Concurrent Session B

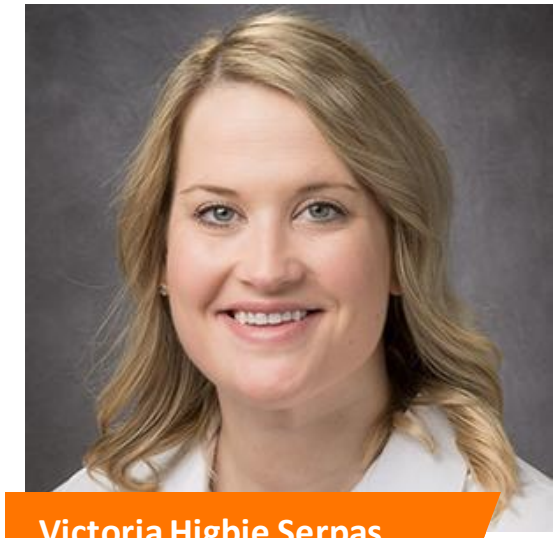
Research Updates on Colorectal Cancer Risk

American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

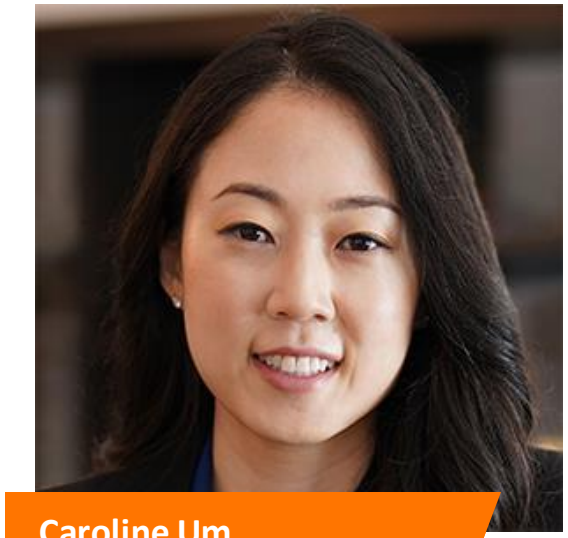
3:30 PM to 4:45 PM

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

Moderator
Keith L. Winfrey
MD, MPH, FACP



Victoria Higbie Serpas
MD



Caroline Um
PhD, MPH, RD

Swati Patel
MD, MS

The Gut Microbiome & Colorectal Cancer

Victoria Higbie, MD

GI Medical Oncology
M. D. Anderson Cancer Center
November 16, 2023

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Outline

Overview of the Gut Microbiome

Colorectal Cancer and the Gut Microbiome

Possible Future Directions

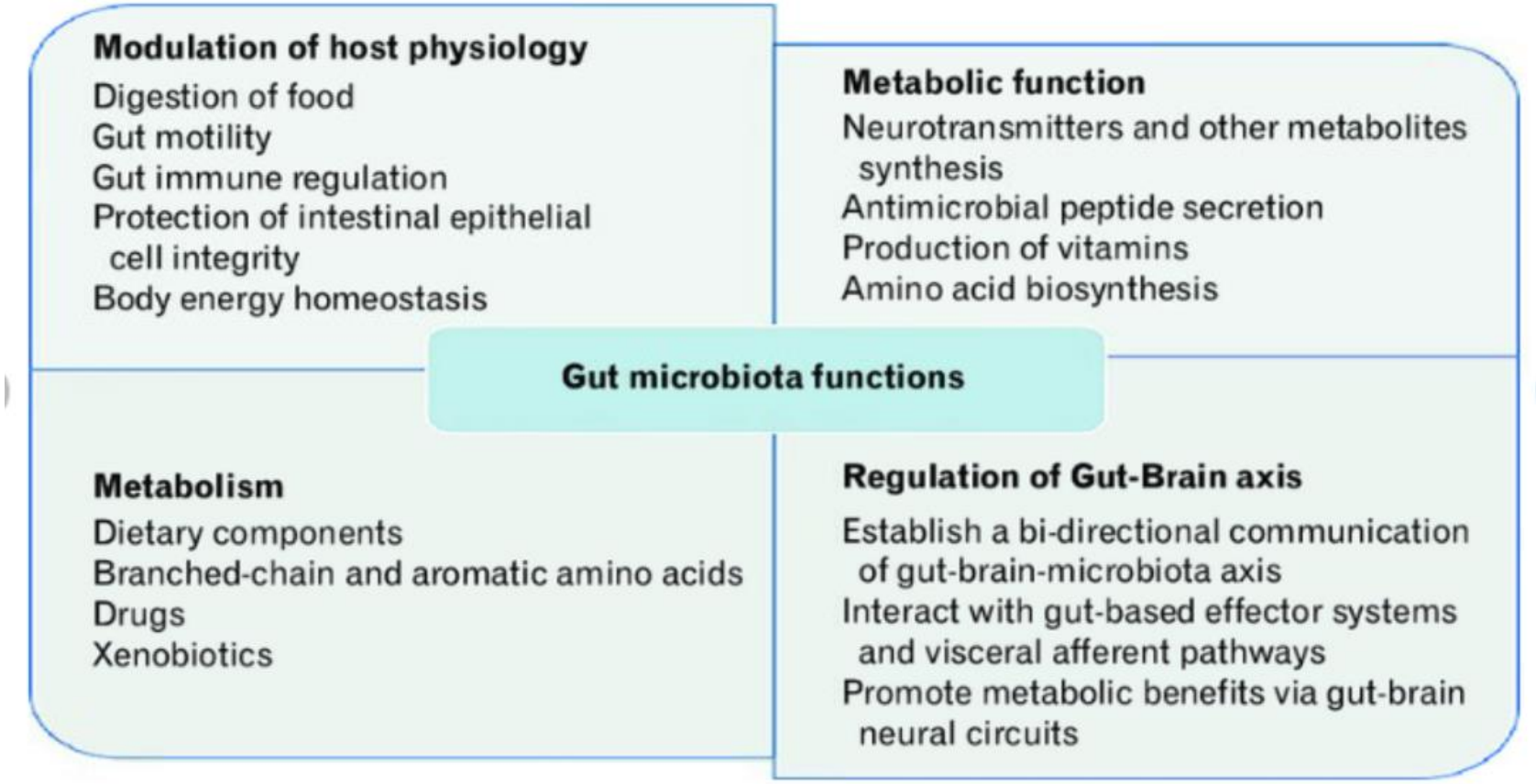
Overview of the Gut Microbiome

What is the gut microbiome?

- Various microorganisms coexist throughout the human body (gut, skin, lung, oral cavity)
- The gut (intestines) microbiome contains trillions of microorganisms- including bacteria as well as viruses, parasites, and fungi
- Dysbiosis is a decrease in variety of microorganisms and/or decrease of beneficial organisms and proliferation of pathogenic organisms

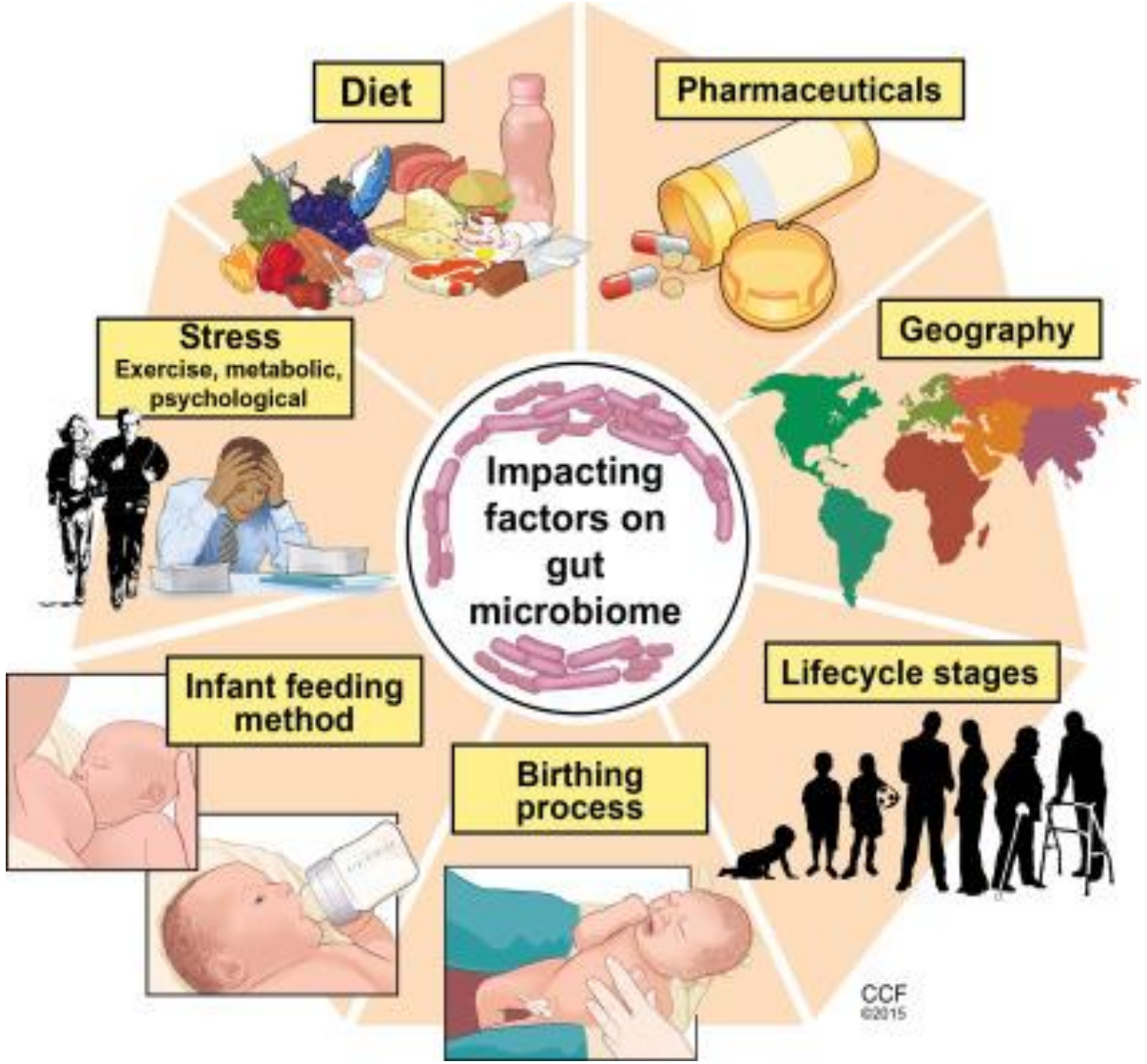
https://www.mybiome.health/news-detail/the-gut-microbiome-how-does-it-work-1

What role does the gut microbiome play?



Singh, et al. Gut Microbiome Dysbiosis, Journal of Neurogastroenterology, 2020.

What impacts the gut microbiome?



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

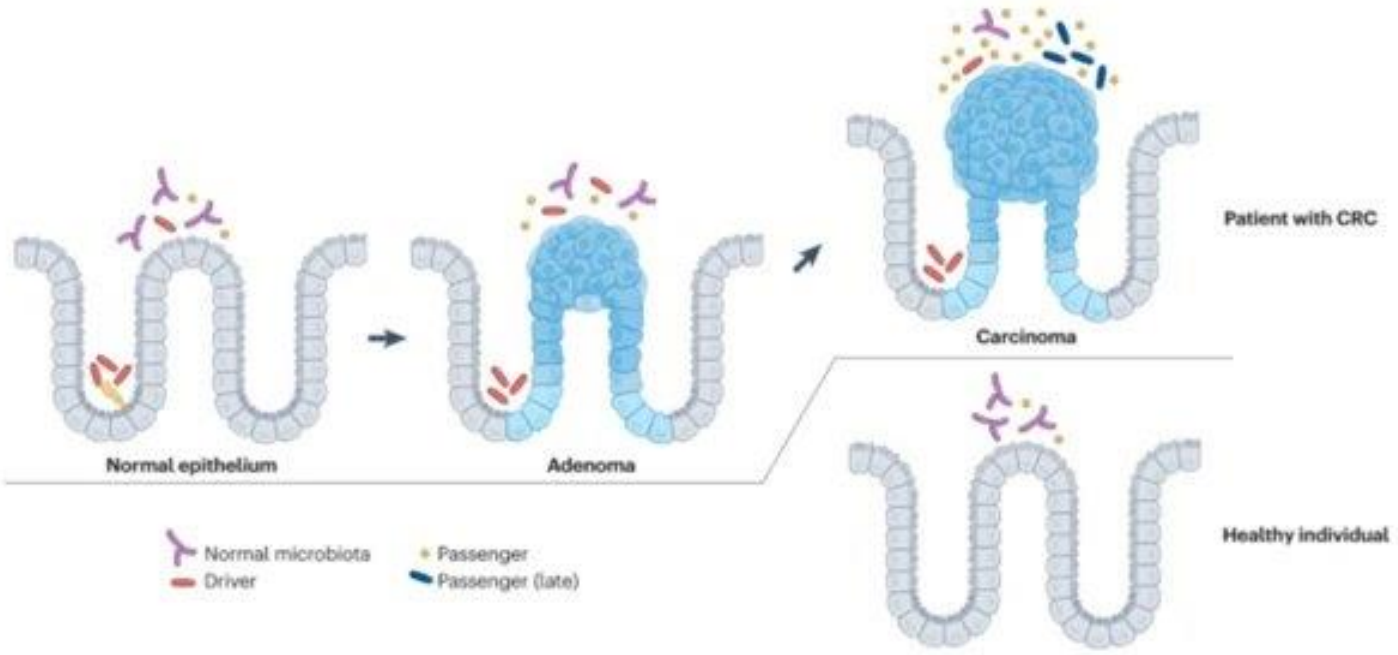
Summary:

- The gut microbiome is diverse and dynamic
- Impacted by many factors including throughout life starting at time of birth
- Plays many roles in digestion, metabolism, and immunity
- Dysbiosis has been linked to many disorders including colorectal cancer
- It's complicated

Role of Microbiome in CRC

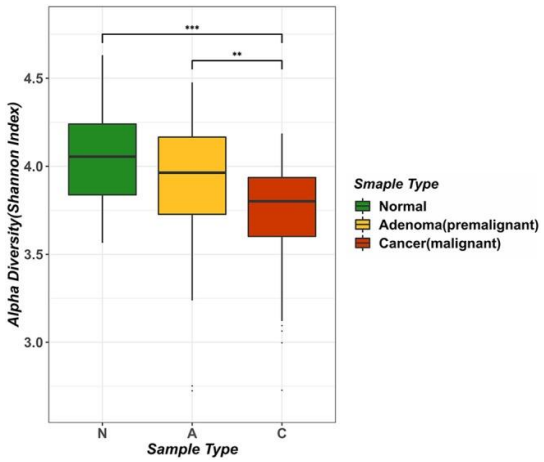
Colorectal cancer and the gut microbiome

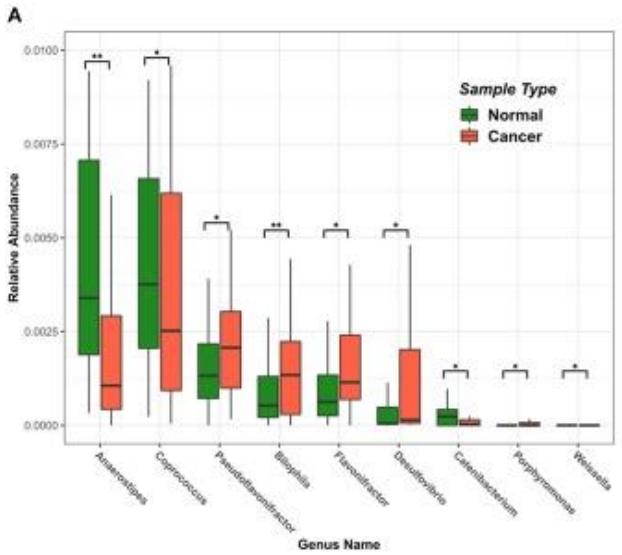
- What do we know?
  - **Differences seen between CRC gut/tumor microbiome vs healthy**

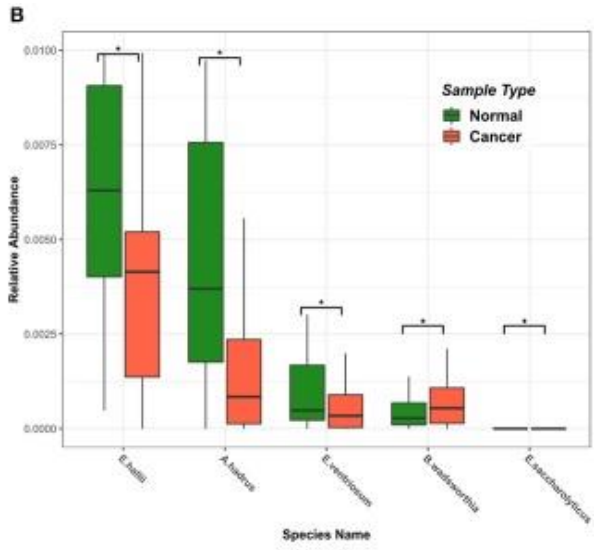


Colorectal cancer and the gut microbiome

- What do we know?
  - Differences seen between CRC gut/tumor microbiome vs healthy
    - Alpha diversity
    - Abundance or loss of certain specific bacteria

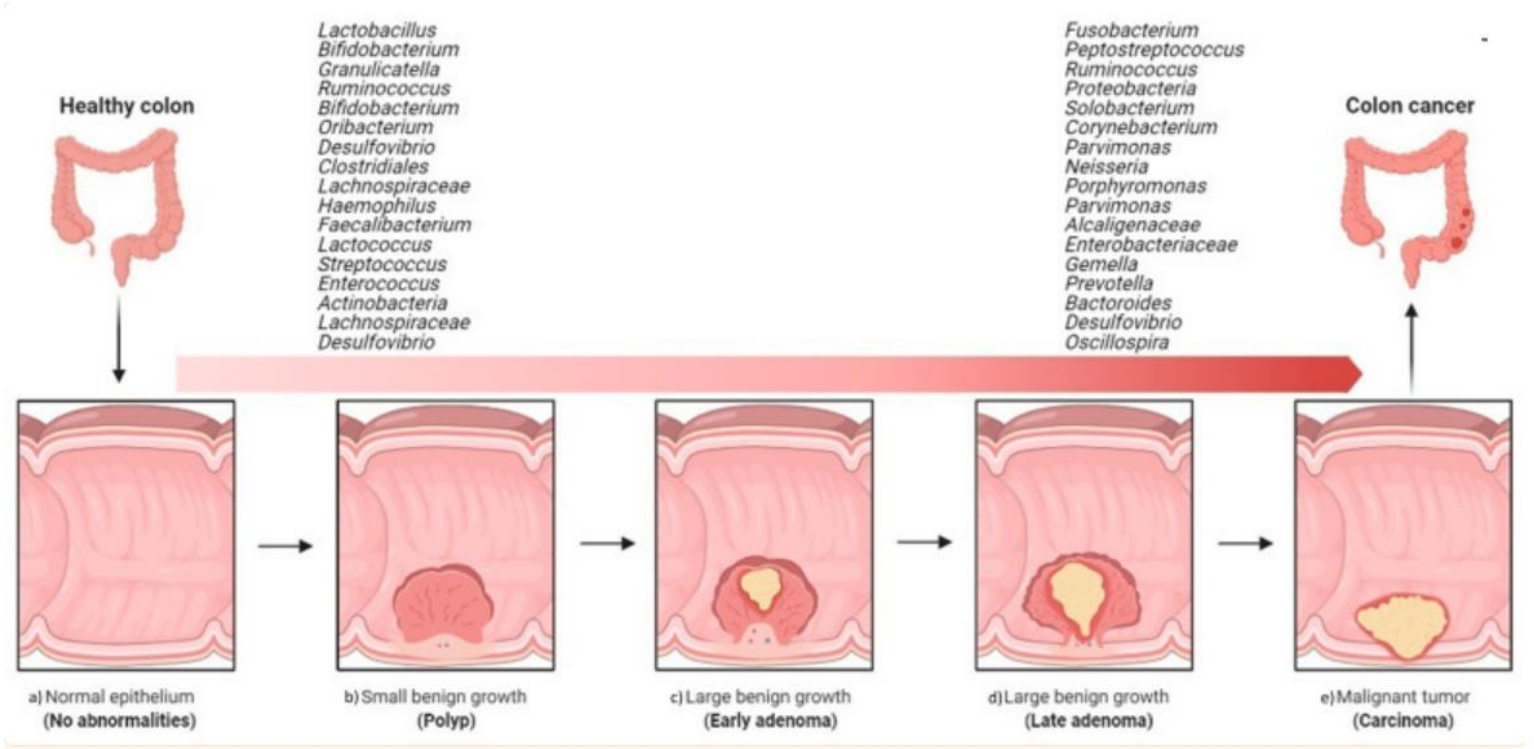






Ai, et al. Front Microbiol. 2019.

