Concurrent Session G

Research Updates on Colorectal Cancer Risk

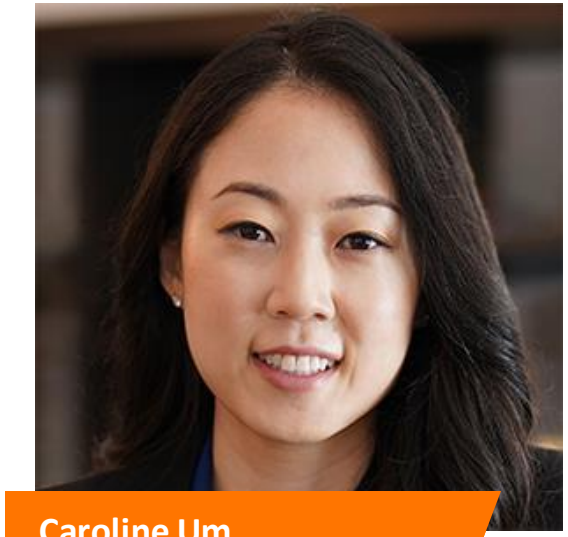
American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

9:55 AM to 11:10 AM

Armchair Conversation: Barriers and Solutions to Reaching American Indian and Alaska Native Communities for Colorectal Cancer Screening

Moderator:
Michael Sapienza

Christopher Lieu
MD



Caroline Um
PhD, MPH, RD

Swati Patel
MD, MS

Colorectal Cancer and the Microbiome

Christopher Lieu, MD
Associate Professor and Associate Director for Clinical Research
University of Colorado

Cancer Center

NCI-DESIGNATED COMPREHENSIVE CANCER CENTER

COLORECTAL CANCER AND THE MICROBIOME

Christopher Lieu, MD
Co-Director, GI Medical Oncology
Associate Director for Clinical Research
University of Colorado

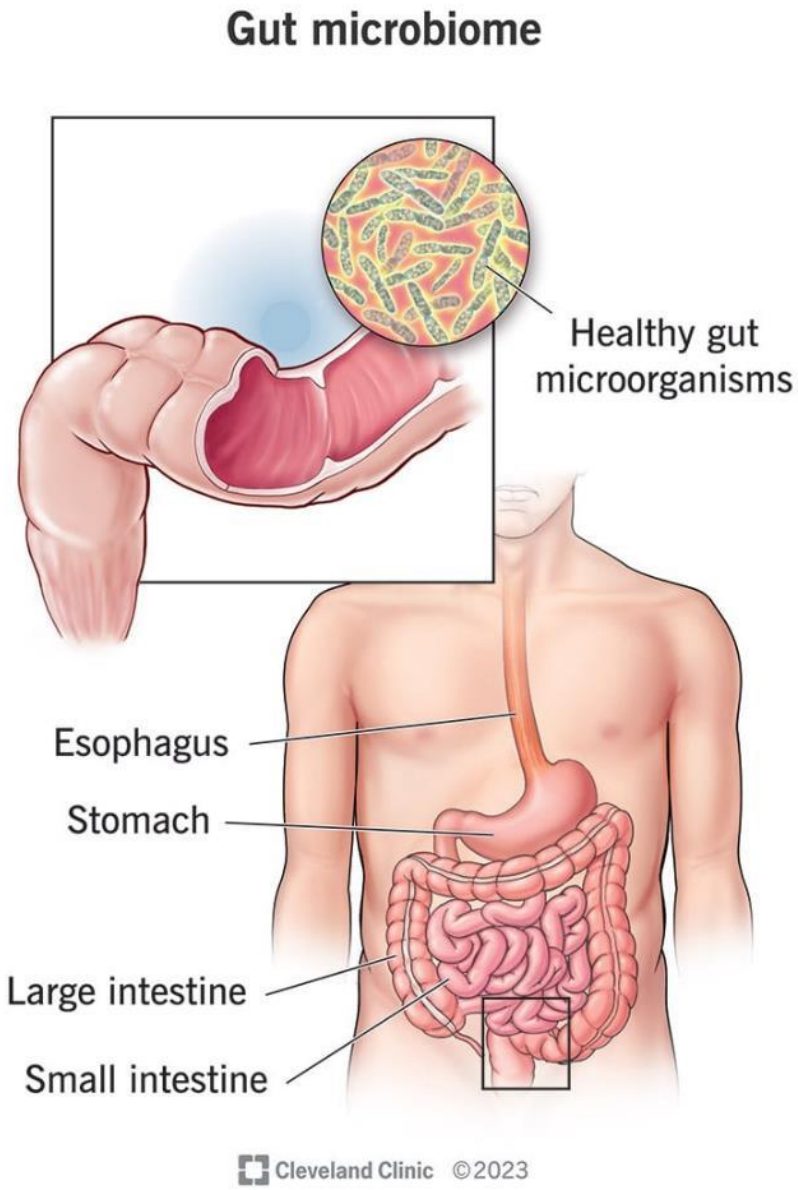
Objectives: What do we know? What do we not know?

- What is the gut microbiome?
- Factors that impact the gut microbiome
- What has been discovered about the gut microbiome and colorectal cancer?
- Future Directions

The Gut Microbiome

What is the gut microbiome?

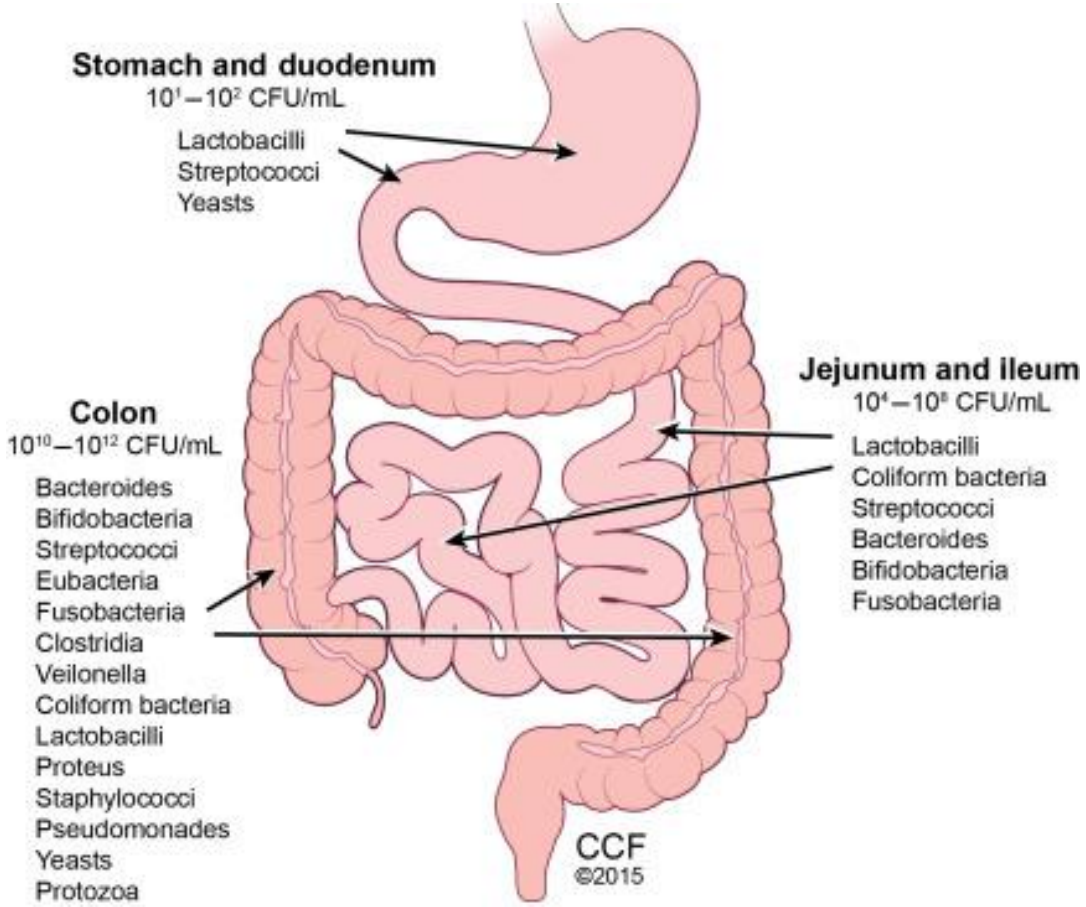
- A biome is a distinct ecosystem characterized by its environment and its inhabitants
- Your gut — inside your intestines — is populated by trillions of microscopic organisms
- These microorganisms include over a thousand species of bacteria, as well as viruses, fungi and parasites



https://my.clevelandclinic.org/health/body/25201-gut-microbiome

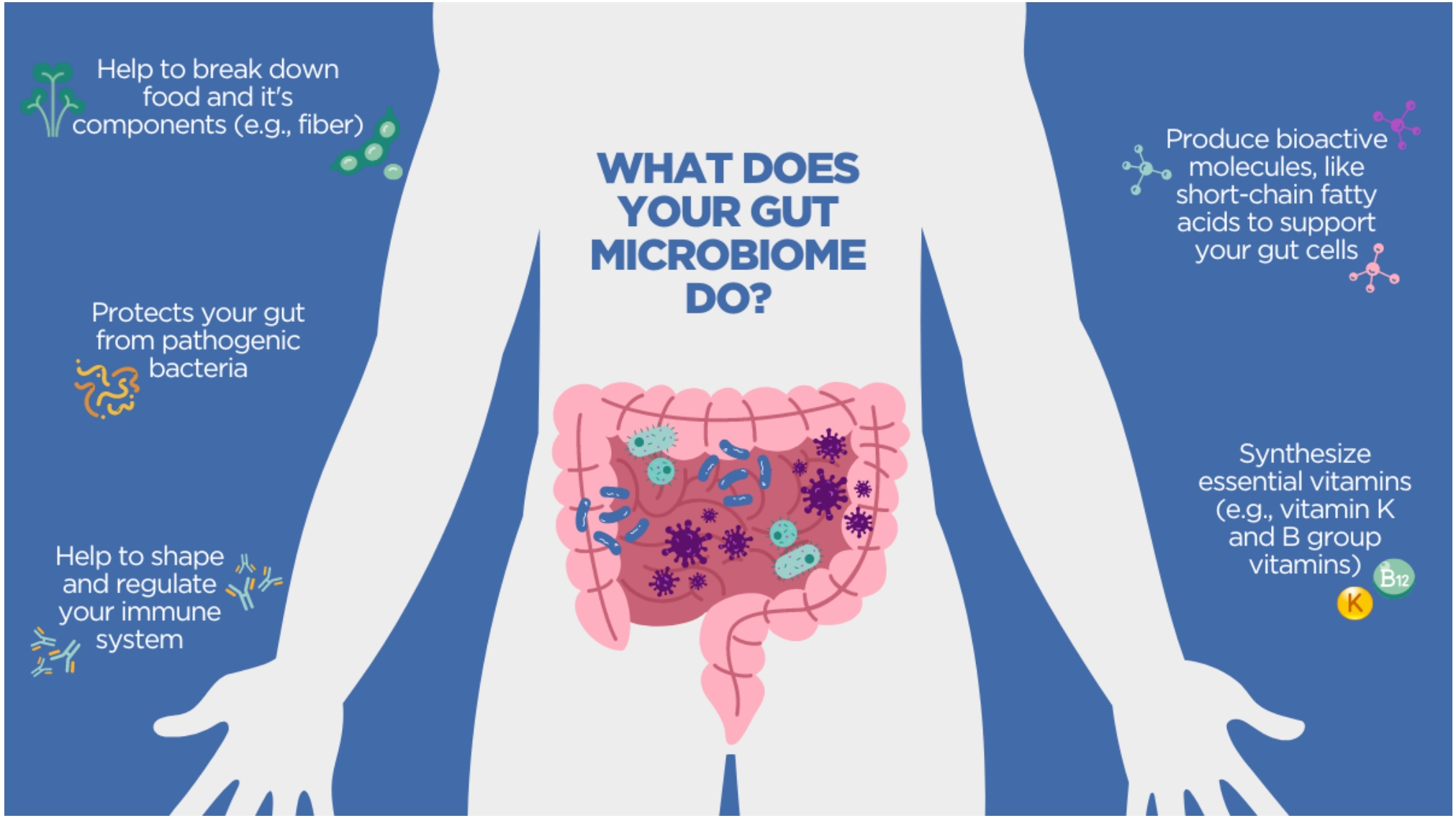
What is the gut microbiome?

- Your gut microbiome is unique to you
- Infants inherit their first gut microbes during vaginal delivery or breastfeeding
- Later, your diet and other environmental exposures introduce new microbes to your biome



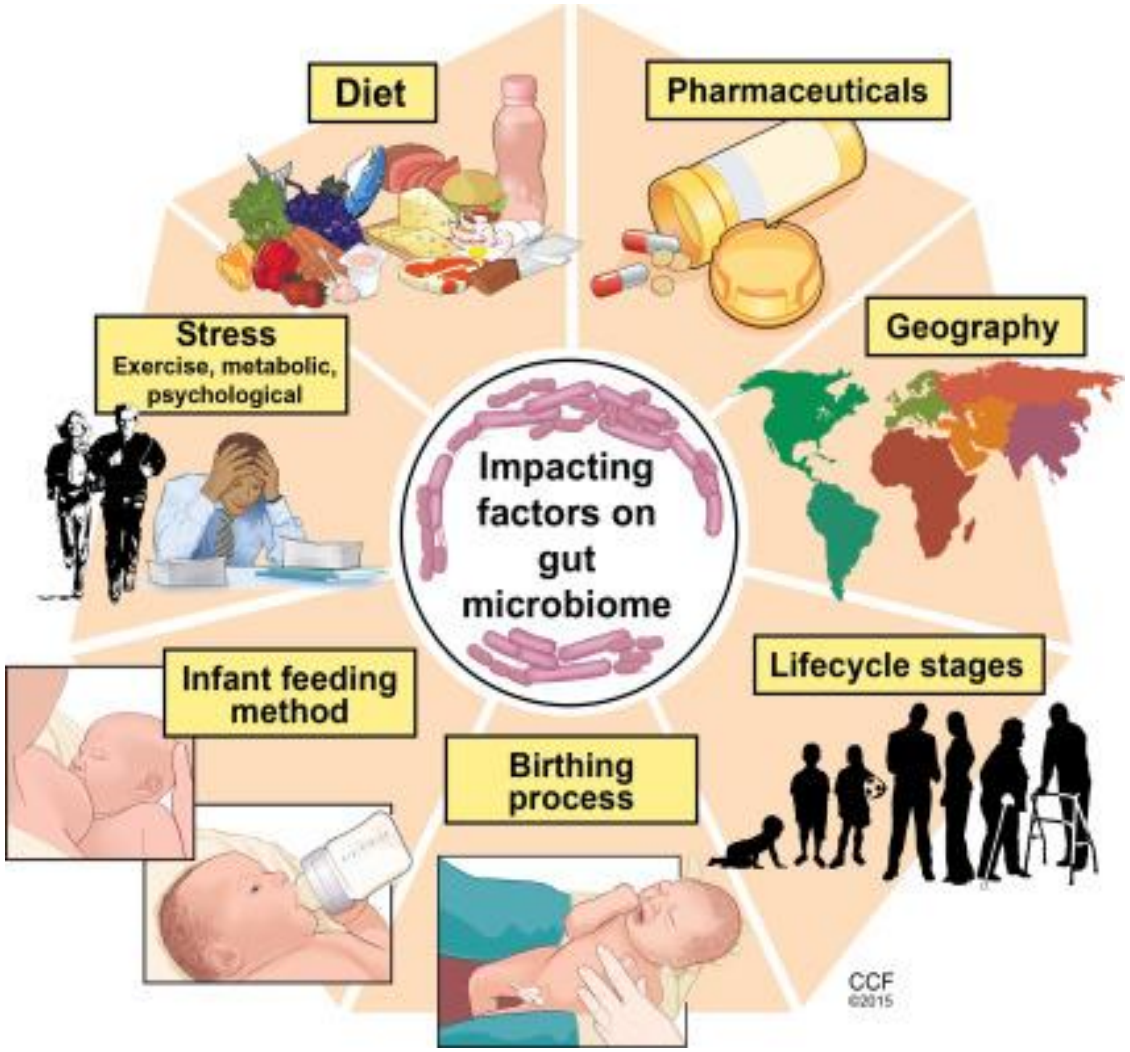
Cresci et al. Adult Short Bowel Syndrome: 2019.

What does the microbiome do?

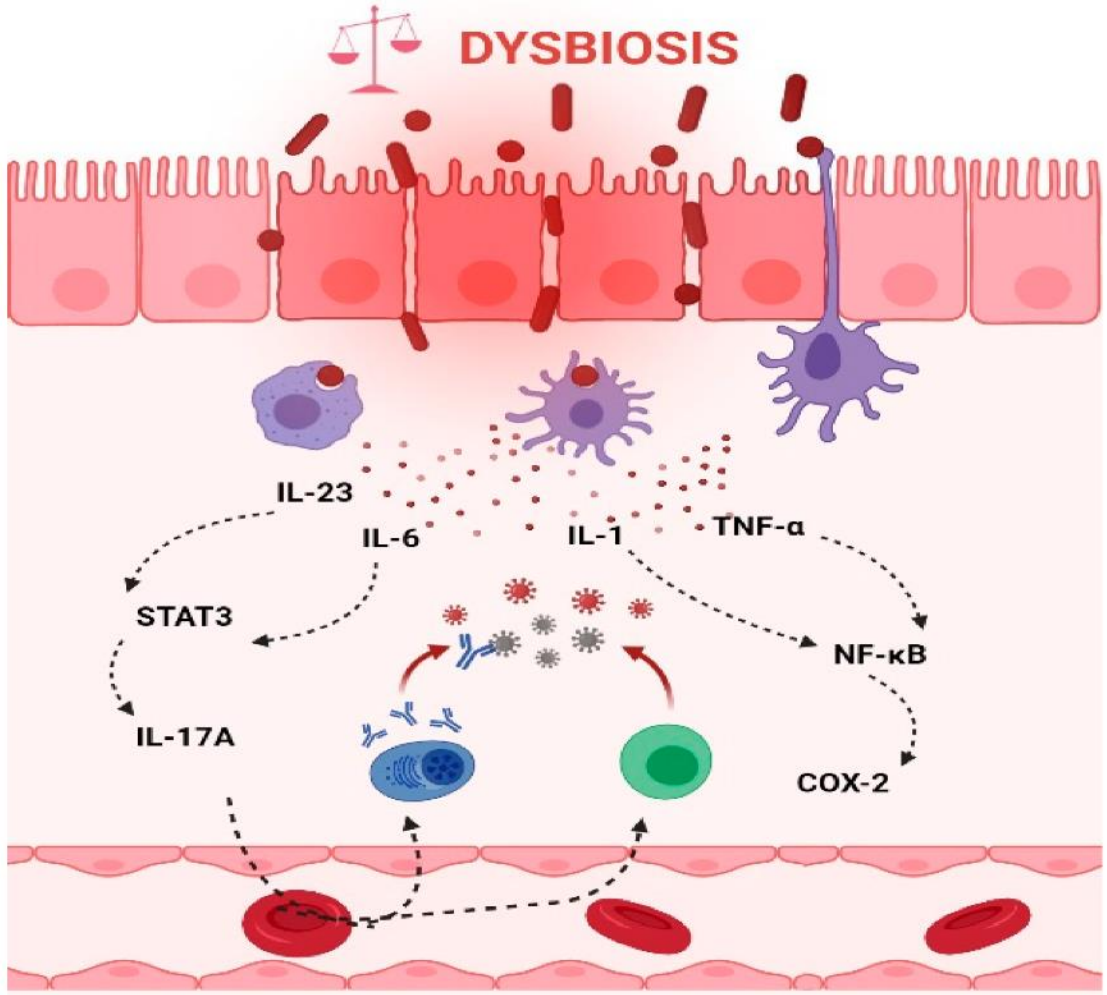


https://omedhealth.com/insights-hub/what-is-the-gut-microbiome/

What Factors Impact the Gut Microbiome?

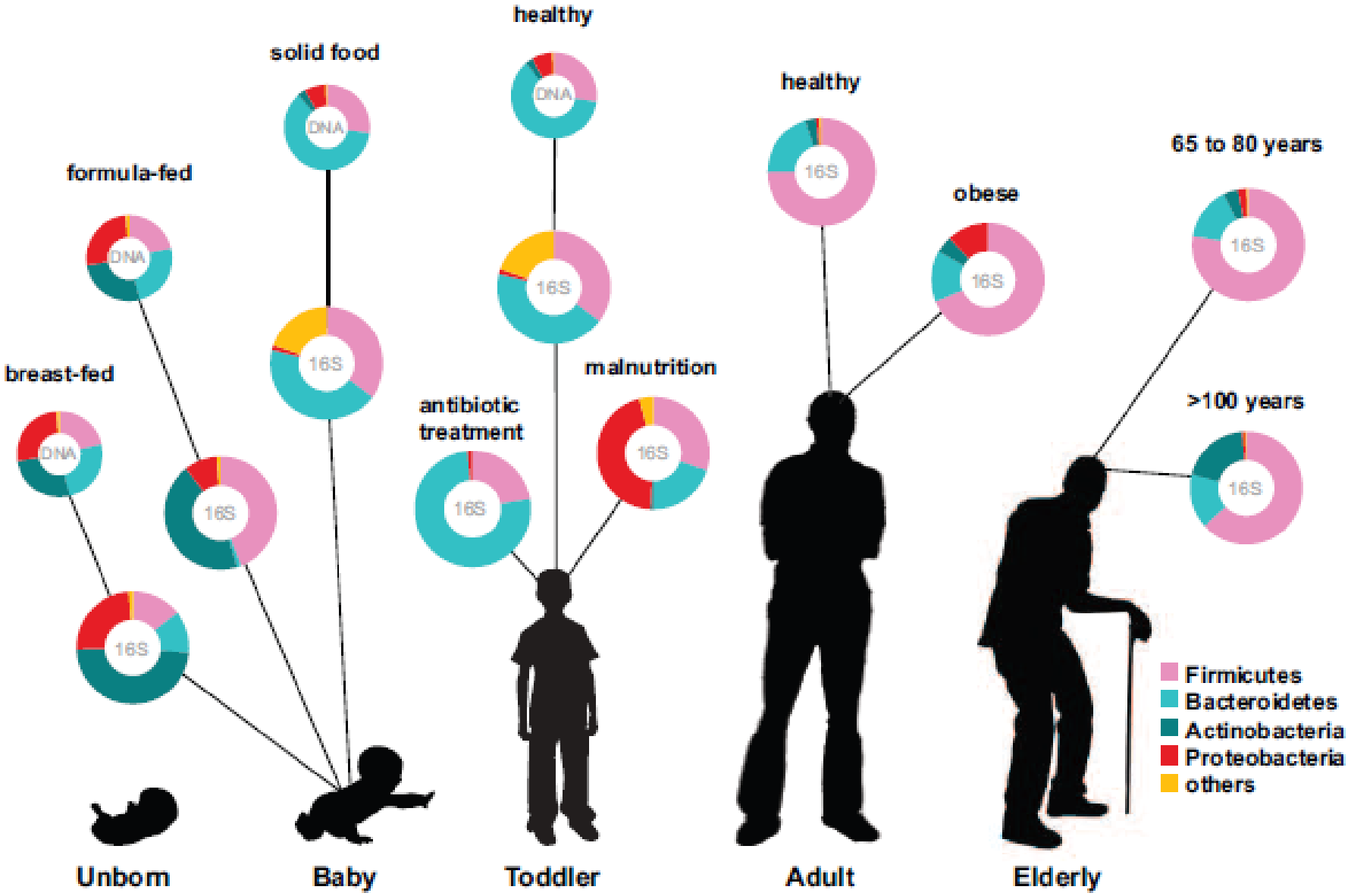


Gut microbiome. Cresci, et al. Adult short bowel syndrome. 2018.



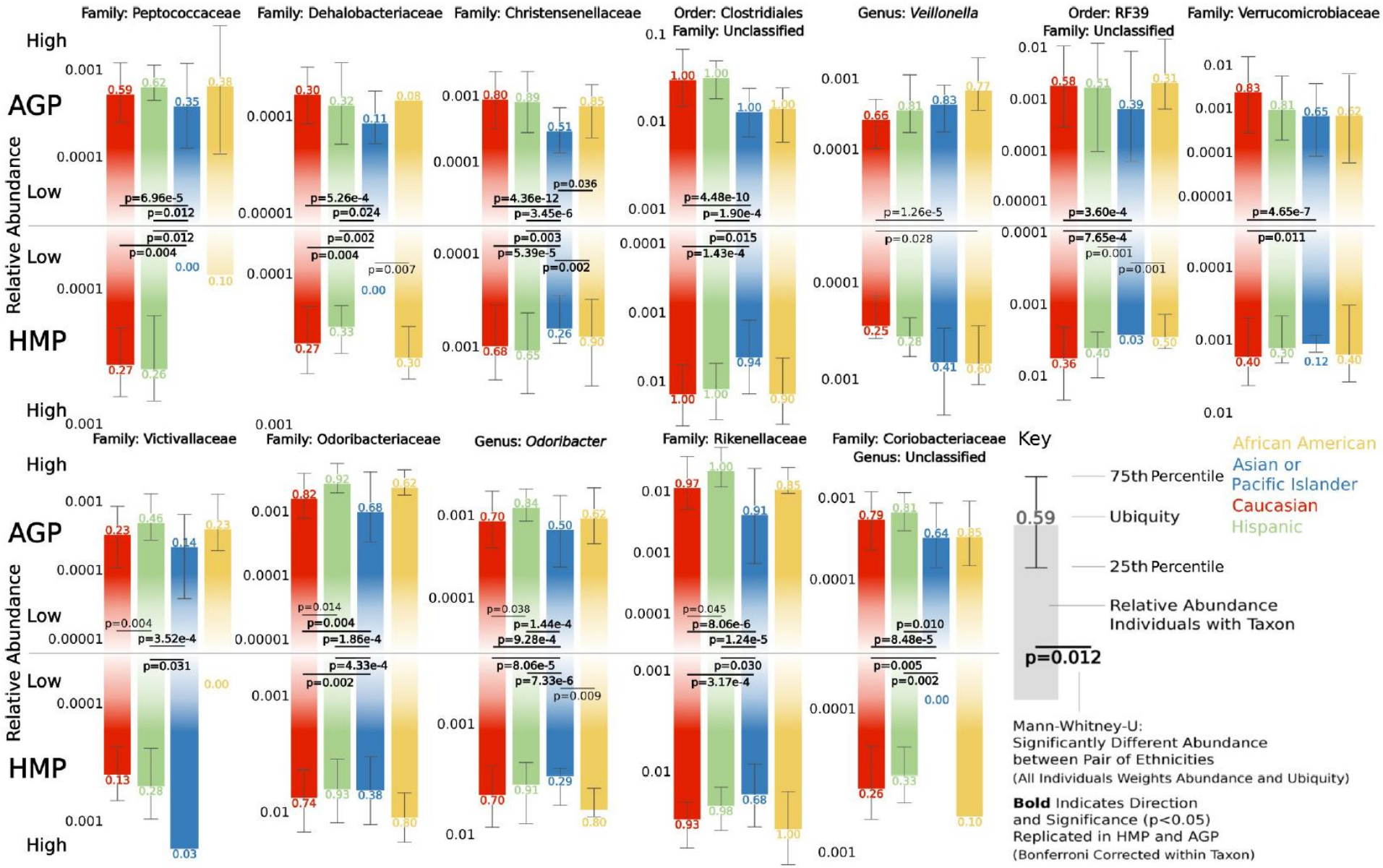
Torres Maravilla, et al. Role of gut microbiota and probiotics in colorectal cancer. Microorganisms. 2021

Gut Microbiome Varies with Age



Ottman et al. *Front Cell Infect Microbiol* 2012.

