

Understanding Early-Onset Colorectal Cancer

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Disclosures

Consultant/Advisory: Merus, Deciphera, SpringWorks Therapeutics, Ipsen, Exelixis

Objectives

Definitions and Epidemiology

Established and emerging risk factors

Diagnosis

Molecular biology and hereditary syndromes

Screening, treatment, and survivorship

Role of dedicated EOCRC centers

Why this matters

Globally, CRC ranks third in cancer incidence and second in cancer deaths.

CRC is now the leading cause of cancer death in US adults younger than 50, both sexes combined.

The rising burden makes timely diagnosis and access to care urgent.

Defining early-onset CRC

Early-onset CRC (EOCRC): diagnosed **before age 50**. Late-onset CRC (LOCRC): diagnosed at age 50 or older.

The age-50 cutoff reflects historical screening practice, **not a biological boundary**.

Risk rises continuously with age; EOCRC spans a spectrum of disease.

CRC is shifting to younger adults

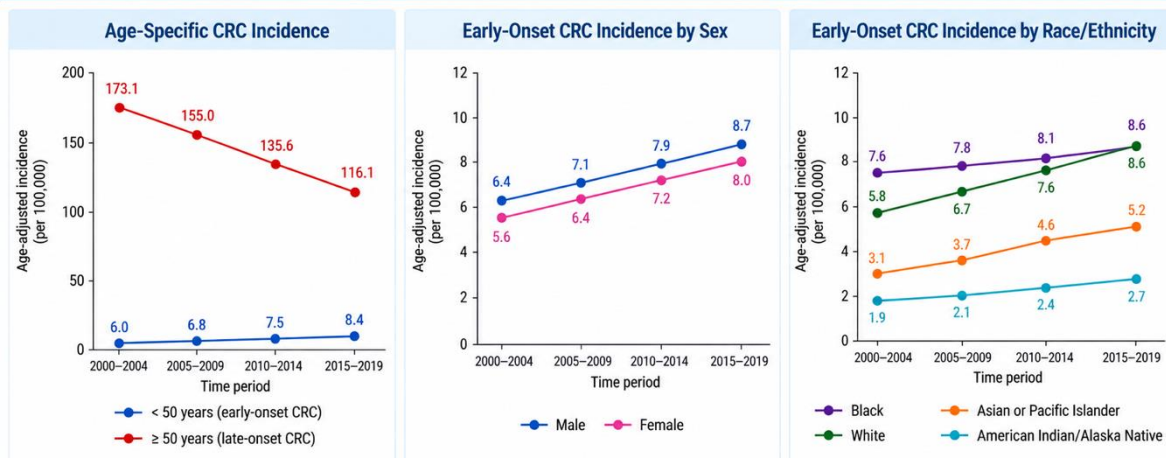
Long-term declines in older adults can obscure rising incidence in younger adults.

US incidence rose ~3% annually at ages 20–49 during 2013–2022.

In the same period, incidence fell ~2.5% annually at ages 65 and older.

US incidence is rising

Incidence of early-onset colorectal cancer in the United States: A population-based analysis (2000–2019).

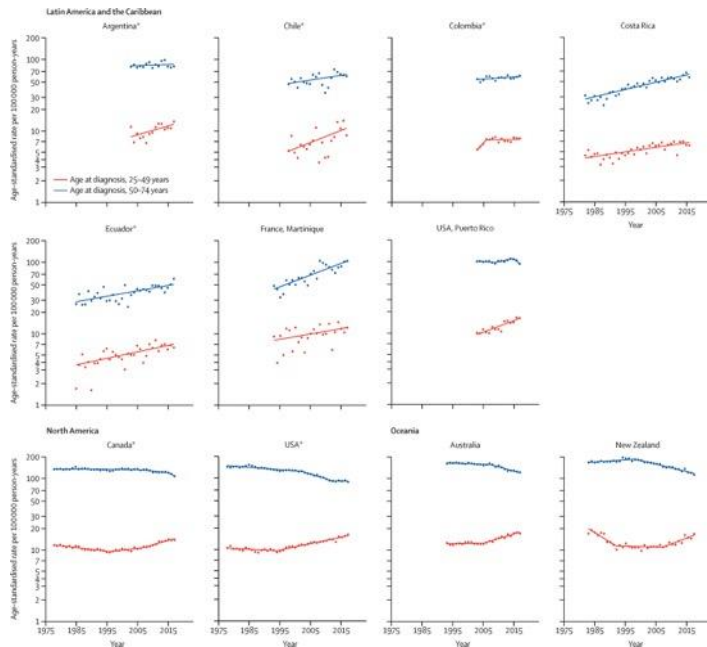


Note: Incidence rates are age-adjusted per 100,000 population.
Source: SEER, 2000–2019.

~**40%** increase in US incidence (2000–2019).

The rise predates screening at 45. Recent diagnosis rates also reflect changing screening uptake.

