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Colorectal cancer in the young: does screening make sense?

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Abstract

Purpose of review: Colorectal cancer (CRC) screening is recommended to reduce CRC mortality. This review outlines key factors to consider when recommending screening, including disease burden, screening benefits and harms, and remaining knowledge gaps.

Recent findings: In response to increasing rates of CRC incidence among younger (age <50 years) adults, the American Cancer Society published guidelines in May 2018 recommending average-risk CRC screening begin at age 45 (vs. 50) years. Rates of young-onset CRC have increased in the U.S. since the early 1990s. However, there is very little empirical evidence of screening effectiveness in younger adults, and few studies have reported harms of routine screening in this age group. Further, we know little about the natural history of CRC in younger adults.

Summary: Uncertainty surrounding the efficacy of CRC screening in younger adults suggest the benefits may be small. Precision cancer screening – or modified screening regimens based on risk – may improve the balance of screening benefits and harms beyond conventional age-based strategies.

Keywords

Colorectal neoplasms; early detection of cancer; mass screening; early-age onset; clinical guidelines

Introduction

Since the late 1980s [1, 2], colorectal cancer (CRC) screening with stool-based tests, flexible sigmoidoscopy, or colonoscopy has been recommended to reduce CRC mortality [3, 4]. Population-wide screening has led to dramatic declines in both incidence and mortality [5], and CRC screening has been touted as one of the most effective preventive health services [6, 7]. Incidence and mortality rates have decreased by more than 30% in the U.S. since 1985, with particularly steep declines among those over age 65 years [8].

Unlike screening for other cancers, where questions linger concerning if, when, how, and how often to screen, historically, there has been consensus across professional organizations

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that CRC screening should start at age 50 years for average risk adults (Table 1). A number of randomized controlled trials and observational studies with mortality endpoints provide strong evidence supporting the effectiveness of guaiac-based fecal occult blood tests (gFOBT) [9, 10], sigmoidoscopy [11-13], and colonoscopy [14, 15]. More recent advances in fecal immunochemical tests (FIT) [16], as well as the availability of CT colonography and FIT-DNA, provide several additional options for screening, all regarded as equally effective [17]. Others have demonstrated efficacy of multi-component interventions [18] to increase patient adherence to screening, including mailed outreach, patient reminders, and reduced structural barriers. Collectively, the field has made enormous progress in understanding CRC biology and screening methods, offering continued support for starting average-risk screening at age 50 years.

In May 2018, the American Cancer Society (ACS) published updated guidelines recommending average-risk CRC screening begin at age 45 years [19]. The ACS commissioned these guidelines in response to increasing rates of CRC incidence among younger (age <50 years) adults [20]. Yet, there is very little empirical evidence of screening effectiveness in those under age 50 years. Nearly all randomized trials of screening efficacy are limited to age ≥50 years, and few or no studies have reported harms of routine screening among 40-year olds. Given the lack of evidence, ACS guidelines rely on simulation models and assumptions [21, 22], extrapolating evidence of screening efficacy and adverse events from older populations. As such, the new recommendation to initiate CRC screening at age 45 years is *qualified* – carrying some uncertainty about the balance of screening benefits and harms in this younger age group.

Screening for any disease in the general population requires thoughtful consideration of disease burden, as well as the benefits and harms of screening. New guidelines have led to an impassioned debate about when to initiate CRC screening among adults at average risk, and many have called for more evidence on screening benefits and harms among 45–49 year olds [23]. Thought leaders in the field have raised concerns about the implications of screening an additional 22 million adults – worsening disparities [24], insufficient endoscopic capacity [25], and cost to the healthcare system [26, 27]. Differences in the ACS and prior guidelines may also cause confusion among patients about what to do in the face of disagreement. Most average-risk adults undergoing CRC screening, even those with abnormal findings, will never develop the disease. The lifetime risk is about 1 in 22 (4.5%), and decisions of who and how often to screen should consider the consequences for the remaining 95% of the population who will never develop cancer. Conflicting guidelines and the surrounding debate raise two related questions:

1. In adults ages 45–49 and 50–75 years, asymptomatic, and at average risk of CRC, what is the balance of benefits and harms in those offered screening compared to those not offered screening?
2. What is the effect of the age at screening initiation on the balance of benefits and harms?

