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CLINICAL PRACTICE GUIDELINES

Delphi Initiative for Early-Onset Colorectal Cancer (DIRECt) International Management Guidelines

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Abbreviations used in this paper: **ADR, adenoma detection rate; CI, confidence interval; CINV, chemotherapy-induced nausea and vomiting; CRC, colorectal cancer; DIRECt, Delphi Initiative Recommendations on EoCRC; eoCRC, early-onset colorectal cancer; ESGE, European Society of Gastrointestinal Endoscopy; ESMO, European Society of Medical Oncology; FIT, fecal immunochemical testing; GI, gastrointestinal; IHC, immunohistochemistry; LE, level of evidence; loCRC, late-onset colorectal cancer; LPV, likely pathogenic variants; LS, Lynch syndrome; MMR, mismatch repair; MMR-d, mismatch repair deficiency; MMR-p, mismatch repair proficiency; MSI, microsatellite instability; MSI-H, microsatellite instability high; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; OR, odds ratio; PICO, population, intervention, comparison, and outcome; PRS, polygenic risk scores; PV, pathogenic variants; RR, relative risk; SNP, single nucleotide polymorphism; USMSTF, U.S. Multi-Society Task Force; USPSTF, U.S. Preventive Service Task Force.**

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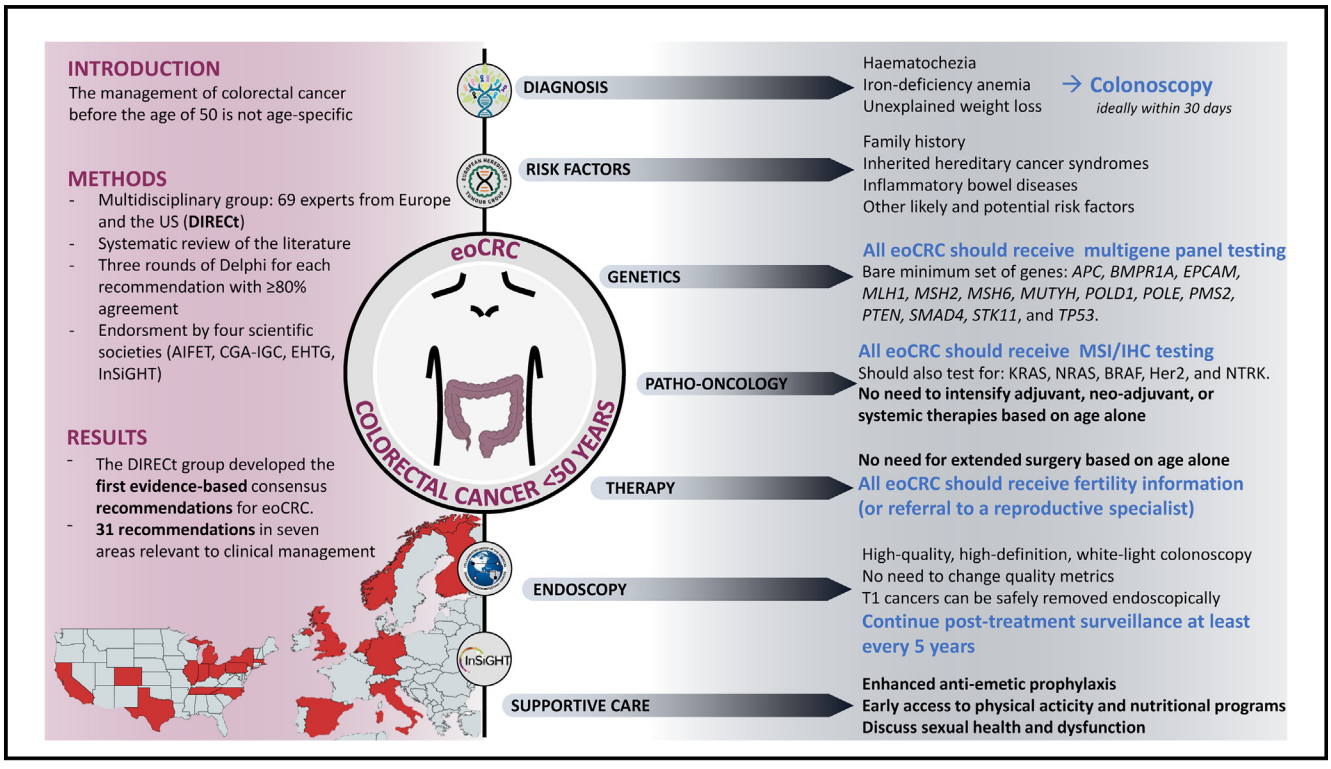
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e7. Upon completion of this module, successful learners will be able to evaluate high-risk symptoms of early-onset colorectal cancer, explain the utility of tumor testing and germline testing in this setting, integrate the oncological management with the fertility management, and cite the surveillance protocol after cure from colorectal cancer <50 years.



BACKGROUND & AIMS: **Patients with early-onset colorectal cancer (eoCRC) are managed according to guidelines that are not age-specific. A multidisciplinary international group (DIRECt), composed of 69 experts, was convened to develop the first evidence-based consensus recommendations for eoCRC.**

METHODS: **After reviewing the published literature, a Delphi methodology was used to draft and respond to clinically relevant questions. Each statement underwent 3 rounds of voting and reached a consensus level of agreement of ≥80%.**

RESULTS: **The DIRECt group produced 31 statements in 7 areas of interest: diagnosis, risk factors, genetics, pathology-oncology, endoscopy, therapy, and supportive care. There was strong consensus that all individuals younger than 50 should undergo CRC risk stratification and prompt symptom assessment. All newly diagnosed eoCRC patients should receive germline genetic testing, ideally before surgery. On the basis of current evidence, endoscopic, surgical, and oncologic treatment of eoCRC should not differ from later-onset CRC, except for individuals with pathogenic or likely pathogenic germline variants. The evidence on chemotherapy is not sufficient to recommend changes to established therapeutic protocols. Fertility preservation and sexual health are important to address in eoCRC survivors. The DIRECt group highlighted areas with knowledge gaps that should be prioritized in future research efforts, including age at first screening for the general population, use of fecal immunochemical tests, chemotherapy, endoscopic therapy, and post-treatment surveillance for eoCRC patients.**

CONCLUSIONS: **The DIRECt group produced the first consensus recommendations on eoCRC. All statements should be considered together with the accompanying comments and literature reviews. We highlighted areas where research should be prioritized. These guidelines represent a useful tool for clinicians caring for patients with eoCRC.**

Keywords: Recommendation; Clinical; Young; 50 Years; Colorectal Cancer.

Colorectal cancer (CRC) diagnosed before the age of 50 is referred to as early-onset CRC (eoCRC). Numerous studies have reported that the epidemiology of eoCRC has changed over the past decades[1]; since the 1990s, there has been an increase in incidence rates of eoCRC across the globe in both high- and low-income countries.[2–4] The rate of increase in eoCRC incidence is accelerating, such that it is projected to become a significant public health threat.[2,3]

In contrast, during the last decades, CRC incidence and mortality rates have decreased in individuals older than 50 living in high-income countries[5] because of effective screening programs[6,7] and healthier lifestyle habits (decreased smoking, increased aspirin use).[8,9] Moreover, advances in surgery, radiotherapy, and systemic therapy have reduced morbidity and increased survival.[10–13] Currently, there is significant interest in determining the most appropriate strategies for diagnosis, treatment, and follow-up of eoCRC. There are several knowledge gaps regarding the appropriate management of eoCRC patients, including whether they should receive different surgical, adjuvant, neoadjuvant, and supportive treatments. In the past decade, sufficient evidence has been gathered to warrant the first international evidence-based consensus guidelines. The primary aims of this document are to collect and summarize all available evidence on eoCRC and to provide high-quality risk assessment and disease management guidance for healthcare professionals who care for eoCRC patients.

These recommendations from the DIRECt group (Delphi Initiative Recommendations on eoCRC) received the endorsement of 4 scientific societies: the Associazione Italiana Familiarità Ereditarietà Tumori (AIFET), the Collaborative Group of the Americas on Inherited Gastrointestinal Cancers (CGA-IGC), the European Hereditary Tumor Group (EHTG), and the International Society for Gastrointestinal Hereditary Tumours (InSiGHT).

Methods

The first 2 consensus votes were held online because of the severe acute respiratory syndrome–associated coronavirus (SARS-CoV2) pandemic. The third voting round was held during the DIRECt22 congress in Milan (September 2022). All votes were registered anonymously. The DIRECt consensus was led by a non-voting chairman (GMC) and included a multidisciplinary, international scientific panel of 69 professionals/experts divided into 7 working groups (Table 1, Supplementary Figure 2). Expertise was defined according to publications and clinical expertise. The scientific panel defined, developed, and reviewed the recommendations. Each recommendation was graded according to the Oxford Center for Evidence Based Medicine levels of evidence (LE) (Supplementary Tables 1 and 2).[14] Unlike other ranking schemes that focus on therapeutic interventions

Table 1. Distribution of Experts

Chairs of the Working Panels	Balaguer F, Hampel H, Kupfer SS, Repici A, Sartore-Bianchi A, Seppälä TT, Valentini V
Consensus non-voting chairman	Cavestro GM
Scientific Board	Boland CR, Brand RE, Caccialanza R, Cascinu S, Dekker E, Daca-Alvarez M, Deni F, Dominguez-Valentin M, Houwen BBSL, Kastrinos F, Mannucci A, Meldolesi E, Möslein G, Murphy CC, Nass K, Ng K, Oliani C, Papaleo E, Patel SG, Puzzono M, Remo A, Ripamonti CI, Syngal S, Turi S, Urso ED, Valle L, Zuppardo RA, Stoffel EM
Consensus participants	Buffart TE, Burke CA, Cannizzaro R, Cercek A, Crosbie EJ, Danese S, Eng C, Goel A, Guillem JG, Kahi C, Kalady MF, Kühn F, Laghi L, Latchford A, Liska D, Lu KH, Lynch P, Malesci A, Mauri G, Møller P, Monahan KJ, Ricciardiello L, Siena S, Singh SK, Stadler ZK, Stanich PP, Vanni VS, Vilar E, Yurgelun MB
Representative of the non-governmental organizations for patients	Davis A, Vitaloni M

and harms, the Oxford system has the additional benefit to appraise evidence on epidemiology, risk factors, accuracy of diagnostic tests, and rare and common harms. Therefore, the Oxford system was preferred because of its distinguishing ability to cover multiple questions. Briefly, in the Oxford system each article receives a LE; systematic reviews receive the highest LE (LE 1A), whereas randomized controlled studies and cohort studies are ranked on the basis of the design (retrospective vs prospective), the length of follow-up, the percentage of follow-up, and the width of confidence intervals (CIs) (LE 1B–2B). Individual case-control studies, ecological studies, outcome studies, non-consecutive cohort studies, and audit studies provide lower LE (LE 2C–4). The lowest LE is represented by expert opinion, bench-research, and "first principle" research (LE 5). After the evaluation of each article, the recommendations are graded (GR) on the basis of the consistency of findings from all studies. If all studies find similar results, the recommendations receive a higher grade. All recommendations were based on a critical appraisal of the available evidence, as summarized in Supplementary Appendices 2–7. The appendices explain the results, interpretation, and LE of all the articles that support each statement. The timeline and methods of the DIRECt recommendations are detailed in Supplementary Figure 1 and Supplementary Appendix 1, respectively.

The agreement/disagreement level was scored on a 6-point scale, with the option of providing anonymous feedback during the first 2 virtual consensus and the third discussion rounds (Supplementary Table 3 and Supplementary Figure 3). The level of agreement was expressed as a percentage of each point of the scale. At the end of at least 3 rounds of voting, statements receiving $\geq$80% agreement were accepted.

The format recommendations comprised the question, statement, LE, strength of recommendation, and final percentage of agreement. All statements are accompanied by qualifying comments, which were written and reviewed by each working group and the entire scientific panel. Statements and their accompanying comments are meant to be read together as a whole.

Results

The DIRECt consensus produced 31 recommendations for patients diagnosed with eoCRC $\geq$18 years old based on 145 articles (summarized in Supplementary Appendices 2–7). When appropriate, issues related to colon or rectal cancers specifically are highlighted; in cases where statements applied to both colon and rectal cancer, the term *colorectal cancer* (CRC) was used. All statements are summarized in Tables 2–4 (Table 2: diagnosis, risk factors, and genetics; Table 3: pathology, oncology; Table 4: endoscopic diagnosis and treatment, therapy, and supportive care). Areas of controversy are described throughout the main text and summarized in Table 5.

Section I – Diagnosis (D)

D.1: Comment. Historically, CRC screening has started at age 50 for average-risk individuals in the United States. As a result, CRC diagnoses in patients aged <50 have been referred to as early- or young-onset in the literature. Some U.S. societies have recently recommended lowering the average-risk population screening age to 45 years.[15–20] For the purpose of continuity and consistency in research, we recommend using the term *early-onset CRC* (eoCRC) and defining this as CRC diagnosed younger than 50 years of age. However, with changes in age for population-based screening, it will be critical to assess whether there are differences in risk factors, diagnosis, and/or outcomes for those age 45 and older compared with those younger than age 45. Several terms have been used to describe CRC in the youngest age groups.[21–23] The Scientific Panel suggested "very early onset" for CRC diagnoses before 35 years based on definitions used in previous studies.[23–26] Age 18 is

Table 2. Statements Pertaining to the Diagnosis (D), Risk Factors (R), and Genetics (G) of Early-Onset Colorectal Cancer

Question and statement	Level of evidence, grade of recommendation, agreement level, and clarity
Diagnosis of early onset colorectal cancer (D)	
D.1: What is the age cutoff to define eoCRC? EoCRC is defined as CRC diagnosed younger than age 50.	LE 2A; GR B Agreement: 91.7% (A+ 50.0%|A 41.7%|A– 8.3%)
D.2: Which symptoms and clinical signs prompt evaluation for eoCRC? Symptoms and signs that should prompt evaluation for eoCRC include (but are not limited to) any of the following: hematochezia, unexplained iron deficiency anemia, or unexplained weight loss.	LE 2B; GR B Agreement: 90.7% (A+ 53.5%| A 37.2%|A– 7.0%|D– 2.3%)
D.3: Which test(s) should be used to evaluate eoCRC signs and symptoms? A diagnostic colonoscopy is recommended for evaluation of alarming symptoms and signs of eoCRC.	LE 2B; GR B Agreement: 85.4% (A+ 56.1%|A 29.3%|A– 7.3%|D– 4.9% |D 2.4%)
D.4: When should colonoscopy be performed for alarming symptoms? A colonoscopy should be expedited, ideally within 30 days after referral to a healthcare professional.	LE 2B; GR C Agreement: 86.5% (A+ 35.1%|A 51.4%|A– 10.8%|D+ 2.7%)
Risk factors of early-onset colorectal cancer (R)	
R.1: Does family history of CRC influence eoCRC detection? A family cancer history can inform risk assessment for syndromic and non-syndromic CRC. Therefore, a thorough family history should be routinely collected for all individuals. In addition, in non-syndromic cases, CRC family history can facilitate the identification of high-risk individuals who may benefit from starting screening at an earlier age.	LE 1A; GR A Agreement: 89.2% (A+ 27.0%|A 62.2%|A– 8.1%|D 2.7%)
R.2: What other risk factors increase the risk of eoCRC? Some studies have identified male sex, race and ethnicity, obesity, diabetes, alcohol consumption, and hyperlipidemia as potential risk factors for eoCRC. However, at this time the evidence is insufficient to recommend earlier CRC screening based on these factors.	LE 1B; GR A Agreement: 92.5% (A+ 27.5%|A 65.0%|A– 7.5%)
Genetics of early-onset colorectal cancer (G)	
G.1: Which eoCRC patients should receive germline genetic testing and when? A. All eoCRC patients should be offered multi-gene panel germline genetic testing and genetic counseling for those with a positive germline finding.	LE 1B; GR A Agreement: 100% (A+ 66.7%|A 33.3%)
B. Genetic testing should be performed before treatment to maximize clinical utility, when feasible, but should not substantially delay treatment.	LE 2A; GR B Agreement: 91.9% (A+ 32.4%|A 59.5%|A– 8.1%)
G.2: What genes should be included in germline multi-gene panel tests for eoCRC patients? Germline genetic testing for CRC patients diagnosed younger than age 50 should include at a minimum: • *APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, MUTYH, POLD1, POLE, PMS2, PTEN, SMAD4, STK11*, and *TP53*. Where available and not cost-prohibitive testing should also include: • The following genes that are reasonably prevalent in CRC and change clinical management: *BRCA1, BRCA2, ATM, CHEK2, PALB2*, and possibly, but less prevalent, *BRIP1, BARD1, CDKN2A, CDH1, RAD51C,* and *RAD51D.* • The following genes that have been associated with CRC or polyposis: *AXIN2, GREM1, MLH3, MSH3, MBD4, NTHL1, RNF43*, and *RPS20.*	LE 1B; GR B Agreement: 97.1% (A+ 38.2%|A 58.8%|A– 2.9%)
G.3: Are polygenic risk scores useful for identifying patients at risk for eoCRC? Although emerging data suggest polygenic risk scores (PRS) may provide information that could improve CRC risk stratification, their performance has not been formally validated, and they are not yet ready for clinical use.	LE 2B; GR B Agreement: 100% (A+ 44.8%|A 55.2%)

conventionally used to distinguish adult- from pediatric/adolescent-onset cancers.

D.2: Comment. The most common symptoms and signs of eoCRC are hematochezia (ie, rectal bleeding) (46%), iron deficiency anemia (13.0%), and weight loss (10.0%).[27–32] Hematochezia and iron deficiency anemia (ferritin <15 ng/dL) confer a hazard ratio of 10.66 and 10.81 for eoCRC, respectively, with higher risk for men compared with women and for ages 40–49 compared with age <30.[33] More rectal cancers were noted among those with hematochezia compared with iron deficiency anemia (38% vs 20%, respectively).[33] It should be noted that the American Gastroenterological Association Practice Guidelines recommend gastrointestinal (GI) evaluation for men and postmenopausal women with iron deficiency anemia; in premenopausal women with iron

Table 3. Statements Pertaining to the Pathology and Oncological Treatment (O) of Early-Onset Colorectal Cancer

Question and statement	Level of evidence, grade of recommendation, agreement level, and clarity
Pathology and oncological treatment of early-onset colorectal cancer (O)	
O.1: Is it necessary to test tumors for mismatch repair deficiency with immunohistochemistry or microsatellite instability analysis? All CRCs should undergo evaluation for mismatch repair (MMR) phenotype (with either immunohistochemistry staining for MMR proteins or microsatellite instability testing) preferably in the pretreatment setting on biopsies when feasible.	LE 1B; GR A Agreement: 100% (A+ 92.6%|A 7.4%)
O.2: Which molecular markers are necessary for targeted treatments in eoCRC? Molecular profiling should not be different in eoCRC compared with CRC in older patients, and it should include testing for DNA mismatch repair phenotype/MSI, KRAS, NRAS, BRAF, Her2, and NTRK.	LE 2B; GR C Agreement: 96.3% (A+ 88.9%|A 7.4%|D– 3.7%)
O.3: What is the adjuvant postoperative treatment in eoCRCs? There is no evidence that adjuvant therapy in resected colorectal cancer (stage II at high risk and stage III) should differ between eoCRC patients and patients older than 50 years.	LE 1B; GR B Agreement: 97.1% (A+ 37.1%|A 60.0%|D– 2.9%)
O.4: What is the role of neoadjuvant and systemic treatment in rectal and colon eoCRC?	LE 1B; GR B Agreement: 93.3% (A+ 40.0%|A 53.3%|A– 6.7%)
A. There is no evidence that neoadjuvant therapy in locally advanced rectal cancer should differ between eoRC patients and patients older than 50 years.	LE 1B; GR B
B. There is no evidence that systemic therapy should differ between eoCRC patients and patients older than 50 years.	Agreement: 93.5% (A+ 35.5%|A 58.1%|A– 6.5%)

deficiency anemia, GI evaluation received a conditional recommendation with several caveats related to patient preferences.[27] In a case-control study of eoCRC, of which 40% were rectal cancers, weight loss of ≥5 kg (≥11 pounds) within 5 years was associated with higher odds of eoCRC (odds ratio [OR], 2.23).[29]

Other common symptoms at CRC diagnosis include abdominal pain, abdominal distention, change in bowel habits, and fatigue.[28,34–38] However, because abdominal pain and changes in bowel habits are common and nonspecific and there is conflicting evidence as to how often abdominal pain and changes in bowel habits are associated with eoCRC,[30,39] endoscopic evaluation is currently not recommended for all young adults without other alarming symptoms or CRC risk factors. The decision to proceed with further diagnostic testing in an individual who presents with abdominal pain, bowel habit changes, or both should be individualized.

The systematic review found 10 studies on anemia, hematochezia, and unexplained weight loss in the literature, 5 of which had LE 2b, with similar results across studies. There were 5 studies on abdominal pain and changes to bowel habits, 2 of which had LE 2b but with significant differences across studies. Two studies compared the differences in symptomatic presentation between eoCRC and late-onset CRC (loCRC), one of which had LE 2b.

D.3: Comment. Colonoscopy is recommended for the diagnostic evaluation of individuals with hematochezia, unexplained iron deficiency anemia, or unexplained weight loss. Colonoscopy should be complete to the cecum and of high quality. The use of colonoscopy for evaluation of other symptoms (including a change in bowel habits or abdominal pain) is discussed in section D.2.

The use of alternative diagnostic modalities, including fecal immunochemical tests (FIT), for symptomatic individuals remains controversial. An expanded statement that included FIT reached 67% agreement only (A+, 30.0%; A, 37.5%, A–, 20.0%; D–, 7.5%; D, 5.0%) and was therefore eliminated ("A diagnostic colonoscopy is recommended for evaluation of alarming symptoms and signs of eoCRC (and in case of FIT positivity)"). Recent studies have found that FIT performs well in both symptomatic and asymptomatic patients younger than age 50.[40–42] However, the reasons for such disagreement include that a positive FIT result would still require a colonoscopy, which may lead to delays in diagnosis. Delays in obtaining a colonoscopy are associated with an increased risk of advanced-stage disease.[43,44] Therefore, FIT is not recommended for symptomatic patients. Triaging patients with low-risk symptoms with FIT may be an option (ie, change in bowel habits or abdominal pain). However, for high-risk symptoms (hematochezia, unexplained iron deficiency anemia, or unexplained weight loss) diagnostic colonoscopy remains the modality of choice.[32]

The systematic review found 3 studies on the use of FIT and colonoscopy for asymptomatic individuals, 2 of whom had LE 1b. However, all studies had a selection bias, and there were inconsistent results across them. There were 2 studies on the use of FIT in symptomatic individuals, both with LE 1b and with similar findings. There was 1 study on the use of colonoscopy in symptomatic individuals, with LE 2b.

D.4: Comment. EoCRC patients are often diagnosed at later stages (stage III/IV). Some studies reported that diagnostic delays contribute to advanced disease at presentation.[44–46] However, recent data suggest that the

Table 4. Statements Pertaining to Endoscopic Detection and Treatment (E), Therapy (T), and Supportive Care (C) of Early-Onset Colorectal Cancer

Question and statement	Level of evidence, grade of recommendation, agreement level, and clarity
Endoscopic detection, diagnosis, and treatment of early-onset colorectal cancer (E)	
E.1: Should additional endoscopic technologies be routinely used to improve the diagnostic capabilities for eoCRC? We suggest high-quality, high-definition white-light endoscopy as the standard modality for colonoscopy. There is currently insufficient evidence for the routine use of adjuncts such as dye or virtual chromoendoscopy, add-on devices, and artificial intelligence systems.	LE 5; GR D Agreement: 96.4% (A+ 42.9%|A 53.6% |D 3.6%)
E.2: Are standard quality metrics for colonoscopy appropriate? Standard quality metrics for diagnostic and surveillance colonoscopy in eoCRC have not been established for adenoma detection rate. However, other established standard key performance indicators should be applied.	LE 2A; GR B Agreement: 93.1% (A+ 27.6 %|A 65.5%|A– 3.4% |D– 3.4%)
E.3: What diagnostic workup is necessary before surgery for eoCRC? Complete evaluation of the colon should be performed before surgical treatment, with colonoscopy preferred to computed tomography–colonography. If complete colonoscopy is not technically feasible, a complete colonoscopy should be done within 3–6 months postoperatively.	LE 2A; GR B Agreement: 96.7% (A+ 23.3%|A 73.3%|D– 3.3%)
E.4: Should T1 CRC receive endoscopic therapy in rectal or colonic eoCRC? There is insufficient evidence to recommend T1 CRC be managed differently in eoCRC.	LE 2B; GR B Agreement: 97.1% (A+ 35.3%|A 61.8%|A– 2.9%)
E.5: What endoscopic follow-up is recommended after treatment? A. Patients with non-syndromic eoCRC should receive standard surveillance after the CRC curative resection (at 1 and 3 years) and should continue colonoscopies at a minimum of every 5 years.	LE 2B; GR C Agreement: 89.7% (A+ 31.0%|A 58.6%|A– 10.3%)
B. Patients diagnosed with hereditary CRC syndromes should receive variant- and phenotype-specific surveillance intervals.	LE 2A; GR B Agreement: 96.8% (A+ 16.1%|A 80.6% |D 3.2%)
Treatment of early-onset colorectal cancer (T)	
T.1: Should the surgical approach differ for eoCRC? A. Standard segmental resections should be offered to eoCRC. Extended surgery to reduce metachronous cancer risk should only be considered for individuals with a demonstrated risk-enhancing predisposition.	LE 2B; GR C Agreement: 96.8% (A+ 22.6%|A 74.2%| D 3.2%)
B. In the presence of a demonstrated risk-enhancing predisposition, an extended colorectal resection should be recommended by incorporating the variant-specific guidance, patient characteristics, and patient preference.	LE 2A; GR B Agreement: 87.0% (A+ 21.7%|A 65.2%|A– 8.7%|D 4.3%)
C. For individuals with eoCRC with high risk of gynecologic cancers (due to specific syndromic likely pathogenic/pathogenic variants), combined surgery with colorectal resection and prophylactic hysterectomy with or without bilateral oophorectomy may be considered (if childbearing has been completed).	LE 2B; GR C Agreement: 93.8% (A+ 18.8%|A 75.0%|A– 6.3%) Clarity: 92.6%
T.2: Which information should patients receive about the risk of infertility related to treatment of eoCRC? Clinicians should provide eoCRC patients with referral to a reproductive medicine specialist before treatment and/or infertility information to discuss: (1) The impact of cancer diagnosis and treatments on reproductive function and on potential risks for infertility. (2) Fertility preservation options, ovarian transposition, and issues related to cryo-preservation storage after fertility preservation. (3) Pregnancy-related and menopause-related issues after gonadotoxic treatment or underlying condition and other childbearing and parenting options.	LE 2B; GR B Agreement: 81.6% (A+ 13.2%|A 68.4%|A– 13.2%|D– 2.6%|D 2.6%)
T.3: Which criteria make patients candidates for fertility preservation? The following criteria should be considered: the estimated risk of gonadotoxicity, the characteristics of the proposed treatment, the patient's characteristics, and the disease stage and severity.	LE 3A; GR C Agreement: 85.7% (A+ 17.1%|A 68.6%|A– 8.6%|D+ 2.9%)

Table 4. Continued

Question and statement	Level of evidence, grade of recommendation, agreement level, and clarity
Supportive care of early-onset colorectal cancer (C)	
C.1: Are there peculiarities in the management of cancer-related symptoms in eoCRC (ie, pain, fatigue, nausea, vomiting, constipation, diarrhea, cachexia)?	LE 1B; GR A Agreement: 96.2% (A+ 30.8%|A 65.4%|D 3.8%)
A. For symptom management, patients with eoCRC should be managed as recommended in the ASCO and ESMO guidelines for the general population with CRC.	LE 3B; GR C Agreement: 100% (A+ 34.6%|A 65.4%)
B. Patients with eoCRC may be more prone to chemotherapy-induced nausea and vomiting (CINV) compared with patients with later-onset CRC, particularly female patients with low body mass index. Therefore, enhanced prophylaxis may be considered.	LE 3B; GR B Agreement: 88.0% (A+ 24.0%|A 64.0%|A– 12.0%)
C. Patients with eoCRC can benefit from early personalized physical activity and nutritional support programs. Such programs could favor the maintenance and recovery of muscle mass.	LE 4; GR D Agreement: 91.3% (A+ 34.8%|A 56.5%|A– 8.7%)
D. Patients with eoCRC benefit from discussions about sexual health and dysfunction resulting from cancer or its treatment. Psychosocial and/or psychosexual counseling should be offered to improve sexual response, body image, intimacy and relationship issues, and overall sexual functioning and satisfaction.	
C.2: How should supportive care programs be organized for eoCRC patients?	LE 4; GR C Agreement: 91.3% (A+ 26.1%|A 65.2%|A– 8.7%)
For eoCRC patients, a multidisciplinary team including psychosocial support and fertility preservation experts should be made available because of the specific psychosocial and informational needs (symptom management, fears, and behavior modifications).	

increased incidence of advanced-stage disease in eoCRC may not be fully explained by delays in workup.[47,48] According to one study, stage III/IV eoCRCs tend to present with alarming symptoms that prompt expedited endoscopic evaluation compared with stage I/II eoCRC.[47] The following recommendations should therefore be followed[49]: assessment of CRC risk, timely workup of symptoms, and referral for colonoscopy. Optimally, colonoscopy should be performed within 30 days of presentation with alarming symptoms.[49]

The systematic review found 4 studies on the diagnostic delay of eoCRC; only one had LE 2b, and the others with lower LE, but all showed consistent results. Three studies evaluated the hypothesis that a longer diagnostic delay was associated with a more advanced disease stage at diagnosis; all 3 studies had LE 3b and provided unconclusive and conflicting results.