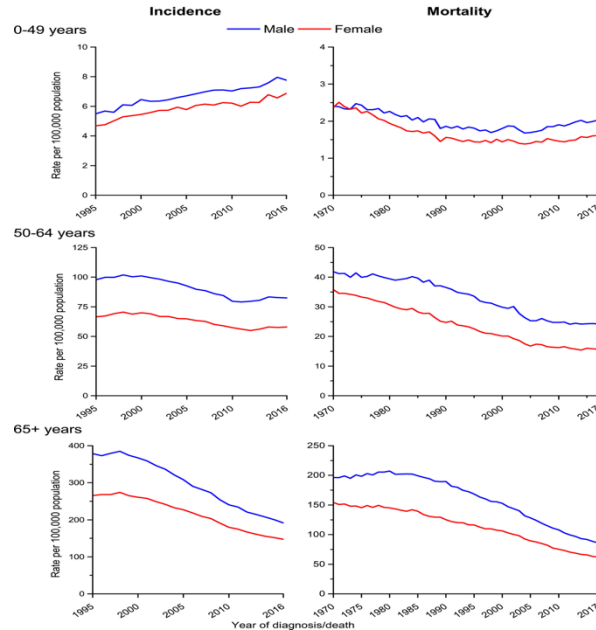
A global rise in incidence



First observed in high-income countries:
Australia, New Zealand, the US, and
South Korea.

Now rising across Latin America, the
Caribbean, Asia, and Eastern Europe.

Mortality is also rising



Colon cancer mortality is increasing in adults younger than 50.

Earlier detection alone does not explain the rise in incidence.

Age, period, and birth cohort

Age effect: risk changes as a person grows older.

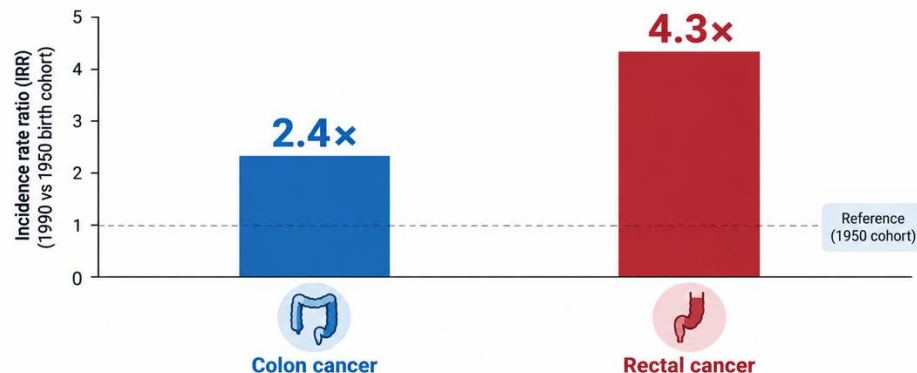
Period effect: an event changes diagnosis or exposure in a calendar period.

Cohort effect: people born in different years have different risk patterns.

Risk in later birth cohorts

Higher Risk of Early-Onset Colorectal Cancer in Later Birth Cohorts

Incidence rate ratios for the 1990 vs 1950 birth cohort



Compared with individuals born around 1950, those born around 1990 had a 2.4-fold higher incidence of early-onset colon cancer and a 4.3-fold higher incidence of early-onset rectal cancer.

Incidence first rose in Western high-income countries in the mid-1990s and has since expanded globally.

Early-life exposures may accumulate over decades.

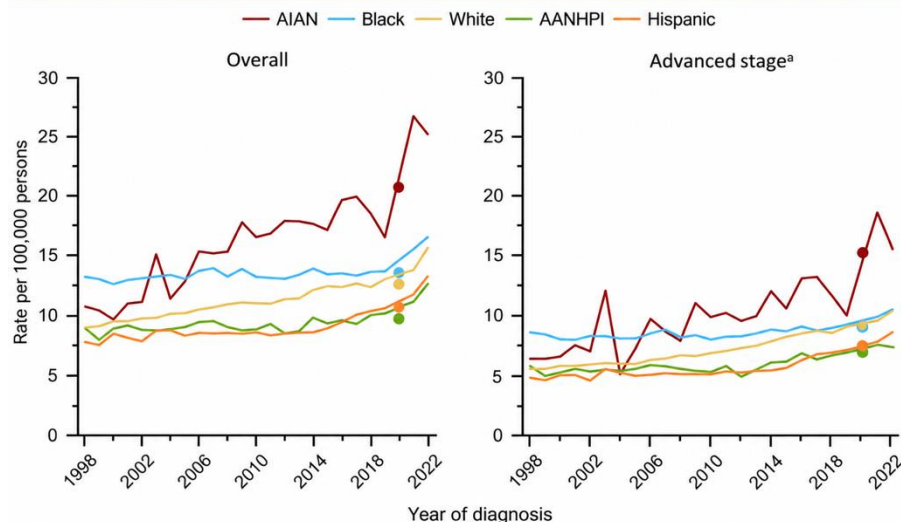
Who is most affected?