This review outlines key factors to consider when addressing these questions, including disease burden and natural history, screening benefits (i.e., effectiveness), screening harms

(i.e., adverse effects), and remaining knowledge gaps. Table 2 also summarizes these key factors.

Disease Burden

Epidemiology of young-onset CRC

CRC incidence and mortality trends have evolved strikingly in recent decades. Despite large declines in older populations (Figure 1), the incidence of CRC has nearly doubled among younger adults since the early 1990s [20]. Incidence rates have risen rapidly among those ages 20–49 years in the U.S., from 8.6 per 100,000 in 1992 to 12.5 per 100,000 in 2015, with the largest absolute increases among 40-year olds (from 18.2 to 26.5 per 100,000) [8]. Mortality rates have only increased slightly during the same period, ranging from 7.2 to 8.3 per 100,000 among the 45–49 year age group. Similar increases in incidence and mortality have occurred across the globe – from France [28] to Canada [29] to Australia [30]. Despite overall population trends in aging, by 2030, about 11% of colon cancers and 23% of rectal cancers in the U.S. will occur in adults younger than age 50 years [31].

Unrecognized hereditary syndromes and family history of CRC or advanced adenomas may explain a substantial proportion of young-onset CRC. About 15% of young adults diagnosed with CRC carry mutations in genes associated with Lynch syndrome or polyposis [32, 33]. Another 5% have mutations in genes not traditionally associated with CRC (e.g., BRCA, ATM), and 15% report a family history of CRC but no known hereditary syndrome. Many of these patients are eligible for earlier screening under existing clinical guidelines – most organizations recommend patients with a first-degree relative with CRC or advanced adenoma start screening at age 40 or 10 years younger than the earliest family diagnosis [34]. Other guidelines make specific recommendations for screening in the setting of hereditary syndromes [35].

Mechanisms contributing to the other 55% of young-onset CRC cases remain largely unknown. The rise in incidence has occurred more rapidly than expected if it were entirely due to genetics, and environmental risk factors likely play a role [36]. And, for those with hereditary syndromes or family history, environmental risk factors may modify penetrance and contribute to younger age at onset. Many have hypothesized that obesity [37] and diet account for the majority of sporadic young-onset CRC, but these risk factors alone cannot fully explain the increase [38]. Identifying additional risk factors, and their synergistic effects, may inform efforts to risk-stratify screening; however, researchers have made little progress in understanding risk factors that may explain young-onset CRC in persons with no family history.

Finally, it is important to recognize that the large, relative increases in young-onset CRC corresponded to an absolute increase of only a few additional cases per 100,000 persons [39]. Rates among younger adults are still low compared to older populations. For example, at age 45–49 years, incidence increased by 36% from 1992–96 to 2011–15, but the absolute difference in rates over the same time period is a modest 8.2 cases per 100,000. Considering the absolute risk of CRC in younger adults is important because when the prevalence of disease is very low, even the best screening test will not be an effective public health

program [40]. Using a screening test in a population with lower disease prevalence decreases the positive predictive value – and increases the number of false positives. Although there is no consensus on what constitutes “very low” disease prevalence, CRC incidence is markedly lower in certain population subgroups (e.g., white, premenopausal women) than in others. Consequently, the balance of screening benefits and harms will shift when screening a population with lower rates of disease.

