Early Onset (Lower) GI Cancers

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Outline

1 Epidemiology

Incidence trends — US & global · clinicopathologic features · features · projections to 2030

2 Risk factors & biology

Common + emerging exposures · birth cohort · molecular landscape · microbiome & immune microenvironment

3 Clinical presentation & management

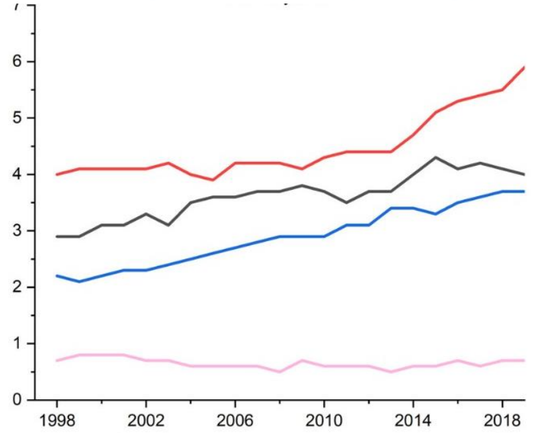
Germline testing + tumor molecular profiling · quality of life · rectal cancer pathways — TNT, surgery, watch & wait · fertility · systemic considerations

4 Survivorship & the future

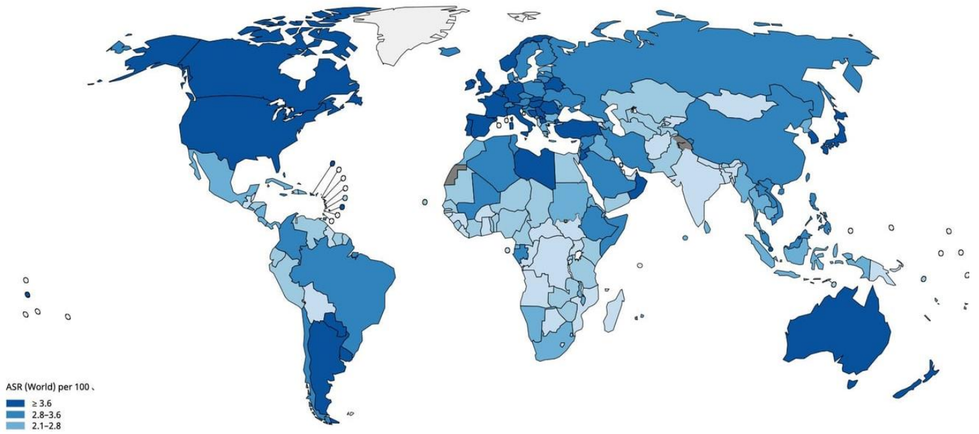
Whole-person care · clinical trials · screening & family history · takeaways for clinic

A US trend, a global trend, and a projection.

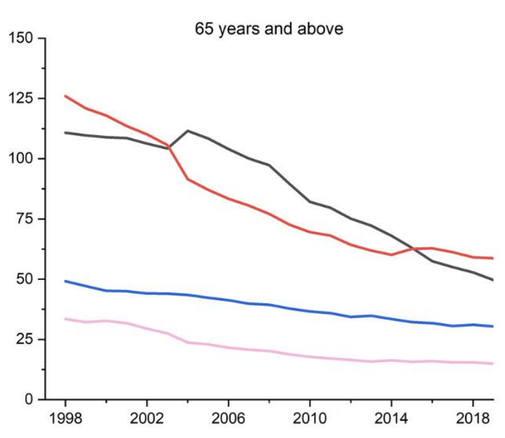
US — ages 20–49 (rising)



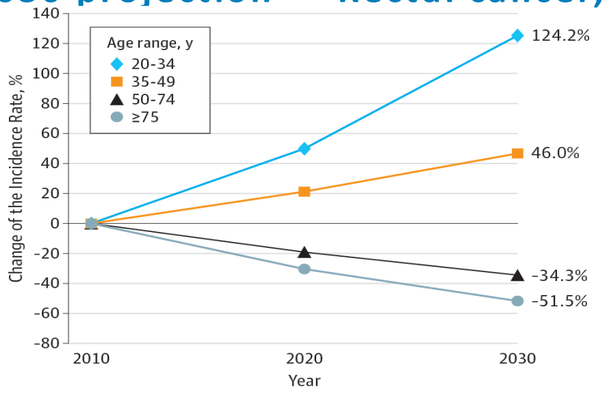
Global — Age-standardized incidence, ages 0–49 (2020)



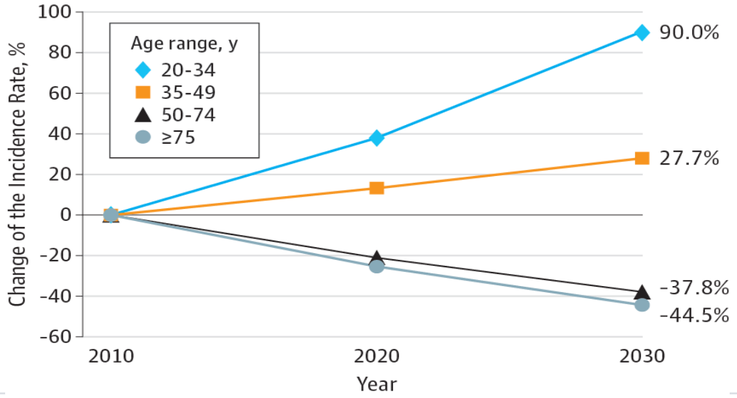
US — ages 65+ (declining)



2030 projection — Rectal cancer, by age



2030 projection — Colon cancer, by age



Projections to 2030

By 2030, rectal cancer in **<50** projected to rise **124%**; colon colon **90%**.

Simultaneous **decline** in ages 50–74 and ≥75.

Bailey CE et al. JAMA Surg 2015.

Siegel RL et al. CA Cancer J Clin 2023 · Sinicrope FA NEJM 2022. · Bailey CE et al. JAMA Surg 2015.

Definition and Anatomic Distribution

Working definition

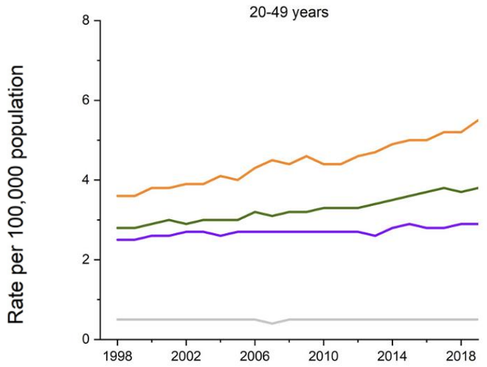
- CRC diagnosed before age 50.