A full summary of relevant evidence for D.2,[28–39,47,50–53] D.3,[32,40–42,54,55] and D.4[33,36,38,45–47,51] is available in Supplementary Appendix 2.

Section II: Risk Factors (R)

R.1: Comment. Family history of cancer should include all cancer diagnoses to identify hereditary syndromes (implicated in 13% of eoCRC),[56,57] as well as to quantify risk for non-syndromic familial CRC. About 28% of patients with eoCRC have a family history of CRC,[58,59] which is not significantly different compared with the loCRC population. Individuals with a family history of CRC should undergo more intensive surveillance than the general population, starting at an earlier age. However, definitions of who should undergo more intensive surveillance vary widely by country. There is a consensus that having at least 2 first-degree relatives with CRC and/or at least 1 first-degree relative diagnosed with CRC before the age of 50–60 years are associated with a significant increase in risk for CRC. In these situations, screening colonoscopy starting at 40 years (or 10 years before the age at diagnosis of the youngest affected relative) is usually recommended. A recent study showed that up to 16% of eoCRC could be prevented[56] if colonoscopy was performed at the age recommended by guidelines based on family history.[17,18,58–60]

Validated risk assessment tools can facilitate family history taking and identification of patients who would benefit from germline genetic testing, such as the Colon Cancer Risk Assessment Tool and the $PREMM_5$.[61,62] The $PREMM_5$ tool can be used to determine the likelihood of a pathogenic variant (PV)/likely pathogenic variant (LPV) in a Lynch syndrome (LS) gene. However, it is recommended that all patients with eoCRC should undergo multigene germline panel testing, regardless of the results of risk assessment tools (see G.1).

The systematic review found 6 studies evaluating the prevalence of a family history of CRC among individuals with eoCRC, 3 of whom had LE 2b, and they all concluded that there was a strong predisposition for having a family history of CRC among younger patients. Five studies evaluated the clinical outcomes of taking family histories, with 2 studies having LE 1a, and they all concluded that a family history of CRC increases the risk of eoCRC.

R.2: Comment. Most patients diagnosed with eoCRC have no obvious risk factors. A minority of eoCRC patients have a predisposing condition such as hereditary CRC syndromes (13% of cases), longstanding

Table 5. Areas of Uncertainty on eoCRC and Proposed Research Agenda

Areas of controversy	Issues raised
Topic: diagnosis of eoCRC	
Fecal immunochemical test	• FIT vs colonoscopy for alarming signs and symptoms: (1) no cost-effectiveness analysis, (2) higher risk of false negatives with FIT, (3) FIT use may prolong diagnostic delays, (4) FIT may be useful for patients with vague symptoms (ie, not alarming) • Positive FIT follow-up: (1) unknown referral rate to colonoscopy after positive FIT, (2) non-zero risk of non-compliance to follow-up colonoscopy • Screening FIT: (1) unknown diagnostic rate, (2) unknown survival benefit, (3) unknown cost-benefit ratio in many countries • Unclear whether a positive FIT is a sign of eoCRC: lack of data
Sigmoidoscopy versus colonoscopy	• Advantages of sigmoidoscopy: (1) eoCRC often left-sided, (2) sigmoidoscopy marginally faster than colonoscopy, (3) no need for a complete bowel preparation • Advantages of colonoscopy: (1) similar overall costs, (2) similar need for hospital access, (3) lower risk of false negatives
Time to colonoscopy	• Diagnostic delay: (1) 30 days are ideal but difficult to achieve under some circumstances (difficult access to care, incomplete insurance coverage), (2) highlight the need for a timely diagnosis • Alarming signs/symptoms + positive FIT: proceed to colonoscopy with the highest priority
Topic: Risk factors of eoCRC	
Family history	• Accuracy of family histories: (1) a 2-generation family history is often difficult to obtain under routine circumstances, (2) dedicated hospitals may have more time for such tasks, (3) risk assessment tools may provide a framework for history taking
Risk factors	• Many risk factors identified, but insufficient evidence to recommend earlier access to screening. Further studies necessary on the additional risk factors to include in CRC screening programs (besides age).
Topic: genetics of eoCRC	
Ranking the genes by importance	• Costs of germline testing: (1) not all healthcare systems may afford large gene panels, (2) prioritize the most important genes if needed, (3) no cost-benefit analysis on additional genes, (4) further studies necessary before recommending large panels in low resources settings
Risk assessment tools	• Utility: (1) all with eoCRC should receive germline testing
Polygenic risk scores	• Utility: (1) potentially estimate lifetime risk of CRC, (2) further evidence and validation studies in diverse populations are needed before clinical use
Topic: Oncological treatment of eoCRC	
Adjuvant therapy	• Aggressive adjuvant therapy: (1) eoCRC often receive more aggressive regimens, (2) increased toxicity, but no evidence of a survival benefit, (3) further randomized clinical trials should include endpoints to evaluate benefits to patients with eoCRC
Neoadjuvant therapy, adding oxaliplatin	• Oxaliplatin addition: (1) post hoc analysis of one large phase II trial suggested that adding oxaliplatin to standard chemoradiotherapy in eoRC improved disease-free survival and overall survival compared with older individuals, (2) no prospectively analyzed randomized clinical trial data, (3) future randomized clinical trials should include endpoints pertaining to eoRC patients specifically.
Rectum, neoadjuvant therapy	• Total neoadjuvant therapy: (1) more and more centers are adopting this strategy as standard management of individuals with rectal cancer, regardless of age, (2) not enough evidence to hypothesize that this should differ for rectal eoCRC, (3) further clinical trials should include endpoints pertaining to eoCRC patients specifically.
Immune checkpoint inhibitors therapy	• Use: (1) not enough evidence to hypothesize a different use for younger patients, (2) higher prevalence of LS among eoCRC, therefore higher likelihood of MSI-H CRC, (3) further clinical trials should include endpoints pertaining to eoCRC patients specifically.
IHC/MMR assessment	• Biopsies vs surgical specimens: (1) ideally, IHC/MMR assessment before treatment, (2) biopsies provide results comparable with staining on surgical specimens, (3) biopsies do not carry a risk of false-negative IHC/MMR results
Targeted therapies	• Use: (1) not enough evidence to hypothesize a different use for younger patients, (2) further clinical trials should include endpoints pertaining to eoCRC patients specifically

Table 5. Continued

Areas of controversy	Issues raised
Topic: Endoscopy of eoCRC	
Clearing colonoscopy	• Ideally, the diagnostic colonoscopy should clear the colon of all synchronous lesions, particularly when multiple polyps are present. It should be emphasized that younger patients do not require an extended surgical resection by default. The scientific panel suggests a clearing colonoscopy to further discourage the use of an extended surgical resection.
Post-treatment follow-up	• Surveillance protocol: (1) insufficient evidence to support an intensified surveillance protocol, (2) insufficient evidence to discharge patients with eoCRC from follow-up, (3) suggestion to continue post-treatment surveillance and not to discharge the patient, (4) significant knowledge gap, (5) further studies necessary on the risk of metachronous CRC and the time of surveillance discharge • Hereditary CRC, family history of CRC, or inflammatory bowel diseases: should receive post-treatment surveillance according to their specific guidelines.
Secondary prevention of CRC	• Aspirin use: (1) insufficient evidence on the secondary prevention of eoCRC, (2) optimal dosage for cancer prevention unclear after CRC • Other medications: (1) insufficient evidence
Topic: Treatment of eoCRC	
Standard vs extensive surgical resections	• Extended surgical resections: (1) no evidence to support more extensive resections, unless a distinctly higher risk of CRC is demonstrated, (2) the scientific panel currently discourages further analysis on extensive colorectal surgeries based on early age alone • Factors besides age: (1) can be considered, including (but not limited to) a polyposis phenotype, a colitis-associated CRC, and a genetically higher risk of CRC. Such characteristics do not pertain to these guidelines.
Synchronous gynecologic surgery	• Indications: (1) eoCRC is not an indication for hysterectomy with or without oophorectomy, (2) however, other indications may justify hysterectomy with or without oophorectomy at the time of CRC surgery, (3) consider age of the patient, risk for gynecologic cancers, and reproductive desires when offering a gynecologic prophylactic surgery • Ovarian transposition: (1) patients requiring radiotherapy may benefit from ovarian transposition at the time of colorectal surgery, (2) further evidence is necessary
Fertility preservation	• Information provider: (1) any healthcare professional, if adequately trained, (2) multidisciplinary teams for eoCRC patients may benefit from having a gynecologist • Ovarian damage: (1) CRC-directed chemotherapeutic agents can be gonadotoxic, (2) female patients with eoCRC should receive information on their ovarian health • Menopause: little to no evidence on the menopausal issues on patients with eoCRC receiving treatment. Research necessary • Male reproductive health: scarce evidence on male factors. Further research necessary on the reproductive needs, issues, and desires
Supportive care of eoCRC	
Nausea and vomiting	• (1) Higher risk of chemotherapy-induced nausea and vomiting, (2) enough evidence to contemplate the use of enhanced antiemetic prophylaxis with new-generation antiemetic, (3) further evidence may be needed.
Nutritional support and physical therapy	• (1) Higher risk of significant weight loss than patients with CRC at an older age, (2) little to no evidence on the use of nutritional support and physical support programs in patients with eoCRC.

inflammatory bowel diseases (<1% of cases), or a family history of CRC (28%)[29,63,64]; however, the majority of individuals affected with eoCRC would have been considered at average risk for colorectal neoplasia.

In the United States, black individuals have a higher CRC incidence and mortality compared with other racial and ethnic groups.[15,65] However, the recent increase in eoCRC is largely driven by an increase in rectal cancer among white males.[66–70] Some studies have proposed other risk factors for eoCRC, including male sex, hyperlipidemia, obesity (especially during adolescence), metabolic syndrome, alcohol consumption, type II diabetes, and high intake of simple sugars.[36,71–75] There is controversial evidence on cigarette smoking, hypertension, chronic kidney disease, dietary patterns, sedentary behavior, and in utero, pediatric, and occupational exposures.[36,72–74,76–87] Although many of these proposed risk factors have been combined to produce CRC risk scores,[88,89] no CRC risk score has received formal validation for clinical use.

The systematic review found 6 studies evaluating the risk of eoCRC among different ethnicities, with 2 studies having LE 1b. They all concluded that black individuals have a higher risk of eoCRC, but the incidence and prevalence of eoCRC have remained the

same in recent years, whereas it has increased among white individuals. Eight studies with LE 1a, 1b, or 2b evaluated the known CRC risk factors (male sex, hyperlipidemia, obesity, metabolic syndrome, alcohol consumption, and type II diabetes), and they generally agreed that these represent risk factors for eoCRC as well. Seventeen more studies evaluated other risk factors, with controversial and inconsistent findings.

A full summary of relevant evidence for R.1[21,30,31,39,42,47,51,53,54,56,59,74,76,78,90–102] and R.[29,30,31,36,65–67,70–89,91,103,104] is available in Supplementary Appendix 3.

Section III: Genetics (G)

G.1: Comment. The advent of next-generation sequencing (NGS) has allowed multigene panel testing to be performed on various cohorts of cancer patients including those with eoCRC. The prevalence of germline LPV and PV in cancer susceptibility genes is 13.0% (range, 9.0%–26.4%) among patients with eoCRC (excluding *MUTYH* heterozygotes), but it is even higher among patients younger than 35 (23.0%).[105] This is comparable with the 18%–24%[106] prevalence of germline LPV/PVs among ovarian cancer patients for whom genetic testing is recommended.

The management of hereditary CRC syndromes should be incorporated into surgical planning. Genetic testing before surgery may permit optimization of the surgical plan,[107–109] including a discussion of extent of colonic resection and indications for gynecologic surgery (section T.1).

Thirteen studies analyzed the prevalence of PV/LPVs in cancer susceptibility genes in individuals with eoCRC. There were 7 studies with LE 2b and 6 studies with LE 1b. The prevalence of LS was variable from 0% to 18.3%. The prevalence of other, non-LS, hereditary predisposition PV/LPV ranged from 2.3% to 26.4%.

G.2: Comment. Among eoCRC patients, 2%–16% have LS, and up to 14% have PV/LPVs in other cancer susceptibility genes.[110–122] LS is the most common genetic diagnosis among eoCRC patients, and LS genes include the DNA-mismatch repair genes *MLH1, MSH2, MSH6,* and *PMS2,* as well as *EPCAM* 3′ deletions. Colorectal polyposis syndromes account for 2%–3% of eoCRC and include familial adenomatous polyposis (associated with PV/LPV in *APC*), MUTYH-associated polyposis (associated with biallelic PV/LPV in *MUTYH*), juvenile polyposis (associated with PV/LPV in *SMAD4, BMPR1A*), and Peutz-Jeghers syndrome (associated with PV/LPV in *STK11*). Some of the newer genes associated with polyposis or CRC (*GREM1, POLE, POLD1, AXIN2, MSH3, MLH3, MBD4, RNF43,* and *RPS20*) were not included in most prior studies because they were discovered relatively recently. Studies have also identified PV/LPVs in other highly actionable high-penetrance genes that have not previously been associated with CRC (*TP53, BRCA1, BRCA2,* and *PALB2*) at a prevalence higher than that of some of the known polyposis genes.[122–124] Notably, there is emerging evidence that *ATM* may be a CRC susceptibility gene.[115] At this time, *RNF43, RPS20*, and *MBD4* do not have actionable recommendations for clinical management. However, they are included in this statement because of their potential association with serrated polyposis syndrome or CRC.

As of the time of writing these guidelines, our recommendations about which genes to include in the multigene panel testing for eoCRC patients are based on their known association with CRC or polyposis, the prevalence of PV/LPVs in each gene among eoCRC patients, and the clinical actionability of genetic findings (Supplementary Tables 4–6). Germline genetic testing for eoCRC patients should include at a minimum the following: *APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, MUTYH, POLD1, POLE, PMS2, PTEN, SMAD4, STK11*, and *TP53*.Where available and not cost-prohibitive, testing should also include the following genes, which are reasonably prevalent in CRC and change clinical management: *BRCA1, BRCA2, ATM, CHEK2, PALB2*, and possibly, but less prevalent, *BRIP1, BARD1, CDKN2A, CDH1, RAD51C,* and *RAD51D,* and the following genes, which have been associated with CRC or polyposis: *AXIN2, GREM1, MLH3, MSH3, MBD4, NTHL1, RNF43*, and *RPS20*.

G.3: Comment. Single nucleotide polymorphisms (SNPs) have been identified through genome-wide association studies as associated with increases or decreases in risk for CRC. A variety of SNPs have been shown to modestly increase the relative risk of CRC (range, 1.46–2.82), and these have been combined (with and without other lifestyle factors) to create polygenic risk scores (PRS). However, the clinical utility of the various PRS remains thus far unproven. Important limitations of PRS include that most were developed using data from predominantly white individuals of European ancestry and have not been validated in diverse populations. One genome-wide association study took data from 12,197 individuals younger than 50 and 95,865 individuals older than 50. It categorized the resulting 95 SNPs into a PRS that could correlate more strongly with eoCRC than with loCRC.

In a subanalysis, the same study conducted a PRS classification to identify individuals who would benefit the most from anticipatory screening at age 45. We encourage further study of the performance of PRS and its validity in non-white non-European individuals.

A full summary of relevant evidence for G.1,[110–122] G.2,[110–122,125,126] and G.3[127–142] is available in Supplementary Appendix 4 and Supplementary Tables 4–6.

Section IV: Pathology and Oncological Treatment (O)

O.1: Comment. All patients with CRCs, regardless of age at diagnosis, must be tested for DNA mismatch repair

deficiency (MMR-d) by immunohistochemistry (IHC) staining for MMR proteins MLH1, MSH2, MSH6, and PMS2 or microsatellite instability (MSI) by polymerase chain reaction or NGS. MMR-d or MSI-high (MSI-H) tumors are associated with LS, a decreased response to 5-fluorouracil–based chemotherapy, an enhanced response to immunotherapy, and in general have an improved prognosis compared with MMR-proficient tumors (MMR-p).[143,144]

Pretreatment MMR-d testing is particularly critical in 2 scenarios. (1) In metastatic CRC, patients with MMR-d metastatic CRC should be treated with immunotherapy as a part of first-line systemic treatment, regardless of age at diagnosis. (2) In non-metastatic CRC, the presence of MMR-d may implicate a diagnosis of LS, for which an extended colectomy may be recommended.[145–148] The longer the life expectancy, determined by the patient's age and disease stage, the greater the benefit of more extensive colonic resection for reducing the risk of metachronous tumors.[145–147]

The rate of MMR-d CRC is higher among eoCRC than among loCRC.[21,64,149] The MMR/MSI status can be assessed on diagnostic colon tumor biopsies or surgical specimens. Although pathologists may prefer to test the surgical specimen to analyze the normal matched mucosa, MMR testing on pretreatment biopsies is usually preferable.[144] IHC/MSI tumor testing results are often available before the results of germline panel testing. In cases of metastatic, non-resectable tumors, MMR testing can be performed on biopsies. Moreover, in locally advanced rectal cancer, MMR testing is best investigated on biopsies collected before neoadjuvant therapy, because the tumor may regress during chemoradiotherapy.[144]

All patients with eoCRC should undergo germline genetic testing and receive genetic counseling, regardless of the results of MMR-d/MSI testing, to identify other high-penetrance PVs beyond LS.[124,150]

The systematic review found 3 cohort studies on the prevalence of IHC/MSI in eoCRC, only one with LE 3b but all with similar findings. Six studies compared the IHC/MSI characteristics of eoCRC against loCRC, 2 with LE 1b and 3 with LE 2b. They all showed similar findings.

O.2: Comment. MMR-d/MSI, *KRAS, NRAS, BRAF,* and *Her2* should be tested in all patients with metastatic CRC, regardless of age at diagnosis, to guide therapy selection. Initial studies noted that eoCRC tumors exhibit fewer somatic mutations in *APC* and *TP53* and exhibit consensus molecular subtype 1 more often than loCRC.[64,151–154] However, when eoCRC was compared with loCRC with complete clinical annotation and the genomics of sporadic eoCRC were analyzed by tumor sidedness, there were no significant differences in the mutational landscape.[105] Moreover, MSI-H eoCRC, particularly MLH1-deficient, non-LS, BRAF-wild-type, MLH1-methylation negative tumors, should be tested for *NTRK*.[50,151,155] Finally, anti-EGFR inhibitors are a reasonable component of first-line treatment for metastatic left-sided (including but not limited to rectal cancer) and RAS/RAF-wild-type eoCRC.

The systematic review found 3 studies with LE 2b–3b supporting the hypothesis that eoCRC has biological markers different than loCRC. However, 2 LE 1b studies showed that there was no statistically significant difference in the biological markers between eoCRC and loCRC.

O.3: Comment. Various reports have suggested that eoCRC may display a more aggressive behavior than CRC of older individuals.[31,156–163] This has been explained by delayed diagnosis resulting in more advanced tumor stage,[164] more aggressive molecular and pathologic subtypes, and/or lower pathologic complete response rates to neoadjuvant chemoradiotherapy.[163] However, recent lines of evidence challenge this observation.[104,152,153,165,166]

Because of their young age and robust performance status, patients with eoCRC often receive more aggressive multimodality treatment.[162,167,168] However, more aggressive treatment strategies have not translated into a statistically significant survival benefit.[50,105,143,155,169,170]

The systematic review found 7 studies that supported that eoCRC is more aggressive than loCRC, with 1 LE 1b study and 3 LE 3b studies. However, 5 studies reported that the survival rates and the prognosis of eoCRC and loCRC do not differ, with 1 LE 1b study and 3 LE 2b studies. Seven studies did not support the use of more aggressive systemic therapies for eoCRC, with 2 studies having LE 1b. Only 2 studies suggested a benefit from more aggressive systemic therapy, but both had a low LE.

O.4: Comment. There is scarce evidence regarding the impact of age on the efficacy of neoadjuvant chemoradiotherapy and the outcomes of locally advanced rectal cancer. Many publications describe a more aggressive attitude of clinicians and surgeons treating stage III and IV eoCRC, as well as on the part of eoCRC patients, but this aggressiveness has often not conferred a significant survival benefit.[165,171] One post hoc analysis suggested that adding oxaliplatin to standard 5-fluorouracil–based chemoradiotherapy for locally advanced rectal cancer may improve disease-free survival and overall survival in patients younger than 60.[172] However, numerous phase III trials have shown no benefit (and increased toxicity) from adding oxaliplatin to neoadjuvant chemoradiotherapy in locally advanced rectal cancer patients of any age, and adding oxaliplatin is thus not part of standard neoadjuvant therapy. In the absence of randomized clinical trial data prospectively comparing eoRC versus loRC, standard 5-fluorouracil–based chemoradiotherapy in eoRC patients does not contain oxaliplatin. Finally, there are data from randomized controlled trials that total neoadjuvant therapy with sequential radiotherapy and combination chemotherapy may improve complete pathologic response rate, disease-free survival, and overall survival compared with standard chemoradiotherapy, but no data specifically on eoRC.[173–176]

Age of onset is not a criterion to change the use of immune checkpoint inhibitors in MSI-H CRC. Likewise,

early age of onset is not a criterion to drive treatment, and the current consensus is that eoCRC and loCRC patients should receive similar systemic treatments.[177–180]

Two cohort studies reported the outcomes of neoadjuvant use on eoRC, and 3 retrospective studies (2 LE 3b, 1 LE 2b) suggested that eoRC has lower response rates to neoadjuvant therapy compared with loRC. However, a case-control study (LE 2b) concluded that there was no significant difference in survival between loCRC and eoCRC.

A full summary of relevant evidence for 0.1,[21,37,64,105,143,151,152,162,167] 0.2,[64,151–154] 0.3,[31,50,104,105,143,152,153,155–162,165–170] and 0.4[162–164,167,171,172,181,182] is available in Supplementary Appendix 5.

Section V: Endoscopy (E)

E.1: Comment. The overall miss rates for colonoscopic detection of adenomas and advanced adenomas are 26% and 9%, respectively.[183–185] To maximize the detection of adenomas and CRC, good bowel preparation and high-quality endoscopic techniques are necessary.[183–185] High-definition white-light endoscopy, dye- or virtual chromoendoscopy, and certain add-on devices can increase the adenoma detection rate (ADR) of colonoscopy exams.[185–187] The degree to which artificial intelligence systems can improve detection of colorectal neoplasia is currently being evaluated. To date, no study has compared these endoscopic techniques for detection of eoCRC or its precursors.

E.2: Comment. Standard endoscopic quality metrics for polyp detection should be applied for colonoscopy exams performed on young patients. A high ADR is associated with decreases in incidence of post-colonoscopy CRC and CRC-related mortality.[188,189] Current guidelines propose a minimum ADR of 25% overall,[183] but there is limited evidence regarding the expected ADR in young patients. Although ADRs in younger age groups are likely lower than the ADR observed in the 50- to 75-year age group (28.4% vs 35.6%, $P < .001$),[190] the absolute difference remains small. Nevertheless, if the number of average risk 45- to 49-year-olds undergoing colonoscopy increases compared with older populations, this could further lower the ADR. We encourage more research to determine a minimum ADR. Other colonoscopy quality metrics (cecal intubation rate, bowel preparation, and post-polypectomy recommendations) should be applied equally regardless of patient age.

The systematic review yielded 2 studies on the prevalence of adenoma, advanced adenoma, and CRC among individuals younger than the age of 50, with 1 LE 1a study. Three studies tested the hypothesis that a lower ADR should be used for individuals younger than 50; 2 LE 1b studies supported a change in the ADR, but 1 LE 2b study did not.

E.3: Comment. The prevalence of synchronous CRCs and adenomas reaches 10% and 60%, respectively,[191] and many of these (43% and 80% of cases, respectively) are located in a different area within the colon.[191,192] Therefore, all patients should undergo a complete colonoscopy exam before surgery if feasible.[193] Alternatively, colonoscopy should be performed intraoperatively or 3–6 months after recovery from surgery to exclude synchronous lesions.

EoCRCs present at a more advanced stage.[182,194] Staging studies for CRC should not differ on the basis of patient age (computed tomography of chest, abdomen, and pelvis, complete blood count, blood chemistries, and carcinoembryonic antigen).[195] Pelvic magnetic resonance imaging or lower endoscopic ultrasound is necessary for rectal cancer staging.[196]

Patients undergoing curative resection for colon cancer should undergo a follow-up colonoscopy 1 year after the resection (or 1 year after the performance of the colonoscopy that was performed to clear the colon of synchronous disease). Patients undergoing curative resection for rectal cancer could undergo rectal ultrasound or flexible sigmoidoscopy every 3–6 months during the first 2 years after resection.[197–202]

E.4: Comment. Compared with surgery, endoscopic resection of colonic T1 CRC may offer a similar 5-year cancer-free survival.[203] However, the long-term risk of recurrence after endoscopic resection of T1 eoCRC is unknown. Therefore, the endoscopic resection modalities and pre-procedural workup should be no different than for other T1 CRCs.[186,187]

High-definition endoscopy and chromoendoscopy (dye- or virtual) are recommended.[185–187] The risk of submucosal invasion depends on size, vascular invasion, glandular pattern, Paris classification, and type of laterally spreading tumor lesions. Rectal lesions should be staged with lower endoscopic ultrasound or pelvic magnetic resonance imaging before initiation of treatment.[196,204] Superficially invasive T1 CRCs (Kudo Vi, Sano IIIa, LST-NG, and rectal LST-GM) should be removed endoscopically en bloc with endoscopic submucosal dissection or endoscopic mucosal resection. Deeply invasive CRCs (Kudo Vn, Sano IIIb) are not amenable to endoscopic resection. Radical surgery with lymphadenectomy is recommended if histopathology shows lymphovascular invasion, submucosal invasion >1000 μm, high-grade budding, positive/non-evaluable vertical margins, or poor differentiation (G3).[186,205] There are limited data on full-thickness resections in eoCRC, but we encourage further investigations.