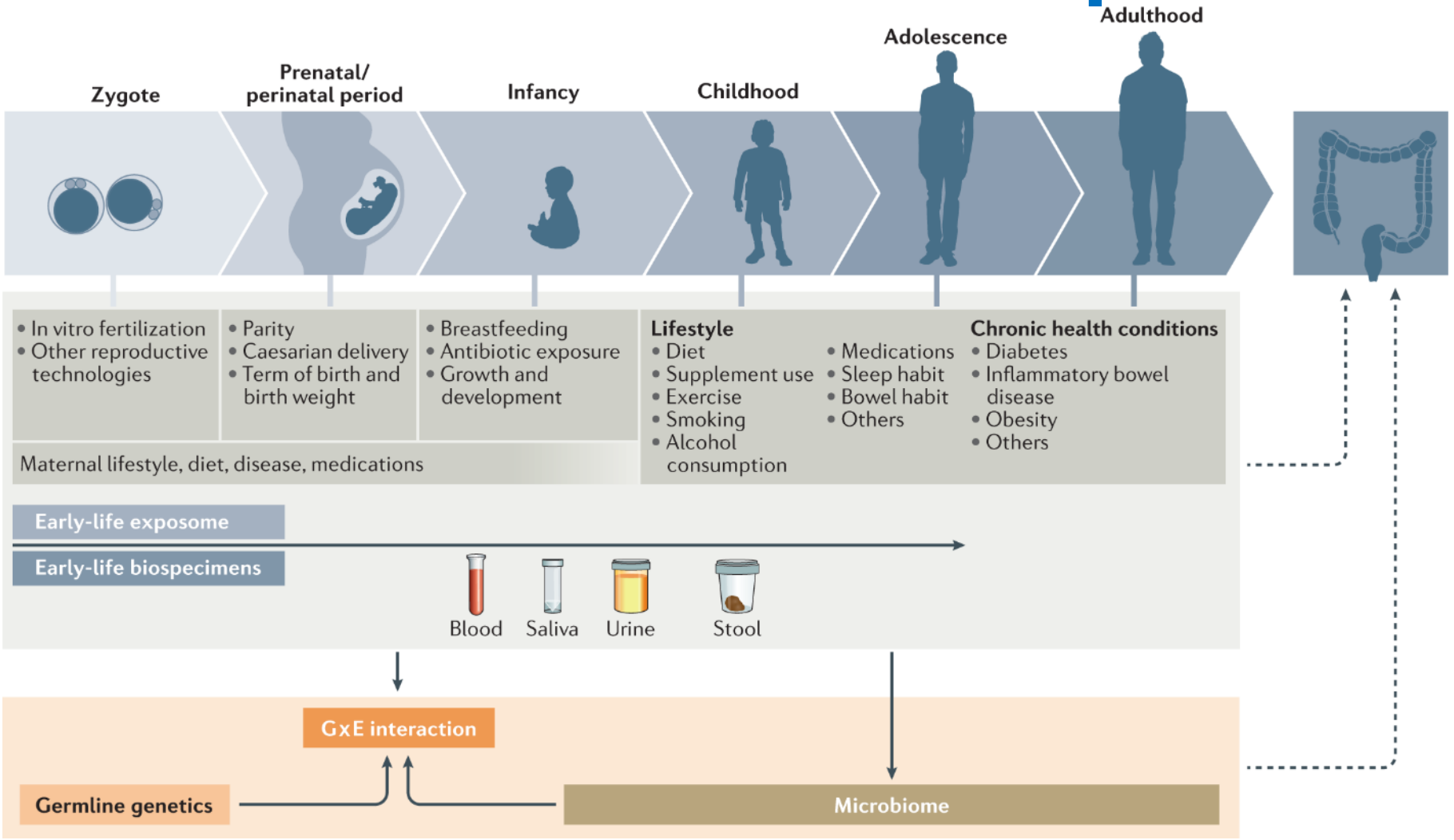
Gut Microbiome Varies with Ethnicity



Brooks et al. *PLoS Biol* 2018.

Prevent and conquer cancer. **Together.**

Life-course exposures with potential effects on CRC development



Akimoto et al. *Nat Rev Clin Oncol* 2020.

TAKE HOME POINTS

The gut microbiome is unique to all individuals

The gut microbiome helps with digestion, protects against other bacteria and illnesses, and helps to shape and regulate the immune system

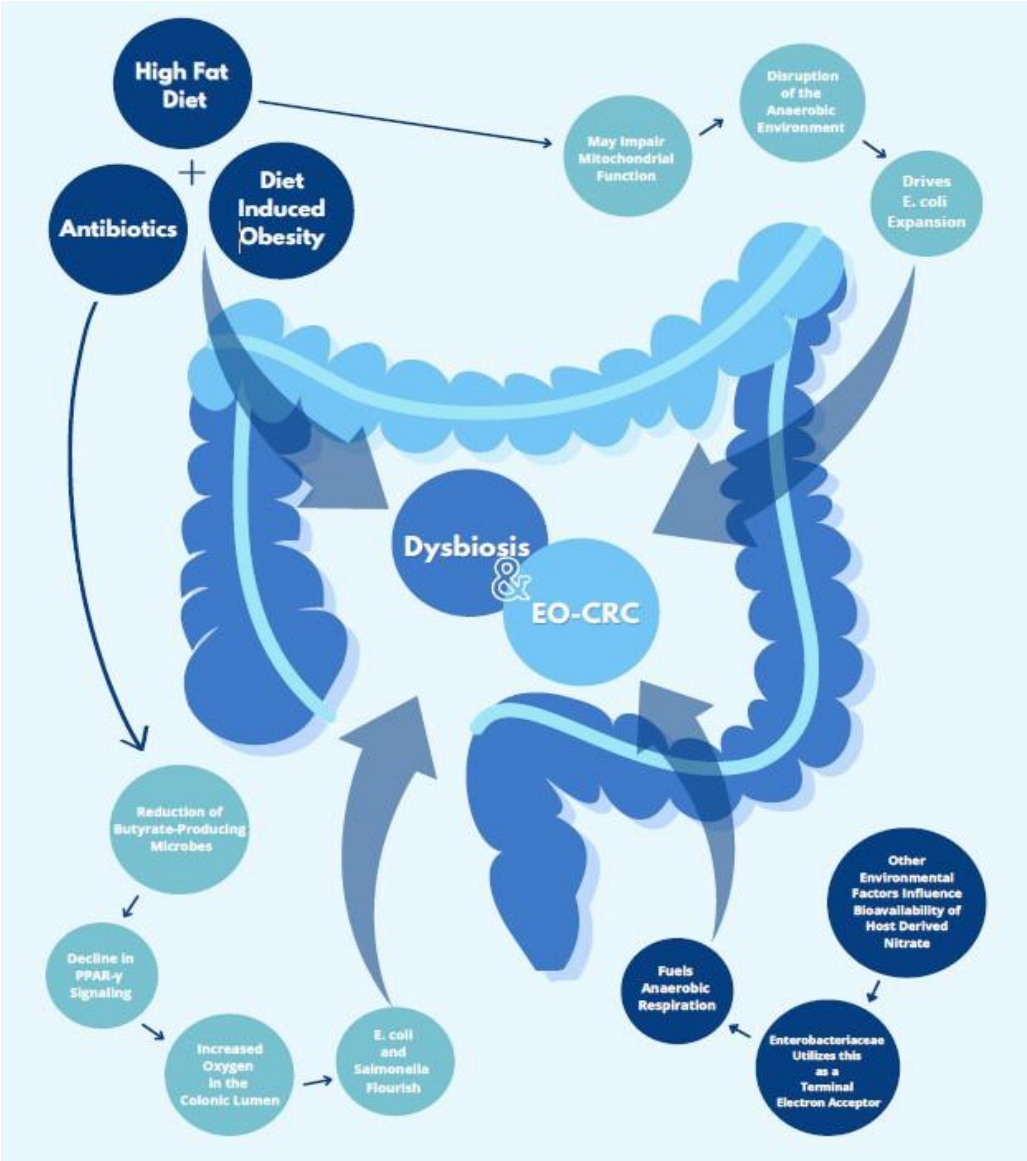
Dysbiosis has been linked to many disorders including colorectal cancer

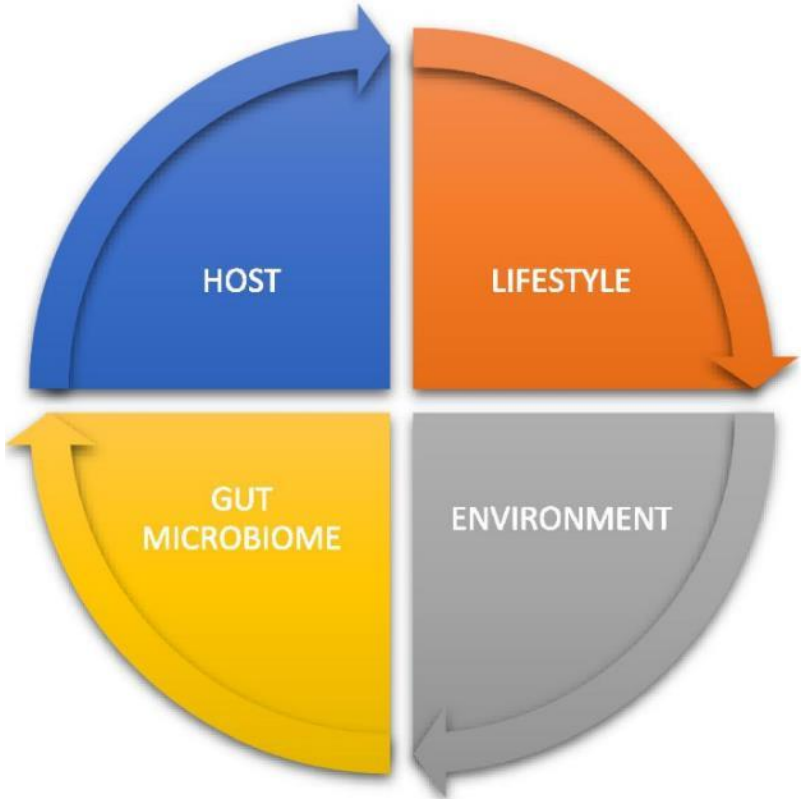
Gut microbiome varies by age and ethnicity, and alterations to the gut microbiome start as early as birth!

The Gut Microbiome and Colorectal Cancer

Christopher Lieu, MD, University of Colorado

CRC: The potential impact of the microbiome

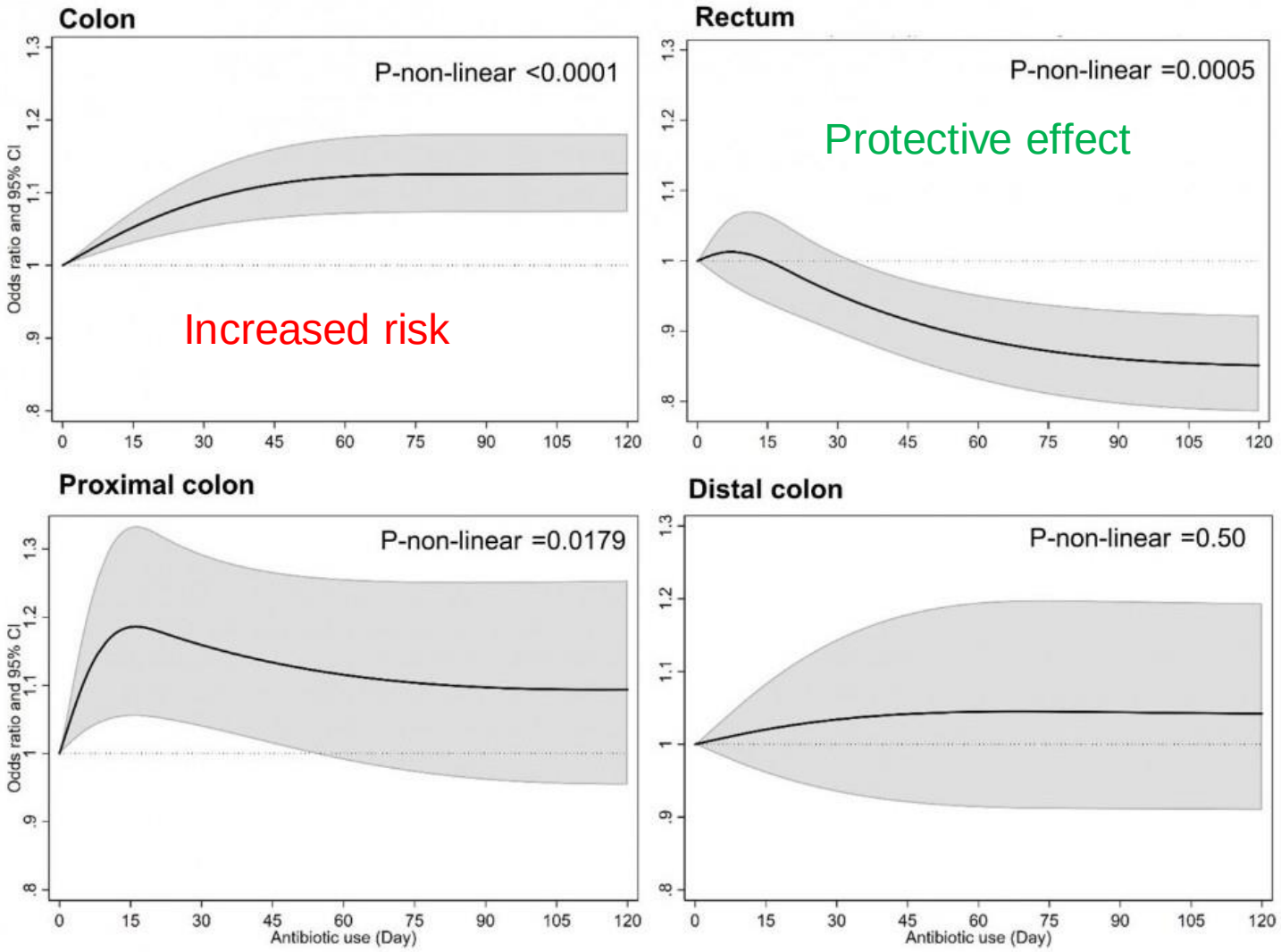




Eng et al. *Lanc Onc* 2022, Rebersek *BMC Cancer* 2021.

Antibiotic use and Colon Cancer Risk

- Matched case-control study of incident CRC cases diagnosed in the UK between 1989 & 2012 and up to 5 unaffected healthy patients
- ~29,000 CRC cases vs. ~137,000 controls
- Risk of colon cancer <u>increased</u> after antibiotic use in dose-dependent fashion, especially penicillins
- Prolonged antibiotic use appeared <u>protective</u> against rectal cancer
- Antibiotic-cancer association occurred after antibiotic exposure > 10 yrs prior to cancer diagnosis

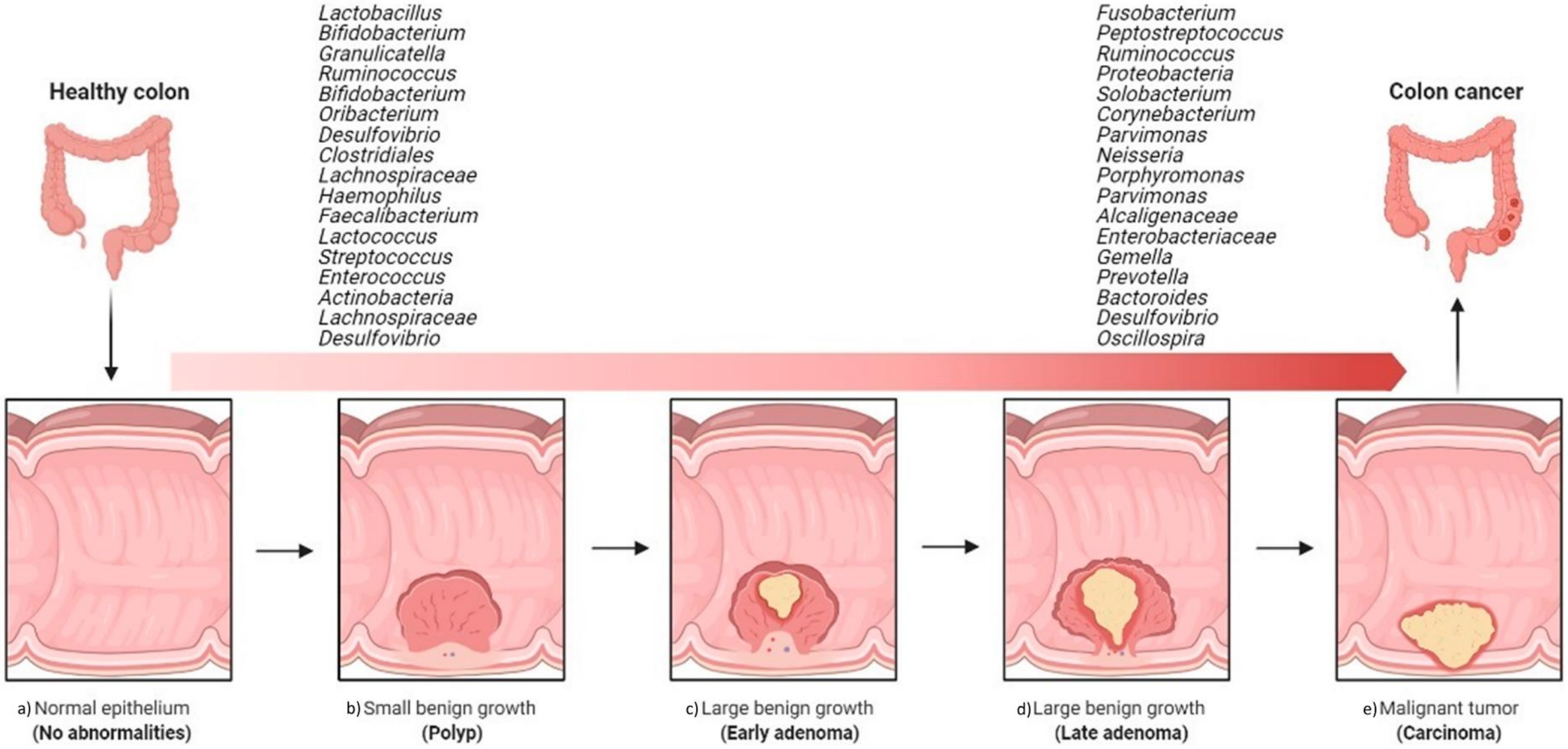


Zhang J et al: Gut. 2019

Factors associated with the microbiome and CRC
a confusing landscape!

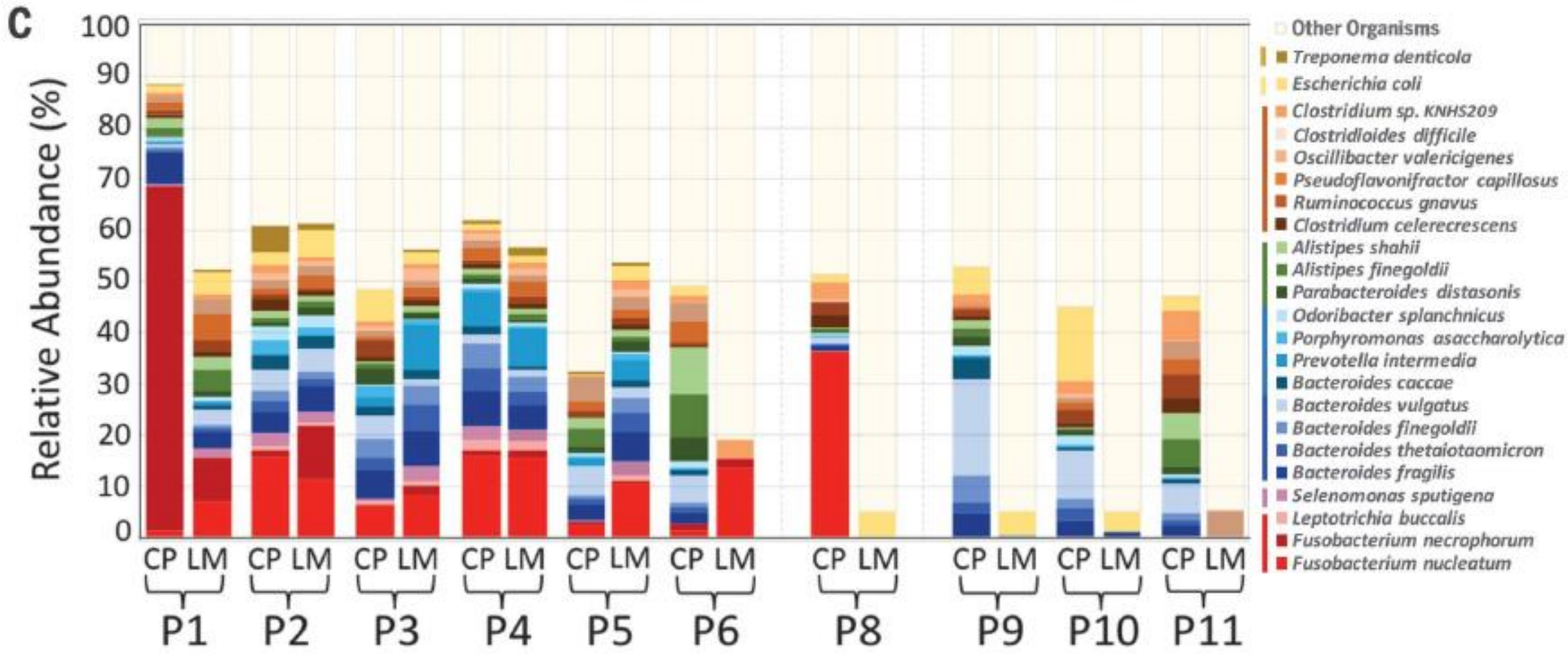
Factor	Outcome	HR
Birth by cesarean delivery *Cao et al. JAMA Netw Open 2023*	Females born by cesarean delivery had **higher** odds of EO-CRC	1.62 (1.01-2.60)
Women with a BMI > 30 *Liu et al. JAMA Onc 2019*	Females with a BMI > 30 had **higher** odds of EO-CRC	1.88 (1.07-3.30)
Obesity in men in childhood *Jensen et al: Int J of Obesity, 2018*	Higher weights in childhood that persist had **higher** odds of EO-CRC	2.62 (1.62-4.25)
BMI: Obesity in veterans *Low et al. Gastroent 2020*	Obesity associated with **lower** odds of EO-CRC	0.69 (0.55-0.86)
Antibiotic use and colon cancer *Zhang J et al: Gut. 2019*	Prolonged antibiotic use resulted in **higher** odds of colon cancer	1.17 (1.10-1.23)
Antibiotic use and rectal cancer *Zhang J et al: Gut. 2019*	Prolonged antibiotic use resulted in **lower** odds of rectal cancer	0.85 (0.79-0.93)

Gut bacteria *shift* from polyp formation to cancer progression



Torres Maravilla, et al. Role of gut microbiota and probiotics in colorectal cancer. Microorganisms. 2021

Bacteria Often Co-Occur in the Primary Lesion and the Liver Metastasis



Bullman et al. *Science* 2017.

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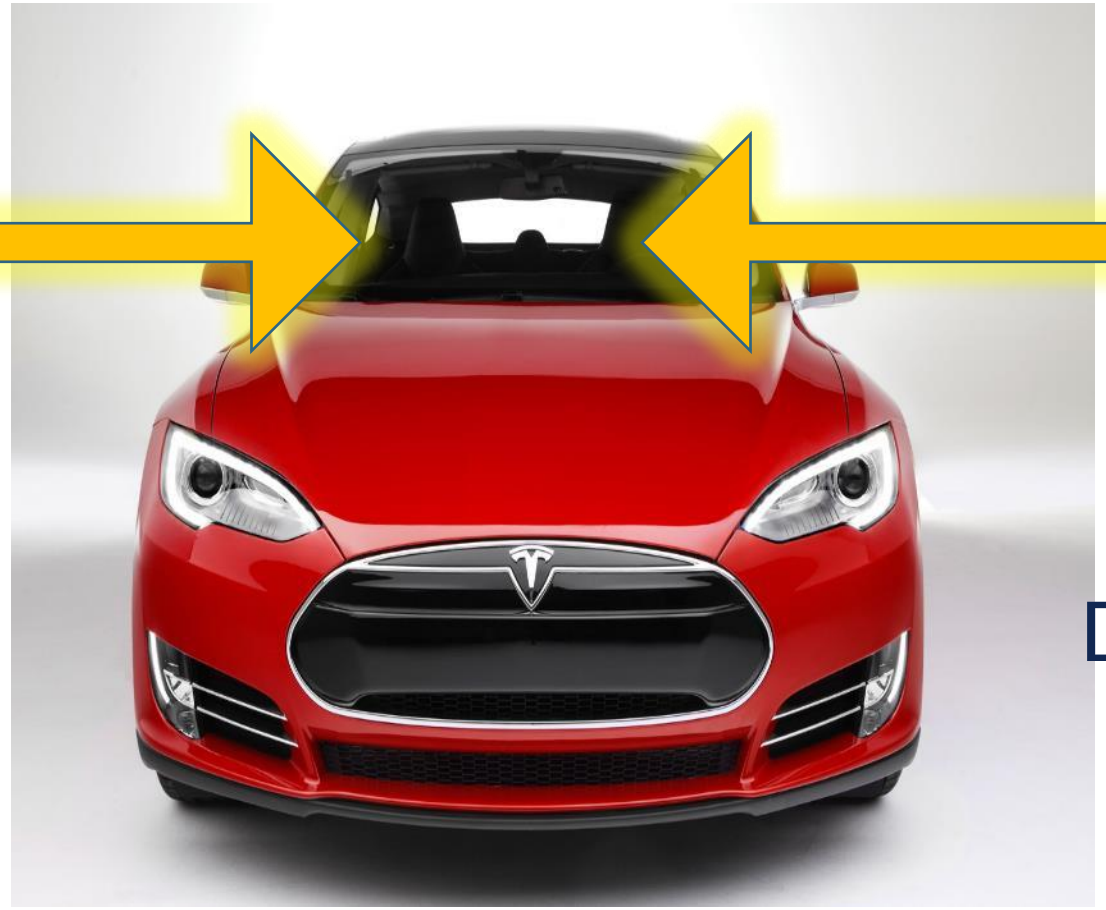
What Do These Bacteria Do to Promote Cancer Growth?



