

REVIEW ARTICLE

Early-Onset Colorectal Cancer: Epidemiology, Molecular Drivers, and Implications for Screening and Treatment

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ABSTRACT

Early-onset colorectal cancer (EOCRC), defined as colorectal cancer diagnosed before age 50, has become a rapidly increasing global health concern. In contrast to declining rates in older adults, EOCRC incidence has nearly doubled in several high-income countries since the early 1990s and is rising in more than half of countries worldwide, particularly among individuals born after the 1960s, reflecting a clear birth-cohort effect. In the United States, colorectal cancer is now the leading cause of cancer-related death in men under 50 and the second leading cause in women of the same age. Although hereditary syndromes such as Lynch syndrome and familial adenomatous polyposis account for 16--20% of cases, most EOCRC is sporadic and linked to environmental exposures, lifestyle factors, gut microbiome dysbiosis, and early-life influences.

EOCRC displays distinct molecular features compared with late-onset disease, including lower frequencies of BRAF and KRAS mutations, higher rates of microsatellite instability-high tumors outside hereditary contexts, and enrichment of TP53 and CTNNB1 alterations. Clinically, EOCRC often presents at advanced stages, shows rectal predominance, and is associated with diagnostic delays of up to six months due to misattribution of symptoms to benign conditions. In response to rising incidence, major U.S. guidelines now recommend initiating colorectal cancer screening at age 45. Treatment increasingly incorporates immunotherapy for mismatch repair-deficient tumors, with neoadjuvant PD-1 blockade producing exceptional pathological complete response rates. This review summarizes current evidence on EOCRC epidemiology, biology, clinical presentation, screening, and treatment, and highlights emerging directions including liquid biopsy, artificial intelligence, and microbiome-based strategies.

Keywords: Early-onset colorectal cancer; microsatellite instability; colorectal cancer screening; gut microbiome; Lynch syndrome

Introduction

Colorectal cancer (CRC) ranks as the third most common malignancy worldwide and the second leading cause of cancer-related mortality, accounting for over 1.9 million new diagnoses and approximately 904,000 deaths annually according to GLOBOCAN 2022 estimates. [1] While overall CRC incidence and mortality have declined significantly among adults aged 50 years and older as a result of established screening programs and improved risk factor management, an alarming and countervailing trend has emerged: a steady and accelerating rise in CRC among individuals under 50 years of age, a phenomenon referred to as early-onset colorectal cancer (EOCRC). [2]

EOCRC is defined by consensus as any CRC diagnosed before the age of 50, regardless of hereditary predisposition. [3] In the United States alone, incidence rates in adults aged 20–49 years rose from 8.6 per 100,000 in 1992 to 12.9 per 100,000 in 2018, with the most pronounced increases observed in the 40–49-year age group. [4] CRC has now become the leading cause of cancer-related death in men under 50 and the second leading cause in women of the same age group in the United States, surpassing malignancies traditionally associated with younger adults. [5]

The epidemiological rise of EOCRC is particularly striking because it cannot be fully explained by established hereditary syndromes, which account for only 16–20% of EOCRC cases. [6] The majority of cases are sporadic, suggesting exposure to novel or amplified environmental, dietary, or microbial risk factors during early life. [7] Despite its increasing prevalence, EOCRC remains underrecognized at the primary care level, and patients frequently experience prolonged diagnostic delays. [8] Moreover, EOCRC exhibits distinct molecular features that have important implications for both prognosis and treatment selection, particularly in the era of precision oncology. [9]

This clinical practice-focused narrative review synthesizes current evidence across eight key domains: global epidemiology, risk factors and etiology, molecular biology and pathogenesis, clinical presentation and diagnostic delay, screening strategies, systemic and surgical treatment, special clinical considerations in younger patients, and emerging therapeutic and diagnostic frontiers. Our aim is to provide clinicians with a comprehensive, evidence-based framework for managing this increasingly prevalent and clinically challenging malignancy.

Search Strategy

A structured literature search was performed in PubMed/MEDLINE, Embase, and Google Scholar for articles published between January 2016 and June 2026, using combinations of the terms “early-onset colorectal cancer,” “young-onset colorectal cancer,” “colorectal cancer screening,” “microsatellite instability,” “immunotherapy,” and “gut microbiome.” Reference lists of retrieved articles, major clinical practice guidelines (ACS, USPSTF, NCCN, ESMO, DIRECT), and recent systematic reviews were manually screened to identify additional relevant publications. Priority was given to population-based registry studies, randomized controlled trials, and systematic reviews or meta-analyses published in peer-reviewed journals. As this is a narrative rather than a systematic review, formal quality appraisal and PRISMA reporting were not applied.