Five studies analyzed the use of endoscopic treatment for T1 CRC among patients younger than 50. Two LE 1a studies, 1 LE 2b study, and 1 LE 3b study all supported the use of endoscopic treatment of T1 eoCRC. Only 1 LE 2b study suggested that T1 eoCRC has a higher propensity for lymph node metastasis and cautioned against endoscopic treatment.

E.5: Comment. Endoscopic surveillance after curative resection of CRC can prevent local recurrences and metachronous CRC.[198] The detection of interval high-risk neoplastic lesions should prompt shortening of the endoscopy intervals (size, number, and histologic features), as should a genetic diagnosis that requires more intensive colonoscopic surveillance. The European Society of Gastrointestinal Endoscopy (ESGE), National Comprehensive Cancer Network (NCCN), and U.S. Multi-Society Task Force (USMSTF) guidelines endorse similar follow-up endoscopic surveillance intervals after CRC resection (at 1, 3, and 5 years).[147,180,185,198] Patients with eoCRC may have a higher risk for metachronous CRC after surgery compared with patients with loCRC,[52] and the risk for metachronous neoplasia may extend further in time.[101,206] Therefore, eoCRC survivors may not be safely dismissed from post-treatment surveillance. Post-CRC colonoscopic surveillance is recommended at similar intervals for eoCRC and loCRC in the absence of interval advanced colorectal neoplasia and/or diagnosis of a genetic condition requiring more intensive surveillance. There is not enough evidence on the effectiveness of aspirin for secondary prevention after eoCRC treatment; the decision to give aspirin should be individualized, and no recommendation could be endorsed at the time of writing this guideline. We acknowledge a significant knowledge gap in this area.

Three studies found that the risk of metachronous CRC is higher in eoCRC patients compared with loCRC, including 1 LE1a and 2 LE2b. Four more studies did not conclude that the risk of metachronous CRC was higher, although with inconsistent observational times and inconsistent follow-ups.

A full summary of relevant evidence for E.2,[39,53,91,190,207] E.3,[156,203,208–211] and E.4[51,91,102,182,206,210,212] is available in Supplementary Appendix 6.

Session VI: Treatment (T)

T.1: Comment. More extensive surgical resection cannot be recommended for eoCRC patients who do not have a distinct risk-enhancing predisposition (particularly a hereditary CRC syndrome or ulcerative colitis).[102,209,213] Although subtotal or total colectomy offers a benefit in reducing risk for metachronous CRC in patients with LS and familial adenomatous polyposis, more extensive surgery did not offer a survival benefit in LS.[107,108,214–216]

For patients with LS, the cumulative incidence of gynecologic cancers (endometrial or ovarian) before 50 years of age is high (the risk of endometrial cancer by age 50 in female carriers of *MSH2* and *MSH6* PV/LPVs exceeds that of CRC, and it is roughly the same among *MLH1* female carriers).[217] One-third of LS patients are diagnosed with CRC before risk-reducing gynecologic surgery.[210] Simultaneous hysterectomy with or without bilateral salpingo-oophorectomy at the time of CRC resection may be an option for female LS carriers age >35 years who have completed childbearing. A decision regarding risk-reducing gynecologic surgery should be individualized, taking into account the woman's age and childbearing status, and must follow a detailed discussion regarding risks and benefits.[218–220] The negative consequences of a surgical menopause preclude bilateral oophorectomy at the time of risk-reducing gynecologic surgery in very young women (<40 years). For women aged 40–50 years undergoing risk-reducing gynecologic surgery, estrogen replacement therapy may be a consideration to prevent the negative sequelae of bilateral salpingo-oophorectomy.

The systematic review gathered 3 studies on the use of more extended surgical resections for patients with eoCRC, and they all concluded that the use of extended surgical resections should be discouraged.

T.2: Comment. Loss of fertility is a known side effect of cancer treatment. Unfortunately, eoCRC survivors often do not receive comprehensive fertility information.[221–223] All patients of reproductive age should receive information on the risk of infertility and the option of fertility preservation before initiation of potentially gonadotoxic treatment.[224] Options for fertility preservation include ovarian transposition before initiation of radiotherapy, sperm banking, and cryopreservation of oocytes, embryos, and ovarian tissue.

Three studies investigated the access to fertility preservation among patients with eoCRC, and they all concluded that patients often receive inadequate counseling and are offered limited access to fertility services. Most patients in these 3 studies were female, which further highlights the lack of fertility care particularly among eoCRC male patients.

T.3: Comment. One of the major issues to consider when choosing a treatment plan includes the risk of gonadal failure and/or uterine damage with the proposed treatment program.[225] The risk of treatment-induced gonadotoxicity depends on the use of alkylating agents,[226] the patient's age,[226,227] and the patient's ovarian reserve.[228] There is no homogeneous definition for premature ovarian failure, but ovarian reserve tests may be useful to assess this (ie, blood levels of anti-Müllerian hormone and the antral follicle count).

Moreover, one also needs to factor in the overall prognosis of the patient, the potential risks of delaying treatment, the impact of pregnancy on the risk of recurrence, and the risk of hormonal manipulation on CRC.[219,229] Studies about fertility preservation generally enroll individuals with eoCRC.[222] However, no interventional study has directly compared the clinical outcomes of different fertility preservation techniques in individuals with eoCRC specifically.

Two small studies (LE 4) evaluated the effects of oxaliplatin on fertility markers. One cohort study analyzed the fertility rates of patients with eoCRC, but with an intrinsic selection bias (all patients had LS).

A full summary of relevant evidence for T.1,[50,104,213] T.2,[221–223] and T.3[226,227,230] is available in Supplementary Appendix 7.

Session VII: Supportive Care (C)

C.1: Comment. The assessment and treatment of pain are important for every patient with cancer, and a comprehensive set of guidelines was recently published by the European Society of Medical Oncology (ESMO).[231] Abdominal pain is common during CRC, particularly within the context of advanced disease. A continuous assessment of pain (characteristics, duration, and intensity) should be an integral part of cancer care using standardized scales. In the absence of vomiting and dysphagia, oral analgesics are preferred. In the case of severe pain, strong opiates may be required for symptom control.[231] Adjuvant drugs, antidepressants, invasive techniques, psychological therapy, and palliative antitumor treatment can also be considered.

The assessment and treatment of fatigue are important and addressed for every patient with cancer, and the recently published ESMO guidelines provide general recommendations on the management of this common cancer-related symptom.[232]

Patients with eoCRC often suffer from chemotherapy-induced nausea and vomiting (CINV), particularly women with low body mass index.[233] Therefore, enhanced prophylactic use of antiemetic drugs can be considered in this population[234,235]; however, there are no data available on the effectiveness of tailored antiemetic regimens specific for eoCRC.

The assessment and treatment of constipation, diarrhea, and cachexia should follow the recently published ESMO and American Society of Clinical Oncology guidelines.[219,236–239] Similar to patients with loCRC, eoCRC patients may be responsive to early physical activity programs and nutritional support to maintain and recover muscle mass and counteract cachexia.[240]

Finally, eoCRC patients may be more reluctant than older patients to discuss concerns about side effects with their healthcare providers and may be especially hesitant to address issues such as sexual dysfunction.[241] Therefore, clinicians and members of the healthcare team should proactively discuss sexual health and potential dysfunction resulting from cancer or its treatment because these issues are particularly relevant for eoCRC survivors.[242]

Three studies assessed the prevalence of comorbidities among eoCRC patients, with 1 LE 1b study. There was 1 LE 1b study supporting the use of physical therapy during and after cancer treatment.

C.2: Comment. Pain should be managed by a multidisciplinary team and should include psychosocial support.[231] Inadequate pain control contributes to poor quality of life and negative emotional status. Young adults and adolescents with cancer can present with needs that are different from those of their adult and pediatric counterparts.[243,244] They may experience similar side effects, but these symptoms may have a greater impact on daily activities including work and childcare.[245] Furthermore, younger patients also have unique psychosocial and informational needs, including those that concern educational/work pursuits and goals.[243] There may also be more difficulties in the management of symptoms, fears, and behavior modifications.[246]

There were 2 LE 4 studies concerning the organization of supportive care programs among individuals with eoCRC, including the management of sleeping, sexual, intimacy, nutritional, and social care.

A full summary of relevant evidence for C.1[38,165,233,240] and C.2[245,247] is available in Supplementary Appendix 8.

Discussion

The DIRECt group provides the first comprehensive, evidence-based, practical consensus recommendations for the best management of patients with eoCRC. There are some important differences in the management of eoCRC compared with loCRC (Table 6). We strongly recommend that the diagnosis of CRC be carefully considered for individuals younger than 50 who present

Table 6. Guideline Differences Between Early-Onset Colorectal Cancer (eoCRC) and CRC Diagnosed After the Age of 50 Years

	CRC before age 50	CRC after age 50
Genetics	Germline multigene panel testing always recommended	Germline multigene panel testing recommended under specific circumstances (tumor and clinical features suggestive of hereditary cancer syndromes)
Family history	Family history: mandatory	Family history: recommended
Surgery	No difference yet	
Chemotherapy	No difference yet	
Targeted therapy	No difference yet	
Fertility	All patients should receive information on fertility preservation options	Most patients are not candidates for fertility preservation
Sexuality	No difference yet	
Nausea and vomiting	Consider enhanced antiemetic prophylaxis	Regular antiemetic prophylaxis
Endoscopic management	No difference yet	
Post-treatment follow-up	Should not be discharged from follow-up	Follow country-specific guidelines for post-treatment surveillance

with alarming symptoms. Risk assessment for CRC includes the presence of a CRC family history and the personal history of individual risk factors and comorbidities. We strongly recommend that all patients with newly diagnosed eoCRC undergo both germline multigene panel testing and IHC/MSI tumor testing, ideally before surgery. There is insufficient evidence to recommend changes to the endoscopic, surgical, and oncologic treatment based on age alone. However, therapeutic decisions should be individualized on the basis of additional factors (ie, higher risk of metachronous CRC, results from germline and somatic testing, fertility desires, concomitant indications for gynecologic cancer, and higher risk of CINV). We recommend that all newly diagnosed eoCRC patients receive counseling on fertility preservation before treatment starts, as well as psychosocial support.

All statements received an agreement rate of at least 80%. The systematic analysis and appraisal of the literature showed that the LE in this disease is low in some specific areas.

The lack of sufficiently high-quality data on some topics demands further investigation (Table 5). During the in-person DIRECt22 meeting in Milan, we identified significant knowledge gaps that should be prioritized in future research agendas, including outcomes of screening in young populations at average and increased risk for CRC (especially in European Union countries, where data remain limited); identification of risk factors for eoCRC; examining outcomes of specific neoadjuvant, adjuvant, and systemic therapy in eoCRC; long-term outcomes after surgery vs endoscopic resections; and appropriate follow-up schedules and surveillance intervals after curative resection. However, there was global consensus regarding the importance of individual risk assessment for determining the optimal age to initiate CRC screening. One topic of discussion was whether the systemic treatment of eoCRC should differ compared with loCRC; at this time data are limited because of the absence of randomized controlled trials specific to eoCRC; therefore, no change to the treatment of CRC should be made on the basis of age alone.

These recommendations resulted from a critical appraisal of the best available evidence and expert evaluation of the most recently published data on eoCRC. A consensus process contributed to their elaboration and validated the conclusions drawn from the literature. The DIRECt guidelines are the first for eoCRC, and they represent a useful tool for diagnosis, management, and prevention of eoCRC in clinical settings.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.12.006.

References

1. Sung H, Siegel RL, Rosenberg PS, et al. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. Lancet Public Heal 2019;4:e137–e147.
2. Vuik FER, Nieuwenburg SAV, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut 2019;68:1820–1826.
3. Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut 2019; 68:2179–2185.
4. Patel SG, Karlitz JJ, Yen T, et al. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. Lancet Gastroenterol Hepatol 2022;7:262–274.
5. Arnold M, Abnet CC, Neale RE, et al. Global burden of 5 major types of gastrointestinal cancer. Gastroenterology 2020; 159:335–349.e15.
6. Breekveldt ECH, Lansdorp-Vogelaar I, Toes-Zoutendijk E, et al. Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study. Lancet Gastroenterol Hepatol 2022;7:60–68.
7. Chiu HM, Jen GHH, Wang YW, et al. Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers. Gut 2021;70:2321–2329.
8. Flor LS, Reitsma MB, Gupta V, et al. The effects of tobacco control policies on global smoking prevalence. Nat Med 2021; 27:239–243.
9. Boakye E, Uddin SMI, Obisesan OH, et al. Aspirin for cardiovascular disease prevention among adults in the United States: trends, prevalence, and participant characteristics associated with use. Am J Prev Cardiol 2021;8:100256.
10. Guillou PJ, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005;365:1718–1726.
11. Modest DP, Karthaus M, Fruehauf S, et al. Panitumumab plus fluorouracil and folinic acid versus fluorouracil and folinic acid alone as maintenance therapy in RAS wild-type metastatic colorectal cancer: the randomized PANAMA trial (AIO KRK 0212). J Clin Oncol 2022;40:72–82.
12. Iveson TJ, Sobrero AF, Yoshino T, et al. Duration of adjuvant doublet chemotherapy (3 or 6 months) in patients with high-risk stage II colorectal cancer. J Clin Oncol 2021;39:631–641.
13. André T, Vernerey D, Mineur L, et al. Three versus 6 months of oxaliplatin-based adjuvant chemotherapy for patients with stage III colon cancer: disease-free survival results from a randomized, open-label, International Duration Evaluation of Adjuvant (IDEA) France, phase III trial. J Clin Oncol 2018;36:1469–1477.
14. Howick J, Chalmers I, Glasziou P, et al. The 2011 Oxford CEBM evidence levels of evidence (introductory document). Oxford Cent Evidence-Based Med, 2011.
15. US Preventive Services Task Force, Davidson KW, Barry MJ, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA 2021; 325:1965–1977.
16. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018; 68:250–281.

17. Shaukat A, Kahi CJ, Burke CA, et al. ACG clinical guidelines: colorectal cancer screening 2021. Am J Gastroenterol 2021; 116:458–479.
18. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2017;112:1016–1030.
19. Shaukat A, Kahi CJ, Burke CA, et al. ACG clinical guidelines: colorectal cancer screening 2021. Am J Gastroenterol 2021;116:458–479.
20. Patel SG, May FP, Anderson JC, et al. Updates on age to start and stop colorectal cancer screening: recommendations from the U.S. Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2022;162:285–299.
21. Khan SA, Morris M, Idrees K, et al. Colorectal cancer in the very young: a comparative study of tumor markers, pathology and survival in early onset and adult onset patients. J Pediatr Surg 2016;51:1812–1817.
22. Djursby M, Madsen MB, Frederiksen JH, et al. New pathogenic germline variants in very early onset and familial colorectal cancer patients. Front Genet 2020;11.
23. Jasperson KW, Vu TM, Schwab AL, et al. Evaluating Lynch syndrome in very early onset colorectal cancer probands without apparent polyposis. Fam Cancer 2010;9:99–107.
24. Durno C, Aronson M, Bapat B, et al. Family history and molecular features of children, adolescents, and young adults with colorectal carcinoma. Gut 2005;54:1146–1150.
25. Terdiman JP, Levin TR, Allen BA, et al. Hereditary nonpolyposis colorectal cancer in young colorectal cancer patients: high-risk clinic versus population-based registry. Gastroenterology 2002;122:940–947.
26. Liu B, Farrington SM, Petersen GM, et al. Genetic instability occurs in the majority of young patients with colorectal cancer. Nat Med 1995;1:348–352.
27. Ko CW, Siddique SM, Patel A, et al. AGA clinical practice guidelines on the gastrointestinal evaluation of iron deficiency anemia. Gastroenterology 2020;159:1085–1094.
28. Vajravelu RK, Mehta SJ, Lewis JD, et al. Understanding characteristics of who undergoes testing is crucial for the development of diagnostic strategies to identify individuals at risk for early-age onset colorectal cancer. Gastroenterology 2021;160:993–998.
29. Low EE, Demb J, Liu L, et al. Risk factors for early-onset colorectal cancer. Gastroenterology 2020;159:492–501.e7.
30. Syed AR, Thakkar P, Horne ZD, et al. Old vs new: risk factors predicting early onset colorectal cancer. World J Gastrointest Oncol 2019;11:1011–1020.
31. Frostberg E, Rahr HB. Clinical characteristics and a rising incidence of early-onset colorectal cancer in a nationwide cohort of 521 patients aged 18-40 years. Cancer Epidemiol 2020;66.
32. Krigel A, Zhou M, Terry MB, et al. Symptoms and demographic factors associated with early-onset colorectal neoplasia among individuals undergoing diagnostic colonoscopy. Eur J Gastroenterol Hepatol 2020;32:821–826.
33. Demb J, Liu L, Murphy CC, et al. Young-onset colorectal cancer risk among individuals with iron-deficiency anaemia and haematochezia. Gut 2021;70:1529–1537.
34. Dozois EJ, Boardman LA, Suwanthanma W, et al. Young-onset colorectal cancer in patients with no known genetic predisposition: can we increase early recognition and improve outcome? Medicine (Baltimore) 2008;87:259–263.
35. Glover M, Mansoor E, Panhwar M, et al. Epidemiology of colorectal cancer in average risk adults 20-39 years of age: a population-based national study. Dig Dis Sci 2019; 64:3602–3609.
36. Leo M Di, Zuppardo RA, Puzzono M, et al. Risk factors and clinical characteristics of early-onset colorectal cancer vs late-onset colorectal cancer. Eur J Gastroenterol Hepatol 2021; 33:1153–1160.
37. Rajagopalan A, Antoniou E, Morkos M, et al. Is colorectal cancer associated with altered bowel habits in young patients? ANZ J Surg 2021;91:943–946.
38. Zhu C, Ji M, Dai W, et al. Clinicopathological characteristics of Chinese colorectal cancer patients under 30 years of age: implication in diagnosis and therapy. Curr Cancer Drug Targets 2015;15:27–34.
39. Butterly LF, Siegel RL, Fedewa SA, et al. Colonoscopy outcomes in average-risk screening equivalent young adults: data from the New Hampshire Colonoscopy Registry. Am J Gastroenterol 2021;116:171–179.
40. D'Souza N, Delisle TG, Chen M, et al. Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: a diagnostic accuracy study. Gut 2020.
41. D'Souza N, Monahan KJ, Benton S, et al. Finding the needle in the haystack: the diagnostic accuracy of the faecal immunochemical test for colorectal cancer in younger symptomatic patients. Colorectal Dis 2021:codi.15786.
42. Jung Y, Park CH, Kim NH, et al. Colorectal cancer screening with the fecal immunochemical test in persons aged 30 to 49 years: focusing on the age for commencing screening. Gastrointest Endosc 2017;86:892–899.
43. Corley D, Jensen CD, Quinn VP, et al. Association between time to colonoscopy after a positive fecal test result and risk of colorectal cancer and cancer stage at diagnosis. JAMA 2017; 317:1631–1641.
44. San Miguel Y, Demb J, Martinez M, et al. Time to colonoscopy after abnormal stool-based screening and risk for colorectal cancer incidence and mortality. Gastroenterology 2021; 160:1997–2005.e3.
45. Sandhu GS, Anders R, Blatchford P, et al. High incidence of prolonged rectal bleeding and advanced stage cancer in early-onset colorectal cancer patients. Color Cancer 2020;9:CRC31.
46. Scott RB, Rangel LE, Osler TM, et al. Rectal cancer in patients under the age of 50 years: the delayed diagnosis. Am J Surg 2016;211:1014–1018.
47. Chen FW, Sundaram V, Chew TA, et al. Advanced-stage colorectal cancer in persons younger than 50 years not associated with longer duration of symptoms or time to diagnosis. Clin Gastroenterol Hepatol 2017;15:728–737.e3.
48. Cavestro GM, Mannucci A, Zuppardo RA, et al. Early onset sporadic colorectal cancer: worrisome trends and oncogenic features. Dig Liver Dis 2018;50:521–532.
49. Burnett-Hartman AN, Lee J, Demb J, et al. An update on the epidemiology, molecular characterization, diagnosis, and screening strategies for early-onset colorectal cancer. Gastroenterology 2021;160:1041–1049.
50. Quah HM, Joseph R, Schrag D, et al. Young age influences treatment but not outcome of colon cancer. Ann Surg Oncol 2007;14:2759–2765.
51. Kim TJ, Kim ER, Hong SN, et al. Long-term outcome and prognostic factors of sporadic colorectal cancer in young patients: a large institutional-based retrospective study. Med (United States) 2016;95.

52. Sandhu GS, Anders R, Blatchford P, et al. High incidence of prolonged rectal bleeding and advanced stage cancer in early-onset colorectal cancer patients. Available at: https://doi.org/10.2217/crc-2020-0012 2020;9:CRC31. Accessed October 13, 2021.
53. Bilal M, Singh S, Le TT, et al. Select group of patients might benefit from early colonoscopic screening for colorectal cancer. Surg Endosc 2020;34:4463–4471.
54. Yeh JH, Lin CW, Wang WL, et al. Positive fecal immunochemical test strongly predicts adenomas in younger adults with fatty liver and metabolic syndrome. Clin Transl Gastroenterol 2021;12:e00305.
55. Kim NH, Park JH, Park DI, et al. The fecal immunochemical test has high accuracy for detecting advanced colorectal neoplasia before age 50. Dig Liver Dis 2017;49:557–561.
56. Stanich PP, Pelstring KR, Hampel H, et al. A high percentage of early-age onset colorectal cancer is potentially preventable. Gastroenterology 2021;160:1850–1852.
57. Daca Alvarez M, Quintana I, Terradas M, et al. The inherited and familial component of early-onset colorectal cancer. Cells 2021;10:710.
58. Leerdam ME van, Roos VH, Hooft JE van, et al. Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Georg Thieme Verlag, 2019:1082–1093.
59. Wong MCS, Chan CH, Lin J, et al. Lower relative contribution of positive family history to colorectal cancer risk with increasing age: a systematic review and meta-analysis of 9.28 million individuals. Am J Gastroenterol 2018;113:1819–1827.
60. Hemminki K, Li X. Familial colorectal adenocarcinoma from the Swedish Family-Cancer Database. Int J Cancer 2001;94:743–748.
61. Kastrinos F, Allen JI, Stockwell DH, et al. Development and validation of a colon cancer risk assessment tool for patients undergoing colonoscopy. Am J Gastroenterol 2009;104:1508–1518.
62. Kastrinos F, Uno H, Ukaegbu C, et al. Development & validation of the PREMM5 model for comprehensive risk assessment of lynch syndrome. J Clin Oncol 2017;35:2165–2172.
63. Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults. Gastroenterology 2020;158:341–353.
64. Willauer AN, Liu Y, Pereira AAL, et al. Clinical and molecular characterization of early-onset colorectal cancer. Cancer 2019;125:2002–2010.
65. Kamath SD, Torrejon N, Wei W, et al. Racial disparities negatively impact outcomes in early-onset colorectal cancer independent of socioeconomic status. Cancer Med 2021;10:7542–7550.
66. Murphy CC, Wallace K, Sandler RS, et al. Racial disparities in incidence of young-onset colorectal cancer and patient survival. Gastroenterology 2019;156:958–965.
67. Rahman R, Schmaltz C, Jackson C, et al. Increased risk for colorectal cancer under age 50 in racial and ethnic minorities living in the United States. Cancer Med 2015;4:1863–1870.
68. Garcia S, Pruitt SL, Singal AG, et al. Colorectal cancer incidence among Hispanics and non-Hispanic whites in the United States. Cancer Causes Control 2018;29:1039.
69. Muller C, Ihionkhan E, Stoffel EM, et al. Disparities in early-onset colorectal cancer. Cells 2021;10:1018.
70. Montminy EM, Zhou M, Maniscalco L, et al. Trends in the incidence of early-onset colorectal adenocarcinoma among black and white US residents aged 40 to 49 years, 2000-2017. JAMA Netw open 2021;4.
71. Breau G, Ellis U. Risk factors associated with young-onset colorectal adenomas and cancer: a systematic review and meta-analysis of observational research. Cancer Control 2020;27.
72. Joh H-K, Lee DH, Hur J, et al. Simple sugar and sugar-sweetened beverage intake during adolescence and risk of colorectal cancer precursors. Gastroenterology 2021;161:128–142.e20.
73. O'Sullivan DE, Sutherland RL, Town S, et al. Risk factors for early-onset colorectal cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2022;20:1229–1240.e5.
74. Lei X, Song S, Li X, et al. Excessive body fat at a young age increases the risk of colorectal cancer: a systematic review and meta-analysis. Nutr Cancer, 2020.
75. Li H, Boakye D, Chen X, et al. Associations of body mass index at different ages with early-onset colorectal cancer. Gastroenterology 2022;162:1088–1097.e3.
76. Khan NA, Hussain M, Rahman AU, et al. Dietary practices, addictive behavior and bowel habits and risk of early onset colorectal cancer: a case control study. Asian Pacific J Cancer Prev 2015;16:7967–7973.
77. Kim JY, Jung YS, Park JH, et al. Different risk factors for advanced colorectal neoplasm in young adults. World J Gastroenterol 2016;22:3611–3620.
78. Kim NH, Jung YS, Yang HJ, et al. Prevalence of and risk factors for colorectal neoplasia in asymptomatic young adults (20–39 years old). Clin Gastroenterol Hepatol 2019;17:115–122.
79. Murphy CC, Cirillo PM, Krigbaum NY, et al. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am J Obstet Gynecol 2022;226:132.e1–132.e14.
80. Zheng X, Hur J, Nguyen LH, et al. Comprehensive assessment of diet quality and risk of precursors of early-onset colorectal cancer. J Natl Cancer Inst 2021;113:543–552.
81. Puzzono M, Mannucci A, Grannò S, et al. The role of diet and lifestyle in early-onset colorectal cancer: a systematic review. Cancers 2021;13:5933.
82. Gausma V, Liang PS, O'Connell K, et al. Evaluation of early-life factors and early-onset colorectal cancer among men and women in the UK Biobank. Gastroenterology 2022;162:981–983.e3.
83. Puzzono M, Mannucci A, Leo M Di, et al. Diet and lifestyle habits in early-onset colorectal cancer. a pilot case-control study. Dig Dis 2022;40:710–718.
84. McDowell R, Perrott S, Murchie P, et al. Oral antibiotic use and early-onset colorectal cancer: findings from a case-control study using a national clinical database. Br J Cancer 2022;126:957–967.
85. Nguyen LH, Liu P-H, Zheng X, et al. Sedentary behaviors, TV viewing time, and risk of young-onset colorectal cancer. JNCI Cancer Spectr 2018;2:1–8.
86. Hur J, Otegbeye E, Joh HK, et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. Gut 2021;70:2330–2336.
87. Kim H, Lipsyc-Sharf M, Zong X, et al. Total vitamin D intake and risks of early-onset colorectal cancer and precursors. Gastroenterology 2021;161:1208–1217.e9.
88. Gu J, Li Y, Yu J, et al. A risk scoring system to predict the individual incidence of early-onset colorectal cancer. BMC Cancer 2022;22:122.