Distinguishing features

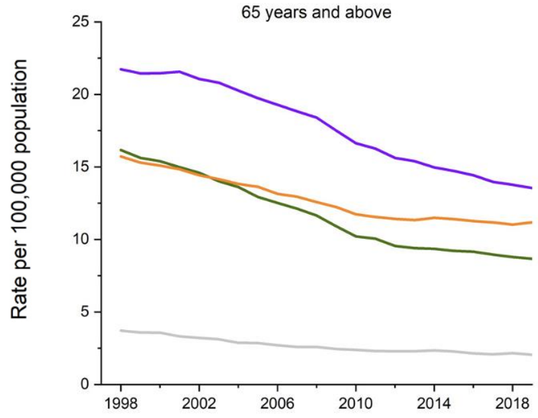
- Predominantly **left-sided** & rectal
- **Advanced stage** at presentation
- More often **poorly differentiated**
- Mostly **sporadic** (~80%)

US trends by anatomic site, 1998–2018

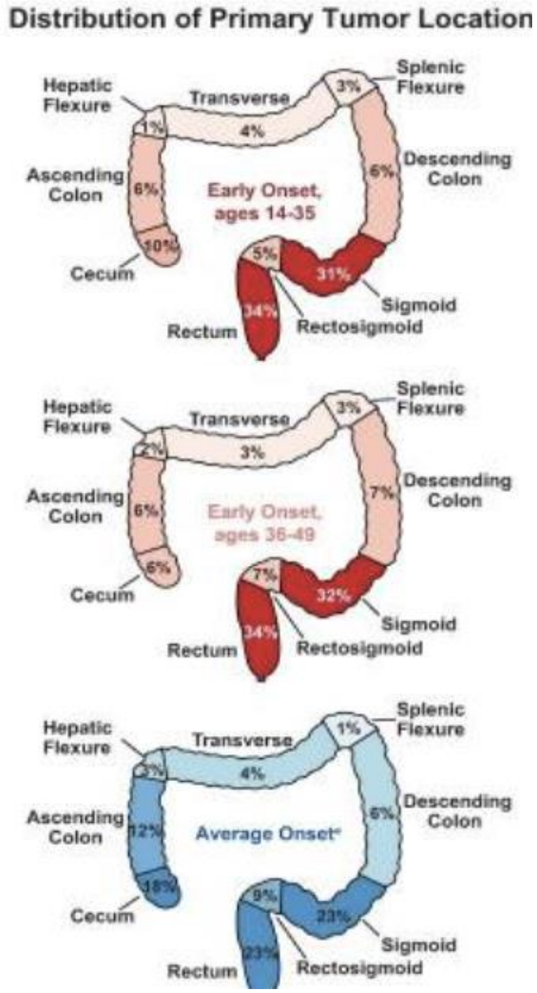
Ages 20–49 — rising in distal colon & rectum



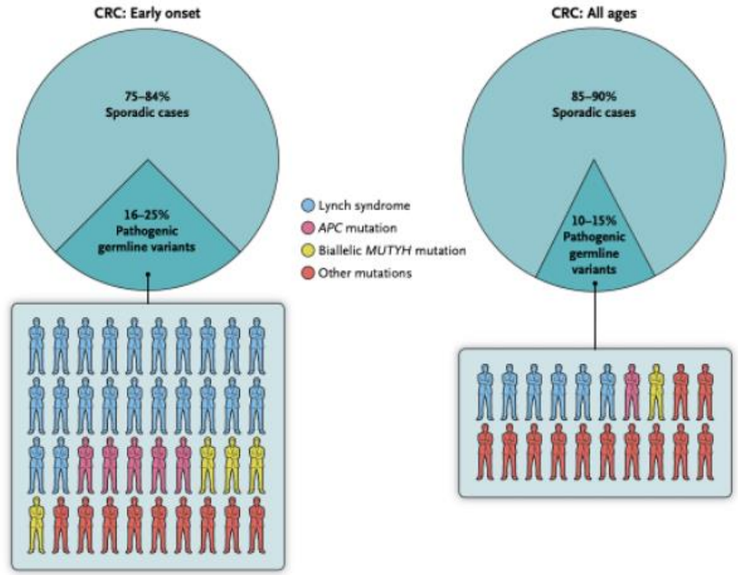
Ages 65+ — declining across sites



Primary tumor location



Sporadic vs. hereditary hereditary — EO vs. all all ages



~20% germline

Cercek et al., JNCI 2021 · Sinicrope, NEJM 2022.

Symptoms at presentation

Symptom-to-dx delay

5–12 mo

typical interval from first symptom to diagnosis.

Screening gap

45

USPSTF screening age — leaves a large **at-risk window.**

Typical presenting symptoms

Hematochezia / occult bleeding — most common, often dismissed as hemorrhoids

Change in bowel habits — chronic diarrhea/constipation, narrow stools

Abdominal pain — often months before workup

Iron-deficiency anemia in a young patient — requires further evaluation

Why the delay matters

First clinician to see these symptoms is usually **primary care or the ED** — not GI. Dominant differential: hemorrhoids or IBS.

Colonoscopy deferred. By diagnosis, regional spread is common.

No single cause. A converging exposome.