Prevalence of colonic neoplasia in younger adults

Screening works best when the natural history of the disease, from latent to symptomatic disease, is adequately understood [41]. This ensures earlier diagnosis and treatment confers a clinical benefit to the patient. For CRC, risk and prevalence of neoplasia across the adenoma-carcinoma sequence [42, 43], including time from initial development of adenoma to preclinical to clinical disease, form the basis of our understanding of natural history. The goal of CRC screening is to intervene upon the life history of CRC by detecting and removing adenomas that may eventually transition to cancer.

A challenge to describing the natural history of young-onset CRC is understanding the prevalence of colonic neoplasia in younger adults. Most estimates derive from autopsy studies performed decades ago [44-46] – and few among 40-year olds. Limited evidence suggests the prevalence of large polyps may be similar between adults ages 40–49 [47] and 50–59 years [48] (3.5% vs. 5.3%). A recent cross-sectional study in Korea shows a very small proportion of 20–29 year olds (0.6%) and 30–39 year olds (0.9%) have advanced neoplasia at colonoscopy [49]. It is not clear whether earlier removal of these lesions impacts important endpoints, like mortality, in younger age groups. An additional challenge is that many colonoscopies performed in younger adults are among those with symptoms or at higher risk of CRC (i.e., due to family history), and the number of lesions identified from these colonoscopies likely does not reflect the true underlying prevalence of neoplasia in this age group. As a result, we know little about whether asymptomatic lesions in younger adults are more or less aggressive or follow a different disease course than those diagnosed in older adults. Information about the expected course and prognosis of young-onset CRC is often extrapolated from the behavior of adenomas and cancers detected in older (asymptomatic) adults.

Benefits and Harms of CRC Screening

Screening benefits

The most direct way of establishing benefits of a screening test is through a randomized trial demonstrating reduction in mortality, or at the very least, reduction in important morbidity [40]. In the 1990s, three trials [50, 10, 9] demonstrated the effectiveness of gFOBT in reducing CRC mortality. Around the same time, case-control studies [51, 52] of sigmoidoscopy showed reductions in CRC mortality of up to 60%. Trials of once-only sigmoidoscopy [53, 54, 11, 55], published after 2010, supported results from these early case-control studies. Although trials of screening colonoscopy are still underway [56-58], support for colonoscopy has evolved from evidence of gFOBT and sigmoidoscopy established in randomized trials, as well as observational studies demonstrating reductions in

CRC incidence and mortality [15, 14]. Consensus quickly developed among professional organizations, and in 1996, the U.S. Preventive Services Task Force endorsed for the first time CRC screening with gFOBT and/or sigmoidoscopy, colonoscopy, or double-contrast barium enema in men and women age 50 years or older [59].

In contrast to evidence accumulated in older populations, very few studies have evaluated CRC screening efficacy in younger adults. Most of the landmark trials of gFOBT and/or sigmoidoscopy are limited to adults older than age 50 years. Notably, the Nottingham trial included adults between the ages of 45 and 74 years and found no mortality benefit of biennial gFOBT among those randomized at age <60 years (RR 0.96, 95% CI 0.85, 1.10) [60]. The trial was not powered to detect differences in outcome by age, but this finding may suggest benefits of screening are most reliably observed in older adults at average risk. Observational studies supporting the effectiveness of screening are also limited to older adults [61]. In clinical practice, most young adults receiving colonoscopy often do so because of symptoms, family history, or reasons other than screening; therefore, it is difficult to determine screening benefits and yield in a younger, asymptomatic population.

To address this lack of data, experts rely on modeling studies. Modeling studies are not new to cancer screening, and in fact, CRC screening may be particularly well suited for models because of data inputs readily available from randomized trials of gFOBT and sigmoidoscopy and observational studies. For example, in the absence of head-to-head comparisons of different screening tests (e.g., colonoscopy vs. FIT), simulation models have shown several screening strategies reduce CRC mortality by a similar magnitude [62, 3]. Healthcare organizations have long used modeling studies to make clinical recommendations and reimbursement decisions, including the U.S. Preventive Services Task Force, Centers for Medicare and Medicaid Services, and World Health Organization.

