Сеченовский Университет

КК МХ

КЛИНИКА КОЛОПРОКТОЛОГИИ И МАЛОИНВАЗИВНОЙ ХИРУРГИИ

Первого МГМУ им. И.М. Сеченова Минздрава России

Hereditary colorectal cancer

Inna Tulina

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(Moscow Russia)

Hereditary CRC – historic viewpoint

- Traditionally – clinical information
  - Familial accumulation
  - Early-onset CRC
  - Multiple tumours
  - Other related cancers
  - Presence of polyposis or multiple polyps
  - Other specific features characterizing specific conditions
    - Adenomatous polyposis
    - Hamartomous polyposis

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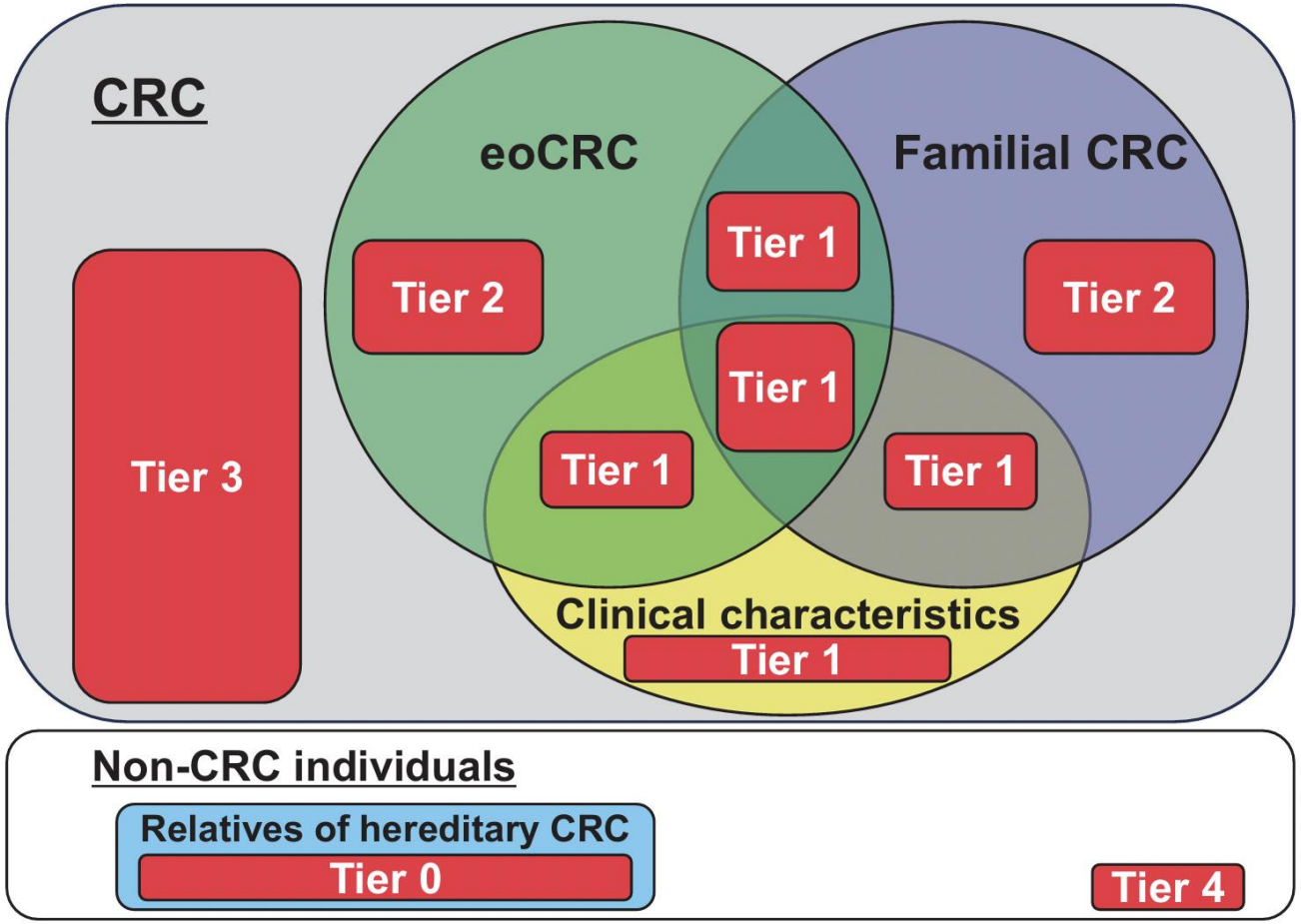
J Anus Rectum Colon 2025; 9(2): 167-178 dx.doi.org/10.23922/jarc.2025-001

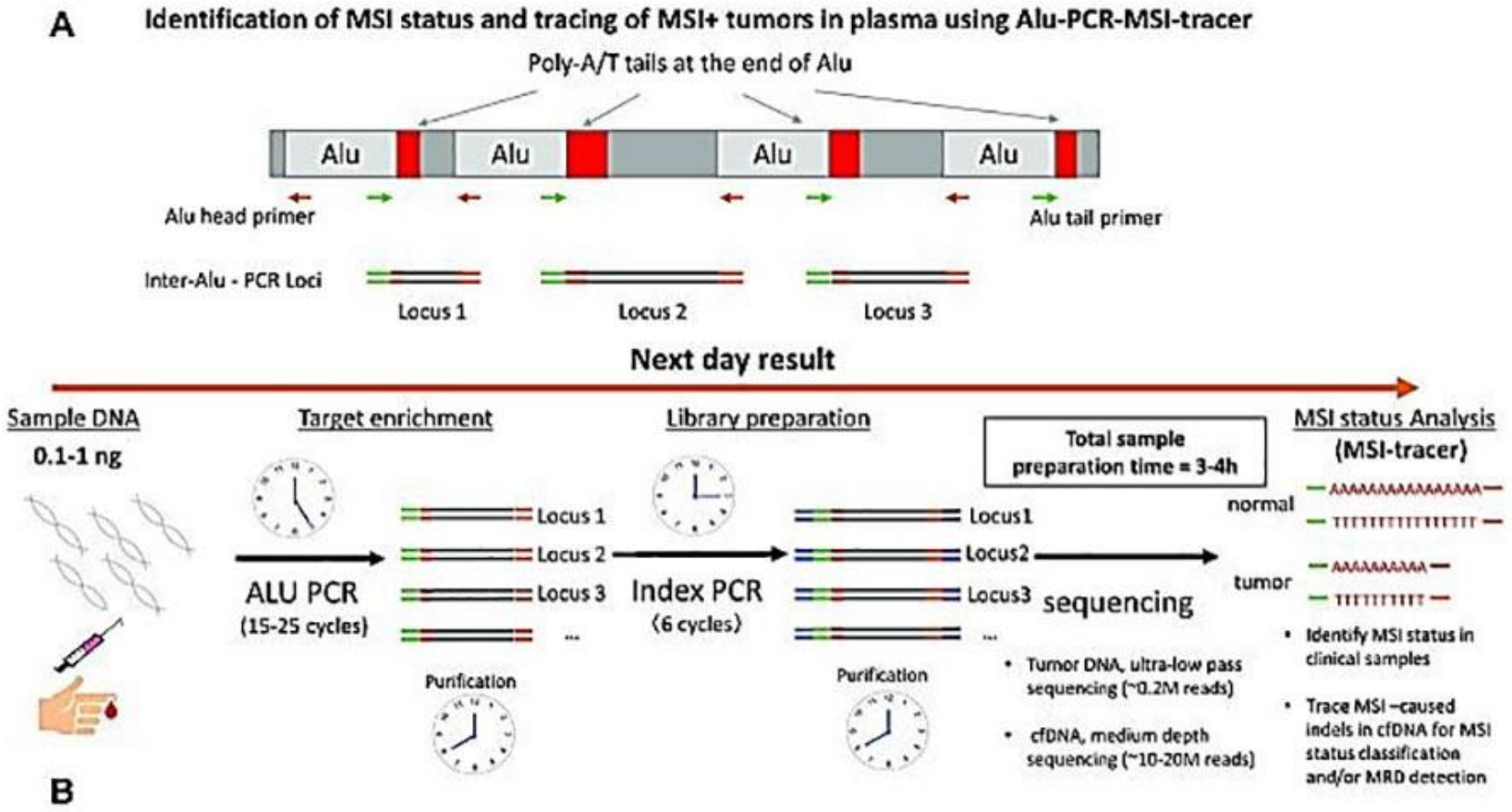


Diagnosis of hereditary CRC

- TIER 1
  - traditional diagnostic criteria specific to each cancer syndrome
  - Amsterdam criteria
- TIER 2
  - revised Bethesda guidelines
- TIER 3 and 4
  - universal tumor testing
  - universal genetic testing
- TIER 0
  - Cascade testing