Passenger?

Driver?

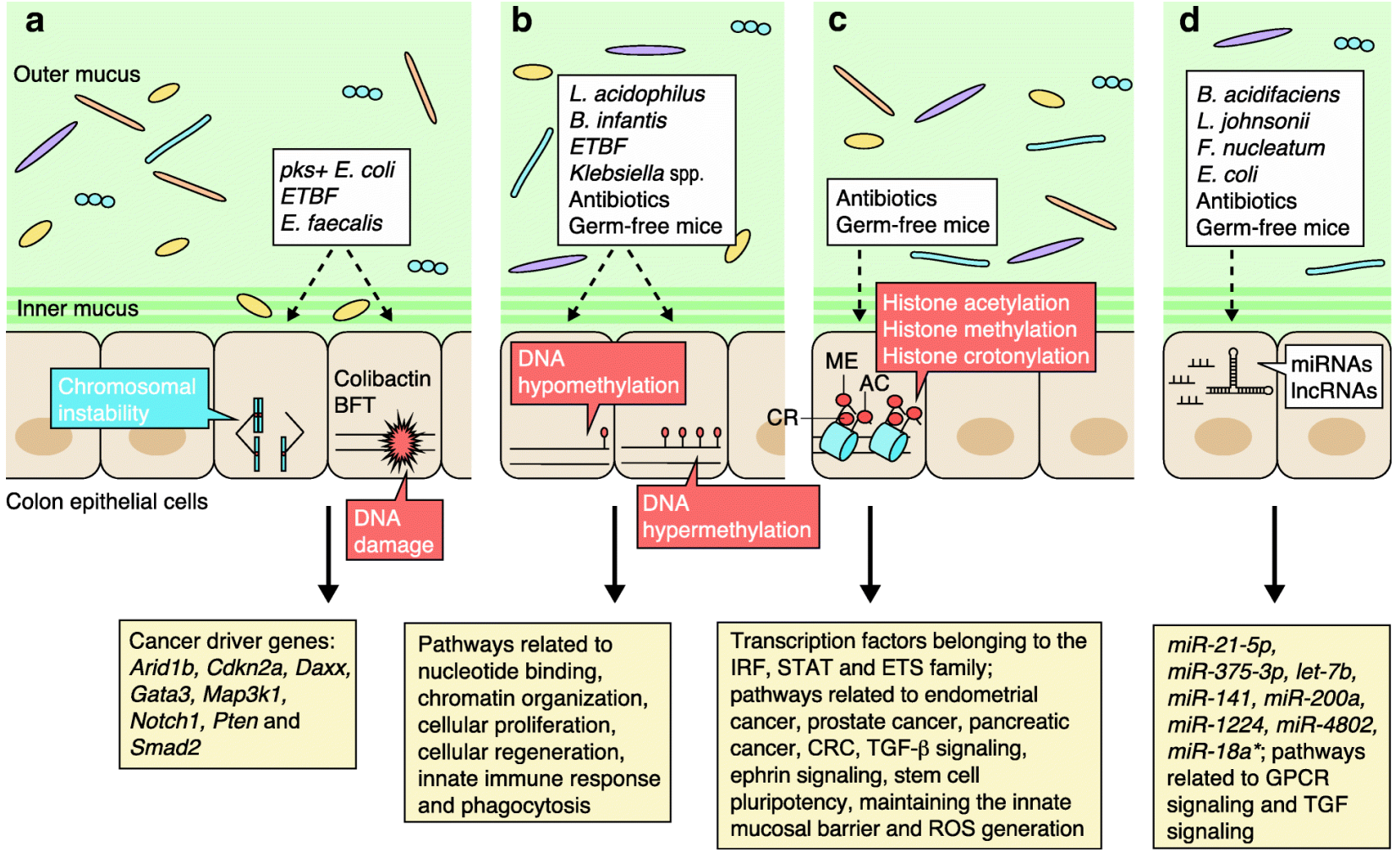
Effect of the gut microbiome on the colon epithelial cell genome and epigenome

CRC- associated bacteria, individually linked to CRC

- *Bacteroides fragilis*
- *Escherichia coli*
- *Enterococcus faecalis*
- *Streptococcus gallolyticus*

CRC- associated bacteria, with increased abundance in faecal and tumour samples

- *Fusobacterium nucleatum*
- *Parvimonas*
- *Peptostreptococcus*
- *Porphyromonas*
- *Prevotella*



Cancer driver genes: *Arid1b, Cdkn2a, Daxx, Gata3, Map3k1, Notch1, Pten* and *Smad2*

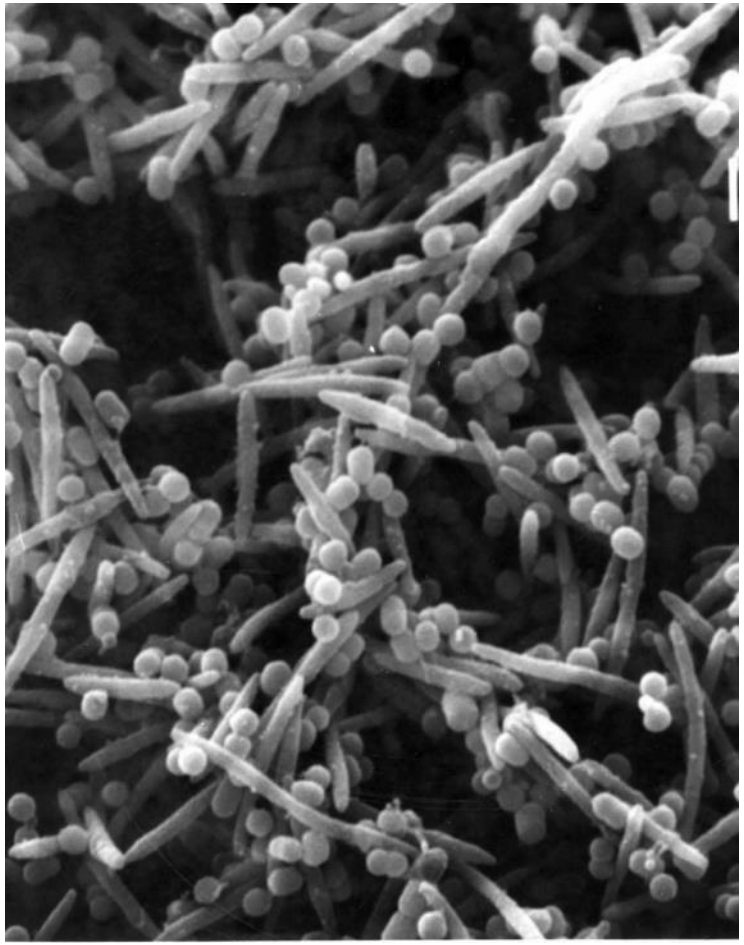
Pathways related to nucleotide binding, chromatin organization, cellular proliferation, cellular regeneration, innate immune response and phagocytosis

Transcription factors belonging to the IRF, STAT and ETS family; pathways related to endometrial cancer, prostate cancer, pancreatic cancer, CRC, TGF-β signaling, ephrin signaling, stem cell pluripotency, maintaining the innate mucosal barrier and ROS generation

*miR-21-5p, miR-375-3p, let-7b, miR-141, miR-200a, miR-1224, miR-4802, miR-18a**; pathways related to GPCR signaling and TGF signaling

Rebersek *BMC Cancer* 2021. Allen and Sears. *Genome Med* 2019.

Fusobacterium nucleatum

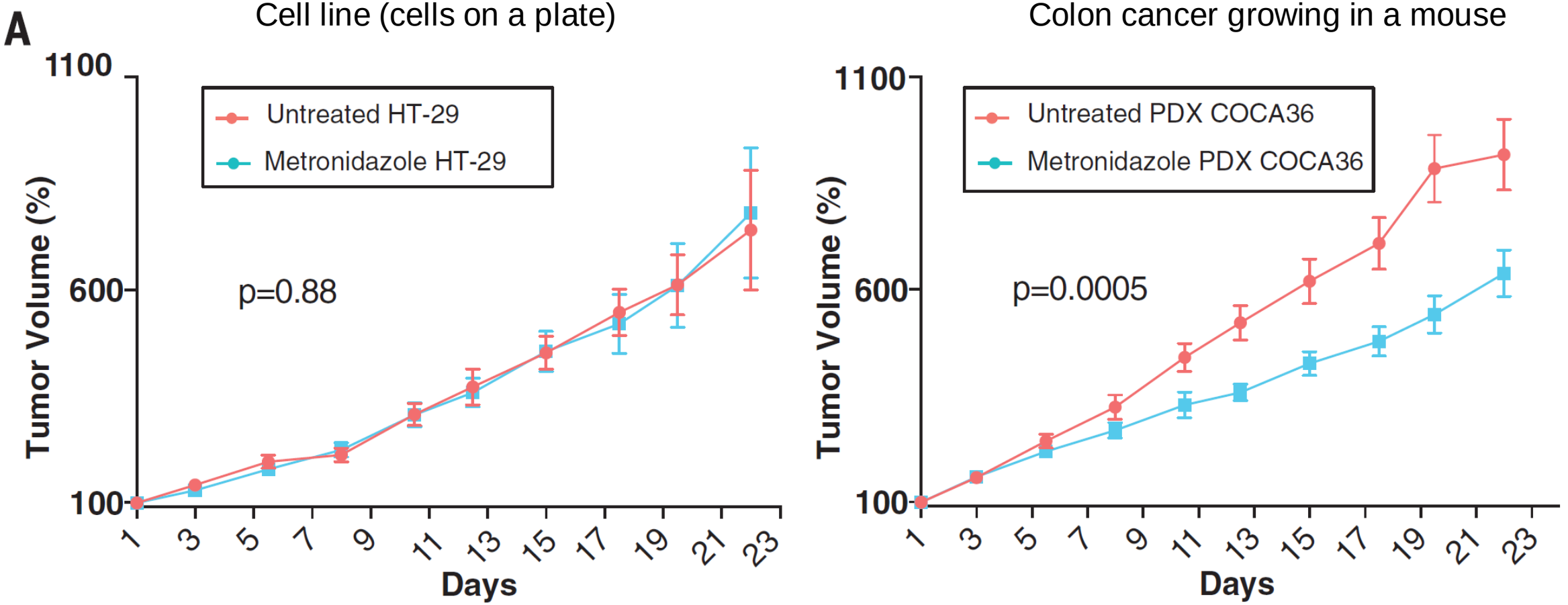


Baylor College of Medicine

- Associated with gingival plaque
- Seen in CRC associated with diets lacking whole grains and dietary fiber
- High levels seen in 7%, low or high levels seen in 15% of CRC
  - mostly right-sided, MSS *(n = 598, mean age 67.2, SD 8.4)*
- Associated with a lower density of immune cells

Mima et al. *JAMA Oncol* 2015, Mehta et al. *JAMA Oncol* 2017, Hamada et al. *Cancer Immunol Res* 2018.

Metronidazole slows tumor growth in *Fusobacterium*-colonized mouse models



Bullman et al. *Science* 2017.

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Is *Fusobacterium*. *nuc*. present in adenomas?

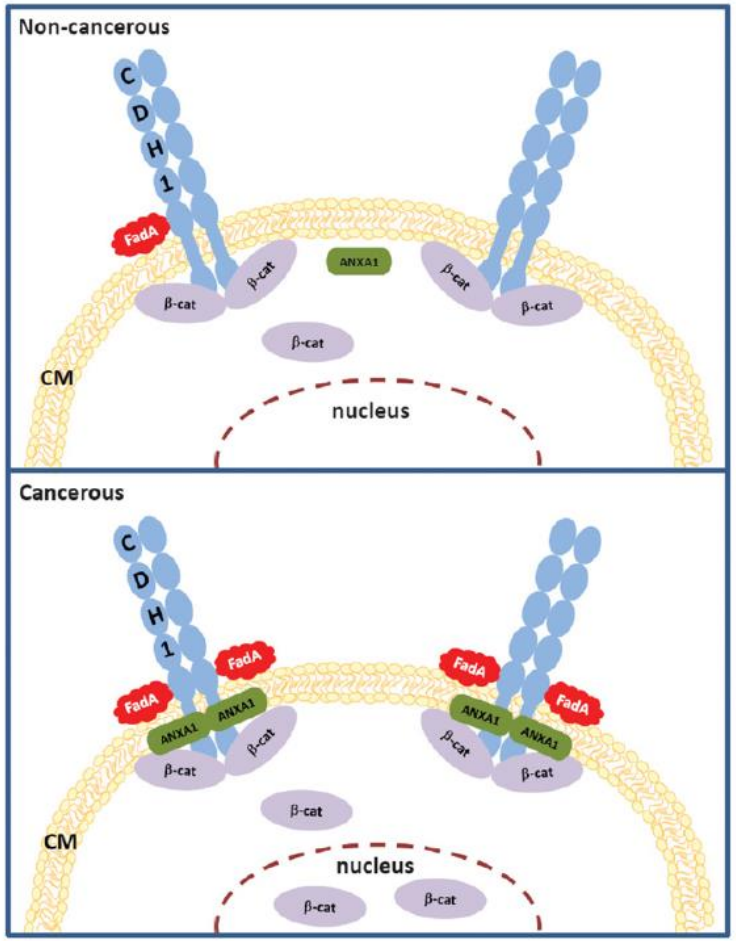
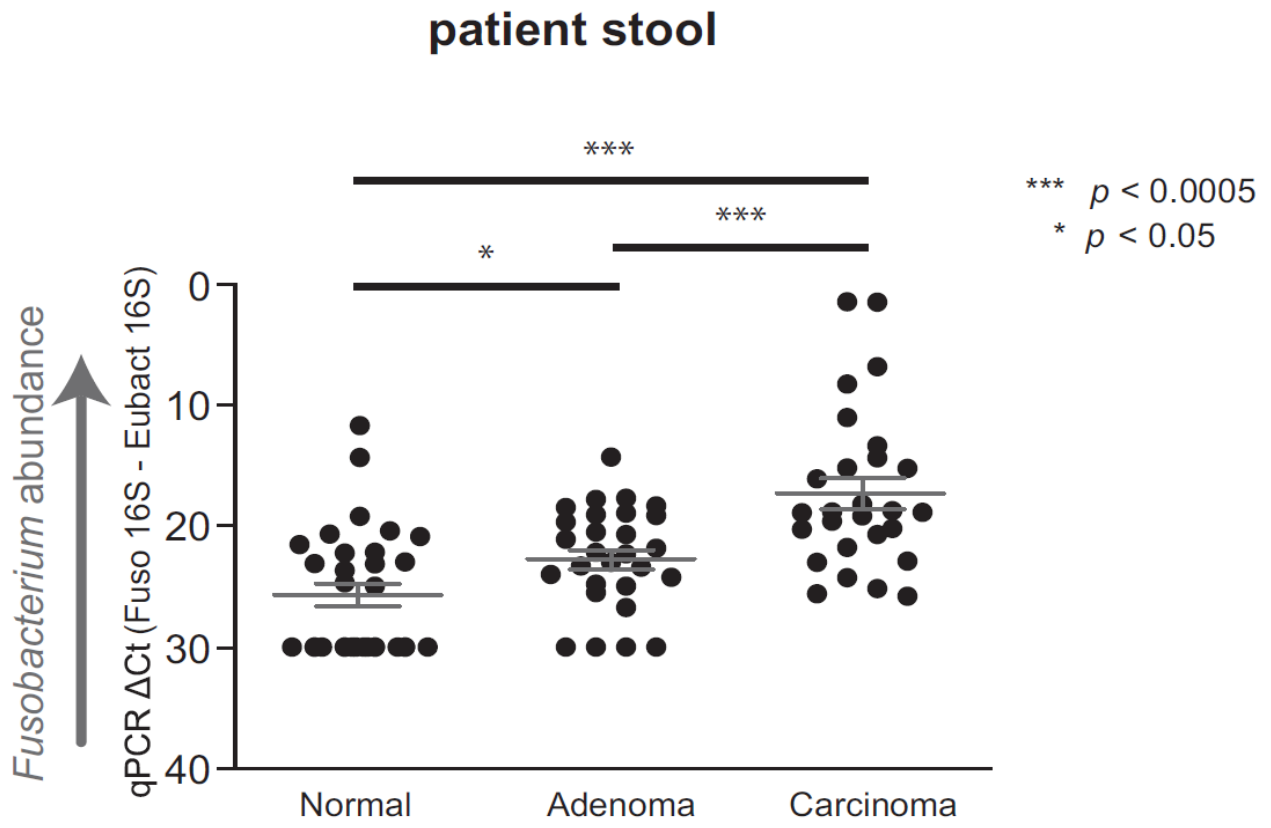


Figure 9. A "two-hit" model for CRC progression stimulated by *F. nucleatum*.

In non-cancerous cells (top panel), there is low level of Annexin A1 (ANXA1) and weak binding of FadA to E-cadherin (CDH1). In cancerous cells (bottom panel), Annexin A1 level increases, FadA binding enhances, FadA–E-cadherin–Annexin A1–β-catenin complex forms, β-catenin is activated, resulting in acceleration of cancer progression. CM, cell membrane.



Rubinstein et al. *EMBO Rep* 2019, Kostic et al. *Cell Host Microbe* 2013.

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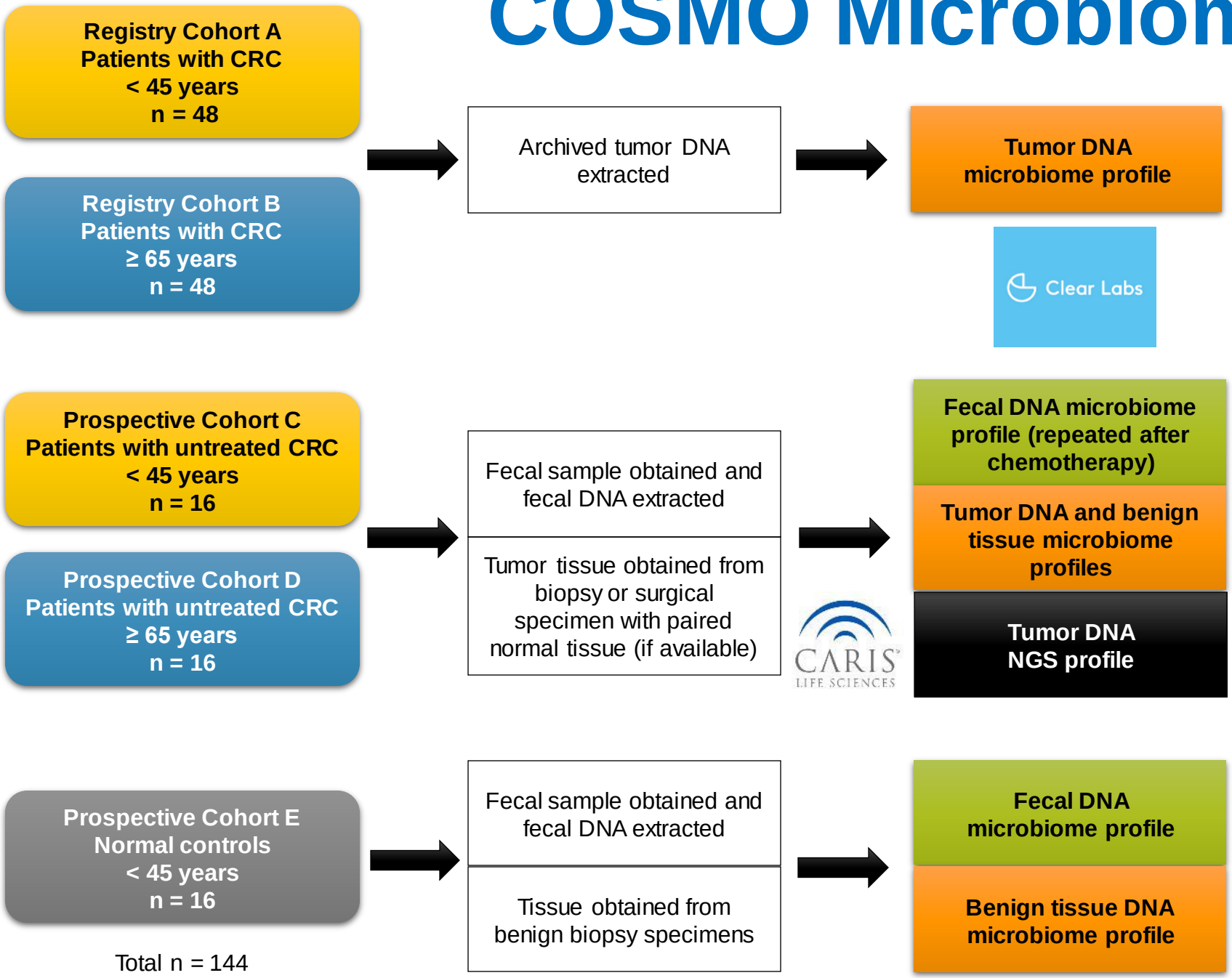
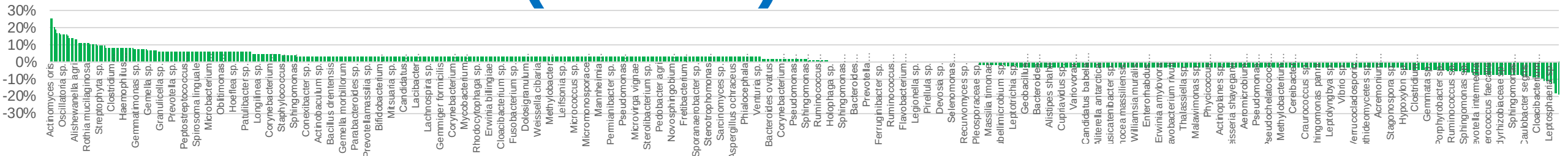
COSMO Microbiome Study

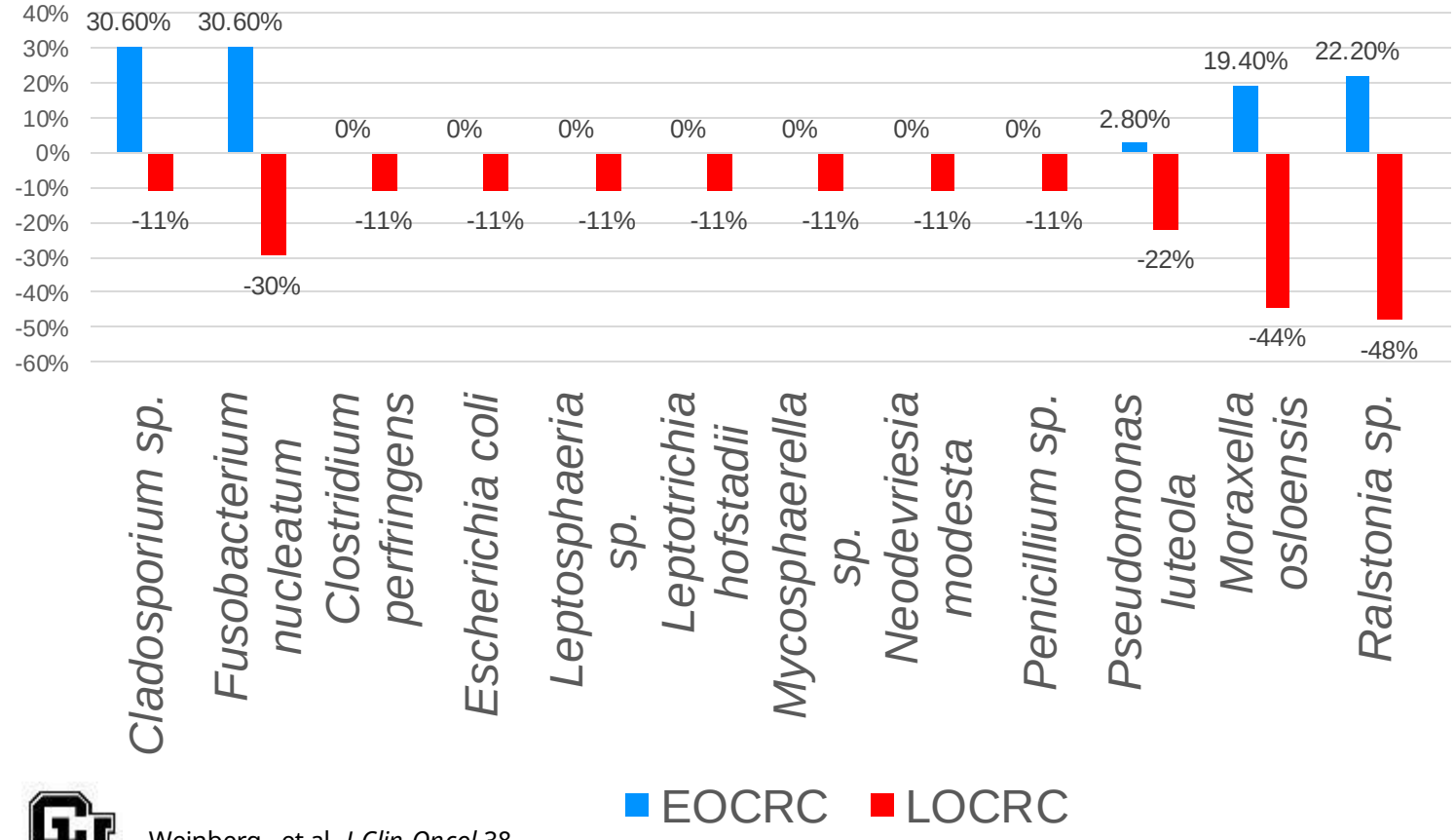


Total n = 144

Weinberg, et al. *J Clin Oncol* 38, no. 4_suppl (February 01, 2020) 241-241.