Male-to-female incidence ratio:
~1.20

Rates are rising in all racial/ethnic groups; historically fastest in non-Hispanic White populations.

Highest absolute rates: **Black and Indigenous** populations.

Trends in early onset colorectal cancer incidence rates by race and ethnicity, 1998–2022, United States

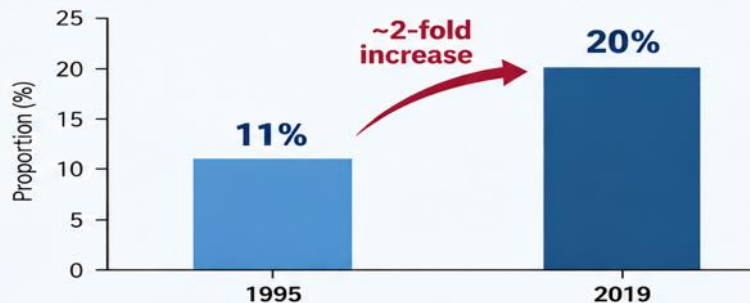


Early-Onset Colorectal Cancer: A Growing Public Health Burden

A growing proportion of colorectal cancers are diagnosed before age 55, and high-risk birth cohorts will reshape overall CRC epidemiology.

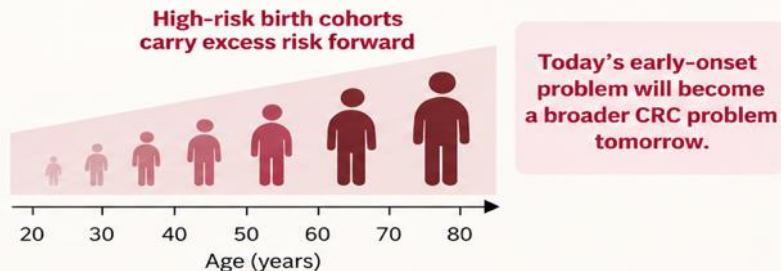
Proportion of CRC diagnosed before age 55

United States, 1995–2019



High-risk birth cohorts will reshape the future CRC burden

As cohorts with elevated early-onset risk age into their 50s–60s, the impact will extend beyond “early-onset” CRC.



One in five CRCs

is now diagnosed before age 55
(20% in 2019 vs 11% in 1995)



Global implications

Rising early-onset incidence is a global phenomenon, and modeling studies project a substantial increase in the overall CRC burden in coming decades unless prevention strategies change.

Framework: Hereditary vs Familial vs Sporadic

Sporadic

~65–80%
of CRC cases



No identifiable hereditary syndrome



Likely driven by a combination of lifestyle and environmental factors



Accounts for most of the increase in early-onset CRC at the population level

Familial

~15–25%
of CRC cases



Reports a family history of CRC (≥ 1 first-degree relative)



No identifiable pathogenic variant



Likely due to shared genes of modest effect and/or shared environmental and lifestyle factors

Hereditary

~5%
of CRC cases



Caused by pathogenic variants in high-penetrance genes (e.g., Lynch syndrome, FAP, MUTYH-associated polyposis)



Higher lifetime risk and often earlier onset



Important for identifying at-risk individuals and targeted surveillance

Most early-onset CRC is sporadic, a smaller proportion is familial without an identifiable gene, and a minority is due to well-defined inherited syndromes.

Metabolic risk factors

Metabolic and Lifestyle Drivers

Obesity, metabolic dysfunction, and sedentary behavior increase the risk of early-onset CRC.



Obesity

Higher risk with increasing BMI:

- Overweight: **OR ~1.32**
- Obese: **OR ~1.88**



Early-life obesity

Childhood, adolescent, and even maternal obesity are implicated in increased risk.



Metabolic syndrome, type 2 diabetes, and sedentary behavior

All associated with higher risk of early-onset CRC.

Exposure across the life course

Adult BMI captures only part of exposure history.

Association does not establish intervention benefit.

Health counseling should avoid blame.

Dietary associations

Diet

Dietary patterns and specific nutrients influence the risk of early-onset CRC.



Western dietary pattern, processed and red meat

Higher intake is associated with increased risk of early-onset CRC.



Sugar-sweetened beverages

≥2 per day: **RR 2.18**



Higher vitamin D intake

Associated with lower risk:
HR ~0.49

Patterns and specific exposures

Diet and metabolic health overlap.

Comparison groups and exposure definitions matter.

A protective association does not establish a supplement benefit.

Other Modifiable Risk Factors for Early-Onset CRC

Smoking and Alcohol

Tobacco and alcohol use, particularly during adolescence and young adulthood, are linked to increased risk of early-onset CRC.