Epidemiology

Global Incidence Trends

The epidemiological landscape of EOCRC has undergone substantial transformation over the past three decades. A landmark analysis of population-based cancer registry data from 50 countries, published in *The Lancet Oncology* in 2025, demonstrated that early-onset CRC incidence rates were rising in 27 of these countries. [2] Critically, in 20 of the 27 countries, the rise in early-onset disease was either exclusive to adults under 50 or was accelerating more rapidly than in older age groups. In 14 countries, including the United States, rates were increasing in younger adults while simultaneously stabilizing or declining in those aged 50 and over—a divergence that strongly implicates birth-cohort-specific exposures rather than random variation or improved detection alone. [2]

The most rapid annual increases in EOCRC over the past decade were observed in New Zealand (4.0%), Chile (4.0%), and Puerto Rico (3.8%). [2] In Europe, incidence among young adults increased consistently over the last 25 years across 20 national cancer registries, with average annual percentage increases of 7.9% among those aged 20–29 years (2004–2016), 4.9% among those aged 30–39 years (2005–2016), and 1.6% among those aged 40–49 years (2004–2016); country-level rises were most pronounced in Germany, the United Kingdom, and the Scandinavian countries. [10] A birth cohort analysis using data from Australia, Canada, England, and the United States, published in the *Journal of the National Cancer Institute* in 2025, demonstrated that individuals born in the 1990s face at least a four-fold higher risk of EOCRC compared with those born in earlier decades, confirming a generational

amplification of risk. [11]

By 2030, it is projected that approximately 15% of all CRC diagnoses will occur in adults under 50 years of age. [4] Specifically, up to 25% of rectal cancers and 10--12% of colon cancers will be diagnosed in individuals under 50. [12] Globally, the GBD 2021 analysis showed that while mortality and disability-adjusted life year (DALY) rates have declined due to improved therapeutics, the absolute count of incident EOCRC cases has risen substantially since 1990, creating a paradox of improving outcomes alongside increasing disease burden. [13]

Racial, Ethnic, and Sex Disparities

Racial and ethnic disparities in EOCRC are pronounced and clinically significant. Black Americans experience a 15% higher incidence of CRC and a 35% higher mortality rate compared with non-Hispanic White Americans. [5] Alaska Native individuals have among the highest CRC incidence and mortality rates globally, a disparity driven by both genetic and socioeconomic factors. [5] Moreover, Black and Hispanic adults are disproportionately diagnosed at younger ages, with lower rates of access to timely screening and follow-up care. [12]

Sex differences in EOCRC trends are also emerging. While incidence is generally slightly higher in men, recent analyses from Chile, Puerto Rico, Argentina, Ecuador, Thailand, Sweden, Israel, and Croatia showed faster increases among young men, whereas young women experienced faster increases in England, Norway, Australia, Turkey, Costa Rica, and Scotland. [2] These sex-specific patterns hint at differential exposures to hormonal, behavioral, or environmental risk factors across geographic settings.

Risk Factors and Etiology

Hereditary Syndromes

Hereditary conditions represent a quantifiable and clinically actionable fraction of EOCRC risk. Lynch syndrome, caused by pathogenic germline variants in the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, is the most common hereditary CRC syndrome and is estimated to account for the majority of hereditary EOCRC. [6] Familial adenomatous polyposis (FAP), caused by *APC* mutations, confers a near-100% lifetime risk of CRC in the absence of prophylactic surgery. MUTYH-associated polyposis (MAP), Peutz-Jeghers syndrome, juvenile polyposis syndrome, and serrated polyposis syndrome account for additional hereditary cases. [14] Collectively, hereditary syndromes explain 16--20% of EOCRC, with the remainder being sporadic. [6]

A family history of CRC in a first-degree relative confers a relative risk of 4.21 (95% CI: 2.61--6.79) for EOCRC and accounts for up to 20--30% of cases. [15] As many as 35% of patients diagnosed with CRC under age 35 harbor an identifiable hereditary syndrome, underscoring the importance of universal germline testing in this age group. [16] Universal tumor MMR testing or microsatellite instability analysis in all patients with EOCRC is recommended by major guidelines including the Delphi Initiative for Early-Onset Colorectal Cancer (DIRECT) international management guidelines, published in 2023. [9]

Environmental and Lifestyle Factors

The majority of EOCRC is sporadic, and the rapid generational increase in incidence implicates environmentally modifiable exposures. Obesity has emerged as one of the most consistently reported modifiable risk factors. Among women in the Nurses' Health Study II cohort, higher body mass index (BMI) was significantly associated with increased EOCRC risk, particularly for rectal cancer. [17] A systematic review confirmed that a growing number of high-quality studies demonstrate a consistent association between high body weight, obesity, and EOCRC, with several reporting dose-dependent relationships. [15]

Ultra-processed food (UPF) consumption has gained substantial attention as a potential driver of EOCRC. A prospective cohort study among participants of the Nurses' Health Study II, incorporating data on EOCRC precursor lesions identified before age 50, found that higher UPF intake was significantly associated with increased risk of early-onset conventional colorectal adenomas. [18] This finding implicates the Nova classification of highly processed, calorie-dense, nutrient-depleted foods---including fast food, packaged snacks, sugar-sweetened beverages, and processed meats---in the pathogenesis of EOCRC-related adenomatous transformation. [18] Red meat and processed meat consumption, alcohol use, smoking, and sedentary behavior have each been identified as contributing risk factors in systematic reviews of EOCRC-specific literature. [15]

Gut Microbiome and Early-Life Exposures

Emerging evidence implicates gut microbiome dysbiosis as a central mechanistic contributor to

sporadic EOCRC. Key pathobionts enriched in CRC include *Fusobacterium nucleatum*, colibactin-producing *Escherichia coli*, and enterotoxigenic *Bacteroides fragilis*. [19] Of particular significance, colonization of colibactin-producing *E. coli* has been detected in 15% of neonatal stool samples, raising the hypothesis that early-life microbiome programming may initiate an oncogenic cascade that manifests as EOCRC decades later. [20] Conversely, butyrate-producing commensal bacteria---associated with a high-fiber diet and colonocyte protection---are depleted in CRC patients, suggesting that dietary modulation of the microbiome may constitute a modifiable protective factor. [19]