Comprehensive Ds of hereditary CRC – recent time

- MSI test
  - PCR
  - NGS
- MMR test
  - IHC



Comprehensive Ds of hereditary CRC – recent time

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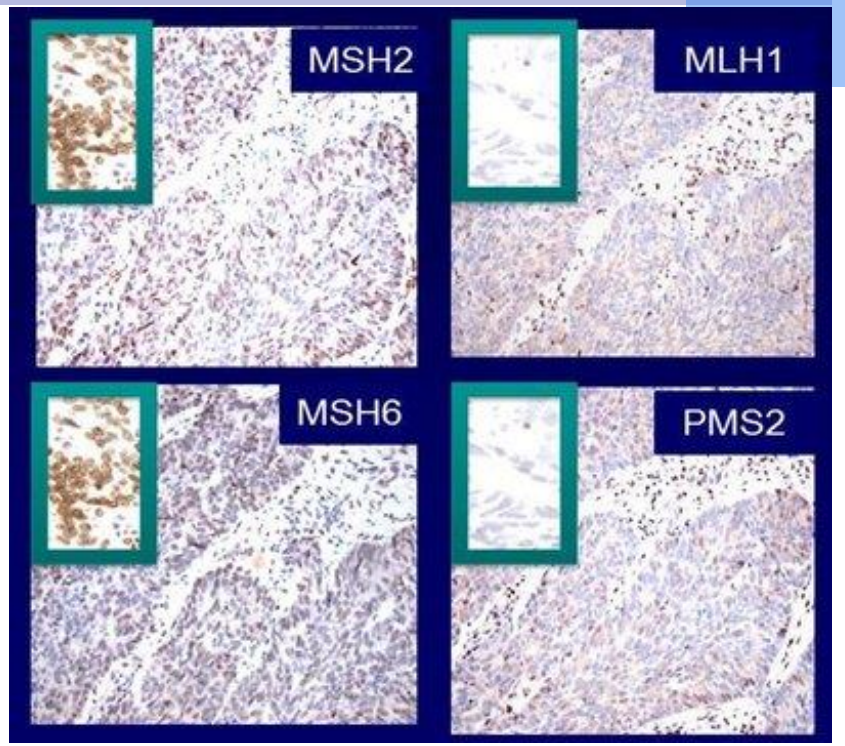
  - PCR
  - NGS
- **MMR test**
  - **IHC**



All CRC

Seppälä TT, Latchford A, Negoi I, et al. European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. Br J Surg. 2021 May; 108(5): 484-98.

All endometrial cancer

Crosbie EJ, Ryan NAJ, Arends MJ, et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med. 2019 Oct; 21(10): 2390-400

European guidelines – localized rectal cancer (2025)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

SPECIAL ARTICLE

Localised rectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

R.-D. Hofheinz[1], E. Fokas[2], L. Benhaim[3], T. J. Price[4], D. Arnold[5], R. Beets-Tan[6], M. G. Guren[7], G. A. P. Hospers[8], S. Lonardi[9], I. D. Nagtegaal[10], R. O. Perez[11], A. Cervantes[12,13] & E. Martinelli[14], on behalf of the ESMO Guidelines Committee*

Recommendations

- MSI and/or MMR status should be assessed in all patients at diagnosis using biopsy material [I, A; ESCAT score: I-B].
- Analysis of *RAS*, *BRAF* V600E, *NTRK* and HER2 status currently has no impact on the treatment of localised tumours and cannot be recommended [IV, D].

Molecular biology

Assessment of mismatch repair (MMR) proteins on biopsies or LE specimens can identify patients with sporadic microsatellite instability-high (MSI-H) tumours or Lynch syndrome, who may benefit from treatment with immunotherapy and, in the case of Lynch syndrome, referral for genetic counselling [see ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) for further details — Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.05.528].

As neoadjuvant therapy can disrupt MMR staining or diminish the number of evaluable tumour cells, baseline biopsy material is preferred. Analysis of *RAS*, *BRAF* V600E, *NTRK* and human epidermal growth factor receptor 2 (HER2) status currently has no impact on the treatment of localised tumours.

Russian guidelines – rectal cancer (2025)

Genetic testing to exclude hereditary rectal cancer

- **Suspected Lynch syndrome:**
  - Amsterdam II or Bethesda criteria
  - MSI or dMMR

1. Hereditary cancer syndromes

Amsterdam II criteria

At least three members of a family with hereditary nonpolyposis or associated (endometrial, small bowel, ureter or renal pelvis cancer) colorectal cancer and the following criteria must be met:	First degree of consanguinity in at least two of the affected members
	Clinical presentation in at least two consecutive generations
	Diagnosis of at least one case of CRC or associated cancers before age 50
	Discarded familial adenomatous polyposis
	Tumors verification through histopathology tests

1. Hereditary cancer syndromes

- **Bethesda criteria**

Tumors of individuals should be screened for microsatellite instability in the following situations:	CRC in a patient diagnosed before age 50
	Presence of synchronous, metachronous or other HNPCC-associated tumors regardless of the age
	CRC with high microsatellite instability (MSI-H) in a patient diagnosed before age 60
	CRC in one or more first-degree relatives with HNPCC or HNPCC-related tumor diagnosed before age 50
	CRC diagnosed in two or more of first or second degree relatives with HNPCC-related tumor regardless of age

Russian guidelines – rectal cancer (2025)

Genetic testing to exclude hereditary rectal cancer

- **Suspected Lynch syndrome:**
  - Amsterdam II or Bethesda criteria
  - MSI or dMMR

  NGS for MLH1, MSH2, MSH6 and PMS2
- **Suspected FAP**
  - >100 polyps
  - 1 first degree relative with diagnosed FAP

  NGS for APC
- **Suspected attenuated FAP**
  - 20-100 polyps and polyps and older persons

  NGS for APC
  - 20-100 polyps but no pathogenic APC

  NGS for MUTYH

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Early-onset colorectal cancer (EO-CRC)

1. Is it really a rising problem?
2. Is it a different disease from LO-CRC?
3. Are the patients different?
4. Should we make something different for these patients?
   - Screening
   - Prevention
   - Diagnosis
   - Treatment
   - Follow-up

CRC epidemiology

- **Median age at diagnosis**
  - Colon cancer **68 years** in men and **72** years in women
  - Rectal cancer **63** years both genders

(Am C Soc 2017, Siegel 2018)

- **Incidence CRC**
  - USA: since 2000 decreased 2-3% per year

(Am C Soc 2017, Siegel 2018)

  - Europe: since 2008-2016 increased 6% annually

(Malvezzi 2018, Vuik 2018)

- **Mortality CRC**
  - Europe: decreased since 2012 by 6,7% in men and 7,5% in women

(Malvezzi 2018, Vuik 2018)

EO-CRC epidemiology – USA

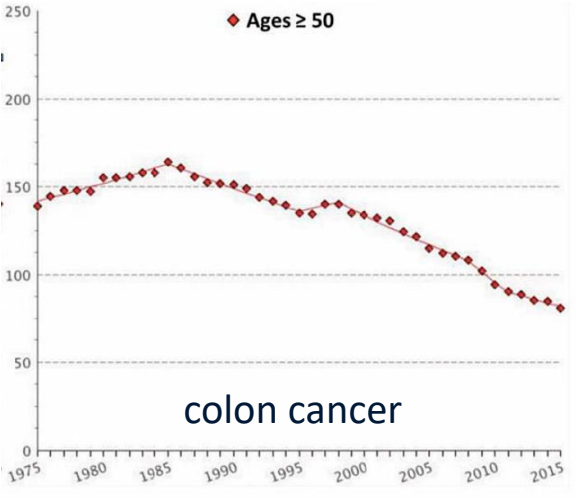
- **SEER database 2018**
  - CRC: 5% diagnosed at age <45 years