Smoking

Associated with higher risk, with stronger associations for initiation and higher exposure in adolescence and young adulthood.



Alcohol

Binge or heavy use, particularly in teens and twenties, is linked to increased risk.

Physical Activity

Greater physical activity is associated with a lower risk of early-onset CRC.



Protective association

Higher levels of physical activity are associated with lower risk.



Both moderate and vigorous activity may be beneficial.



Reducing sedentary behavior is also important.

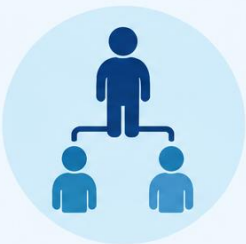


Avoiding tobacco and excessive alcohol use and maintaining regular physical activity may help reduce the risk of early-onset CRC.

Family history of CRC

Family History of CRC

A first-degree relative with CRC is associated with a substantially higher risk of early-onset CRC.



First-degree relative with CRC

Meta-analytic OR up to

~5.9



A positive family history should prompt earlier and more vigilant screening.

Details that change risk assessment

Which relative had cancer?

How old were they at diagnosis?

Were polyps or other cancers also present?

Inflammatory bowel disease

Inflammatory Bowel Disease (IBD)

IBD is more common in young CRC patients compared with the general population.



Prevalence of IBD

EOCRC patients

3%

General population

0.4%



Chronic colitis remains an important risk context for early-onset CRC.

A different surveillance context

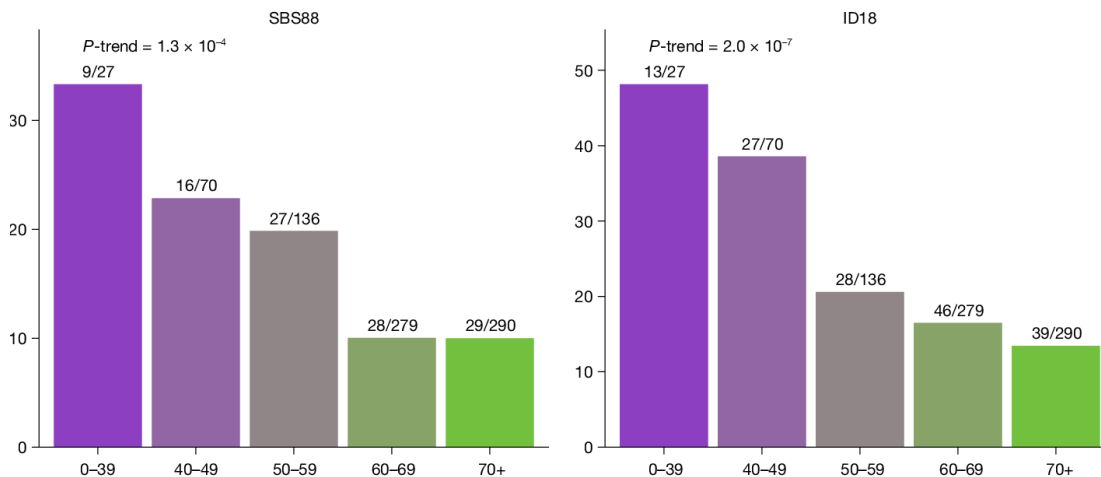
Colitis requires a disease-specific risk assessment.

Surveillance depends on the individual clinical history.

Average-risk screening rules do not cover this group.

E. coli and colibactin mutagenesis

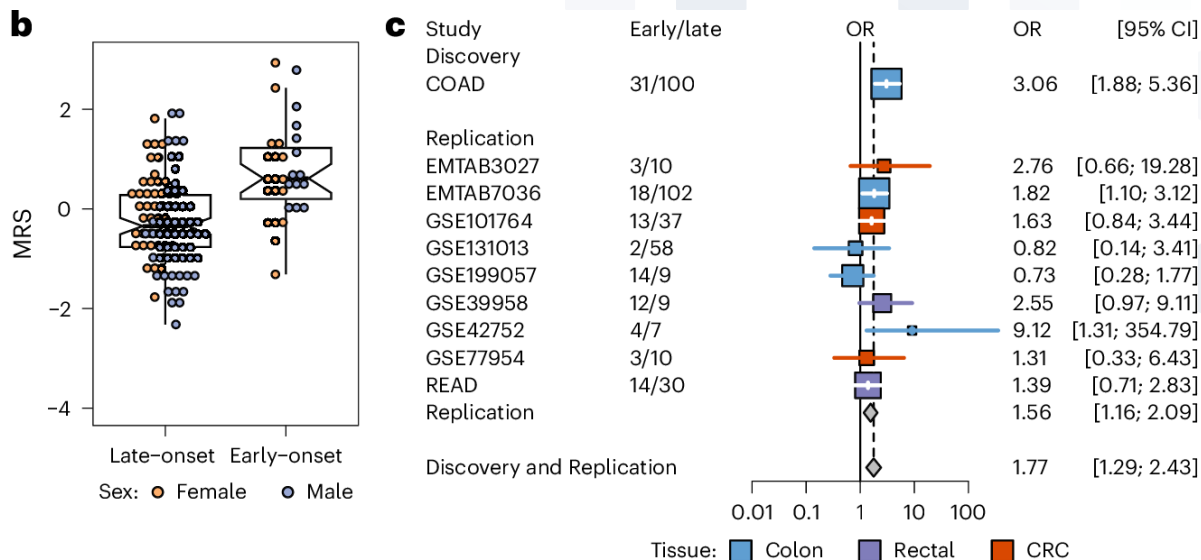
Signature prevalence (%) by age at diagnosis (years)