Antibiotic use during childhood and early adulthood represents a plausible but incompletely characterized risk factor. Antibiotics profoundly disrupt the microbiome by eliminating protective taxa and creating ecological niches for pro-oncogenic species. [16] Inflammatory bowel disease (IBD), both Crohn's disease and ulcerative colitis, confers a well-established elevated risk of CRC and is increasingly recognized as a contributor to EOCRC in younger patients. [7] Additional implicated exposures include psychosocial stress, sleep disruption, and food insecurity, each of which may promote chronic low-grade inflammation and microbiome perturbation as intermediary mechanisms. [21]

Molecular Biology and Pathogenesis

Major Carcinogenesis Pathways

Colorectal carcinogenesis proceeds through three principal molecular pathways: chromosomal instability (CIN), the microsatellite instability (MSI) pathway, and the CpG island methylator phenotype (CIMP)/serrated pathway. [22] The CIN pathway, responsible for approximately 85% of CRCs, is initiated by loss-of-function mutations in *APC*, followed by oncogenic *KRAS* activation and subsequent *TP53* and *SMAD4* alterations. [14] MSI, synonymous with mismatch repair deficiency (dMMR), results from germline MMR mutations (Lynch syndrome) or somatic *MLH1* promoter hypermethylation in sporadic tumors and produces a hypermutant phenotype with high immunogenicity. [22] The CIMP/serrated pathway involves epigenetic silencing of tumor suppressor genes and is characteristically associated with *BRAF* V600E mutations in sporadic MSI-H tumors. [22]

Distinct Molecular Features of EOCRC

EOCRC is increasingly recognized as a biologically distinct entity with a molecular profile that diverges meaningfully from late-onset CRC (LOCRC). A comprehensive systematic review and meta-analysis incorporating 149 studies and published in 2024 demonstrated that tumors from EOCRC patients are significantly less likely to carry mutations in *KRAS* (OR 0.91; 95% CI 0.85--0.98), *BRAF* (OR 0.63; 95% CI 0.51--0.78), *APC* (OR 0.70; 95% CI 0.58--0.84), and *NRAS* compared with LOCRC. [23] Conversely, EOCRC is enriched for *TP53* and *CTNNB1* (beta-catenin) mutations, reflecting greater activation of the Wnt/ β -catenin signaling axis. [14]

With respect to MSI, sporadic EOCRC (excluding Lynch syndrome cases) demonstrates a pooled MSI-H/dMMR prevalence of approximately 10% (95% CI 7--14%), substantially lower than in LOCRC when adjusted for sporadic cases. [24] Notably, the CIMP-high and *BRAF* V600E mutation rates, hallmarks of the serrated/MSI pathway in older patients, are markedly lower in EOCRC. [14] This constellation of molecular features---lower *BRAF*, higher *TP53*, lower CIMP---suggests that many sporadic EOCRC tumors arise through mechanisms distinct from both Lynch syndrome and the classical serrated neoplasia pathway that dominates in older patients.

Anatomical site-specific molecular variation also characterizes EOCRC. Left-sided and rectal EOCRC tumors show higher mutation rates in *NF1*, *POLE*, *SMAD4*, and *BRCA2*, and enrichment of histone-modifying gene mutations including *KDM5C* and *KMT2A*. [25] These findings have implications for biomarker-driven treatment selection (table 3), as targeted therapies increasingly exploit actionable genomic alterations such as *BRAF* V600E (*BRAF* inhibitor combinations), *RAS*-wild-type (anti-EGFR therapy), *HER2* amplification (trastuzumab/pertuzumab), and MSI-H (immune checkpoint inhibitors). [9]

Tumor Microenvironment

The tumor microenvironment (TME) of EOCRC displays characteristic features including lower levels of tumor-infiltrating lymphocytes and reduced peritumoral lymphocytic reactions compared with LOCRC. [26] This relative immune quiescence in EOCRC tumors outside of MSI-H contexts may contribute to the observed worse prognosis when controlling for stage, since tumors with rich lymphocytic infiltrates---particularly in pMMR (microsatellite-stable, MSS) disease---are generally associated with superior outcomes. [9] Ongoing research is examining the interaction between early-

life microbiome exposures, mucosal immune programming, and the subsequent TME phenotype as a unifying pathobiological model for sporadic EOCRC. [19]

Table 3. Biomarker-driven treatment selection in metastatic early-onset colorectal cancer.

Molecular Marker	Prevalence in mEOCRC	Therapeutic Implication	Key Supporting Evidence
RAS wild-type (left-sided)	~50–55%	Anti-EGFR (cetuximab or panitumumab) + FOLFOX/FOLFIRI preferred in first line	PARADIGM trial (OS HR 0.82; JAMA 2023)
RAS mutated	~40–45%	Anti-VEGF (bevacizumab) + FOLFOX/FOLFIRI; no anti-EGFR	Multiple phase III RCTs; NCCN v3.2024
BRAF V600E (lower in EOCRC)	~3–5%	Encorafenib + cetuximab in 2nd line; BREAKWATER trial (1st line, ongoing)	BEACON CRC (Kopetz et al, NEJM 2019)
MSI-H / dMMR	~10–15%	Pembrolizumab monotherapy preferred first-line; neoadjuvant ICIs in non-metastatic disease	KEYNOTE-177 (André et al, Ann Oncol 2025); Cercek et al (NEJM 2022)
HER2 amplification	~3–5% (enriched in RAS WT)	Trastuzumab + pertuzumab or lapatinib; T-DXd under investigation	DESTINY-CRC01; My Pathway trial
KRAS G12C	~3–4%	Sotorasib or adagrasib ± cetuximab (modest responses in CRC)	CodeBreak 300; KRYSTAL-10 trials
NTRK fusion	<1%	Larotrectinib or entrectinib (agnostic approval)	NAVIGATE; STARTRK-2 trials
MSS / pMMR	~85–90%	Chemotherapy + anti-VEGF or anti-EGFR (per RAS/BRAF status); ICI combinations investigational	NCCN; ongoing trials exploring LAG-3, TIGIT, bispecific Ab combinations