(CRC – Cancer Stat Facts 2018)

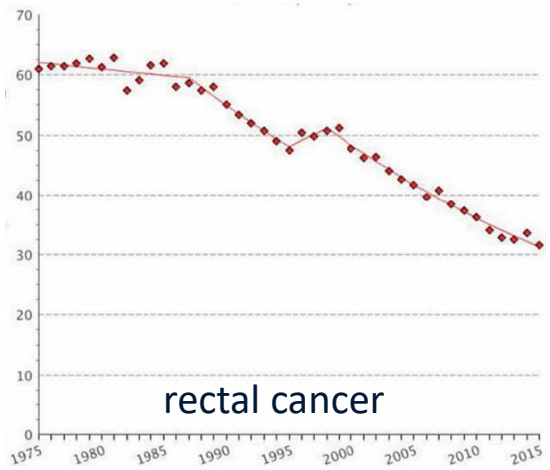
  - Rectal cancer: 18% diagnosed at age <50 years

(Ahnen 2014)

- **EO-CRC in USA**
  - Since 1994 incidence in pts <55 y.o. increasing by 2% per year



colon cancer



rectal cancer

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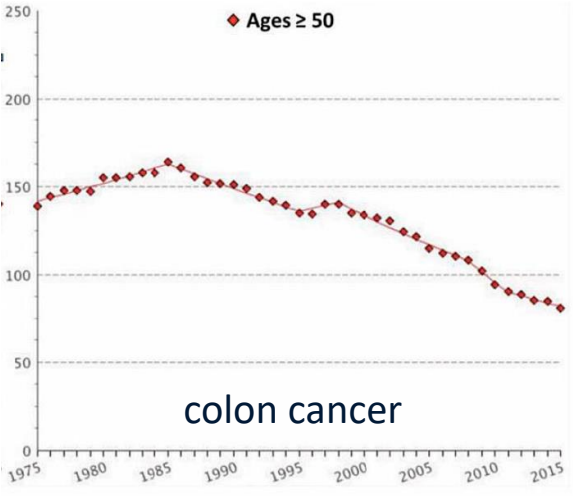

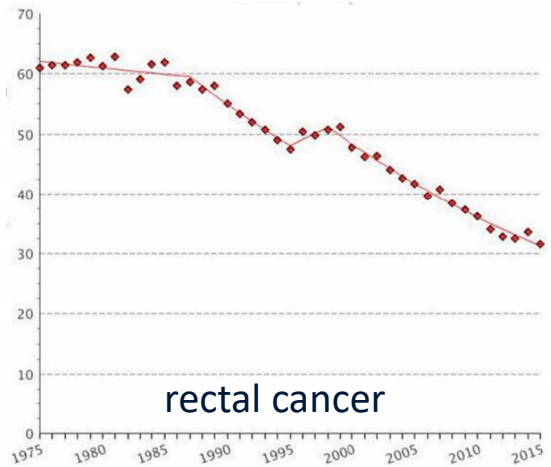

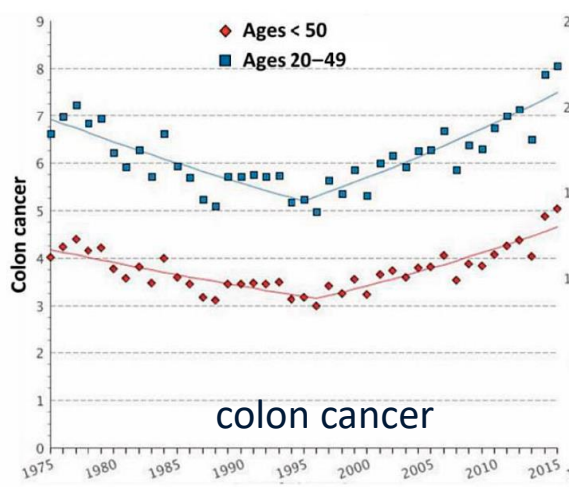

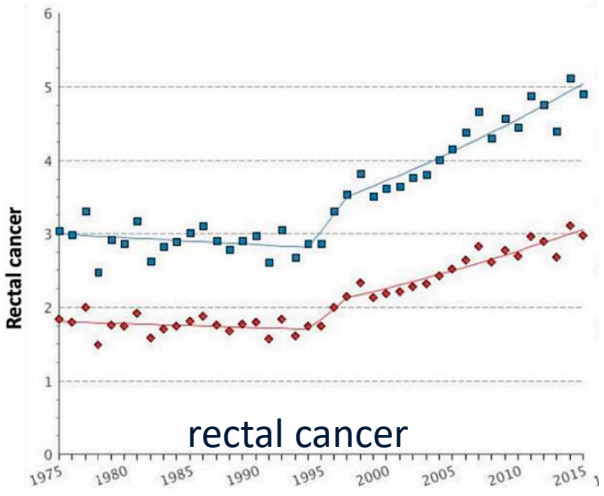

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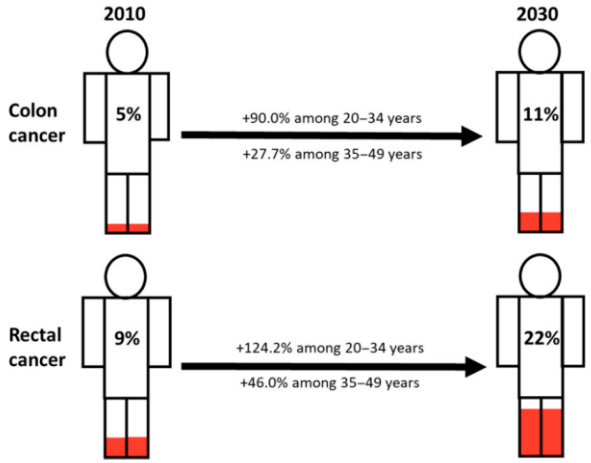
- **EO-CRC in USA**
  - Since 1994 incidence in pts <55 y.o. increasing by 2% per year
  - 2015: **4%** colon ca **9%** rectal ca
  - 2030 (prognosis): **10%** colon ca **22%** rectal ca

(Bailey 2015)