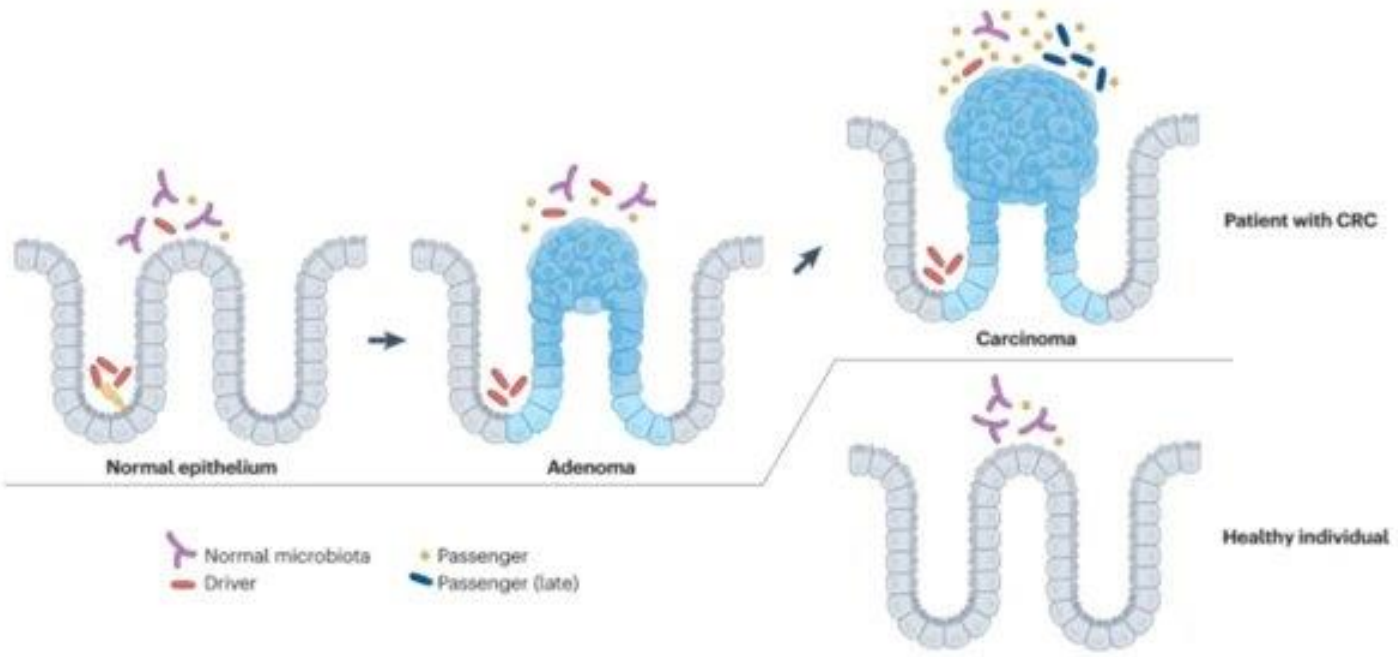
Colorectal cancer and the gut microbiome

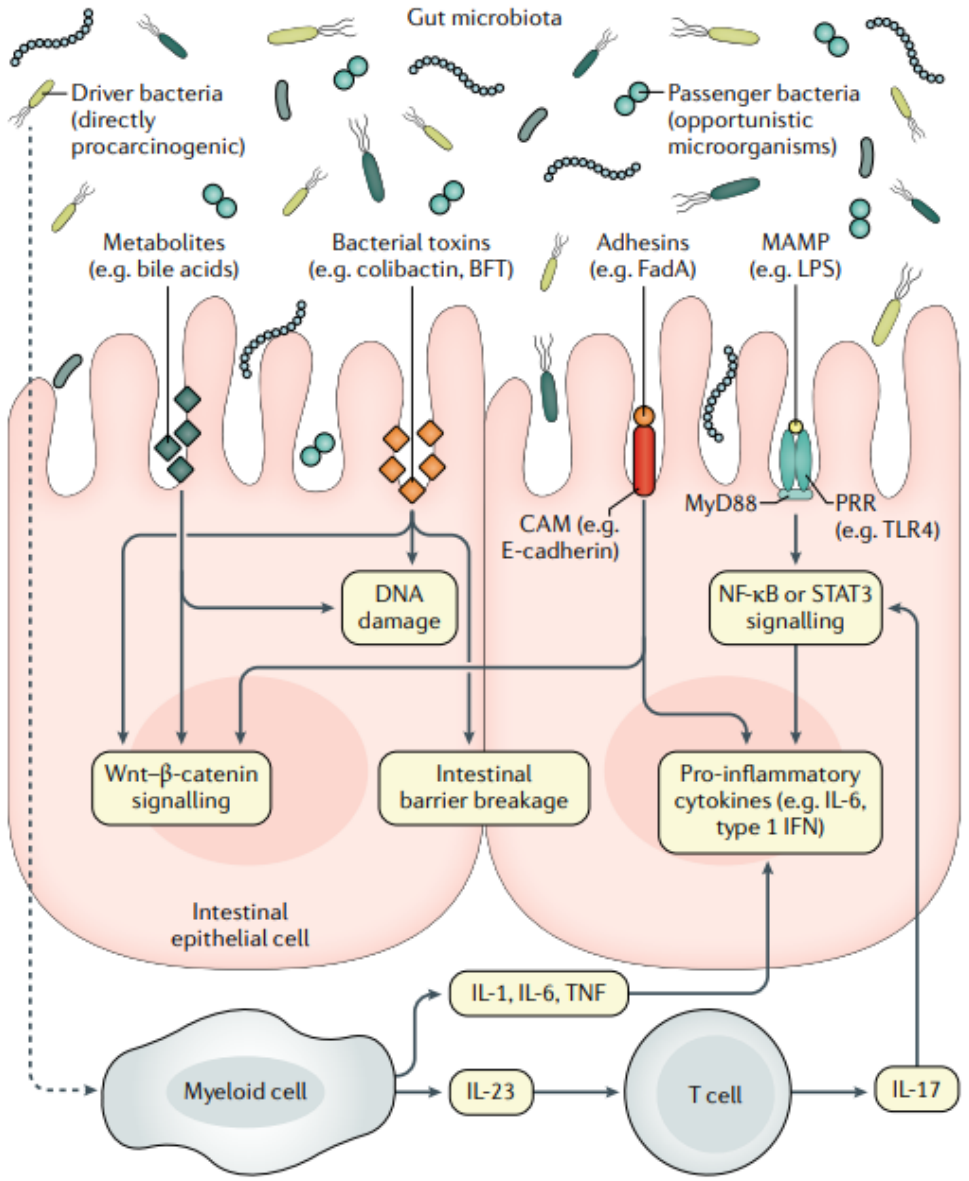


Torres Maravilla, et al. Role of gut microbiota and probiotics in colorectal cancer. Microorganisms. 2021

Colorectal cancer and the gut microbiome

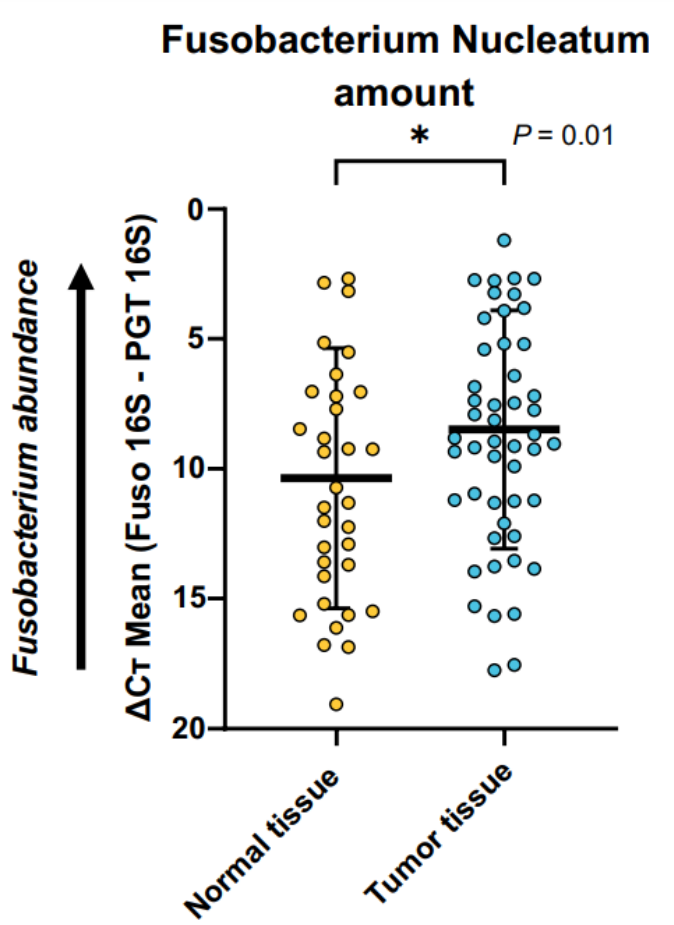
- What do we know?
  - Differences seen between CRC gut/tumor microbiome vs healthy
  - **Some microorganisms appear to have some role in carcinogenesis**



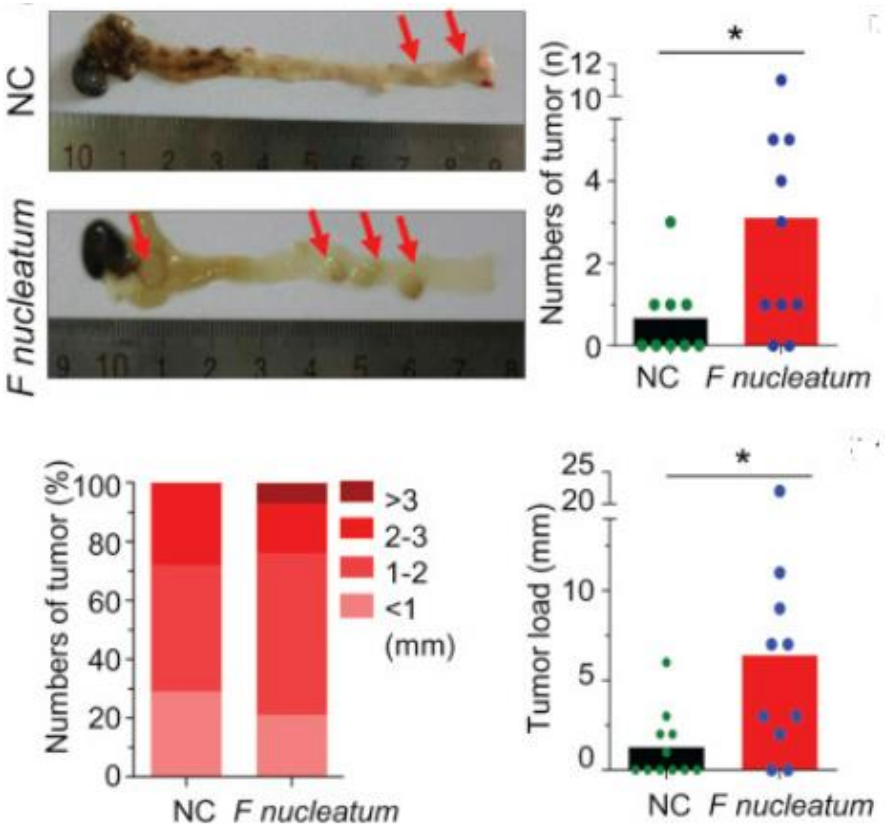


Wong, et al. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nature. 2019.

Fusobacterium in colorectal cancer

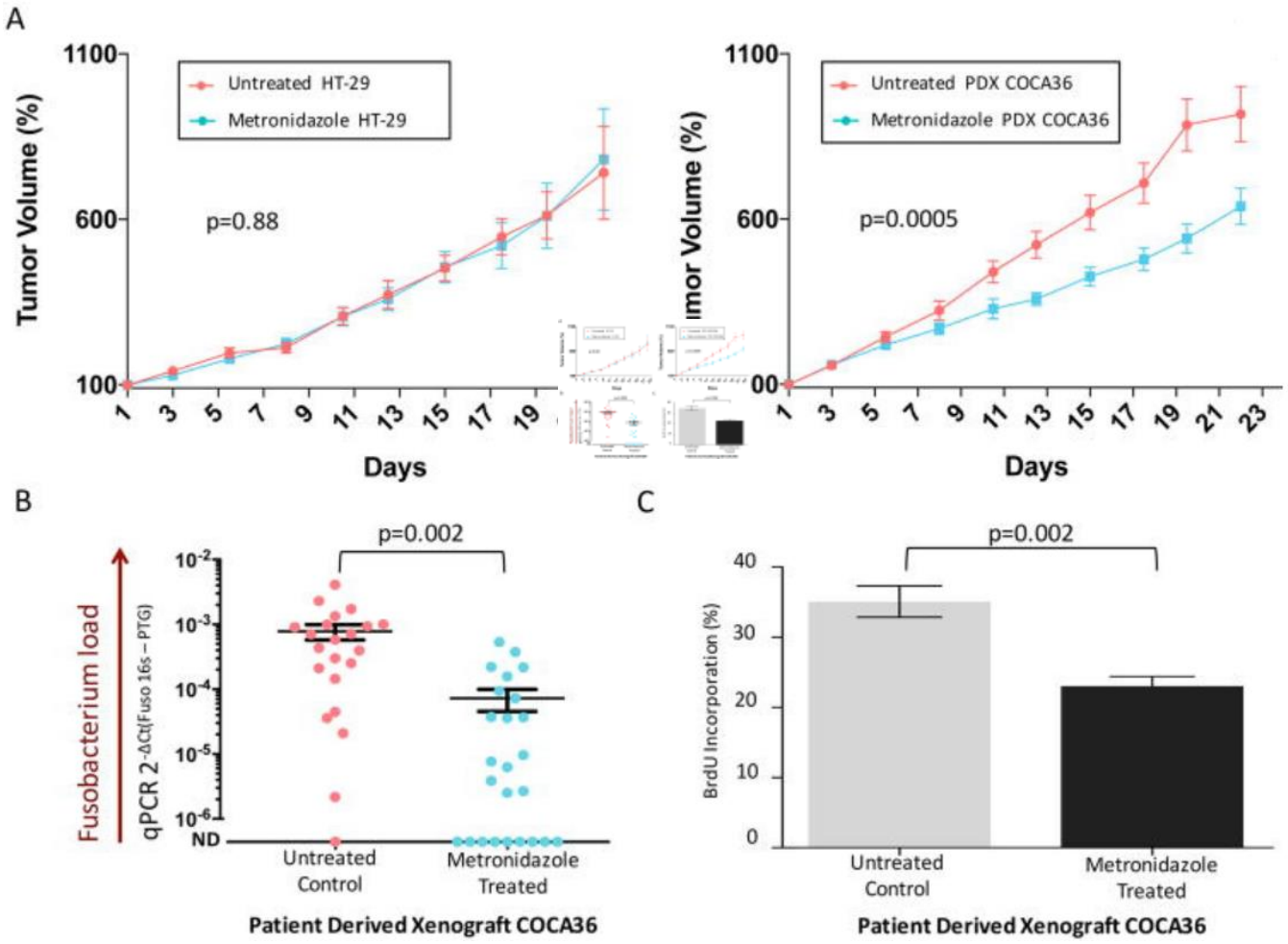


Lee, et al. Associations between Fusobacterium and prognosis in metastatic colon cancer. Scientific Reports. 2021.



Yang, et al. Fusobacterium nucleatum increase proliferation of colorectal cancer cells. Gastroenterology. 2017.