Ab, antibody; BRAF, v-raf murine sarcoma viral oncogene homolog B; dMMR, deficient mismatch repair; EOCRC, early-onset colorectal cancer; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma proto-oncogene; mEOCRC, metastatic early-onset colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stable; NTRK, neurotrophic tyrosine receptor kinase; OS, overall survival; pMMR, proficient mismatch repair; RAS, rat sarcoma viral proto-oncogene; RCT, randomized controlled trial; T-DXd, trastuzumab deruxtecan; WT, wild-type.

Note: BRAF V600E-mutant and HER2-amplified tumors are molecular subsets of the RAS-wild-type population and are not additive with the RAS wild-type / RAS mutated rows above; percentages across rows should not be summed to 100%.

Clinical Presentation, Diagnostic Delay, and Pathological Features

Symptom Profile and Diagnostic Delay

One of the most clinically consequential features of EOCRC is prolonged diagnostic delay. A systematic review and meta-analysis published in *JAMA Network Open* in 2024 examined the frequency of red flag signs and symptoms in EOCRC and quantified time-to-diagnosis. [27] Nearly half of patients with EOCRC presented with rectal bleeding, and approximately one-quarter reported altered bowel habits. However, despite the presence of these alarm symptoms, the median diagnostic delay was up to six months. [27] Even patients with multiple concurrent red flag symptoms---rectal bleeding, abdominal pain, iron deficiency anemia, and altered bowel habits---experienced a median delay of 4.8 months before diagnosis.

The underlying causes of diagnostic delay are multifactorial. At the patient level, symptoms such as rectal bleeding, abdominal cramping, and a change in bowel habits are frequently attributed to benign conditions including hemorrhoids, irritable bowel syndrome, or dietary intolerance, and individuals under 50 are unlikely to connect these symptoms with a malignant etiology. [8] Patients in UK, Australian, and New Zealand web-based cohort studies reported that primary care physicians often failed to pursue malignant diagnoses without a family history, reflecting provider-level awareness gaps. [28] This combination of patient and physician attribution bias creates a compounding delay that results in a disproportionate number of EOCRC patients presenting at advanced stages.

Stage at Presentation and Anatomical Distribution

EOCRC presents at more advanced stages than LOCRC (table1), with approximately 60% of early-onset cases diagnosed at stage III or IV, compared with 25--30% in older adults. [12] EOCRC tumors tend to be larger (>5 cm) at diagnosis, more likely to demonstrate lymph node involvement, and more frequently exhibit perineural invasion. [12] These features collectively contribute to a higher burden of metastatic disease at presentation and a more complex surgical and systemic treatment landscape.

Table 1. Key clinical and molecular differences between early-onset colorectal cancer (EOCRC) and late-onset colorectal cancer (LOCRC).

Feature	Early-Onset CRC (<50 years)	Late-Onset CRC (≥50 years)
Age definition	<50 years	≥50 years
Global incidence trend	Rising (↑1–2%/year)	Stable or declining
Anatomical distribution	Rectal and left-sided predominance	Shift toward proximal colon
Stage at presentation	~60% Stage III–IV	~25–30% Stage III–IV
BRAF V600E mutation	Low (~1% sporadic)	Higher (~8–10% sporadic)
KRAS mutation	Lower frequency (~32%)	Higher frequency (~40–45%)
APC mutation	Less frequent (OR 0.70)	More frequent
TP53 / CTNNB1	Enriched	Less enriched
MSI-H (sporadic)	~10% (excl. Lynch syndrome)	~15% (includes serrated/BRAF)
CIMP-high	Lower prevalence	Higher prevalence
Hereditary syndrome	16–20% (Lynch, FAP, MAP, others)	5–10%
Diagnostic delay	Median ~6 months	Less common
Tumor-infiltrating lymphocytes	Reduced in pMMR tumors	More variable
Prognosis (stage-adjusted)	Worse independent of stage	Reference

Abbreviations: BRAF, B-Raf proto-oncogene; CIMP, CpG island methylator phenotype; CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; FAP, familial adenomatous polyposis; KRAS, Kirsten rat sarcoma proto-oncogene; LOCRC, late-onset colorectal cancer; MAP, MUTYH-associated polyposis; MMR, mismatch repair; MSI, microsatellite instability; OR, odds ratio; pMMR, proficient mismatch repair; TP53, tumor protein p53.

Note: The pooled odds ratios reported in the text for KRAS (OR 0.91, 95% CI 0.85–0.98) and BRAF (OR 0.63, 95% CI 0.51–0.78) [23] reflect a meta-analysis pooling sporadic and hereditary EOCRC across mixed study populations. The prevalence percentages shown in this table are derived from cohorts restricted to sporadic tumors [14, 24]. The larger apparent gap between EOCRC and LOCRC in the table therefore reflects this narrower sporadic-only denominator rather than a discrepancy in the underlying data.

