ages of 50 and 75 years."	"Clinicians should discontinue screening for colorectal cancer in average-risk adults older than 75 years or in adults with a life expectancy of 10 years or less."
ACS, 2018 (52)	"The ACS recommends that adults aged 45 and older with an average risk of CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on non-colonoscopy screening tests should be followed up with timely colonoscopy."	"Average-risk adults in good health with a life expectancy of greater than 10 years continue CRC screening through the age of 75 years (qualified recommendation)."
	"The recommendation to begin screening at age 45 is a qualified recommendation."	Clinicians should "individualize CRC screening decisions for individuals aged 76 through 85 years based on patient preferences, life expectancy, health status, and prior screening history (qualified recommendation)."
	"The recommendation for regular screening in adults aged 50 y and older is a strong recommendation."	Clinicians should "discourage individuals over age 85 years from continuing CRC screening (qualified recommendation)."

MSTF, Multi-Society Task Force; NCCN, National Comprehensive Cancer Network; USPSTF, U.S. Preventative Services Task Force; ACP, American College of Physicians; ACS, American Cancer Society; CRC, colorectal cancer; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Table 5. Areas of future work to refine recommendations on when to start and stop CRC screening

Areas	Recommendations
Patient selection	Starting age: Should age to start be the same for general population or determined by precision screening? Stopping age: Relative impact of age, prior screening history, CRC risk. patient preference, and comorbidities
Provider acceptance	Provider attitudes and behaviors regarding starting screening earlier, test selection, and stopping screening
Screening test selection	Menu of equivalent options vs tiered approach vs hybrid approach
Access, equity, compliance	Track disparities in access to and use of screening tests, diagnostic tests, and treatment Interventions to address screening underuse in medically underserved populations
Primary prevention	Populations that benefit from chemoprevention Optimal dietary and lifestyle recommendations

CRC, Colorectal cancer.

models or risk stratification strategies that can also inform appropriate and safe use of screening for elderly populations. Approaches to screening test modalities have also been understudied in populations over age 75.

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Abbreviations: CMS, consensus molecular subtype; CRC, colorectal cancer; EAO-CRC, early-age onset colorectal cancer; FIT, fecal immunochemical test; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LAO-CRC, later-age onset colorectal cancer MSTF, U.S. Multi-Society Task Force; QALY, quality-adjusted life-year; SEER, Surveillance, Epidemiology, and End Results

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