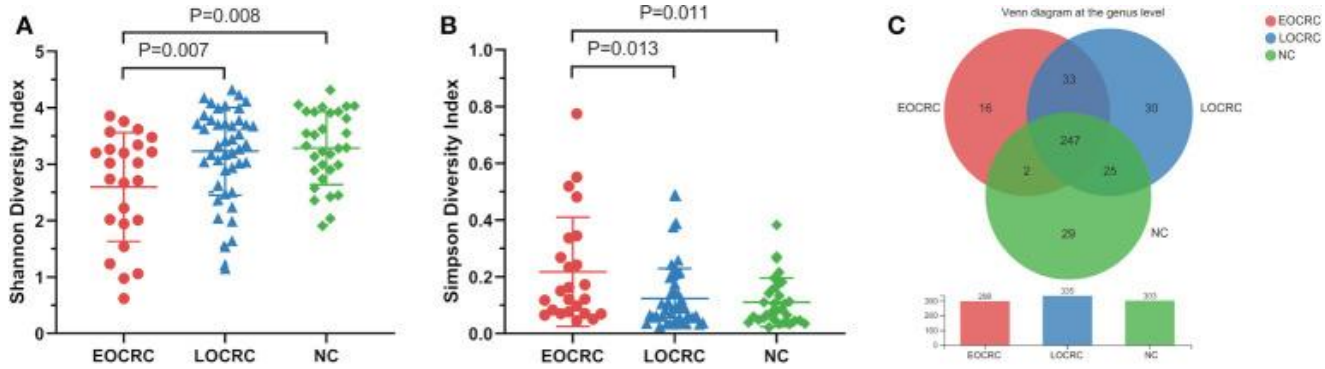
Fusobacterium in colorectal cancer



Bullman, et al. Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. Science. 2017.

Colorectal cancer and the gut microbiome

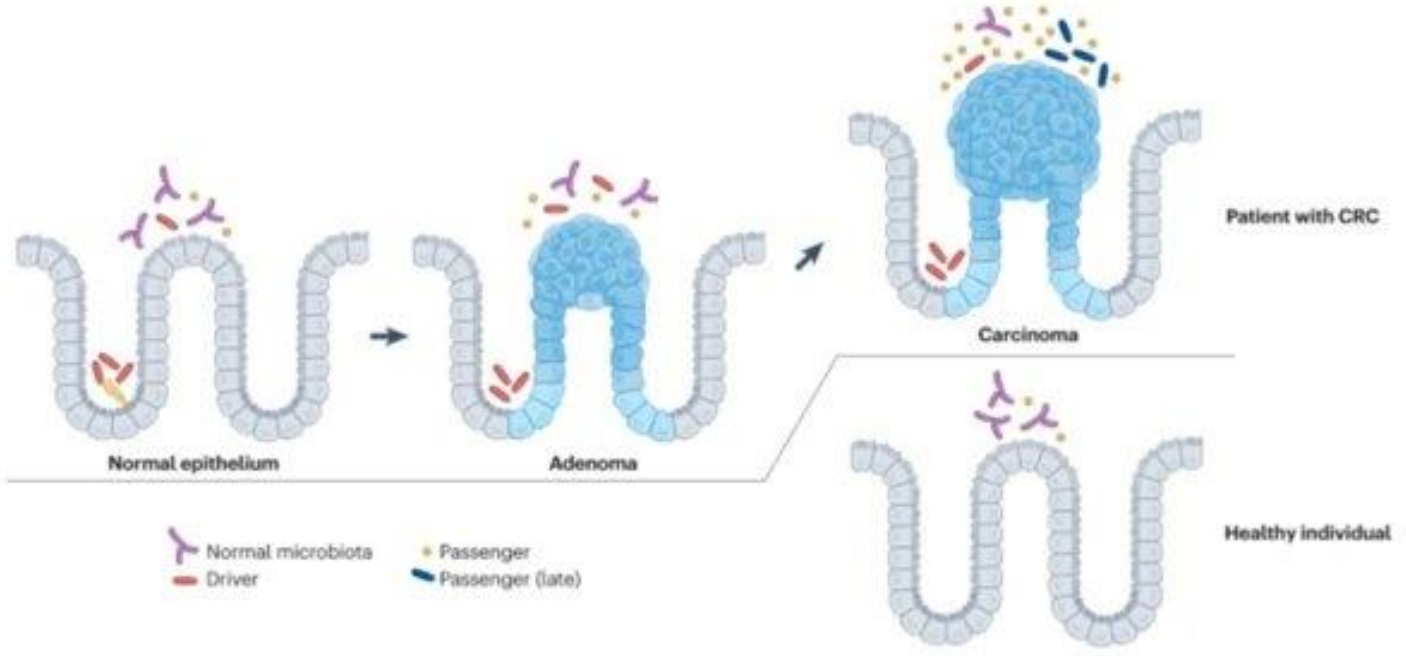
- What do we know?
  - Differences seen between CRC gut/tumor microbiome vs healthy
  - Some microorganisms appear to have some role in carcinogenesis
  - **Difference also seen between EOCRC and LOCRC**



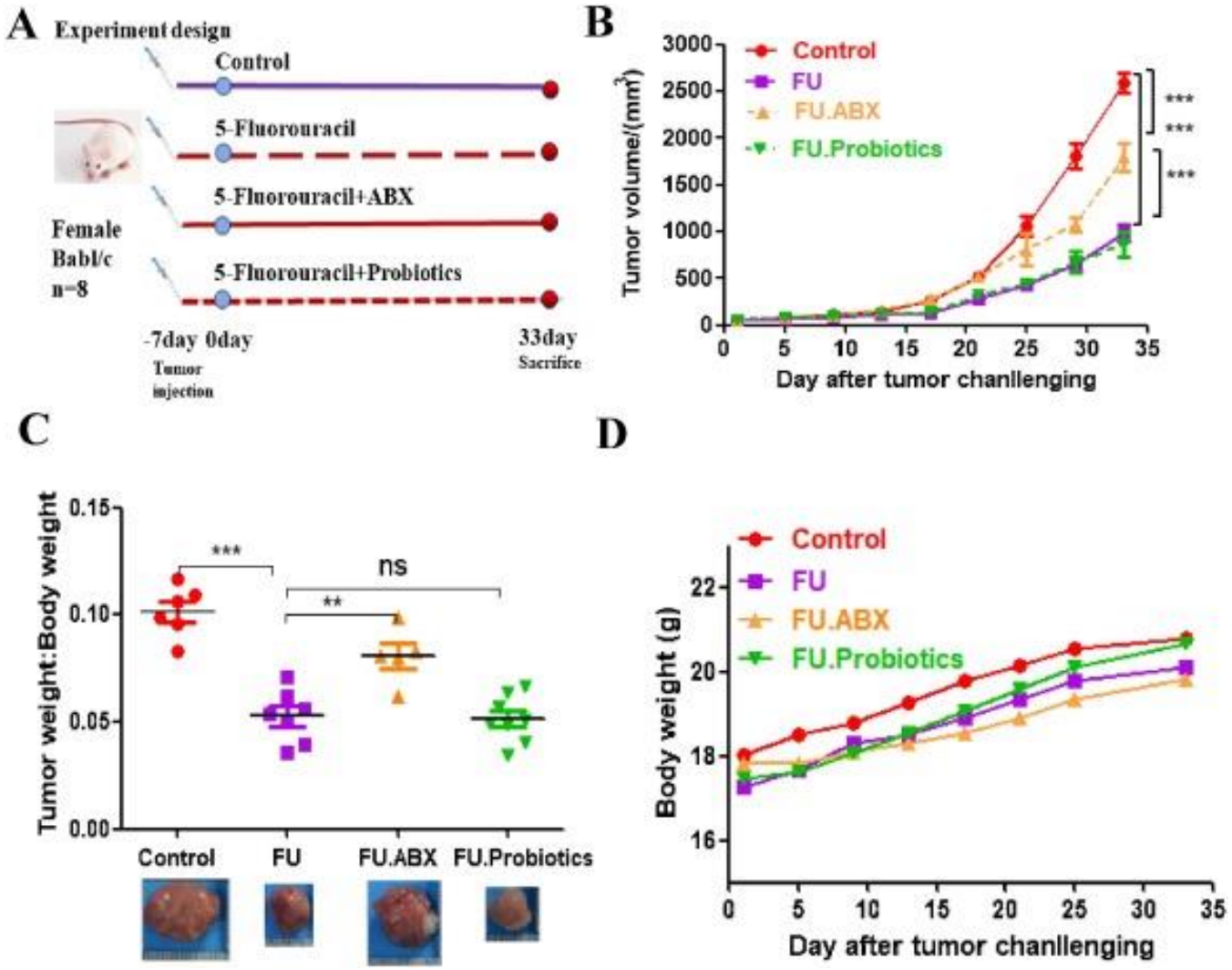
Xiong, et al. Front Cell Infect Microbio. 2022.

Colorectal cancer and the gut microbiome

- What do we know?
  - Differences seen between CRC gut/tumor microbiome vs healthy
  - Some microorganisms appear to have some role in carcinogenesis
  - Difference also seen between EOCRC and LOCRC
  - **Microbiome can affect treatment response**



Microbiome and treatment response: chemotherapy



Yuan, et al. The influence of gut microbiota dysbiosis to the efficacy of 5-Fluorouracil treatment on colorectal cancer. Biomedicine & Pharmacotherapy. 2018.

Microbiome and treatment response: immunotherapy

Table 1. Summary of current available studies addressing the impact of ATB on cancer patients receiving ICI, presented in order of similar ATB timing

Publication	Cancer type *N* = 1804	Immunotherapy	Prior line of therapy	ATB window	Outcome	*P*-values
Routy, Science 2018	NSCLC *n*=140 RCC *n*=67 UC *n*=32	Anti-PD-1	>1	2 months PRE or 1 month POST	↓ PFS (0.6 months) ↓ OS (9.1 months)	0.017 0.001
Rubio, IASLC 2018	NSCLC *n*=168	Anti-PD-1	>1	2 months PRE or 1 month POST	↓ PFS (2.3 months) ↓ OS (3.8 months)	0.028 0.026
Kaderbhai, Anticancer Res 2017	NSCLC *n*=74	Anti-PD-1	Not reported	3 months PRE	No change in PFS OS not reported	0.72
Ouaknine, IASLC 2018	NSCLC *n*=72	Anti-PD-1	Not reported	2 months PRE or 1 month POST	↓ OS (8.3 months)	0.03
Lalani, ASCO GU 2018	RCC *n*=146	Anti-PD-1, anti-PDL-1	0 to >1	2 months PRE or 1 month POST	↓ ORR (21.9%) ↓PFS (5.5 months)	0.026 0.08
Galli, IASLC 2018	NSCLC *n*=157	Anti-PD-1, anti-PDL-1, anti-PD-1 + CTLA-4	0 to >1	1 month PRE or 3 months POST	↓ PFS in patients with ↑ AE* (5.5 months) ↓ OS in patients with ↑ AE* (11.4 months)	0.0001 0.0004
Derosa, Annals 2018	NSCLC *n*=249 RCC *n*=121	Anti-PD-1, anti-PD-1 + CTLA-4	0 to >1	1 month PRE	NSCLC: ↓ PFS (1.9 months) ↓OS (16.7 months) RCC: ↑ PD (53%) ↓ PFS (5.5 months) ↓OS (13.3 months)	0.03 0.01 0.01 0.01 0.03
Elkrief, OncoImmunology 2018	Melanoma *n*=74	CTLA-4 with chemo-therapy, CTLA-4 alone, anti-PD-1	0 to >1	30 days PRE	↓RR (34%) ↓PFS (4.9 months)	0.01 0.01
Do, ASCO 2018	NSCLC *n*=109	Anti-PD-1	Not reported	1 month PRE or 1 month POST	↓OS (11.8 months)	0.0004
Huemer, Oncotarget 2018	NSCLC *n*=30	Anti-PD-1	>1	1 month PRE or 1 month POST	↓ PFS (0.2 months) ↓OS (7.6 months)	0.031 0.021
Tinsley, ASCO 2018	Melanoma *n*=201 NSCLC *n*=58 RCC *n*=46	Anti-PD-1, anti-PD-1 + CTLA-4	0 to >1	14 days PRE or 42 days POST	↓ PFS (2.7 months) ↓OS (11 months)	0.049 0.001
Ahmed, OncoImmunology 2018	Various cancers (*n*=60)	ICI with chemother-apy, anti-PD-1 and anti-PDL-1	0 to >1	14 days PRE or 2 weeks POST	↓RR (36%) ↓PFS	0.02 0.012

NSCLC, non-small-cell lung cancer; RCC, renal cell cancer; UC, urothelial cancer; PFS, progression-free survival; OS, overall survival; PD, progressive disease; ORR, objective response rate.
*AE (antibiotic exposure rate), a numerical value determined by the following calculation: number of days of ATB use divided by the number of days of ICI use.

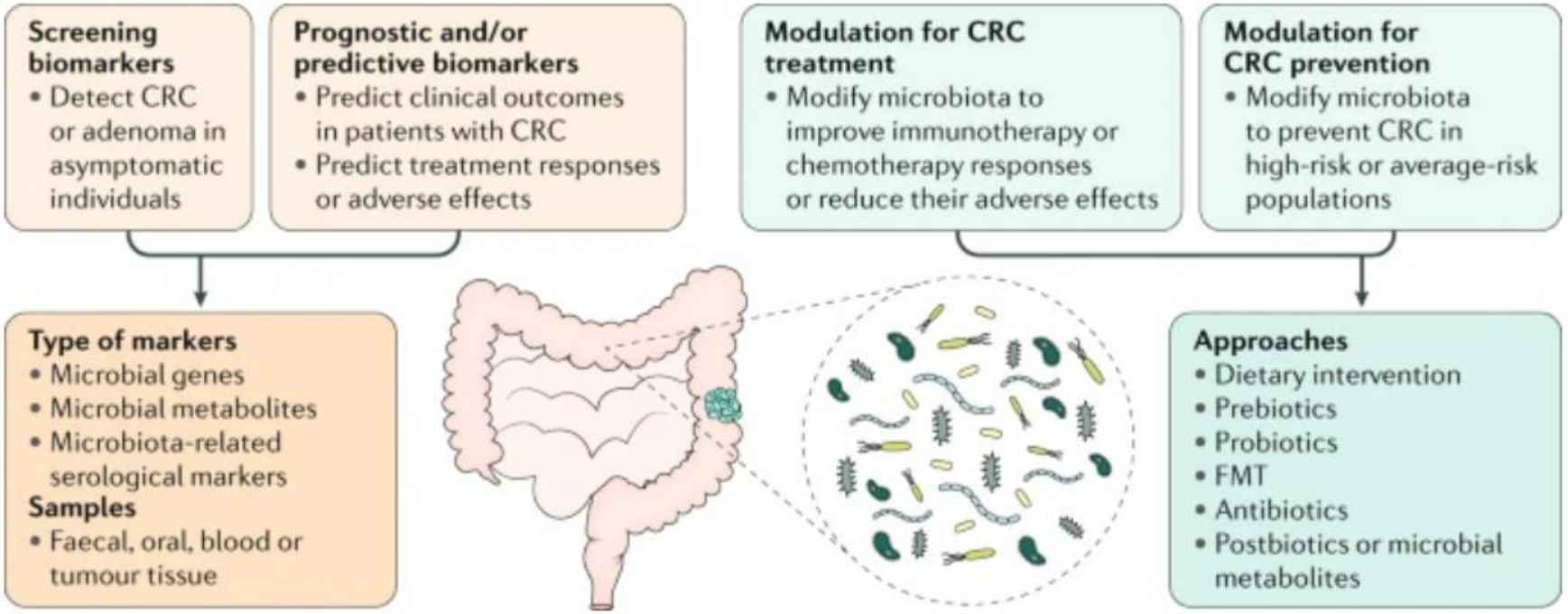
•Elkrief, et al. Annals of Oncology. 2019.

Summary:

- Differences in gut microbiome diversity and profile seen in CRC versus healthy
- Certain bacteria, i.e. fusobacterium, have been linked to colorectal pathogenesis and progression
- Microbiome diversity and profile has also been linked to response to chemo and immunotherapy
- It's complicated