Final Results (N = 63)





- *Cladosporium sp.* seen more in early-onset CRC
- *F. nuc.* was found in 30% of early and average-onset CRC (p = 0.94)

- Others were seen significantly more commonly in average-onset CRC (p < 0.05):
  - *Pseudomonas luteola*
  - *Ralstonia sp.*
  - *Moraxella osloensis*
  - *Clostridium perfringens*
  - *Escherichia coli*
  - *Leptotrichia hofstadii*
  - *Mycosphaerella sp.*
  - *Neodevriesia modesta*
  - *Penicillium sp.*
  - *Leptosphaeria sp.*

Weinberg, et al. *J Clin Oncol* 38, no. 4_suppl (February 01, 2020) 241-241.

What we know:

We now know that various microbes (and microbial communities) are found more frequently in the stool and mucosa of individuals with CRC

Gut bacteria shift from polyp formation to cancer development

Certain bacteria (*fusobacterium)* have been linked to colorectal cancer development

We also know that these microbes induce tumors in various mouse models

What we don't know:

We know little about how the microbiome impacts colon epithelial cells (CECs) directly

AND

How these interactions might lead to modifications at the genetic and epigenetic levels that trigger and propagate tumor growth

The future of the gut microbiome and colorectal cancer

Christopher Lieu, MD, University of Colorado

Potential Clinical Applications:
Targeting or Using the Gut Microbiome

Screening biomarkers
- Detect CRC or adenoma in asymptomatic individuals

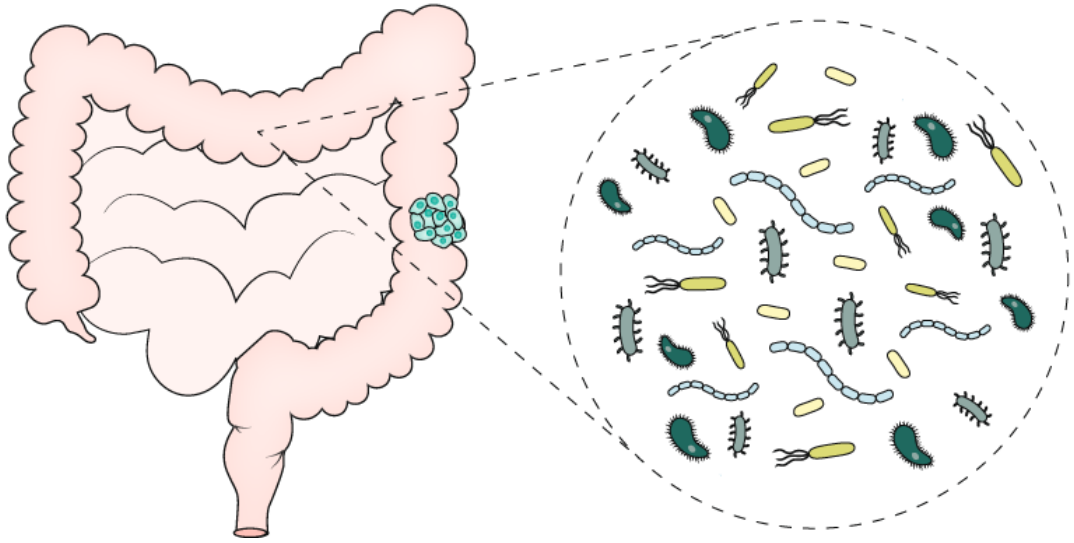
Prognostic and/or predictive biomarkers
- Predict clinical outcomes in patients with CRC
- Predict treatment responses or adverse effects

Modulation for CRC treatment
- Modify microbiota to improve immunotherapy or chemotherapy responses or reduce their adverse effects

Modulation for CRC prevention
- Modify microbiota to prevent CRC in high-risk or average-risk populations

Type of markers
- Microbial genes
- Microbial metabolites
- Microbiota-related serological markers

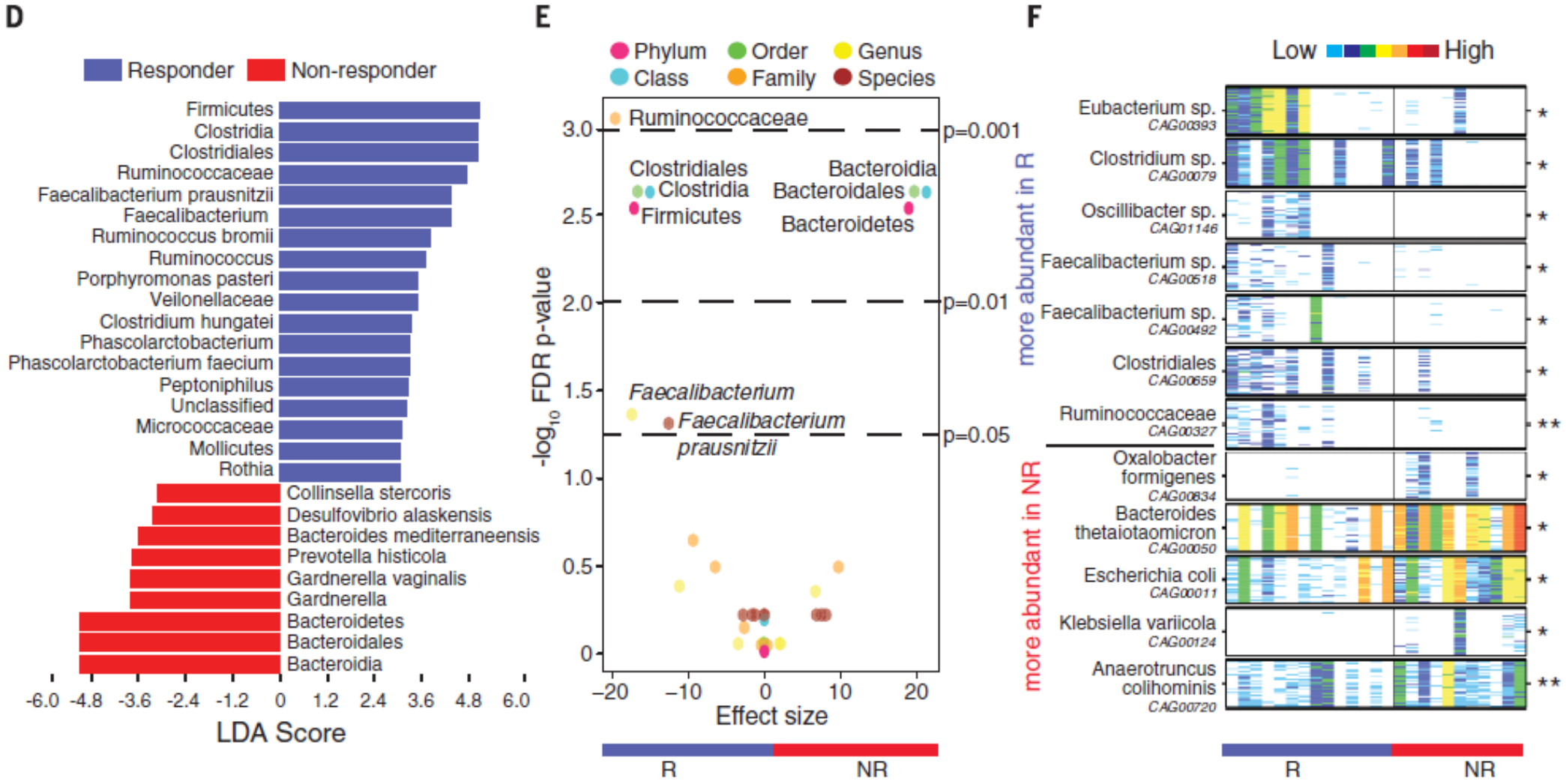
Samples
- Faecal, oral, blood or tumour tissue



Approaches
- Dietary intervention
- Prebiotics
- Probiotics
- FMT
- Antibiotics
- Postbiotics or microbial metabolites

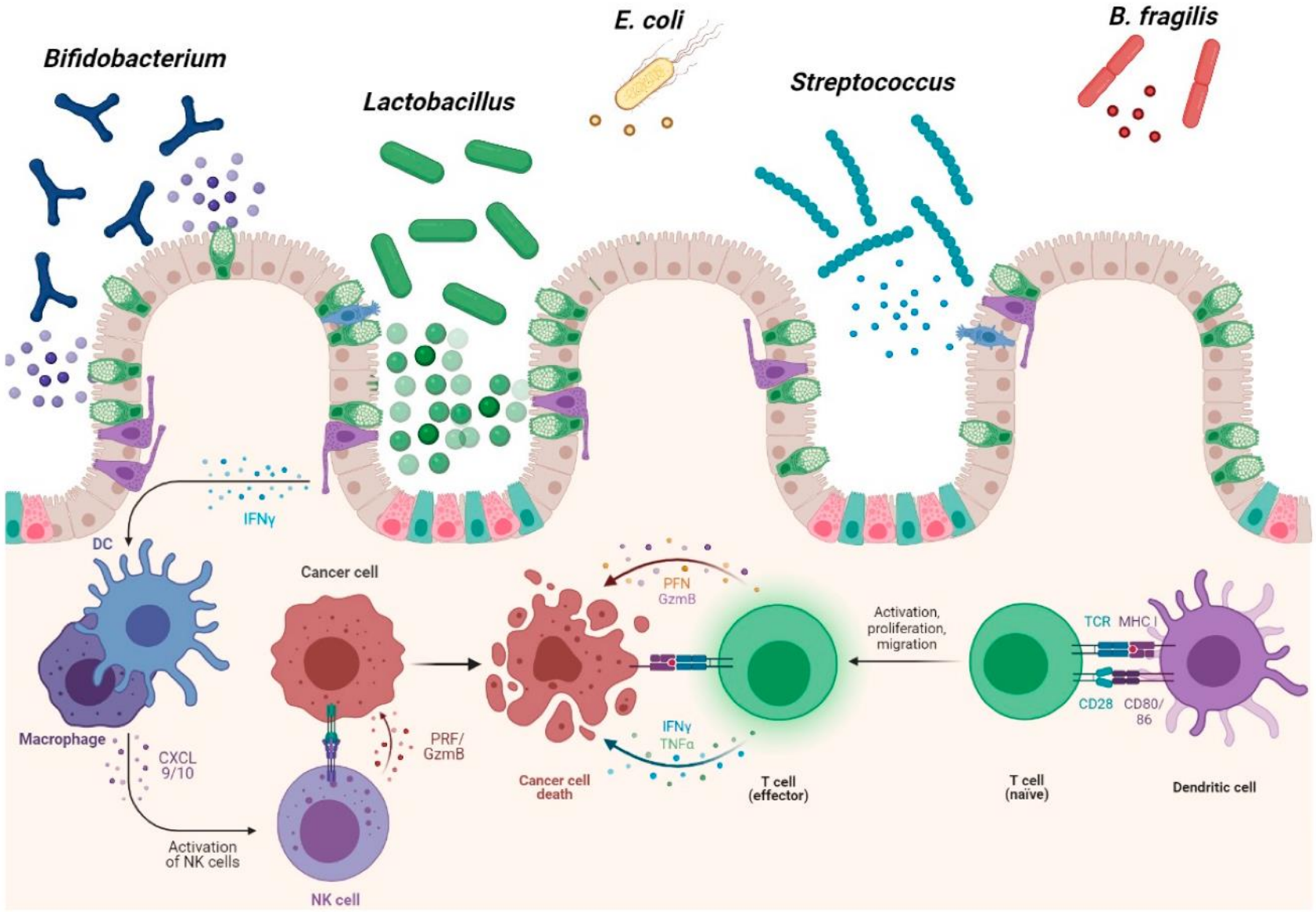
Wong, et al. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nature. 2019.

Gut Microbiome Modulates Response to Anti-PD-1 Immunotherapy in Patients with Melanoma



Gopalakrishnan et al. *Science* 2018.

Positive effects of microbiota and probiotics in CRC

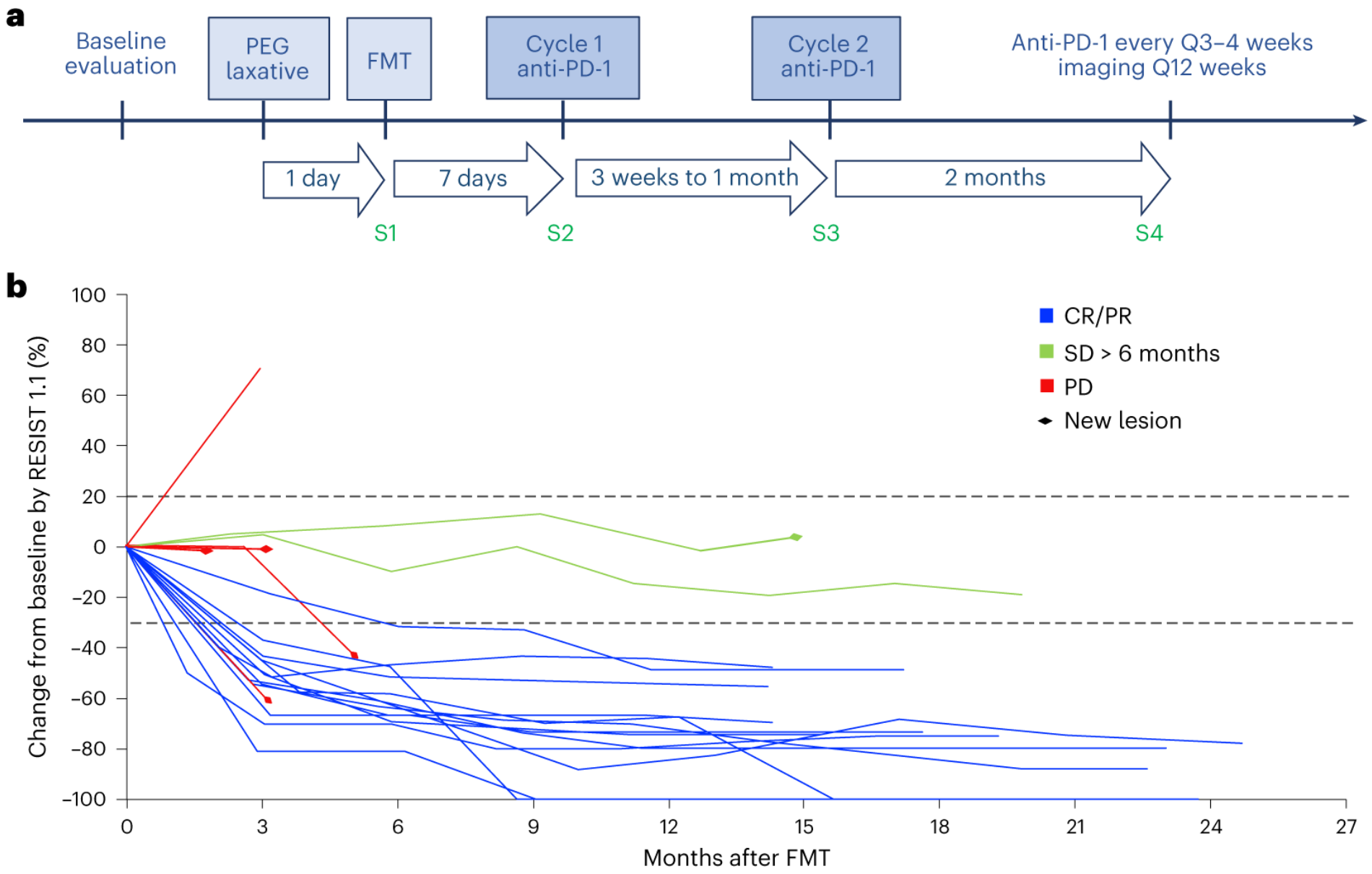


Torres Maravilla, et al. Role of gut microbiota and probiotics in colorectal cancer. Microorganisms. 2021

Fecal Microbiota Transplant Capsules

- Guideline approved for recurrent/refractory *C. difficile* infections (2013)
- Fecal Microbiota Transplant can improve immunotherapy-induced colitis
- Phase I study of patients with melanoma receiving immunotherapy and a fecal microbiota transplant (n = 40 patients)
  - 65% of the patients who retained the donors' fecal microbiota had clinical responses to the combination treatment

Routy et al. *Nature* 2023.



Routy et al. *Nature* 2023.

What we need:

Need to implement more standardized analysis strategies

Collate data from multiple studies and institutions (a ton of data!)

This is an area where machine learning and AI may be helpful!

Utilize CRC mouse models to better assess these effects, understand their functional relevance, and leverage this information to improve patient care

Cancer Center

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Prevent and conquer cancer. **Together**.

Thank You

American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

Thank You

nccrt.org @NCCRTnews #80inEveryCommunity

Diet, Nutrition, & Colorectal Cancer Research in the ACS Cancer Prevention Studies

Caroline Um, PhD, MPH, RD
Principal Scientist, Epidemiology Research
American Cancer Society

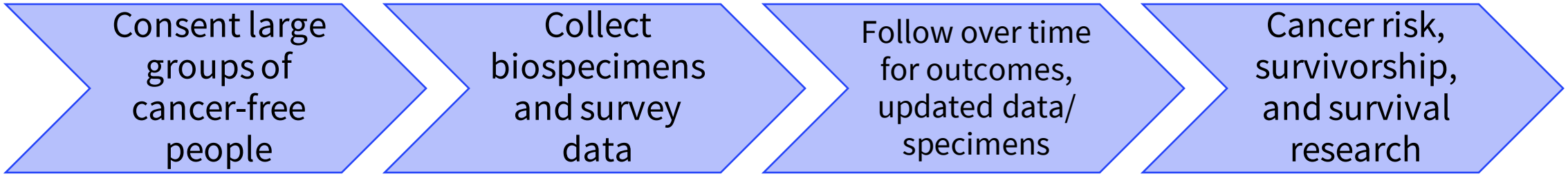
Diet, Nutrition, & Colorectal Cancer Research in the ACS Cancer Prevention Studies

Caroline Um, PhD, MPH, RD

National Colorectal Cancer Roundtable Annual Meeting
November 15-17, 2023

THE CANCER PREVENTION STUDIES (CPS)

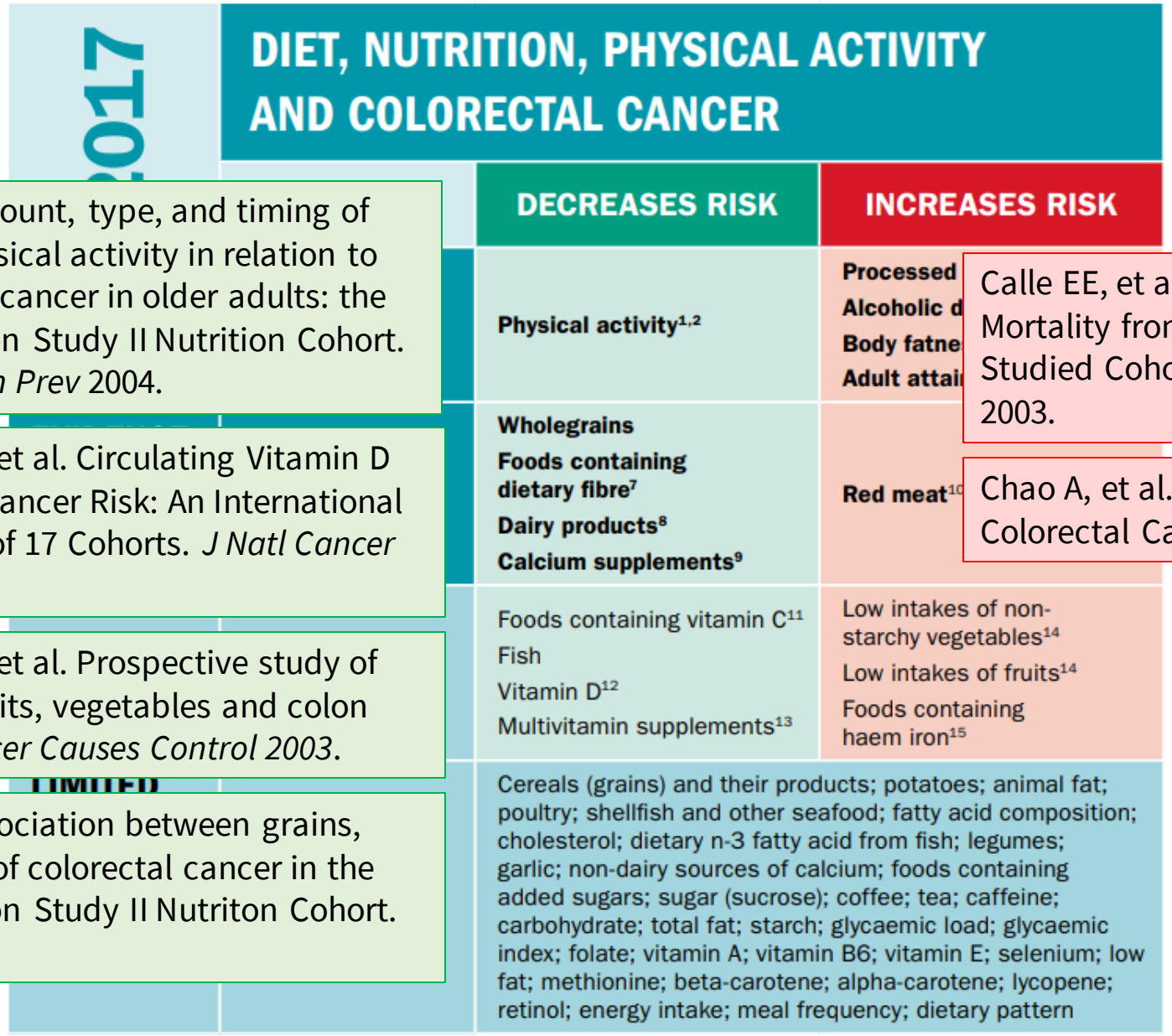
For nearly 70 years, the American Cancer Society has conducted some of the world's largest prospective epidemiologic cohort studies to understand risk factors for cancer risk as well as progression, quality of life, and survival after a cancer diagnosis.



	Hammond-Horn	CPS-I	CPS-II*	CPS-3*
Years	1952-1955	1959-1972	1982-2022	2006-present
Participants	188,000	1,000,000	1,200,000	304,000
Volunteers	22,000	68,000	77,000	25,000
With blood (or DNA)	n/a	n/a	40,000 (70,000)	297,000

** Tumor tissue for selected cancer types collected*

DIET & NUTRITION RESEARCH FROM CPS



DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER

	DECREASES RISK	INCREASES RISK
	Physical activity[1,2]	**Processed** **Alcoholic d** **Body fatne** **Adult attai**
	Wholegrains **Foods containing dietary fibre**[7] **Dairy products**[8] **Calcium supplements**[9]	**Red meat**[10]
	Foods containing vitamin C[11] Fish Vitamin D[12] Multivitamin supplements[13]	Low intakes of non-starchy vegetables[14] Low intakes of fruits[14] Foods containing haem iron[15]
LIMITED	Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine; beta-carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern	

Chao A, et al. Amount, type, and timing of recreational physical activity in relation to colon and rectal cancer in older adults: the Cancer Prevention Study II Nutrition Cohort. *Cancer Epid Biom Prev* 2004.

McCullough ML, et al. Circulating Vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts. *J Natl Cancer Inst* 2019.

McCullough ML, et al. Prospective study of whole grains, fruits, vegetables and colon cancer risk. *Cancer Causes Control 2003*.

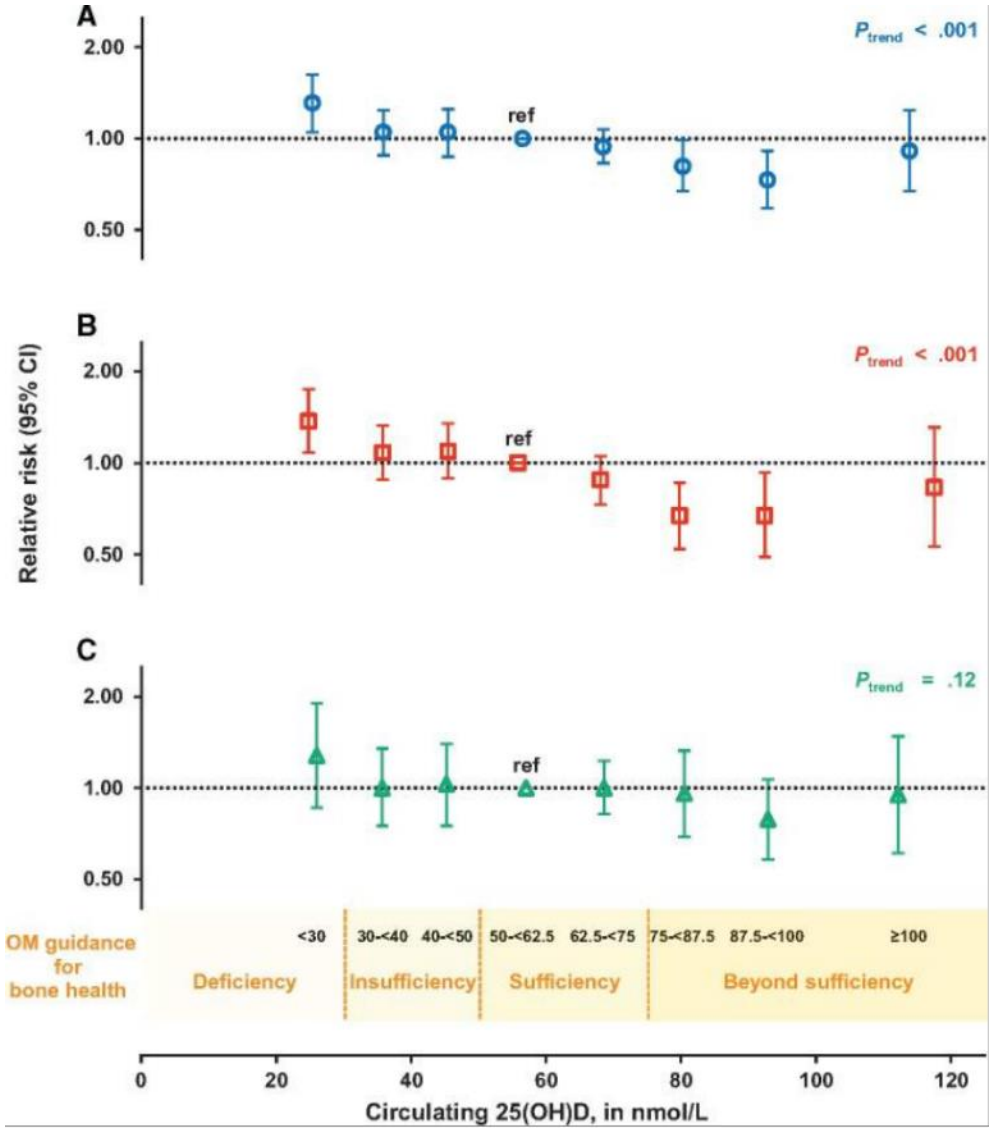
Um CY, et al. Association between grains, gluten, and risk of colorectal cancer in the Cancer Prevention Study II Nutriton Cohort. Eur J Nutr *2003*.