Of course, simulation models perform only as well as the data inputs are accurate. Models often incorporate assumptions not based on any real evidence (e.g., 100% screening adherence, natural history derived from decades' old autopsy studies), and these assumptions may lead to unrealistic recommendations. Examining the choice and consequences of model-recommended strategies vs. empirical evidence is left to the discretion of the guideline-making organization. Two of the three simulation models used by the U.S. Preventive Services Task Force recommended screening initiation at age 45 years [62], but given the limited empirical data to support screening 45–49 year olds, the Task Force presented screening strategies with the age to initiate screening of 50 or 55 years. Using the same three simulation models, albeit with slightly different data inputs, the ACS recommended screening initiation at age 45 years. These differing recommendations underscore the importance of exercising caution when allowing modeling studies to guide health policy decisions affecting millions, particularly in the absence of empirical evidence.

Screening harms

Harms of a screening test can affect multiple domains, from medical complications to anxiety over abnormal results to a cascade of follow-up tests and treatment. Because colonoscopy is the most common (and invasive) screening test, harms of CRC screening are typically measured as the number of lifetime colonoscopies and any resulting complications,

such as colonic perforation or major bleeding. Guidelines recommending screening initiation at age 50 years estimate about 4,100 lifetime colonoscopies per 1,000 persons screened [62]. Lowering the screening age to 45 years requires an additional 1,400 colonoscopies for a total of 5,600 lifetime colonoscopies per 1,000 screened [22]. These estimates assume screening occurs predominantly by colonoscopy, with few or no stool-based tests or CT colonographies. Lifetime colonoscopies can be an ambiguous screening harm, particularly to patients, and the impact on clinical practice of additional colonoscopies required by new guidelines is not yet clear.

Other studies of CRC screening harms describe incidence of perforation and bleeding, mostly derived from adverse events reported in trials [63] or large, population-based cohort studies [64, 65]. Risk of screening harms generally increases with age [4], but few studies describe these harms specifically in younger adults. Among those that do, risk of perforation and bleeding is slightly lower or about the same as in older populations (risk of perforation: 6 per 10,000 colonoscopies among ages 18–49 years [66], risk of bleeding: 2 per 1,000 colonoscopies [65]; see Table 2).

Another dimension of screening harms is cost. The U.S. Preventive Services Task Force and other guideline panels make the deliberate decision to exclude cost from assessments of screening benefits and harms, in part to avoid the appearance that screening guidelines limit health care based on cost [67]. However, cost is still an important consideration for patients, payers, and healthcare systems, particularly in the U.S because insurance coverage widely varies. Although there is no formal cost-effectiveness analysis of initiating screening at age 45 years, for illustration, we can assume screening with a mix of colonoscopy and stool-based tests costs $250 per person and reduces CRC mortality by 50% [26]. The direct cost to prevent 13,600 CRC deaths among 45–75 year olds would be $2.0 million per death averted, compared to about $1.8 million per death averted when screening ages 50–75 years. There may also be indirect costs to the patient (e.g., time off work, lost productivity) and healthcare system (e.g., shifting diagnostic colonoscopies to screening colonoscopies [24]). Indirect costs may be especially important to adults in their 40s – an age group arguably in the most productive years of their life [20].

Conclusion

The goal of any population-wide screening program should be to match risk of disease with the benefits and harms of screening. It is tempting to believe that, because more young adults are diagnosed with CRC, screening must have an equally as large impact. Increases in young-onset CRC are real and important, but increases in incidence alone do not provide any evidence supporting the efficacy of screening –or the potential harms of screening that need to be offset by benefits to be useful. Uncertainty surrounding the efficacy of CRC screening in younger adults, combined with their much lower incidence of CRC, suggest the benefits of screening **all 22 million** 45–49 year olds may be small.