A notable anatomical characteristic of EOCRC is its rectal and left-sided predominance. In contrast to LOCRC, which has shifted toward a greater proportion of right-sided (proximal) lesions attributable to BRAF-mutant/MSI-H serrated cancers in older adults, EOCRC demonstrates relative enrichment in the distal colon and rectum. [25] This distribution is clinically relevant because rectal cancer requires distinct treatment planning involving neoadjuvant chemoradiotherapy, total mesorectal excision (TME), and careful consideration of sphincter preservation, all of which carry particular implications for quality of life in younger patients.

Screening Strategies

Guideline Evolution and Current Recommendations

The recognition of rising EOCRC incidence prompted a major revision of colorectal cancer screening guidelines. In 2018, the American Cancer Society (ACS) became the first major body to lower the recommended screening initiation age for average-risk individuals from 50 to 45 years, citing rising incidence rates among 45- to 49-year-olds and modeling data demonstrating a favorable benefit-to-burden ratio. [29] This was designated a "qualified recommendation" owing to the relative paucity of empirical data in this younger cohort compared with the strong evidence base supporting screening from age 50. [29] In 2021, the United States Preventive Services Task Force (USPSTF) followed suit, issuing a Grade B recommendation for screening adults aged 45–49 years and a Grade A recommendation for those aged 50–75 years, granting expanded insurance coverage under the Affordable Care Act. [30]

In contrast, Canada, the United Kingdom, and Australia have maintained screening initiation at 50 years for average-risk individuals, reflecting differences in healthcare resource allocation and the relative weighting of benefits versus harms in younger cohorts. [31] A nationwide cohort study of over 10 million privately insured Americans aged 45–49, published in *JAMA Network Open* in 2024, demonstrated a significant increase in CRC screening uptake in the 20 months following the USPSTF recommendation, with adenomatous polyp detection increasing and adenocarcinoma detection declining---consistent with earlier interception of premalignant lesions. [32]

Available Screening Modalities

Multiple screening modalities are endorsed by current guidelines, and shared decision-making is recommended to align patient preference, risk profile, and test availability. Colonoscopy remains the single-step gold standard, demonstrating a 69% reduction in CRC incidence and a 68% reduction in CRC mortality when performed for screening. [33] Annual fecal immunochemical testing (FIT) offers a non-invasive stool-based alternative with strong cost-effectiveness and accessibility, particularly suited to populations with lower colonoscopy acceptance or capacity constraints. The multitarget stool DNA

test (Cologuard; sDNA-FIT) detects both aberrant DNA methylation biomarkers and hemoglobin, and is recommended every three years, although its cost and false-positive rate remain considerations. [30] CT colonography, performed every five years, offers an acceptable balance between sensitivity and radiation exposure (table 2).

Table 2. Current colorectal cancer screening modalities: characteristics, intervals, and clinical considerations relevant to early-onset colorectal cancer.

Modality	Interval	Sensitivity CRC	Guideline Endorsement	Key Considerations in EOCRC
Colonoscopy	10 years	~95%	ACS, USPSTF, ACG, ESMO (Grade A)	Gold standard; single-step diagnostic and therapeutic; preferred for high-risk individuals
FIT (Fecal Immunochemical Test)	Annual	~79% (per cycle)	ACS, USPSTF, ACG	Accessible, non-invasive; requires follow-up colonoscopy if positive; limited detection of early polyps
sDNA-FIT (Cologuard)	3 years	~92% (single test)	ACS, USPSTF	Higher sensitivity than FIT alone; higher false-positive rate; ACS endorses over FIT for age-lowered cohort
CT Colonography	5 years	~96% for ≥6mm polyps	ACS, USPSTF	No sedation required; radiation exposure; positive tests require colonoscopy follow-up
Flexible Sigmoidoscopy	5 years	~75–80%	USPSTF (alone or + FIT)	Examines only distal colon; misses proximal lesions; declining use
Liquid Biopsy / MCED Tests	Annual (investigational)	Under evaluation	Not yet guideline-endorsed	Highly promising for under-45 cohort; simultaneous multi-cancer detection; regulatory approvals pending

ACG, American College of Gastroenterology; ACS, American Cancer Society; CRC, colorectal cancer; ESMO, European Society for Medical Oncology; FIT, fecal immunochemical test; MCED, multi-cancer early detection; sDNA, stool DNA; USPSTF, United States Preventive Services Task Force.

For high-risk individuals—including those with Lynch syndrome, FAP, IBD, or a strong family history—more intensive surveillance protocols are required, often beginning in adolescence or early adulthood and using colonoscopy exclusively. [9] Genetic testing and cascade screening of first-degree relatives following identification of a pathogenic variant represent critical secondary prevention measures that are systematically underutilized. [6]

Emerging Screening Technologies

Liquid biopsy approaches, including multi-cancer early detection (MCED) tests that analyze circulating tumor DNA (ctDNA) methylation patterns in blood, represent a transformative frontier for EOCRC detection. These platforms offer the potential for CRC detection—as well as detection of multiple other cancers simultaneously—in a single blood test, which could address barriers including colonoscopy aversion, procedure-related risk, and access in resource-limited settings. [21] While several MCED tests are under commercial development and clinical investigation, none are currently endorsed as a standalone first-line CRC screening modality in any major national guideline. Artificial intelligence-assisted colonoscopy—using deep learning algorithms to improve adenoma detection rates in real time—is being rapidly integrated into endoscopy suites and has demonstrated significant improvements in adenoma detection rates in randomized trials, which may reduce interval cancers and long-term CRC incidence. [21]