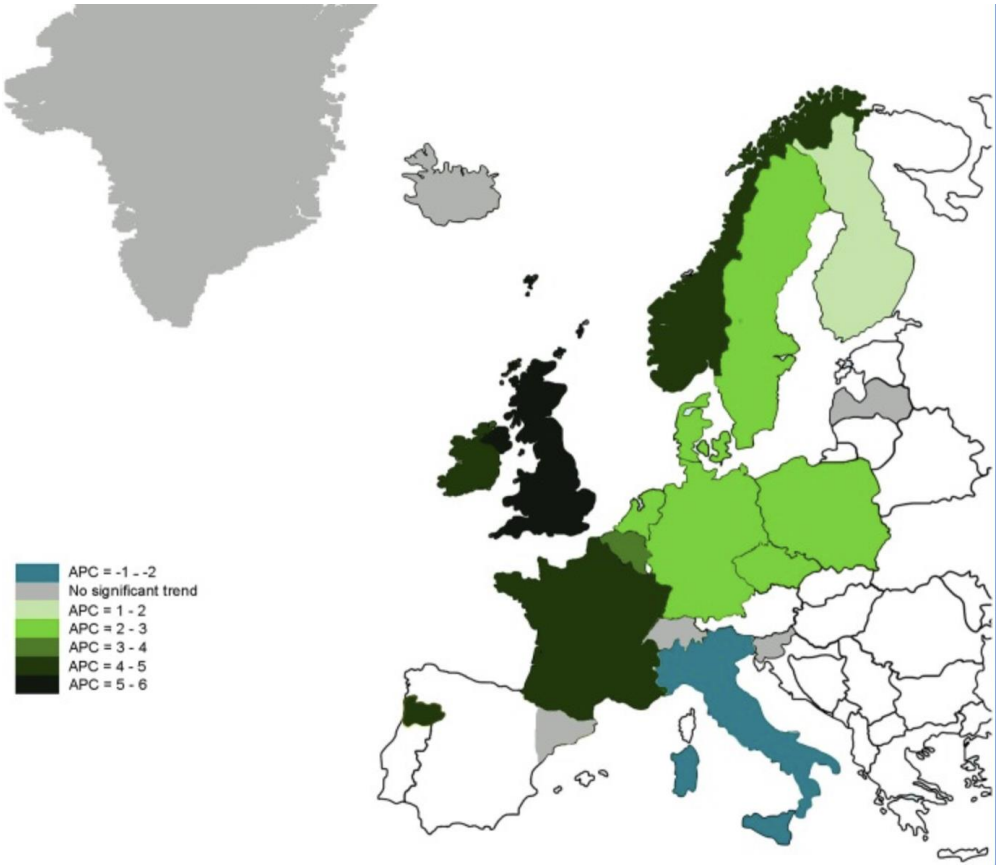


⇒ screening age **45 years**

EO-CRC epidemiology – Europe

Vuik et al. Gut 2019

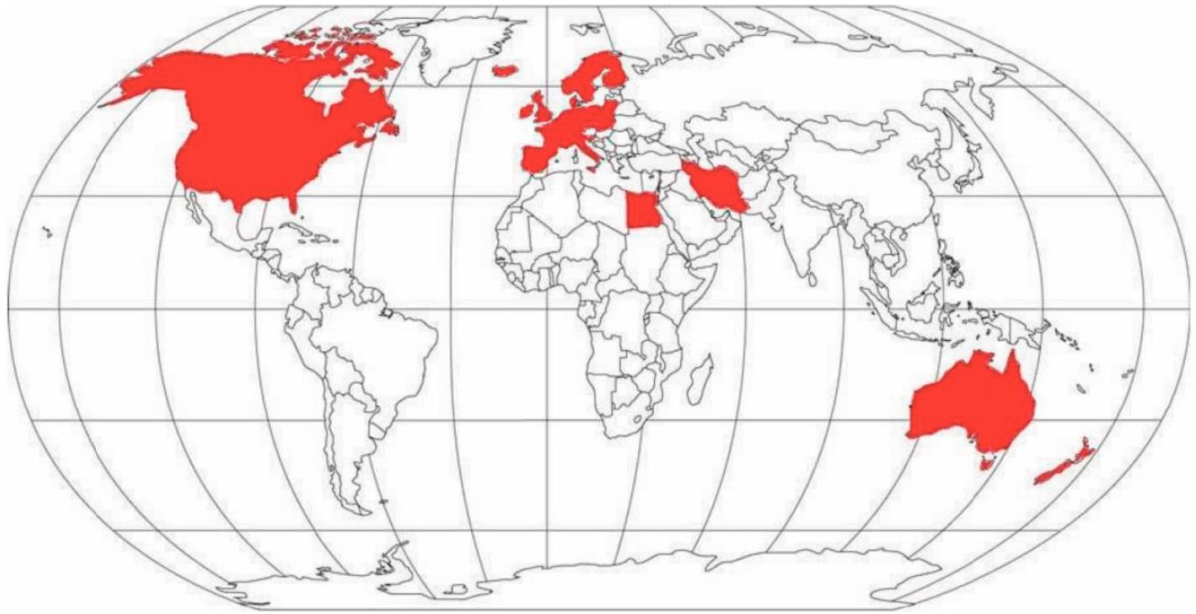
- **20 European countries** – EO-CRC
  - Increasing incidence: 14
  - Stable: 5
  - Decreasing: 1 (Italy)



EO-CRC epidemiology – worldwide

Siegel et al. Am Soc Clin Oncol Educ Book 2016

- 36 countries on 5 continents – EO-CRC
  - Incresing incidence: 19
  - Stable: 14
  - Decreasing: 3 (Austria, Italy, Lithuania)



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EO-CRC vs. LO-CRC

- Clinical presentation
- Pathomorphology
- Outcomes

Clinical presentation

- **Diagnosis 6 months later the onset of symptoms** (1,2,3)
  - Low level of suspiciousness by probands and clinicians
  - Sense of invincibility in young adults
  - Lack of medical insurance
- **Diagnosed at stage III-IV**
  - **61%** in pts <50 years (4)
  - **76%** in pts <30 years (5,6,7)
  - **46-50%** in pts >50 years (4,7,8)

1. Bleyer et al. Nat Rev Cancer 2008
2. Hill et al. J Clin Oncol 2007
3. O'Connell Am J Surg 2004
4. Kneuertz et al. JAMA Surg 2015
5. Indini et al. Pediatr Blood Cancer 2017
6. Kam et al. Colorectal Dis 2004
7. Khan et al. J Pediatr Surg 2016
8. Ferrari et al. Pediatr Blood Cancer 2008

Pathomorphology

Signet cell CRC

▶ <30 y.o.	**6.1-6.4%**	(1,2)
▶ 30-39 y.o.	**2.3-2.4%**	(1,2)
▶ 40-49 y.o.	**1.0%**	(2)
▶ >50 y.o.	**1.0-1.6%**	(2, 3, 4)

1 Holowatyj et al. J Clin Oncol 2019 (31259751)
2 Willauer et al. Cancer 2019 (30854646)
3 Kneuertz et al. JAMA Surg 2015 (25806815)
4 Inamura et al. Ann Surg Oncol 2015 (25326395)

Survival – conflicting data

- **Poorer prognosis**
  - <30 y.o. compared to >50 y.o. (1,2,3)
  - the younger the patient, the worse the prognosis (4)
  - Different biological background likely underlies earlier and faster CRC progression (1,5,6,7)

1. Khan 2016
2. Lieu 2014
3. Sultan 2010
4. Lieu 2014
5. Ferrari 2008
6. Indini 2017,
7. Zhao 2017

Survival – conflicting data

- **Comparable or better prognosis**
  - <50 y.o. compared to >50 y.o. – better prognosis

1. Kneuertz 2015,
2. Kolarich 2018
3. Vatandoust 2016
4. Wang 2015

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Potential genetic scenarios in EO-CRC

1. Known hereditary cancer syndromes
2. De novo germline hereditary cancer mutations
3. Familial colorectal cancer
4. Non-hereditary and non-familial CRC

1. Hereditary cancer syndromes

22% among EO-CRC
2-5% among general population

(Chang 2012, Jasperson 2010, Mork 2015)

- **Lynch syndrome (#1)**
  - Most frequent, 1/3 among pts <35 years old *(Mork 2015, Pearlman 2017, Stoffel 2018)*
  - 70% lifetime risk of CRC, 40% onset before age 40 *(Lynch 2008)*
- **Adenomatous polyposis syndromes**:
  - **Familial adenomatous polyposis (FAP) #2**
    lifetime risk of CRC 100%, median age of onset 39 years *(Zbuk 2009)*
  - **Polymerase proofreading-associated polyposis (PAAP)**
  - **MutYH-associated polyposis (MAP)**
    10-50 polyps around age 40
    28-fold risk CRC <60 years old
  - **NTHL1-associated polyposis (NAP)**
- **Li-Fraumeni syndrome**
  (germline *TP53* mutation) <1% cases

MCRA - multiple colorectal adenoma

British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)

- lifetime total of ≥ 10 colonic adenomas under the age of 60

or

- a lifetime total of ≥ 20 adenomas

or

- ≥ 10 adenomas plus a family history of either colorectal cancer or polyposis

- Stanich PP, Pearlman R, Hinton A, Gutierrez S, LaDuca H, Hampel H et al (2019) Prevalence of germline mutations in polyposis and colorectal cancer-associated genes in patients with multiple colorectal polyps. Clin Gastroenterol Hepatol 17(10):20082015.e3.
- Mak S, Alexander JL, Clark SK, Hawkins M, Cuthill V, Latchford A et al (2024) The diagnostic yield of genetic testing in patients with multiple colorectal adenomas: a specialist center cohort study. Clin Transl Gastroenterol 15(1):1–8

1. Hereditary cancer syndromes

- **Screening programmes**
  - Adherence is low
    Promote strong adherence
  - In LS reduces the risk of death by 65%

(Jarvinen 2000)

- **Preventive aspirin regimen**
  reduce the risk of CRC incidence

(Burn 2011)

