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Genetic risk factors contributing to young-onset colorectal cancer (YOCRC)

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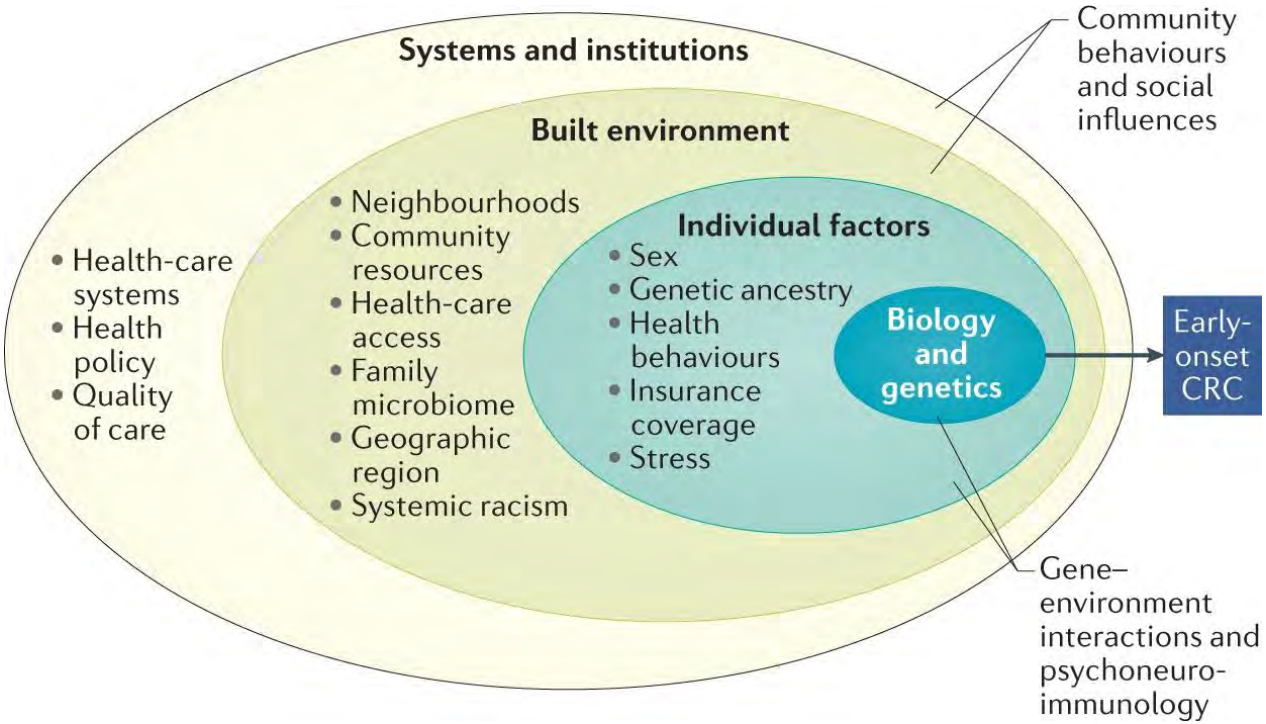
Disclosures

I have no relevant financial disclosures.