Calle EE, et al. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. *N Engl J Med* 2003.

Chao A, et al. Meat Consumption and Risk of Colorectal Cancer. *JAMA* 2005.

CPS-II

Circulating vitamin D and colorectal cancer risk: Pooled analysis of 17 prospective cohorts



All

Women

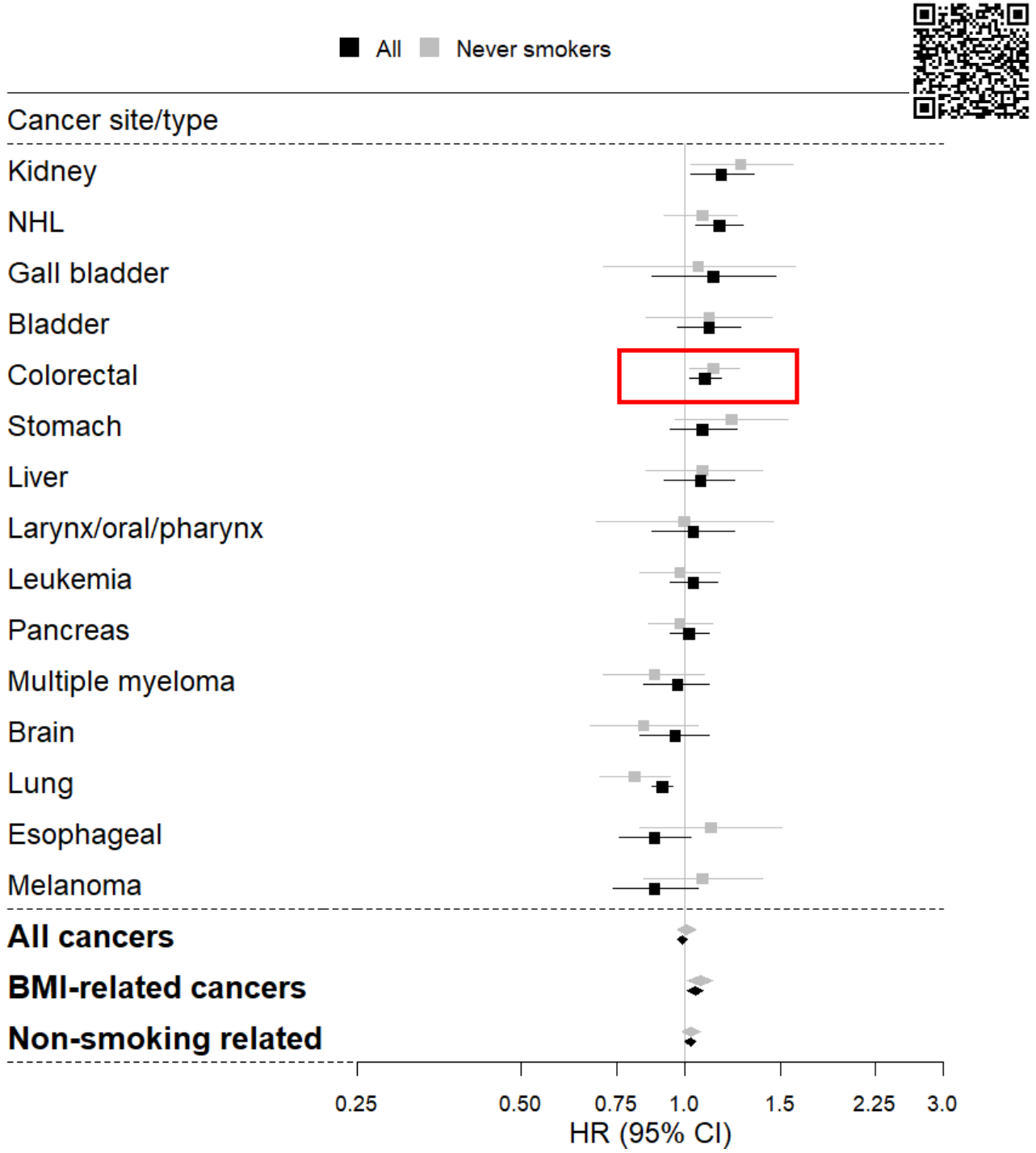
Men

Lower risk with circulating levels between 75-100 nmol/L

McCullough ML, et al. Circulating vitamin D and colorectal cancer risk: A pooled analysis of 17 prospective cohorts. *J Natl Cancer Inst* 2019.

CPS-II

Sugar sweetened beverage consumption and risk of cancer mortality among adults in CPS-II (1982-2017)



McCullough ML, et al. Sugar- and Artificially-Sweetened Beverages and Cancer Mortality in a Large U.S. Prospective Cohort. *Cancer Epid Biom Prev* 2022.

Diet and Activity Guidelines to Reduce Cancer Risk

Staying at a healthy weight, being physically active throughout life, following a healthy eating pattern, and avoiding or limiting alcohol may greatly reduce your risk of developing or dying from cancer.

EXCESS BODY WEIGHT, POOR NUTRITION, PHYSICAL INACTIVITY, AND EXCESS ALCOHOL CONSUMPTION = ABOUT **1** IN **5** **CANCER CASES**

OVERWEIGHT OR OBESITY RAISES A PERSON'S RISK OF GETTING ONE OR MORE OF **13** **TYPES OF CANCER**

The American Cancer Society Diet and Physical Activity Guidelines for Cancer Prevention provide recommendations for weight control, physical activity, diet, and alcohol consumption to reduce cancer risk.

The American Cancer Society recommends the following:

GET TO AND STAY AT A HEALTHY BODY WEIGHT THROUGHOUT LIFE.

BE PHYSICALLY ACTIVE.

EXERCISE

ADULTS should get 150-300 minutes moderate-intensity activity/week
or
75-150 Minutes vigorous-intensity activity/week
or
a combination of the two through the week

CHILDREN AND TEENS should get at least 1 hour of moderate- or vigorous-intensity activity each day.

LIMIT SEDENTARY BEHAVIOR

- Screen-based entertainment
- Sitting around
- Lying down

FOLLOW A HEALTHY EATING PATTERN.

MORE FRUITS AND VEGGIES ... LESS JUNK

- **Foods high in vitamins, minerals, and other nutrients in amounts that help you get to and stay at a healthy body weight**
- **A colorful variety of vegetables – dark green, red, and orange**
- **Fiber-rich beans and peas**
- **A colorful variety of whole fruits**
- **Whole grains, like whole wheat bread and brown rice**

- **Red meats such as beef, pork, and lamb and processed meats such as bacon, sausage, deli meats, and hot dogs**
- **Sugar-sweetened beverages**
- **Highly processed foods and refined grain products**

IT IS BEST NOT TO DRINK ALCOHOL

- **If you do choose to drink alcohol, women should have no more than one drink per day and men should have no more than two drinks per day.**
- **A drink is 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits.**

Many environments – where people live, learn, work, shop and play – are not supportive of making healthy choices.

The American Cancer Society recommends that public, private, and community organizations work together to increase access to affordable, healthy foods and provide safe, enjoyable and accessible opportunities for physical activity.

YOU CAN MAKE YOUR COMMUNITY HEALTHIER BY:

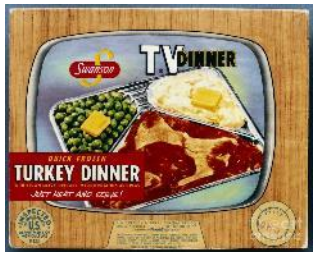
- **Asking for healthier meal and snack choices at school or work**

- **Speaking up at city council and other community meetings about the need for sidewalks, bike lanes, parks, and playgrounds to help make easier to walk, bike, and enjoy a variety of physical activities**

- **Supporting stores and restaurants that sell or serve healthy options**

WHAT'S AHEAD IN CPS

~2 million yrs ago
Hunter-gatherers



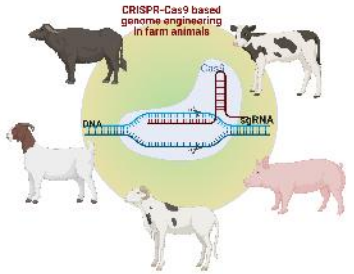
1950s
Convenience foods

2010s
Plant-based meat products

EVOLUTION OF FOOD

~12,000 yrs ago
Agriculture & farming

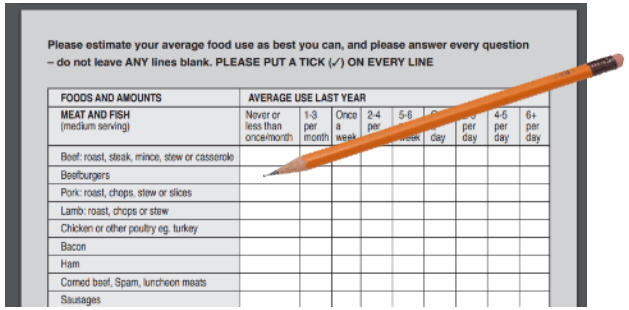
1980s
Genetic engineering



WHAT'S AHEAD IN CPS

Improved dietary assessment

EVOLUTION OF DIETARY ASSESSMENT



WHAT'S AHEAD IN CPS

Multi-omics research

- Lifestyle, environmental, & social factors
- Host genetics
- Oral and gut microbiomes
- Host and fecal metabolomes

Baseline Cohort: 1.2 million followed for mortality

Nutrition Cohort: 184,000 followed for cancer incidence & mortality

1982 1992 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017 2022

Blood
(n ≈ 37,000)

Buccal cell
(n ≈ 70,000)

Tumor tissue collection

Deaths through 2022

Cancer Prevention Study-II

Enrollment

Follow-up

2006 2009 2011 2013 2015 2018 2019 2020 2021 2023 2024

Enrollment
(survey, blood, waist measure)
n ≈ 303,000

Beginning in 2015
- National Death Index linkage and state cancer registry linkages (every 2 years)
- Triennial follow-up surveys

Validation studies (2015-2016)

Substudies (2019-)

Cancer Prevention Study-3

(2015-)
Tumor tissue & digital pathology

(2019-2023)
Accelerometry (n~20,000)

(2020-)
Participant portal (n=75,000)

(2020-2023)
Microbiome (n=10,000)

(2020-)
COVID-19 app (n=10,000)

(2022-2023)
HEALED (n=400)

(2024-2025)
Repeat blood (n=10,000)

WHAT'S AHEAD IN CPS

Racially/ethnically diverse participants

VOICES OF BLACK WOMEN

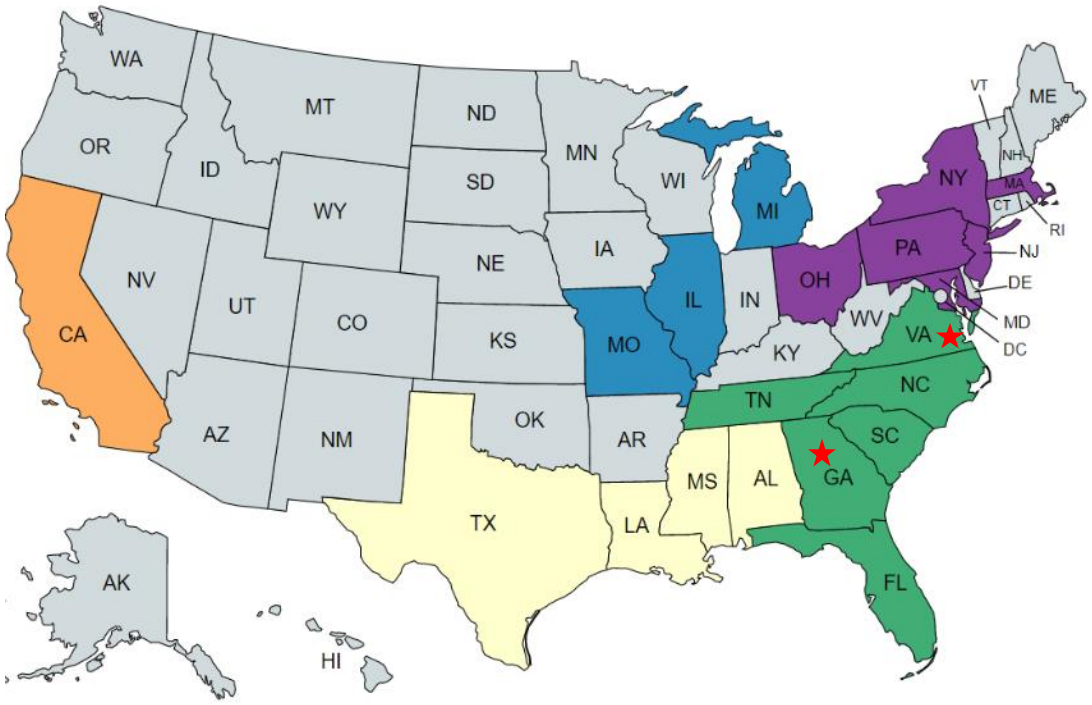
Enrolling Participant Groups:

Cancer-free cohort arm: *(Pilot launched Oct 2023)*

- 85,000 women between ages 25-55 years
- No cancer history (except basal or squamous skin cancer)

Survivor cohort arm: *(Pilot launching Fall 2024)*

- 15,000 women previously diagnosed with breast, endometrial, or colon cancer
  - 95% of excess cancer deaths for Black women attributed to these 3 cancers
- Age <65 years at diagnosis



★ **2023 Pilot Sites:**
Atlanta, GA
Hampton Roads, VA

Recruiting:

- Postdoctoral Fellows
- Study Management staff
- Data analysts

American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

Thank You

nccrt.org @NCCRTnews #80inEveryCommunity

Updates in Genetics and Family History

Swati Patel, MD, MS
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Updates in Genetics & Family History

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Disclosures

Olympus America (research support)

(NCCN Colorectal Cancer Screening Panel)

(US-MTSF on Colorectal Cancer)

Potential Impact of Family History–Based Screening Guidelines on the Detection of Early-Onset Colorectal Cancer

Samir Gupta, MD, MDCS, AGAF [1,2,3]; Balambal Bharti, MBBS, MPH, PhD[2,3]; Dennis J. Ahnen, MD[4,5]; Daniel D. Buchanan, PhD[6,7,8]; Iona C. Cheng, PhD, MPH[9]; Michelle Cotterchio, PhD[10]; Jane C. Figueiredo, PhD [11]; Steven J. Gallinger, MD, MSc[12]; Robert W. Haile, DrPH, MPH[11]; Mark A. Jenkins, PhD[7,13]; Noralane M. Lindor, MD[14]; Finlay A. Macrae, MD, AGAF[15]; Loïc Le Marchand, MD, PhD[16]; Polly A. Newcomb, PhD, MPH[17]; Stephen N. Thibodeau, PhD[18]; Aung Ko Win, MBBS, MPH, PhD[7,13]; and Maria Elena Martinez, PhD [3,19]

BACKGROUND: Initiating
for the prevention and de
limited. The authors asse
The authors conducted a
(772 individuals) incident
ity of family history–based
the American College of Radiology in 2008 for early screening, an
screening initiation if these criteria had been applied. **RESULTS:** Fa
25% of cases (614 of 2473 cases) and 10% of controls (74 of 772 co
ing EOCRC cases aged 40 to 49 years. Among 614 individuals me
screening initiation at an age younger than the observed age of
4 met family history–based early screening criteria, and nearly all
(or possibly even prevented) if earlier screening had been implem
are needed to improve the detection and prevention of EOCRC f

***Cancer* 2020;126:3013-3020**. © *2020 American Cancer Society*.

KEYWORDS: case-control study, family history, guidelines, sensitivi

I wish we had more time…

Check for up

Health Record Encourage Referrals for Genetic Counseling and Testing Among Patients at High Risk for Hereditary Cancer Syndromes?

Kristin K. Zorn, MD[1]; Melinda E. Simonson, ScM[1]; Jennifer L. Faulkner, MS[1]; Cyndee L. Carr, BS[1]; Joshua Acuna, MPH[1]; Tiffany L. Hall, RN[1]; John F. Jenkins, MBA[1]; Karen L. Drummond, PhD[1]; and Geoffrey M. Curran, PhD[1]

Updates in Genetics & Family History

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Updates in *Genetics* & Family History

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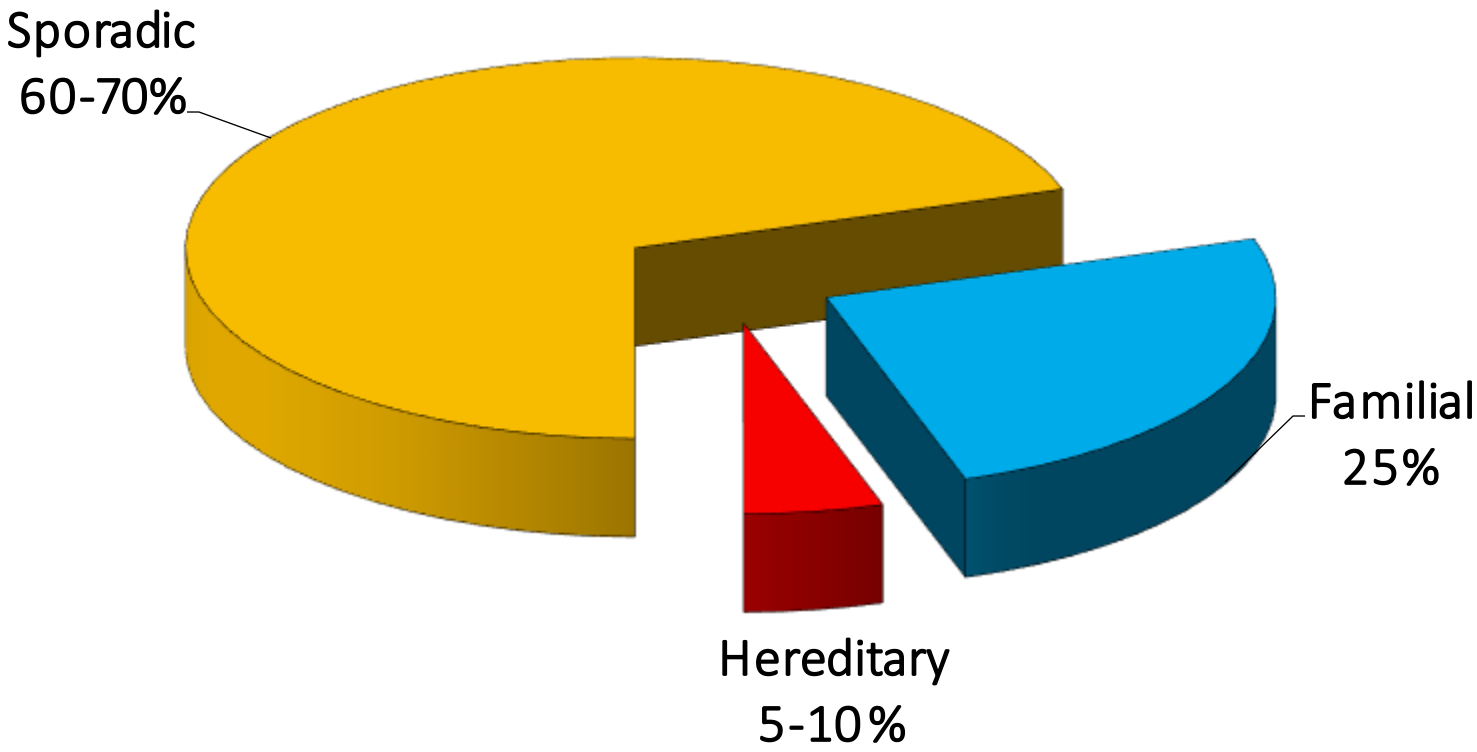
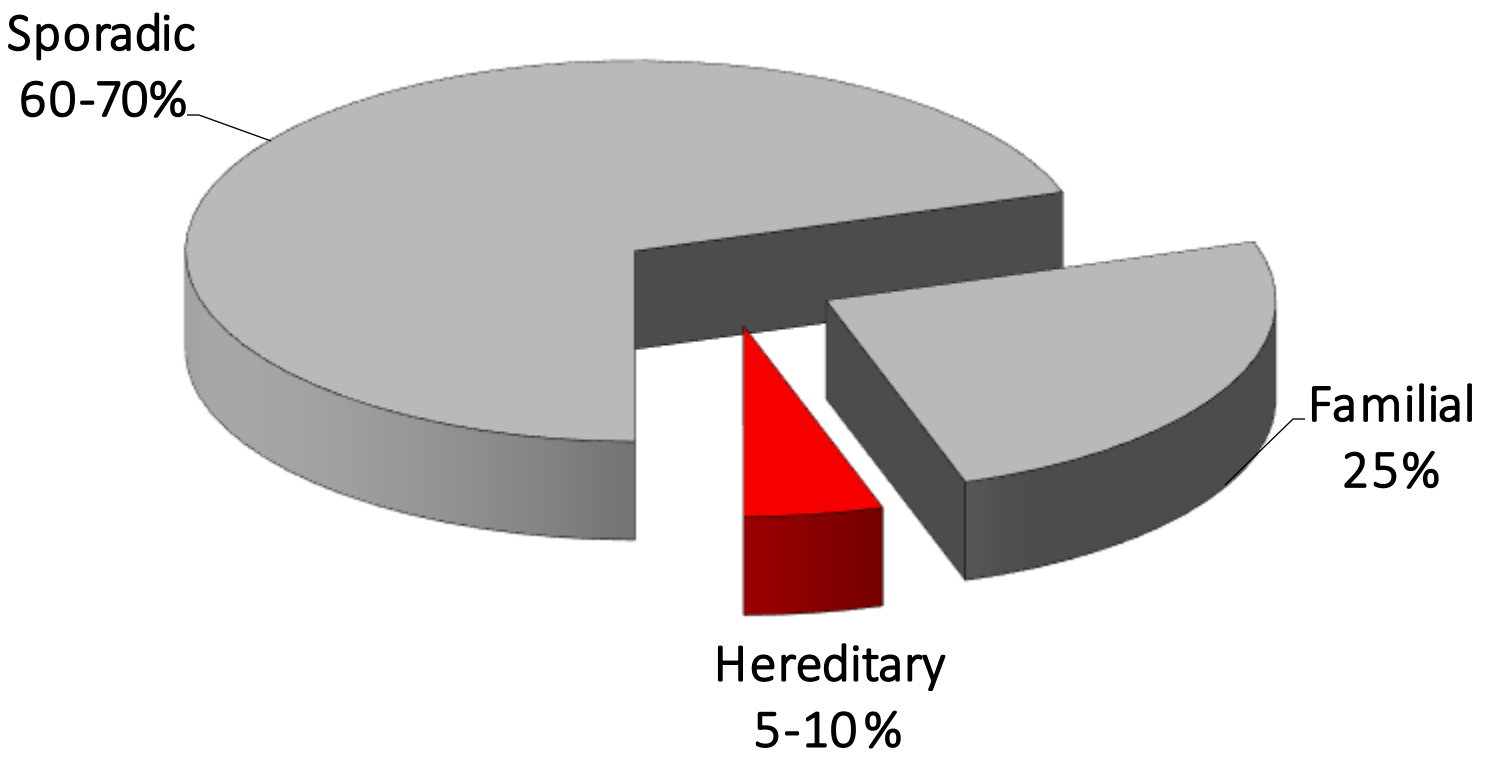
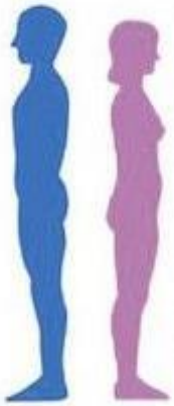
Approach to Hereditary Risk Assessment
Exercise Interventions
Dietary Interventions
Medication Interventions


Sporadic
60-70%
Familial
25%
Hereditary
5-10%


Sporadic
60-70%
Familial
25%
Hereditary
5-10%

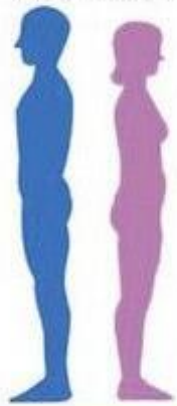
Estimated New Cases*

Males			Females		
Prostate	217,730	28%	Breast	207,090	28%
Lung & bronchus	116,750	15%	Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%	Colon & rectum	70,480	10%
Urinary bladder	52,760	7%	Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%	Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%	Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%	Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%	Kidney&renal pelvis	22,870	3%
Leukemia	24,690	3%	Ovary	21,880	3%
Pancreas	21,370	3%	Pancreas	21,770	3%
All sites	**789,620**	**100%**	**All sites**	**739,940**	**100%**