2. De novo germline hereditary cancer mutations

- **Only a half EO-CRC pts report CRC in a first-degree relative**
- So they are the first to be diagnosed with a cancer-predisposing syndrome *(Stoffel 2018)*
- Other genes (2-10% in EO-CRC) *(Pearlamn 2017, Stoffel 2018)*
  - *SMAD4*
  - *BRCA1-2*
  - *ATM*
  - *BUB1-2*
  - *BRF1*
  - *CHEK2*
- **Genetic councelling is recommended for all pts with extreme EO-CRC <35 years** *(Mork 2015)*

3. Familial EO-CRC

- Familial CRC not affected by hereditary CRC syndromes:
  - Amsterdam criteria I or II (+)
  - Bethesda criteria (+)
  - No Lynch Syndrome

  = Familial Colorectal Cancer Syndrome Type X

  (Nejadtaghi 2017, Umar 2004, Vasen 1991, 1999)
- Ideal group to extend molecular screening to find potentially actionable gene alterations
  - To confer survival benefit if receiving appropriately targeted agents
  - Garre 2015:
    - 48 EO-CRC pts Amsterdam criteria II (+)
    - 29 (60%) had BRCA2 germline mutation (point and frame)
    - If metastatic CRC these pts might benefit from platinum or PARP-inhibitor based regimens

Familial Colorectal Cancer Syndrome Type X

- linked to an increased risk of CRC
- no association with an increased risk of extracolonic cancer
- Compared with LS, CRCs in FCCTX have characteristic clinicopathological features, including
  - older age at diagnosis
  - more likely left-sided location
  - not linked to poorly differentiated or mucinous histology
- **Colonoscopic surveillance significantly reduces CRC incidence and improves survival** among asymptomatic members of FCCTX families

Familial Colorectal Cancer Syndrome Type X

- The genetic causes of FCCTX are heterogeneous have not yet been fully elucidated
- Putative caused:
  - germline pathogenic variants in BRCA2, BMPR1A, FAN1, MUTYH, OGG1, RSP20, SEMA4A, and SETD6
  - co-segregation of germline variants in the BRCA1 and RNF 43 genes with CRC

4. Non-hereditary and non-familial EO-CRC

- **About 50% of pts**

  (Mork 2015, Stoffel 2018)

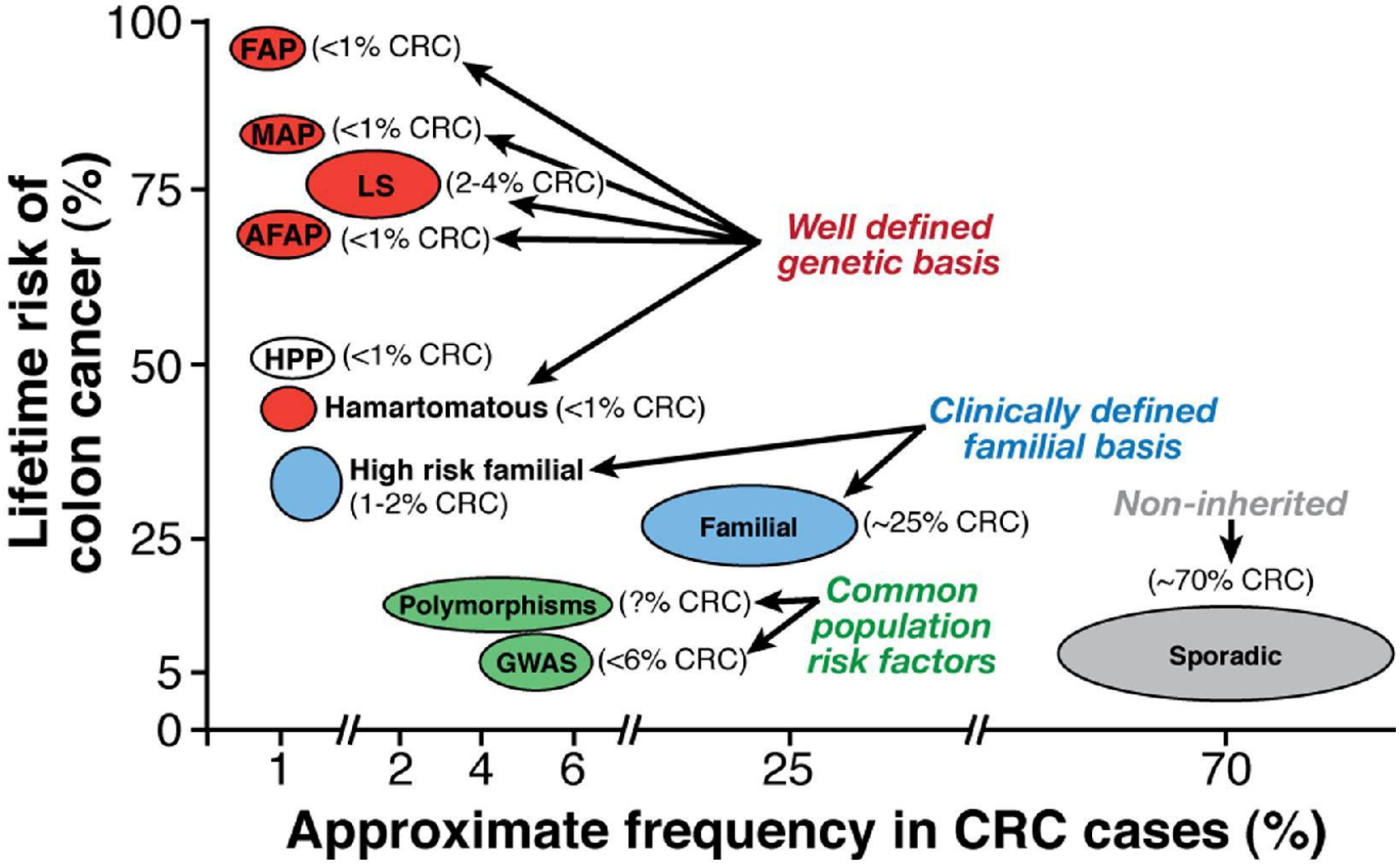
- Not included in screening programmes
- Often diagnosed at later stages
- Specific characteristics:
  - Different alterations in genes:
    TNFR1, EIF4E, LTBP4, CYR61, UCHL1, FOS, FOS B

    (Berg 2010, Hong 2007, Kirzin 2014)
  - Different expression of immune activation genes (*CLC, IFNAR1*)

    (Agesen 2011)
  - Higher prevalence of MMR, POLE, POLD1 abberations
    more pts could potentially benefit from immunotherapy in mts setting

    (Pai 2017)