89. Archambaut AN, Jeon J, Lin Y, et al. Risk stratification for early-onset colorectal cancer using a combination of genetic and environmental risk scores: an international multi-center study. J Natl Cancer Inst 2022;114:528–539.
90. Kolb J, Hu J, DeSanto K, et al. Early-age onset colorectal neoplasia in average-risk individuals undergoing screening colonoscopy: a systematic review and meta-analysis. Gastroenterology 2021;161:1145–1155.e12.
91. Enweren, Cho MY, Demb J, et al. Systematic review of prevalence, risk factors, and risk for metachronous advanced neoplasia in patients with young-onset colorectal adenoma. Clin Gastroenterol Hepatol 2021;19:680–689.e12.
92. Ladabaum U, Mannalithara A, Meester RGS, et al. Cost-effectiveness and national effects of initiating colorectal cancer screening for average-risk persons at age 45 years instead of 50 years. Gastroenterology 2019;157:137–148.
93. Chen C, Stock C, Hoffmeister M, et al. Optimal age for screening colonoscopy: a modeling study. Gastrointest Endosc 2019; 89:1017–1025.e12.
94. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US preventive services Task Force. JAMA 2016;315:2595–2609.
95. Trivedi PD, Mohapatra A, Morris MK, et al. Prevalence and predictors of young-onset colorectal neoplasia: insights from a nationally representative colonoscopy registry. Gastroenterology 2022;162:1136–1146.e5.
96. Reif de Paula T, Haas EM, Keller DS. Colorectal cancer in the 45-to-50 age group in the United States: a National Cancer Database (NCDB) analysis. Surg Endosc 2022;36:6629–6637.
97. Shen J, Wu Y, Mo M, et al. Risk factors associated with early-onset colorectal neoplasm in Chinese youth: a prospective population-based study. Front Oncol 2021;11.
98. Imperiale TF, Wagner DR, Lin CY, et al. Results of screening colonoscopy among persons 40 to 49 years of age. N Engl J Med 2002;346:1781–1785.
99. Yip B, Holub J, Lieberman D. Increasing prevalence of polyps > 9 mm in young adults aged 40 to 59 years undergoing colonoscopy from 2002 to 2014. Gastroenterology 2021; 160:1863–1865.e1.
100. Yen T, Scolaro J, Montminy E, et al. Spectrum of advanced colorectal neoplasia and anticipated yield of average-risk screening in veterans under age 50. Clin Gastroenterol Hepatol 2021.
101. Levin TR, Jensen CD, Chawla NM, et al. Early screening of African Americans (45–50 years old) in a fecal immunochemical test–based colorectal cancer screening program. Gastroenterology 2020;159:1695–1704.e1.
102. Chen FW, Yang L, Cusumano VT, et al. Early-onset colorectal cancer is associated with a lower risk of metachronous advanced neoplasia than traditional-onset colorectal cancer. Dig Dis Sci 2022;67:1045–1053.
103. Yeo H, Betel D, Abelson JS, et al. Early-onset colorectal cancer is distinct from traditional colorectal cancer. Clin Colorectal Cancer 2017;16:293–299.e6.
104. Abdelsattar ZM, Wong SL, Regenbogen SE, et al. Colorectal cancer outcomes and treatment patterns in patients too young for average-risk screening. Cancer 2016;122:929–934.
105. Cercek A, Chatila WK, Yaeger R, et al. A comprehensive comparison of early-onset and average-onset colorectal cancers. J Natl Cancer Inst 2021;113:1683–1692.
106. Norquist BM, Harrell MI, Brady MF, et al. Inherited mutations in women with ovarian carcinoma. JAMA Oncol 2016;2:482–490.
107. Malik SS, Lythgoe MP, McPhail M, et al. Metachronous colorectal cancer following segmental or extended colectomy in Lynch syndrome: a systematic review and meta-analysis. Fam Cancer 2018;17:557–564.
108. Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut 2011;60:950–957.
109. Duraes L, et al. Role of genetic testing in surgical decision making for patients with HNPCC. Fam Cancer 2017; 16:S101–S102.
110. LaDuca H, Polley EC, Yussuf A, et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. Genet Med 2020; 22:407–415.
111. Jiang T, Wang F, Wang Y, et al. Germline mutational profile of Chinese patients under 70 years old with colorectal cancer. Cancer Commun 2020;40:620–632.
112. Zhunussova G, Afonin G, Abdikerim S, et al. Mutation spectrum of cancer-associated genes in patients with early onset of colorectal cancer. Front Oncol 2019;9.
113. You YN, Borras E, Chang K, et al. Detection of pathogenic germline variants among patients with advanced colorectal cancer undergoing tumor genomic profiling for precision medicine. Dis Colon Rectum 2019;62:429–437.
114. Mork ME, Rodriguez A, Bannon SA, et al. Outcomes of disease-specific next-generation sequencing gene panel testing in adolescents and young adults with colorectal cancer. Cancer Genet 2019;235–236:77–83.
115. AlDubayan SH, Giannakis M, Moore ND, et al. Inherited DNA-repair defects in colorectal cancer. Am J Hum Genet 2018; 102:401–414.
116. Stoffel EM, Koeppe E, Everett J, et al. Germline genetic features of young individuals with colorectal cancer. Gastroenterology 2018;154:897–905.e1.
117. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. JAMA Oncol 2017;3:464–471.
118. DeRycke MS, Gunawardena S, Balcom JR, et al. Targeted sequencing of 36 known or putative colorectal cancer susceptibility genes. Mol Genet Genomic Med 2017;5:553–569.
119. Chubb D, Broderick P, Dobbins SE, et al. Rare disruptive mutations and their contribution to the heritable risk of colorectal cancer. Nat Commun 2016;7:1–7.
120. Mork ME, You YN, Ying J, et al. High prevalence of hereditary cancer syndromes in adolescents and young adults with colorectal cancer. J Clin Oncol 2015;33:3544–3549.
121. Toh MR, Chiang JB, Chong ST, et al. Germline pathogenic variants in homologous recombination and DNA repair genes in an Asian cohort of young-onset colorectal cancer. JNCI Cancer Spectr 2018;2.
122. Yurgelun MB, Kulke MH, Fuchs CS, et al. Cancer susceptibility gene mutations in individuals with colorectal cancer. J Clin Oncol 2017;35:1086–1095.
123. Chang PY, Chang SC, Wang MC, et al. Pathogenic germline mutations of DNA repair pathway components in early-onset sporadic colorectal polyp and cancer patients. Cancers (Basel) 2020;12:1–12.

124. Jansen AML, Ghosh P, Dakal TC, et al. Novel candidates in early-onset familial colorectal cancer. Fam Cancer 2020;19.
125. Uson PLS, Riegert-Johnson D, Boardman L, et al. Germline cancer susceptibility gene testing in unselected patients with colorectal adenocarcinoma: a multicenter prospective study. Clin Gastroenterol Hepatol 2022;20:e508–e528.
126. Fernández-Rozadilla C, Álvarez-Barona M, Quintana I, et al. Exome sequencing of early-onset patients supports genetic heterogeneity in colorectal cancer. Sci Rep 2021;11:11135.
127. Middeldorp A, Jagmohan-Changur S, Eijk R Van, et al. Enrichment of low penetrance susceptibility loci in a Dutch familial colorectal cancer cohort. Cancer Epidemiol Biomarkers Prev 2009;18:3062–3067.
128. Song N, Shin A, Park JW, et al. Common risk variants for colorectal cancer: an evaluation of associations with age at cancer onset. Sci Rep 2017;7.
129. Giráldez MD, López-Dóriga A, Bujanda L, et al. Susceptibility genetic variants associated with early-onset colorectal cancer. Carcinogenesis 2012;33:613–619.
130. Holst S Von, Picelli S, Edler D, et al. Association studies on 11 published colorectal cancer risk loci. Br J Cancer 2010; 103:575–580.
131. He J, Wilkens LR, Strain DO, et al. Generalizability and epidemiologic characterization of eleven colorectal cancer GWAS hits in multiple populations. Cancer Epidemiol Biomarkers Prev 2011;20:70–81.
132. Huyghe JR, Bien SA, Harrison TA, et al. Discovery of common and rare genetic risk variants for colorectal cancer. Nat Genet 2019;51:76–87.
133. Archambault AN, Su YR, Jeon J, et al. Cumulative burden of colorectal cancer–associated genetic variants is more strongly associated with early-onset vs late-onset cancer. Gastroenterology 2020;158:1274–1286.e12.
134. Northcutt MJ, Shi Z, Zijlstra M, et al. Polygenic risk score is a predictor of adenomatous polyps at screening colonoscopy. BMC Gastroenterol 2021;21:65.
135. Thomas M, Sakoda LC, Hoffmeister M, et al. Genome-wide modeling of polygenic risk score in colorectal cancer risk. Am J Hum Genet 2020;107:432–444.
136. Li X, Timofeeva M, Spiliopoulou A, et al. Prediction of colorectal cancer risk based on profiling with common genetic variants. Int J Cancer 2020;147:3431–3437.
137. Jia G, Lu Y, Wen W, et al. Evaluating the utility of polygenic risk scores in identifying high-risk individuals for eight common cancers. JNCI Cancer Spectr 2020;4.
138. Guo F, Weigl K, Carr PR, et al. Use of polygenic risk scores to select screening intervals after negative findings from colonoscopy. Clin Gastroenterol Hepatol 2020;18:2742–2751.e7.
139. Carr PR, Weigl K, Edelmann D, et al. Estimation of absolute risk of colorectal cancer based on healthy lifestyle, genetic risk, and colonoscopy status in a population-based study. Gastroenterology 2020;159:129–138.e9.
140. Saunders CL, Kilian B, Thompson DJ, et al. External validation of risk prediction models incorporating common genetic variants for incident colorectal cancer using UK Biobank. Cancer Prev Res 2020;13:509–520.
141. Fahed AC, Wang M, Homburger JR, et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. Nat Commun 2020;11:1–9.
142. Schmit SL, Edlund CK, Schumacher FR, et al. Novel common genetic susceptibility loci for colorectal cancer. J Natl Cancer Inst 2019;111:146–157.
143. Jin Z, Dixon JG, Fiskum JM, et al. Clinicopathological and molecular characteristics of early-onset stage III colon adenocarcinoma: an analysis of the ACCENT database. J Natl Cancer Inst 2021;113:1693–1704.
144. Remo A, Fassan M, Lanza G. Immunohistochemical evaluation of mismatch repair proteins in colorectal carcinoma: the AIFEG/GIPAD proposal. Pathologica 2016;108:104–109.
145. Monahan KJ, Bradshaw N, Dolwani S, et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut 2020; 69:411.
146. Seppälä TT, Latchford A, Negoi I, et al. European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. Br J Surg 2021;108:484–498.
147. Benson AB, Venook AP, Al-Hawary MM, et al. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2021;19:329–359.
148. Møller P, Seppälä T, Bernstein I, et al. Incidence of and survival after subsequent cancers in carriers of pathogenic MMR variants with previous cancer: a report from the prospective Lynch syndrome database. Gut 2017;66:1657–1664.
149. Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path-MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut 2018;67:1306–1316.
150. Mannucci A, Sloane Furniss C, Ukaegbu CI, et al. Comparison of colorectal and endometrial microsatellite instability tumor analysis and Premm 5 risk assessment for predicting pathogenic germline variants on multigene panel testing. J Clin Oncol 2020; 38:4086–4094.
151. Liang JT, Huang KC, Cheng AL, et al. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. Br J Surg 2003;90:205–214.
152. Chen Y, Chen Z, Huang J, et al. Clinicopathological and molecular characteristics of early-onset vs late-onset colorectal cancer according to tumor location. Int J Clin Oncol 2022.
153. Narayan RR, Aveson VG, Chou JF, et al. Association of genomic profiles and survival in early onset and screening-age colorectal cancer patients with liver metastases resected over 15 years. J Surg Oncol 2022.
154. Jácome AA, Vreeland TJ, Johnson B, et al. The prognostic impact of RAS on overall survival following liver resection in early versus late-onset colorectal cancer patients. Mol Diagnostics Br J Cancer 2021;124.
155. Manjelievskaia J, Brown D, McGlynn KA, et al. Chemotherapy use and survival among young and middle-aged patients with colon cancer. JAMA Surg 2017;152:452–459.
156. Tang C-T, Guo Z-X, Wang P, et al. Higher LNM rate and poorer prognosis of early-onset compared to late-onset T1 stage colorectal cancer: a large-population based study. Am J Cancer Res 2021;11:3176–3188.
157. Wang H, Lu H, Yang H, et al. Impact of age on risk of lymph node positivity in patients with colon cancer. J Cancer 2019; 10:2102–2108.
158. Lieu CH, Renfro LA, Gramont A De, et al. Association of age with survival in patients with metastatic colorectal cancer: analysis from the ARCAD clinical trials program. J Clin Oncol 2014; 32:2975–2982.

159. Foppa C, Tamburello S, Maroli A, et al. Early age of onset is an independent predictor for worse disease-free survival in sporadic rectal cancer patients: a comparative analysis of 980 consecutive patients. Eur J Surg Oncol 2022;48:857–863.
160. McClelland PH, Liu T, Ozuner G. Early-onset colorectal cancer in patients under 50 years of age: demographics, disease characteristics, and survival. Clin Colorectal Cancer 2021.
161. Chen JN, Zhang QW, Pan YB, et al. Young-onset early colorectal cancer had similar relative survival to but better overall survival than conventional early colorectal cancer: a large population-based study. Front Oncol 2020;10.
162. Georgiou A, Khakoo S, Edwards P, et al. Outcomes of patients with early onset colorectal cancer treated in a UK specialist cancer center. Cancers (Basel) 2019;11.
163. Zhang Y, Yan L, Wu Y, et al. Worse treatment response to neoadjuvant chemoradiotherapy in young patients with locally advanced rectal cancer. BMC Cancer 2020;20:854.
164. Zhang Y, Wang Y, Liu X, et al. Worse prognosis in young patients with locally advanced rectal cancer following neoadjuvant chemoradiotherapy: a comparative study. Medicine (Baltimore) 2020;99:e21304.
165. Blanke CD, Bot BM, Thomas DM, et al. Impact of young age on treatment efficacy and safety in advanced colorectal cancer: a pooled analysis of patients from nine first-line phase III chemotherapy trials. J Clin Oncol 2011;29:2781–2786.
166. Wang L, Hirano Y, Heng G, et al. Better cancer-specific survival in younger patients with stage III colorectal cancer: a propensity score matching study from Japan. Anticancer Res 2020;40:4365–4372.
167. Zaborowski AM, Murphy B, Creavin B, et al. Clinicopathological features and oncological outcomes of patients with young-onset rectal cancer. Br J Surg 2020;107:606–612.
168. Xie X, Yin J, Zhou Z, et al. Young age increases the risk for lymph node metastasis in patients with early colon cancer. BMC Cancer 2019;19.
169. Fontana E, Meyers J, Sobrero A, et al. Early-onset colorectal adenocarcinoma in the IDEA database: treatment adherence, toxicities, and outcomes with 3 and 6 months of adjuvant fluoropyrimidine and oxaliplatin. J Clin Oncol 2021;39:4009–4019.
170. Kneuertz PJ, Chang GJ, Hu CY, et al. Overtreatment of young adults with colon cancer: more intense treatments with unmatched survival gains. JAMA Surg 2015;150:402–409.
171. Lipsyc-Sharf M, Zhang S, Ou FS, et al. Survival in young-onset metastatic colorectal cancer: findings from Cancer and Leukemia Group B (Alliance)/SWOG 80405. J Natl Cancer Inst 2022;114:427–435.
172. Hofheinz RD, Arnold D, Fokas E, et al. Impact of age on the efficacy of oxaliplatin in the preoperative chemoradiotherapy and adjuvant chemotherapy of rectal cancer: a post hoc analysis of the CAO/ARO/AIO-04 phase III trial. Ann Oncol 2018;29:1793–1799.
173. Bahadoer RR, Dijkstra EA, Etten B van, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:29–42.
174. Fokas E, Schlenska-Lange A, Polat B, et al. Chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for patients with locally advanced rectal cancer: long-term results of the CAO/ARO/AIO-12 randomized clinical trial. JAMA Oncol 2022;8.
175. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol 2022;18.
176. Conroy T, Bosset JF, Etienne PL, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:702–715.
177. Cutsem E Van, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386–1422.
178. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 2.2018 clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2018;16:874–901.
179. Yoshino T, Arnold D, Taniguchi H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol 2018;29:44–70.
180. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 6.2020: featured updates to the NCCN guidelines. J Natl Compr Cancer Netw 2020;18:807–815.
181. Calderillo G, Herrera M, Lopez H, et al. Impact of age on efficacy of neoadjuvant chemoradiotherapy (CRT) in locally advanced rectal cancer (LARC). Ann Oncol 2016;27:ii38.
182. You YN, Dozois EJ, Boardman LA, et al. Young-onset rectal cancer: presentation, pattern of care and long-term oncologic outcomes compared to a matched older-onset cohort. Ann Surg Oncol 2011;18:2469–2476.
183. Kaminski MF, Thomas-Gibson S, Bugajski M, et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) quality improvement initiative. Endoscopy 2017;49:378–397.
184. Dekker E, Houwen BBSL, Puig I, et al. Curriculum for optical diagnosis training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) position statement. Endoscopy 2020;52:899–923.
185. Bisschops R, East JE, Hassan C, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) guideline—update 2019. Endoscopy 2019;51:1155–1179.
186. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015;47:829–854.
187. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy 2017;49:270–297.
188. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298–1306.
189. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;362:1795–1803.
190. Shaukat A, Rex DK, Shyne M, et al. Adenoma detection rates for 45-49 year old screening population. Gastroenterology 2022;162:957–959.e1.

191. Krause C, Kruis W. Synchronous pathologic findings in patients with colorectal cancer and preoperative incomplete colonoscopy. Int J Colorectal Dis 2019;34:1407–1412.
192. Isler JT, Brown PC, Lewis GF, et al. The role of preoperative colonoscopy in colorectal cancer. Dis Colon Rectum 1987; 30:435–439.
193. Ito S, Hotta K, Imai K, et al. Ultrathin colonoscopy can improve complete preoperative colonoscopy for stenotic colorectal cancer: prospective observational study. Dig Endosc 2021; 33:621–628.
194. Healy M, Bednarski BK, Eng C, et al. Higher propensity for nodal metastases among young-onset rectal cancers. Dis Colon Rectum 2019;62:E322–E322.
195. Alawadi Z, Phatak UR, Hu CY, et al. Comparative effectiveness of primary tumor resection in patients with stage IV colon cancer. Cancer 2017;123:1124–1133.
196. Taylor FGM, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY Study. J Clin Oncol 2014;32:34–43.
197. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130:1865–1871.
198. Kahi CJ, Boland CR, Dominitz JA, et al. Colonoscopy surveillance after colorectal cancer resection: recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2016;150:758–768.e11.
199. Pita-Fernández S, Alhayek-Aí M, González-Martín C, et al. Intensive follow-up strategies improve outcomes in non-metastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. Ann Oncol 2015; 26:644–656.
200. Green BL, Marshall HC, Collinson F, et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 2013;100:75–82.
201. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. CA Cancer J Clin 2006;56:160–167.
202. Anon AGA. institute guidelines for colonoscopy surveillance after cancer resection: clinical decision tool. Gastroenterology 2014;146:1413–1414.
203. Cao B, Min L, Zhu S, et al. Long-term oncological outcomes of local excision versus radical resection for early colorectal cancer in young patients without preoperative chemoradiotherapy: a population-based propensity matching study. Cancer Med 2018;7:2415–2422.
204. Fernández-Esparrach G, Ayuso-Colella JR, Sendino O, et al. EUS and magnetic resonance imaging in the staging of rectal cancer: a prospective and comparative study. Gastrointest Endosc 2011;74:347–354.
205. Lugli A, Kirsch R, Ajioka Y, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol 2017;30:1299–1311.
206. Kim SB, Lee HJ, Park SJ, et al. Comparison of colonoscopy surveillance outcomes between young and older colorectal cancer patients. J Cancer Prev 2017;22:159–165.
207. Karsenti D, Tharsis G, Burtin P, et al. Adenoma and advanced neoplasia detection rates increase from 45 years of age. World J Gastroenterol 2019;25:447–456.
208. Oh EH, Kim N, Hwang SW, et al. Comparison of long-term recurrence-free survival between primary surgery and endoscopic resection followed by secondary surgery in T1 colorectal cancer. Gastrointest Endosc 2021;94:394–404.
209. Zhang Q, Sun L, Tang C, et al. Inverse association of age with risk of lymph node metastasis in superficial colorectal cancer: a large population-based study. Oncologist 2020;25.
210. Dang H, Dekkers N, Cessie S le, et al. Risk and time pattern of recurrences after local endoscopic resection of T1 colorectal cancer: a meta-analysis. Clin Gastroenterol Hepatol 2022; 20:e298–e314.
211. Yeh JH, Tseng CH, Huang RY, et al. Long-term outcomes of primary endoscopic resection vs surgery for T1 colorectal cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2020;18:2813–2823.e5.
212. Anderson JC, Robinson CM, Butterly LF. Young adults and metachronous neoplasia: risks for future advanced adenomas and large serrated polyps compared with older adults. Gastrointest Endosc 2020;91:669–675.
213. Klos CL, Montenegro G, Jamal N, et al. Segmental versus extended resection for sporadic colorectal cancer in young patients. J Surg Oncol 2014;110:328–332.
214. Renkonen-Sinisalo L, Seppälä TT, Järvinen HJ, et al. Subtotal colectomy for colon cancer reduces the need for subsequent surgery in Lynch syndrome. Dis Colon Rectum 2017; 60:792–799.
215. Heneghan HM, Martin ST, Winter DC. Segmental vs extended colectomy in the management of hereditary nonpolyposis colorectal cancer: a systematic review and meta-analysis. Color Dis 2015;17:382–389.
216. Anele CC, Adegbola SO, Askari A, et al. Risk of metachronous colorectal cancer following colectomy in Lynch syndrome: a systematic review and meta-analysis. Color Dis 2017; 19:528–536.
217. Dominguez-Valentin M, Sampson JR, Seppälä TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med 2020;22:15–25.
218. Seppälä TT, Dominguez-Valentin M, Crosbie EJ, et al. Uptake of hysterectomy and bilateral salpingo-oophorectomy in carriers of pathogenic mismatch repair variants: a Prospective Lynch Syndrome Database report. Eur J Cancer 2021;148:124–133.
219. Crosbie EJ, Ryan NAJ, Arends MJ, et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med 2019;21:2390–2400.
220. Schmeler KM, Lynch HT, Chen L, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354:261–269.
221. Stal J, Yi S, Cohen-Cutler S, et al. Fertility preservation discussions between young adult rectal cancer survivors and their providers: sex-specific prevalence and correlates. Oncologist 2022;27:579–586.
222. Selter J, Huang Y, Grossman Becht LC, et al. Use of fertility preservation services in female reproductive-aged cancer patients. Am J Obstet Gynecol 2019;221:328.e1–328.e16.
223. Rogers JE, Woodard TL, Dasari A, et al. Fertility discussions in young adult stage III colorectal cancer population: a single-

center institution experience. Support Care Cancer 2021; 29:7351–7354.
224. Holowatyj AN, Eng C, Lewis MA. Incorporating reproductive health in the clinical management of early-onset colorectal cancer. JCO Oncol Pract 2022;18:169–172.
225. Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. Futur Oncol 2016;12:2333–2344.
226. Cercek A, Siegel CL, Capanu M, et al. Incidence of chemotherapy-induced amenorrhea in premenopausal women treated with adjuvant FOLFOX for colorectal cancer. Clin Colorectal Cancer 2013;12:163–167.
227. Stupart D, Win AK, Winship IM, et al. Fertility after young-onset colorectal cancer: a study of subjects with Lynch syndrome. Colorectal Dis 2015;17:787–793.
228. Overbeek A, Berg MH van den, Leeuwen FE van, et al. Chemotherapy-related late adverse effects on ovarian function in female survivors of childhood and young adult cancer: a systematic review. Cancer Treat Rev 2017;53:10–24.
229. Anon. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertil Steril 2018;110:380–386.
230. Levi M, Shalgi R, Brenner B, et al. The impact of oxaliplatin on the gonads: from bedside to the bench. Mol Hum Reprod 2015; 21:885–893.
231. Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO clinical practice guidelines. Ann Oncol 2018;29:iv166–iv191.
232. Fabi A, Bhargava R, Fatigoni S, et al. Cancer-related fatigue: ESMO clinical practice guidelines for diagnosis and treatment. Ann Oncol 2020;31.
233. Fontana E, Meyers JP, Sobrero AF, et al. Early-onset colorectal adenocarcinoma in the IDEA database: treatment adherence, toxicities, and outcomes with 3 and 6 months of adjuvant fluoropyrimidine and oxaliplatin. J Clin Oncol 2021;39:4009–4019.
234. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO guideline update. J Clin Oncol 2020;38:2782–2797.
235. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 2016;27:v119–v133.
236. Larkin PJ, Cherny NI, Carpia D La, et al. Diagnosis, assessment and management of constipation in advanced cancer: ESMO clinical practice guidelines. Ann Oncol 2018;29:iv111–iv125.
237. Bossi P, Antonuzzo A, Cherny NI, et al. Diarrhoea in adult cancer patients: ESMO clinical practice guidelines. Ann Oncol 2018; 29:iv126–iv142.
238. Roeland EJ, Bohlke K, Baracos VE, et al. Management of cancer cachexia: ASCO guideline. J Clin Oncol 2020;38:2438–2453.
239. Arends J, Strasser F, Gonella S, et al. Cancer cachexia in adult patients: ESMO clinical practice guidelines. ESMO Open 2021; 6:100092.
240. Munsie C, Ebert J, Joske D, et al. The benefit of physical activity in adolescent and young adult cancer patients during and after treatment: a systematic review. J Adolesc Young Adult Oncol 2019;8:512–524.
241. Carter J, Lacchetti C, Andersen BL, et al. Interventions to address sexual problems in people with cancer: American Society of Clinical Oncology clinical practice guideline adaptation of Cancer Care Ontario guideline. J Clin Oncol 2018; 36:492–511.
242. Averyt JC, Nishimoto PW. Addressing sexual dysfunction in colorectal cancer survivorship care. J Gastrointest Oncol 2014; 5:388–394.
243. Rogers JE, Johnson B. The reality of early-onset colorectal cancer: highlighting the needs in a unique but emerging population. Dig Med Res 2021;4:63–63.
244. Sansom-Daly UM, Wakefield CE, Patterson P, et al. End-of-life communication needs for adolescents and young adults with cancer: recommendations for research and practice. J Adolesc Young Adult Oncol 2020;9:157–165.
245. Rogers JE, Woodard TL, Gonzalez GMN, et al. Colorectal cancer during pregnancy or postpartum: case series and literature review. Obstet Med 2022;15:118–124.
246. Barr RD, Ferrari A, Ries L, et al. Cancer in adolescents and young adults: a narrative review of the current status and a view of the future. JAMA Pediatr 2016;170:495–501.
247. Perl G, Nordheimer S, Lando S, et al. Young patients and gastrointestinal (GI) tract malignancies: are we addressing the unmet needs? BMC Cancer 2016;16.

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Conflicts of interest
Refer to the online form to see conflicts of interest.

Supplementary Appendix 1. Search Strategy and Population, Intervention, Comparison, and Outcome (PICOs)

MP, RAZ, and AM carried out the first systematic search of the literature on each topic up to May 15, 2021 by using PubMed, Embase, and Scopus. From May 2021 to January 2022, monthly systematic revisions of newly published literature were conducted by AM (using PubMed, Embase, and Scopus). New findings and newly published articles were sent to each Working Group to support statement writing. All the literature published was added as needed. The numbers below refer to the most recent literature systematic review (completed January 28, 2022).