Established

Lifestyle & metabolic

Obesity — esp. childhood/adolescent

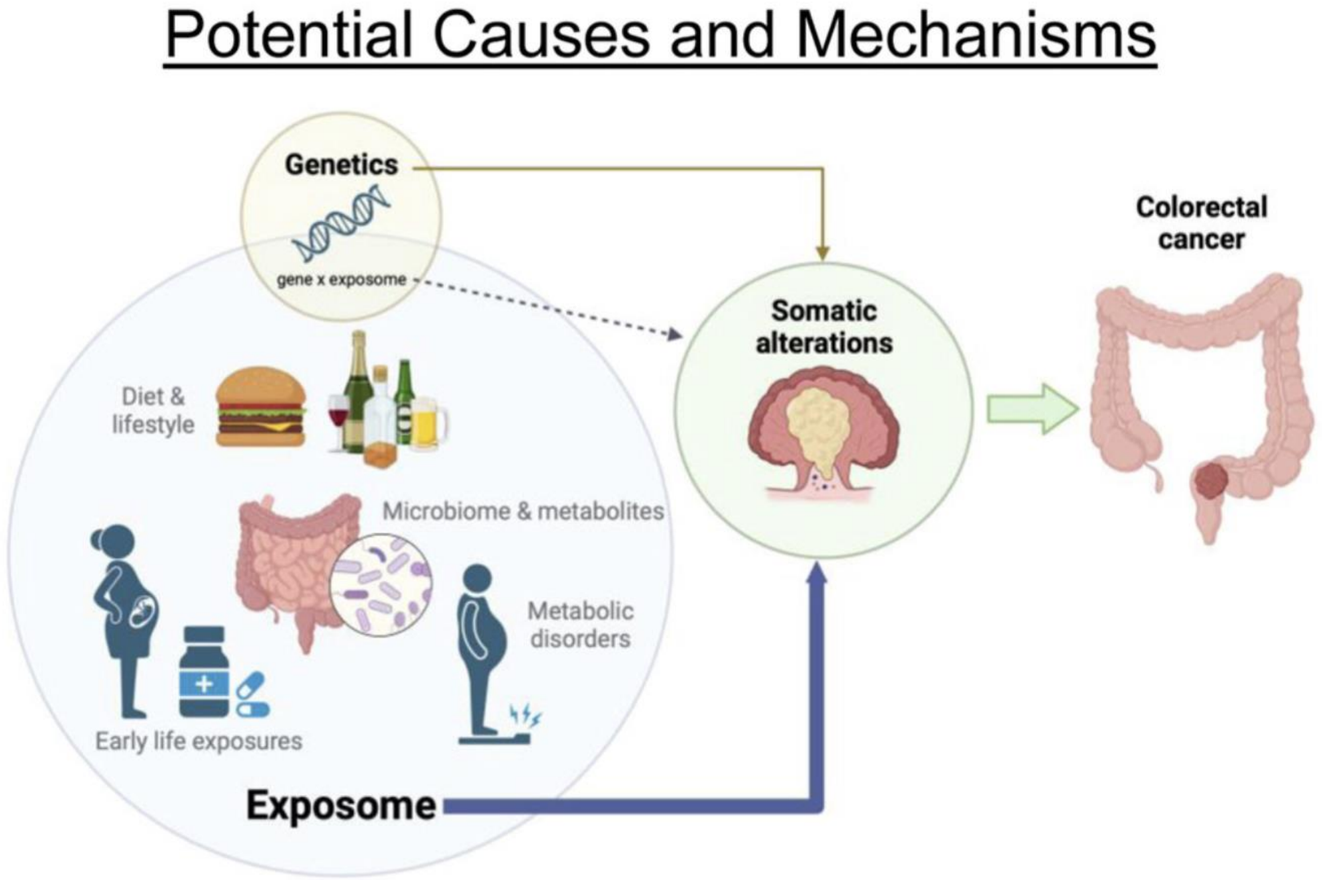
Western diet — high red/processed meat, low fiber

Ultra-processed foods — independent signal

Physical inactivity, sedentary time, TV time

Alcohol, tobacco

Type 2 diabetes, metabolic syndrome



Gupta S, et al., Clin Gastroenterol Hepatol 2023
Hofseth LJ et al, Nat Rev Gastroenterol Heapotol 2023