Moving toward precision CRC screening

Rather than debate the age to initiate CRC screening, we could instead learn from a discussion of how to better define subgroups at increased risk – a concept now referred to as

precision cancer screening [68]. Precision screening uses a combination of genetic factors, environmental and lifestyle exposures, and prior screening to determine the expected benefit of screening for any individual person. Indeed, some organizations have already recommended earlier CRC screening for higher-risk subgroups: African Americans and Alaska Natives, those with family history of CRC or advanced adenomas, and those with inflammatory conditions such as Crohn's disease or ulcerative colitis (Table 1). In our current clinical practice, we can and should do a better job of identifying those at higher risk, particularly because familial risk (genetic syndrome, family history of either CRC or advanced adenomas) accounts for nearly half of cases diagnosed in younger adults. Meanwhile, research efforts must focus on better understanding the biology of young-onset CRC and associated risk factors, which will facilitate and expand risk-stratified screening in the future.

We should also be mindful of the challenges of precision cancer screening. There are clearly some 45 year-olds who will benefit from earlier CRC screening, but identifying those at higher risk (beyond the subgroups listed above) from a pool of 22 million is difficult. Implementing precision screening must take into account a number of factors: endoscopic capacity, management of additional, screen-detected cancers, availability of genetic and environmental information to calculate risk, communication strategies for patients and providers, and the potential impact on disparities. Considering these challenges while the evidence base still accumulates may allow for rapid uptake if precision strategies prove beneficial [68].

Better risk assessment– and modified screening regimens based on risk – may improve the ratio of benefit to harm over conventional age-based strategies. As genetic information becomes increasingly available, efforts are underway to develop and validate models of CRC risk based on lifestyle, environmental, and genetic risk factors [69], with hopes of identifying the optimal age to begin screening. For example, a recent study showed risk calculation models that included genetic and environmental factors have greater accuracy than family history and age alone [69]. Our goal should be to translate these scientific findings into actionable, clinical information that informs precision cancer screening. Small improvements in risk calculation models can translate into large improvements in risk stratification and recommendations for the age to initiate CRC screening.