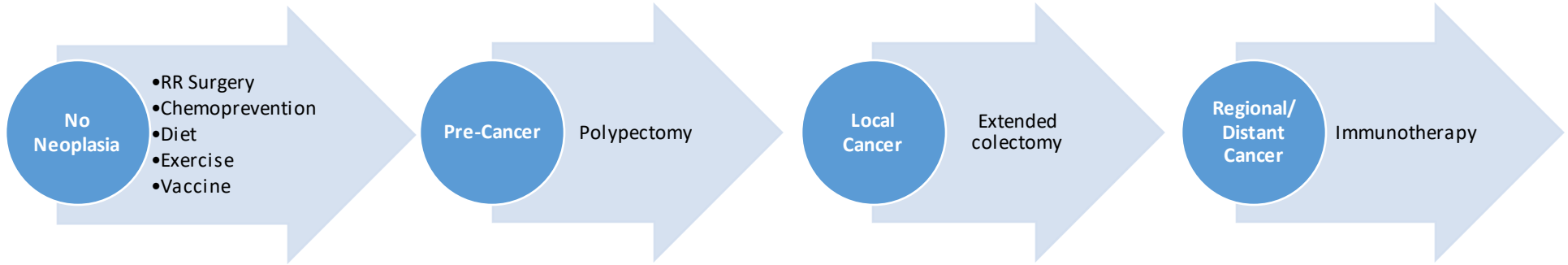


Estimated Deaths

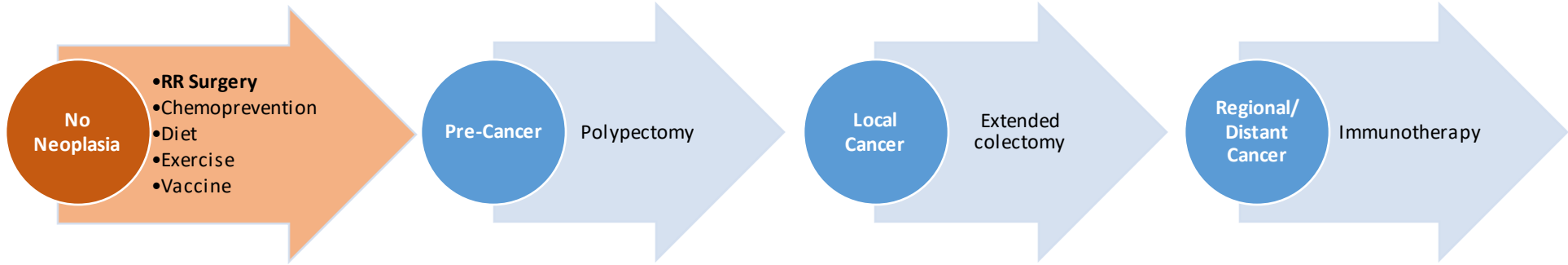
Males			Females		
Lung & bronchus	86,220	29%	Lung & bronchus	71,080	26%
Prostate	32,050	11%	Breast	39,840	15%
Colon & rectum	26,580	9%	Colon & rectum	24,790	9%
Pancreas	18,770	6%	Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%	Ovary	13,850	5%
Leukemia	12,660	4%	Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%	Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%	Uterine corpus	7,950	3%
Urinary bladder	10,410	3%	Multiple myeloma	6,190	2%
Kidney & renal pelvis	8,210	3%	Brain & other nervous system	5,720	2%
All sites	**299,200**	**100%**	**All sites**	**270,290**	**100%**

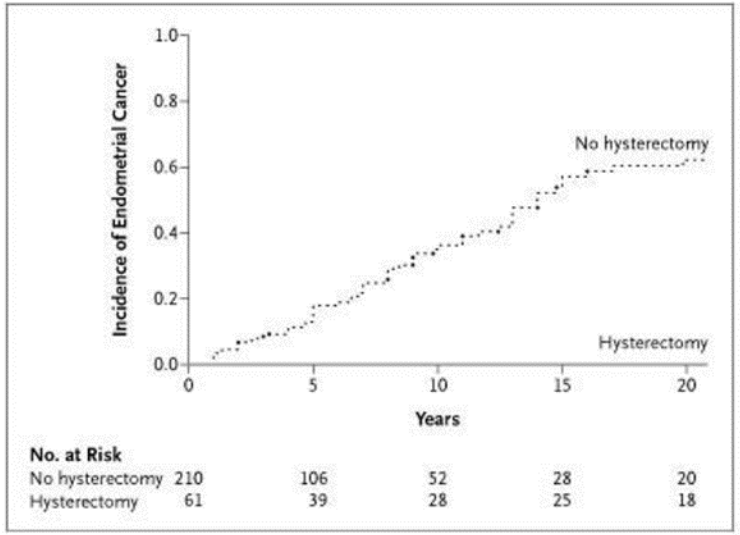


Opportunities for Intervention



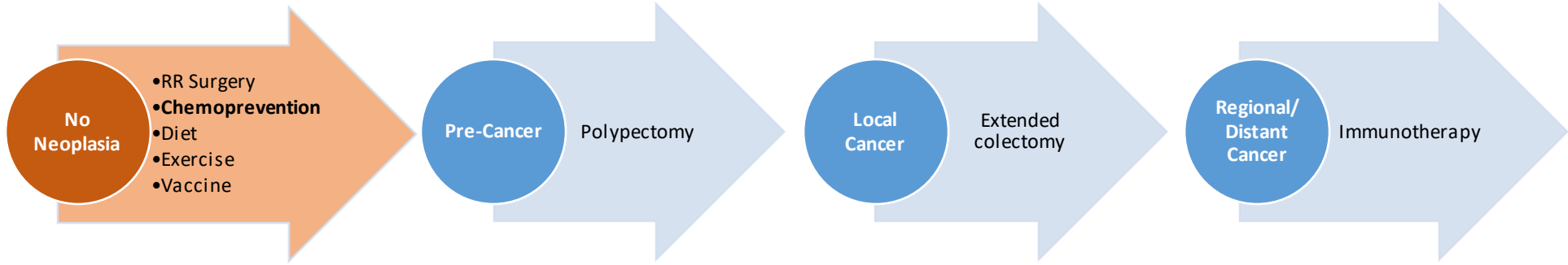
Opportunities for Intervention

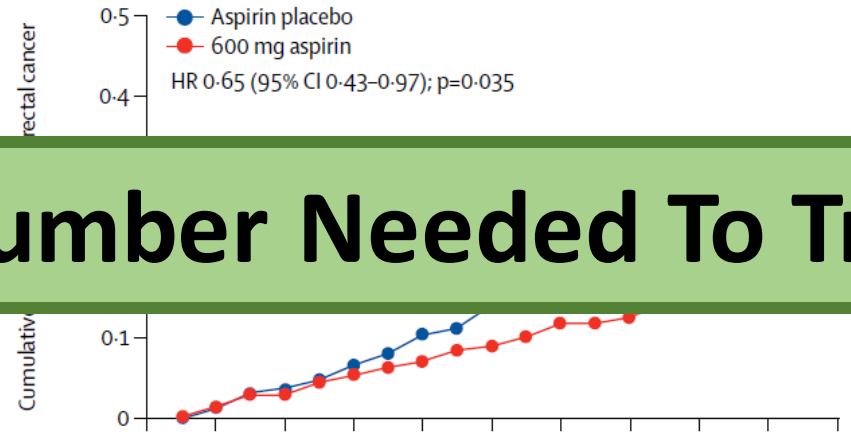




Schmeler et al. N Engl J Med 2006; 354:261-269.

Opportunities for Intervention

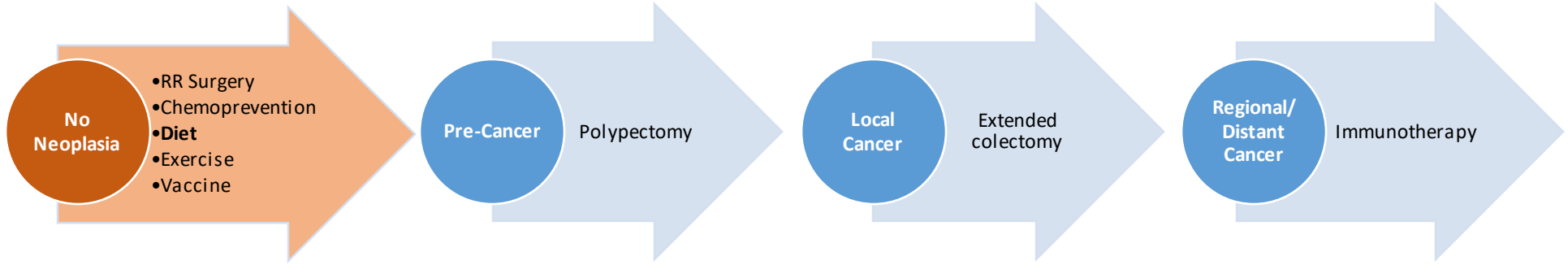


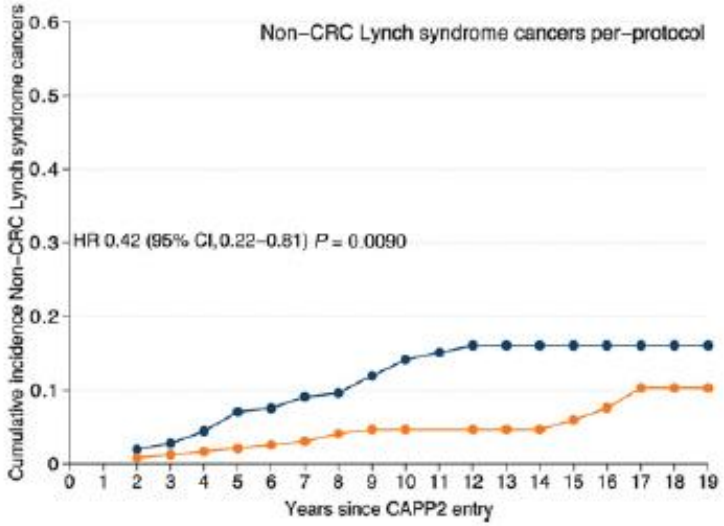


Number Needed To Treat to Prevent 1 CRC = 24

Burn et al. Lancet 2020, 395(10240): 1855-63.

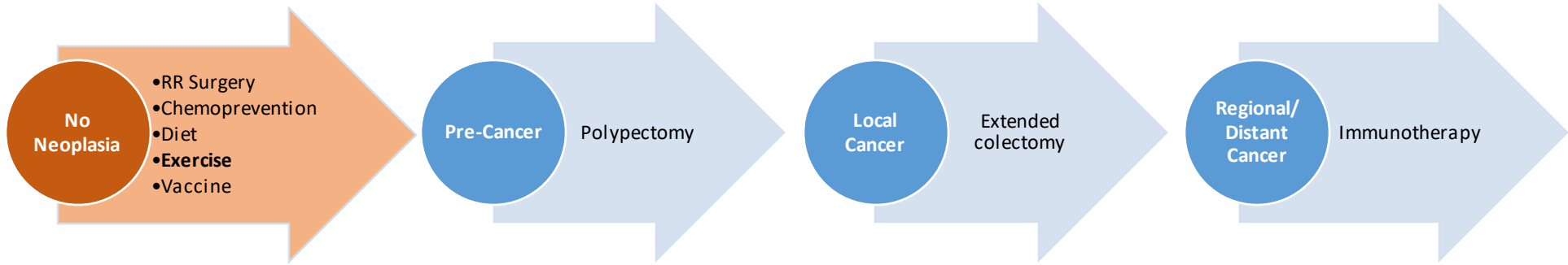
Opportunities for Intervention

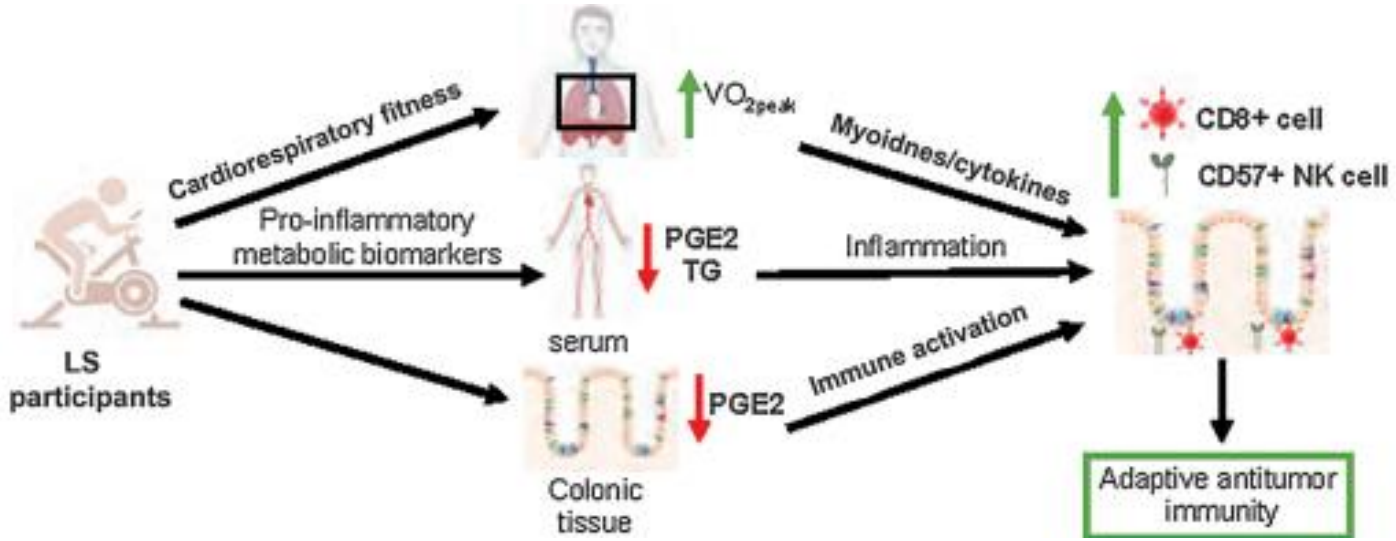




Mathers et al. Cancer Prev Res 2022;15:623-34.

Opportunities for Intervention





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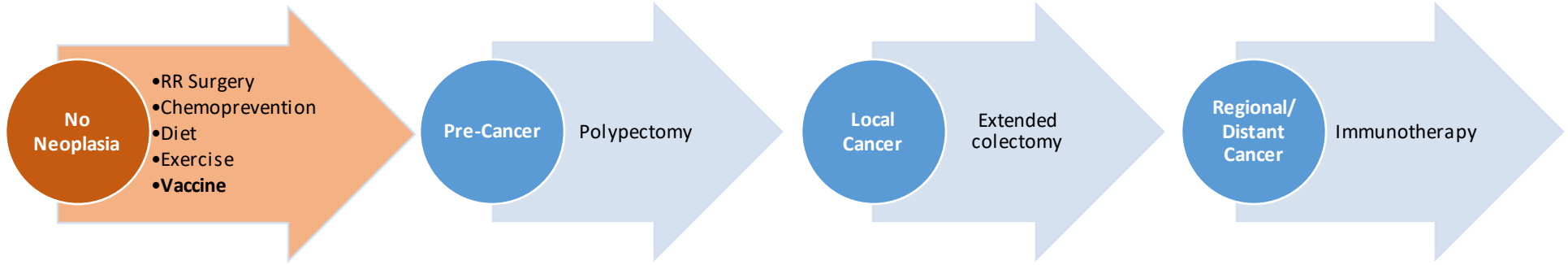
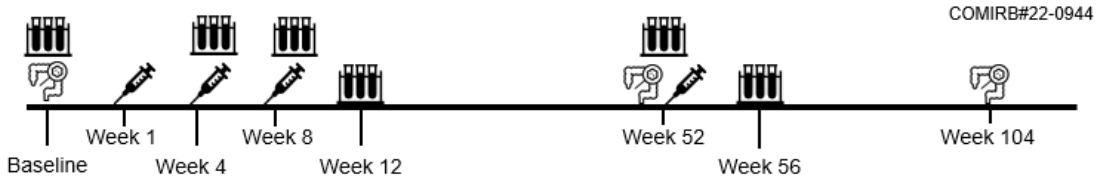




Standard of Care Colonoscopy

Vaccine Administration

Research Blood Draw

ELIGIBILITY

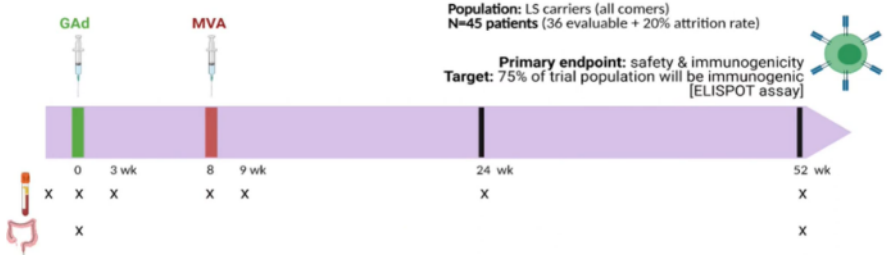
- Lynch Syndrome Diagnosis
- Able to partake in research blood draws and colonoscopies
- 18 years of age
- Able to commit to 2 years of research-related appointments

PRIMARY OUTCOME

- Cumulative colorectal neoplasia

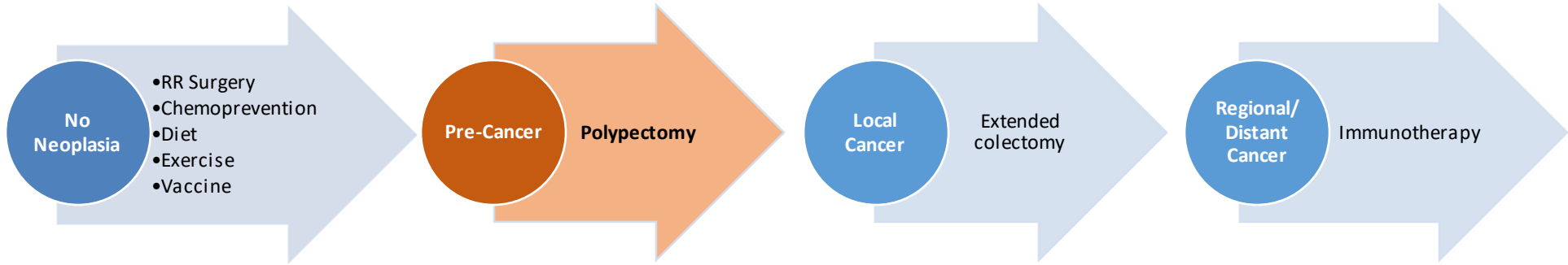
	cMS type	Mutation frequency (CRC)[3]	Mutation frequency (EC)[3]
TAF1B(−1)	A11	74.6%	50.0%
HT001(−1)	A11	86.2%	92.9%
AIM2(−1)	A10	81.6%	71.4%

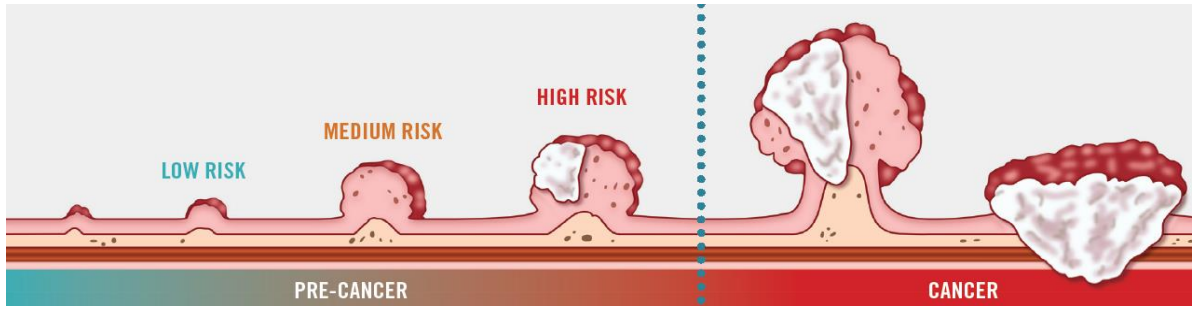
TAF1B(−1): H-NTQIKALNRGLKKKTILKKAGIGMCVKVSSIFFINKQKP-OH
AIM2(−1): H-HSTIKVIKAKKKHREVKRTNSSQLV-OH
HT001(−1): H-EIFLPKGRSNSKKKGRRNRIPAVLRTEGEPLHTPSVGMRETTGLGC-OH

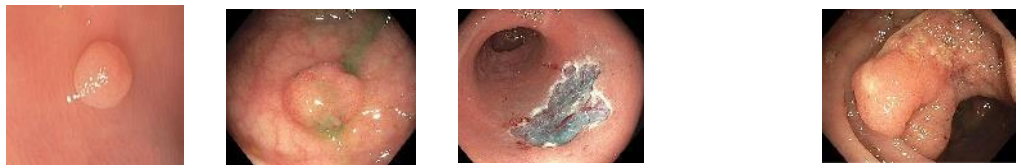


Kloor et al. Clin Cancer Res 2020;26(17):4503-10.
Vilar-Sanchez et al. NCT05078866.
Bansal & Vilar-Sanchez et al. NCT05419011.

Opportunities for Intervention





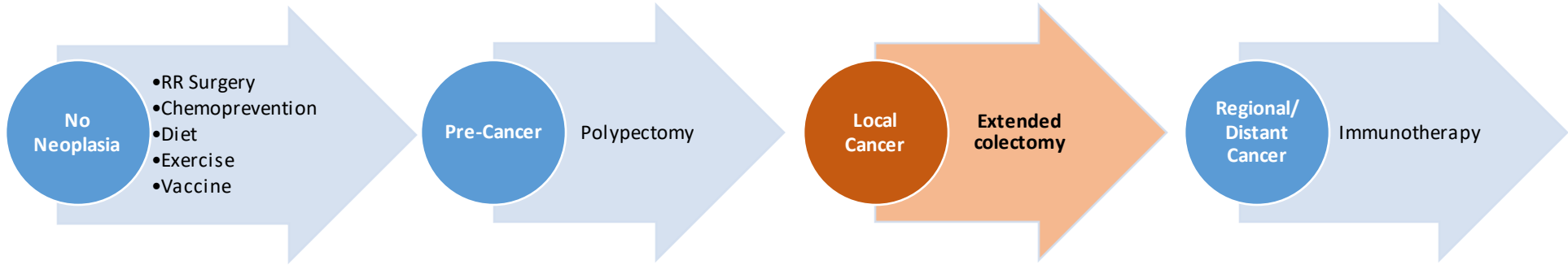


62% reduction in CRC Incidence

72% reduction in CRC Mortality

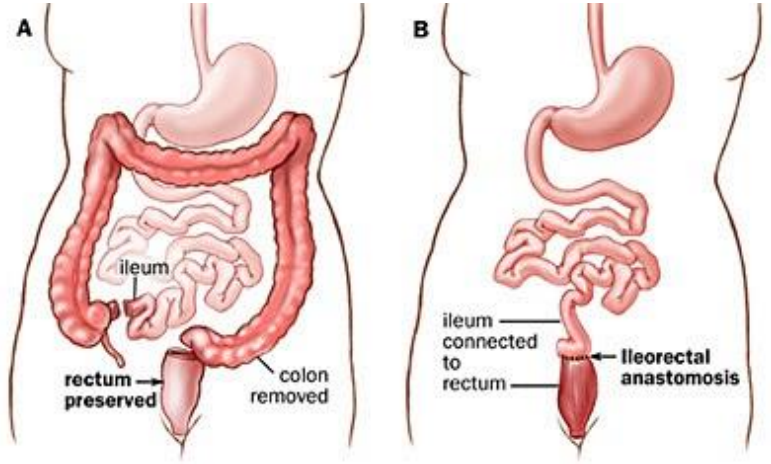
Jarvinen et al. Gastroenterol. 2000. 118(5):829-34.
Dove-Edwin et al. BMJ. 2005. 331(7524):1047.

Opportunities for Intervention



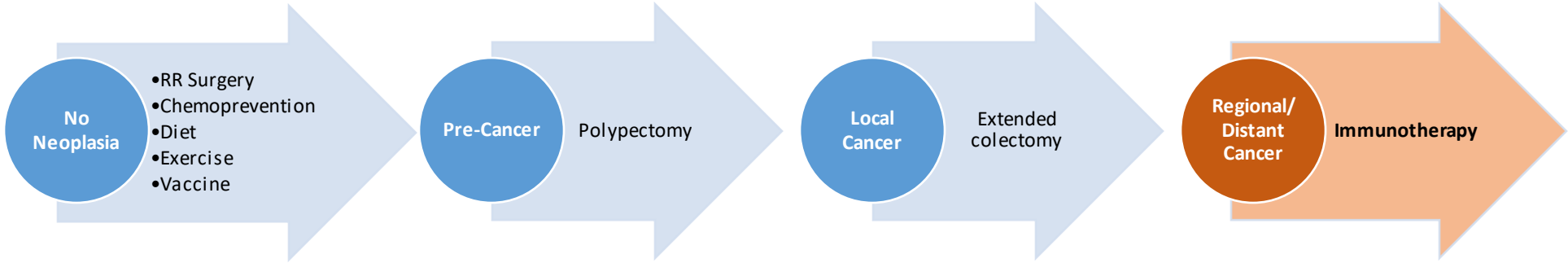
- Cumulative risk of metachronous CRC at 10, 20, 30 years is 16%, 41%, 62%, respectively

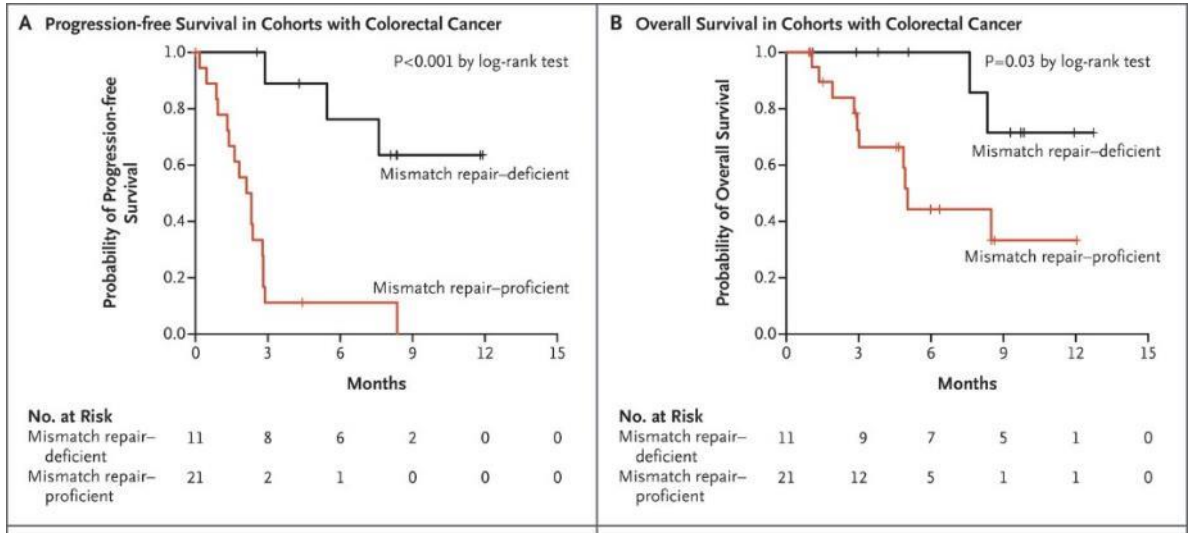
- Extensive colectomy vs segmental
  - Extensive: 0/50 metachronous tumors
  - Segmental: 74/322 (22%) metachronous tumors



Parry et al. Gut. 2011; 60:950-7.
Win et al. Ann Surg Onc. 2013; 20:1829-36.
Edelstein et al. Clin Gastroenterol Hep. 2011;9:340-43.