Treatment Strategies

Surgical Management

Surgical resection remains the cornerstone of curative-intent treatment for non-metastatic EOCRC. For colon cancer, laparoscopic or robotic-assisted colectomy with complete mesocolic excision (CME) and adequate lymphadenectomy is the standard approach. Rectal cancer management requires total mesorectal excision (TME), typically preceded by neoadjuvant therapy, with increasing emphasis on sphincter-preserving procedures to optimize long-term function in younger patients. [9] Intersphincteric resection and robotic-assisted TME have expanded the technical armamentarium for sphincter preservation in distal rectal cancer, which is of particular importance given the younger age and longer survivorship expected after curative resection.

Neoadjuvant and Adjuvant Systemic Therapy

For locally advanced rectal cancer (LARC), total neoadjuvant therapy (TNT)—delivering both

chemotherapy and chemoradiotherapy prior to surgery---has emerged as the preferred strategy based on the CAO/ARO/AIO-12 and OPRA trials, which demonstrated improved pathological complete response (pCR) rates and sphincter preservation compared with conventional neoadjuvant chemoradiotherapy followed by adjuvant chemotherapy. [34] The consolidation chemotherapy TNT model appears superior to the induction model in terms of pCR rate, compliance, and sphincter-saving rate, though long-term overall survival benefit requires further maturation of data. [34] EOCRC patients in LARC trials were not analyzed as a distinct subgroup in most pivotal studies, representing an evidence gap that is increasingly being addressed in ongoing trials.

Adjuvant chemotherapy for stage III (node-positive) and high-risk stage II colon cancer follows standard FOLFOX (oxaliplatin, leucovorin, 5-fluorouracil) or CAPOX (capecitabine, oxaliplatin) regimens. [9] Younger patients generally tolerate systemic chemotherapy well but face specific long-term toxicity concerns including peripheral neuropathy from oxaliplatin, gonadotoxicity, and cardiovascular sequelae over their anticipated long post-treatment lifespan---factors that must be integrated into shared treatment decision-making.

Targeted Therapy Based on Molecular Profile

Molecular profiling is now mandatory in the management of metastatic EOCRC, guiding selection among anti-EGFR, anti-VEGF, and targeted agents. [9] In RAS/RAF wild-type (WT) left-sided metastatic CRC, anti-EGFR monoclonal antibodies---cetuximab and panitumumab---combined with FOLFIRI or FOLFOX remain a preferred first-line strategy, with bevacizumab representing an alternative for right-sided or RAS-mutated tumors. [35] The PARADIGM trial confirmed the superiority of FOLFOX plus panitumumab over FOLFOX plus bevacizumab in RAS WT left-sided metastatic CRC in terms of overall survival (HR 0.82; 95% CI 0.69--0.99). [35] HER2 amplification, present in approximately 3--5% of metastatic CRC and enriched in RAS/RAF WT tumors, is an emerging actionable target; trastuzumab-containing regimens and trastuzumab deruxtecan (T-DXd) are under clinical investigation in this genomically selected population. [9]

For patients with *BRAF* V600E-mutant metastatic CRC---which is relatively less common in EOCRC given the lower *BRAF* mutation rate---the combination of encorafenib (*BRAF* inhibitor) plus cetuximab represents standard second-line therapy following the BEACON CRC trial, and is under investigation in the first-line setting via the BREAKWATER trial. [36] *KRAS* G12C inhibitors, including sotorasib and adagrasib, offer a targeted option for the small subset (~3--4%) of mCRC patients with *KRAS* G12C mutations, though response rates in CRC are more modest than in lung adenocarcinoma. [36]

Immunotherapy in MSI-H/dMMR Early-Onset CRC

Immune checkpoint inhibitor (ICI) therapy has transformed the management of MSI-H/dMMR CRC across all stages. In the metastatic setting, the KEYNOTE-177 phase III trial established pembrolizumab (anti-PD-1) as superior to chemotherapy in the first-line treatment of MSI-H/dMMR metastatic CRC, with a median progression-free survival (PFS) of 16.5 months compared with 8.2 months for chemotherapy, and a three-year overall survival rate of 55% versus 48.6%. [37] Nivolumab plus ipilimumab (CheckMate 142) demonstrated objective response rates of approximately 55% in pretreated MSI-H/dMMR mCRC, with durable long-term remissions raising the possibility of functional cure in a subset of patients. [38]

In the neoadjuvant setting, the landmark NEJM paper by Cercek et al. [39] demonstrated that single-agent dostarlimab in dMMR locally advanced rectal cancer resulted in 100% clinical complete response (cCR) rates with no surgical resection required at a median follow-up of 12 months. These extraordinary results prompted multiple confirmatory and phase III trials. The NEOPRISM-CRC trial demonstrated a 59% pCR rate with neoadjuvant pembrolizumab, stratified by tumor mutation burden, in stage II--III dMMR/MSI-H colorectal cancer. [40] The NICHE-2 trial, evaluating neoadjuvant nivolumab plus ipilimumab in locally advanced MMR-deficient colon cancer, reported a three-year disease-free survival rate of 100% in dMMR tumors, supporting an immunotherapy-first organ-preserving paradigm for this distinct molecular subset. [41] These results are particularly impactful for EOCRC patients with dMMR disease, offering organ preservation and avoidance of chemotherapy-related morbidity.