Complex factors contributing to the rise in YOCRC

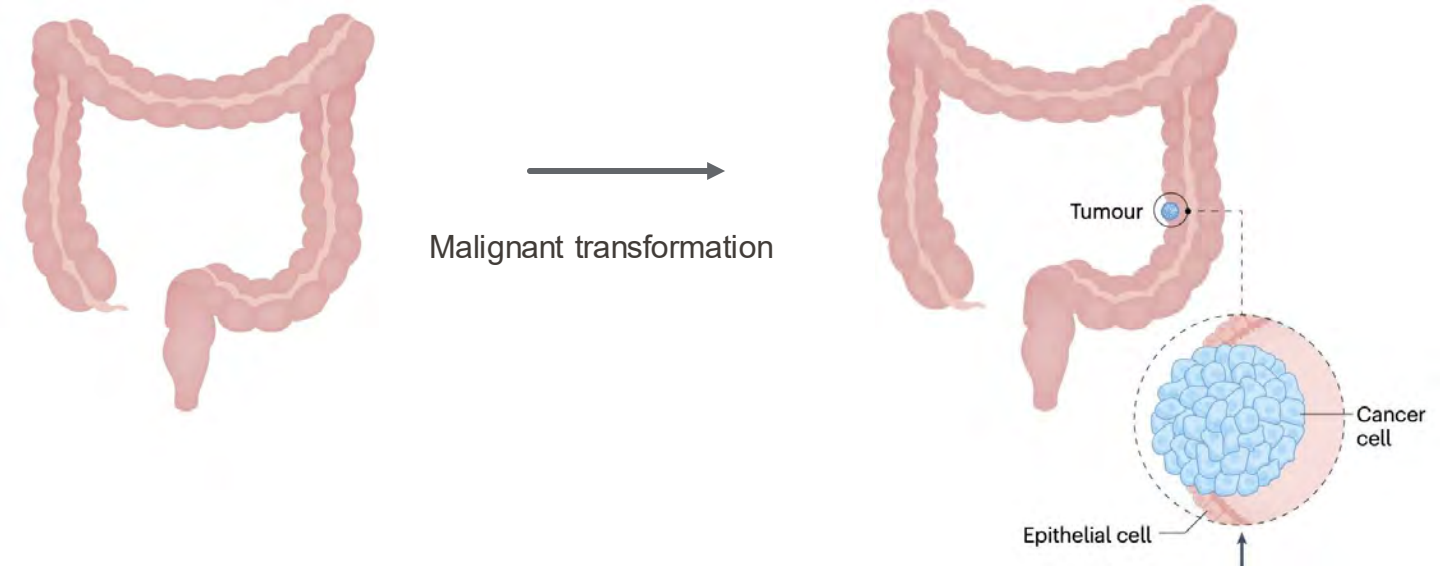


Holowatyj A, et al. Nature Reviews Cancer, 2021

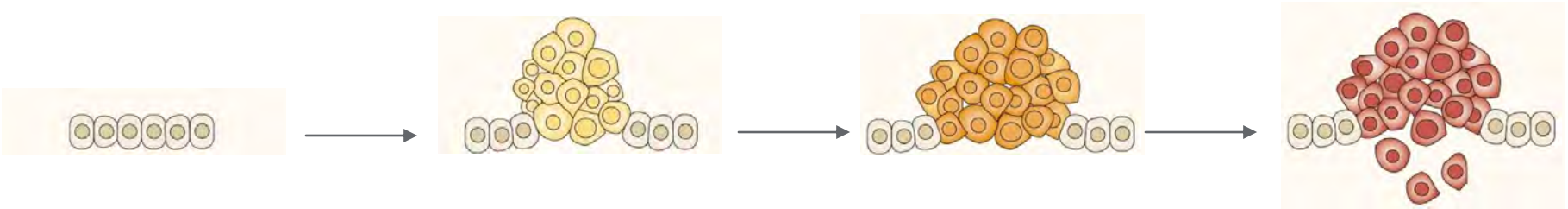
Outline

1) Genetic changes during colorectal cancer development
2) Hereditary versus non-hereditary (somatic) genetic factors: what's the difference?
3) What we know about YOCRC and hereditary cancer syndromes
4) Conclusions

Colorectal cancer represents a physical and molecular transformation of healthy cells



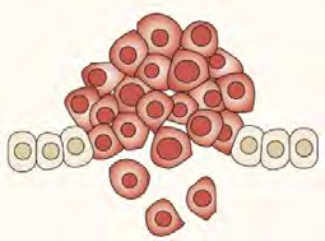
Spaander M.C.W, et al. Nature Reviews: Disease Primers, 2023



Normal colorectal tissue → Early adenoma (polyp) → Advanced adenoma → Colorectal cancer

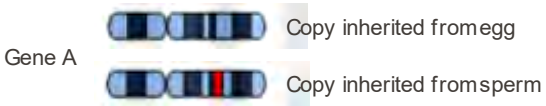
http://nature.com

Colorectal cancer represents a physical and molecular transformation of healthy cells



Normal colorectal tissue/cells

- Each cell carries two copies of every genes in the human genome
- We **inherit** one copy of a gene from each parent