Birth cohort effect

Emerging

Environment & exposome

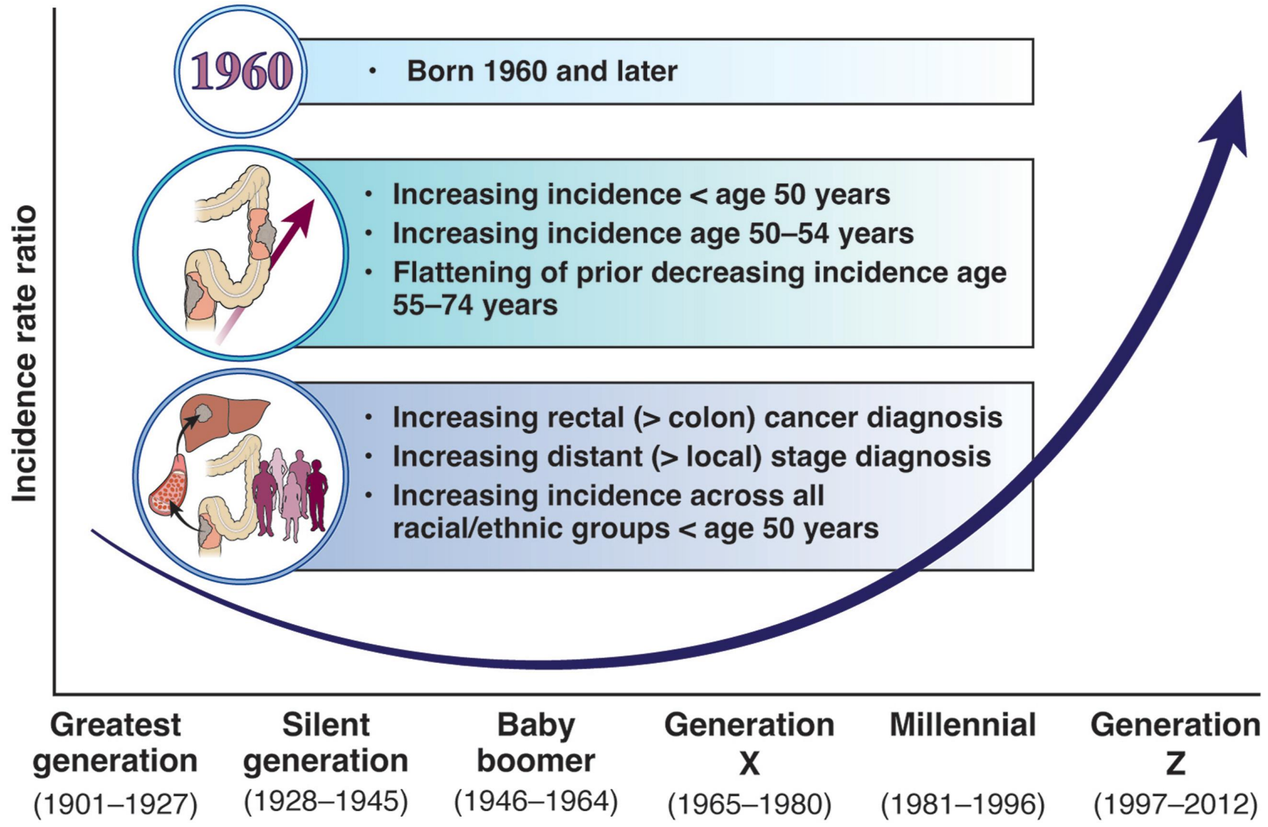
Microbiome dysbiosis

Microplastics, endocrine disruptors

Drinking-water byproducts and pesticides

Industrial exposures — rubber, dyes

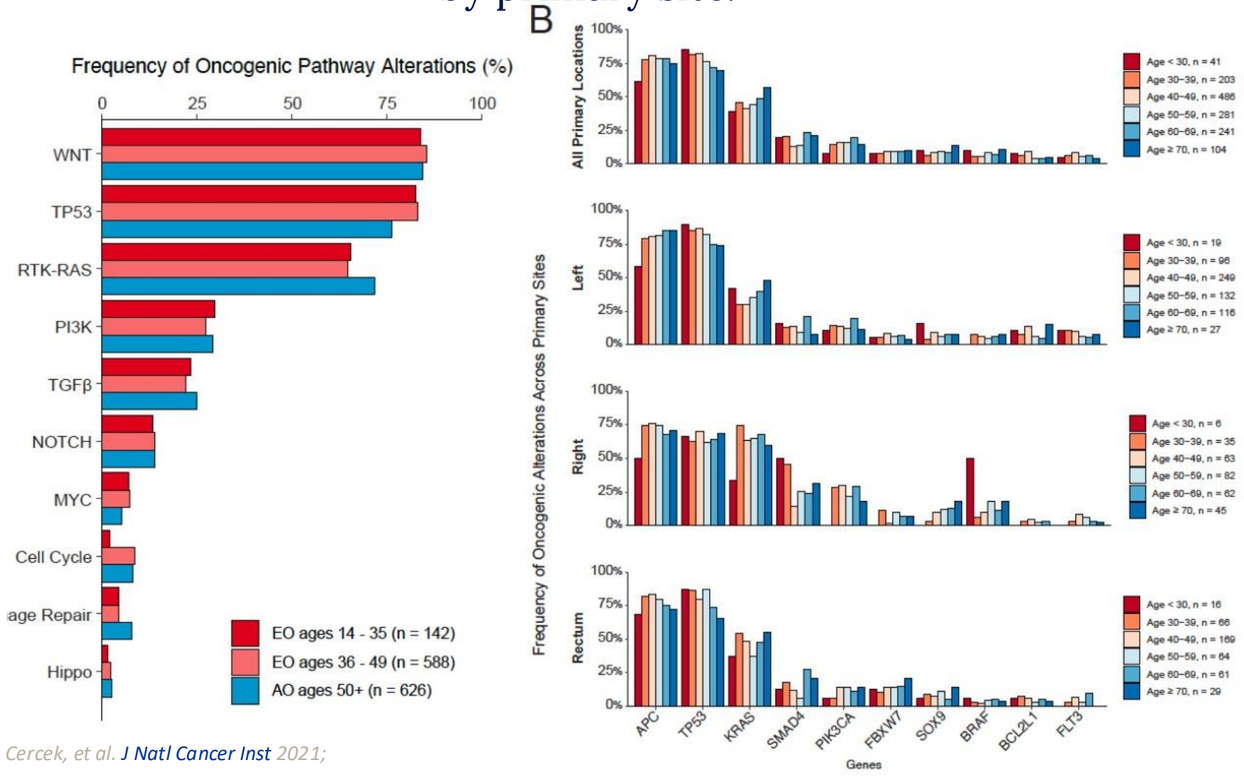
Birth-cohort effect — post-1950 *in utero* exposures



Gupta S, et al., Clin Gastroenterol Hepatol 2023
Hofseth LJ et al, Nat Rev Gastroenterol Heapotol 2023
Mass et al, Nature Med 2026

Distinct disease — or genomically indistinguishable?

Oncogenic pathway alterations by age band, by primary site.



Cercek, et al. J Natl Cancer Inst 2021;

Clinical: EO-CRC presents **more left-sided** (~84% vs 64%) and with **rectal bleeding** (41% vs 26%) and **abdominal pain** (37% vs 27%) ·

Genomic: Initial signal — ↑*TP53*, ↓*RTK-RAS* — **disappeared after adjusting for sidedness.** No difference at gene or pathway level. **TMB, FGA, WGD, LOH** all equivalent.

Outcomes: Response to 1L chemo (~62–72%) and OS (~47 / 56 / 55 mo) **equivalent across age cohorts**. Age not associated with survival on multivariate.

Germline: Pathogenic variants in **23.3% of ≤35 yrs** vs 14.1% AO (P=.01) — high-penetrance genes (MMR, *APC*, *POLD1*) drive the gap. **Test everyone <50.**

Authors' Conclusion: EO-CRCs are clinically & genomically indistinguishable from AO-CRCs after adjusting for sidedness. sidedness.

Aggressive treatment based on age alone is not warranted.

Differences in mutations

Argument: distinct biology

Genomic landscape

4,983 EOCRC vs. 12,150 LOCRC

(8 countries · target panel + WES)

Higher mutation frequency in 137 genes — incl. **TP53, TCF7L2, CTNNB1**

Lower mutation frequency in 6 genes — incl. **BRAF, RNF43, SOX9, AXIN2, HNF1A, ELF3**

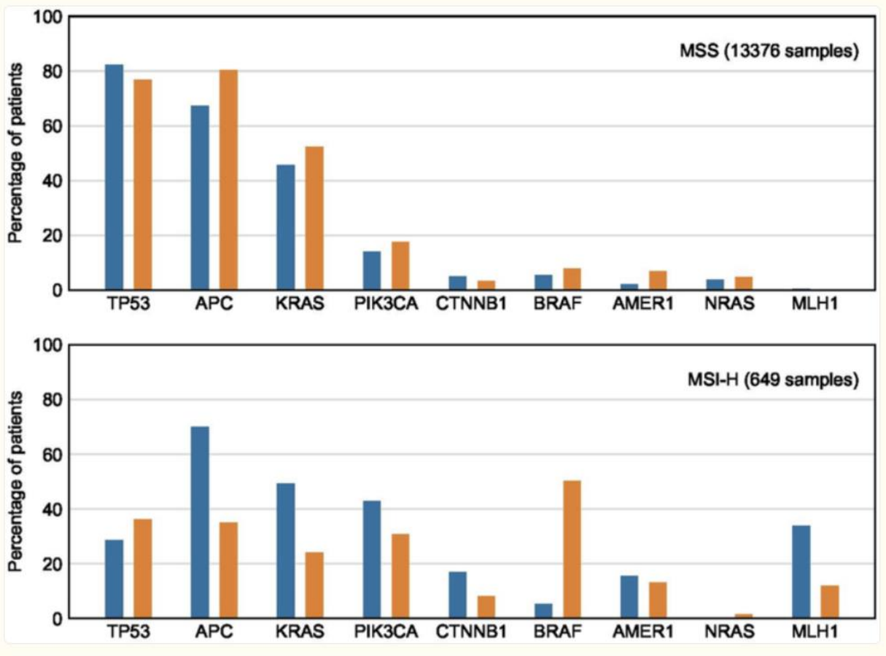
EOCRC vs LOCRC — split

Hypermutated: ↑ KRAS, CTNNB1, BRAF, RNF43

Non-hypermutated: ↑ TP53, ↓ BRAF, KRAS

Li et al. Lancet Oncology 2025. · Lieu CH et al. Clin Cancer Res 2019.

Alteration rate — EOCRC (blue) vs. LOCRC (orange)



alteration rate, EO <40y vs LO ≥50y in MSS & MSI-H series.

Takeaways:

Same actionable biomarkers — **MMR/MSI, KRAS/NRAS, BRAF, HER2, NTRK**.

EOCRC enriched for **TP53, CTNNB1** — modest absolute differences.

Lower **APC** frequency in some left-sided series.