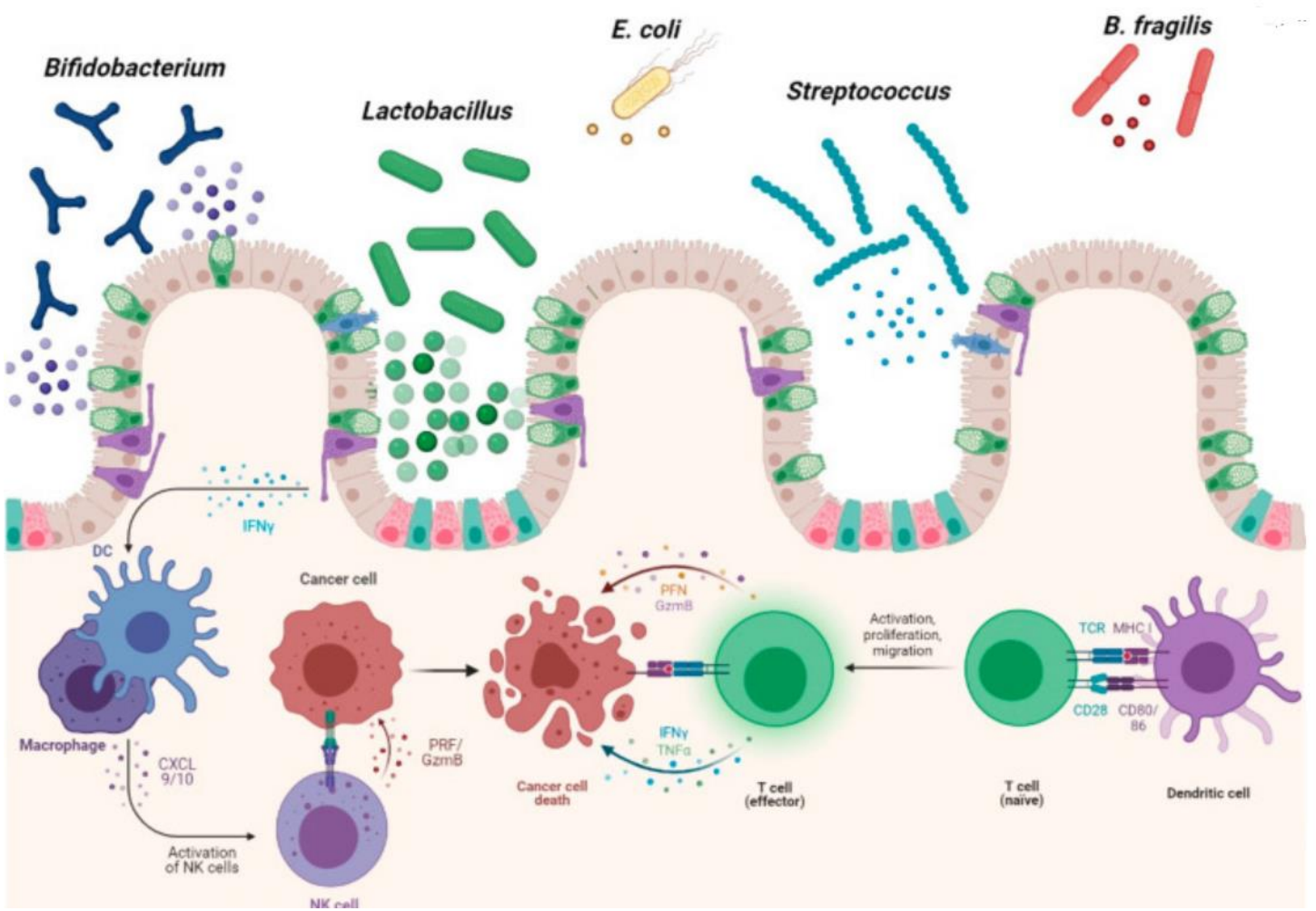
Potential Future Directions

Potential Clinical Applications



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

Probiotics affect microbiome



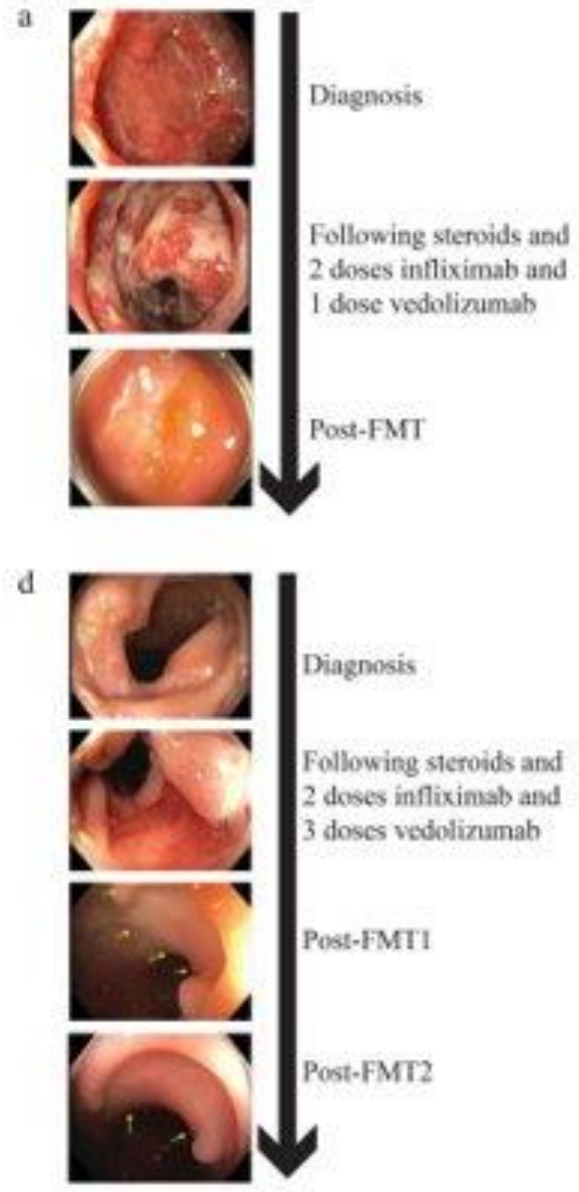
Torres Maravilla, et al. Role of gut microbiota and probiotics in colorectal cancer. Microorganisms. 2021

Microorganism	Function	Mechanism	Year	Reference
acidophilus	Reduction in tumor in colitis-associated CRC models	Activation of immune response by enhancing Th1 helper lymphocytes and M1 macrophages	2013	[91]
			2019	[92]
L. acidophilus strain MTCC 5401	Alleviation of gut inflammation	Decreasing the expression of the inflammation-associated genes; reducing the levels of TNF-α, IL-6, and malonaldehyde; increasing the levels of superoxide and catalase	2018	[93]
L. acidophilus	Protection against H. pylori	Inhibition of *H. pylori* adherence through the production of acetic acid and other bactericidal substances.	2019	[94]
L. bulgaricus		Prevention of TLR4/NF-κB signaling, and production of the IL-8 pro-inflammatory cytokine		
L. acidophilus	Inhibition of the incidence of colonic lesions	Elevation of IFN-γ and IL-10 serum levels and the number of $CD4^+$ and $CD8^+$ cells	2019	[95]
B. bifidum				
L. acidophilus	Cytotoxic effect on tumor cells	Stimulation of immune response, effect on apoptosis, and inactivation of NF-κB inflammatory pathway	2018	[96]
L. acidophilus	Prevention of the formation of advanced aberrant crypt foci and CRC	Inhibition of pre-neoplastic lesions and reduction in the activity of antioxidant enzymes (SOD) and apoptosis-related proteins (caspase-3 and Bcl-2)	2019	[97]
B. animalis subsp. lactis				
L. acidophilus CL1285	Protection against toxic and reactive chemical species and inhibition of colon cancer (HT-29) cell proliferation	Stimulation of quinone reductase activity	2020	[98]
L. casei LBC80R				
L. rhamnosus CLR2				
L. reuteri	Reduction of enteropathogenic *E. coli* (EPEC) infection	Creation of a strong physical barrier against EPEC infection by binding to the mucus layer	2016	[99]
Lactobacillus EPSs	Anticancer effect on colon cancer cells	Induction of apoptosis by increasing the expression of Caspase 3, Caspase 9, and BAX, and reducing the levels of Bcl-2	2019	[100]
L. casei	Protection against CRC development	Regulation of cancer cells proliferation and apoptosis through modulation of IL-22 and upregulation of caspase-7, respectively	2017	[101]
L. lactis	Prevention of CRC development	Restoration of T cell populations and regulation of IFN-γ production in the $CD4^+$ T cell population	2020	[102]
L. plantarum	Inhibition of colitis-associated carcinogenesis	Suppression of inflammation and apoptosis, and elevation of IgA secretion	2015	[103]
L. plantarum	Prevention of CRC development	Upregulation of IL-18 production	2020	[104]
L. salivarius				
B. longum	Colon cancer treatment	Reduction in the elevated expression of miR-155 and onco-miR miR-21a, elevation in the levels of tumor-suppressing miR-145 and miR-15a, and downregulation in NF-κb and miR-146a	2019	[105]
B. longum (BB536-y)	Inhibition of CRC growth	Enhancement of SCFAs production and reducing the amount of *Bacteroides fragilis* enterotoxin	2018	[106]
Lactobacilli cocktail	Prevention and treatment of colon cancer	Modulation of Notch- or Wnt/β-catenin signaling pathway, apoptosis, and downregulation of cell proliferation	2020	[107]
L. rhamnosus KCTC 12202BP	Inhibition of intestinal epithelial apoptosis and suppression of CRC cell proliferation	Regulation of p53-p21-Cdk1/Cyclin B1 signaling pathway by downregulating the expression of Cyclin B1 and Cdk1	2019	[108]
L. rhamnosus MD 14	Anticancer effect	Reducing fecal procarcinogenic enzymes, oxidants, and aberrant crypt foci, downregulating numerous oncogenes, and upregulating tumor-suppressing p53	2020	[109]
L. casei ATCC334	Inhibition of CRC cell growth	Induction of apoptosis by upregulation of DDIT3	2021	[110]
VSL#3	Reduction in the size and number of pre-neoplastic lesions in a model of colitis-associated cancer	Regulation of the intestinal barrier integrity and endogenous antioxidant defense system by increasing the level of SCFAs and enzymes, and alterations in the general composition of the intestinal microbiota	2020	[111]
L. lactis subsp. lactis	Anti-metastatic effects on multiple colon cancer cell lines	Regulation of apoptosis by changing the intracellular calcium concentrations, and downregulating the expression of CEA, CEAM6, and matrix metalloproteinases (MMP2 and MMP9)	2018	[112]
butyricum	Inhibition of intestinal tumor development	Decreasing proliferation, increasing apoptosis, suppressing the Wnt/β-catenin signaling pathway, and modulating the composition of gut microbiota	2020	[113]
P. pentosaceus FP3	Inhibition of colon cancer cell proliferation	Production of SCFAs (propionic and butyric acid)	2013	[114]
L. salivarius FP35 and FP25				
E. faecium FP51				
L. gasseri 505	Improvement of CRC	Downregulating pro-inflammatory cytokines and anti-apoptotic factors, and upregulating anti-inflammatory cytokines and pro-apoptotic factors	2020	[115]
	Prevention of hepatic toxicity induced by CRC		2020	[116]
A. muciniphila	Cancer immunotherapy treatments	Improvement of anti-PD-1 blockade efficacy	2018	[117]
B. pullicaecorum	Prevention of necrotic enteritis and CRC	Reducing pathogen abundance in the cecum and ileum	2018	[118]
	Anticancer effect and inhibition of CRC cell growth	Production of butyrate and upregulation of SLC5A8 and GPR43	2020	[119]

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

FMT to Reverse Dysbiosis

- Guideline approved for recurrent/refractory C. difficle infections (2013)
- Also being used in treatment of IBD
- Exciting work in steroid- and infliximab- refractory ICI-related colitis
- Being explored in many areas involving anti-cancer therapy



Wang, et al. JCO. 2018.

Summary:

- Probiotics can alter microbiome
- FMT has been shown to reverse dysbiosis
- Lots more to learn

Take Home Points

Gut microbiome plays an important role in colorectal pathogenesis, progression, and response to therapy

We are working on ways to utilize the microbiome for potential screening and treatment stragies

It's complicated and we still have a lot to learn!

Thank you!
Questions or Comments?

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

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

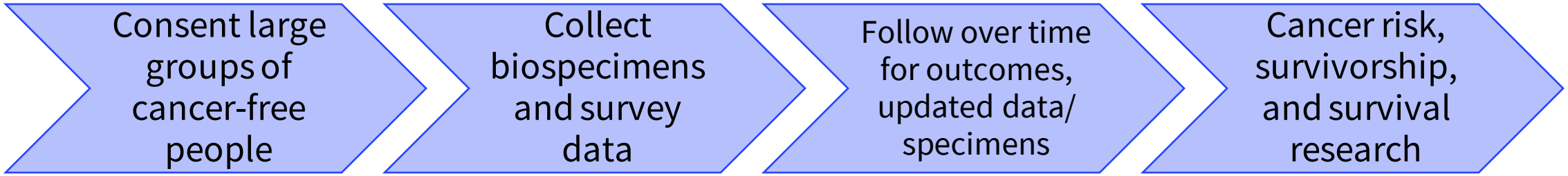
Diet, Nutrition, & Colorectal Cancer Research in the ACS Cancer Prevention Studies

Caroline Um, PhD, MPH, RD

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

THE CANCER PREVENTION STUDIES (CPS)

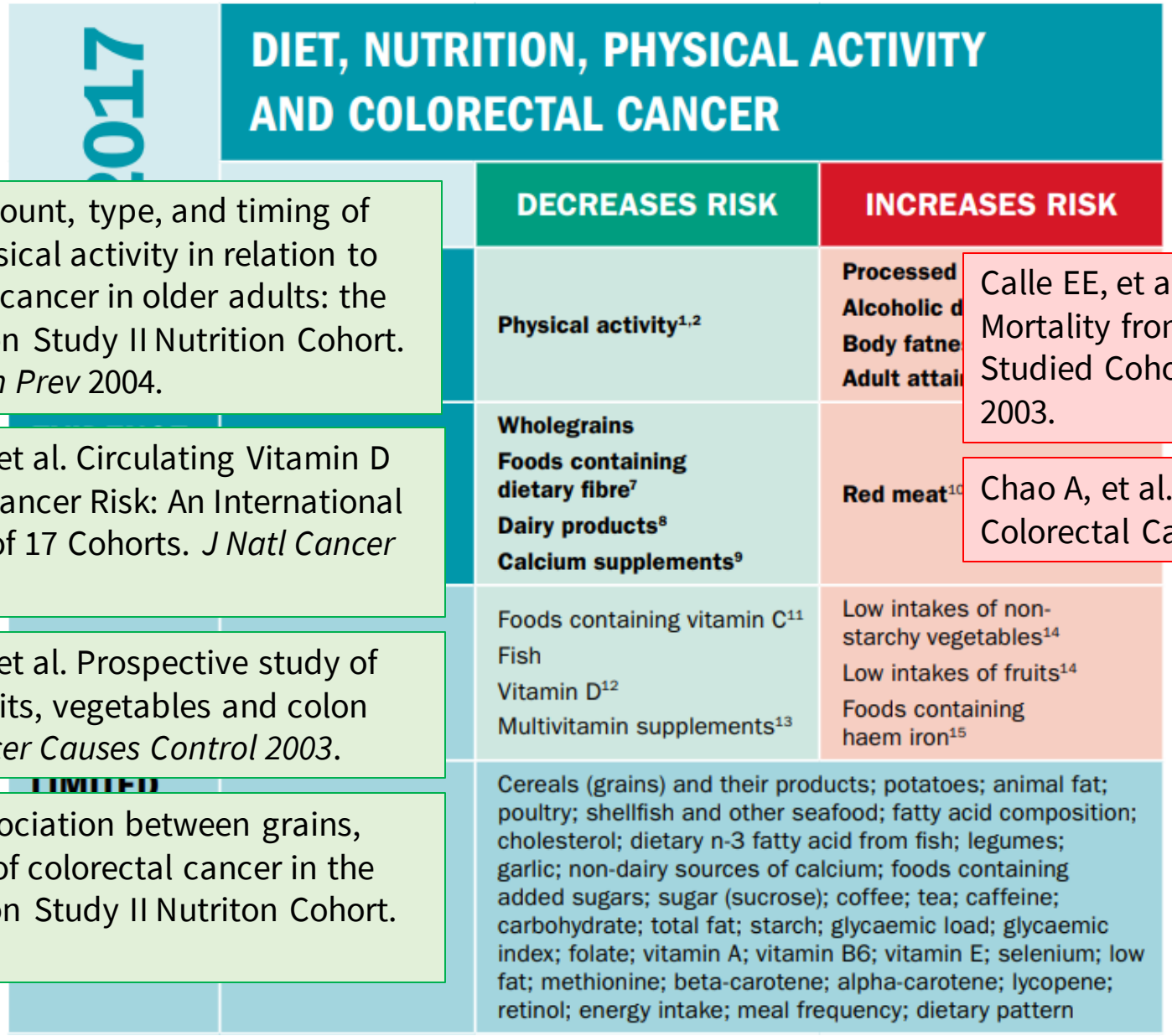
For nearly 70 years, the American Cancer Society has conducted some of the world's largest prospective epidemiologic cohort studies to understand risk factors for cancer risk as well as progression, quality of life, and survival after a cancer diagnosis.



	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*.

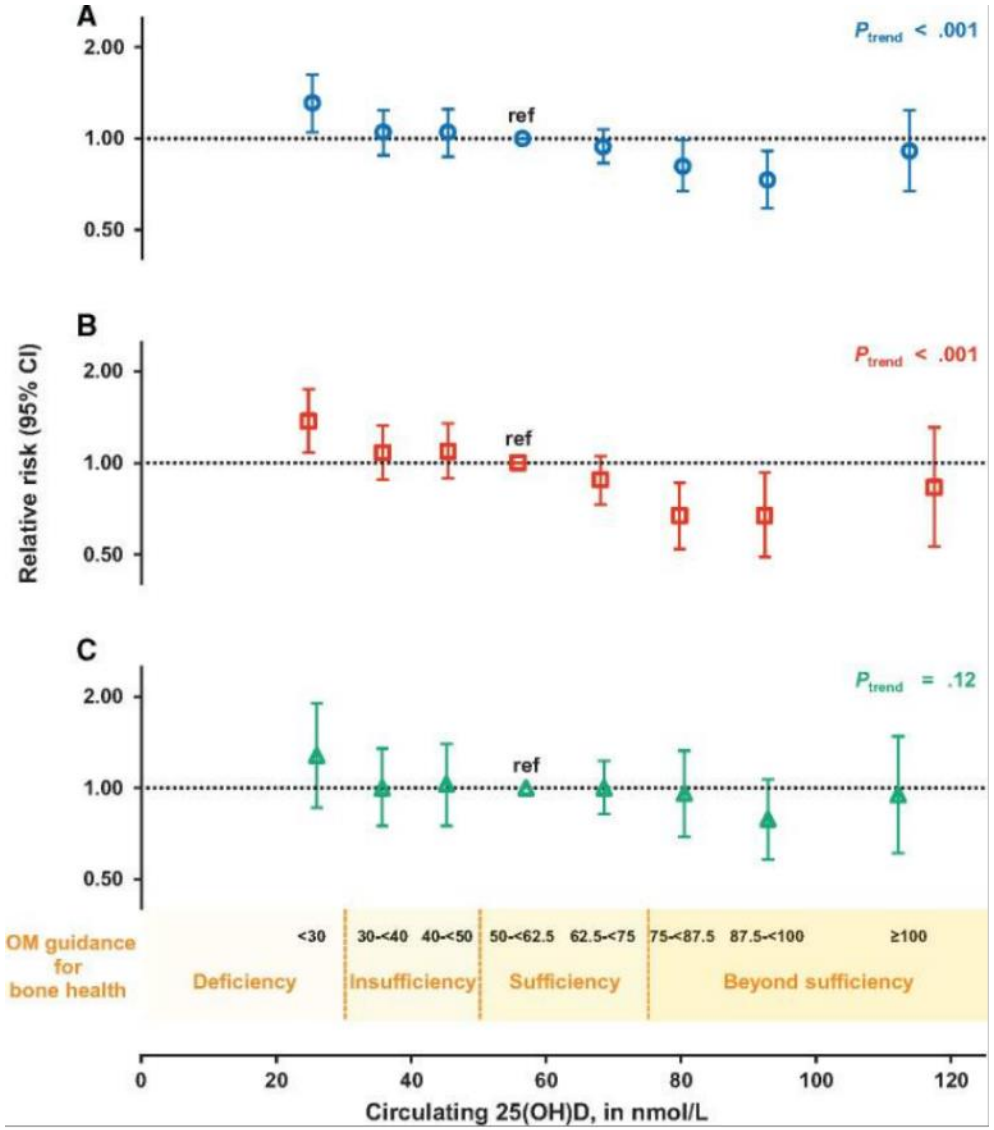
Um CY, et al. Association between grains, gluten, and risk of colorectal cancer in the Cancer Prevention Study II Nutriton Cohort. Eur J Nutr *2003*.