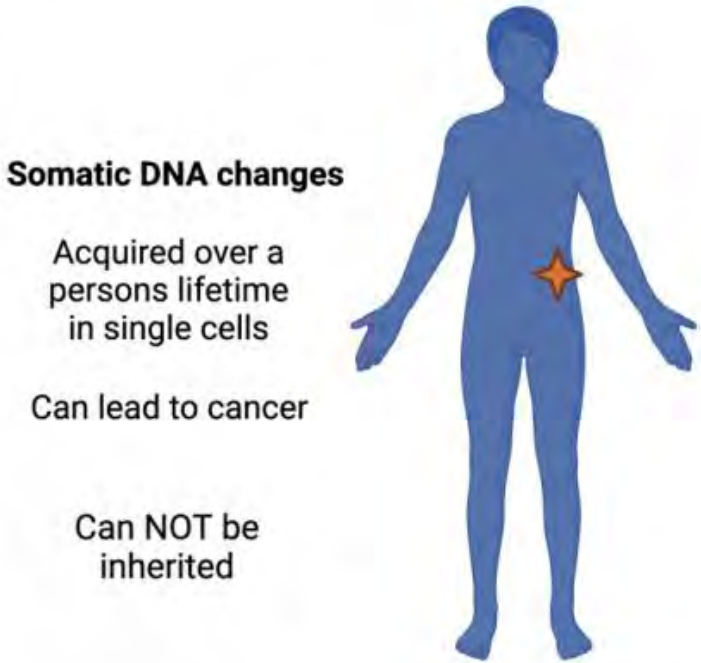
- Some copies of a gene may contain a ”variant” (mutation) that affects the normal function of that gene

- Accumulation of **somatic** mutations in pre-cancerous and cancerous cells

Colorectal cancer

- Each cancer cell contains an altered genome
- An individual gene may be mutated in a way that greatly affects its function (e.g., stimulate cancer growth and metastases)

Differences between hereditary (germline) and non-hereditary (tumor/somatic) testing