Microbial implications

Young-onset CRC

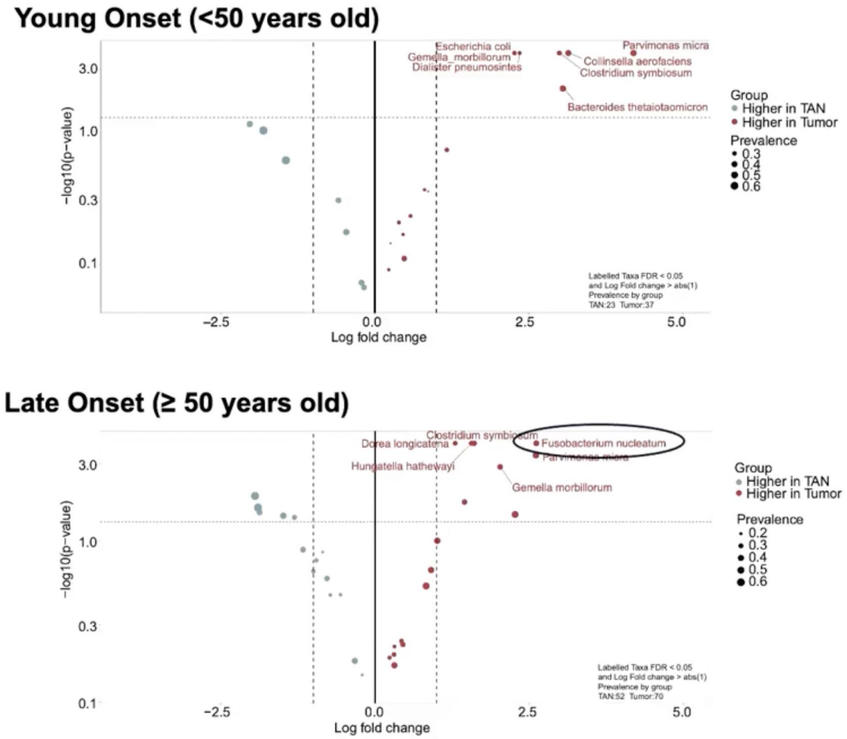
E. coli · pks+ · colibactin

pks+ *E. coli* over-represented in YOCRC tumors
Produces **colibactin** — DNA-damaging genotoxin
Signature mutational footprint on epithelium
Possible **early-life exposure** window

Late-onset / older CRC

Fusobacterium nucleatum

Fusobacterium dominant in LOCRC tumors
Drives **immune evasion**, chemoresistance
Prognostic — higher load → worse outcomes
Different niche than pks+ *E. coli*



Barrier biology — why the bug story matters

Dysbiosis & loss of commensal bacteria

Early-life antibiotics, Western diet, low fiber → depletion of protective commensal bacteria (e.g. *Faecalibacterium*, butyrate producers). Niche opens for pks+ *E. coli*, *Fusobacterium*.

Mucosal barrier & gut permeability

Mucus layer thinning, tight-junction disruption — "leaky gut." Microbial products (LPS, peptidoglycan) translocate from lumen into lamina propria

Endotoxemia & chronic inflammation

Low-grade systemic LPS exposure drives TLR4 drives TLR4 activation, NF-κB signaling, insulin insulin resistance. Chronic mucosal inflammation primes the epithelium for transformation.

Proposed causal chain (YOCRC)

Early-life antibiotics → **dysbiosis** → loss of commensals + colibactin damage → **barrier breakdown** → endotoxemia + insulin resistance → polyps → **CRC at 35.**

Clinical presentation and management considerations

Vignette

"A 37-year-old elementary school teacher, two kids, no family history. Six months of rectal bleeding, "hemorrhoids." Now MRI shows a T3N2 mid-rectal mass. She and her husband are in the room. ***Where do we go next?****"*

Staging	CT C/A/P · MRI pelvis (rectal) · CEA · colonoscopy w/ biopsies · signet-ring/mucinous → consider PET · liver-protocol MRI if equivocal.
Tumor molecular	**MMR/MSI by IHC + PCR** · KRAS/NRAS/BRAF · HER2 · NTRK · broad NGS panel (stage IV, NCCN). Tumor MMR doubles as Lynch screen.
Germline	**All patients <50 → multigene panel (NCCN).** Refer genetic counseling. Polyposis + non-polyposis genes. Implications: surgery extent, surveillance, family.
Fertility	**Refer BEFORE chemo/RT starts.** Sperm/oocyte/embryo banking. Lynch: hyst/BSO timing. Pelvic RT planning — gonadal shielding.
Psychosocial & financial	Social work · financial navigation · YA survivorship intake · childcare logistics · employer/FMLA. Loop in early.

Every patient <50 · multigene panel · what changes if positive?

NCCN — Genetic/Familial High-Risk Assessment: Colorectal

CRC dx <50 → multigene germline panel, regardless of family history.

What's on the panel

Non-polyposis

- **MLH1, MSH2, MSH6, PMS2, EPCAM** (Lynch)
- **TP53** (Li-Fraumeni)
- **STK11** (Peutz-Jeghers)
- **BMPR1A, SMAD4** (Juvenile polyposis)
- **CHEK2, ATM, PALB2** — moderate risk

Polyposis

- **APC** (FAP / AFAP)
- **MUTYH** (MAP, biallelic)
- **POLE, POLD1** (polymerase proofreading)
- **NTHL1, MSH3, AXIN2, GREM1**

If positive — treatment considerations

Lynch / dMMR

Immunotherapy as first line option

FAP / AFAP / MAP

Total / subtotal colectomy ± IPAA discussion. Upper GI surveillance (duodenal). Desmoid risk.

POLE / POLD1

Ultra-hypermutated phenotype → strong **IO candidates** even when MMR-proficient.

Family cascade

First-degree relative testing, counseling, surveillance timing. Risk-reducing hyst/BSO conversation in Lynch (timing vs. family completion).

NCCN Genetic/Familial High-Risk Assessment: Colorectal v.1.2025.

Tumor Molecular Profiling

Biomarker	When to send	What it changes
MMR / MSI *IHC + PCR/NGS*	Every patient, all stages	dMMR/MSI-H → **immunotherapy**.
KRAS / NRAS	Stage IV (NCCN)	WT → anti-EGFR candidate (left-sided). KRAS G12C → sotorasib/adagrasib
BRAF V600E	Stage IV (NCCN)	Encorafenib + cetuximab. Prognostic; right-sided enriched.
HER2 *IHC / FISH / NGS*	Stage IV, RAS/BRAF WT	Tucatinib + trastuzumab; Pertuzumab + trastuzumab
NTRK fusions	Pan-tumor; esp. MSI-H	Larotrectinib / entrectinib. Rare but disease-changing.

NCCN — colon and rectal cancer, suspected/proven distant mets

- **Biomarker testing ordered as rapidly as possible following diagnosis, including[f,n]:**
  - ***KRAS, NRAS,* and *BRAF* V600E mutations; HER2 (*ERBB2*) overexpression/amplification; MMR or MSI status (if not previously done)**
  - **Testing should be conducted as part of multigene panel testing (MGPT), which would identify rare and actionable mutations and gene fusions such as *POLE/POLD1*, *RET*, and *NTRK 1/2/3*.**

Distinguish: tumor MMR/MSI = Lynch screen + IO eligibility · germline panel = inherited risk + family cascade. *Order both* in patients <50.