Opportunities for Intervention





Le et al. NEJM. 2015;372:2509-20.

Capturing Family Members: Cascade Testing

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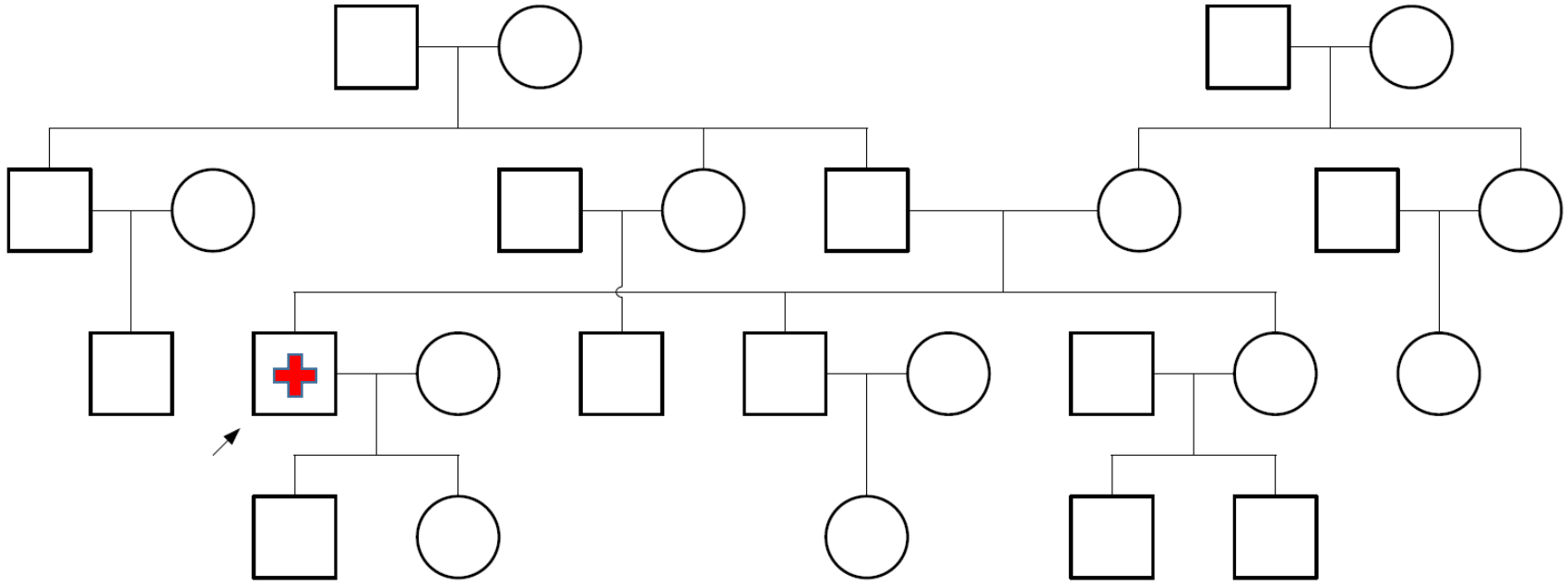
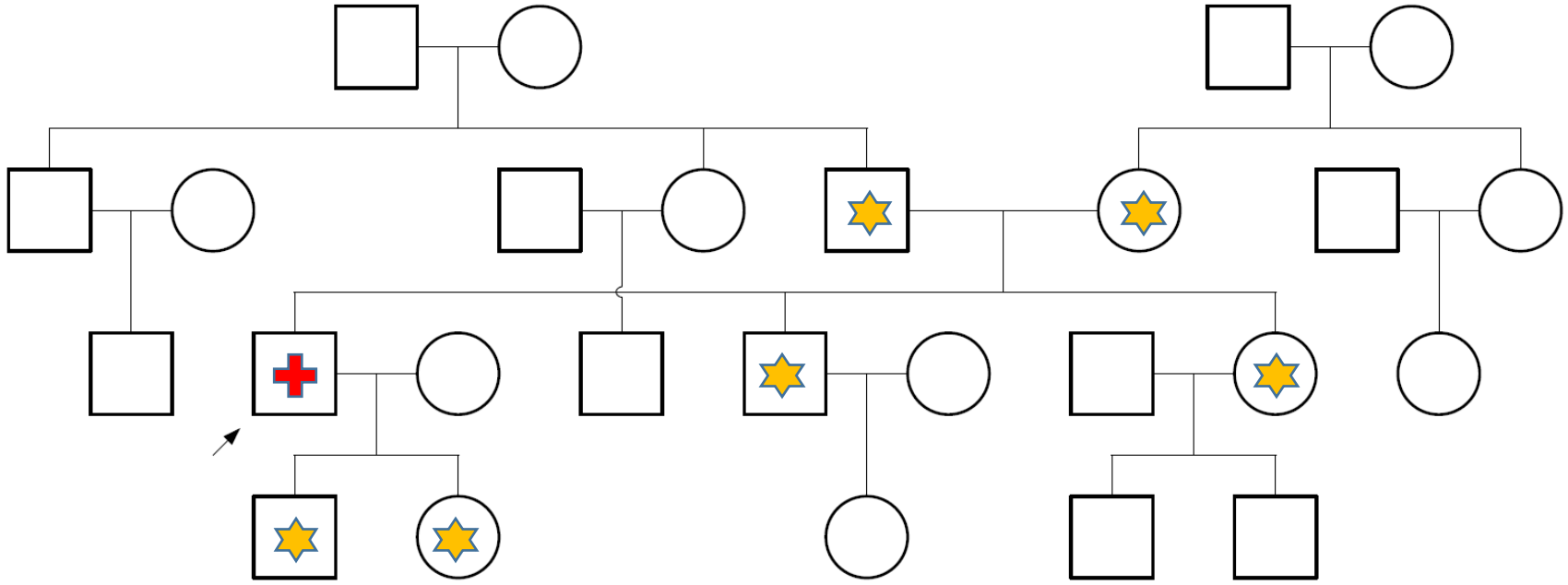


Capturing Family Members: Cascade Testing



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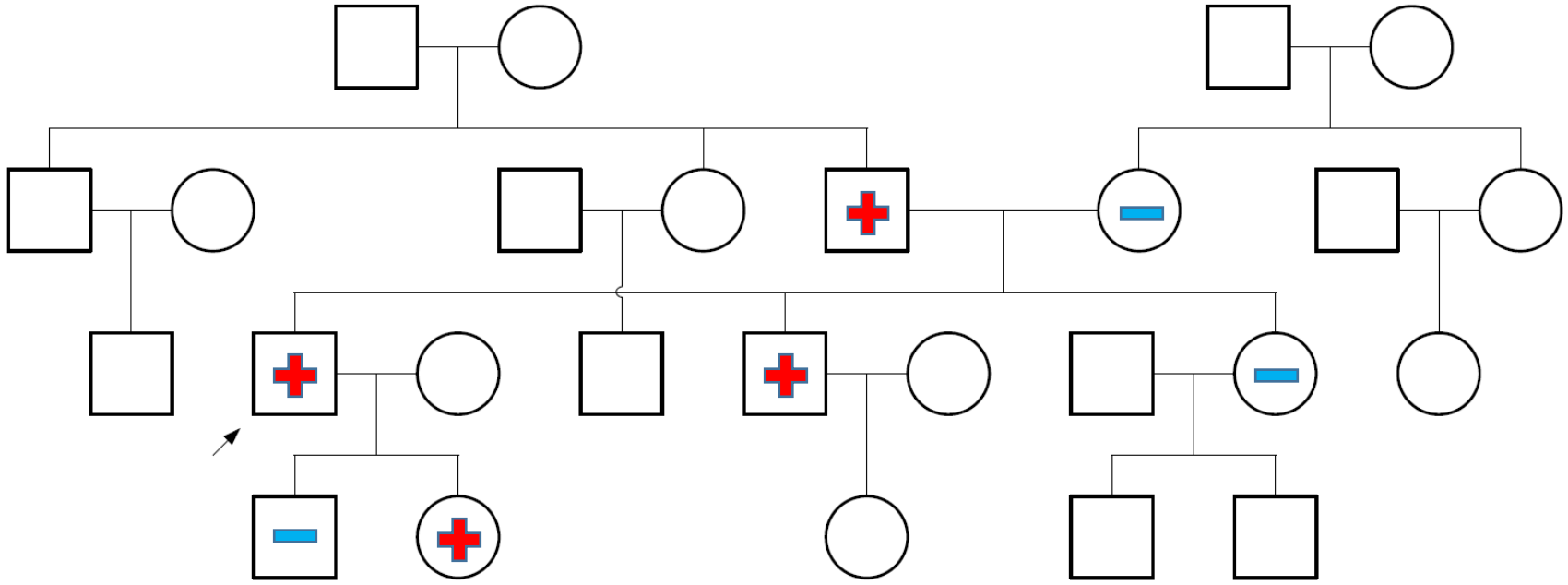

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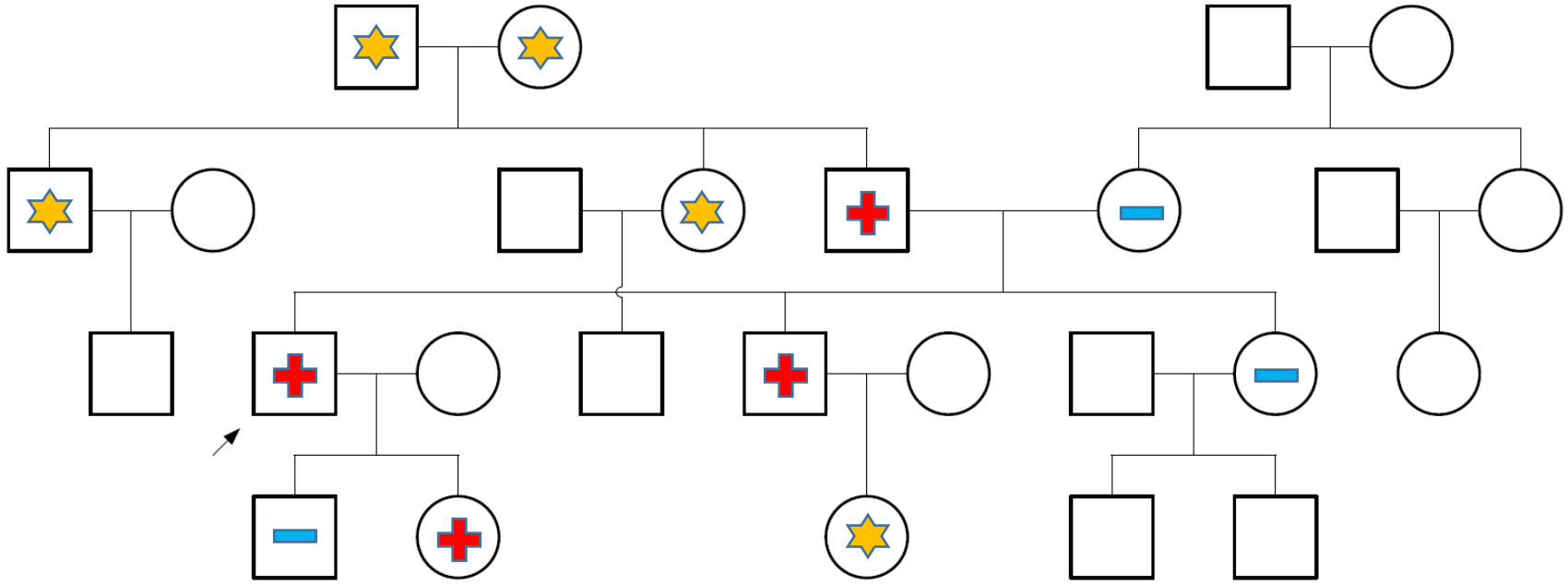

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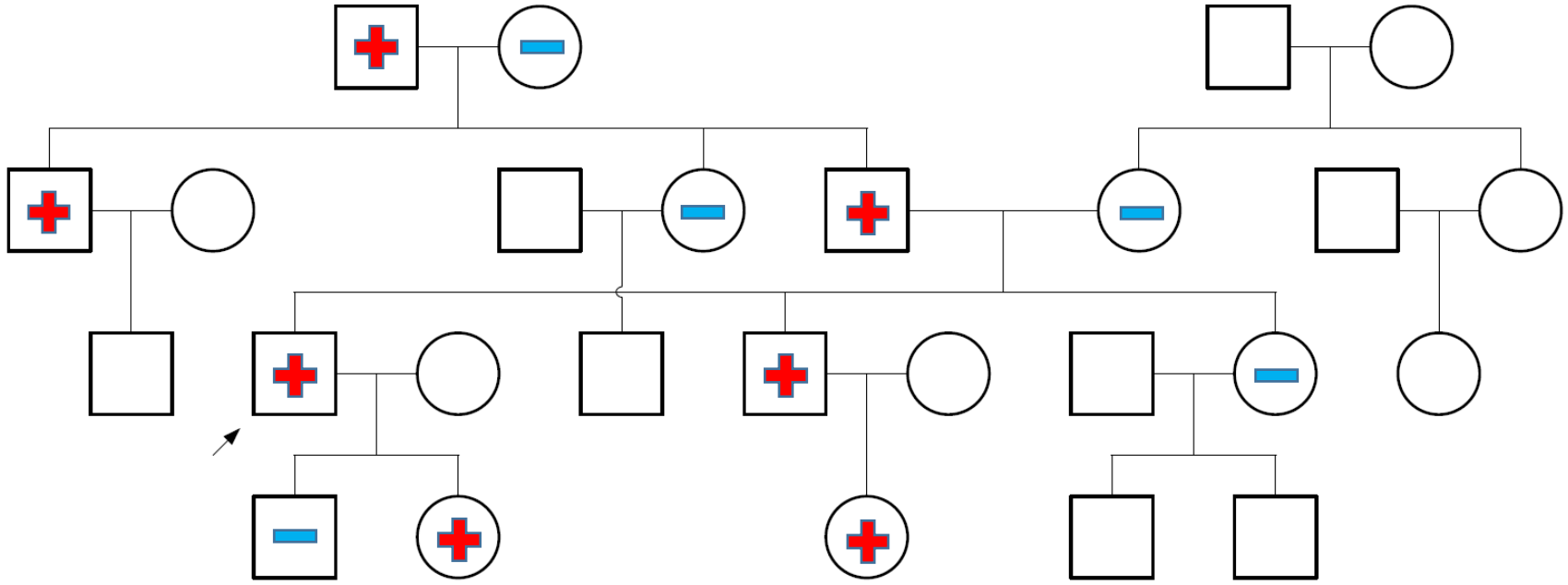

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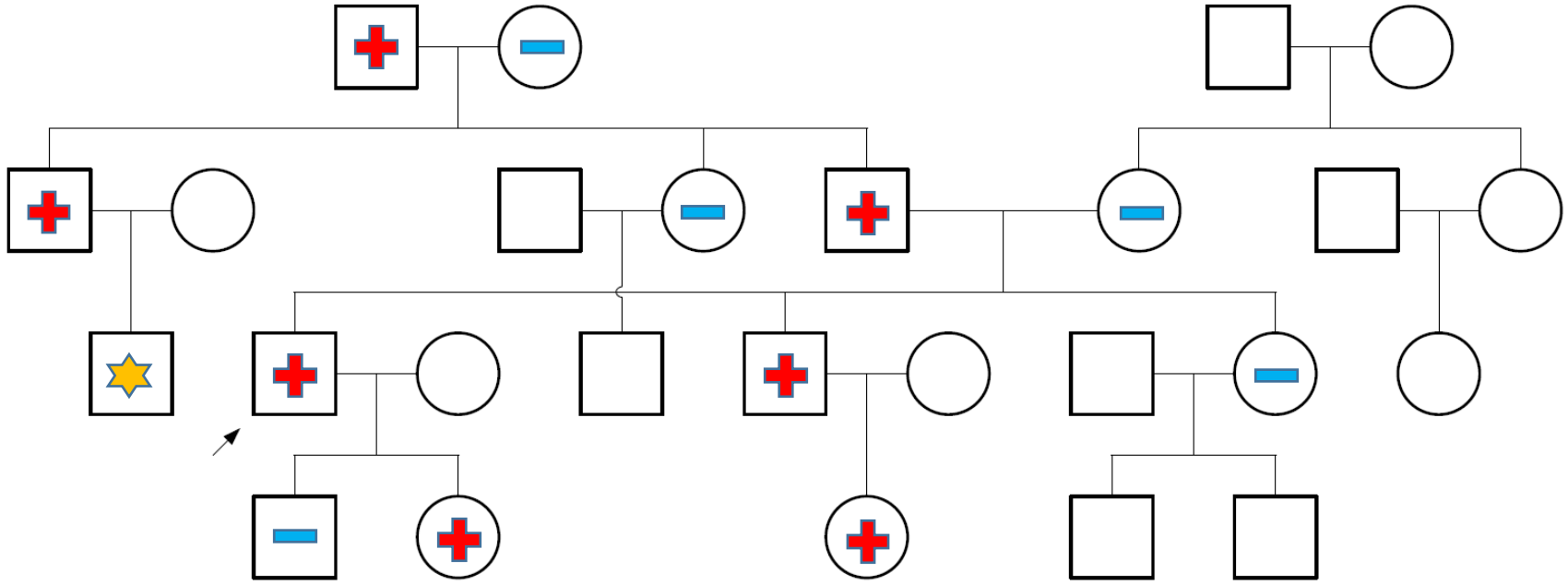
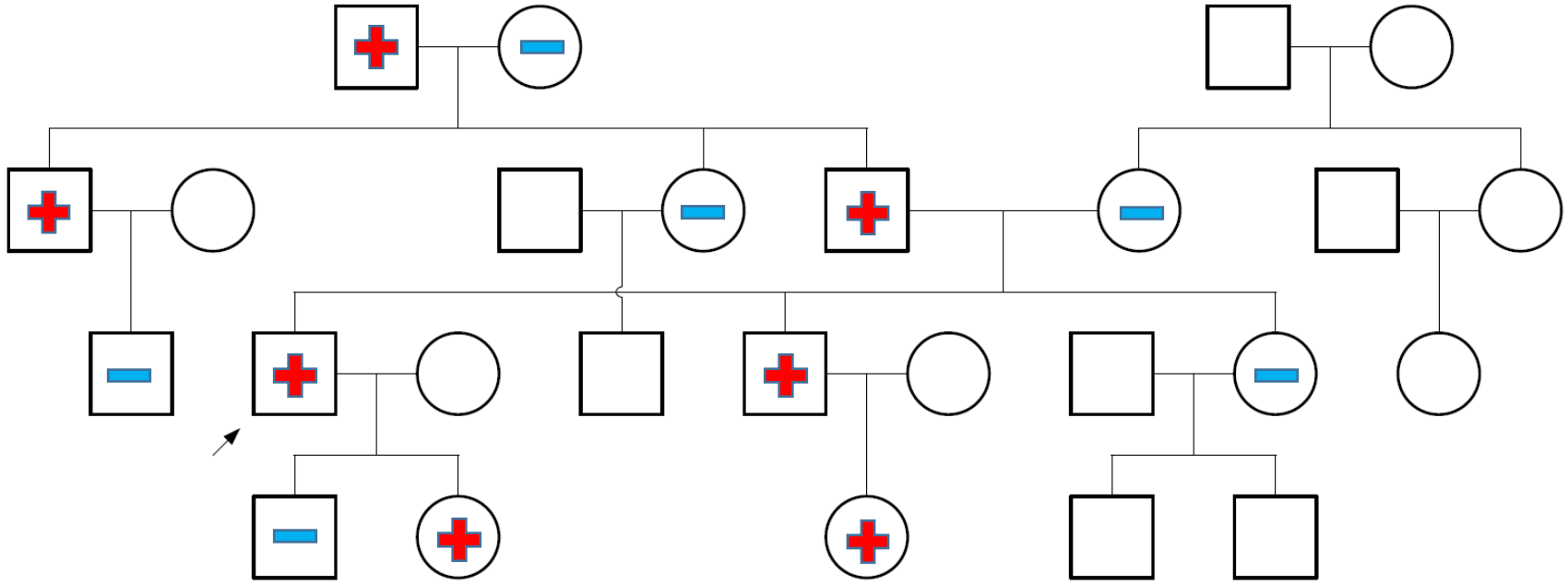
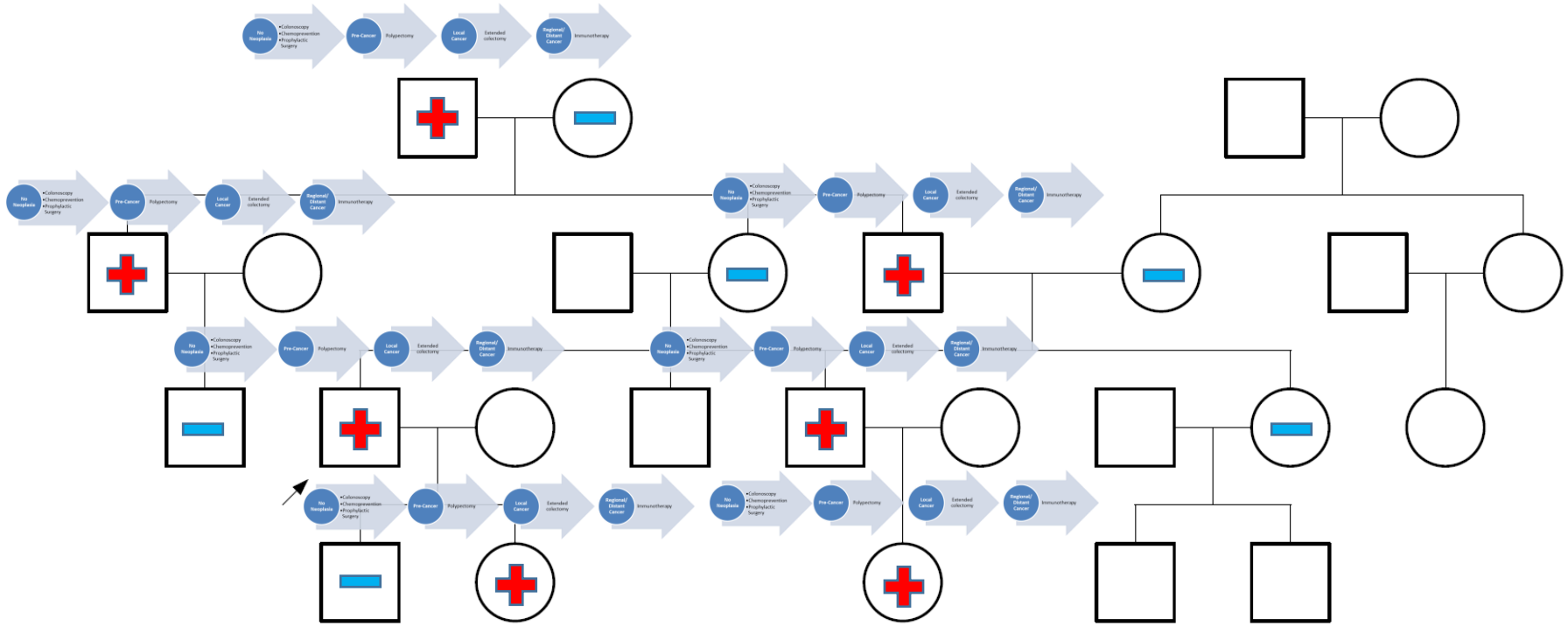


Capturing Family Members: Cascade Testing

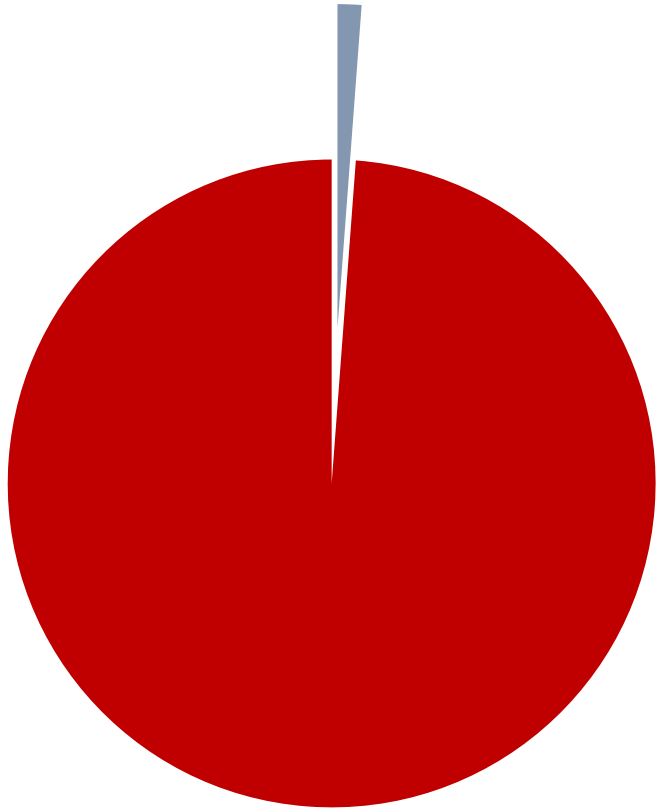


Capturing Family Members: Cascade Testing



Lynch Syndrome is Grossly Under-Recognized

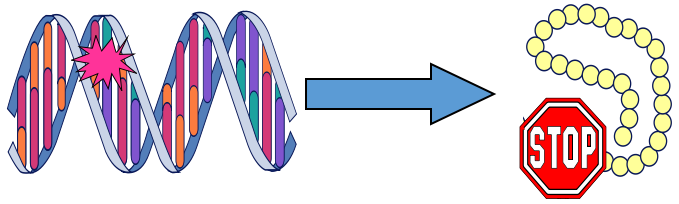
Only ~1.2% (10K/830K) Lynch mutation carriers in the US are aware of their diagnosis



Hampel et al. Cancer Prev Res. 2011. 4:1-5.