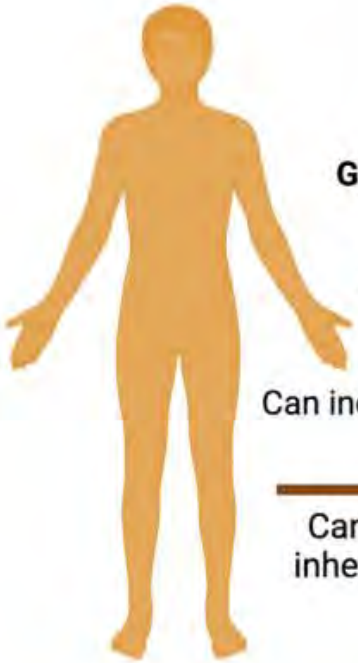


Somatic DNA changes

Acquired over a persons lifetime in single cells

Can lead to cancer

Can NOT be inherited



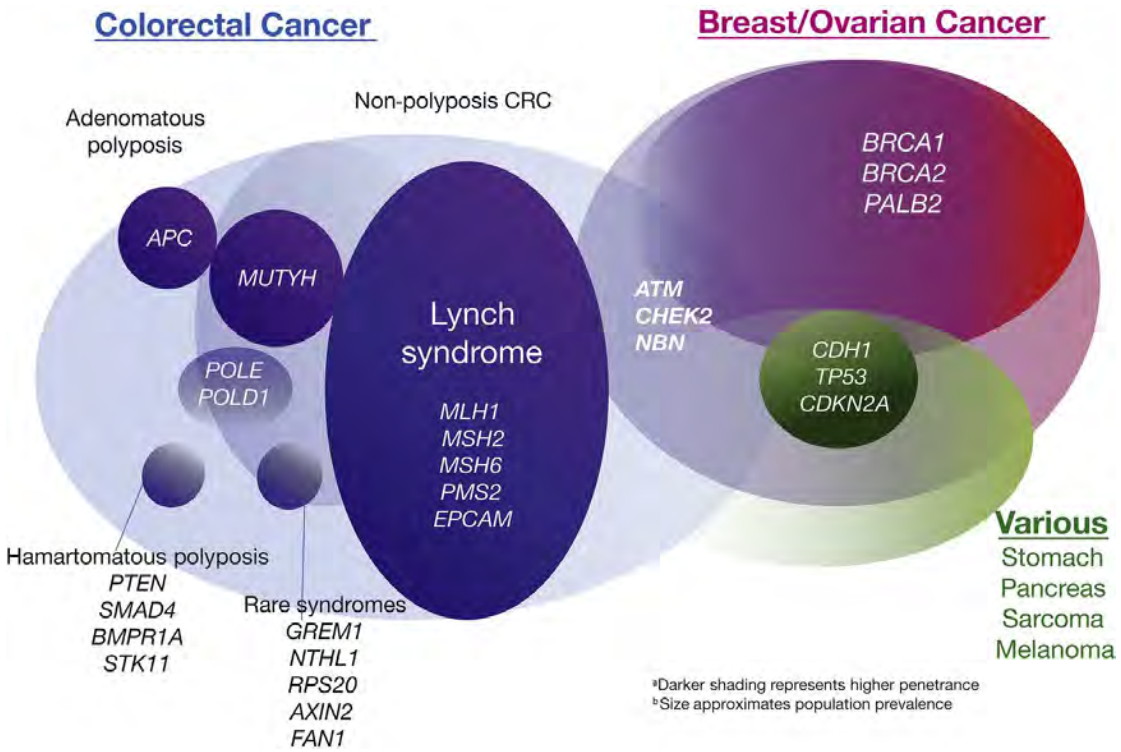
Germline DNA changes

Present in every cell of the body including egg and sperm

Can increase cancer susceptibility

Can be inherited

Known hereditary cancer syndromes



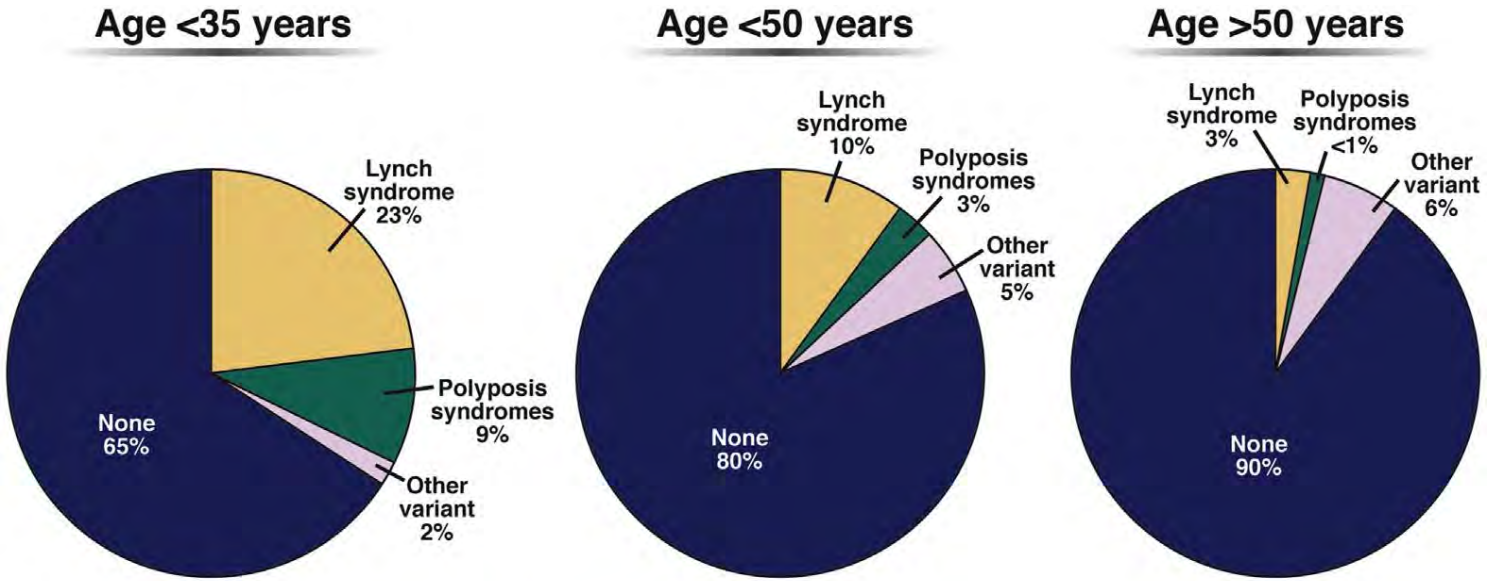
Stoffel EM, et al. Gastroenterology. 2018

Testing for known hereditary cancer syndromes

- Must be ordered by a clinician
- A sample of DNA is extracted from healthy tissue (such as blood or saliva) using a test kit. This represents the DNA a person inherits.
- DNA undergoes genetic sequencing (”spell checking”) to detect mutations/variations present within a panel of genes that are linked to hereditary colon cancer
- A mutation is categorized based on its impact on gene function and predisposition to cancer
- Results are reported back to patients and their clinicians

- Examples of testing kits/companies:

Hereditary colon cancer syndromes are found more often in people with YOCRC



Stoffel EM, Murphy CC. Gastroenterology. 2020

	Cohort characteristics	Genes tested	Pathogenic or likely pathogenic variants
Mork et al[56]	193 patients aged ≤35 years; mean age at diagnosis 29 years	Phenotype driven; all patients had been referred for genetic counselling	44/193 (23%)
Yurgelun et al[57]	336 patients aged <50 years selected from 1058 consecutive patients with colorectal cancer of all ages with mean age at diagnosis 56 years	25-gene panel	52/336 (14%)
Pearlman et al[58]	450 patients aged <50 years; mean age at diagnosis 43 years	25-gene panel	75/450 (16%)
Stoffel et al[59]	430 patients aged <50 retrospectively selected from genetic counseling service; mean age at diagnosis 40 years	124-gene or 67-gene panel	79/315 (25%)
Uson et al[60]	124 patients aged <50 years; mean age at diagnosis 43 years	83-gene or 84-gene panel	33/124 (22%)
Toh et al[61]	88 patients aged <50 years; mean age at diagnosis 41 years	64-gene panel, excluding MMR genes	12/88 (14%)

Patel, SW, et al., Lancet Gastroenterology and Hepatology, 2022

How often are people with YOCRC found to have a hereditary cancer syndrome?	**14-25%**
What is the most common hereditary cancer syndrome among people with YOCRC	**Lynch syndrome**
I don't have a family history of colorectal cancer. Could I still have a hereditary cancer syndrome?	**Yes!**
My tumor was already tested for biomarkers/genes that can determine treatment options. Could I still benefit from hereditary genetic testing?	**Yes!**