Sporadic CRC – risk factors



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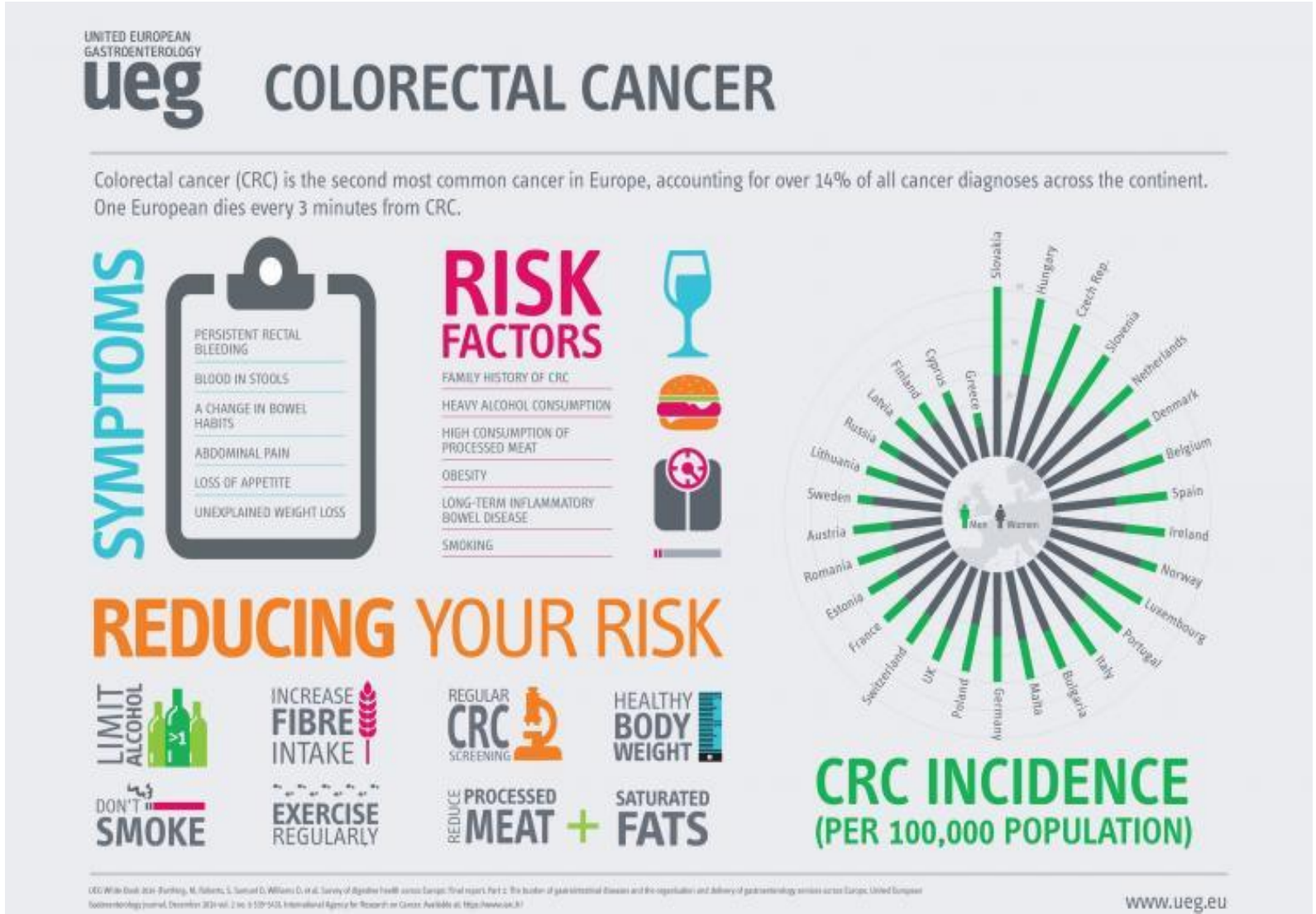


Sporadic EO-CRC – modifiable risk factors

- **Obesity** – 20% higher risk of EO-CRC

  (Liu 2019)

- **Obesity at early age** – higher risk of colon cancer
  - Proinflammatory cytokines produced by adipose tissue
  - Chronic exposure to hyperinsulinemia and IGF-1

  (Hidayat 2018)

- **Diabetes mellitus** – 30% increased risk

  (Larsson 2005)

- **Alcohol and tobacco**, especially together

  (Zisman 2006, Rosato 2013)

Sporadic EO-CRC – modifiable risk factors

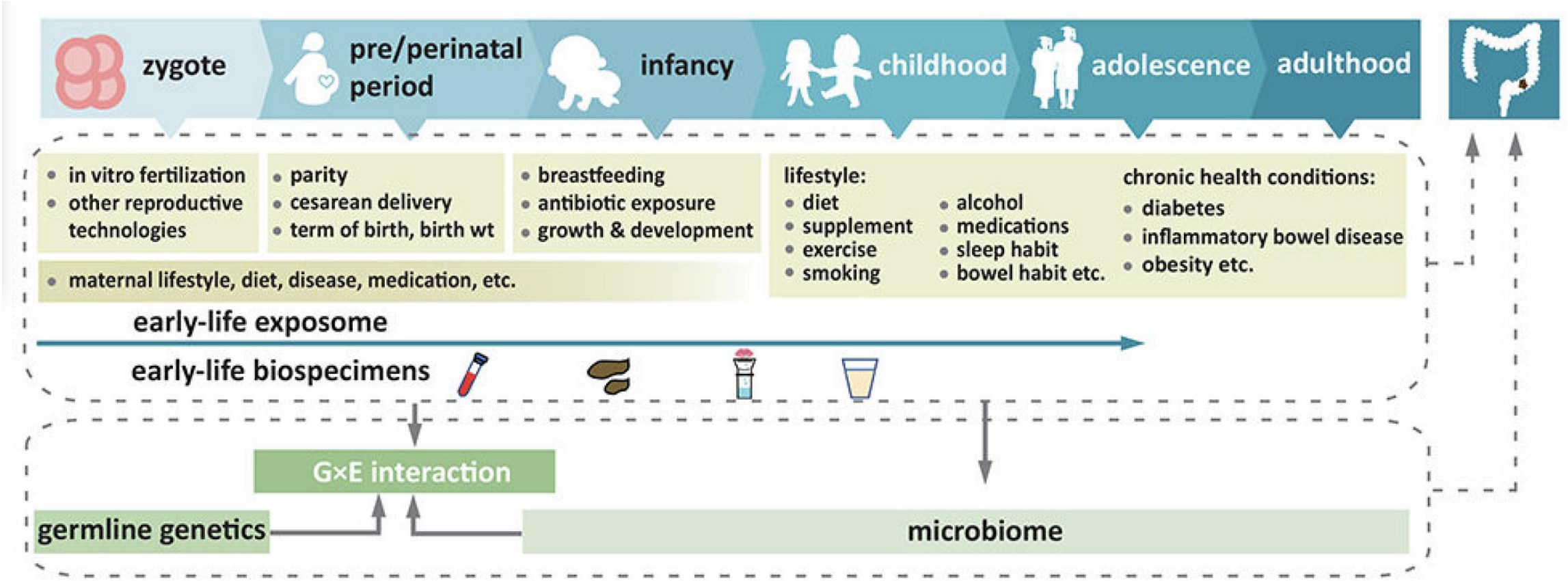
- **Diet**
  - Red and processed meat — *Vieira 2017, Parr 2013, Chao 2005*
  - Sugar sweetened beverages — *Fuchs 2014*
  - Fiber
    short-chain fatty acids – anti-inflammatory effect — *Glover 2019, Wu 2013*
  - dairy, fruit, vegetables — *Vieira 2017*
  - Fish, beta-carotene, vitamin C, vitamin D, folate — *Rosato 2013, Ma 2011*
- **Aspirin and NSAIDs**
  inhibition of COX - anti-inflammatory effect
- **Antibiotics**
  used repeatedly or in early ages — *Dik 2016, Cao 2018*

Sporadic EO-CRC – modifiable risk factors

- **Microbiota**
  - Cesarian section
  - Appendectomy
  - Diet (colorants and preservatives – direct carcinogenesis)
  - Extensive use of antibiotics in agriculture and medicine
- **Immune system**
  - Alter the development and its capacity for cancer surveillance (Reduced breast-feeding)