Colibactin signatures are enriched in younger MSS tumors.

A tumor DNA footprint supports prior mutagenesis, not a clinical infection.

Picloram and an epigenetic signal



EOCRC <50 vs LOCRC ≥70. Replication: 83 vs 272 patients.

Exposure proxy and association. Individual exposure and causation remain unproven.

What the exposure studies establish

Colibactin: a mutational signature links a bacterial toxin to DNA damage in a subset of CRC.

Picloram: tumor methylation and county-level data identify an association to investigate.

Neither study establishes a patient-level prevention strategy or a routine exposure test.

Presenting symptoms

Rectal bleeding

45%

Abdominal pain

40%

Altered bowel habits

27%

Pooled prevalence among patients with EOCRC. Symptoms can overlap.

The interval to diagnosis

A 4–6 month interval from symptom onset to diagnosis is common.

Persistent symptoms need a clear follow-up plan.

Resolution or further evaluation should close the diagnostic loop.

Diagnostic evaluation

Symptoms below age 45 require their own assessment

Persistent rectal bleeding or bowel changes warrant evaluation at any age.

A benign initial explanation needs reassessment if symptoms persist.

The follow-up plan should name the next step and who will review results.

Site and stage at diagnosis

Distal colon and rectum predominate.

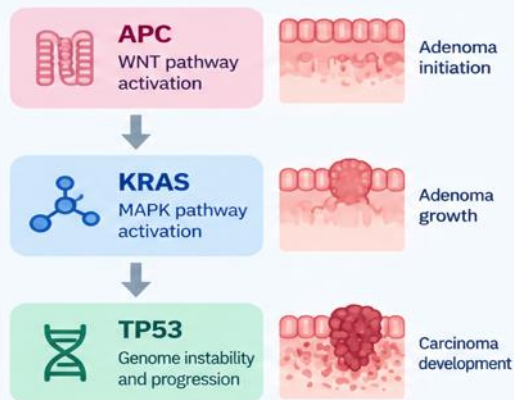
~**60%** present at **stage III–IV**, compared with ~49% in LOCRC.

Mucinous, signet-ring, and poorly differentiated histology are more common.

Is EOCRC Biologically Distinct?

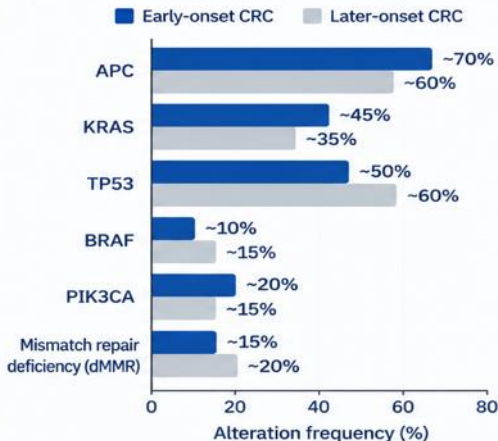
Shares the Canonical CRC Pathways

EOCRC uses the same core molecular framework as later-onset CRC.



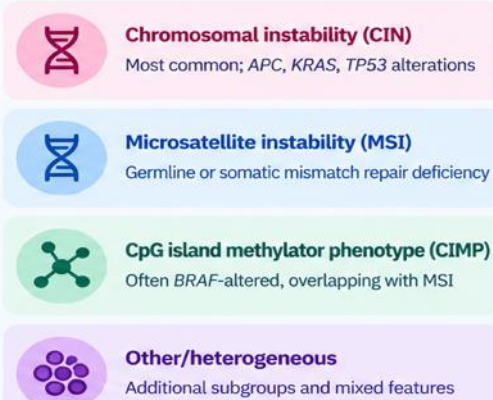
Alteration Frequencies Differ

The relative frequency of key alterations varies between EOCRC and later-onset CRC.



Multiple Biologic Subgroups

EOCRC comprises several molecular subtypes, not a single defining signature.



EOCRC is not a single new molecular entity.

It shares canonical CRC pathways, with a shifted distribution of alterations and multiple biologic subgroups.

