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

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Abstract

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.

Graphical Abstract

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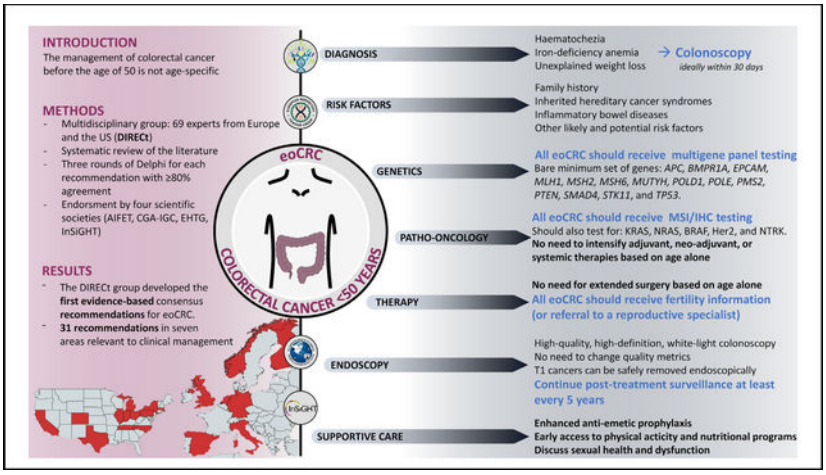
Conflicts of interest

Refer to the online form to see conflicts of interest.

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.

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.



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 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, nonconsecutive 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 ≥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 ≥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 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 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 non-specific 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 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 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

PeutzJeghers 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 MMRd 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 O.1,[21,37,64,105,143,151,152,162,167] O.2,[64,151–154] O.3,[31,50,104, 105,143,152,153,155–162,165–170 162–164,167,171,172,181,182] and O.4 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 meta-chronous 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] andE.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 antiMüllerian 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 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

Refer to Web version on PubMed Central for supplementary material.

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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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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, Moller 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

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. B. Genetic testing should be performed before treatment to maximize clinical utility, when feasible, but should not substantially delay treatment.	LE 1B; GR A Agreement: 100% (A+ 66.7%|A 33.3%) 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%)

Question and statement	Level of evidence, grade of recommendation, agreement level, and clarity
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%)

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? A. There is no evidence that neoadjuvant therapy in locally advanced rectal cancer should differ between eoRC patients and patients older than 50 years. B. There is no evidence that systemic therapy should differ between eoCRC patients and patients older than 50 years.	LE 1B; GR B Agreement: 93.3% (A+ 40.0%|A 53.3%|A− 6.7%) LE 1B; GR B Agreement: 93.5% (A+ 35.5%|A 58.1%|A− 6.5%)

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%IA− 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. B. Patients diagnosed with hereditary CRC syndromes should receive variant- and phenotype-specific surveillance intervals.	LE2B; GRC Agreement: 89.7% (A+ 31.0%|A 58.6%|A− 10.3%) 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. 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. 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: 96.8% (A+ 22.6%|A 74.2%| D 3.2%) LE 2A; GR B Agreement: 87.0% (A+ 21.7%|A 65.2%|A− 8.7%|D 4.3%) 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%)
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)? 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 1B; GR A Agreement: 96.2% (A+ 30.8%|A 65.4%|D 3.8%) LE 3B; GR C Agreement: 100% (A+ 34.6%|A 65.4%)

Question and statement	Level of evidence, grade of recommendation, agreement level, and clarity
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. 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. 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.	LE 3B; GR B Agreement: 88.0% (A+ 24.0%|A 64.0%|A− 12.0%) LE 4; GR D Agreement: 91.3% (A+ 34.8%|A 56.5%|A− 8.7%)
C.2: How should supportive care programs be organized for eoCRC patients? 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).	LE 4; GR C Agreement: 91.3% (A+ 26.1%|A 65.2%|A− 8.7%)

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

Areas of controversy	Issues raised
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
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 posttreatment 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.

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