Working Group I. Diagnosis of eoCRC

Database searched	Years of coverage	References	Total
Embase	1971–Present	2409	9950
Pubmed.gov	1946–Present	4084	
Scopus	1992–Present	3457	
Remaining after de-duplication (5725)			4225
First round of literature screening: exclusion	Cell studies	935	1672
	Animal studies	482	
	Case reports	255	
Remaining after first round of exclusion			2561
Second round of literature screening: exclusion	Not pertinent/review	735	2416
	Incorrect study population	421	
	Incorrect study intervention	421	
	Incorrect study comparison	404	
	Incorrect study outcomes	435	
References sent to the Working Group			145
References selected	Statement D2		17
	Statement D3		6
	Statement D4		7

PubMed search strings:

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (age OR cut-off OR epidemiolog* OR young*)

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (symptom* OR sign* OR (clinical AND (feature* OR sign* OR presentation* OR characteristic*))) AND (diagnos*)

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (diagnos* OR diagnostic test* OR (screening AND strateg*))

Embase:

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('age'/exp OR age OR 'cut off' OR epidemiolog* OR young*)

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND (symptom* OR sign* OR (('clinical'/exp OR clinical) AND (feature* OR sign* OR presentation* OR characteristic*))) AND diagnos*

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ((diagnos* OR 'diagnostic'/exp OR diagnostic) AND test* OR (('screening'/exp OR screening) AND strateg*))

Scopus:

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (age OR cut-off OR epidemiolog* OR young*))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (symptom* OR sign* OR (clinical AND (feature* OR sign* OR presentation* OR characteristic*))) AND (diagnos*))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (diagnos* OR diagnostic AND test* OR (screening AND strateg*)))

D.1	P	Colorectal cancer
	I	N/A
	C	N/A
	O	Early-onset
D.2	P	Early-onset colorectal cáncer
	I	Symptom assessment
	C	Hematochezia, pain, fatigue, anemia, diarrea, constipation, abdominal pain
	O	Diagnosis
D.3	P	Early-onset colorectal cancer
	I	Diagnostic approach
	C	N/A
	O	Diagnosis
D.4	P	Early-onset colorectal cancer
	I	Time frame from symptom onset to endoscopy
	C	30 days vs 60 days vs longer times
	O	Time to diagnosis

eoCRC, early-onset colorectal cancer; N/A, not applicable.

Working Group II. Risk factors for eoCRC

Database searched	Years of coverage	References	Total
Embase	1971–Present	2083	16,287
Pubmed.gov	1946–Present	12,346	
Scopus	1992–Present	1858	
Remaining after de-duplication (7562)			8725
First round of literature screening: exclusion	Cell studies	470	958
	Animal studies	252	
	Case reports	236	
Remaining after first round of exclusion			7767
Second round of literature screening: exclusion	Not pertinent/ review	1509	7668
	Incorrect study population	1358	
	Incorrect study intervention	2706	
	Incorrect study comparison	470	
	Incorrect study outcomes	1625	
References sent to the Working Group			99
References selected	Statement R1		26
	Statement R2		31

PubMed search strings:

(colorectal AND (cancer* OR neoplasia OR tumor*)) AND (screening AND age)

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND screening

(family cancer history) AND (((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND diagnos*)

(risk factor*) AND ((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC)

Scopus:

((colorectal AND (cancer* OR neoplasia OR tumor*)) AND (screening AND age) ((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND screening)

((family AND cancer AND history) AND (((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND diagnos*))

((risk AND factor*) AND ((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc))

Embase:

colorectal AND (cancer* OR 'neoplasia'/exp OR neoplasia OR tumor*) AND ('age'/exp OR age) AND (colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('screening'/exp OR screening)

('family cancer history' OR (('family'/exp OR family) AND ('cancer'/exp OR cancer) AND ('history'/exp OR history))) AND (colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND diagnos*

('risk'/exp OR risk) AND factor* AND (colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc)

R.1	P	Individuals with a family history of colorectal cancer
	I	Family history taking
	C	N/A
	O	Incidence and mortality reduction
R.2	P	Individuals younger than 50 years
	I	N/A
	C	Presence or absence of risk factors for eoCRC
	O	Risk of eoCRC

eoCRC, early-onset colorectal cancer; N/A, not applicable.

Working Group III. Genetics of eoCRC

Database searched	Years of coverage	References	Total
Embase	1971–Present	978	2894
Pubmed.gov	1946–Present	925	
Scopus	1992–Present	991	
Remaining after de-duplication (2319)			575
First round of literature screening: exclusion	Cell studies	139	320
	Animal studies	23	
	Case reports	158	
Remaining after first round of exclusion			255
Second round of literature screening: exclusion	Not pertinent/ reviews	91	180
	Incorrect study population	18	
	Incorrect study intervention	33	
	Incorrect study comparison	3	
	Incorrect study outcomes	35	

Continued

Database searched	Years of coverage	References	Total
References sent to the Working Group			75
References selected	Statement G1		13
	Statement G2		13
	Statement G3		12

PubMed search strings:

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND ((genetic OR germline) AND test*)

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (germline AND (mutation* OR variant*))

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (multigene AND panel*)

(risk AND (tool* OR calculator*)) AND ((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC)

(polygenic risk score*) AND ((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC)

Scopus:

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND ((genetic OR germline) AND test*))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (germline AND (mutation* OR variant*)))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (multigene AND panel*))

((risk AND (tool* OR calculator*)) AND ((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc))

((polygenic AND risk AND score*) AND ((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc))

Embase:

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('genetic'/exp OR genetic OR germline) AND test*

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND germline AND (mutation* OR variant*)

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND multigene AND panel*

('risk'/exp OR risk) AND (tool* OR calculator*) AND (colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc)

polygenic AND ('risk'/exp OR risk) AND score* AND (colo* AND ('cancer'/exp OR cancer) AND young AND onset OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc)

G.1	P	Individuals with newly diagnosed eoCRC
	I	Genetic testing
	C	N/A
	O	Diagnostic rate of a hereditary cancer syndrome
G.2	P	Individuals with newly diagnosed eoCRC
	I	What genes should be included for testing
	C	Multipanel gene testing
	O	Diagnostic rate of a hereditary cancer syndrome
G.3	P	Individuals at risk for eoCRC
	I	Use of polygenic risk scores
	C	Various risk scores
	O	Genetic risk stratification

eoCRC, early-onset colorectal cancer; N/A, not applicable.

Working Group IV. Pathlogy and Oncology of eoCRC

Database searched	Years of coverage	References	Total
Embase	1971–Present	1021	2942
Pubmed.gov	1946–Present	826	
Scopus	1992–Present	1095	
Remaining after de-duplication (2188)			754
First round of literature screening: exclusion	Cell studies	231	513
	Animal studies	78	
	Case reports	114	
Remaining after first round of exclusión			241
Second round of literature screening: exclusion	Not pertinent/ reviews	71	154
	Incorrect study population	73	
	Incorrect study intervention	3	
	Incorrect study comparison	0	
	Incorrect study outcomes	7	

Continued

Database searched	Years of coverage	References	Total
References sent to the Working Group			87
References selected	Statement O1		9
	Statement O2		5
	Statement O3		21
	Statement O4		8

PubMed search strings:

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND ((mismatch repair OR MMR) AND (immunohistochemistry OR IHC))

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (microsatellite instability OR MSI)

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (molecular AND (marker* OR profile* OR characteristic*))

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND ((BRAF OR KRAS) AND mutation*)

(((colo* OR rect*) AND cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (adjuvant AND (therapy OR chemotherapy OR radiotherapy OR chemoradiotherapy))

(((colo* OR rect*) AND cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (neoadjuvant AND (therapy OR chemotherapy OR radiotherapy OR chemoradiotherapy))

Scopus:

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND ((mismatch AND repair OR mmr) AND (immunohistochemistry OR ihc)))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (microsatellite AND instability OR msi))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (molecular AND (marker* OR profile* OR characteristic*)))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND ((braf OR kras) AND mutation*))

((((colo* OR rect*) AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (adjuvant AND (therapy OR chemotherapy OR radiotherapy OR chemoradiotherapy)))

((((colo* OR rect*) AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (neoadjuvant AND (therapy OR chemotherapy OR radiotherapy OR chemoradiotherapy)))

Embase:

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('mismatch repair'/exp OR 'mismatch repair' OR (mismatch AND ('repair'/exp OR repair)) OR 'mmr'/exp OR mmr) AND ('immunohistochemistry'/exp OR immunohistochemistry OR ihc)

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('microsatellite instability'/exp OR 'microsatellite instability' OR (('microsatellite'/exp OR microsatellite) AND ('instability'/exp OR instability)) OR msi)

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND molecular AND (marker* OR profile* OR characteristic*)

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND (braf OR kras) AND mutation*

((colo* OR rect*) AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('adjuvant'/exp OR adjuvant) AND ('therapy'/exp OR therapy OR 'chemotherapy'/exp OR chemotherapy OR 'radiotherapy'/exp OR radiotherapy OR 'chemoradiotherapy'/exp OR chemoradiotherapy)

((colo* OR rect*) AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND neoadjuvant AND ('therapy'/exp OR therapy OR 'chemotherapy'/exp OR chemotherapy OR 'radiotherapy'/exp OR radiotherapy OR 'chemoradiotherapy'/exp OR chemoradiotherapy)

O.1	P	Individuals with newly diagnosed eoCRC
	I	Tumor testing with either IHC and/or MSI
	C	IHC versus MSI
	O	MMR-d or MSI-H
O.2	P	Individuals with newly diagnosed eoCRC
	I	Tumor testing with additional assays
	C	N/A
	O	Prognosis and therapeutic changes
O.3	P	Individuals with newly diagnosed eoCRC
	I	Adjuvant therapy
	C	Use vs non-use; selection of different regimens
	O	Survival, progression, and recurrence rates
O.4	P	Individuals with newly diagnosed eoCRC
	I	Neoadjuvant therapy
	C	Use vs non-use; selection of different regimens
	O	Survival, progression, and recurrence rates

eoCRC, early-onset colorectal cancer; N/A, not applicable.

Working Group V. Endoscopy of eoCRC

Database searched	Years of coverage	References	Total
Embase	1971–Present	1312	3720
Pubmed.gov	1946–Present	1588	
Scopus	1992–Present	820	
Remaining after de-duplication (1934)			1786
First round of literature screening: exclusion	Cell studies	168	516
	Animal studies	50	
	Case reports	298	
Remaining after first round of exclusión			1270
Second round of literature screening: exclusion	Not pertinent/ reviews	154	1222
	Incorrect study population	568	
	Incorrect study intervention	94	
	Incorrect study comparison	83	
	Incorrect study outcomes	323	
References sent to the Working Group			48
References selected	Statement E1		N/A
	Statement E2		5
	Statement E3		10
	Statement E4		6
	Statement E5		7

PubMed search strings:

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (endoscopy OR chromoendoscopy* OR artificial intelligence)

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND ((adenoma* OR polyp* OR serrated lesion*) AND detection rate)

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (endoscopic AND (therapy OR dissection OR resection OR treatment))

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (follow-up OR surveillance)

Scopus:

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (endoscopy OR chromoendoscopy* OR artificial AND intelligence))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND ((adenoma* OR polyp* OR serrated AND lesion*) AND detection AND rate))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (endoscopic AND (therapy OR dissection OR resection OR treatment)))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (follow-up OR surveillance))

Embase:

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('endoscopy'/exp OR endoscopy OR chromoendoscopy* OR 'artificial intelligence'/exp OR 'artificial intelligence' OR (artificial AND ('intelligence'/exp OR intelligence)))

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND (adenoma* OR polyp* OR serrated) AND lesion* AND ('detection rate'/exp OR 'detection rate' OR (('detection'/exp OR detection) AND rate))

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND endoscopic AND ('therapy'/exp OR therapy OR 'dissection'/exp OR dissection OR 'resection'/exp OR resection OR 'treatment'/exp OR treatment)

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('follow up'/exp OR 'follow up' OR 'surveillance'/exp OR surveillance)

E.1	P	Individuals younger than 50 undergoing colonoscopy
	I	Additional endoscopic techniques/ chromoendoscopy/artificial intelligence
	C	Standard high-definition colonoscopy
	O	Improvement of diagnostic rate/adenoma detection rate
E.2	P	Individuals younger than 50 undergoing colonoscopy
	I	Standard quality indicators of colonoscopy/ adenoma detection rate/advanced adenoma detection rate/serrated lesion detection rate
	C	N/A
	O	Appropriateness
E.3	P	Patients with newly diagnosed eoCRC
	I	Diagnostic workup before surgery
	C	N/A
	O	N/A
E.4	P	T1 stage eoCRC
	I	Endoscopic therapy
	C	Surgery
	O	Radical resection, mortality rate, progression rate, recurrence rate

Continued

E.5	P	Early-onset colorectal cancer/young-onset colorectal cancer
	I	Standard follow-up/surveillance schedule
	C	Non-standard follow-up schedule
	O	Survival, recurrence

eoCRC, early-onset colorectal cancer; N/A, not applicable.

Working Group VI. Therapy of eoCRC

Database searched	Years of coverage	References	Total
Embase	1971–Present	1393	2734
Pubmed.gov	1946–Present	894	
Scopus	1992–Present	447	
Remaining after de-duplication (1696)			1038
First round of literature screening: exclusion	Cell studies	422	601
	Animal studies	35	
	Case reports	144	
Remaining after first round of exclusion			437
Second round of literature screening: exclusion	Not pertinent/ review	124	376
	Incorrect study population	156	
	Incorrect study intervention	48	
	Incorrect study comparison	25	
	Incorrect study outcomes	23	
References sent to the Working Group			61
References selected	Statement T1		3
	Statement T2		3
	Statement T3		3

PubMed search strings:

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (diagnostic workup) AND (surgery OR (surgical AND (therapy OR treatment)))

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (surgery OR (surgical AND (therapy OR treatment)))

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (fertility preservation)

((colorectal AND (cancer* OR neoplasia OR tumor*)) AND reproductive-age*) AND (surg* OR chemotherapy OR radiotherapy) AND (fertility preservation)

Scopus:

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (diagnostic AND workup) AND (surgery OR (surgical AND (therapy OR treatment))))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (surgery OR (surgical AND (therapy OR treatment))))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (fertility AND preservation))

(((colorectal AND (cancer* OR neoplasia OR tumor*)) AND reproductive-age*) AND (surg* OR chemotherapy OR radiotherapy) AND (fertility AND preservation))

Embase:

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('diagnostic workup' OR (('diagnostic'/exp OR diagnostic) AND workup)) AND ('surgery'/exp OR surgery OR (surgical AND ('therapy'/exp OR therapy OR 'treatment'/exp OR treatment)))

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('surgery'/exp OR surgery OR (surgical AND ('therapy'/exp OR therapy OR 'treatment'/exp OR treatment)))

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('fertility preservation'/exp OR 'fertility preservation')

colorectal AND (cancer* OR 'neoplasia'/exp OR neoplasia OR tumor*) AND 'reproductive age*' AND (surg* OR 'chemotherapy'/exp OR chemotherapy OR 'radiotherapy'/exp OR radiotherapy) AND ('fertility preservation'/exp OR 'fertility preservation' OR (('fertility'/exp OR fertility) AND ('preservation'/exp OR preservation)))

T.1	P	Patient with eoCRC fit for surgery
	I	Surgery
	C	Extended vs standard surgery
	O	Disease-free survival, progression-free survival, overall survival
T.2	P	Patients with eoCRC scheduled for chemo/radiotherapy
	I	Information about fertility preservation
	C	N/A
	O	N/A
T.3	P	Patients with eoCRC scheduled for chemoradiotherapy desiring fertility preservation
	I	Selection of candidates for fertility preservation
	C	Biochemical and clinical parameters
	O	Fertility preservation after eoCRC treatment

eoCRC, early-onset colorectal cancer; N/A, not applicable.

Working Group VII. End-Stage Disease

Database searched	Years of coverage	References	Total
Embase	1971–Present	53	233
Pubmed.gov	1946–Present	157	
Scopus	1992–Present	23	
Remaining after de-duplication (54)			179
First round of literature screening: exclusion	Cell studies	2	17
	Animal studies	4	
	Case reports	11	
Remaining after first round of exclusión			162
Second round of literature screening: exclusion	Not pertinent/ review	29	144
	Incorrect study population	36	
	Incorrect study intervention	26	
	Incorrect study comparison	16	
	Incorrect study outcomes	37	
References sent to the Working Group			18
References selected	Statement C1		4
	Statement C2		2

PubMed search strings:

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND (end stage AND (therap* OR management))

((colo* cancer AND young onset) OR (early onset colorectal cancer) OR eoCRC) AND ((palliative OR supportive) AND care)

Scopus:

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND (end AND stage AND (therap* OR management)))

(((colo* AND cancer AND young AND onset) OR (early AND onset AND colorectal AND cancer) OR eocrc) AND ((palliative OR supportive) AND care))

Embase:

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND ('end stage' OR (end AND stage)) AND (therap* OR 'management'/exp OR management)

(colo* AND ('cancer'/exp OR cancer) AND ('young onset' OR (young AND onset)) OR 'early onset colorectal cancer'/exp OR 'early onset colorectal cancer' OR (early AND onset AND colorectal AND ('cancer'/exp OR cancer)) OR eocrc) AND (palliative OR supportive) AND ('care'/exp OR care)

C.1	P	Patients with eoCRC undergoing curative therapy
	I	Management of morbidity and needs
	C	N/A
	O	Symptom relief
C.2	P	Patients with eoCRC
	I	N/A
	C	Support of eoCRC versus loCRC
	O	Supportive care, palliative care, and symptom relief

eoCRC, early-onset colorectal cancer; loCRC, late-onset colorectal cancer; N/A, not applicable.

Supplementary Appendix 2. Summary of Available Evidence on Session I (Diagnosis of eoCRC)

Summary of available evidence for D.2: Seventeen studies, focused on eoCRC, were considered sufficiently important to be included in the discussion below.

Studies on iron deficiency anemia, hematochezia, and unexplained weight loss	
LE: 2b	A registry-based, retrospective, cohort study among U.S. veterans aged 18–49 evaluated the cumulative incidence of eoCRC among 653,740 patients presenting with hematochezia and 239,000 patients presenting with iron deficiency anemia.[33] Patients with hematochezia had a significantly higher 5-year cumulative incidence of eoCRC than those without hematochezia (0.33% vs 0.03%, a risk difference of 0.30% and a corresponding hazard ratio of 10.66, 95% confidence interval [CI], 8.76–12.97). The number needed to screen for hematochezia was 322 (95% CI, 293.4–359.1) and it was significantly lower for men than for women (308 vs 471.1).[33] Patients with iron deficiency anemia also had a significantly higher 5-year cumulative incidence of eoCRC than those without iron deficiency anemia (0.45% vs 0.05%, with a risk difference of 0.39% and a hazard ratio of 10.81, 95% CI, 8.15–14.33). The number needed to screen for iron deficiency anemia was 259.8 (95% CI, 226.8–301.6) but it was significantly lower for men than for women (140.3 vs 1056.5). For patients presenting with iron deficiency anemia, the risk difference was more pronounced for men (0.78%; 95% CI, 0.64%–0.92%) than for women (0.08%; 95% CI, 0.03%–0.13%).[33] The presence of both iron deficiency anemia and hematochezia provided a 5-year cumulative incidence of eoCRC of 2.50%, corresponding to a risk difference of 2.39% for the presence of either.[33]
LE: 2b	In a retrospective cohort study of a medical claims, 46% of eoCRC complained of rectal bleeding at diagnosis, and 47% complained of abdominal pain.[28]
LE: 2b	A case-control study in U.S. veterans aged 18–49 found that being overweight or obese was significantly associated with decreased odds of eoCRC. The post hoc analysis found that a weight loss of 5 kg (11 pounds) or more within 5 years of diagnosis was associated with higher odds of eoCRC (odds ratio, 2.23; 95% CI, 1.76–2.83).[29]
LE: 2b	In a retrospective cohort study of 253 eoCRC and 232 loCRC, most patients presented with 1 symptom, but approximately one-third presented with 2 symptoms; the most common were hematochezia in rectal cancer and abdominal pain in colon cancer, without significant differences between eoCRC vs loCRC.[47]
LE: 2b	A retrospective cohort study compared the clinical presenting symptoms of 1680 patients with CRC at age 18–39 and 92,260 patients with CRC at age >40.[35] The same study also compared patients with eoCRC with almost 8 million healthy age-matched individuals. Individuals with eoCRC presented symptoms more likely than healthy age-matched controls (including abdominal pain, anemia, hematochezia, diarrhea, constipation, malaise and fatigue, weight loss, nausea, and decreased appetite).[36] Compared with older individuals, the prevalence of hematochezia, diarrhea, and constipation was not significantly different.[35]
LE: 3b	In a retrospective cohort study of 54 eoCRC and 494 loCRC, patients with eoCRC more commonly reported weight loss (10.0% vs 2.9%, $P = .03$). However, eoCRC less commonly presented with anemia (6.0% and 18.5%, respectively; $P = .03$) and positive FIT (2.0% and 23.0%, respectively; $P < .0001$).[36]
LE: 4	In a retrospective cross-sectional study of 2059 individuals aged 40–49 years undergoing colonoscopy,[53] the most common indications for colonoscopy were hematochezia (34.5%), abdominal pain (6.2%), and a change in bowel habits (15.7%).[53]
LE: 4	In a retrospective case series of 693 patients with CRC at ≤45 years,[51] 80.5% had symptoms before the diagnosis; the most common symptom was hematochezia.
LE: 4	In a retrospective case series of 209 patients with eoCRC,[52] 42.5% of patients had a history of rectal bleeding, with a median time to diagnosis of 180 days. It was noticed that longer duration of symptoms occurred in individuals with more advanced stages at diagnosis, especially in stage IV.[52]
LE: 4	In a retrospective case series of 83 patients with CRC at age <30 years,[38] the most common presenting symptom was hematochezia, which occurred in 66.3% of patients. Patients with a metastatic disease more commonly complained of fatigue but less commonly reported an alteration of bowel habits.[38]
Studies on abdominal pain and change of bowel habits	
LE: 2b	In a large retrospective registry-based cohort study, patients with eoCRC more commonly presented with abdominal pain (OR, 4.73; 95% CI, 4.49–4.98), rectal pain (OR, 7.48; 95% CI, 6.42–8.72), altered bowel function (OR, 5.51; 95% CI, 5.19–5.85), rectal bleeding (OR, 9.83; 95% CI, 9.12–10.6), or weight loss (OR, 7.43; 95% CI, 6.77–8.15).[30] This population-based cohort analysis concluded that abdominal pain, rectal pain, altered bowel function, rectal bleeding, and weight loss are possible risk factors for eoCRC.[30]
LE: 4	In one study, abdominal pain and constipation were not associated with a higher risk for eoCRC.[39]

Continued

LE: 4	In a retrospective study of 75 patients aged 18–45 years,[37] 56% presented with altered bowel habits (irregular, 17%; constipation, 17%; diarrhea, 31%), but no symptom had a statistically significant association with eoCRC.[37] Constipation approached significance in association with left-sided colonic cancer. Comparing right- and left-sided eoCRC, right-sided eoCRC less likely presented with bleeding ($P = .002$; OR, .06) or constipation ($P < .001$).
LE: 2b	In a registry study of 4333 colonoscopies performed on symptomatic individuals,[32] 8.4% had any adenoma or eoCRC, and 0.6% had eoCRC. The multivariate analysis showed that anemia of unknown origin was associated with higher risk of adenoma or eoCRC (OR, 3.11; 95% CI, 1.32–7.34). On the other hand, abdominal pain, diarrhea, and constipation were not associated with a lower risk of adenoma or eoCRC (OR, 0.69; 95% CI, 0.50–0.95).
LE: 4	In a retrospective case series of 1025 patients with eoCRC,[34] the most common symptoms at presentation were hematochezia (51%), a change in bowel habits (18%), abdominal pain (32%), weight loss (13%), nausea/vomiting (7%), and melena (2%).[35] Asymptomatic patients with eoCRC presented with anemia (14%), positive fecal occult blood test (7%), an abdominal mass (2%), or a mass on a digital rectal exam (2%). The absence of a healthy age-matched cohort limits the interpretability of such findings.
Studies on the symptoms of eoCRC vs loCRC	
LE: 3b	A retrospective case-control study on patients with stage I–III colon cancer (68 diagnosed ≤40 years versus 1259 after >40 years) could not find statistically significant differences in the presenting symptoms.[50]
LE: 2b	In a retrospective, registry-based, Dutch case-control study (521 patients with CRC at <40 years and 15,000 with CRC at ages 66–75),[31] both age groups presented with abdominal pain, hematochezia, weight loss, and a change in bowel habits. However, younger individuals were significantly more likely to complain of hematochezia (81% vs 65%) and abdominal pain. There were no significant differences in the proportions of individuals with weight loss or having a change in bowel habits.

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Summary of available evidence for D.3: Six studies, focused on eoCRC, were considered sufficiently important to be included in the discussion below.

Studies on fecal immunochemical testing in asymptomatic individuals	
LE: 1b	In a record-based retrospective evaluation of 19,808 asymptomatic individuals aged 30–49 undergoing FIT and colonoscopy as part of a screening program, FIT had a positive predictive value for adenoma or CRC of 2.9% (95% CI, 1.1%–7.4%), 9.7% (95% CI, 5.8%–15.6%), 7.7% (95% CI, 4.5%–12.8%), and 14.6% (95% CI, 8.7%–23.5%) for subgroups aged 30–34, 35–39, 40–44, and 45–49 years, respectively. However, most of these cases were adenomas or advanced adenomas. The prevalence of cancer was very low for these age groups (0.0%, 0.02%, 0.02%, and 0.06% for subgroups aged 30–34, 35–39, 40–44, and 45–49 years, respectively.[42]
LE: 2b	In a single-center, retrospective, cohort study of 3307 individuals aged <50 years and 3150 aged >50, individuals with a positive FIT had a significantly higher risk of advanced adenoma or cancer, compared with FIT-negative individuals (14.5% vs 3.7%, $P < .001$). Interestingly, a positive FIT conferred a higher risk of advanced adenoma or cancer in younger participants compared with individuals older than 50 with a positive FIT (14.5% vs 9.8%, $P = .028$). Finally, the risk of having an adenoma, an advanced adenoma, or cancer was significantly higher for FIT-positive individuals who also had additional risk factors such as nonalcoholic fatty liver disease (OR, 2.60; 95% CI, 1.27–5.34; $P = .001$) or metabolic syndrome (OR, 3.46; 95% CI, 1.66–7.21; $P = .001$).[54]
LE: 1b	A retrospective, registry-based Korean study compared the diagnostic accuracy of FIT in 21,942 asymptomatic individuals <50 years against 4374 asymptomatic individuals ≥50 years.[55] Specifically, there was no statistically significant difference in sensitivity for CRC ($P = .999$, respectively). However, the specificity of FIT was marginally higher for younger individuals (for ages 30–39: 97.1%, 95% CI, 96.8%–97.5%; for ages 40–49: 97.0%, 95% CI, 96.8%–97.4%; for ages ≥50: 96.3%, 95% CI, 95.7%–96.8%; $P = .013$).
Studies on fecal immunochemical testing in symptomatic individuals	
LE: 1b	A multicenter, double-blinded diagnostic accuracy study in patients with suspected CRC symptoms in England found high sensitivity and specificity for fecal immunochemical testing (FIT) with an area under the receiver operating characteristic curve of 0.93, although only 16 CRC were identified in patients aged 30–49, limiting the generalizability of the findings to this age group.[40]
LE: 1b	In a prospective, multicenter, diagnostic accuracy study of FIT among 1103 symptomatic individuals younger than 50 years, FIT had a sensitivity of 87.5% (95% CI, 61.7%–98.4%), 81.3% (54.4%–96.0%), and 68.8% (41.3%–89.0%) at f-Hb cutoffs of 2, 10, and 150 μg/g. The positive predictive value for eoCRC increased from 4.2% (2.3%–6.9%) to 11.5% (5.9%–19.6%) at cutoffs of 2 and 150 μg/g.[41]

Continued

Studies on diagnostic yield of colonoscopy in symptomatic individuals	
LE: 2b	In a registry study of 4333 colonoscopies performed on symptomatic individuals,[32] 8.4% had any adenoma or eoCRC. The diagnostic rate of advanced adenoma or eoCRC was 1.1%. Risk factors for eoCRC were obesity (OR, 1.44; 95% CI, 1.04–2.01), smoking (OR, 1.63; 95% CI, 1.18–2.23), and anemia of unknown origin (OR, 3.11; 95% CI, 1.32–7.34).