Patel, SW, et al., Lancet Gastroenterology and Hepatology, 2022

Under-utilization of hereditary genetic testing in YOCRC

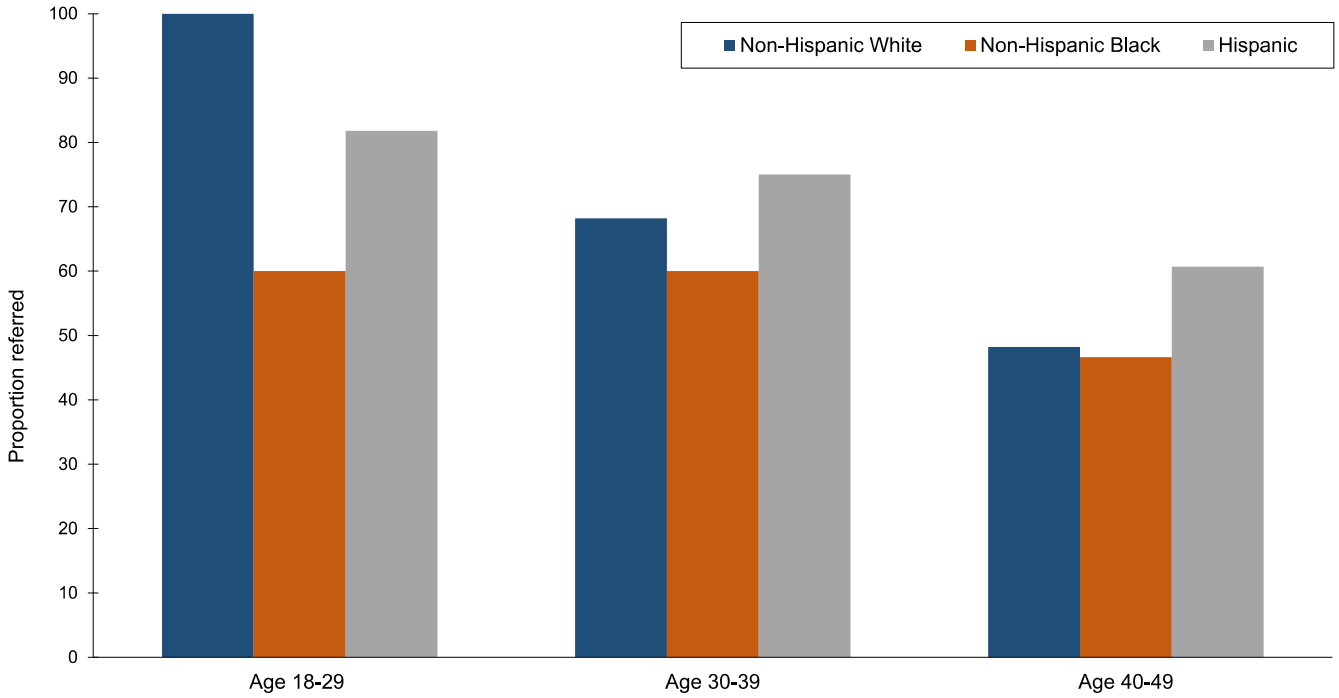


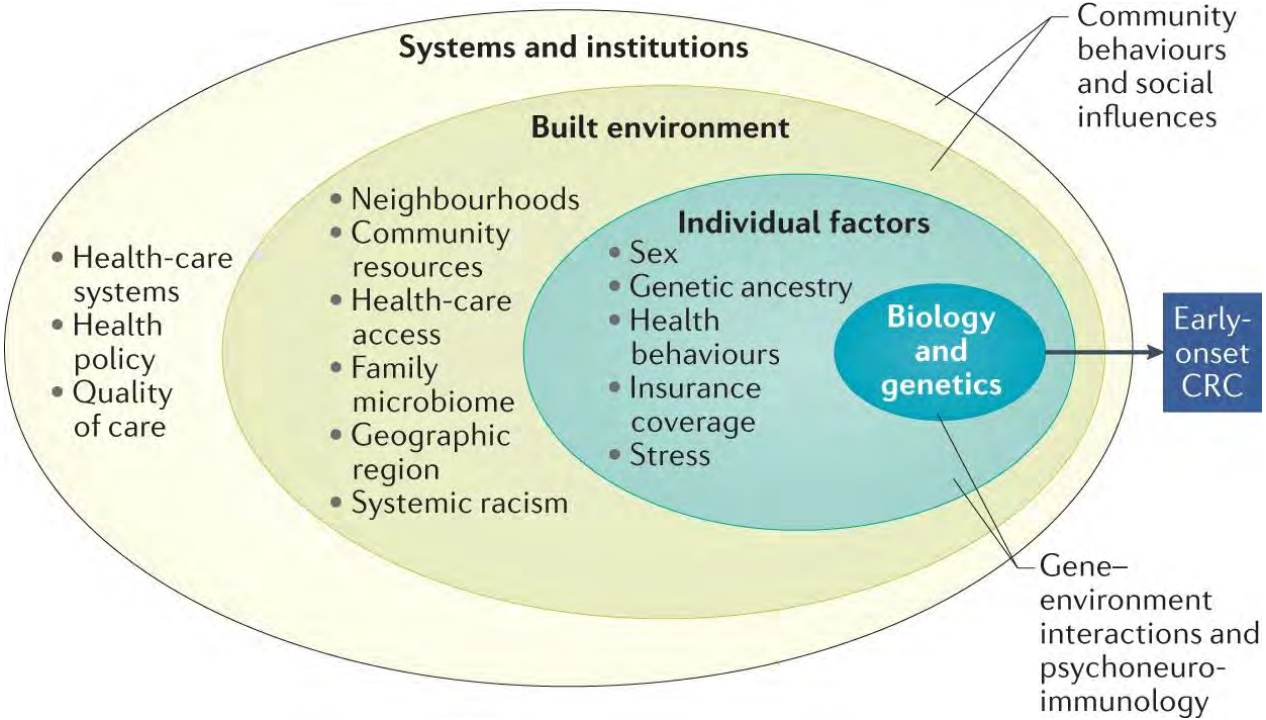
Figure 2. Proportion of patients referred to genetic counseling by race/ethnicity and age (n = 225).

Dharwadkar, P., et al., Clinical Gastroenterology and Hepatology, 2022

Conclusions

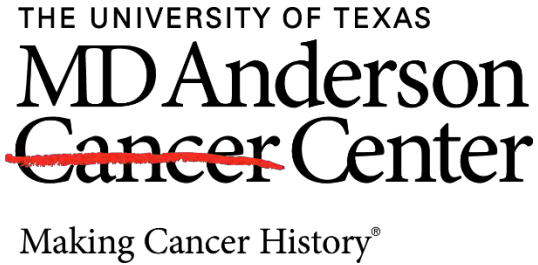
- People with YOCRC have an estimated ~14-25% risk of carrying a hereditary colon cancer syndrome
- Genetic testing should be offered and strongly considered for all individuals with YOCRC

Next frontier: how to hereditary factors interact with environmental factors?



Thank you

Questions?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