NCCN Colon Cancer v.2.2026 · NCCN Rectal Cancer v.2.2026 ·

What goal(s) are we chasing after?

Juggling Balls in the Air

Costs of treatment — a 38-year-old pays for decades

Radiation

Pelvic RT → ovarian failure, premature menopause, vaginal stenosis, erectile dysfunction, secondary malignancy decades later.

Chemotherapy — long-term

Oxaliplatin neuropathy — a surgeon, an electrician, a musician, a parent who carries a child —fine-motor professions change with persistent neuropathy. 5-FU cardiotoxicity. Cognitive effects.

Surgery — sexual & urinary

Pelvic dissection → autonomic injury · erectile dysfunction, retrograde ejaculation, dyspareunia, bladder dysfunction. Peri-operative decision making — what do patients hear vs. what we say.

Surgery — bowel function

LARS · frequency, urgency, fragmentation, soiling. Stoma vs. no stoma.

Which goals are we prioritizing? Balancing oncologic cure with functional quality of life.

Conversations that can't wait.

Male

Sperm cryopreservation — fast, low burden, often single visit

Refer **before** first cycle of chemo

Pelvic RT — counsel re: gonadal shielding limits

Document baseline semen analysis

Female

Oocyte / embryo cryopreservation — 2-week stim cycle

GnRH agonist co-admin — partial ovarian protection

Pelvic RT — ovarian transposition consideration

Lynch: **risk-reducing hyst/BSO** timing — family completion vs. age

Workflow

First visit: ask reproductive goals

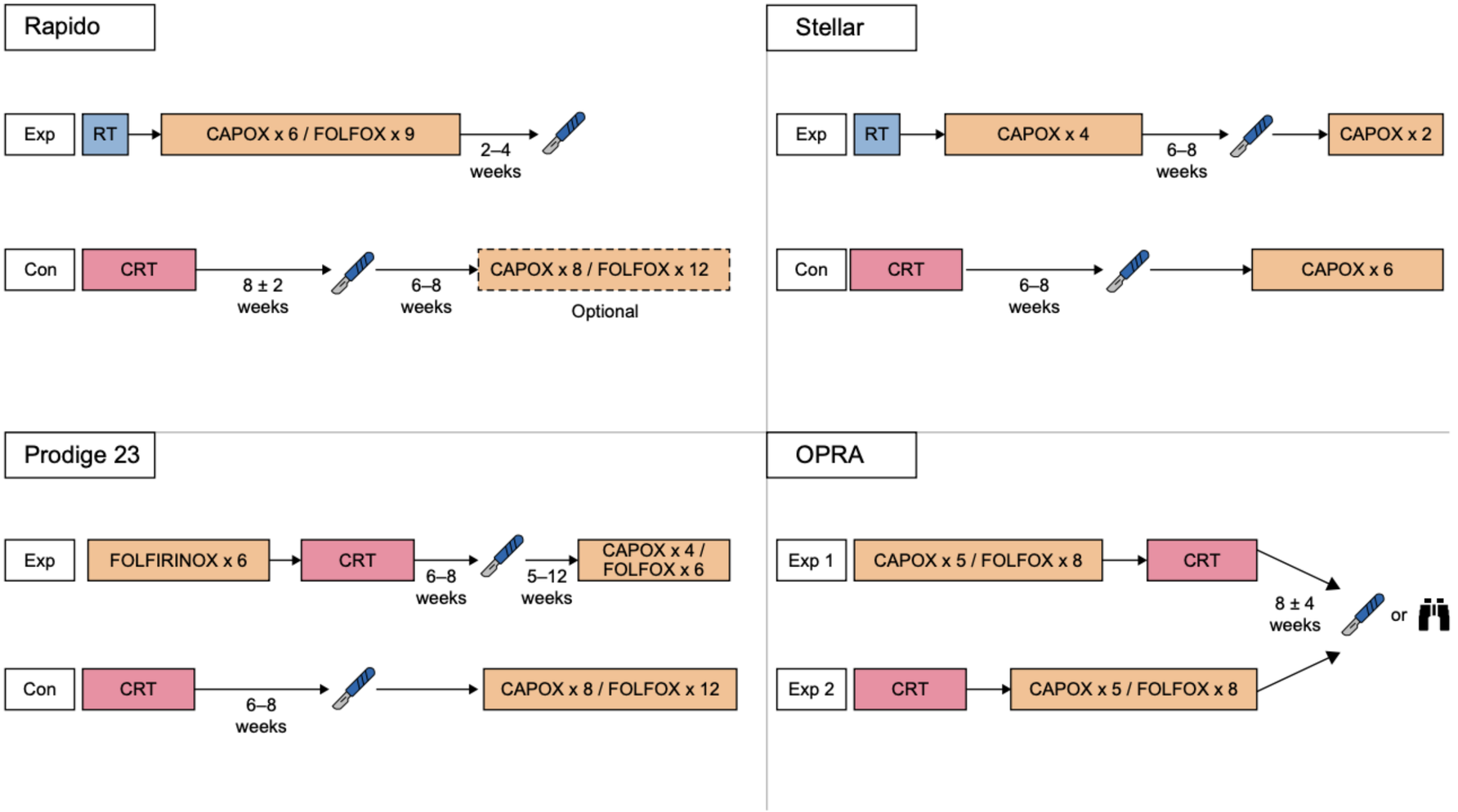
Same-day referral to reproductive endo

REI can usually slot in **~2 weeks**

If insurance is the barrier: **Livestrong / Alliance** funds

ASCO Fertility Preservation Guideline 2018 (update 2024) · NCCN AYA Oncology v.2024.

TNT sequencing strategies.



Neoadjuvant treatment of colorectal cancer: comprehensive review. BJS Open 2024 May 8;8(3):zrae038. PMID 38747103.

Surgical and non-surgical options.

Standard

Total Mesorectal Excision

Gold-standard oncologic resection. Best loco-regional control.

Risks

~50% major LARS at 1 year (sphincter-sparing)
Sexual dysfunction — autonomic injury
Urinary dysfunction
Potential permanent stoma (APR for distal)

Indications

Locally advanced; non-responders to to neoadjuvant;
patients who can't adhere to W&W
W&W surveillance.

GRECCAR 2 · OPRA · STAR-TREC · IWWD · Cercek NEJM 2022.