Birth-cohort effect

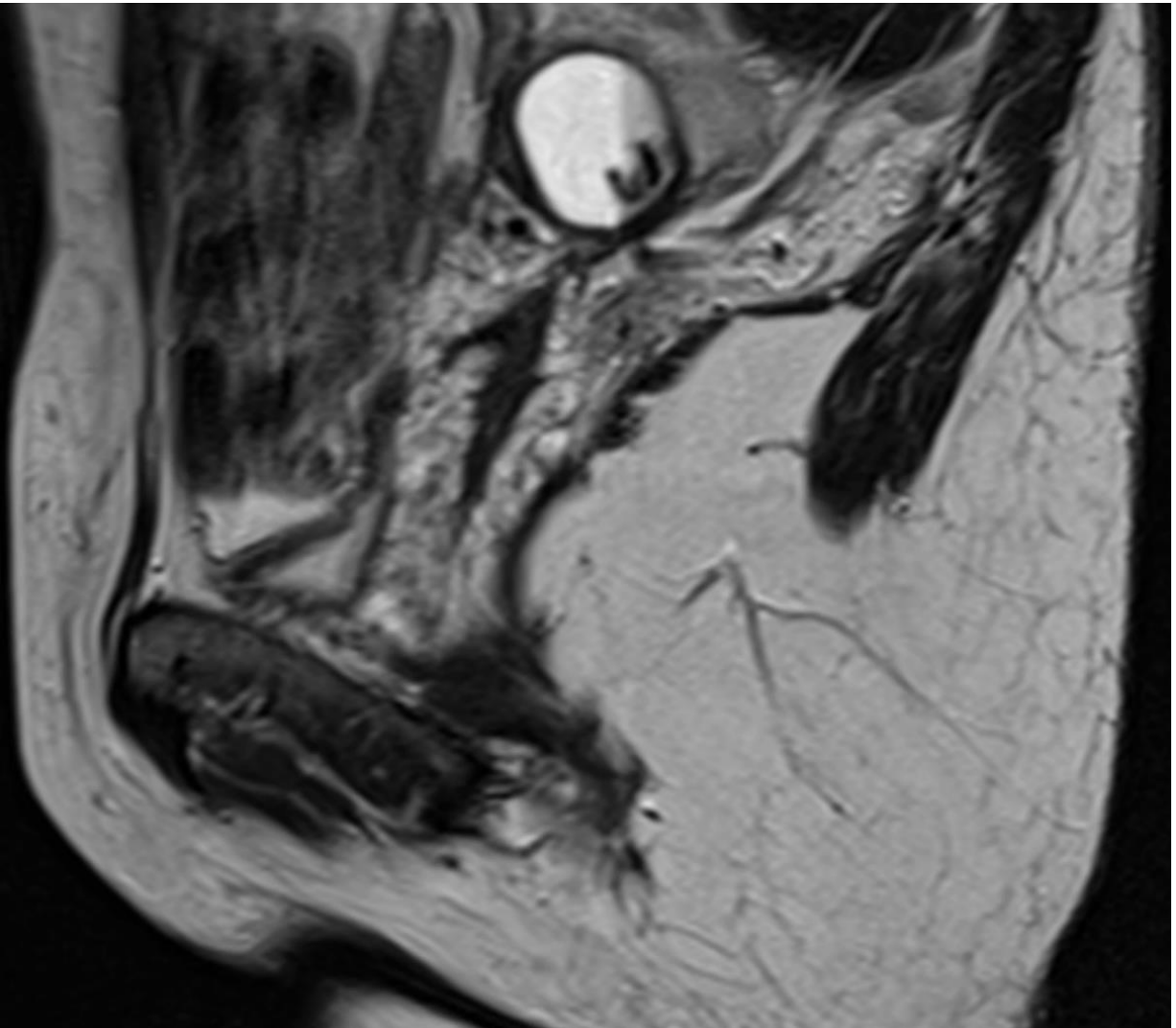
Akimoto Nat Rev Clin Oncol 2021

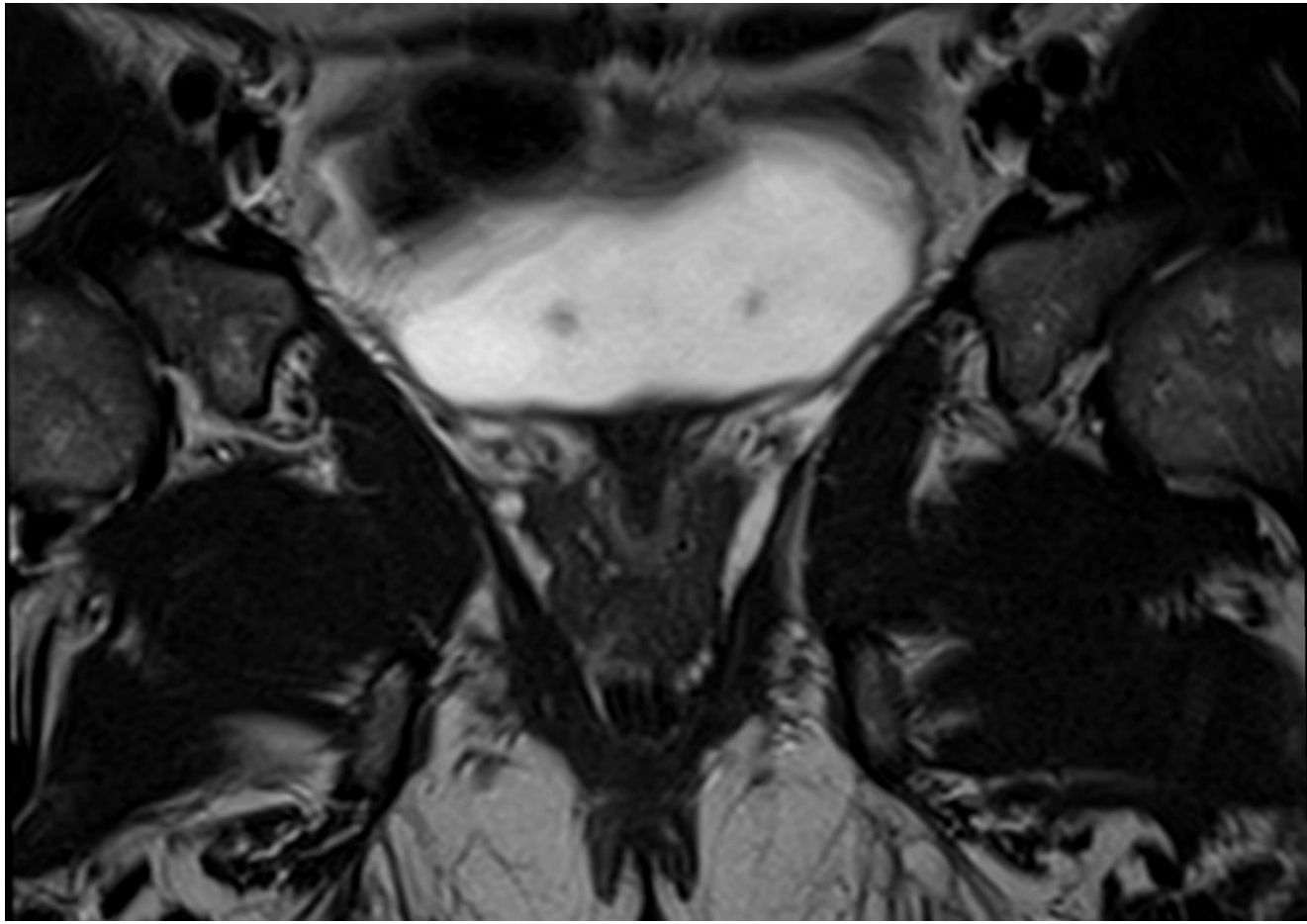


Long-term effects

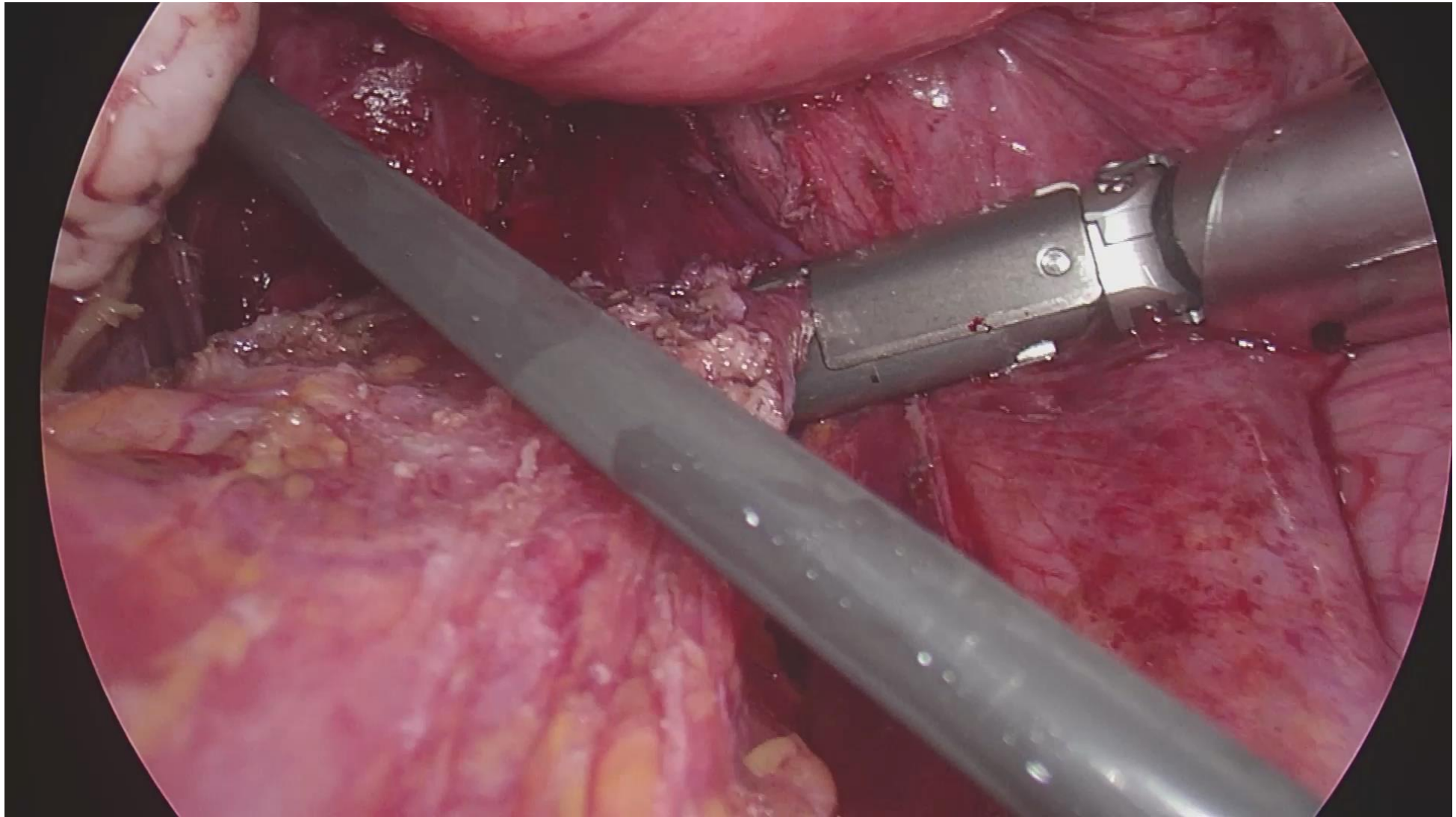
- Sexual dysfunction
- Fertilty
- Anal incontinence
- Body image acceptance
- Depression