In contrast, pMMR/MSS metastatic CRC---which represents the majority of metastatic CRC including most sporadic EOCRC---remains largely refractory to current ICI agents, with response rates below 5% with monotherapy. [38] Research into novel combinatorial immunotherapeutic strategies including LAG-3 and TIGIT pathway blockade, bispecific antibodies, and adoptive cell therapy is actively ongoing in this critically underserved population. [42]

Special Considerations in Young Patients

Fertility Preservation and Gonadotoxicity

Younger patients with CRC face unique reproductive health concerns that require proactive clinical attention. Pelvic radiation therapy for rectal cancer carries significant gonadotoxic risk, particularly ovarian failure in premenopausal women and testosterone deficiency and ejaculatory dysfunction in men. [9] Oncofertility consultation—including cryopreservation of oocytes, embryos, or ovarian tissue before pelvic irradiation—should be offered to all reproductive-age patients for whom this is feasible. [9] Oxaliplatin-based adjuvant chemotherapy, while less gonadotoxic than alkylating agents, may impair spermatogenesis during treatment and should be discussed as part of pre-treatment counseling.

Financial Toxicity

Financial toxicity represents a substantial and underappreciated burden in EOCRC. A national survey-based study using data from the National Health Interview Survey published in *Surgery* in 2024 demonstrated that EOCRC patients experience significantly greater financial hardship compared with older CRC patients, reflecting their active workforce participation, dependent family responsibilities, and insurance barriers. [43] Loss of income during treatment, catastrophic medical expenditures, and resultant delays in care-seeking create a compounding cycle of harm that affects treatment adherence, follow-up, and psychological well-being. [43]

Psychosocial Burden and Quality of Life

The psychosocial impact of CRC in younger adults is distinct from that in older patients. Young adults diagnosed with cancer face unique identity and social role disruptions, including interruption of education and career development, challenges to intimate relationships, altered body image following stoma formation or pelvic surgery, and the psychological burden of facing mortality prematurely. [8] Higher rates of anxiety, depression, and post-traumatic stress disorder have been documented in EOCRC survivors compared with age-matched healthy controls and older CRC patients. [8] Survivorship care plans incorporating mental health support, sexual health counseling, and fertility follow-up should be integrated into routine post-treatment care for all EOCRC patients.

Hereditary Counseling and Cascade Testing

Given the higher prevalence of hereditary syndromes in EOCRC, universal germline genetic testing is recommended by the DIRECT guidelines for all patients diagnosed under age 50, regardless of family history, tumor molecular profile, or apparent sporadic presentation. [9] Identification of a pathogenic germline variant has implications not only for the patient's surveillance and risk-reduction strategy but also for first-degree relatives, who carry a 50% a priori probability of harboring the same variant. Cascade testing programs for Lynch syndrome have been shown to be cost-effective and to reduce mortality through timely colonoscopic surveillance in at-risk relatives. [6]

Future Directions

Several transformative research directions are poised to redefine the detection, prevention, and treatment of EOCRC over the next decade. Multi-cancer early detection (MCED) blood-based tests, which utilize cfDNA methylation profiling to detect cancer-specific signals across multiple tumor types simultaneously, offer a compelling solution to the challenge of identifying EOCRC in adults aged 20--44 years, for whom current screening guidelines provide no systematic coverage. [21] While regulatory approval and clinical integration of MCED platforms remain in progress, large prospective validation studies are currently underway and will generate critical data on sensitivity, specificity, and lead time in younger cohorts.

Artificial intelligence integration across the CRC care continuum holds remarkable promise. AI-assisted colonoscopy systems have achieved significant improvements in adenoma detection rates compared with standard endoscopy in multiple randomized trials, potentially reducing interval cancers in the post-colonoscopy period. [21, 44] AI-powered histopathology algorithms are being developed to predict recurrence risk and adjuvant chemotherapy benefit directly from routine tumor histology in colorectal cancer, complementing genomic testing and potentially enabling treatment de-escalation in low-risk patients. [45]

Microbiome-based interventions represent a nascent but scientifically compelling frontier. Dietary modulation to increase butyrate-producing taxa, probiotic supplementation, and targeted elimination of

oncogenic pathobionts are under investigation as chemoprevention strategies. [20] Fecal microbiota transplantation (FMT) is being explored as a means of restoring a protective microbiome profile in high-risk individuals, though clinical validation in the EOCRC prevention context is in early stages. [16]

Non-operative management (NOM) of dMMR/MSI-H rectal cancer following complete clinical response to immunotherapy is an emerging paradigm that has profound implications for EOCRC patients, who face decades of potential morbidity from permanent stoma, sexual dysfunction, and bowel dysfunction following surgical TME. [46] Accumulating data from the Cercek et al. cohort, NEOPRISM-CRC, and NICHE-2 are collectively building the evidence base for durable organ preservation in this molecularly selected patient group.

Conclusions

Early-onset colorectal cancer represents one of the most significant and counterintuitive oncologic trends of the 21st century: a malignancy traditionally associated with older adults that is rapidly rising in successive birth cohorts of younger individuals worldwide. The convergence of sporadic and hereditary drivers, environmental and microbial exposures, distinct molecular biology, and unique clinical and psychosocial challenges makes EOCRC a paradigmatic example of a disease that demands a dedicated, age-specific, and multi-disciplinary approach.