Selective

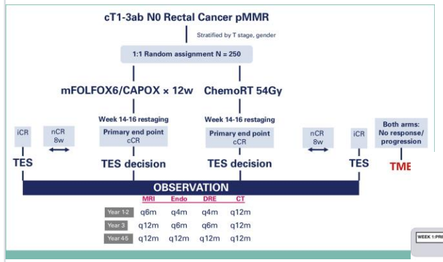
Local Excision

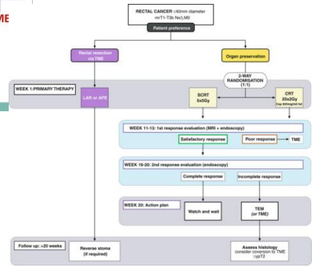
TEM / TAMIS / TES — full-thickness resection without TME.

Risks

Less LARS, less sexual/urinary dysfunction
Higher local recurrence vs. TME if not selected well
May still need salvage TME

NEO-RT / STAR-TREC





Organ-preservation

Watch & Wait

→ Clinical CR after TNT → **DRE + endoscopy + MRI**
→ Restaging MRI w/ no residual / ypT0 features
→ Patient who can **adhere to surveillance**
→ Multidisciplinary review

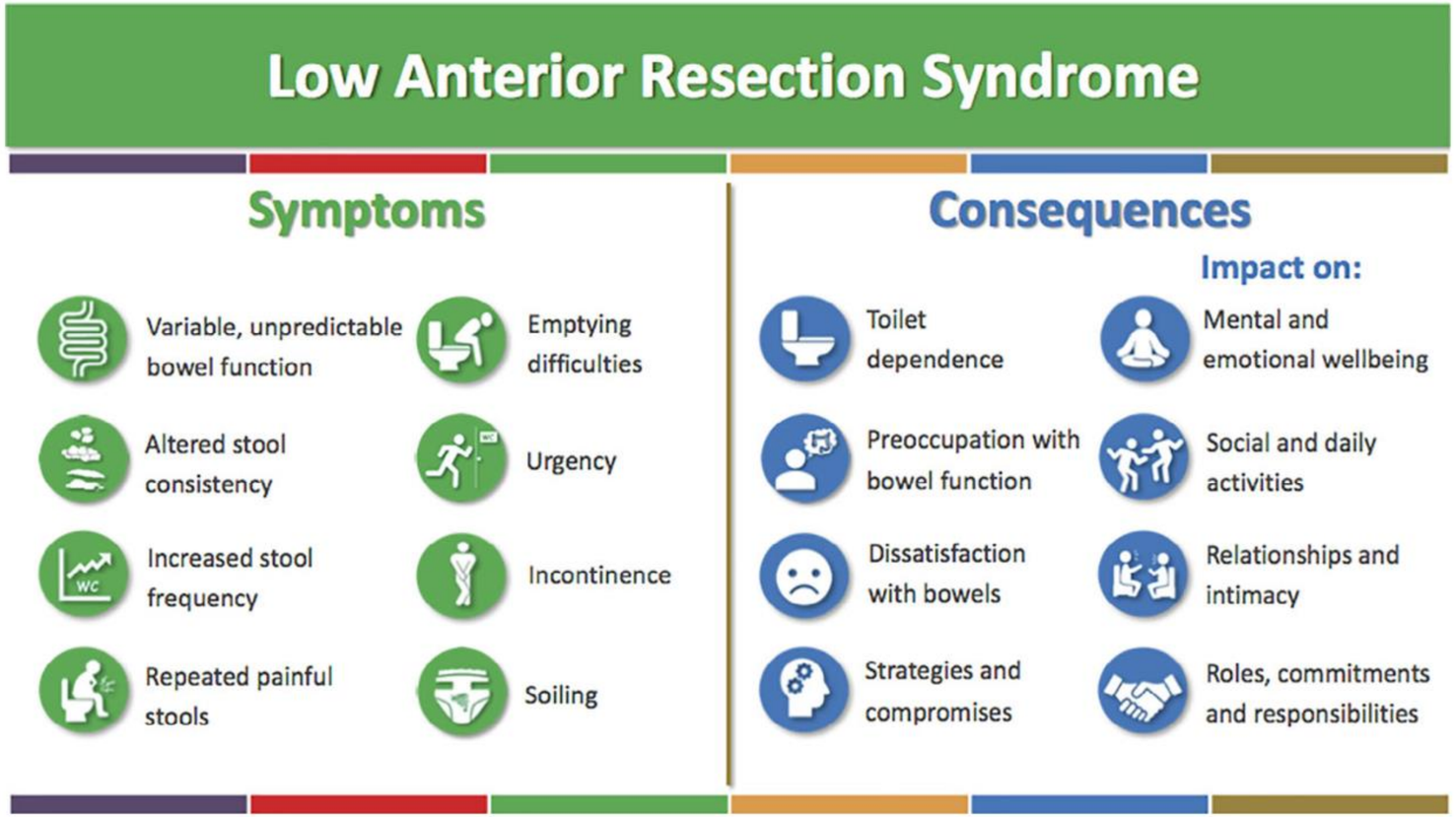
Risks

→ Local regrowth **~25–30%** — most salvageable
→ Surveillance intensity burden
→ Patient must be reliable

Evidence

→ **IWWD** registry — outcomes comparable
→ **OPRA** — pathway-defining trial
→ **Cercek 2022** — dMMR --> IO

Unspoken Realities and Finding a "New Normal."



Keane et al. Dis Colon Rectum. 2020

By the numbers

~50%

major LARS at 1 year after sphincter-sparing surgery.

Lasts years

persistent for many — often the dominant survivorship issue at 5+ years.

In a young patient's life

Work — bathroom proximity
Parenting — school, sports
Intimacy — body image & partners
Mental health — anxiety, withdrawal

Use the LARS score at follow-up — it gives patients vocabulary they don't otherwise have.