Somatic Differences in Early-Onset CRC

MSS vs. MSI-H Tumors

MSS Tumors

(Microsatellite stable)

Compared with later-onset CRC, MSS tumors in young patients show a different pattern of somatic alterations.

Alteration	Early-onset MSS (relative frequency)	Later-onset MSS (relative frequency)
TP53	↑ Higher	Lower
CTNNB1	↑ Higher	Lower
PIK3CA	↑ Higher (in some series)	Lower
APC	↓ Lower	Higher
KRAS	↓ Lower	Higher
BRAF	↓ Lower	Higher



Less CpG-island methylator phenotype (CIMP)



Serrated pathway not a major driver



Consistent with a left-sided, chromosomal instability phenotype

MSI-H / dMMR Tumors

(Microsatellite instability-high / mismatch repair deficient)

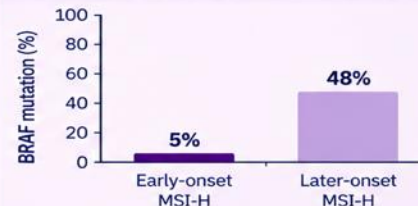


~10–20% of EOCRC is MSI-H, predominance due to Lynch syndrome.



A young patient with MSI-H tumor should undergo **germline testing** (regardless of family history).

BRAF Mutation in MSI-H Tumors



Among MSI-H tumors, **BRAF** mutation is **much less common in young patients** (5% vs 48%).



EOCRC is not a single molecular entity, but shows characteristic somatic differences by molecular subtype, with distinct patterns in MSS and MSI-H tumors.

Germline and tumor testing

Germline testing addresses inherited susceptibility and family implications.

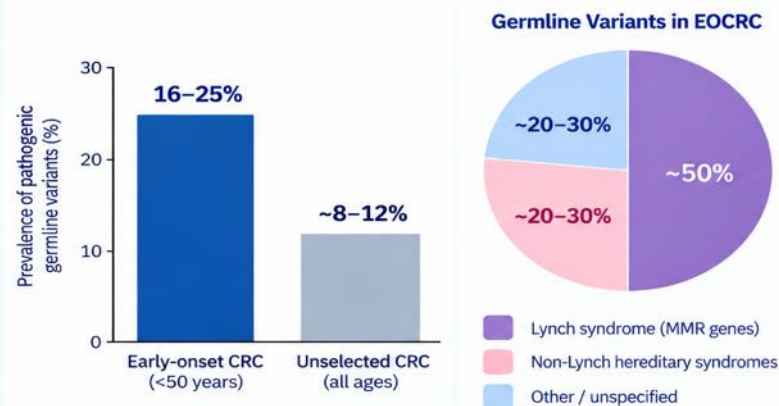
Tumor MMR/MSI testing characterizes mismatch repair in the cancer.

The two tests answer different clinical questions.

Germline Variants in Early-Onset CRC

Prevalence of Pathogenic Germline Variants

Pathogenic germline variants are found in ~16–25% of EOCRC, roughly double the rate in unselected CRC.



Hereditary Syndromes in EOCRC

Multiple actionable syndromes account for germline risk, with Lynch syndrome being the most common.



Lynch syndrome

MLH1, MSH2, MSH6, PMS2, EPCAM

Most common germline cause of EOCRC (~50% of germline variants)



Familial adenomatous polyposis (FAP)

APC

Rare, but important; thousands of adenomas and very high CRC risk



MUTYH-associated polyposis (MAP)

MUTYH

Biallelic *MUTYH* variants; adenomatous polyposis phenotype



Polymerase-proofreading associated polyposis

POLE, POLD1

Increased CRC risk, often multiple adenomas



Hamartomatous syndromes

STK11 (Peutz-Jeghers)
SMAD4/BMPR1A (juvenile polyposis)
PTEN (Cowden syndrome)

Distinct clinical features and extracolonic risks



~1 in 5 to 1 in 6 young patients with CRC carries a pathogenic germline variant, and about half are due to Lynch syndrome.

These findings support universal germline testing in all patients with EOCRC.

Germline testing for every EOCRC patient

Offer germline multigene panel testing at diagnosis, regardless of family history or tumor MMR status.

Results may guide surveillance, surgical discussions and testing of relatives.

Genetic counseling supports interpretation. A variant of uncertain significance is not an actionable diagnosis.

Average-risk screening

Screening begins at age 45 for asymptomatic adults at average risk.

USPSTF: grade B for ages 45–49 and grade A for ages 50–75.

Symptoms and increased-risk histories require their own assessment.

Screening options in 2026

Preferred test options	Interval
Colonoscopy	10 years
FIT or high-sensitivity gFOBT	1 year
Multi-target stool DNA or stool RNA	3 years
CT colonography or sigmoidoscopy	5 years

Blood-based testing: an alternative for those who decline preferred tests.

Any positive non-colonoscopy test requires timely colonoscopy.