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; f-Hb, fecal hemoglobin; FIT, fecal immunochemical tests; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Summary of available evidence for D.4.: Seven retrospective studies, focused on eoCRC, were considered sufficiently important to be included in the discussion below.

Studies on time to colonoscopy for eoCRC	
LE: 3b	In a retrospective, registry-based, cohort study on 8482 US veterans aged 18–49 years, only 28% received a colonoscopy within 60 days of diagnosis of iron deficiency anemia.[33] Among those with hematochezia, 46% received a colonoscopy within 5 years of follow-up, but only 59% within 60 days of diagnosis.[33]
LE: 4	In a retrospective case series of 83 patients with CRC at age <30 years,[38] the average time from symptom onset to diagnosis was 4.6 months.
LE: 3b	In a case-control study of 54 eoCRC and 494 loCRC, patients with eoCRC had a longer time to diagnosis. Only 40.7% of patients with eoCRC received a diagnosis within 6 months from the start of symptoms, compared with 85.6% of loCRC ($P < .0001$).[36]
LE: 2b	In a retrospective cohort study of 693 patients with CRC ≤45 years and 1823 aged 56–65 years,[51] younger patients had symptoms for more days before reaching a diagnosis (52.9 days vs 33.2 days). Moreover, there was a higher rate of a delayed diagnosis (≥3 months) in the young group (14.9% vs 7.9%, $P < .001$).[51]
Studies supporting the hypothesis that diagnostic delay accounts for the advanced stage at diagnosis	
LE: 3b	In a retrospective study of 209 patients with eoCRC,[45] the median time to diagnosis was 180 days, and a longer duration of symptoms was associated with more advanced stage at diagnosis ($P = .004$), especially with stage IV disease (median duration of bleeding was 333.5 days for stage IV versus 30 days for stage I, $P = .05$).[45]
Studies conflicting with the hypothesis that diagnostic delay accounts for the advanced stage at diagnosis	
LE: 3b	In a retrospective case-control study of 253 eoCRC vs 232 loCRC, patients with eoCRC demonstrated significantly longer median time to diagnosis (128 vs 79 days; $P < .05$), longer symptom duration (60 vs 30 days; $P < .01$), and time of evaluation (31 vs 22 days; $P < .05$). Patients with eoCRC had 27% more visits than patients with loCRC before diagnosis. However, patients who experienced longer symptom duration did not have a higher stage at diagnosis. Patients with stage III/IV eoCRC had a significantly shorter workup period than those with stage I/II eoCRC.[47]
LE: 3b	In a case-control study of 56 eoCRC and 56 loCRC,[46] younger individuals had a longer time to treatment after symptom recognition (217 vs 29.5 days, $P < .0001$). The two age groups had a similar stage at diagnosis. The 5-year survival did not differ between groups (64% vs 71%; $P = .54$).

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Supplementary Appendix 3. Summary of Available Evidence on Session II (Risk Factors)

Summary of available evidence for R.1.: Ten studies, focused on eoCRC and the family history of CRC, were considered sufficiently important to be included in the discussion below.

Studies on the prevalence of family history for CRC in individuals younger than 50	
LE: 4	In a case series of 94 patients with CRC before the age of 30, 57% did not report any family history of CRC, and less than 5% fulfilled the Amsterdam II criteria.[21]
LE: 2b	In a registry-based retrospective study of 5710 eoCRC and 11,800,420 age-matched healthy controls, patients with eoCRC more commonly had a family history of cancer (OR, 11.66; 95% CI, 10.97–12.39), gastrointestinal malignancy (OR, 28.67; 95% CI, 26.64–30.86), and polyps (OR, 8.15; 95% CI, 6.31–10.52).[30] Compared with patients with loCRC, patients with eoCRC also more commonly had a family history of any cancer (OR, 1.78; 95% CI, 1.67–1.90,), gastrointestinal malignancy (OR, 2.36; 95% CI, 2.18–2.55), and polyps (OR, 1.41; 95% CI, 1.08–1.20).[30]
LE: 3b	In a retrospective, case-control study of 253 eoCRC and 232 loCRC, patients with eoCRC were more likely to report a family history of CRC (25% vs 17%; $P = .03$) or to have a hereditary cancer syndrome (7% vs 1%; $P < .01$).[47]
LE: 2b	In a retrospective study of 693 patients with CRC $\leq$45 years and 1823 aged 56–65 years,[51] younger patients more often had a family history of CRC.[51]
LE: 3b	In a retrospective case-control study (107 eoCRC and 139 loCRC), patients with eoCRC more commonly had a family history of CRC (30% vs 16%, $P = .02$).[102]
LE: 2b	In a retrospective, registry-based, Dutch case-control study (521 patients with CRC at <40 years and 15,000 with CRC at ages 66–75),[31] younger patients were more likely to report a positive family history (24.1% vs 12.4%; $P < .0001$).
Clinical outcomes of family history taking	
LE: 4	In a prospective case series on 713 eoCRC, 97 (13.6%) had a positive family history of CRC that should have led them to a colonoscopy before the age of 50. It was estimated that correct adherence to guidelines on family history could have led to the early diagnosis of 80 patients (82.5%), and it could have prevented 65 cases (67.0%).[56]
LE: 3b	In a retrospective cross-sectional study of 2059 individuals aged 40–49 years undergoing colonoscopy,[53] 15.4% had a family history of CRC in a first-degree relative. Patients with a family history of CRC had a higher polyp detection rate (51.7% vs 38.3%, $P = 0.0001$) and a higher adenoma detection rate (27.8% vs 19.7%; $P = .001$), but there was no difference in the prevalence of adenomas $\geq$1 cm.
LE: 3b	A national colonoscopy registry[95] compared 225,932 colonoscopies on individuals aged <50 with 336,627 colonoscopies on individuals aged 50–54. Among patients aged 45–49, 32% had premalignant or malignant lesions, 7.5% had advanced adenomas, and 0.58% had eoCRC. Moreover, the prevalence of adenoma, advanced adenoma, and eoCRC increased since 2014 across all age groups.[95] Rates were similar in those aged 40–44. Family history, male sex, white race, and hematochezia were significant risk factors for the presence of advanced adenoma. Family history increased the risk of eoCRC.
LE: 1a	In a large meta-analysis of 9,280,000 subjects from 63 studies, a family history of CRC in first-degree relatives confers a higher risk of CRC in younger individuals (RR, 3.29; 95% CI, 1.67–6.49 for <40 years versus RR, 1.42; 95% CI, 1.24–1.62 for $\geq$40 years; $P = .017$; RR, 2.81; 95% CI, 1.94–4.07 for <50 years versus RR, 1.47; 95% CI, 1.28–1.69 for $\geq$50 years; $P = .00$).[59]
LE: 1a	In a meta-analysis of 20 studies, a family history of CRC in first-degree relatives was a significant risk factor for eoCRC (RR, 4.21; 95% CI, 2.61–6.79).[74] There was substantial heterogeneity in risk estimates (I^2 >60%), but there was limited evidence of publication bias on family history.

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio; RR, relative risk.

Summary of available evidence for R.2: Thirty-one studies, focused on eoCRC and the risk factors for CRC, were considered sufficiently important to be included in the discussion below.

Ethnicity as a risk factor	
LE: 1b	An analysis of the Surveillance, Epidemiology, and End Results database compared the incidence of colon and rectal cancer between 31,859 white individuals with eoCRC and 5203 black individuals with eoCRC.[66] In whites, the eoCRC incidence increased from 7.5 to 11.0 per 100,000 from 1992–1996 to 2010–2014. In blacks, the increase was comparatively small (from 11.7 to 12.7 per 100,000).[66] The largest increase in incidence was for rectal cancer in whites (from 2.7 to 4.5 per 100,000) but not blacks (from 3.4 to 4.0 per 100,000). In fact, the authors concluded that the increasing incidence of eoCRC is largely dependent on an increase in rectal cancers among white individuals.[66]
LE: 1b	In an analysis of the Surveillance, Epidemiology, and End Results database, the percentage of patients diagnosed with eoCRC in each racial/ethnic minority was almost twice that of white individuals.[67] Trend analysis revealed a significant increase in eoCRC in all racial and ethnic groups except for African American.[67]
LE: 2b	In a retrospective, registry-based, case-control study of 330,009 patients with loCRC and 39,787 with eoCRC,[103] eoCRC was more prevalent among black (14.6% vs 11.0%; $P < .001$) and Hispanic patients (14.7% vs 8.3%; $P < .001$). Diabetes, obesity, and excessive drinking were not significantly associated with increased rates of eoCRC (P values 0.5812, 0.6465, and 0.6649, respectively).[103]
LE: 2b	In a retrospective, registry-based study of 37,847 eoCRC and 220,177 loCRC,[104] younger patients were more likely to be African American (14.8% vs 12%), American Indian/Alaska Native, or Asian/Pacific Islander (10.6% vs 8.5%; all $P < .001$).
LE: 1b	In an incidence rate analysis of 18 registries on 45,429 eoCRCs, the incidence rate among whites increased since 2000 (annual percentage change, APC, 1.6; 95% CI, 1.3–1.9).[70] The incidence rate was stable for blacks (APC, –0.03; 95% CI, –0.5 to +0.5). After 2017, the incidence rate of rectal cancer was 39% higher among whites than blacks.[70]
LE: 2b	In a U.S. registry study of 108,058 eoCRC,[65] black patients had a worse median OS than whites (58.3 vs 67.0 months; $P < .0001$).
Definitive and likely risk factors	
LE: 1b	In a population-based registry cohort analysis of 68,860 patients with CRC (5710 with eoCRC), the risk for eoCRC was higher for the African-American race (OR, 1.18; 95% CI, 1.09–1.27, $P < .001$).[30] Comparing patients with eoCRC with 11,800,420 age-matched controls, the risk of eoCRC increased for males (OR, 1.34; 95% CI, 1.27–1.41), whites (OR, 1.48; 95% CI, 1.40-1.57), African Americans (OR, 1.25; 95% CI, 1.17–1.35), weight loss (OR, 7.43; 95% CI, 6.77–8.15), tobacco use (OR, 2.46; 95% CI, 2.33–2.59), alcohol use (OR, 1.71; 95% CI, 1.62–1.80), presence of colitis (OR, 4.10; 95% CI, 3.79–4.43), and obesity (OR, 2.88; 95 % CI, 2.74–3.04).[30]
LE: 2b	In a case-control study of 68,067 U.S. veterans aged <50 with colonoscopy exposure, 651 had eoCRC, and 67,416 were healthy controls.[29] Risk factors for eoCRC included older age (for every additional year in age, OR, 1.05; 95% CI, 1.03–1.07), male gender (OR, 2.21; 95% CI, 1.68–2.91), non-aspirin use (aspirin use, OR, 0.66; 95% CI, 0.52–0.84), and lower BMI (overweight: OR, 0.69; 95% CI, 0.55–0.87; obese: OR, 0.69; 95% CI, 0.55–0.86) (all comparisons $P < .05$).[29] There was no significant difference in odds of eoCRC across racial/ethnic subgroups.[29] In post hoc analysis, controls had a tendency to increase their 10-year body weight, but patients with eoCRC had a tendency to lose weight 5 years before baseline colonoscopy. A weight-loss of >5 kg increased the odds of eoCRC (odds ratio, 2.23; 95% CI, 1.76–2.83).[29]
LE: 1a	In a meta-analysis of 20 studies,[74] significant risk factors for eoCRC included hyperlipidemia (RR, 1.62; 95% CI, 1.22–2.13), obesity (RR, 1.54; 95% CI, 1.01–2.35), and alcohol consumption (high vs non-drinkers) (RR, 1.71; 95% CI, 1.62–1.80). Smoking was a suggestive risk factor, but the association did not reach statistical significance (RR, 1.35; 95% CI, 0.81–2.25).[74] White ethnicity was associated with a relative risk of 1.31 (95% CI, 1.06–2.07).
LE: 1a	In a meta-analysis of 6 studies on the risk factors for CRC and adenoma before the age of 50, smoking and alcohol consumption were significant risk factors.[71] Smoking conferred a pooled OR of 1.69 (95% CI, 1.44–1.99), whereas alcohol conferred a pooled OR of 1.48 (95% CI, 1.40–1.57). Obesity had a pooled OR for eoCRC and adenoma of 1.45 (95% CI, 1.37–1.52), whereas metabolic syndrome had a pooled OR of 1.56 (95% CI, 1.44–1.68). Hyperglycemia was associated with an OR of 1.69 (95% CI, 1.27–2.25), whereas diabetes type 2 had a similar pooled OR of 1.60 (95% CI, 1.32–1.95). Hypertension had a pooled OR of 1.56 (95% CI, 1.31–1.86).[71]
LE: 1b	In a meta-analysis of 28 studies involving patients younger than 50 years with colorectal adenoma,[91] risk factors for adenoma development included BMI, male sex, and current smoking status.[91] Among patients younger than 50 with an adenoma, only 1 patient developed a subsequent (metachronous) CRC among 9341 patients (0.01%).
LE: 1b	In a systematic review[81] of 26 studies pertaining to diet and lifestyle, 17 studies investigated the role of obesity on the risk of eoCRC. Obesity appeared to be a risk factor for eoCRC, although with inconsistent results across studies.[81] Twelve studies found a statistically significant risk of eoCRC among obese individuals, with higher risk for patients with a higher BMI. Three studies could not find a statistically significant association between obesity and eoCRC. Two studies reported a decreased risk for eoCRC among obese adults.[81]

Continued

LE: 2b	A case control study of 747 patients and 621 healthy controls younger than 55 years analyzed the risk of CRC according to BMI.[75] Higher BMI was strongly associated with a higher risk of eoCRC. Obesity at ages 20 and 30 increased the risk for eoCRC development (adjusted OR, 2.56; 95% CI, 1.20–5.44; adjusted OR, 2.06; 95% CI, 1.25–3.40, respectively). Obesity in the 10 years before diagnosis was also a risk factor for eoCRC (adjusted OR, 1.88; 95% CI, 1.30–2.73).[75]
LE: 2b	In a cross-sectional study of 72,356 asymptomatic individuals aged 20–39 who underwent colonoscopy, study investigators detected 11 eoCRC. The prevalence of CRC was 0.01% in the 20–29 age group and 0.02% in the 30–39 age group.[78] Age, smoking (OR, 1.29; 95% CI, 1.21–1.38), alcohol intake (OR, 1.25; 95% CI, 1.17–1.33), obesity (OR, 1.26; 95% CI, 1.19–1.34), and abdominal obesity (OR, 1.32; 95% CI, 1.23–1.40) were independent risk factors for adenoma, advanced adenoma, and eoCRC. Regular exercise was an independent protective factor (OR, 0.89; 95% CI, 0.81–0.97).
Risk factors under investigation	
LE: 2b	In a prospective study of 33,106 individuals who provided adolescent dietary information,[72] 2909 conventional adenomas and 2355 serrated lesions were reported, conferring an increased risk of conventional adenoma, especially rectal adenoma. Per each increment of 5% of calories, total fructose intake during adolescence was positively associated with the risk of a high-risk adenoma <50 years. For adolescent intake of sugary drinks, there was a positive association with rectal adenoma <50 years, albeit smaller.[72] Authors concluded that a high intake of simple sugars and sugar-sweetened beverages during adolescence is associated with increased risk of conventional adenoma, especially rectal adenomas.[72]
LE: 3b	In a case-case study comparing 54 eoCRC with 494 loCRC, patients with eoCRC were less likely to be smokers (53.7% vs 38.9%), diabetic (0.0% vs 16.2%), or obese (5.6% vs 14.7%).[36]
LE: 3b	In a prospective study of 1157 early-onset adenomas with 375 high-risk adenomas,[80] Western diet conferred the highest risk of developing such precancerous lesions. The association was strongest for high-risk adenomas, reaching OR, 1.67; 95% CI, 1.18–2.37.[80]
LE: 2b	In a retrospective, registry-based, Dutch case-control study (521 patients with CRC at <40 years and 15,000 with CRC at ages 66–75),[31] younger patients displayed a statistically significant lower consumption of alcohol and cigarettes ($P < .0001$ for both).
LE: 3b	In a Pakistani questionnaire-based case-control study of 74 eoCRC and 148 age-matched controls,[76] a diet rich in fats and poor in vegetables conferred a higher risk of eoCRC. Other risk factors included smoking (OR, 2.12), paan consumption (OR, 2.92), and alcohol use (OR, 3.9).[76]
LE: 2b	An occupational cohort offered colonoscopy through company benefits to 70,428 individuals from Korea (59,782 younger than 50 and 10,646 older than 50).[77] Risk factors associated with advanced adenoma development before 50 years included current smoking (OR, 1.37; 95% CI, 1.15–1.63), CRC family history (OR, 1.46; 95% CI, 1.01–2.10), diabetes (OR, 1.27; 95% CI, 1.06–1.54), obesity (OR, 1.23; 95% CI, 1.03–1.47), and dyslipidemia (OR, 1.01; 95% CI, 1.01–1.02).[77]
LE: 1b	For the other risk factors, a systematic review and meta-analysis demonstrated that significant risk factors for eoCRC include CRC history in first-degree relatives (RR, 4.21; 95% CI, 2.61–6.79), hyperlipidemia (RR, 1.62; 95% CI, 1.22–2.13), obesity (RR, 1.54; 95% CI, 1.01–2.35), and alcohol consumption (high vs non-drinkers) (RR, 1.71; 95% CI, 1.62–1.80).[36,73,74] Another meta-analysis associates type 2 diabetes as an additional risk factor for eoCRC (OR, 1.60; 95% CI, 1.32–1.95).[71]
LE: 1b	In a systematic review[81] of 26 studies pertaining to diet and lifestyle, significant risk factors for the development of eoCRC included the consumption of red and processed meat and sugary drinks. This evidence supports the hypothesis that a Western diet increases the risk of eoCRC.[81] There was conflicting evidence on alcohol consumption; 6 studies supported the hypothesis that alcohol is a risk factor for eoCRC, but 4 studies could not find a statistically significant risk of eoCRC.[81] There was controversial evidence on physical activity as well. Three studies suggested that sedentary behavior increases the risk of eoCRC, but 4 studies could not reach such conclusions.[81]
LE: 1b	A large prospective cohort and biobank study (451,615 UK residents) explored the hypothesis of risk factors during early life.[82] It could not find any statistically significant association between eoCRC and 6 variables of interest (breastfeeding in infancy, maternal smoking at birth, comparative body size and height at age 10 years, age at menarche for women, and relative age of first facial hair for men). Authors concluded that these factors are unlikely to drive carcinogenesis of eoCRC.[82]
LE: 2b	A prospective case-control study of the Child Health and Development Studies explored the role of maternal exposure to 17α-hydroxyprogesterone caproate among 18,751 individuals born in 1959–1967.[79] There was a dose-specific increased risk for CRC among the exposed ones (adjusted HR, 3.45; 95% CI, 1.08–11.00), and it was higher if exposed during the first trimester of pregnancy (adjusted HR, 5.51; 95% CI, 1.73–17.5). However, the median age of cancer diagnosis was similar.[79]

Continued

LE: 3b	Gu et al[88] used a Rothman–Keller model to construct an individualized risk appraisal model for eoCRC. The simulation was informed by data extracted from 10 published studies (32,843 cases and 25,806,408 controls). By using 9 risk factors, the authors simulated 10,000 subjects.[88] However, there was no real-life validation of this study.
LE: 3b	In a case control study[83] (47 eoCRC and 71 healthy controls), the consumption of fresh and processed meat and dairy products was significantly associated with eoCRC compared with controls. Smoking was associated with the development of eoCRC. The risk of eoCRC was not increased by BMI, physical activity, dietary supplements, and nutritional supplements.
LE: 2b	Archambault et al[89] combined data from 13 population-based studies (3486 cases, 3890 controls) to build a risk prediction model for eoCRC. This study incorporated 141 variables into an environmental risk score and a polygenic risk score. The polygenic risk score had a higher discriminatory capacity than the environmental risk score. The two approaches combined reached an area under the curve of 0.631 (95% CI, 0.615–0.647). Authors concluded that the absolute number of cases expected was modest.
LE: 2b	In a case-control study of 7903 CRC (445 eoCRC) and 30,418 healthy controls,[84] antibiotic consumption was associated with CRC in both age groups. Such association seemed strongest for the development of eoCRC (adjusted OR, 1.49; 95% CI, 1.07–2.07; $P = .018$). However, the risk difference between eoCRC and loCRC was not statistically significant. Authors concluded that antibiotic use may be associated with CRC development at any age.[84]
LE: 2b	In a registry-based cohort study (Nurses' Health Study II) comprising 116,430 female nurses ages 25–42 years at enrollment in 1989, subjects were followed up for more than 22 years (1,262,540 person-years), there were 118 incident cases of eoCRC.[85] Compared with age-matched individuals, cases were more likely to have longer sedentary TV viewing time, even after adjustment for obesity and physical inactivity.[85] Women reporting >7.1 h/week of TV time had a higher risk of eoCRC than those reporting <7 h/week (RR, 1.12; 95% CI, 0.72–1.75). Women reporting >14 h/week had an even higher risk (RR, 1.69; 95% CI, 1.07–2.67, *P* trend ¼ .03). Such risk was seen in patient with no CRC family history. The risk was higher for eoRC (RR for >14 vs 7 h/week, 2.44; 95% CI ¼, 1.03–5.78, *P* trend ¼ .04).[85]
LE: 2b	In a registry-based cohort study (Nurses' Health Study II) comprising 116,430 female nurses ages 25–42 years at enrollment in 1989, subjects were followed up for more than 22 years (1,262,540 person-years), and they reported their beverage intakes every 4 years with a semiquantitative food-frequency questionnaire since 1991.[86] There were 109 incident cases of eoCRC.[86] Women reporting ≥2 servings of sugar-sweetened beverages per day had a higher risk of eoCRC (RR, 2.18; 95% CI, 1.10–4.35; *P* trend = .02). The risk was dependent on the quantity, with 16% higher risk (RR, 1.16; 95% CI, 1.00–1.36) per serving/day increase.[86]
LE: 2b	In a registry-based cohort study (Nurses' Health Study II) comprising 116,430 female nurses ages 25–42 years at enrollment in 1989, subjects were followed up for more than 22 years (1,250,560 person-years), there were 111 incident cases of eoCRC.[87] The risk of eoCRC was significantly lower for females receiving a higher dosage of vitamin D (≥450 IU/day vs <300 IU/day; HR, 0.49; 95% CI, 0.26–0.93). Every 400 IU increase in daily vitamin D supplementation was associated with a further reduction in HR of 0.46 (95% CI, 0.26–0.83).[87] Dietary sources of vitamin D seemed to provide a more substantial protection for eoCRC (HR, 0.34; 95% CI, 0.15–0.79) than supplemental vitamin D (HR, 0.77; 95% CI, 0.37–1.62).

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Supplementary Appendix 4. Summary of Available Evidence on Session III (Genetics)

Summary of available evidence for G.1.: Thirteen studies analyzed the prevalence of PV/LPVs in cancer susceptibility genes in individuals with eoCRC. Next-generation sequencing revealed that the prevalence of PVs in cancer genes is 9.0%–35% among patients with eoCRC. There were 7 studies with a level of evidence 2b and 6 studies with a level of evidence 1b. The prevalence of LS was variable from 0% to 18.3%. The prevalence of other, non-LS, hereditary predisposition PV/LPV ranged from 2.3% to 23.1%. Other study characteristics are listed in Supplementary Table 4.

Summary of available evidence for G.2: Thirteen studies reported the prevalence of PV/LPV in cancer susceptibility genes with moderate and high penetrance. There were 7 studies with level of evidence 2b and 6 studies with level of evidence 1b. The study characteristics are reported in Supplementary Table 4. Estimating the impact of PVs in eoCRC predisposition is an active field of research. With massive use of multigene panel testing, some recent trials have reported a significant number of unexpected diagnoses. These include PVs in *TP53*, *CDKN2A*, *CDH1*, and *BRCA1/2*, which are considered clinically actionable, and other genes have been reported in patients with eoCRC, as listed in Supplementary Table 6.[116,125]

In 1 trial with 165,000 patients with CRC of any age,[110] PVs in *ATM* and *BRCA1* were unexpectedly associated with a moderate risk for CRC (about 2-fold increase).

In one recent study of patients with eoCRC,[126] whole genome sequencing of 20 patients with eoCRC identified 8 candidate genes (*CHAD, CHD1L, ERCC6, IGTB7, PTPN13, SPATA20, TDG*, and *TGS1*). These genes were then re-sequenced in 304 patients with eoCRC, but the results could not claim any of these as CRC predisposing genes.

Summary of available evidence for G.3: Research has characterized about 100 SNPs with a relative risk of CRC (1.46–2.82).[127–131] Among these, a few smaller studies on 10–33 SNPs pointed to some loci specifically linked to eoCRC.

Details on the studies investigating polygenic risk scores for CRC (eoCRC and loCRC both) are summarized in Supplementary Table 5.

One genome-wide association study took data from 12,197 individuals younger than 50 and 95,865 individuals older than 50.[132] It categorized the resulting 95 SNPs into a PRS that could correlate more strongly with eoCRC than with late-onset CRC. This provides the first evidence that patients with eoCRC have a different genetic background, which consists of low-penetrance and common genetic polymorphisms.

In a subanalysis, the same study[132] conducted a PRS classification to identify individuals who would benefit the most from anticipatory screening at age 45. Authors could conclude that among individuals with a high score on PRS, only 10.5% had a family history of CRC. They implied that this PRS could identify additional individuals, compared with family history alone.

Supplementary Appendix 5. Summary of Available Evidence on Session IV (Pathology and Oncology)

Summary of available evidence for O.1: Nine retrospective studies, focused on the immunohistochemistry of eoCRC, were considered sufficiently important to be included in the discussion below.

Prevalence studies on IHC and MSI among eoCRC	
LE: 4	In a retrospective case series of 241 patients with eoCRC,[162] 90% of patients had MMR proficient tumors. The prevalence of MMR deficiency according to the stage at diagnosis was 12% for stage II, 16% for stage III, and 2% for stage IV. Sixty-five percent of patients with MMR deficiency had Lynch syndrome.[162]
LE: 4	In a retrospective case series of 75 patients aged 18–45 years undergoing surgical resection,[37] 20% presented with microsatellite instability.
LE: 3b	In a study comparing 94 patients with CRC before the age of 30 with 275 patients with CRC after the age of 50,[21] MSI was more prevalent before the age of 30 (27% vs 13%; $P < .01$), and it was not associated with MLH1/PMS2 loss or BRAFV600E mutations ($P < .01$). However, the MSS/BRAF V600E genotype was more prevalent before the age of 30 (12% vs 3%; $P < .01$).[21] Such genotype is associated with stage III–IV.
Studies comparing eoCRC with loCRC histopathologic features	
LE: 3b	In a retrospective case-control study[151] of 138 consecutive patients with CRC <40 years and 339 patients with CRC >60 years, younger patients had a significantly higher percentage of MSI-H tumors (29.4% versus 6.3%; $P < .001$). Additional histopathologic characteristics of younger patients included a higher rate of mucin-producing (14.5% versus 4.7%; $P < .001$) and poorly differentiated (7.2% versus 3.3%; $P = .015$) tumors.[151]
LE: 2b	In a study of 797 patients with rectal cancer, patients with eoCRC had a significantly higher risk of microsatellite instability (9% vs 1.6%; $P = .003$), compared with patients with loCRC.[167]
LE: 2b	In a retrospective study comprising more than 36,000 patients with CRC, patients with eoCRC more likely displayed microsatellite instability ($P = .038$) and had fewer BRAF V600 mutations ($P < .001$) compared with patients with loCRC.[64]
LE: 1b	In a prospective cohort study of 947 eoCRC and 3521 loCRC,[152] patients with eoCRC more commonly had an MMR-d status (18.1% vs 8.04%; OR, 2.52; $P < .001$). This risk was consistent for all MMR proteins (OR_{MLH1}, 2.11; $P < .001$; OR_{MSH2}, 4.31; $P < .001$; OR_{MSH6}, 3.40; $P < .001$; OR_{PMS2}, 1.83; $P < .001$).[152]
LE: 2b	In a case control study of 759 eoCRC and 687 loCRC,[105] younger patients more commonly had left-sided tumors presenting with hematochezia or abdominal pain. Microsatellite stable CRC did not differ by age in terms of tumor genomics, response to chemotherapy, and survival. At multivariate analysis, there was no statistically significant difference for TP53 and RTK-RAS pathway alterations. Authors concluded that age alone does not represent sufficient criteria to intensify treatments.
LE: 1b	The ACCENT database contains individual data from 25 randomized studies on 35,713 patients with stage III colon cancer.[143] Patients with stage III eoCRC were more likely to have MMR-d (16.4% vs 11.5%) and less likely to have BRAFV600E (5.6% vs 14.0%). This finding is consistent with a higher likelihood of LS in this cohort. Moreover, patients with eoCRC had a statistically superior overall survival (HR, 0.81; 95% CI, 0.74–0.89), disease-free survival (HR, 0.91; 95% CI, 0.84–0.98), and survival after recurrence (HR, 0.88; 95% CI, 0.80–0.97). However, at multivariate analysis, age of onset lost its prognostic value when adjusted for molecular markers. Authors concluded that tumor biology matters more than age for the prognosis.[143]

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; MSI-H, microsatelite instability high; MSI-L, microsatellite instability low; MMR, mismatch repair; MMR-D, mismatch repair deficiency; MMR-P, mismatch repair proficiency; OR, odds ratio.