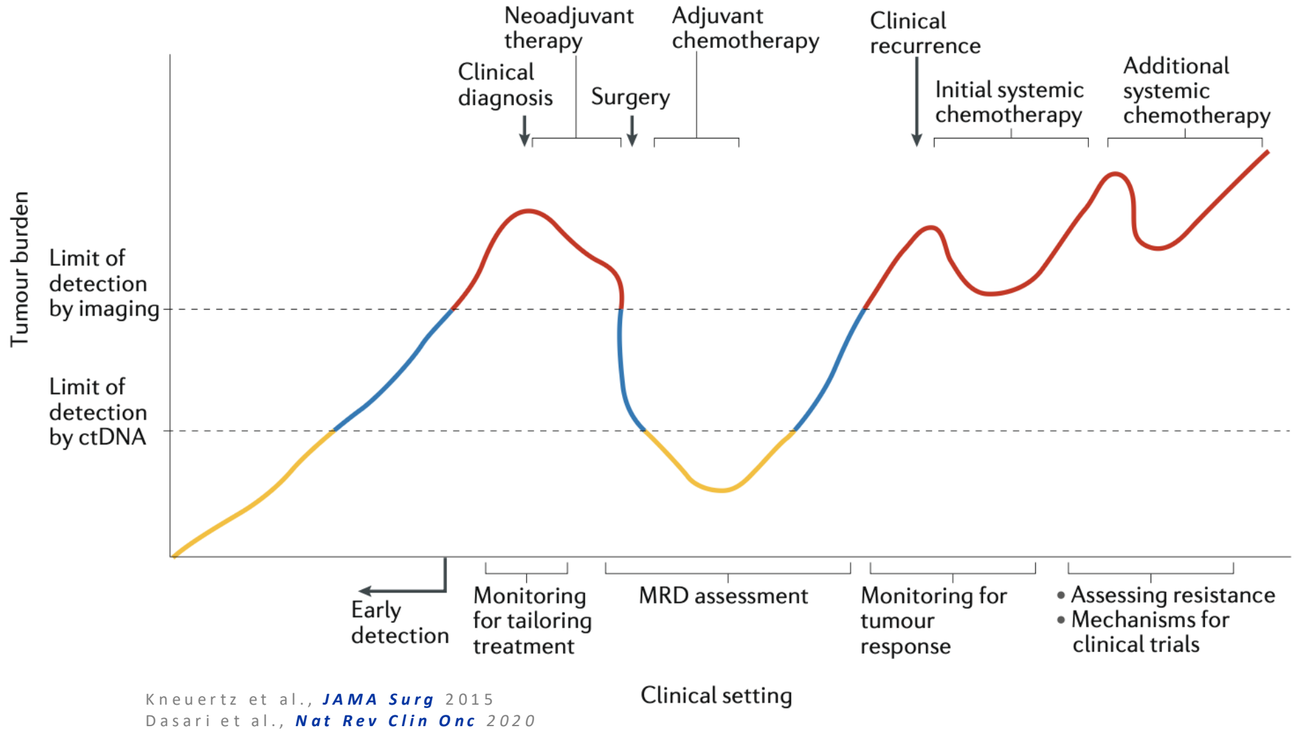
Personalized medicine — who really needs adjuvant?

Overtreatment of Young Adults With Colon Cancer More Intense Treatments With Unmatched Survival Gains

Table 2. Likelihood of Receiving Postoperative Systemic Chemotherapy and Multiagent Regimens for Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers[a]

Patients Who Received Chemotherapy	Any Chemotherapy, No. (%)	Odds Ratio for Receiving Chemotherapy (95% CI)	Multiagent Regimens, No. (%)	Odds Ratio for Receiving Multiagent Regimen (95% CI)
Stage I				
Ages 65-75 y (n = 8991)	162 (1.8)	1 [Reference]	52 (43.0)	1 [Reference]
Ages 18-49 y (n = 1926)	109 (5.7)	2.88 (2.21-3.77)	43 (48.3)	1.38 (0.71-2.68)
Stage II Overall				
Ages 65-75 y (n = 11 011)	2748 (25.0)	1 [Reference]	773 (41.7)	1 [Reference]
Ages 18-49 y (n = 3083)	1732 (56.2)	3.93 (3.58-4.31)	670 (54.9)	1.71 (1.48-1.97)
Stage II Low Risk				
Ages 65-75 y (n = 4822)	923 (19.1)	1 [Reference]	313 (39.6)	1 [Reference]
Ages 18-49 y (n = 1636)	826 (50.5)	4.22 (3.70-4.81)	388 (52.5)	1.67 (1.34-2.09)
Stage II High Risk				
Ages 65-75 y (n = 6189)	1825 (29.5)	1 [Reference]	677 (42.7)	1 [Reference]
Ages 18-49 y (n = 1447)	906 (62.6)	3.69 (3.23-4.20)	454 (57.0)	1.77 (1.46-2.14)
Stage III				
Ages 65-75 y (n = 11 202)	8175 (73.0)	1 [Reference]	4209 (59.4)	1 [Reference]
Ages 18-49 y (n = 4780)	4132 (86.4)	2.42 (2.18-2.68)	2590 (71.5)	1.75 (1.58-1.93)
Stage IV				
Ages 65-75 y (n = 5803)	3652 (62.9)	1 [Reference]	2567 (80.4)	1 [Reference]
Ages 18-49 y (n = 3313)	2710 (81.8)	2.74 (2.44-3.07)	2136 (88.6)	1.90 (1.60-2.26)

MRD framework with ctDNA



Kneuertz et al., *JAMA Surg* 2015
Dasari et al., *Nat Rev Clin Onc* 2020

MRD / adjuvant-calibration trials: ***DYNAMIC*** · ***DYNAMIC-III*** · ***COBRA*** · ***CIRCULATE-US*** · ***GALAXY/CIRCULATE-Japan.***

Goal: identify the role of ctDNA for adjuvant chemotherapy

Supporting the Journey.

QLACS framework

Quality of Life in Adult Cancer Survivors

Avis NE et al., Qual Life Res 2005.

Generic
- Negative feelings
- Positive feelings
- Cognitive problems
- Sexual problems
- Physical pain
- Fatigue
- Social avoidance

Cancer-specific
- Appearance concerns
- Financial problems
- Distress-recurrence
- Distress-family
- Benefits of cancer

Financial toxicity

Two incomes, young debt debt load. Engage financial financial navigator early.

Mental health

Anxiety + depression higher in higher in YOCRC vs. older-onset. Screen every visit.

Sexual health

Pelvic RT + surgery → dysfunction. Ask directly. Sex therapy, pelvic floor PT.

Family / kids

Childcare during treatment. Caregiver burden.

Late treatment effects

Neuropathy, cardiotoxicity, secondary malignancy, ostomy. Decades-long.

Reintegration

Return to work, identity rebuild. YOCRC support groups/communities.

Exercise as treatment-adjunct

Movement on treatment shifts the survival curve.

CHALLENGE (Courneya et al., 2024) — structured exercise during/after adjuvant chemo improves DFS in stage III colon. **Prescribe exercise.**

Bottom line

Survivorship begins on Day 1. Engage resources — social work, mental health, sex therapy, pelvic floor PT, financial navigators — at initial visit.

Avis NE et al., Qual Life Res 2005. · Courneya KS et al. NEJM 2024 (CHALLENGE).

What to take back to clinic.

Suspect it. Rectal bleeding, change in bowel habits, or iron-deficiency anemia in an adult <50 is colon cancer until proven otherwise.

Test everyone <50. Germline multigene panel *per* NCCN, regardless of family history. Tumor molecular profiling.

Early fertility referrals. Should run concurrent to staging prior to treatment.

Run workup in parallel. Staging, genetics, tumor profile, fertility, psychosocial.

Frame trade-offs honestly. YOCRC patients patients are choosing between cures *and and* between post-treatment sequelae — — oncologic cure, fertility, sexual function, function, LARS, stoma.

Build the 30-year plan. Survivorship — financial, mental health, sexual, late toxicity — starts early.

Prescribe movement. Exercise during & after adjuvant shifts the survival curve.

Refer for clinicals trial. YOCRC patients ask.

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