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

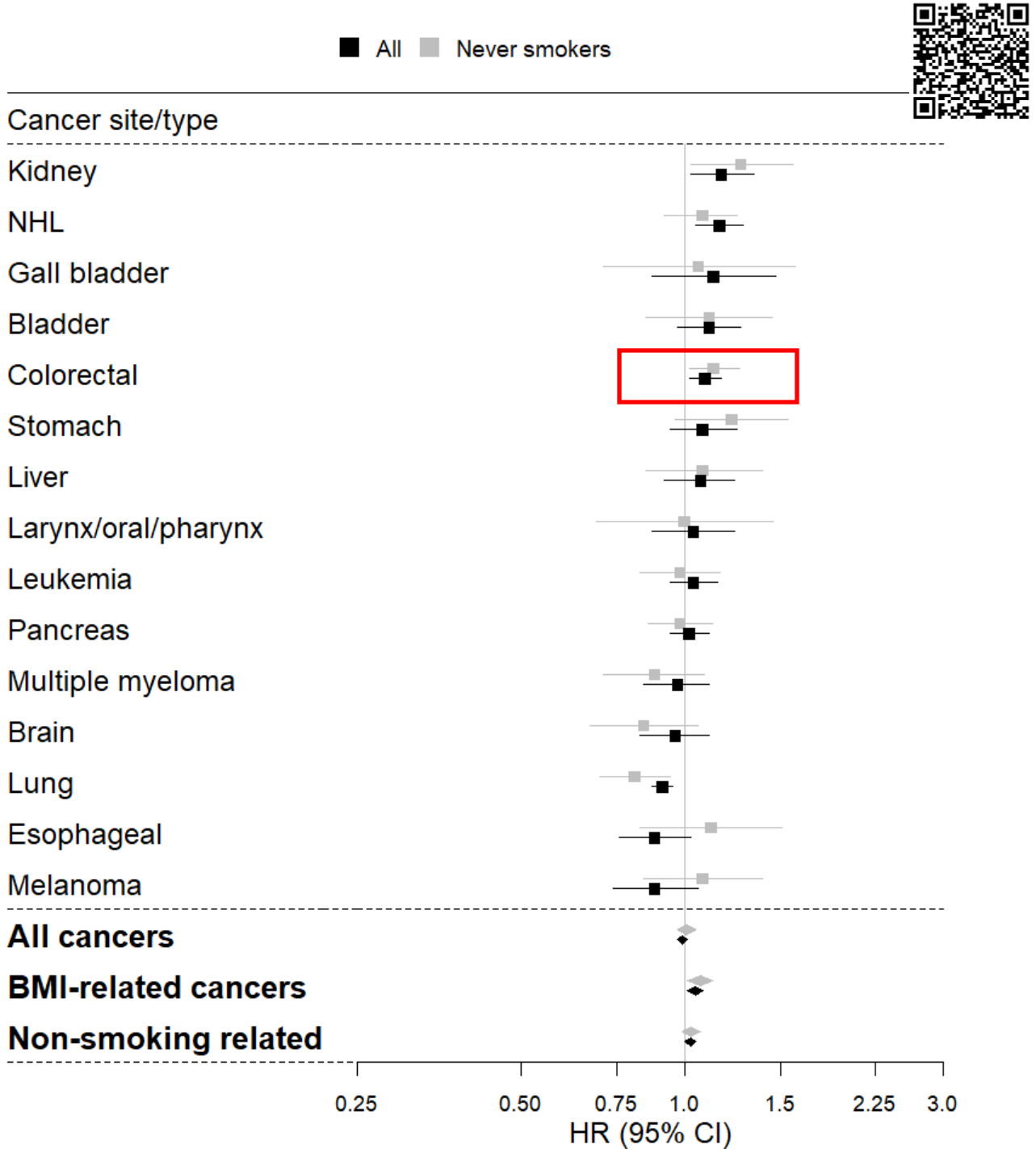
Men

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**

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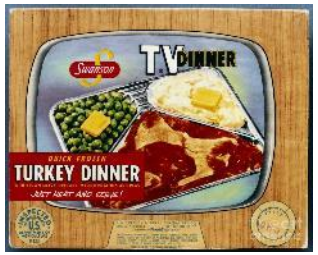
WHAT'S AHEAD IN CPS

~2 million yrs ago
Hunter-gatherers



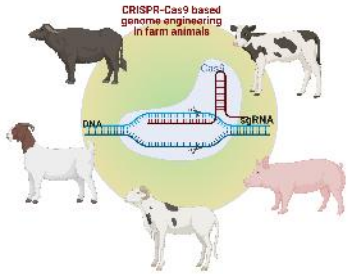
1950s
Convenience foods

2010s
Plant-based meat products

EVOLUTION OF FOOD

~12,000 yrs ago
Agriculture & farming

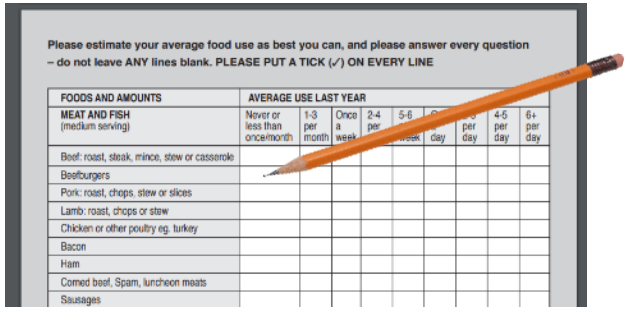
1980s
Genetic engineering



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

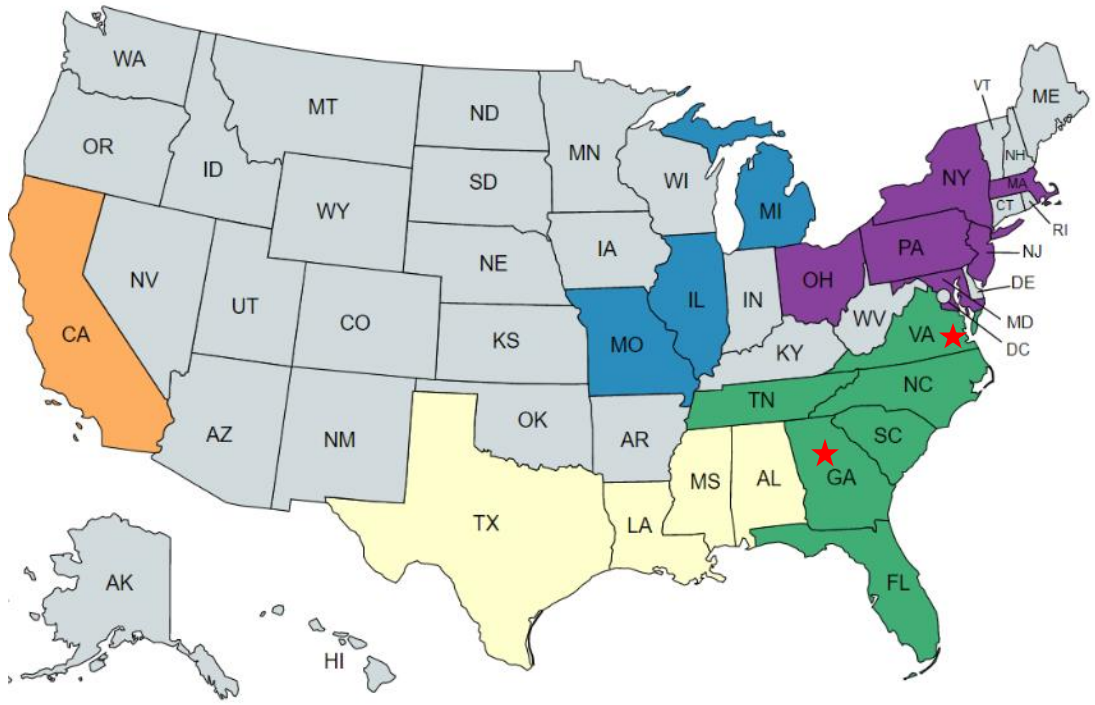
Enrolling Participant Groups:

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
Associate Professor and Director, Gastrointestinal Hereditary Cancer Program
University of Colorado Anschutz Medical Center

Updates in Genetics & Family History

Swati G. Patel, MD MS
Associate Professor of Medicine
Division of Gastroenterology & Hepatology
Director, Gastrointestinal Cancer Risk and Prevention Center
University of Colorado Anschutz Medical Center
Rocky Mountain Regional Veterans Affairs Medical Center
Swati.Patel@cuanschutz.edu

@swatigp

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

Swati G. Patel, MD MS
Associate Professor of Medicine
Division of Gastroenterology & Hepatology
Director, Gastrointestinal Cancer Risk and Prevention Center
University of Colorado Anschutz Medical Center
Rocky Mountain Regional Veterans Affairs Medical Center
Swati.Patel@cuanschutz.edu

@swatigp

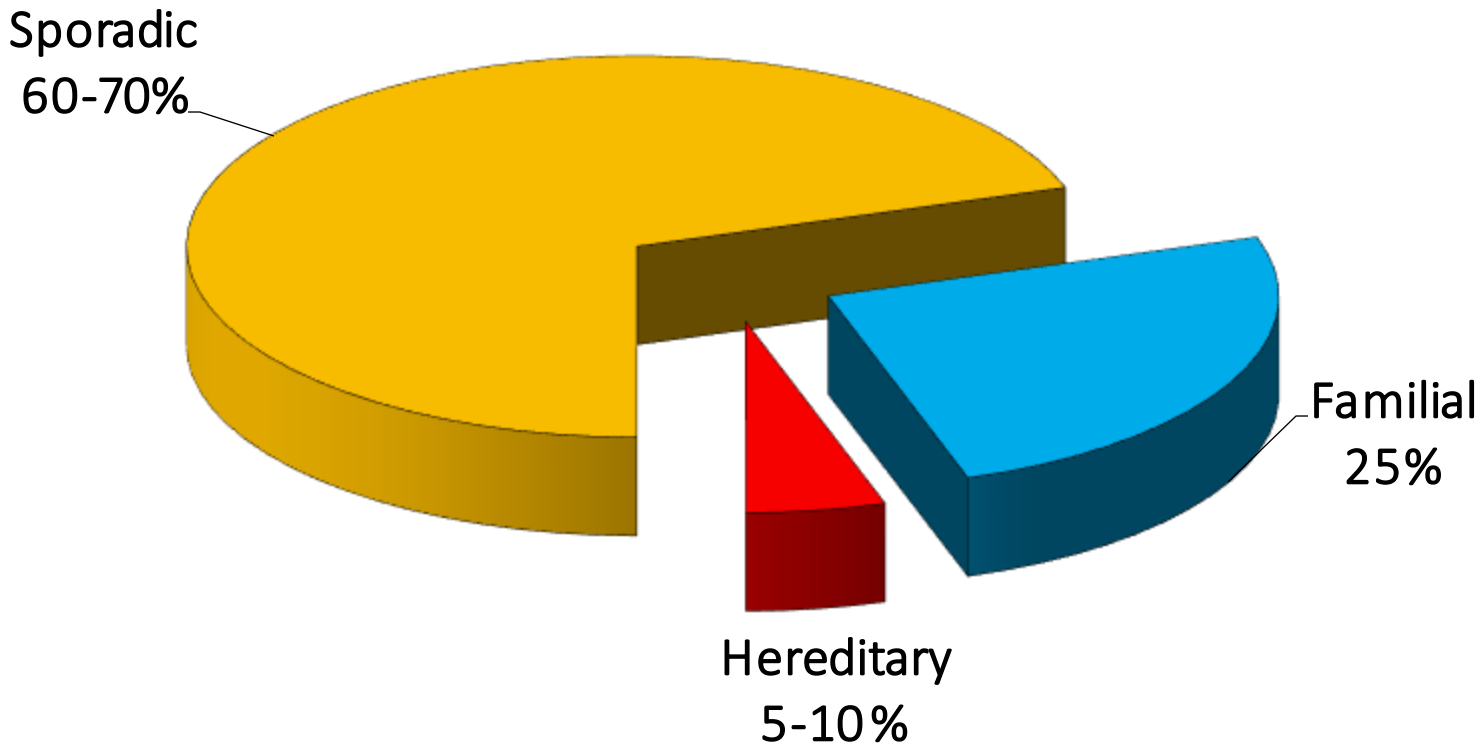
Updates in *Genetics* & Family History

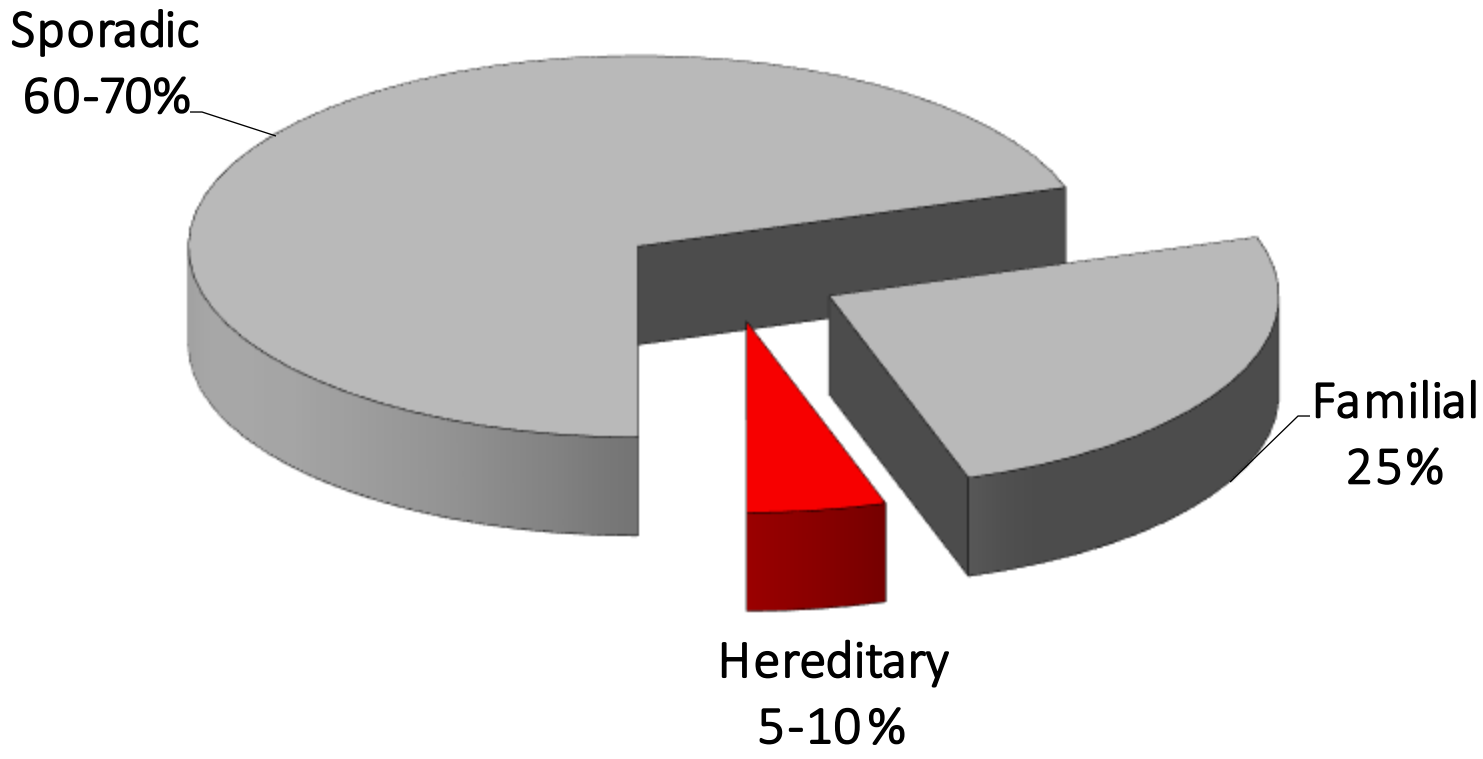
Swati G. Patel, MD MS
Associate Professor of Medicine
Division of Gastroenterology & Hepatology
Director, Gastrointestinal Cancer Risk and Prevention Center
University of Colorado Anschutz Medical Center
Rocky Mountain Regional Veterans Affairs Medical Center
Swati.Patel@cuanschutz.edu

@swatigp

@swatigp

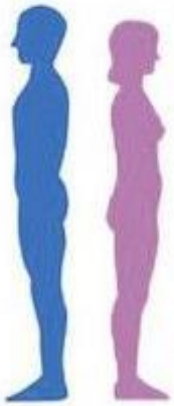

Approach to Hereditary Risk Assessment
Exercise Interventions
Dietary Interventions
Medication Interventions