ACS guideline update, May 2026.

Average-risk, asymptomatic adults. Intervals assume a negative, adequate test.

Screening with a family history

One first-degree relative diagnosed before 60, or two at any age:

Begin colonoscopy at 40 or 10 years before the youngest diagnosis, whichever is earlier. Repeat every **5** years.

Other family histories require a tailored schedule. Hereditary syndromes and IBD have separate guidance.

Screening case at age 35

When should screening begin, and which test would you offer?

A 35-year-old asymptomatic adult has never undergone CRC screening.

Their mother developed colorectal cancer at age 45.

No hereditary syndrome is known. Should screening wait until age 45?

Treatment considerations

Age alone does not justify more intensive cancer treatment.

Use **stage**, tumor **biomarkers**, **fitness** and **patient goals** to select therapy.

More intensive treatment in young adults has not shown a matching survival gain simply because of age.

Include long-term toxicity and function in the initial treatment discussion.

Fertility before treatment

Reproductive goals belong in the initial treatment conversation.

Counseling and specialist referral should occur before potentially gonadotoxic treatment when feasible.

Fertility care can continue during survivorship as goals and options change.

Early-Onset Colorectal Cancer

Standard Treatment with Key Additional Considerations

Treatment is based on stage and tumor biology, with important age-specific considerations in younger patients.



Germline Genetic Testing

- Offer multigene panel testing to all patients with CRC <50 years, regardless of family history.
- Identifies hereditary cancer syndromes (e.g., Lynch, APC, MUTYH, POLE/POLD1).
- Guides treatment, surveillance, and risk-reducing strategies.
- Enables cascade testing for relatives.



Somatic Tumor Profiling

- Perform comprehensive somatic profiling (e.g., NGS).
- Identifies actionable alterations (e.g., RAS, BRAF, HER2, NTRK, MSI, TMB).
- Informs prognosis and treatment selection.
- Guides clinical trial eligibility.



MSI/MMR Testing

- Test all tumors for MSI/dMMR (due to higher prevalence in EOCRC).
- Identifies Lynch syndrome.
- Predicts benefit from immunotherapy.
- Informs prognosis and treatment selection.



Fertility Considerations

- Discuss reproductive goals early in the treatment course.
- Refer to fertility specialists before chemotherapy, radiation, or surgery when possible.
- Consider options for sperm/egg or embryo preservation.
- Discuss potential impact of treatment on fertility and timing of family building.



Function-Preserving Surgery and Radiation

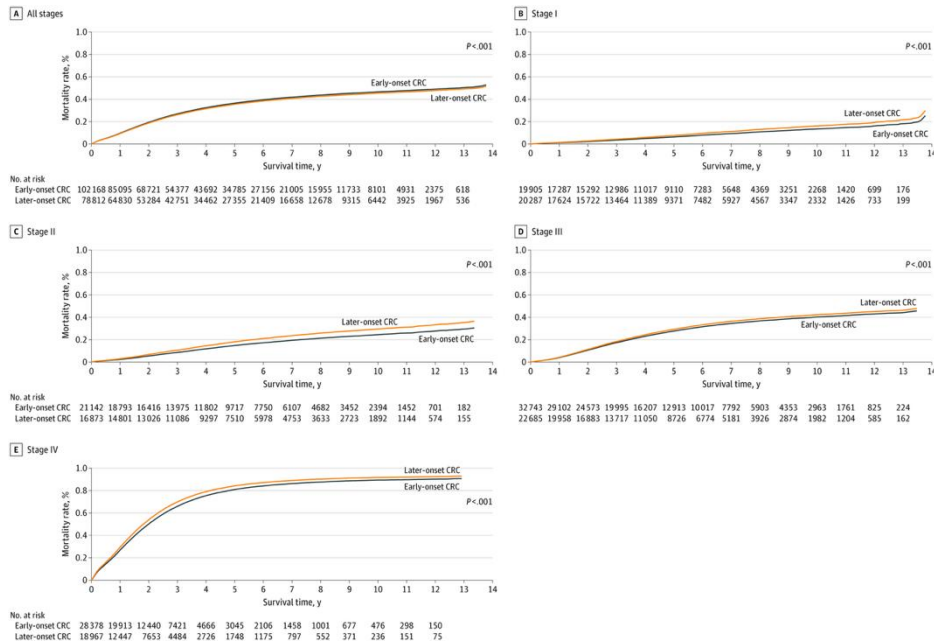
- Consider long-term functional outcomes, given decades of survivorship.
- Prioritize sphincter preservation when oncologically appropriate.
- Consider organ-preserving approaches for rectal cancer (e.g., total neoadjuvant therapy, nonoperative management in select patients).
- Address long-term bowel, urinary, and sexual function.
- Involve a multidisciplinary team (surgery, radiation oncology, GI, urology/gynecology, supportive care).