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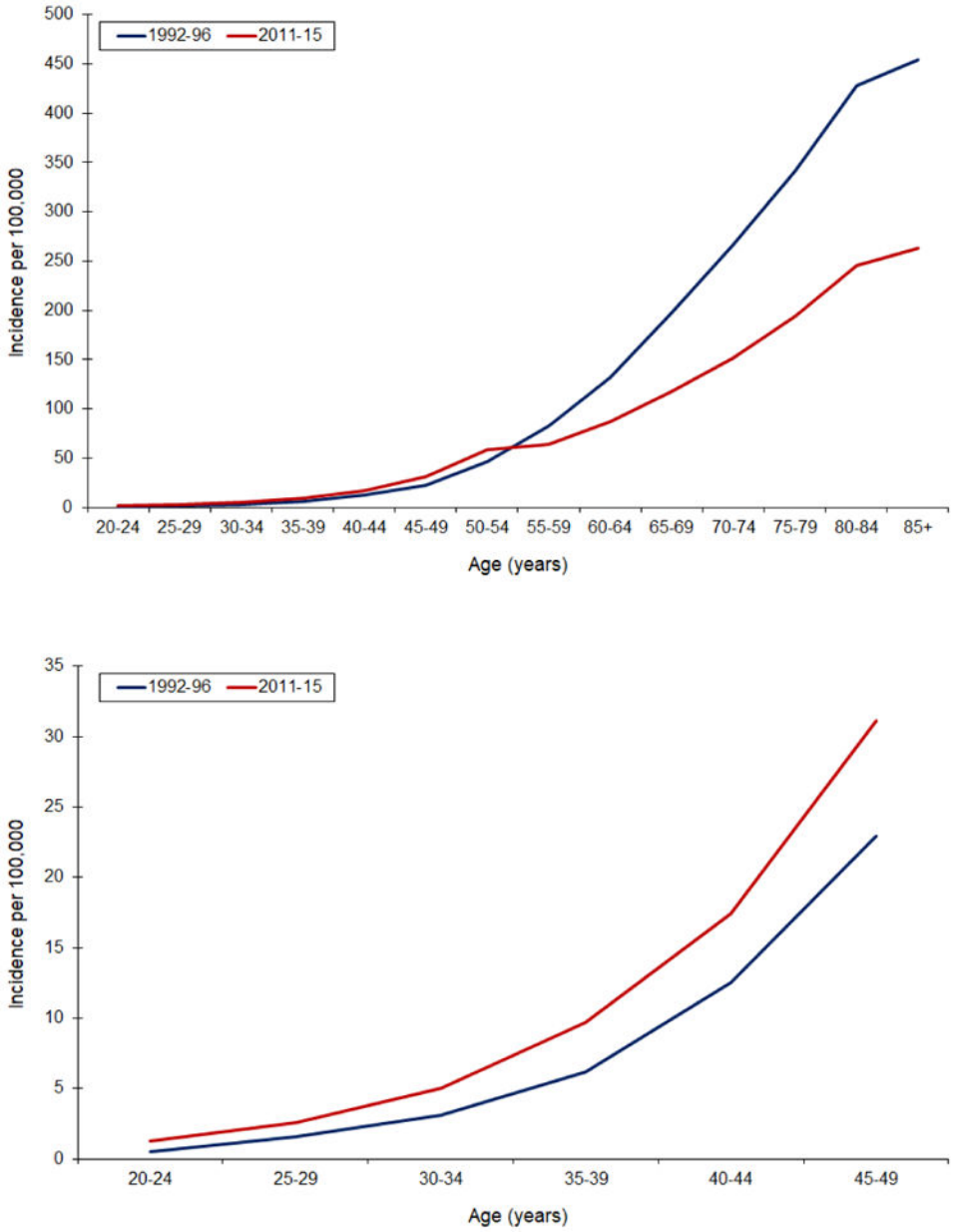

Figure 1.

Age-specific incidence rates of colorectal cancer by time period (1992-96 vs. 2011-15), overall (A) and in ages <50 years (B), SEER 13, 1992 – 2015

Table 1:

Recommendations for colorectal cancer screening across professional organizations

Professional organization	Recommended screening tests	Age to initiate screening	Age to stop screening	Other considerations
U.S. Preventive Services Task Force (2016) [70]	gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, sigmoidoscopy	50	75	
U.S Multi-Society Task Force on Colorectal Cancer (2017) [71]	FIT, colonoscopy (Tier 1) *	50	75	Screening at age 45 years for African Americans; AGA endorses Canadian guidelines on screening in setting of family history[34]
National Comprehensive Cancer Network (2018) [72]	gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, sigmoidoscopy	50	75	Focused guidelines address screening for high-risk syndromes[35]
American College of Physicians (2012) [73]	gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, sigmoidoscopy, DCBE	50	75	
Canadian Task Force on Preventive Health Care (2016) [74]	gFOBT, FIT, sigmoidoscopy	50	74	Weak recommendation for screening in ages 50-59 years
American Cancer Society (2018) [19]	gFOBT, FIT, FIT-DNA, colonoscopy, CT colonography, sigmoidoscopy	45	75	Qualified recommendation for initiating screening at age 45 years – uncertainty regarding ratio of benefits to harms

* Tier 2 tests include CT colonography, FIT-DNA, flexible sigmoidoscopy

Table 2.