Summary of available evidence for O.2: Five retrospective studies, focused on the molecular biology of eoCRC, were considered sufficiently important to be included in the discussion below.

Studies supporting different biological signatures of eoCRC	
LE: 2b	In a retrospective cohort study comprising more than 36,000 patients with CRC, patients with eoCRC had fewer APC somatic mutations (OR, 0.56; 95% CI, 0.35–0.90; $P = .015$) and more likely had signet ring histology (OR, 4.89; 95% CI, 3.23–7.39; $P < .0001$).[64] The most prevalent consensus molecular subtype among patients younger than 40 years was the CMS1, whereas CMS 3 and CMS4 were rare.[64]
LE: 2b	In a retrospective case-control study[151] of 138 consecutive patients with CRC <40 years and 339 patients with CRC >60 years, younger patients less commonly displayed TP53 overexpression. However, there were no significant differences for KRAS mutations and loss of heterozygosity between age groups.[151]

Continued

LE: 3b	A retrospective case-control study of 192 eoCRC vs 381 loCRC analyzed results of metastatic liver resection according to the tumor mutational status.[154] RAS mutated tumors had poorer survival. Among RAS-mutated liver-metastatic CRC, young patients had a higher mortality than older patients, especially among those younger than 40 years.
Studies supporting similar biological signatures between eoCRC and loCRC	
LE: 1b	A prospective study compared tumor genomic profiles of liver-only metastases from 570 stage IV eoCRC and 1252 stage IV loCRC.[153] No single gene (including APC, TP53, KRAS, and PIK3CA) or pathway alteration (Wnt, p53, RTK/RAS, RAS, and PI3K) was enriched in either age group.
LE: 1b	In a prospective cohort study of 947 eoCRC and 3521 loCRC,[152] patients with eoCRC more often had PIK3CA mutations (14.1% vs 11.7%; OR, 1.24; $P = .041$), especially at exon 20 (OR, 1.88; $P < 0.001$).[152] On the other hand, there were no significant differences for BRAF or KRAS mutations.[152]

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Summary of available evidence for O.3: Twenty-one studies discussed the need for adjuvant chemotherapy in eoCRC and they were considered sufficiently important to be included in the discussion below.

Studies reporting worse outcomes for eoCRC compared with loCRC	
LE: 3b	In a retrospective, registry-based, Dutch case-control study (521 patients with CRC at <40 years and 15,000 with CRC at ages 66–75),[31] younger patients more commonly presented with more advanced disease (stage II: $P < .001$; III: $P = .01$; and IV: $P < .01$).[31]
LE: 2b	In a retrospective, registry-based, case-control study on patients with CRC confined to the mucosa or submucosa undergoing surgery,[161] patients with eoCRC (n = 4634) had a similar 5-year relative survival, compared with patients with loCRC (96.7% vs 96.3%).[161] However, patients with eoCRC had higher overall survival (HR, 0.18; 95% CI, 0.16–0.20; $P < .001$).[161]
LE: 2b	In a registry-based study of 35,084 eoCRC and 205,688 loCRC,[160] the 2 cohorts had similar 5-year disease-specific survival (68.2% vs 66.4%; $P = .31$). However, the 20–29 years cohort had the lowest 5-year disease-specific survival (59.0%; $P < .001$). Male sex, advanced stage, and rectal and/or cecal primary were independent predictors of poor survival for both age cohorts.
LE: 3b	In a retrospective study of 163 rectal eoCRC and 830 rectal loCRC,[159] patients with eoCRC more commonly presented with stage III/IV. Recurrence and progression rates were higher among individuals with eoCRC (HR, 1.55; 95% CI, 1.07–2.24). At multivariate analysis, young age of onset was an independent risk factor for disease progression among individuals with rectal cancer. Cancer-specific and overall survival did not differ across age groups.[159]
LE: 1b	The ARCAD database contains data from 20,023 patients from 24 first-line clinical trials.[158] Patients with metastatic eoCRC (n = 3051) had a higher risk of death (19%; 95% CI, 7%–33%) and progression (22%; 95% CI, 10%–35%) compared with patients with metastatic loCRC. After adjusting for performance status, sex, and site of metastasis, age remained a prognostic factor for overall survival but not for progression-free survival.
LE: 2b	In a retrospective, registry-based, population study of 257,334 patients with colon cancer, younger age was a significant risk factor for positive lymph node metastasis for each T stage. Specifically, compared with patients aged >80 years, individuals with CRC at age <40 had an OR for lymph node positivity of 3.06 for stage T1 (95% CI, 2.09–4.48), 2.46 for stage T2 (95% CI, 2.00–3.02), 1.77 for stage T3 (95% CI, 1.62–1.93), and 1.68 for stage T4 (1.51–1.86).[157]
LE: 3b	In a retrospective, population-based study of 1040 patients with eoCRC and 12,044 patients with loCRC,[156] patients with eoCRC more commonly had positive lymph node metastases. Risk factors for lymph node metastases were T1b stage, poor differentiation, lymphatic invasion, and black race.
Studies reporting that clinical outcomes are not significantly worse for eoCRC	
LE: 1b	A meta-analysis of 9 phase III trials for stage III/IV colon cancer[165] comprised 793 eoCRC. In this study, age was prognostic for a lower progression-free survival (median, 6.0 vs 7.5 months; hazard ratio, 1.10; $P = .02$). However, age did not cause a difference in overall survival (15.8 vs 16.6 months; HR, 1.03; $P = .48$) or in the relapse rate (42% vs 43%; OR, 1.02; $P = .84$). During chemotherapy, patients with eoCRC more often developed nausea (10% vs 7%; OR, 1.38; $P = .01$) but less commonly manifested diarrhea (11% vs 14%; OR, 0.68; $P = .001$) and neutropenia (23% vs 26%; OR, 0.64; $P < .001$).[165]

Continued

LE: 3b	In a retrospective study of 3095 Japanese patients with CRC stage I–III,[166] individuals younger than 45 years (n = 139) showed better cancer-specific survival overall, but there was no difference in stage I and II subgroups, only in stage III.[166]
LE: 2b	In a prospective cohort study of 947 eoCRC and 3521 loCRC,[152] patients with eoCRC had a higher 3-year overall survival rate (82.58% vs 76.98%; $P = .001$), although with similar 3-year disease-free survival rates (70.90% vs 75.05%; $P = .028$).[152]
LE: 2b	In a prospective evaluation of 1822 liver-only metastatic CRC (570 eoCRC and 1252 loCRC),[153] the median overall survival (5.8 years; 95% CI, 5.5–6.2) and the 5-year overall survival (55.9%; 95% CI, 53.3–58.7) did not differ by age at diagnosis.
LE: 2b	In a retrospective, registry-based study comparing treatment patterns in 258,024 CRC patients (37,847 eoCRC vs 220,177 loCRC),[104] patients with eoCRC stage III/IV more often received surgery (70.8% vs 66.6%; $P < .001$). Patients with eoCRC had a significantly higher 5-year cancer-specific survival across all stages (95.1% vs 91.9% for stage I/II; $P < .001$; 76% vs 70.3% for stage III, $P < .001$, and 21.3% vs 14.1% for stage IV, $P < .001$).[104]
Studies reporting that eoCRC receive more adjuvant therapy	
LE: 4	In a retrospective case-control study of 797 patients with rectal cancer, patients with eoCRC were more likely to receive adjuvant chemotherapy (41% vs 24.2%; $P = .006$), compared with patients with loCRC.[167]
Studies that do not support intensifying adjuvant treatment	
LE: 3b	A retrospective case-control study of stage I–III colon cancer compared treatments and outcomes in 68 patients with CRC ≤40 years and 1259 patients with CRC >40 years.[50] Young patients were more likely to receive adjuvant chemotherapy. The difference was most pronounced in stage II colon cancer (39% vs 14%; $P = .003$). These differences in treatment did not translate into superior disease-specific survival (5-year disease-specific survival: 86% vs 87%).
LE: 2c	A retrospective, registry-based, case-control study compared chemotherapy use and survival outcomes in patients with stage I–III colon cancer stratified by age (671 diagnosed ≤49 years, 1599 diagnosed ≤64 years, and 873 diagnosed >65 years).[155] Younger patients more often received adjuvant chemotherapy than older patients across all tumor stages (stage I: OR, 7.98; 95% CI, 2.88–22.11; stage II: OR, 4.22; 95% CI, 2.23–7.98; stage III: OR, 2.30; 95% CI, 1.01–5.22; stage IV: OR, 2.43; 95% CI, 1.26–4.70).[155] Younger patients were also more likely to receive multi-agent adjuvant chemotherapy (OR, 2.48; 95%CI, 1.42–4.32). However, these differences in treatment did not yield stage-specific survival benefits.[155]
LE: 1b	In a reevaluation of individual patient data from 6 randomized clinical trials, Fontana et al[169] compared 1564 stage II/III eoCRC with 14,785 stage II/III loCRC. Younger patients more likely completed the treatment plan (83.2% vs 78.2%; $P < .01$) and received more intense treatments, especially with 6-month regimens.[169] For high-risk, stage III eoCRC, the prognosis was poorer. Younger patients experienced lower 3-year relapse-free rate (54% v 65%; HR, 1.33; $P < .01$) and higher 5-year cancer-specific mortality rate (24% vs 20%; HR, 1.21; $P < .06$).[169] Authors concluded that age is a poor prognostic factor in high-risk stage III CRC, despite more intense and more complete treatments.[169]
LE: 2b	In a nationwide cohort study with 13,102 eoCRC and 37,007 loCRC,[170] younger patients were more likely to receive more intensive therapy for all stages (stage I: OR, 2.88; 95% CI, 2.21–3.77; stage II: OR, 3.93; 95% CI, 3.58–4.31; stage III: OR, 2.42; 95% CI, 2.18–2.68; stage IV: OR, 2.74; 95% CI, 2.44–3.07). The more intense treatment strategies did not result into a survival benefit. Authors concluded that eoCRC survivors have distinct needs compared with older patients.
LE: 3b	In a case control study of 759 eoCRC and 687 loCRC with microsatellite stability,[105] there was no statistically significant difference for response to chemotherapy and survival. Authors concluded that age alone does not represent sufficient criteria to intensify treatments.
LE: 1b	In an ACCENT database study (35,713 patients with stage III colon cancer),[143] patients with eoCRC had statistically superior overall survival (HR, 0.81; 95% CI, 0.74–0.89), disease-free survival (HR, 0.91; 95% CI, 0.84–0.98), and survival after recurrence (HR, 0.88; 95% CI, 0.80–0.97). However, age of onset lost its prognostic value when adjusted for molecular markers. Authors concluded that tumor biology matters more than age for prognosis.[143]
Studies that support intensifying treatment for younger patients	
LE: 4	In a retrospective, registry-based, case-series study of patients with T1-2 CRC undergoing standard surgery,[168] patients with eoCRC (n = 3191) had a higher risk of lymph node metastasis for the right and left colon cancer both. Patients with CRC ≤40 years had a 30.1% risk of lymph node positivity, and patients with CRC at 41–50 years had a 22.1% risk.[168] At multivariate analysis, increasing age conferred a protective role for lymph node metastasis of T1-2 CRC (HR, 0.976–0.982; $P < 0.001$).[168]

Continued

LE: 3b	In a retrospective study of 241 patients with eoCRC,[162] 60% of patients with stage II received adjuvant chemotherapy, with 5-year relapse-free survival of 82.2%. Eighty-eight percent of patients with a III disease received adjuvant chemotherapy, with a 5-year relapse-free survival of 74.1%.[162] One hundred three had metastatic disease, and 99% received, as first-line chemotherapy, doublet chemotherapy, with bevacizumab or an anti-EGFR antibody in 57% of cases, providing a median overall survival of 20.1 months (95% CI, 15.9–23.2). Fourteen percent of patients had curative resection of a metastatic lesion and obtained a statistically significant longer median overall survival (79.5 vs 16.2 months; $P < .001$), compared with patients who did not.

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Summary of available evidence for O.4: Eight studies discussed the use for neoadjuvant and systemic therapy in eoCRC, and they were considered sufficiently important to be included in the discussion below.

Studies reporting the use of neoadjuvant chemoradiotherapy on eoCRC	
LE: 4	In a retrospective case-series study of 241 patients with eoCRC,[162] 80% of patients with stage II/III rectal cancer underwent neoadjuvant chemoradiotherapy.
LE: 3b	In a retrospective case-control study of 797 patients with rectal cancer, patients with eoCRC were more likely to receive neoadjuvant chemoradiotherapy (67% vs 53.3%; $P = .003$) compared with patients with loCRC.[167] In the same group, univariate analysis, but not multivariate analysis, demonstrated that neoadjuvant chemoradiotherapy was associated with better disease-specific survival among patients with eoCRC.[167]
According to these studies, young patients respond less to neoadjuvant therapy.	
LE: 3b	A retrospective study on 901 patients with locally advanced rectal cancers undergoing neoadjuvant radiochemotherapy and surgery assessed the impact of age on survival (75 patients ≤40 years and 826 >40 years).[163] Survival analysis demonstrated a poorer prognosis for young patients compared with older ones. After neoadjuvant chemoradiotherapy, younger patients had lower 3-year overall survival (71.6% vs 88.3%; $P = .01$) and lower 3-year disease-free survival (68.6% vs 83.8%; $P = 0.204$).[163]
LE: 3b	In a retrospective, case-control analysis of 413 patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiotherapy (80 patients <40 years and 333 >40 years),[181] among eoCRC there was a higher percentage of disease progression (15% vs 7.8%) and non-resectability (11.25% vs 9.3%).[181]
LE: 2b	A retrospective study on 572 patients with locally advanced rectal cancer (164 younger than 50 years and 408 older than 50 years) assessed the effects of neoadjuvant chemoradiotherapy and surgery.[164] Younger patients had a lower 5-year disease-free survival (72.7% vs 78.0%; $P = .023$) and a higher 5-year cumulative local recurrence rate (8% vs 2%; $P = .003$).[164]
According to these studies, age does not cause significant difference in outcomes of neoadjuvant therapy.	
LE: 2b	In a retrospective case-control study of 333 eoCRC and 675 loCRC (>65 y) with rectal cancer, younger patients more often presented in stage III/IV (15.3% vs 9.0%; $P < .001$).[182] Younger patients more commonly received chemotherapy (67.3% vs 47.6%; $P < .001$), preoperative radiotherapy (24.8% vs 18.5%; $P < .001$), and postoperative radiotherapy (36.6% vs 23.6%; $P < .001$).[182] There was no statistically significant difference in the 5-year disease-free survival across all stages.[182]
According to one post hoc analysis, addition of oxaliplatin to neoadjuvant chemoradiotherapy may provide benefit to eoRC.	
LE: 1b	A post hoc analysis of a German phase III trial CAO/ARo/AIO-04 assessed the age-specific impact of 5-fluorouracil plus oxaliplatin chemoradiotherapy and adjuvant chemotherapy in patients with locally advanced rectal cancer.[172] In this study, after a median follow-up of 50 months, patients aged <60 years receiving oxaliplatin–5-fluorouracil demonstrated significantly superior 3-year disease-free survival (78% vs 67%; $P = .011$) and overall survival (93% vs 87%; $P = .044$) versus older individuals.[172] In general, however, multiple phase III trials have shown increased toxicity and lack of benefit from adding oxaliplatin to standard 5-fluorouracil–based chemoradiotherapy as neoadjuvant for treatment of locally advanced rectal cancer (irrespective of age), and thus the use of oxaliplatin as part of neoadjuvant chemoradiotherapy is not standardly recommended for eoRC.

Continued

No significant differences in survival of metastatic eoCRC vs metastatic loCRC	
LE: 2b	One post hoc subanalysis of a multicenter randomized controlled study (CALGB/SWOG 80405 trial comparing mFOLFOX6 or FOLFIRI in combination with biologics cetuximab and/or bevacizumab as first-line treatment of metastatic CRC) compared 541 eoCRC patients with 1812 loCRC patients.[171] There was a statistically significant difference in the daily time being physically active (median of 6.9 h/week for eoCRC vs 2.9 h/week for loCRC; $P < .001$).[171] There was no statistically significant difference in performance status (61.9% with ECOG 0 vs 57.6%; $P = .08$). There were no statistically significant differences in median overall survival (27.07 months, 95% CI, 25.04–30.06 vs 26.12 months, 95% CI, 24.94–27.30; $P = .12$) or median progression-free survival (10.87 months, 95% CI, 9.99–11.50 vs 10.55 months, 95% CI, 10.12–10.94; $P = .67$) in eoCRC patients vs loCRC patients.[171]

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Supplementary Appendix 6. Summary of Available Evidence on Session IV (Endoscopy)

Summary of available evidence for E.2: Five studies considered the use of different quality metrics during colonoscopy for individuals younger than 50, and they were considered sufficiently important to be included in the discussion below.

These studies report the prevalence of adenoma, advanced adenoma, and CRC among individuals younger than 50 years.	
LE: 3b	In a retrospective cross-sectional study of 2059 individuals aged 40–49 years undergoing colonoscopy,[53] the overall polyp detection rate was 40.3%, and the adenoma detection rate was 20.9%. Having a family history of CRC increased the polyp detection rate (51.7% vs 38.3%; $P = .0001$) and the adenoma detection rate (27.8% vs 19.7%; $P = .001$).[53] At multivariate analysis, risk factors for increased adenoma detection rates included male sex (OR, 1.6; $P < .001$, 95% CI 1.3–2.1), family history (OR, 1.5; $P = .002$, 95% CI, 1.1–2.0), adequate bowel preparation (OR, 1.8; $P = .04$, 95% CI, 1.02–3.4), chronic kidney disease (OR, 2.2; $P = .01$, 95% CI, 1.1–4.3), and obesity (OR, 1.8; $P = 0.001$, 95% CI, 1.2–2.6).[53]
LE: 1a	In a meta-analysis of 28 studies comprising 23,142 individuals, the pooled prevalence of young-onset adenoma was estimated at 9.0% (95% CI, 7.1%–11.4%).[91] Since 1995, the pooled prevalence of young-onset adenoma increased from 4.2% (95% CI, 7.4%–12.0%) to 10.0% (95% CI, 7.8%–12.8%).[91]
One study supports the hypothesis that the adenoma detection rate should not change for younger individuals.	
LE: 2b	By comparing colonoscopy outcomes from 1869 patients aged 45–49 with 21,482 patients aged 50–54, Butterly et al[39] could not find significant differences in the prevalence of advanced adenoma (3.3% in the 45- to 49-year group vs 3.6% in the 50- to 54-year group; $P = .50$). The prevalence of both advanced neoplasia and clinically significant serrated polyps was also similar in the 2 age groups.[39]
These studies support the hypothesis that adenoma detection rate should be lower for younger individuals.	
LE: 1b	Shaukat et al[190] tested the hypothesis of a lower ADR among younger individuals undergoing colonoscopy. They conducted a retrospective study of 159,817 screening colonoscopies in patients 45–75 years of age (with 4841 in the 45–49 age group and 58,914 in the 50–54 age group). They found a small absolute difference in overall ADR, advanced ADR (AADR), and adenomas per colonoscopy (APC) for 45- to 49-year-olds compared with 50-54-year-olds (ADR: 28.4% vs 31.1%; $P < .001$; AADR: 3.28% vs 3.43%; $P = .68$; APC: 0.44 vs 0.49; $P < .001$). In this study, the adenoma detection rate increased with age (28.4% at age 45–49, 31.1% at age 50–54, and 35.6% at age 50–75; all $P < .001$).[190] There was a larger absolute difference in ADR, AADR, and APC compared with the entire screening population of 50- to 75-year-olds (ADR: 28.4% vs 35.6%; $P < .001$; AADR: 3.28% vs 3.5%; $P = .56$; APC: 0.44 vs 0.59; $P < .001$).[190] The adenoma per colonoscopy increased with age (0.44 for ages 45–49, 0.49 for ages 50–54, and 0.59 for ages 50–75; $P < .001$).[190] The advanced adenoma detection rate followed a similar trend without reaching significance (3.28% for ages 45–49, 3.43% for ages 50–54, and 3.5% for ages 50–75; all $P > .05$).[190] Authors concluded that if screening coverage of 45- to 49-year-old individuals increases to 25%, the overall adenoma detection rate would decrease to 33.7%.[190]
LE: 1b	In an observational cohort study of 6027 individuals undergoing colonoscopy (897 younger than 50),[207] the adenoma detection rate increased with age (9.7% for ages 40–44, 21.2% for ages 45–49; $P < .001$). The advanced adenoma detection rate also increased from 3.1% in patients aged 40–44 to 6.4% in those aged 45–49 years ($P < .03$).[207] Comparing individuals aged 45–49 years with those ≥50 years undergoing colonoscopy, younger individuals were significantly more likely to have a lower polyp detection rate (29.1% vs 40.0%; $P < .001$), adenoma detection rate (21.2% vs 34.6%; $P < .001$), and advanced neoplasia detection rate (6.4% vs 11.8%; $P < .001$).[207]

AADR, advanced adenoma detection rate; ADR, adenoma detection rate; CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Summary of available evidence for E.3: Ten studies discussed the need for staging studies and the need for immunohistochemistry in individuals with eoCRC.[31,50,156,157,162,166,168,182] These are already reported in Supplementary Appendix 5, sections 0.1., 0.3., and 0.4.

Summary of available evidence for E.4: Six studies investigated the endoscopic treatment of T1 eoCRC, and they were considered sufficiently important to be included in the discussion below. There were 2 retrospective population studies, 3 retrospective record-based studies, and 2 meta-analyses.

These studies support surgical therapy over endoscopic therapy for eoCRC.	
LE: 2b	In a retrospective, registry-based study of differentiated CRC confined to the mucosa or submucosa (3052 eoCRC and 31,545 loCRC), rates of lymph node metastasis decreased with older age at diagnosis ($P < .001$).[209] Patients aged 18–39 had the highest risk of lymph node metastasis from superficial CRC (15.74%). The older age groups had progressively lower risks for lymph node metastasis (age 40–49: OR, 0.90 [0.71–1.15; $P = .376$]; age 50–59: OR, 0.69 [0.56–0.87; $P = .001$]; age 60–69: OR, 0.54 [0.43–0.68; $P < .001$]; age 70–79: OR, 0.47 [0.38–0.60; $P < .001$]).[209]
These studies support endoscopic therapy in eoCRC.	
LE: 2b	A population-based propensity matching study on 1719 patients with CRC at <45 years compared the outcomes of endoscopic vs surgical treatment (573 and 1146 patients, respectively).[203] For colon cancer, there was no statistically significant difference in the 5-year and 10-year cancer-specific survival (93.4% vs 96.7% and 91.4% vs 94.0%, respectively; $P = .149$).[203] For rectal cancer, there was no statistically significant difference in the 5-year and 10-year cancer-specific survival (96.6% vs 98.4% and 92.8% vs 96.7%, respectively; $P = .067$). At multivariable analysis, endoscopic treatment had a non-inferior cancer-specific survival for both colon (HR, 1.74; $P = .090$) and rectal cancer (HR, 2.16; $P = .052$).[203]
LE: 3b	A retrospective, record-based study investigated whether endoscopic resection of T1 CRC before surgery affects recurrence-free survival compared with upfront surgical treatment.[208] Of 852 patients (388 primary surgery and 464 endoscopic treatment followed by surgery), the use of endoscopy before surgery did not increase the recurrence risk. This study did not stratify results according to age (mean age, 60.1 ± 10.5).[208]
LE: 1a	In a meta-analysis of 71 studies with 5167 patients with T1 CRC undergoing endoscopic treatment,[210] the pooled cumulative incidence of CRC recurrence was 3.3% (95% CI, 2.6%-4.3%; $I^2 = 54.9\%$). This meta-analysis did not stratify results on the basis of age.
LE: 1a	In a meta-analysis of 17 studies with 19,979 patients comparing endoscopic vs surgical treatment of T1 CRC,[211] there was no significant difference in overall survival (HR, 1.10; 95% CI, 0.84–1.45), recurrence-free survival (HR, 1.28; 95% CI, 0.87–1.88), or disease-specific survival (HR, 1.09; 95% CI, 0.67–1.78). In this study, with a mean age of 67.9 years, authors did not observe an association between age and recurrence.[211]
Risk factors for lymph node invasion after endoscopic therapy	
LE: 2b	In a retrospective, population-based study of 1040 patients with eoCRC and 12,044 patients with loCRC,[156] risk factors for lymph node metastases included T1b stage, poor differentiation, lymphatic invasion, and black race.[156]

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Summary of available evidence E.5: Seven studies have evaluated the need for more intensive surveillance in patients with eoCRC after surgical resection with conflicting results.