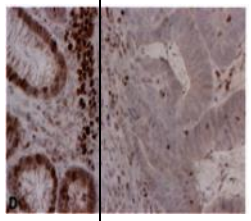
Lynch Syndrome Diagnosis: Tumor Screening

Immunohistochemistry for MMR Protein Loss



Abnormal Gene (MSH2)

Abnormal or missing MSH2 protein

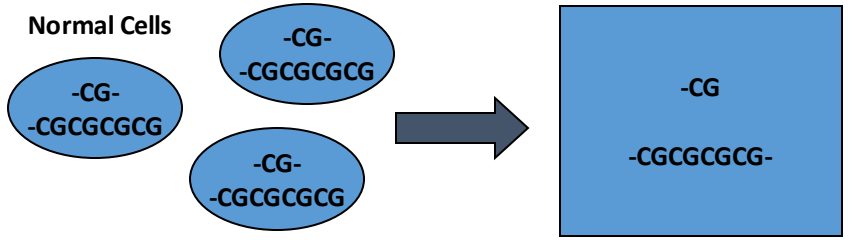


MSH2 +

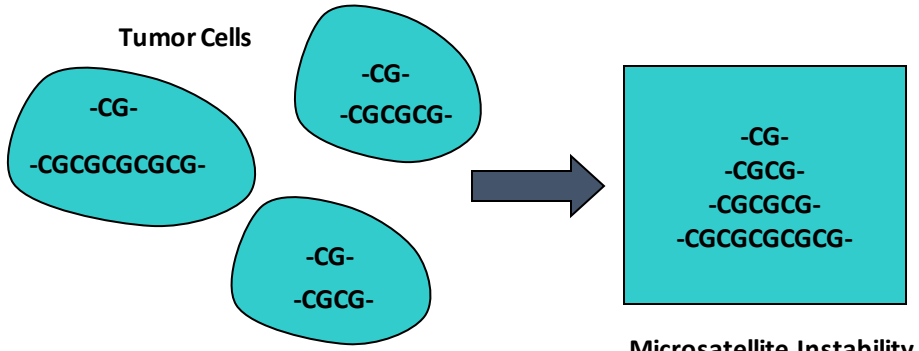
MSH2- Lack of MSH2 expression, negative IHC staining for MSH2 protein

Normal tissue | Tumor tissue

PCR for Microsatellite Instability Markers



Normal Microsatellites



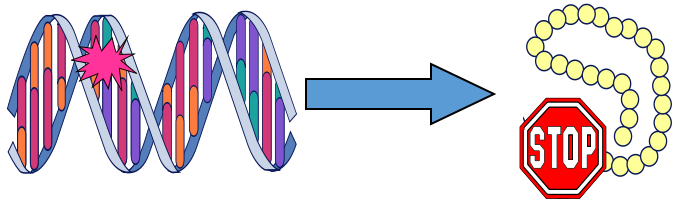
Microsatellite Instability

Lynch Syndrome Diagnosis: Universal Tumor Testing

"The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer (CRC) to reduce morbidity and mortality in relatives."

Lynch Syndrome Diagnosis: Tumor Screening

Immunohistochemistry for MMR Protein Loss



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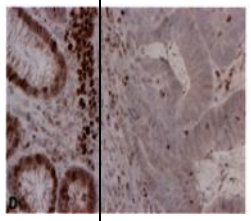

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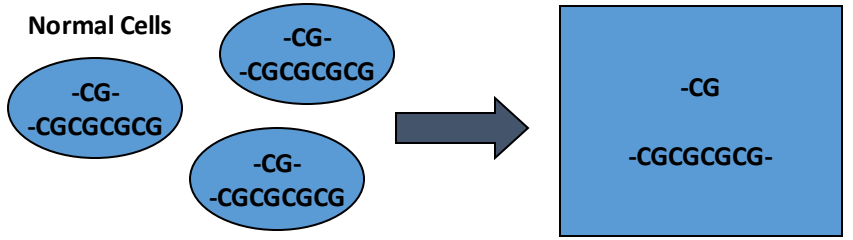

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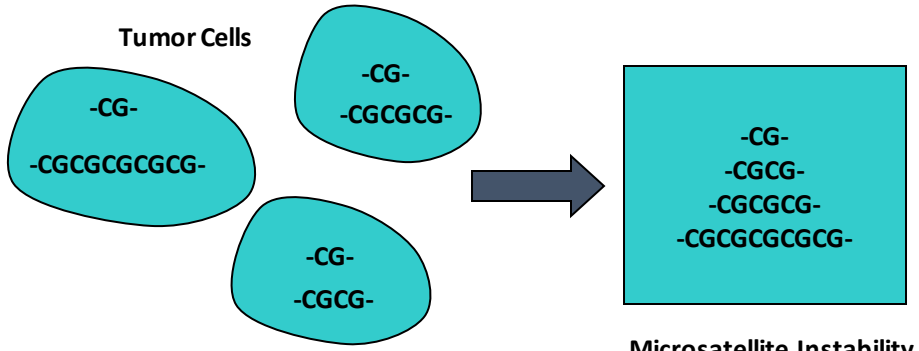
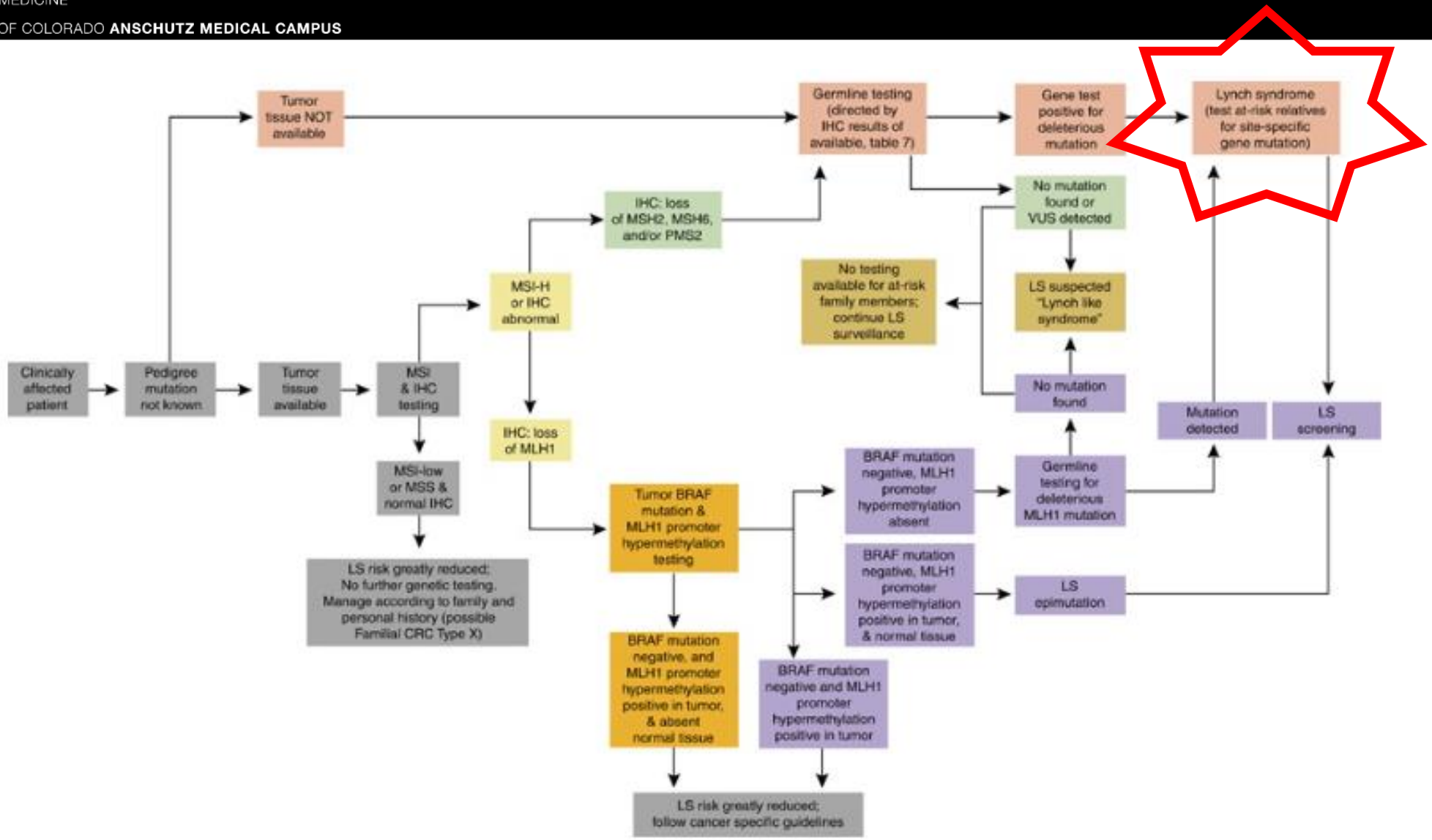


Microsatellite Instability



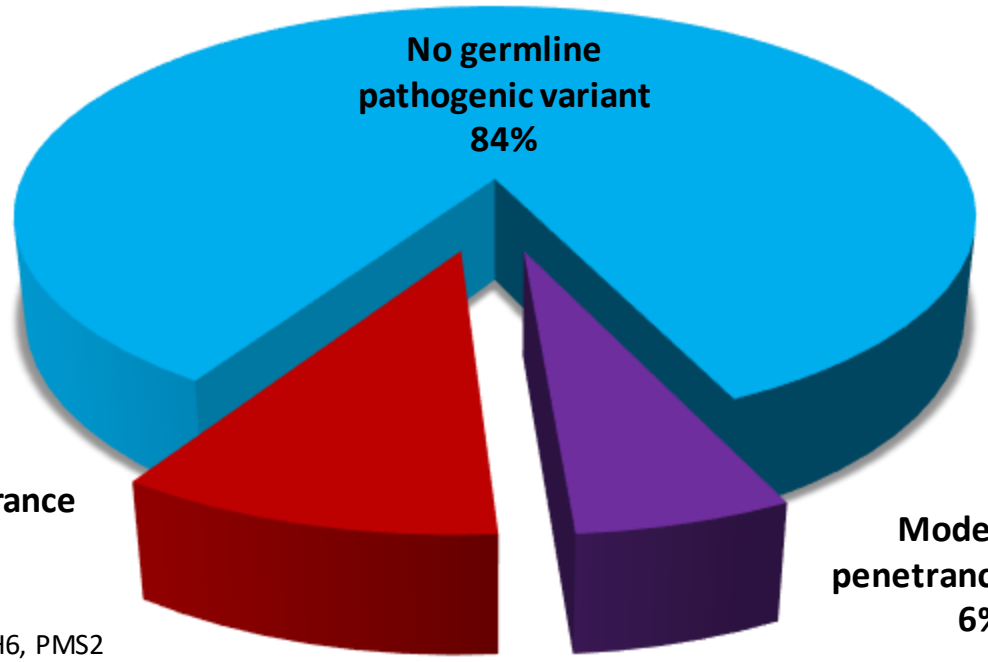
Lynch Syndrome: US-MSTF 2014.

Low Referral Rate for Genetic Testing in Racially and Ethnically Diverse Patients Despite Universal Colorectal Cancer Screening

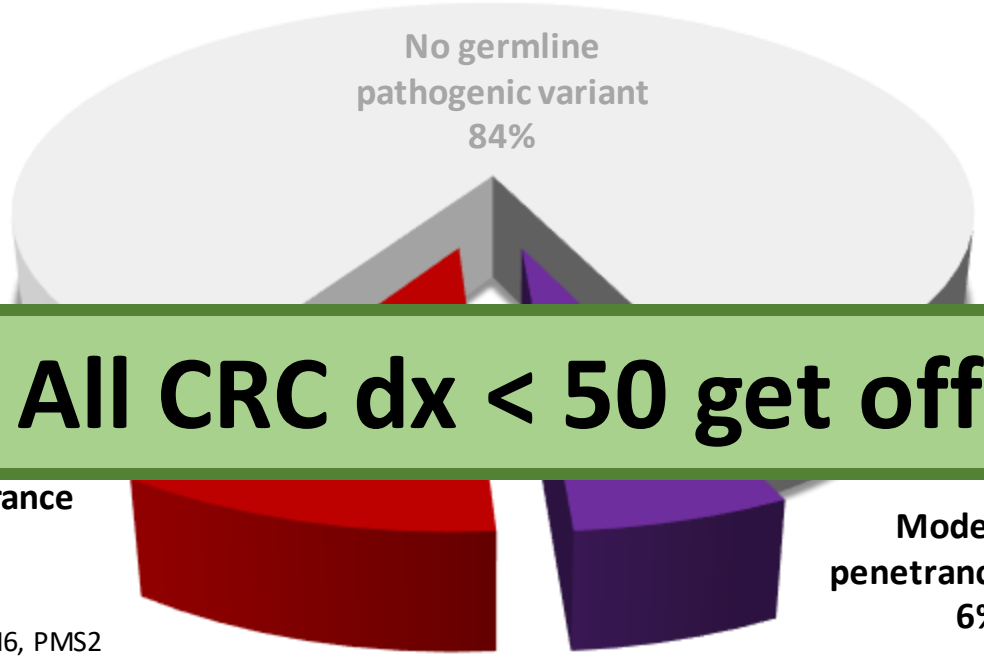
Charles Muller,* Sang Mee Lee,* William Barge,‡ Shazia M. Siddique,§ Shivali Berera,‖ Gina Wideroff,‖ Rashmi Tondon,§ Jeremy Chang,* Meaghan Peterson,* Jessica Stoll,* Bryson W. Katona,§ Daniel A. Sussman,‖ Joshua Melson,‡ and Sonia S. Kupfer*

Overall, 92% of colorectal tumors were analyzed for mismatch repair deficiency without significant differences among races/ethnicities. However, minority patients were significantly less likely to be referred for genetic evaluation (21.2% for NHW patients vs 16.9% for African American patients and 10.9% for Hispanic patients; $P = .02$). Rates of genetic testing were also lower among minority patients (10.7% for NHW patients vs 6.0% for AA patients and 3.1% for Hispanic patients; $P < .01$). On multivariate analysis, African American race, older age, and medical center were independently associated with lack of referral for genetic evaluation and genetic testing.

Muller et al. Clin Gastroenterol & Hepatol 2018;16:1911-18.



Pearlman et al. JAMA Oncology 2017. 3(4):464-71.



Since 2017: All CRC dx < 50 get offered MGPT

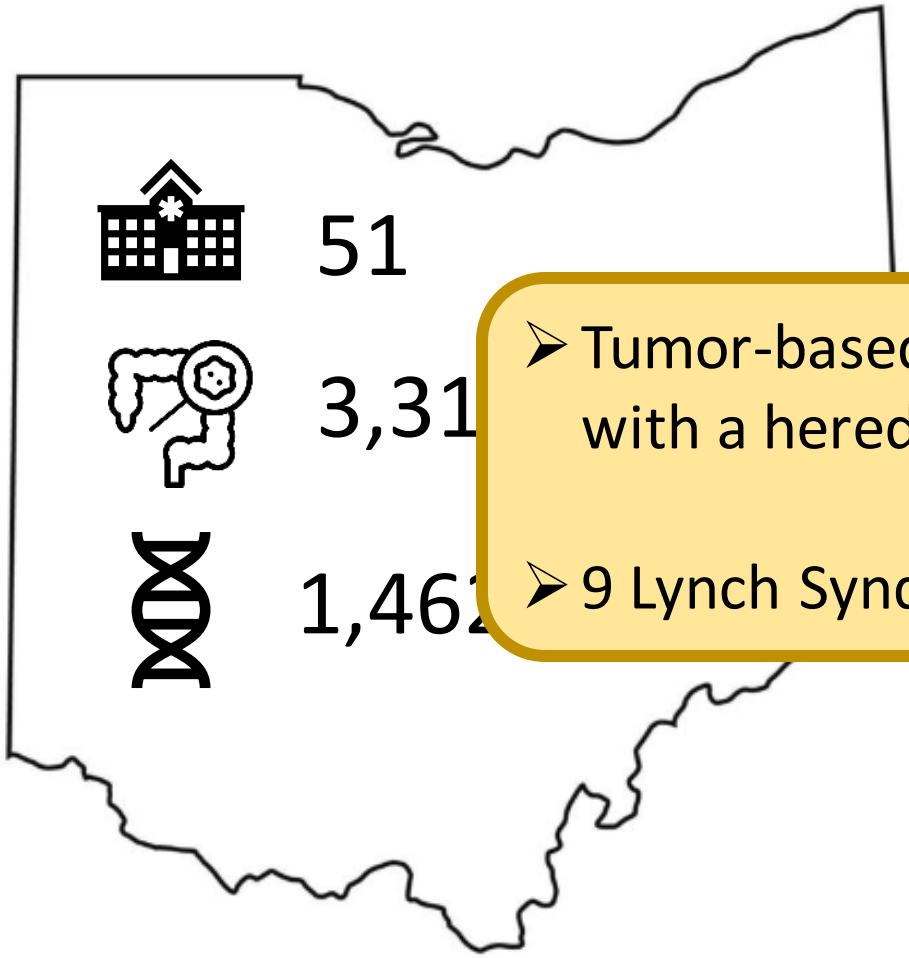
High-penetrance variant 10%

MLH1, MSH2, MSH6, PMS2
Biallelic MUTYH
APC
SMAD4
BRCA1, BRCA2
CDKN2A

Moderate-penetrance variant 6%

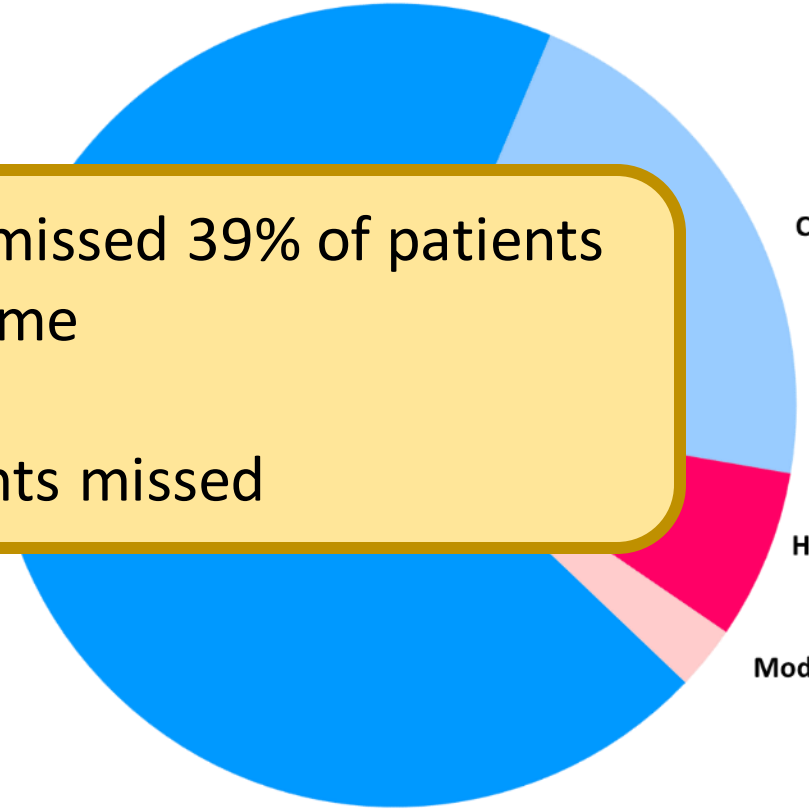
ATM
PALB2
Monoallelic MUTYH
APC I1307K
CHEK2

Pearlman et al. JAMA Oncology 2017. 3(4):464-71.
NCCN Genetic/Familial High-Risk Assessment: Colorectal 2017.

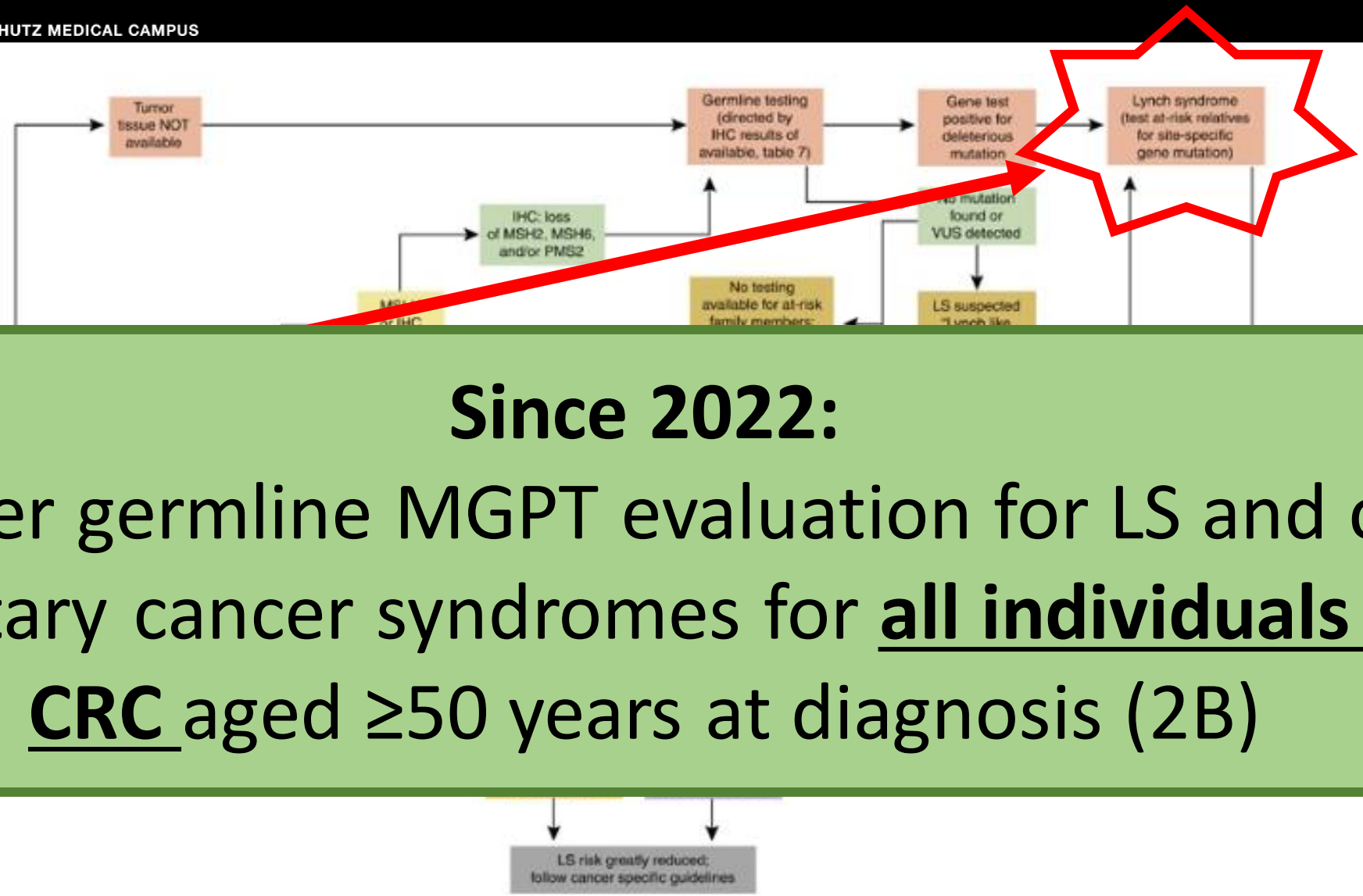


- Tumor-based screening missed 39% of patients with a hereditary syndrome
- 9 Lynch Syndrome patients missed

Spectrum of Pathogenic Variants found in Patients with CRC



Pearlman et al. JCO-PO 2021 5:779-91.



Since 2022:

Consider germline MGPT evaluation for LS and other hereditary cancer syndromes for **all individuals with CRC** aged ≥50 years at diagnosis (2B)

Challenges that lie ahead

- Cost & care delivery burden

Accepted: 5 September 2023
DOI: 10.1111/1471-0528.17675

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

Patient decision aids in mainstreaming genetic testing for women with ovarian cancer: A prospective cohort study

Ann Surg Oncol (2023) 30:5990–5996
https://doi.org/10.1245/s10434-023-13888-4

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Check for updates

ORIGINAL ARTICLE – BREAST ONCOLOGY

A Randomized Trial Comparing the Effectiveness of Pre-test Genetic Counseling Using an Artificial Intelligence Automated Chatbot and Traditional In-person Genetic Counseling in Women Newly Diagnosed with Breast Cancer

Challenges that lie ahead

- Cost & care delivery burden
- Expertise needed

RESULT: NO PATHOGENIC VARIANTS IDENTIFIED

Variant(s) of Uncertain Significance identified.

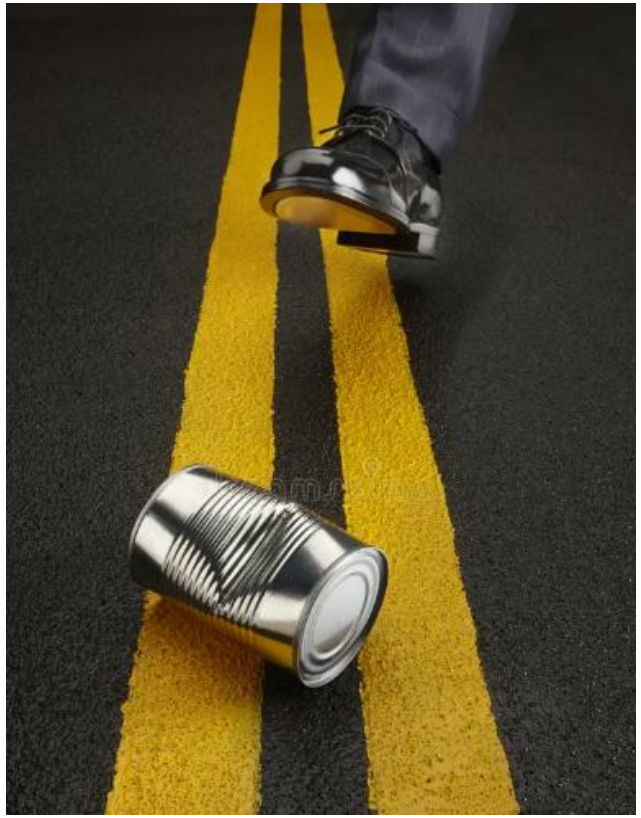
GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BRIP1	c.3302C>T (p.Pro1101Leu)	heterozygous	Uncertain Significance
DICER1	c.278G>A (p.Gly93Glu)	heterozygous	Uncertain Significance
GATA2	c.460A>G (p.Ser154Gly)	heterozygous	Uncertain Significance
MSH3	c.3382A>G (p.Met1128Val)	heterozygous	Uncertain Significance
RECQL4	c.2836C>T (p.Arg946Cys)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 84 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Challenges that lie ahead

- Cost & care delivery burden
- Expertise needed
- May push disparities downstream



Final Thoughts

- Exciting developments in diet, lifestyle and medications
- Universal germline testing has the potential to significantly improve diagnosis of hereditary syndromes
- Operationalizing this for the 3rd most commonly diagnosed cancer will require
  - Adapting to new models of genetic counseling & testing
  - Training a workforce
  - Attention to health equity

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American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

Thank You

nccrt.org @NCCRTnews #80inEveryCommunity