Standard Oncologic Management

Stage-appropriate therapy (surgery, chemotherapy, radiation, targeted therapy, immunotherapy)

Stage-adjusted prognosis



Stage-adjusted survival is similar to or slightly better than in LOCRC.

Survivorship: physical recovery

Neuropathy, fatigue, and cognitive concerns can limit daily function.

Bowel urgency, continence, and ostomy needs merit specific assessment.

Fertility goals and reproductive health remain relevant after treatment.

Survivorship: life after treatment

Sexual health, intimacy, and body image deserve direct discussion.

Work demands, insurance, and financial strain can complicate recovery.

Distress, fear of recurrence, parenting, and family risk require support.

Survivorship care planning

A shared plan for oncology, primary care, and the patient

Document treatment exposures and a stage-appropriate surveillance plan.

Assess persistent symptoms and their effect on daily function.

Identify the team responsible for each concern and the route for earlier review.

Why EOCRC centers are needed

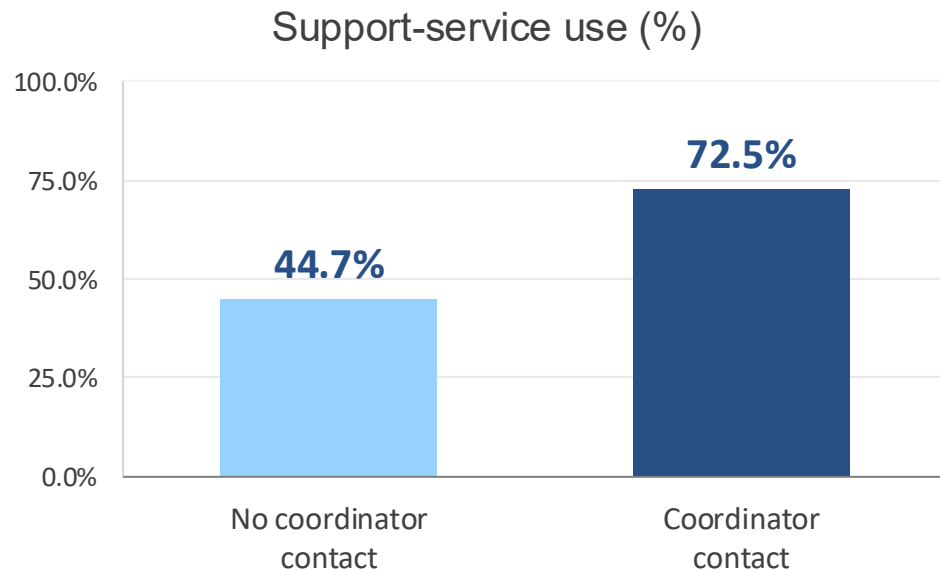
Young adults face cancer alongside **parenting, careers, family planning**, and long-term health.

Patients and caregivers report feeling overwhelmed, isolated, and in need of **navigation and psychosocial support**.

DIRECTt recommends **germline testing** for every newly diagnosed patient and attention to fertility and sexual health.

Dedicated centers can make **coordinated, age-relevant care** routine.

Evidence for care coordination



1,250 patients under 50 in a single-center pragmatic trial.

27.4% reported clinically significant distress.

Higher support-service use was **associated** with coordinator contact.

Care at diagnosis

A named navigator and a coordinated oncology plan

Early genetics and reproductive care

Assessment of distress and practical barriers

Support through follow-up

Symptom management, nutrition, and pelvic rehabilitation

Peer support, social work, and financial guidance

Survivorship planning with a named contact for unresolved needs

Huntsman: care and discovery

An existing model: Huntsman's Integrated Center for EOCRC combines multidisciplinary treatment with support for younger adults.

Support across life domains: fertility, genetics, mental health, finances, rehabilitation, and sexual health.

Care linked to research: ColoCare and clinical trials support studies of causes, treatment, and long-term outcomes.

The opportunity: make comprehensive care accessible while learning how to prevent and better treat EOCRC.

Measuring a center's impact

Time to evaluation and completion of priority referrals

Access to genetics, reproductive care, and support services

Patient-reported distress, function, and unmet needs

Differences in access and outcomes across patient groups

What the evidence tells us

EOCRC incidence is rising across birth cohorts and many countries.

EOCRC is biologically heterogeneous. Exposure studies provide clues, with causal questions still open.

Later-stage presentation contributes to worse unadjusted outcomes. Adjusted prognosis can be similar or better.

Young adults need cancer care that also addresses years of future health and function.

What this means in practice

Assess persistent alarm symptoms at any age and ensure diagnostic follow-up.

Begin average-risk screening at 45. Use earlier, tailored screening for increased-risk histories.

Offer germline testing for EOCRC and tumor MMR/MSI testing for every CRC.

Integrate fertility, function, psychosocial support and survivorship into care from diagnosis.

Thank you!

Questions and discussion