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


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

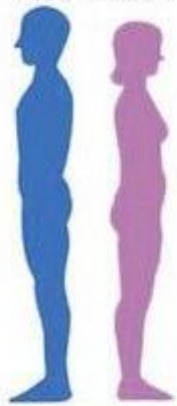
Estimated New Cases*

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%**

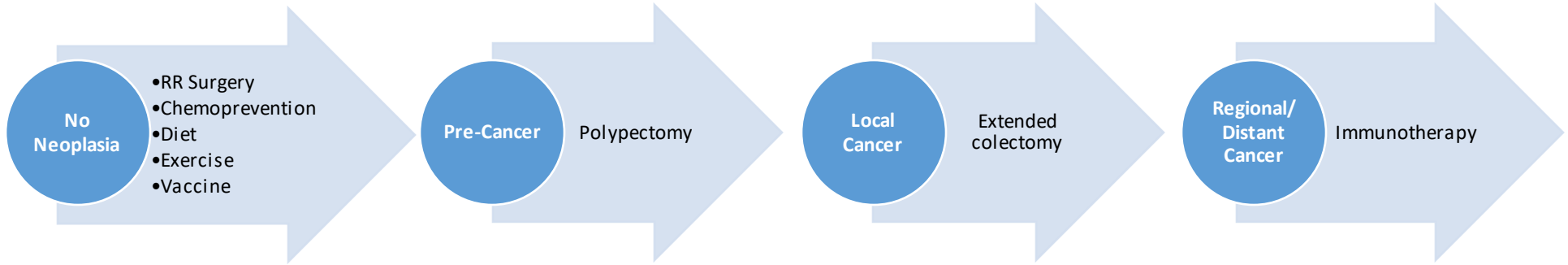


Estimated Deaths

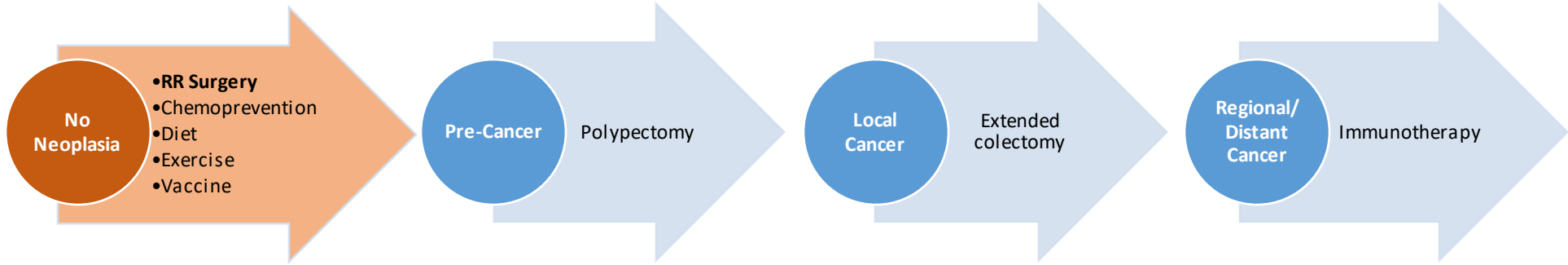
Males			Females		
Lung & bronchus	86,220	29%	Lung & bronchus	71,080	26%
Prostate	32,050	11%	Breast	39,840	15%
Colon & rectum	26,580	9%	Colon & rectum	24,790	9%
Pancreas	18,770	6%	Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%	Ovary	13,850	5%
Leukemia	12,660	4%	Non-Hodgkin lymphoma	9,500	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%**

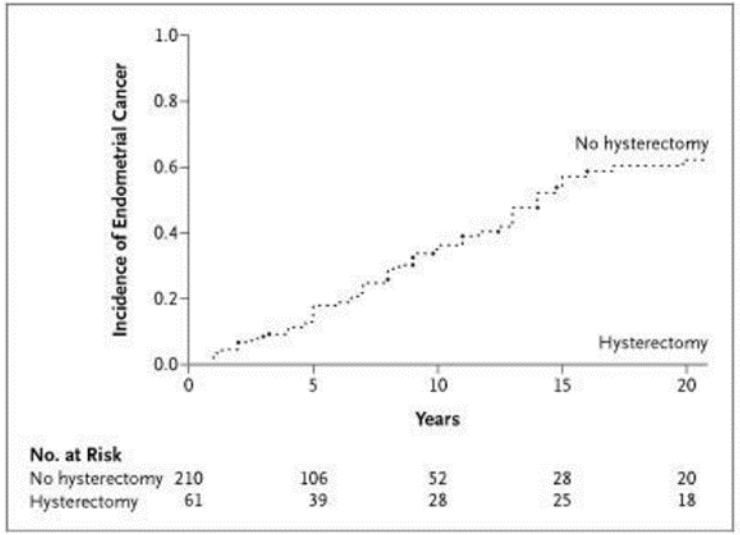


Opportunities for Intervention



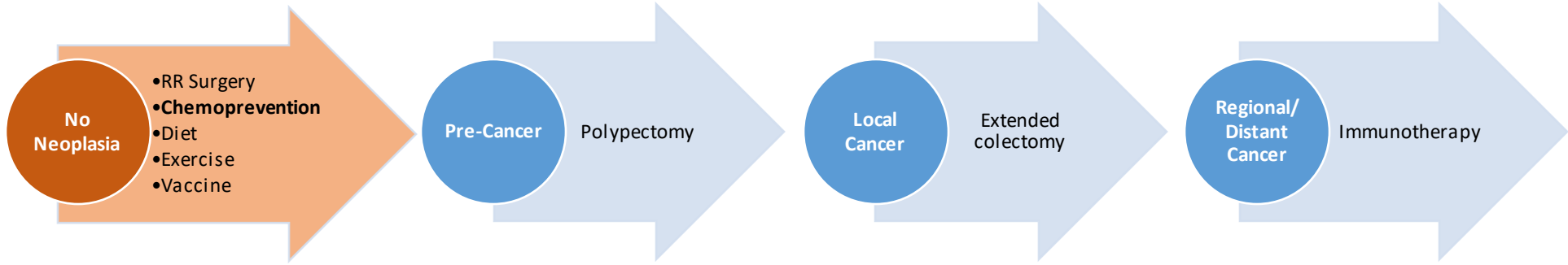
Opportunities for Intervention

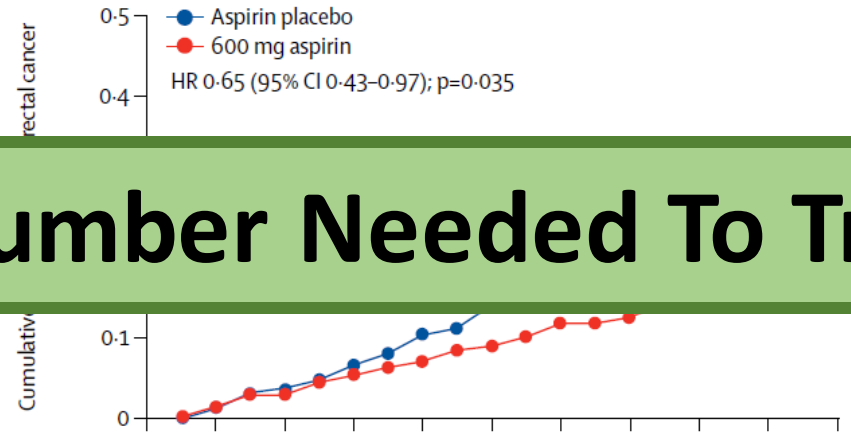




Schmeler et al. N Engl J Med 2006; 354:261-269.

Opportunities for Intervention

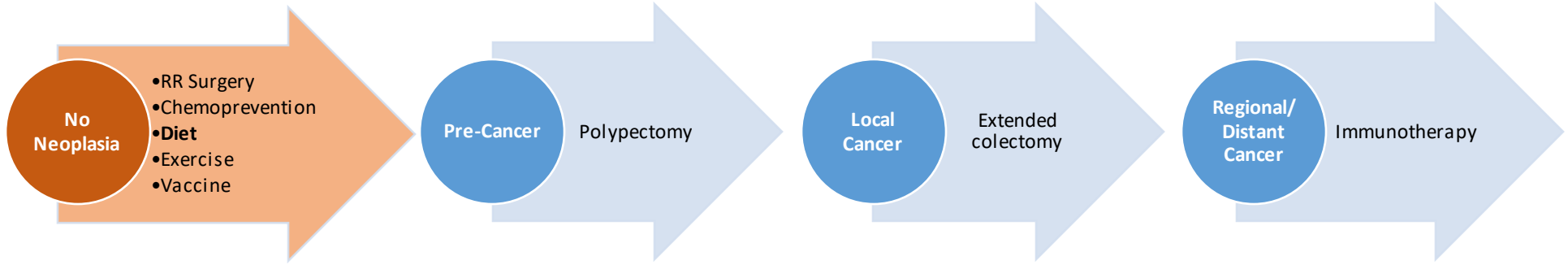


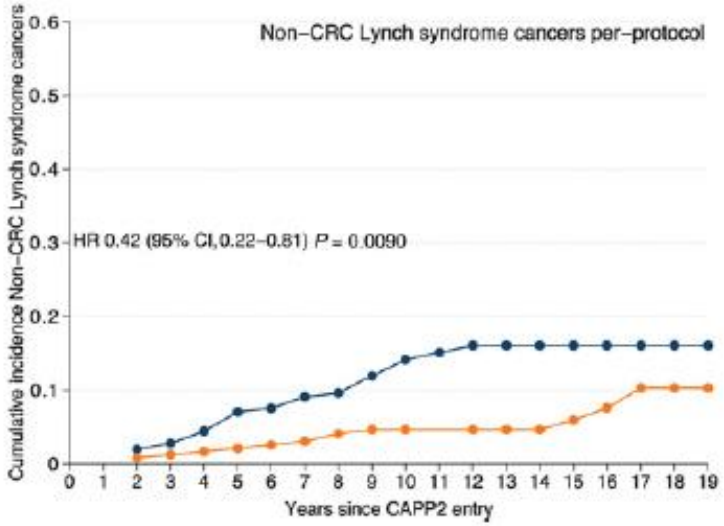


Number Needed To Treat to Prevent 1 CRC = 24

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

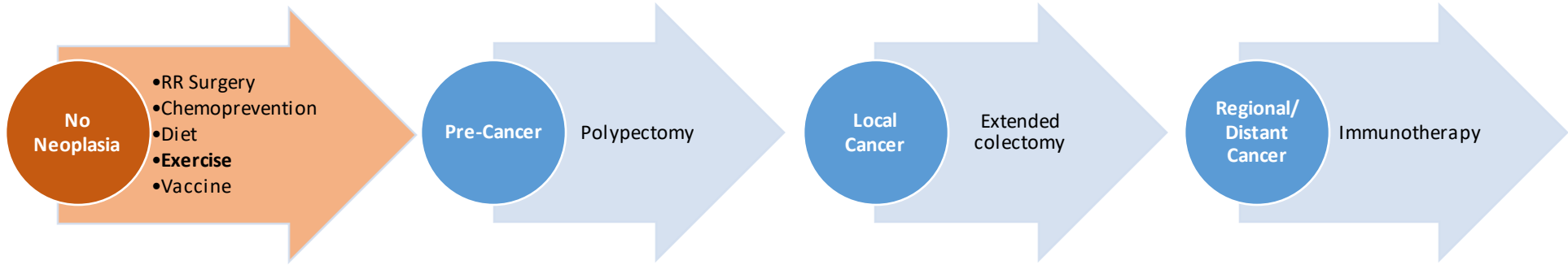
Opportunities for Intervention

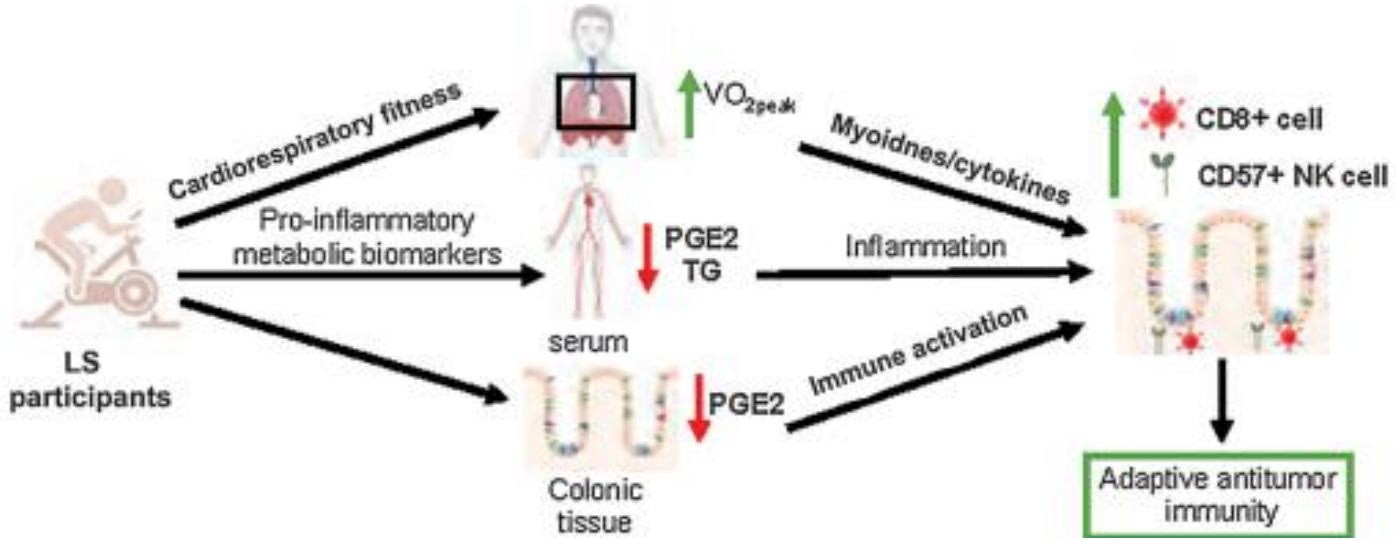




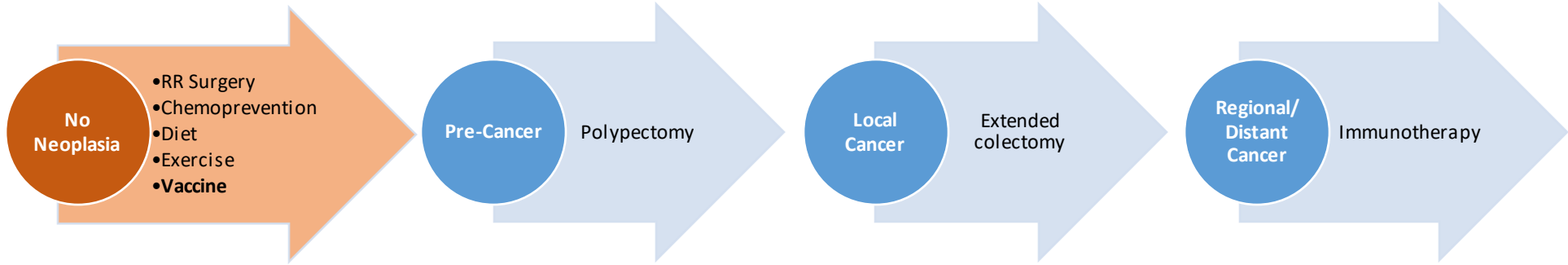
Mathers et al. Cancer Prev Res 2022;15:623-34.

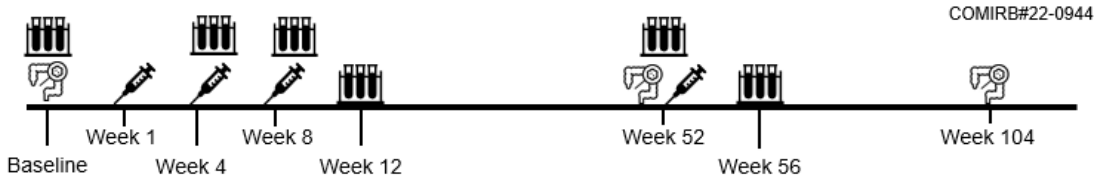
Opportunities for Intervention





Opportunities for Intervention





Standard of Care Colonoscopy

Vaccine Administration

Research Blood Draw

ELIGIBILITY

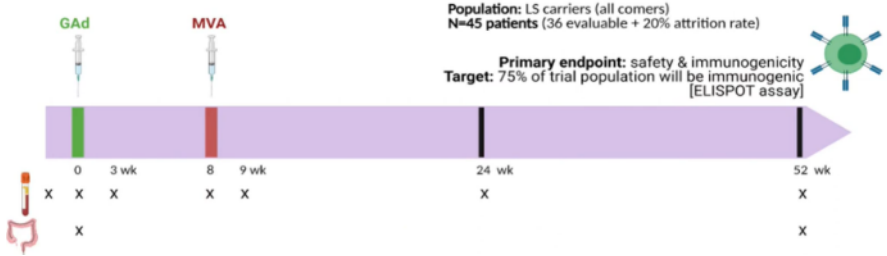
- Lynch Syndrome Diagnosis
- Able to partake in research blood draws and colonoscopies
- 18 years of age
- Able to commit to 2 years of research-related appointments

PRIMARY OUTCOME

- Cumulative colorectal neoplasia

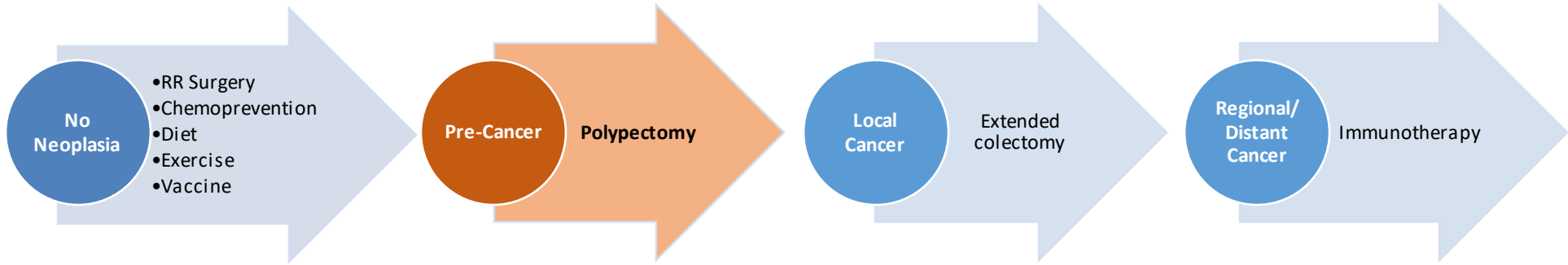
	cMS type	Mutation frequency (CRC)[3]	Mutation frequency (EC)[3]
TAF1B(−1)	A11	74.6%	50.0%
HT001(−1)	A11	86.2%	92.9%
AIM2(−1)	A10	81.6%	71.4%

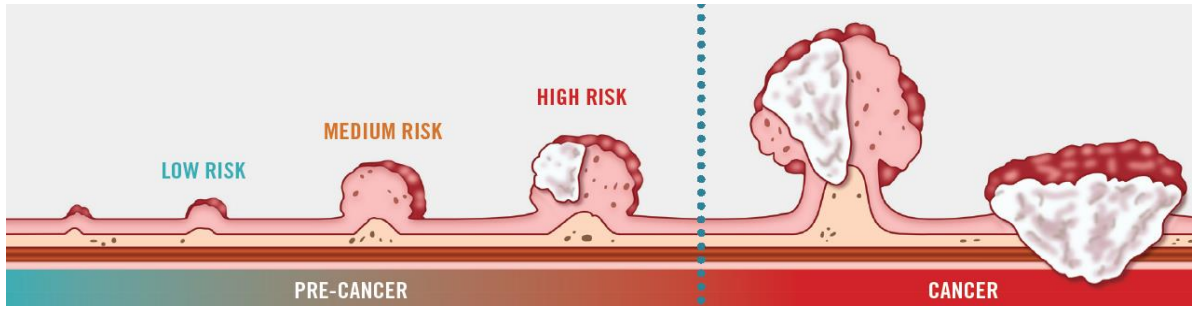
TAFB(−1): H-NTQIKALNRGLKKKTILKKAGIGMCVKVSSIFFINKQKP-OH
AIM2(−1): H-HSTIKVIKAKKKHREVKRTNSSQLV-OH
HT001(−1): H-EIFLPKGRSNSKKKGRRNRIPAVLRTEGEPLHTPSVGMRETTGLGC-OH

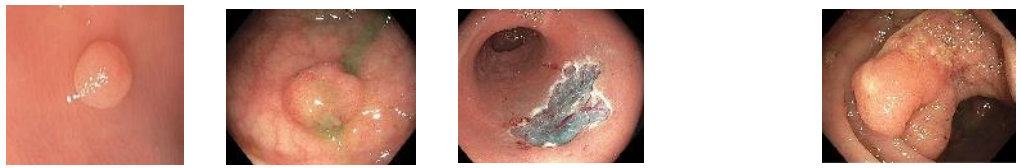


Kloor et al. Clin Cancer Res 2020;26(17):4503-10.
Vilar-Sanchez et al. NCT05078866.
Bansal & Vilar-Sanchez et al. NCT05419011.