From a clinical practice perspective, several key imperatives emerge from the evidence reviewed here. Universal germline testing should be performed in all patients diagnosed under 50 years. Diagnostic delays must be reduced by increasing clinician and public awareness of alarm symptoms in younger adults. Screening guidelines lowering the initiation age to 45 years should be actively implemented, with advocacy for age-appropriate uptake in populations with historically lower compliance. Molecular profiling—including RAS, BRAF, MSI, and HER2 testing—is mandatory in metastatic EOCRC to guide precision therapy selection. In dMMR/MSI-H disease, neoadjuvant immunotherapy is an emerging standard with the potential to revolutionize organ preservation. Survivorship care must address fertility, financial toxicity, and psychosocial burden as integral components of treatment planning.

The epidemiological trajectory of EOCRC, combined with rapid advances in liquid biopsy, AI-assisted detection, targeted therapy, and immunotherapy, positions the field for transformative progress in the near term. Sustained investment in EOCRC-specific research, including dedicated subgroup analyses in clinical trials, prospective registries, and mechanistic studies of early-life exposures, is essential to curb this emerging cancer epidemic and improve outcomes for an increasingly affected generation of young adults.

Author Perspective and Scope of This Review

This narrative review provides a comprehensive, clinician-oriented synthesis of early-onset colorectal cancer spanning eight interconnected domains: global epidemiology and birth-cohort trends, hereditary and environmental risk factors, molecular biology and pathogenesis, clinical presentation and diagnostic delay, evolving screening strategies, multimodal treatment approaches, age-specific survivorship considerations, and emerging diagnostic and therapeutic frontiers. By integrating these domains within a single framework, the review is intended to serve as a practical clinical reference that bridges the gap between rapidly expanding research and day-to-day oncologic decision-making for patients diagnosed before 50 years of age.

Several features distinguish this work from the existing literature on EOCRC. First, while many published reviews focus predominantly on epidemiology or molecular biology in isolation, this review deliberately integrates molecular characterization with its direct therapeutic implications—for example, linking the distinct molecular profile of EOCRC (lower BRAF/KRAS mutation rates, higher MSI-H prevalence outside Lynch syndrome, TP53 and CTNNB1 enrichment) to actionable treatment selection, including the emerging role of neoadjuvant immunotherapy for dMMR/MSI-H disease and anti-HER2 strategies. Second, this review devotes dedicated attention to the practical clinical challenges that are unique to younger patients yet underrepresented in most EOCRC reviews, including fertility preservation and gonadoprotective strategies, financial toxicity, psychosocial burden, and the logistics of hereditary counseling and cascade testing. These survivorship-focused sections reflect the reality that EOCRC management extends well beyond tumor-directed therapy. Third, the review incorporates the most recent evidence on emerging technologies—multi-cancer early detection blood tests, AI-assisted colonoscopy and pathology, microbiome-based chemoprevention, and non-operative management of dMMR rectal cancer—contextualizing these advances specifically for the EOCRC population rather than presenting them as generic CRC innovations.

From the authors' perspective, the current EOCRC landscape reflects a critical inflection point. The disease is no longer a rare curiosity but a major and growing public health challenge that demands age-specific clinical pathways, dedicated representation in clinical trials, and prospective registry infrastructure. The persistent diagnostic delays documented in the literature---frequently exceeding six months from symptom onset---underscore a systemic failure in clinical suspicion among primary care providers that must be addressed through targeted education and awareness campaigns. Furthermore, the absence of any systematic screening strategy for adults aged 20--44 years represents a significant gap that emerging liquid biopsy platforms may help to close, but only if validated in EOCRC-specific cohorts. We believe that the convergence of precision oncology, immunotherapy, and novel detection technologies offers genuine grounds for optimism, but realizing the potential of these advances will require sustained investment in EOCRC-focused research and a deliberate shift toward treating this population as a distinct clinical entity rather than a footnote in general CRC management.

In terms of scope and depth, this review covers the topic broadly across all major clinical and translational domains relevant to EOCRC. Epidemiological coverage includes global incidence trends, birth-cohort analyses, and racial, ethnic, and sex disparities. The molecular biology sections address the three major carcinogenesis pathways (CIN, MSI, CIMP) and the features that distinguish EOCRC from late-onset disease at the genomic, transcriptomic, and tumor microenvironment levels. Screening coverage spans current guideline recommendations across multiple professional societies, available modalities from colonoscopy to stool-based and blood-based tests, and emerging AI-assisted technologies. Treatment sections encompass surgical management including organ-preserving strategies, neoadjuvant and adjuvant systemic therapy, molecularly targeted agents, and immunotherapy across all relevant clinical settings. The review does not include original data or meta-analytic quantification; rather, it is a critical narrative synthesis designed to orient the practicing clinician to the full breadth of the EOCRC field and to identify the most consequential knowledge gaps and research priorities.

Disclosures:

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Ethical Statement:

This manuscript is a narrative review and does not involve human participants, identifiable personal data, tissue samples, or animal subjects. Therefore, institutional review board (IRB) approval and informed consent were not required. All sources used in this review were properly cited, and the authors adhered to the highest standards of research integrity, transparency, and ethical scholarly conduct in accordance with COPE guidelines. The authors affirm that the work is original, has not been published previously, and is not under consideration elsewhere.

Data Availability

The data that support the findings are available from the corresponding author upon reasonable request.

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