Female 44 y.o.





Female 44 y.o.



Female 44 y.o.

Pathology report

- pT2
- pN0 (0/30)
- LVI (-)
- PNI (-)

Stage I

Early-onset colorectal cancer (EO-CRC)

1. **Is it really a rising problem?** **yes**
2. **Is it a different disease from LO-CRC?** **in some way**
3. **Are the patients different?**
   ***50% genetic predisposition**
   ***modifiable risk factors**
   ***long-term effects**
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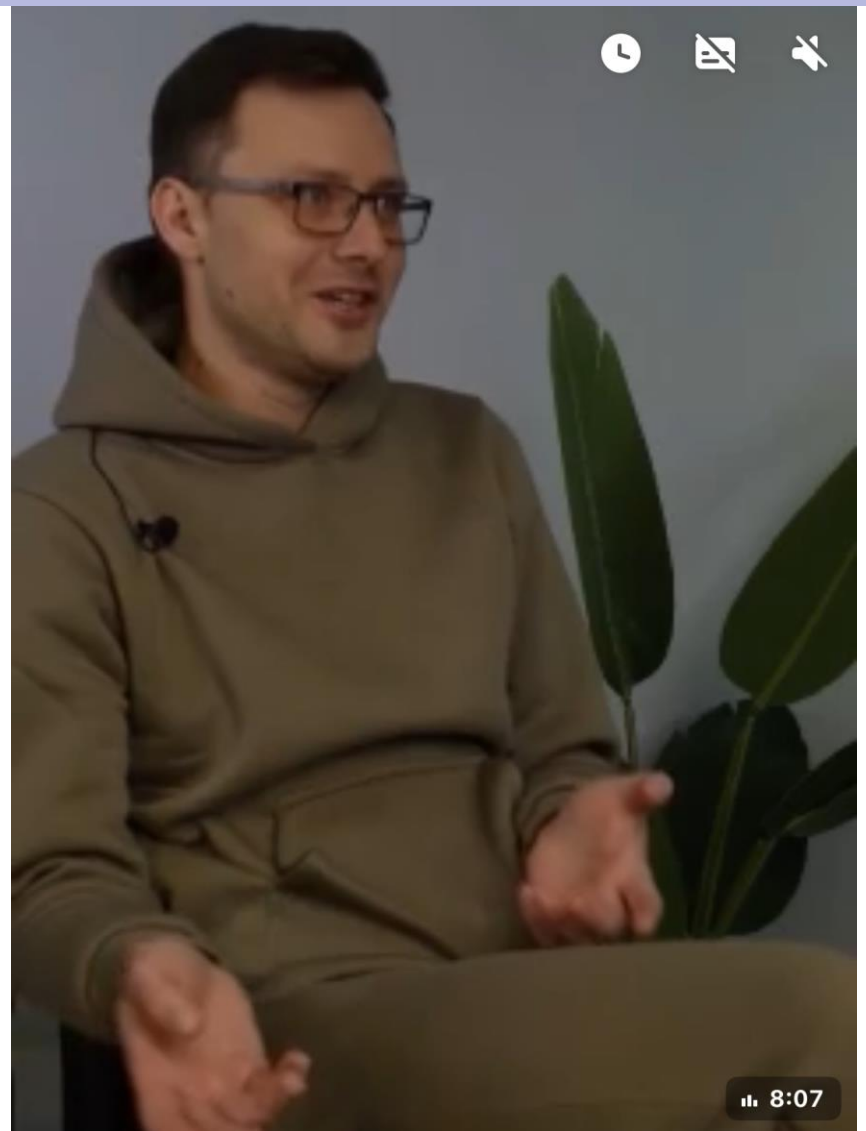
Screening, prevention EO-CRC

- **Colonoscopy** + **polypectomy** (!!!)
  - No symptoms
    no relatives with CRC — **45 y.o.**
  - No symptoms
    relatives with CRC — **40 y.o.**
    Relative age at diagnosis **–10 years**
  - Persistent symptoms:
    diarrhea/constipation
    unintentional weight loss
    bloating/gas/dyspepsia — **no minimum age**

Male, 34 y.o.



- Bloating, dyspepsia
  - 2-3 weeks
- Changed lifestyle and diet, cancelled alcohol
  - 2-3 weeks
  - No improvement
- Gastroenterologist – medical treatment
  - 4 weeks
  - No improvement
- Patient insisted on colonoscopy (gastroenterologist didn’t suggest – no “red flags”)
  - Splenic flexure cancer

Diagnosis EO-CRC

- Standard protocol
  - Colonoscopy
  - Contrast CT chest+abdomen
  - Contrast MRI pelvic
- Genetic councelling
  - <35 y.o. especially
  - Whole genome sequencing
- MSI testing

Treatment EO-CRC

- Balance:
  aggressive treatment vs long-term consequences
  - Careful diagnosis (early vs advanced cancer)
  - Sphincter-preserving surgery
  - Avoidance of abundant CRT

Treatment EO-CRC

- EO-CRC pts consistently receive more aggressive treatment

  Kneuertz 2015, Rodriguez 2018, Yang 2012, Quah 2007, Hubbard 2012, Kolarich 2018, Abdelsattar 2016

- Military Health System:
  pts with EO-CRC receive **2-8 times more adjuvant CT**

  Manjelievskaia 2017

- It remains unclear whether aggressive treatment of EO-CRC
  - Can improve survival

    Rodriguez 2018, Orsini 2015

  - Does not improve survival

    Kneuertz 2015, Manjelievskaia 2017, Kolarich 2018

- Rectal cancer pts <50 y.o.
  surgery vs neoadj CRT + surgery – no benefit

  (Kolarich 2018)

Early-onset colorectal cancer (EO-CRC)

1. **Is it really a rising problem?** **yes**
2. **Is it a different disease from LO-CRC?** **in some way**
3. **Are the patients different?**
   ***50% genetic predisposition**
   ***modifiable risk factors**
   ***long-term effects**
4. **Should we make something different for these patients?**
   - Screening **colonoscopy**
   - Prevention **colonoscopy, genetic councelling**
   - Diagnosis **genetic councelling, genome sequencing**
   - Treatment **if early cancer – avoid aggressive overtreatment**

Genetic screening and councelling

- All patients with CRC <35 years of age
- >10 colonic adenoma in young people
- >20 lifetime colonic adenoma
- Familial Colorectal Cancer Syndrome Type X - ???

Strict colononoscopic surveillance!!!