Key factors to consider when making recommendations of when to initiate CRC screening

	Keep screening at age 50 – screen ages 50 to 75	**Lower screening to age 45 – screen ages 45 to 75**
What is the burden of CRC in the population?	• 79,860 diagnoses and 25,500 deaths at ages 50-75 years • Most frequently diagnosed cancer among 65-74 year olds • Incidence and mortality rates accelerate at age 50 years (Figure 1)	• 7,000 diagnoses and 1,720 deaths at ages 45-49 • Incidence among 45-49 year olds increased by 36% since early 1990s (Figure 1); mortality remained stable during same time period
What is the natural history of CRC and prevalence of neoplasia?	• Most CRCs arise from adenoma-carcinoma sequence • Autopsy studies show prevalence of neoplasia of about 20%, increases with age [75] • Prevalence of advanced adenomas ranges from 5-12% among asymptomatic adults [76]	• Few studies describe prevalence of colonic neoplasia in asymptomatic adults age <50 years • Little information about the aggressiveness or disease course of asymptomatic lesions in younger adults, extrapolated from the behavior of adenomas and CRC detected in older adults
What is the effectiveness of screening?	• Reduces risk of CRC death by 10-45% [4] • Reduces CRC incidence by 25% [61] • 17-24 deaths averted for every 1,000 people screened [70]	• No empirical evidence showing reductions in incidence and mortality for 45-49 year olds, extrapolated from benefits of screening older populations • Nottingham trial: no mortality benefit of biennial FOBT among those randomized at age 45-60 years (RR 0.96, 95% CI 0.85, 1.10) at 20-year follow-up [60]
What are the adverse effects or harms of screening?	• Risk of colonic perforation: 7-10 per 10,000 colonoscopies among age ≥50 years, increases with age [66] • Risk of bleeding: 2 per 1,000 colonoscopies [77] • *Cost: $1.8 million per death averted • 4,100 lifetime colonoscopies per 1,000 screened [70] • Overdiagnosis [78] and overtreatment of small lesions	• Risk of colonic perforation: 6 per 10,000 colonoscopies among ages 18-49 years [66] • Risk of bleeding: 2 per 1,000 colonoscopies [65] • *Cost: $2.0 million per death averted [26] • 5,600 lifetime colonoscopies per 1,000 screened [22] • Overdiagnosis [79] and overtreatment of small lesions
What types of studies provide evidence on benefits and harms of screening?	• Randomized controlled trials (FIT/FOBT, flexible sigmoidoscopy) • Prospective cohort studies with mortality endpoints, case-control studies (colonoscopy) • Trials of screening colonoscopy for average-risk adults underway (NordICC [56], COLONPREV [57], CONFIRM[58])	• Microsimulation models [22, 21] incorporating recent increase in CRC incidence among adults age <50 years
What are the key gaps in the evidence?	• Head-to-head comparative trials of competing screening strategies (e.g., FIT vs. colonoscopy) and CRC mortality	• Natural history of colonic neoplasia in younger adults • Empirical evidence supporting screening efficacy and test performance in 40-year olds

	Keep screening at age 50 – screen ages 50 to 75	Lower screening to age 45 – screen ages 45 to 75
		• Environmental risk factors for young-onset CRC • Proportion of cases explained by genetic syndrome, family history of CRC or advanced adenoma, covered under previous guidelines
Other considerations	• Earlier screening for higher-risk subgroups: African Americans,[80] Alaska Natives, those with family history of CRC or advanced adenomas or inherited syndrome, those with inflammatory bowel disease • Concentrate efforts on the 35% of 50-75 year-olds not yet screened	• Insurance coverage • Endoscopic capacity to screen 22 million 45-49 year olds • Obviates need for targeted screening in subgroups by race/ethnicity or family history • Encourages earlier discussion of screening and risk assessment • Positive predictive value depends upon prevalence of disease – incidence still low in 45-49 year olds

* For illustration, cost estimates assume screening with a mix of colonoscopy and stool testing costs $250 per person and reduces CRC mortality by 50%; in 2017, there were 25,505 CRC deaths among those age 50-75 years (total population size 90,600,000) and 27,225 deaths among those age 45-75 years (total population size 111,400,000).