Opportunities for Intervention





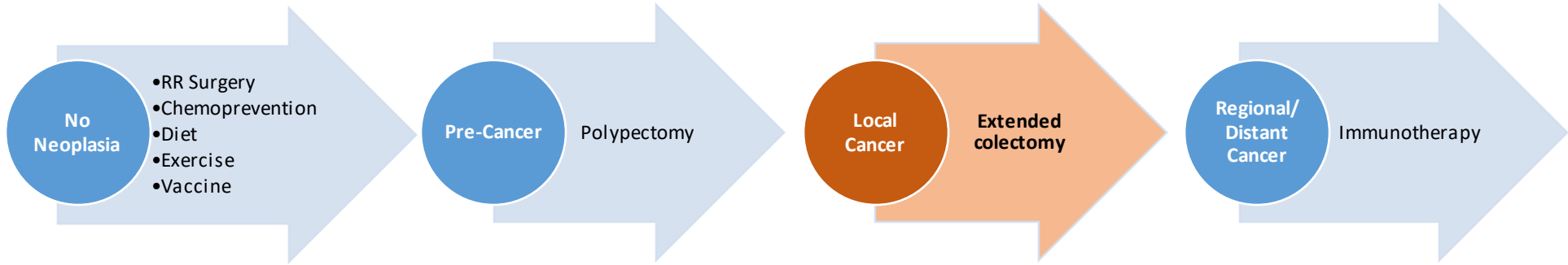


62% reduction in CRC Incidence

72% reduction in CRC Mortality

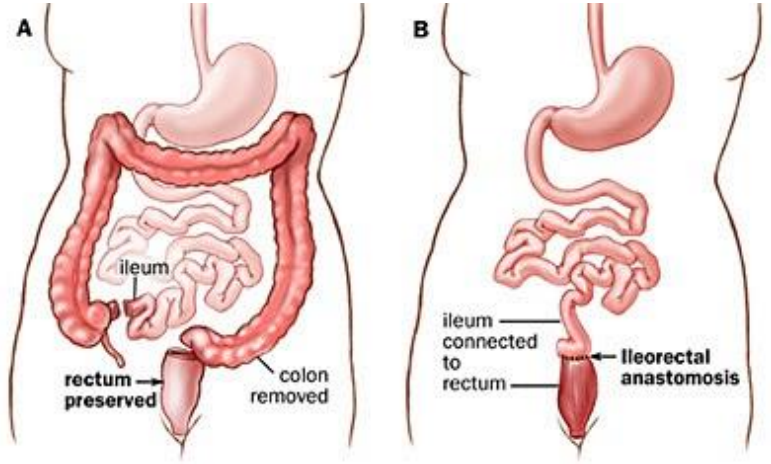
Jarvinen et al. Gastroenterol. 2000. 118(5):829-34.
Dove-Edwin et al. BMJ. 2005. 331(7524):1047.

Opportunities for Intervention



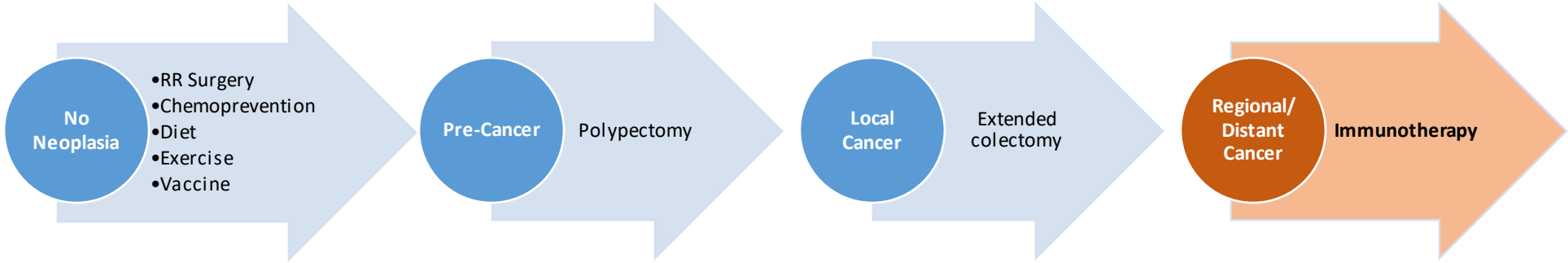
- Cumulative risk of metachronous CRC at 10, 20, 30 years is 16%, 41%, 62%, respectively

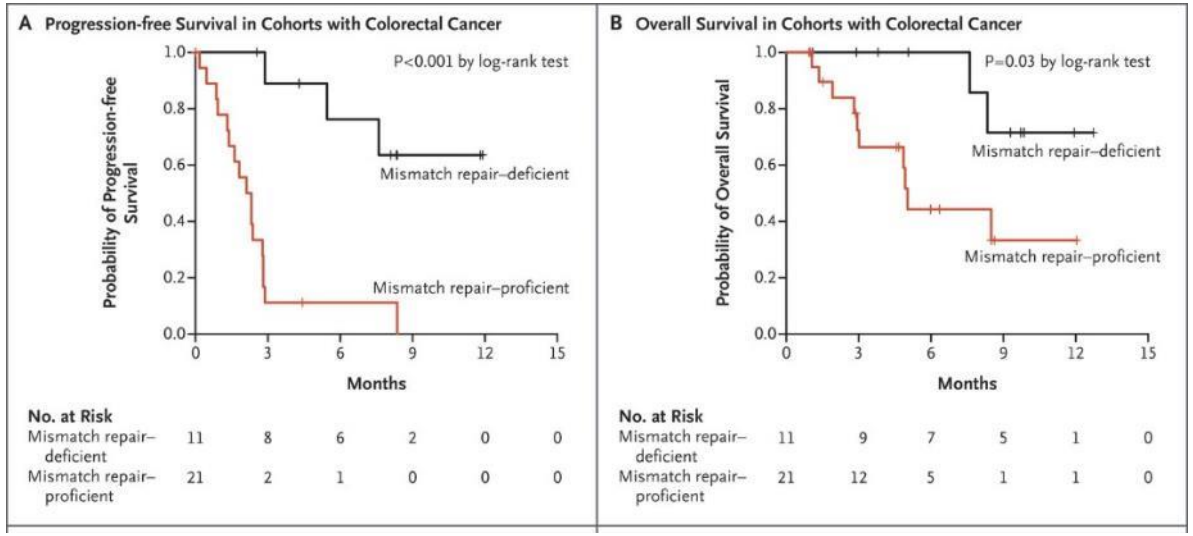
- Extensive colectomy vs segmental
  - Extensive: 0/50 metachronous tumors
  - Segmental: 74/322 (22%) metachronous tumors



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

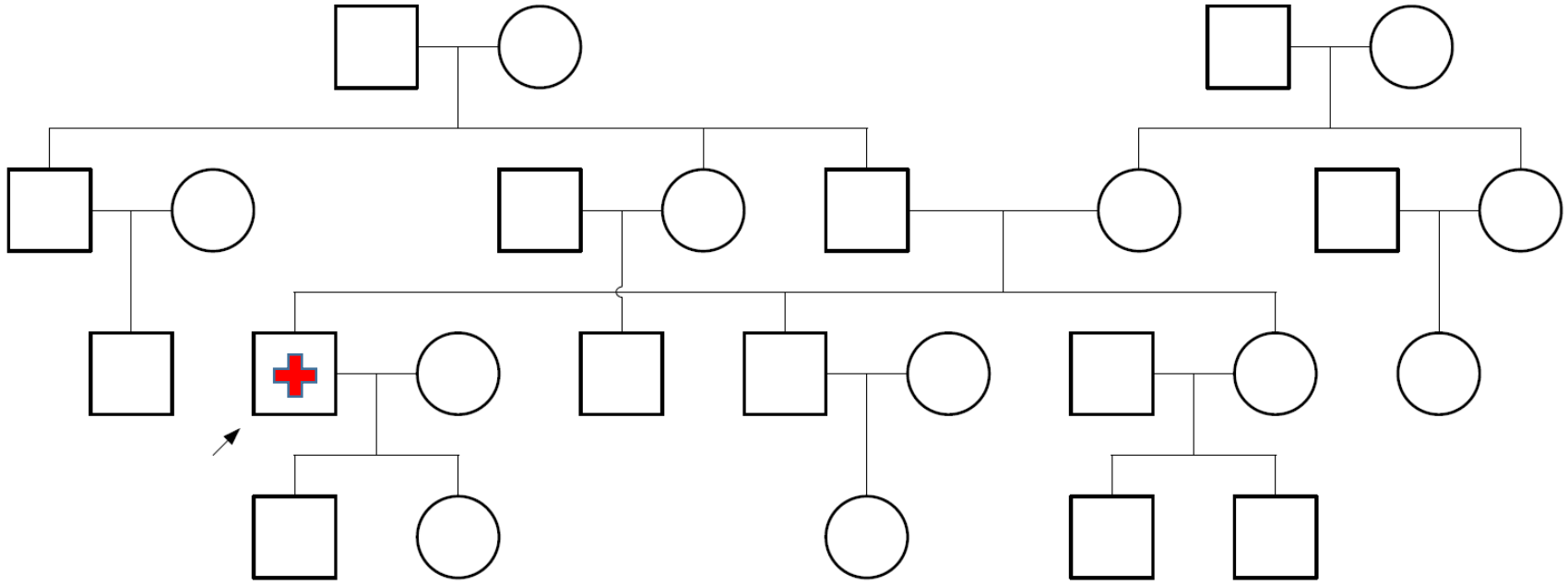




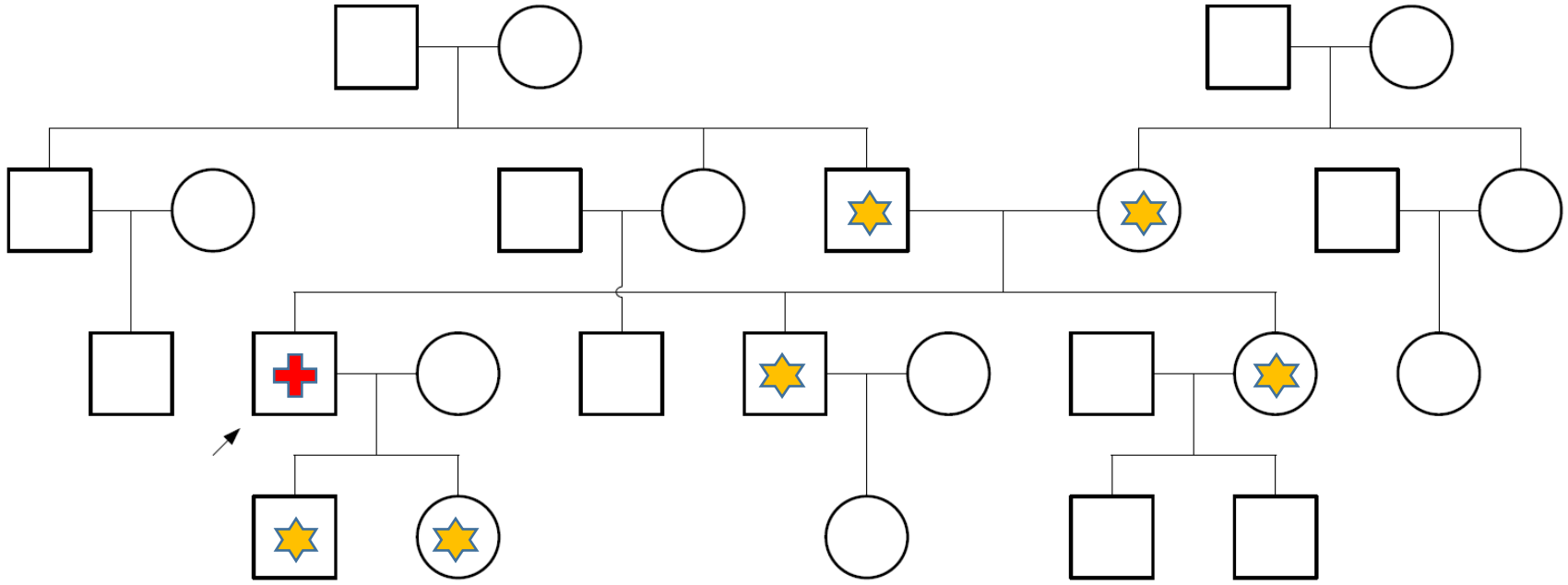
Le et al. NEJM. 2015;372:2509-20.

Capturing Family Members: Cascade Testing

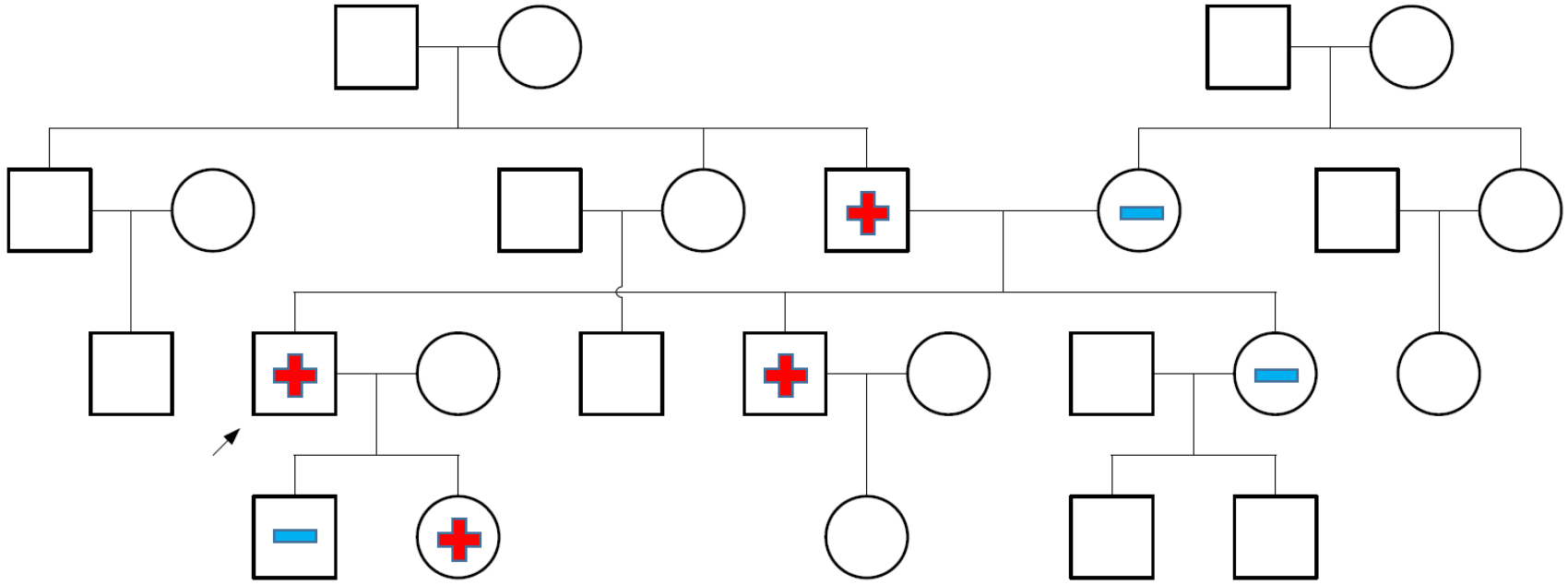
Capturing Family Members: Cascade Testing



Capturing Family Members: Cascade Testing



Capturing Family Members: Cascade Testing



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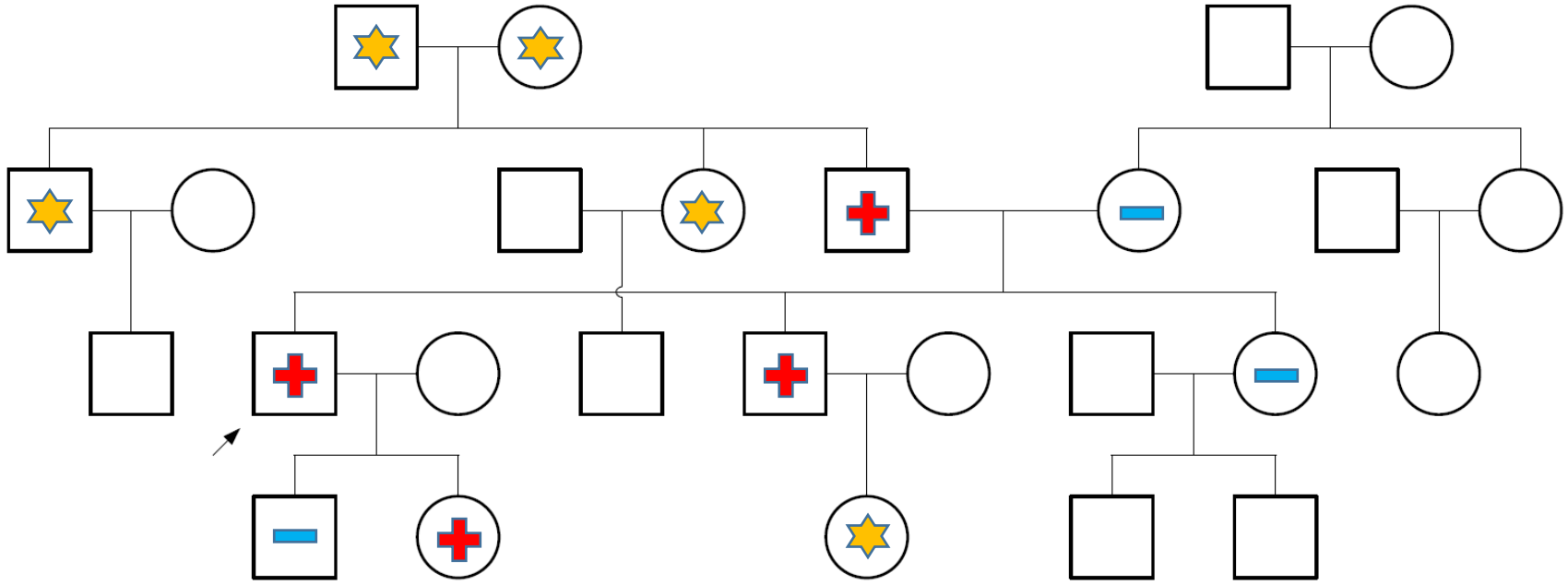