EoCRC vs loCRC: these studies report a higher risk of metachronous neoplasia among eoCRC	
LE: 2b	Kim et al[51] conducted a retrospective case-control study of 693 patients with CRC ≤45 years and 1823 aged 56-65 years. In this study, younger patients had higher CRC recurrence rate for stage I/II (8.8% vs 2.7%; $P < .001$) but not for stage III/IV (27.5% vs 27.9%, $P = 0.325$). Young patients more commonly developed metachronous cancers (1.4% vs 0.6%; $P = .038$).[51]
LE: 2b	In a retrospective case-control study of 333 eoCRC and 675 loCRC (>65 y) with rectal cancer,[182] patients with eoCRC more commonly developed distant disease recurrence during follow-up (24.6% vs 13.9%; $P < .001$). Patients with eoCRC were more likely to develop metastatic recurrence both within 5 years from surgery (19.5% vs 11.3%; $P < .001$) and after 5 years from diagnosis (8.8% vs 6.2%; $P < .001$). However, the time to first recurrence did not differ between age groups (median time to recurrence: 4.7 years vs 4.3 years; $P = .079$).[182]

Continued

EoCRC vs loCRC: these studies report a lower risk of metachronous neoplasia among eoCRC	
LE: 2b	A retrospective, registry-based study with 12,380 adults with at least 1 polyp on index colonoscopy analyzed the risk of metachronous advanced adenoma and large serrated polyps and stratified results on the basis of age.[212] Compared with individuals ≥60 years, younger individuals with ≥1 polyps had a significantly lower risk of metachronous advanced adenoma (<40 years: OR, 0.19; 95% CI, 0.05–0.80; 40-49 years: OR, 0.61; 95% CI, 0.41–0.92; ≥50 years: OR, 0.71; 95% CI, 0.58–0.86). Similarly, younger individuals had lower risk for metachronous CRC than older ones: <40 (0.0%), 40–49 (0.2%), 50–59 (0.2%), ≥60 (0.4%; $P = .04$).[212]
LE: 3b	In a retrospective case-control study of 569 patients with stage I–III CRC (95 eoCRC and 474 loCRC), patients received a similar schedule for surveillance colonoscopy after curative resection.[206] Younger individuals had lower risk of metachronous advanced adenoma or CRC (16.8% vs 44.1%; $P = .001$). Risk factors for the development of metachronous advanced adenoma or CRC included age ≥50 years (OR, 3.56; 95% CI, 1.08–11.74; $P = .04$) and a family history of CRC (OR, 2.66; 95% CI, .29–5.48; $P = .008$).[206] Moreover, this study reported a longer time to development of metachronous advanced neoplasia in patients with eoCRC. Those younger individuals who developed an advanced adenoma or CRC developed it after more time than individuals with loCRC (99.2 ± 3.7 months vs 84.4 ± 2.5 months; $P = .03$).[206]
LE: 3b	In a retrospective case-control study (107 eoCRC and 139 loCRC), patients received similar recommendations for endoscopic surveillance after curative surgery, but patients with eoCRC were more adherent to recommendations (71% versus 55%; $P = .01$).[102] The risk of metachronous advanced adenoma or CRC after curative resection was lower for patients with eoCRC (adjusted HR, 0.44; 95% CI, 0.22–0.88).[102] The 5-year event rate for metachronous advanced adenoma and CRC was lower for patients with eoCRC (5.8% vs 16.1%; $P = .07$).[102]
LE: 1a	In a systematic review of 28 studies on patients younger than 50 years with an adenoma,[91] only 1 patient developed a subsequent (metachronous) CRC among 9341 patients (0.01%). The authors could not determine the impact on incidence and mortality from CRC of surveillance colonoscopy in patients with adenoma at <50 years.[91]
Metachronous cancer risk	
LE: 1a	In a meta-analysis of 71 studies (5167 patients) assessing the risk of recurrence after endoscopic treatment of T1 CRC,[210] the pooled cumulative incidence of CRC recurrence was 3.3% (95% CI, 2.6%–4.3%; $I^2 = 54.9\%$). This meta-analysis did not stratify results on the basis of age.

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Supplementary Appendix 7. Summary of Available Evidence on Therapy

Summary of available evidence for T.1: Three studies explored the surgical outcomes of individuals with eoCRC, and they were considered sufficiently important to be included in the discussion below.

EoCRC vs loCRC: these studies suggest that the surgical management should not differ	
LE: 3b	A retrospective case-control study of stage I–III colon cancer (68 at ≤40 years and 1259 at >40 years) could not find statistically significant differences in the surgical treatment offered to patients of different age. A similar proportion of patients underwent subtotal or total colectomy in both groups.[50]
LE: 4	In a retrospective case-series of 301 patients with eoCRC undergoing segmental surgery (n = 271) vs extended surgery (n = 30),[213] there was a non-statistically significant difference in the risk of metachronous CRC development (3.3% vs 0%; $P = .61$). Recurrence and mortality did not differ in the 2 groups, and authors concluded that the type of surgery in eoCRC does not modify disease-free or overall survival.[213]
LE: 2b	In a retrospective, registry-based study comparing treatment patterns in 258,024 CRC patients (37,847 eoCRC vs 220,177 loCRC),[104] patients with eoCRC stage III/IV more often received surgery (70.8% vs 66.6%; $P < .001$). Patients with eoCRC had a significantly higher 5-year cancer-specific survival across all stages (95.1% vs 91.9% for stage I/II, $P < .001$; 76% vs 70.3% for stage III, $P < .001$; and 21.3% vs 14.1% for stage IV, $P < .001$).[104]

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Summary of available evidence for T.2: Three studies investigated the use of fertility preservation among patients with eoCRC.

These studies report that patients with eoCRC do not receive adequate fertility counseling.	
LE: 4	A retrospective, registry-based study analyzed the referral to fertility services among 18,781 women with various cancers including CRC.[222] Among female patients aged 18–35 years only 11.7% underwent evaluation, 13.7% were tested, and 6.3% pursued fertility-preserving procedures. These percentages were even lower for female patients aged 36–40 (3.3%, 7.5%, and 1.9%, respectively) and those aged 41–45 (0.5%, 7.2%, and 0.3%, respectively).
LE: 4	According to a cross-sectional study of 234 eoCRC survivors (male, 61.9%; white, 77.9%), more than 50% male and female survivors did not have any discussion on fertility options after treatment, and 75% did not preserve eggs/embryos/sperm before therapy.[221]
LE: 4	In a retrospective study with 103 stage III CRC at age 18–40,[223] 27% of patients lacked documentation regarding fertility before treatment start. Authors concluded that most patients received sufficient information on fertility preservation. However, the single-center design of this study limits the interpretability of the findings.

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Summary of available evidence for T.3: Three studies investigated outcomes of fertility preservations within a population of eoCRC.

Effects of oxaliplatin on fertility	
LE: 4	In a prospective study, 19 patients with eoCRC (11 female, 8 male) had hormonal level assessment before and 6 months after oxaliplatin therapy.[230] Among female patients, anti-Mullerian hormone levels (an estimate of ovarian reserve) decreased, whereas follicle-stimulating hormone levels increased. All patients remained menstruating. In men, inhibin B (a testicular function estimate) slightly decreased after treatment.
LE: 4	In a retrospective, questionnaire-based study of 49 female patients with stage II/III eoCRC receiving adjuvant FOLFOX, 41% experienced amenorrhea.[226] Amenorrhea was more common among female patients aged 40–49 than those aged <40 (59% vs 31%; $P = .075$). After chemotherapy completion, both age groups had statistically similar rates of amenorrhea (24% vs 13%; $P = .42$).
Effects of age on fertility	
LE: 3b	In a retrospective cohort study of 467 patients with LS and eoCRC,[227] age-specific fertility rate decreased among female survivors aged 20–24 (1.2 vs 2.2; $P = .0011$). The fertility rate did not decrease for other age groups and for men with LS and eoCRC.

CI, confidence interval; CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; HR, hazard ratio; loCRC, late-onset colorectal cancer (>50 y); LE, level of evidence; OR, odds ratio.

Supplementary Appendix 8. Summary of Available Evidence on Session VII (Supportive Care)

Summary of available evidence for L.1: Four studies explored the management peculiarities of individuals with eoCRC, and they were considered sufficiently important to be included in the discussion below.

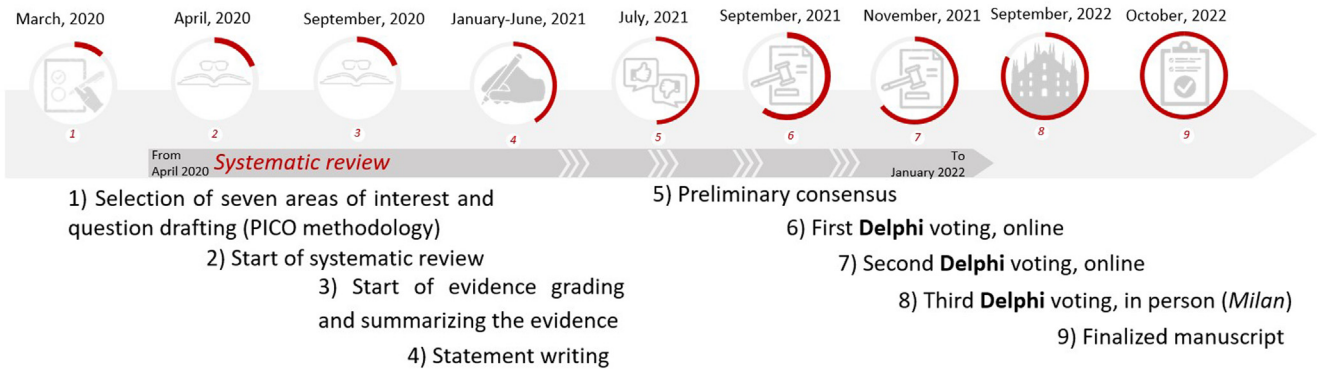
Prevalence of morbidity among patients with eoCRC	
LE: 3b	In a retrospective analysis of 83 patients with CRC at age <30 years,[38] patients with metastatic disease more commonly complained of fatigue (31.0% vs 5.8%; $P = .002$) but less commonly complained of altered bowel habits (38.0% vs 65.4%; $P = .017$).[38]
LE: 1b	In a meta-analysis of 9 phase III trials for stage III/IV colon cancer[165] comprising 793 eoCRC, during chemotherapy, patients with eoCRC more often developed nausea (10% vs 7%; OR, 1.38; $P = .01$) but less commonly manifested diarrhea (11% vs 14%; OR, 0.68; $P = .001$) and neutropenia (23% vs 26%; OR, 0.64; $P < .001$).[165]
LE: 3b	Fontana et al[233] reported that younger age increased the risk of nausea or vomiting from adjuvant chemotherapy (nausea, 58% vs 45%, $P < .01$; vomiting, 22% vs 16%; $P < .01$).
These studies support the use of physical therapy during disease treatment for eoCRC.	
LE: 1b	In a systematic review on the benefit of physical activity during and after cancer treatment in young adults (not necessarily affected by CRC),[240] six studies of inconsistent quality provided sufficient evidence for a potential positive impact of physical activity in this cohort.[240]

CRC, colorectal cancer; eoCRC, early-onset colorectal cancer; LE, level of evidence.

Summary of available evidence for L.2: Two studies explored organization of supportive care programs.

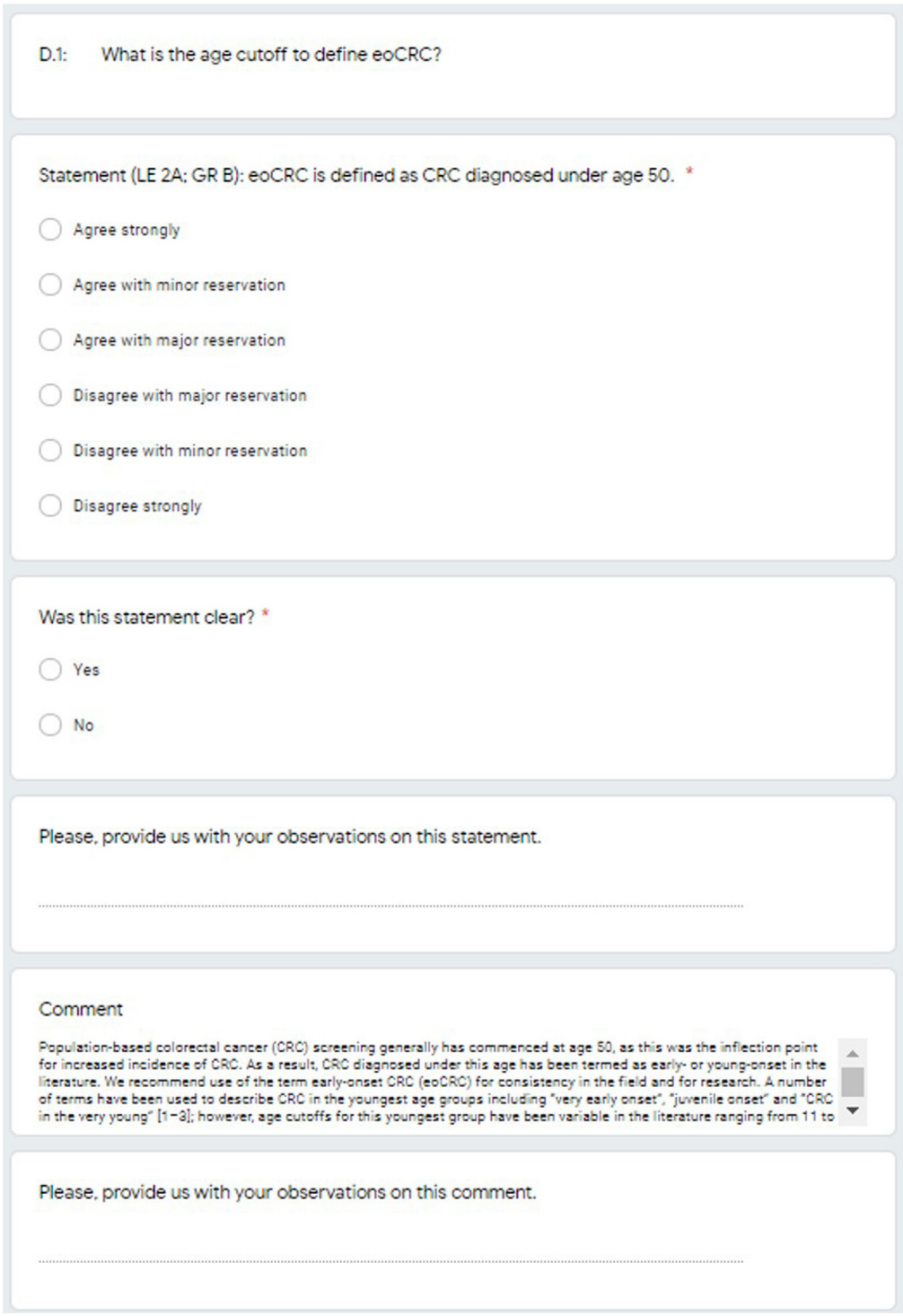
Studies on age-specific needs and peculiarities	
LE: 4	A retrospective cases series assessed the needs of 50 patients with gastrointestinal malignancies diagnosed before 40 years by using a questionnaire.[247] Patients reported sleeping problems (32%), sexual dysfunction (40%), and deterioration of occupational activities and childcare. Female patients more commonly had unmet nutritional and psychological needs. Patients receiving more intensive treatment (chemoradiotherapy and surgery) more commonly had unmet needs (76% vs 48%; $P = .03$)
LE: 4	In a retrospective case series of 42 female patients with eoCRC diagnosed during pregnancy or immediately after delivery,[245] 93% had stage III/IV at diagnosis. Authors concluded that the overlapping symptoms of CRC and pregnancy (abdominal pain) may contribute to the advanced stage at presentation.

eoCRC, early-onset colorectal cancer; LE, level of evidence.



Supplementary Figure 1. Timeline of the DIRECt recommendations. Step 1: The scientific panel selected 7 main areas of interest in eoCRC: diagnosis, risk factors, genetics, pathology and oncology, endoscopy, targeted therapy, and supportive care. Seven working groups were created. Experts were assigned to specific topics according to their clinical expertise and/or area of research. Each working group consisted of at least 4 experts who drafted clinically relevant, clear, and answerable questions that were focused on areas of controversy and clinical interest. Steps 2 and 3: MP, RAZ, and AM carried out the first systematic search of the literature on each topic up to May 15, 2021, by using PubMed, Embase, and Scopus. From May 2021 to January 2022, monthly systematic revisions of newly published literature were conducted by AM. The most recent systematic review update to the literature was done on January 28, 2022. All articles included for statement writing were then graded according to Oxford levels of evidence. The most notable findings from each article were summarized in the appendices. During the consensus process, new findings and articles were sent to each working group to support statement writing. All the literature published was added as needed. Step 4: The task of the working group was to develop clear, unequivocal, and sufficiently short statements that could be applied to clinical practice. The working groups independently developed the initial statements by June 11, 2021. Statements were attributed a grade (strength) of recommendation (GR), from A to D, consistent with the level of evidence (Supplementary Table 2).[13] Moreover, each statement was accompanied by a comment motivating the recommendation and the level of evidence. Step 5: During the first round of consensus, all experts received an invitation to vote on the first draft of the statements using a simplified Delphi technique. This voting round was held online because of the SARS-CoV-2 pandemic, and all participants could vote from June 16 to July 2, 2021. Each expert received an online questionnaire to vote the statements on the basis of agreement with a simplified scale (agreement/disagreement) and clarity (clear/not clear). Below each statement, the members had the option to provide written feedback on each statement. All voting rounds were hosted on an online platform (https://www.google.com/forms/, Supplementary Figure 3). Votes and comments were anonymously recorded. At this stage, only one author (E.P.) asked not to vote, because of his area of expertise (reproductive medicine). At the end of the first round of voting with the simplified Delphi, all statements reached a sufficiently high level of consensus except for 2 statements from the pathology-oncology session. Therefore, these 2 statements underwent significant redrafting, were merged into a single statement (O.1), and then underwent a second round of anonymous voting, which the statements passed. Step 6: Each working group received the results, including the percentage of agreement, how clear the statement was perceived, and anonymous written feedback from other panel members. The second round of consensus voting was held virtually on an online platform (https://www.google.com/forms/) from September 17 to September 27, 2021. Statements were sent to the global consensus group for the first round of anonymous voting without requiring any explanation or justification. Step 7: Each working group was obliged to acknowledge the suggestions received; they could decide to review the statements according to the suggestions they received, or they could decide to address such concerns in the comments. The working groups could then change the statements accordingly or address the concerns in the comments accompanying the statements. The working groups then wrote a final version, which was submitted to the scientific panel before sending the statements for consensus through another online Delphi procedure. Step 8: Additional experts were brought into the working groups to expand the consensus of all topics. Specifically, more oncologists, more surgeons, and more gynecologists were included to provide further perspectives and further feedback on the areas discussed. Each new member had full access to the entire manuscript and the data available. Each new member could suggest changes to the working group leader, who would approve or reject such suggestions. All statements, whether modified or unchanged from step 7, were submitted to a final round of voting after a face-to-face discussion (DIRECt22 meeting in Milan). All statements with a consensus >80% were considered for publication. Areas of controversy were highlighted for further studies.

Supplementary Figure 2. Geographical distribution of participating centers. Red, site of the coordinating center. Blue, sites of the participating centers.



Supplementary Figure 3. Example of the Delphi consensus online platform.

Supplementary Table 1. Level of Evidence Based on the Oxford Center for Evidence-Based Medicine[13]

Level	Therapy, prevention, etiology	Prognosis	Diagnosis	Symptom prevalence study	Economic and decision
1A	SR (with homogeneity) of RCTs	SR (with homogeneity) of inception cohort studies; CDR validated in different populations	SR (with homogeneity) of level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of level 1 economic studies
1B	Individual RCT (with narrow confidence interval)	Individual inception cohort study with >80% follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical center	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1C	All or none	All or none case-series	Absolute SpPins and SnNouts	All or none case-series	Absolute better-value or worse-value analyses
2A	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of level >2 diagnostic studies	SR (with homogeneity) of 2b and better studies	SR (with homogeneity) of level >2 economic studies
2B	Individual cohort study (including low-quality RCT; eg, <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR or validated on split-sample only	Exploratory cohort study with good reference standards; CDR after derivation or validated only on split-sample or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2C	"Outcomes" research; ecological studies	"Outcomes" research		Ecological studies	Audit or outcomes research
3A	SR (with homogeneity[a]) of case-control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3B	Individual case-control study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor-quality cohort and case-control studies)	Case-series (and poor-quality prognostic cohort studies)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"				

CDR, clinical decision rule; RCT, randomized controlled trial; SnOuts, sensitivity is so high that a negative result rules out the diagnosis; SpIn, specificity is so high that a positive result rules in the diagnosis; SR, systematic review.

[a]Homogeneity implies a systematic review without worrisome variations (heterogeneity) in the directions and degrees of results across studies.

Supplementary Table 2. Grade of Recommendation Based on the Oxford Center for Evidence-Based Medicine[13]

Grade	Evidence base
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolation from level 1 studies
C	Level 4 studies or extrapolation from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Supplementary Table 3. Agreement Scale Used for the Delphi Votes

Vote	Explanation
A+	Strong agreement
A	Agreement with minor reservations
A–	Agreement with major reservations
D–	Disagreement with minor reservations
D	Disagreement with major reservations
D+	Strong disagreement

Supplementary Table 4. Articles Providing the Prevalence of PV/LPV in Cancer Susceptibility Genes Among Early-Onset Colorectal Cancer Patients

Article	Ascertainment	Age (*y*)	No. of genes included in MGPT	PV/LPV	Cohort	Prevalence of Lynch síndrome (%)	Prevalence of PV/LPV in non-Lynch syndrome cancer genes (%)	Overall prevalence of PV/LPV in cancer susceptibility genes (%)	Evidence level
Laduca[110] 2020	U.S. commercial laboratory	<50 subset	5–49	362	4017	5.3	4.7	9.0	2b
Jiang[111] 2020	Chinese high-risk clinic based	<50 subset	14	47	261	15.7	2.3	18	2b
Zhunussova[112] 2019	Kazakhstan population-based	<50	94	20	125	2.4	13.6	16	1b
You[113] 2019	U.S. clinic based	<50 metastatic	46	10	67	2.9	12.0	14.9	1b
Mork[114] 2019	U.S. high-risk clinic	≤35	≥1, varied	24	136	18.3[a]	11.1	29.4	2b
AlDubayan[115] 2018	Nurses Health Study & Health Professionals Follow-up Study population-based	<50 subset	54	5	35	0	14.3	14.3	1b
Stoffel[116] 2018	U.S. high-risk clinic based	<50	≥1, varied	85	430	13.5	6.5	20	2b
Pearlman[117] 2017	U.S. population based	<50	25	72	450	8	8	16	1b
DeRycke[118] 2017	U.S. Australian Colon Cancer Family Registry	<50	36	88	333	13.5	12.9	26.4	2b
Chubb[119] 2016	UK National Study of Colorectal Cancer Genetics	≤55 with ≥1 FDR with CRC	WES	158	1006	11	4.7	15.7	2b
Mork[120] 2015	U.S. high-risk clinic based	<35	≥0, varied	67	193	11.9	23.1	35	2b
Toh[121] 2018	Singapore oncology clinic	<50 MMR-p	64	12	88	0	13.6	13.6	1b
Yurgelun[122] 2017	U.S. clinic based	<50 subset	25	40	336	6.3	5.6	11.9	1b

Note. Lynch syndrome: PV/LPV in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*.
CRC, colorectal cancer; LPV, likely pathogenic variant; MMR-p, mismatch repair proficient; PV, pathogenic variant; UK, United Kingdom; WES, whole exome sequencing.
[a]Excludes one case with constitutional MLH1 promoter hypermethylation.

Supplementary Table 5. Publications Including Information About Polygenic Risk Scores and Colorectal Cancer

Article		No. of CRC patients	No. of controls	No. of SNPs	RR	AUC	Outcome	Evidence level
Northcutt[134] 2021	White American	0	1769	22	1.02 vs 0.97		Genetic risk score was significantly associated with adenomatous polyps in patients undergoing screening colonoscopy	2b
Thomas[135] 2020	European	55,105	65,079	1.2 M	2.19–2.82	0.654	Based on their PRS, they can identify 30% of individuals without a family history have a risk similar to those with a family history of CRC. Whereas PRS using the known 140 GWAS variants identified only the top 10% as having a similar relative risk.	2b
Li[136] 2020	Scottish	6478	11,043	116	1.46	0.61	The authors first performed a meta-analysis of 11 GWAS studies (see separate row) to capture CRC susceptibility variants. A weighted PRS using 116 SNPs was then used on this Scottish dataset and validated in the UK Biobank (OR, 1.49 per SD increase, c-statistic 0.61).	2b
Jia[137] 2020	European	2543	386,228	95	2.36 (top 5%)	0.609	A large proportion of the general population can be identified at an elevated cancer risk by PRS, supporting potential clinical utility of PRS.	1b
Guo[138] 2020	German	3827	2641	90	2.52 high vs low tertile PRS with no colonoscopy (0.32–0.85 for those with a colonoscopy)	N/A	This study addressed CRC risk according to PRS and time since last negative colonoscopy. Found no need to shorten the 10-year interval among people with high PRS but could potentially be prolonged for individuals with a low or medium PRS.	2b
Carr[139] 2020	German	4220	3338	90	2.23 women and 2.24 men with high PRS		Individuals with a history of colonoscopy, healthy lifestyle, and low PRS score had very low 30-year risks for CRC (0.9%–1.2%). Individuals with no colonoscopy, unhealthy lifestyle, and high PRS score had highest 30-year risk for CRC (10.6%–13.4%).	2b
Saunders[140] 2020	UK	2679	441,209	120	1.60/SD	0.62 women 0.64 men	Adding phenotypic risk factors without age to the PRS improved discrimination in men but not women. Among individuals in UK, PRS discriminate moderately well between those who do and do not develop colorectal cancer over 6 y.	2b

Supplementary Table 5. Continued

Article		No. of CRC patients	No. of controls	No. of SNPs	RR	AUC	Outcome	Evidence level
Archambault[133] 2020	European	50,023 (discovery cohort) 1093 (replication cohort)	58,039 (discovery cohort) 72,573 (replication cohort)	95	Highest PRS quartile compared with lowest 3.7 for eoCRC vs 2.9 for loCRC	0.64–0.65	PRS successfully identifies individuals at increased risk for eoCRC particularly among individuals without a family history.	2b
Fahed[141] 2020	European	76 individuals with Lynch syndrome	48,736	95	1.65/SD	1	PRS for colorectal cancer modify risk among individuals with Lynch syndrome with an OR of 8.41–117.80 from the lowest to highest risk individuals. Absolute risks to 75 ranged from 11.3%–79.7% for carriers and 0.7%–8.7% for noncarriers.	2b
Huyghe[132] 2019	European	1439 (discovery cohort) 58,131 (validation cohorts)	720 (discovery cohort) 67,347 (validation cohorts)	95	—	—	In a combined meta-analysis of 125,478 individuals, we identified 40 new independent signals at $P < 5 \times 10^{-8}$, bringing the number of known independent signals for CRC to approximately 100.	2b
He[131] 2019	Scotland	5675	—	130	HR: 1.00 Survival based on PRS	—	Common variants associated with CRC risk that have been identified to date are unlikely to have clinically relevant effect on survival outcomes for patients diagnosed with CRC.	2b
Schmit[142] 2019	European + multiethnic validation cohort	36,948 (discovery cohort) 12,952 European & 12,085 multiethnic (validation cohort)	30,864 (discovery cohort) 48,383 European & 22,083 multiethnic (validation cohort)	11 in discovery; 9 validated	—	—	PRS identified 4.3% of the population at an odds ratio for developing CRC of at least 2.0.	2b

AUC, area under the receiver operator curve; CRC, colorectal cancer; eoCRC, early-onset CRC; GWAS, genome-wide association studies; HR, hazard ratio; OR, odds ratio; PRS, polygenic risk score; RR, relative risk; SD, standard deviation; SNP, single nucleotide polymorphism; UK, United Kingdom.

Supplementary Table 6. Data From All Published Articles Regarding the Prevalence of PV/LPVs in Each Gene Among Early-Onset Colorectal Cancer Patients[a]

Gene	Positive	Total tested	Prevalence (%)
Colorectal cancer genes			
LS genes (*MLH1, MSH2, MSH6, PMS2*, & *EPCAM*)	551	7168	7.7
APC	93	7058	1.3
Biallelic *MUTYH*	47	7087	0.7
SMAD4	11	7055	0.2
BMPR1A	6	7055	0.09
STK11	2	7128	0.03
PTEN	2	7188	0.03
GREM1	1	2366	0.04
AXIN2	—	—	—
POLE/POLD1	4	3687	0.1
Other actionable cancer genes			
BRCA1/2	50	4142	1.2
CHEK2	56	6709	0.8
ATM	29	4065	0.7
TP53	14	6737	0.2
PALB2	7	4105	0.2
BRIP1	5	4097	0.1
CDKN2A	3	3399	0.09
CDH1	6	6685	0.09

LS, Lynch syndrome.

[a]Articles where we could not deduce the total number of eoCRC patients tested for each gene were excluded.