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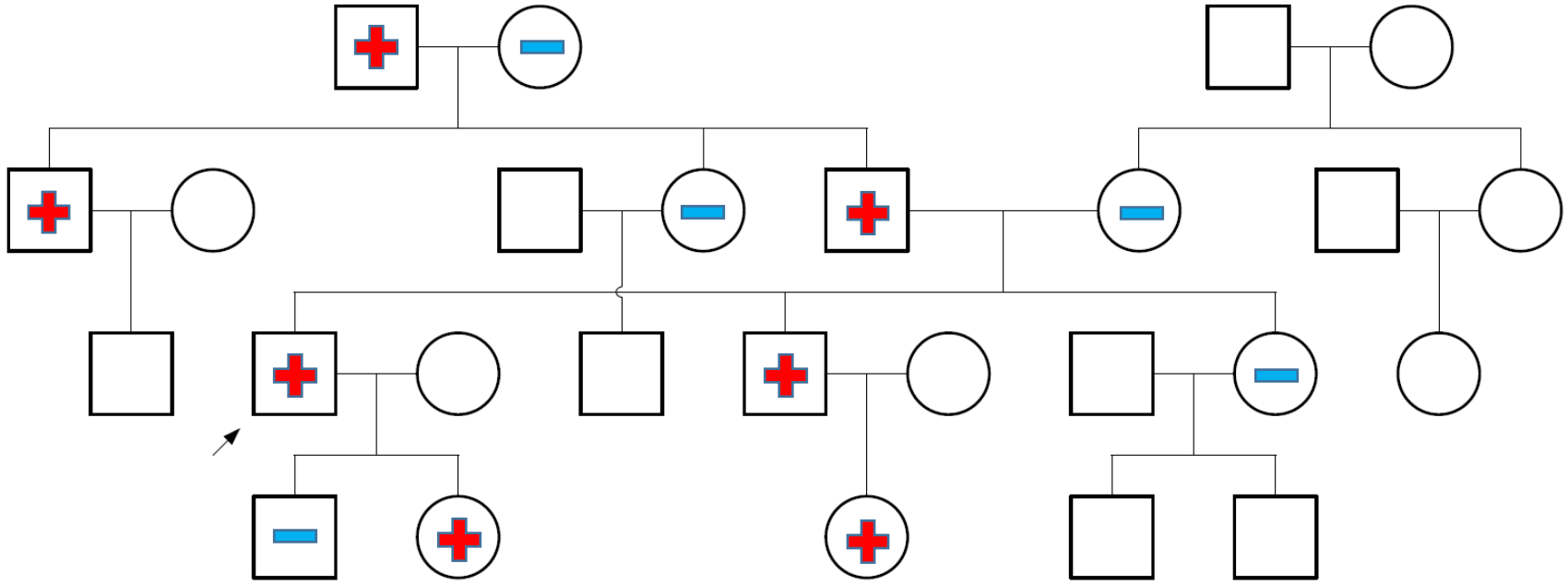

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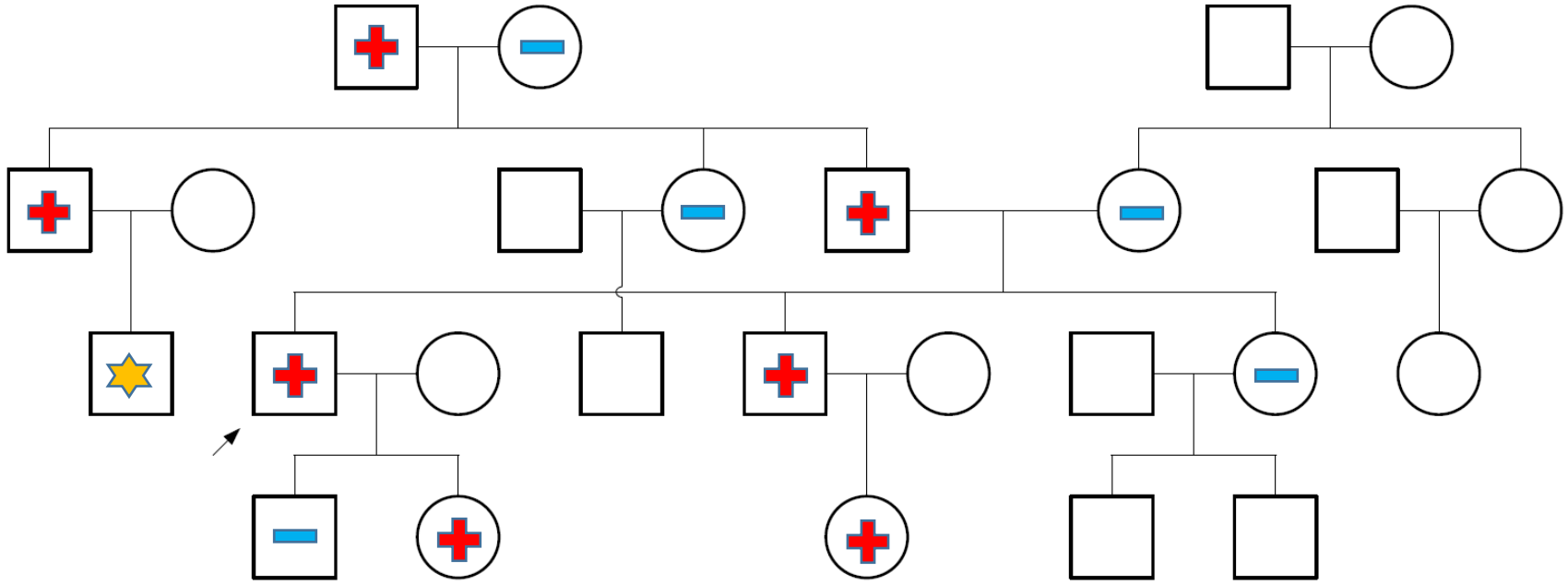
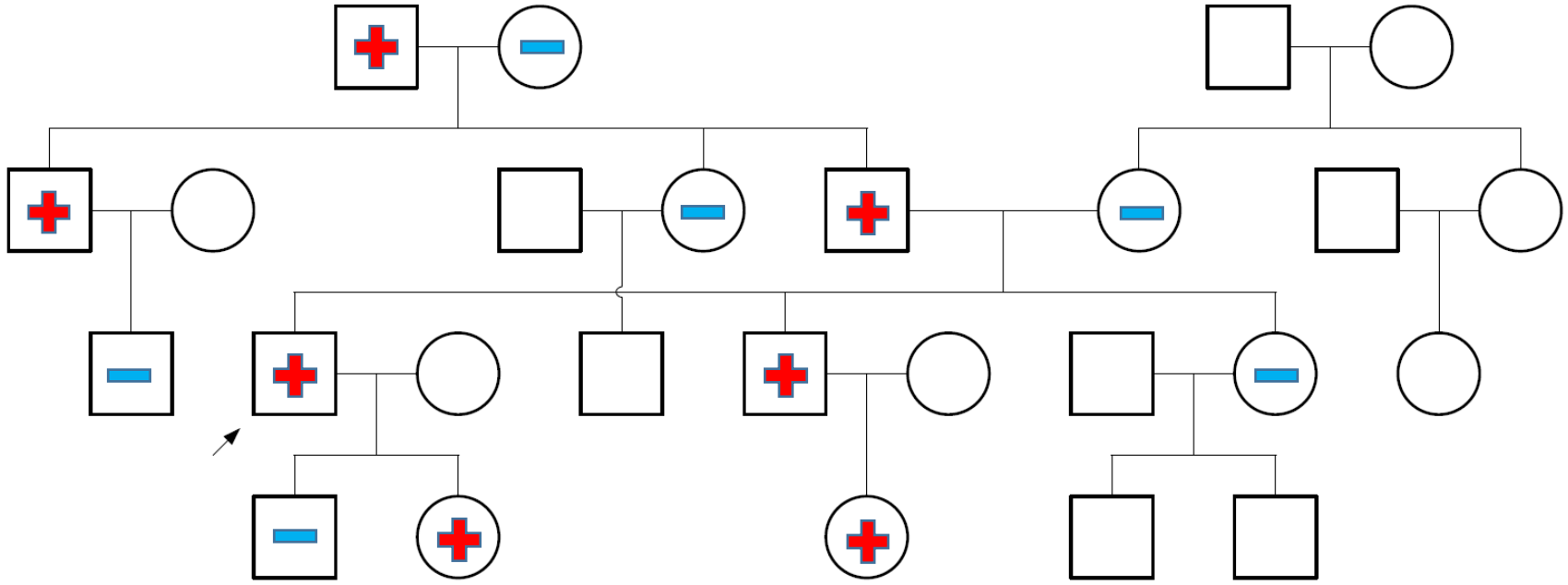


Capturing Family Members: Cascade Testing



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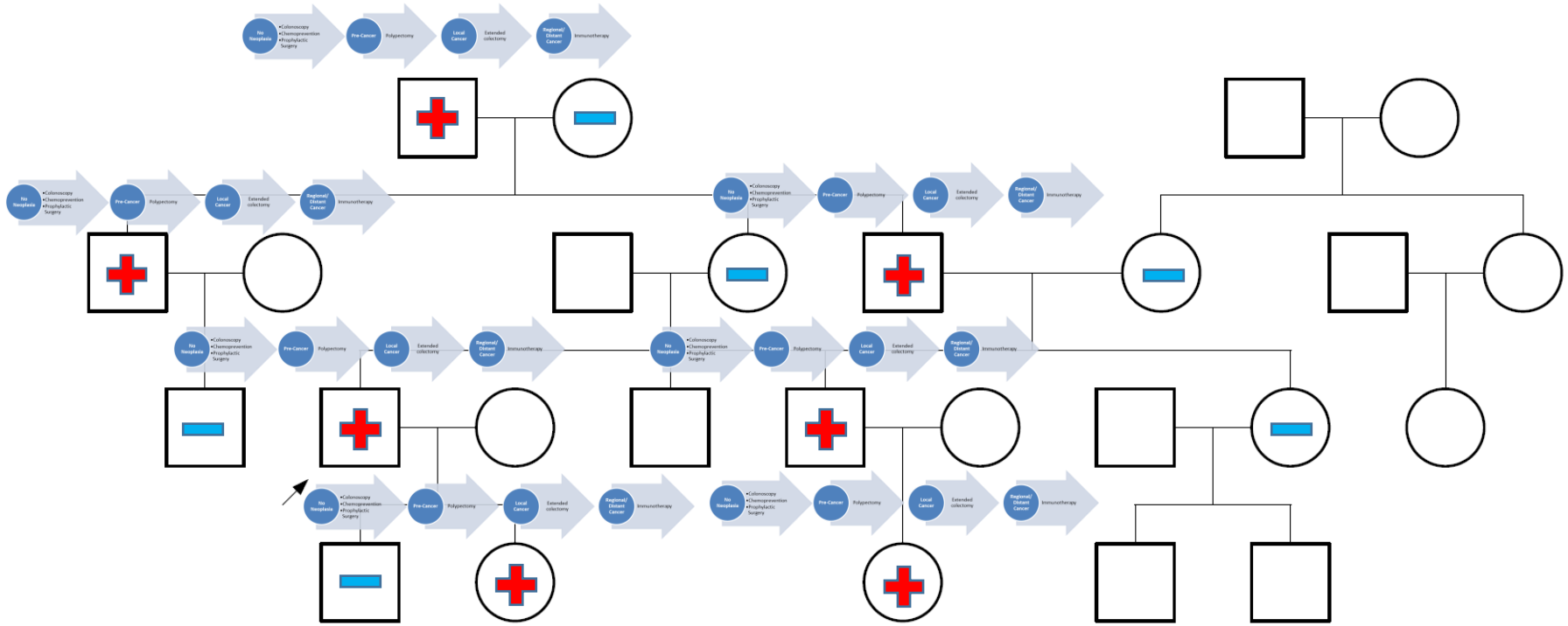
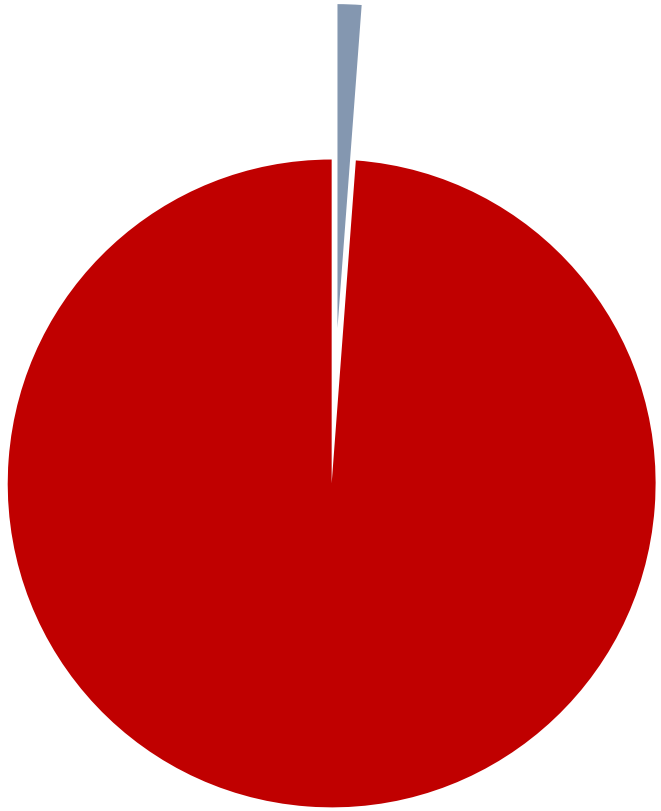


Lynch Syndrome is Grossly Under-Recognized

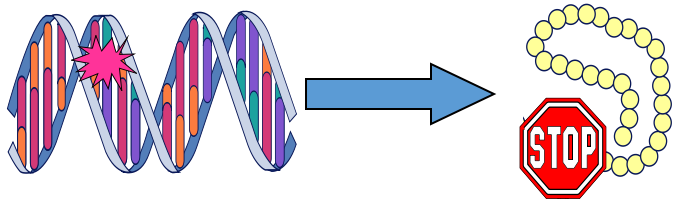
Only ~1.2% (10K/830K) Lynch mutation carriers in the US are aware of their diagnosis



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

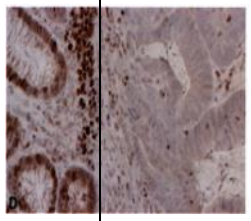
Lynch Syndrome Diagnosis: Tumor Screening

Immunohistochemistry for MMR Protein Loss



Abnormal Gene (MSH2)

Abnormal or missing MSH2 protein

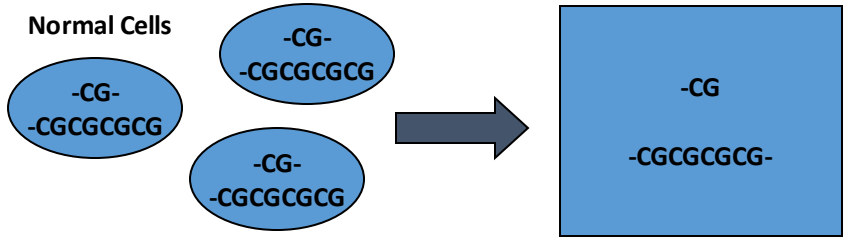


MSH2 +

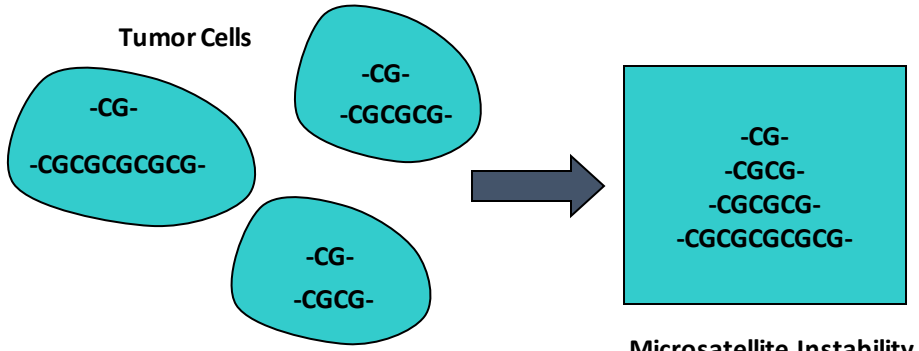
MSH2- Lack of MSH2 expression, negative IHC staining for MSH2 protein

Normal tissue | Tumor tissue

PCR for Microsatellite Instability Markers



Normal Microsatellites



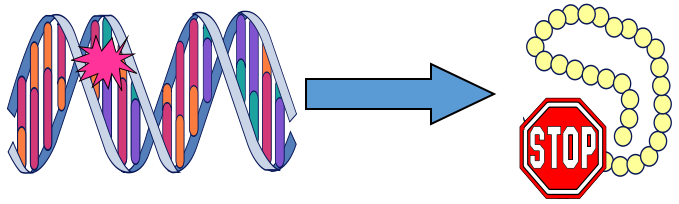
Microsatellite Instability

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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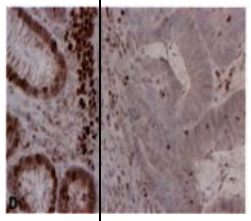

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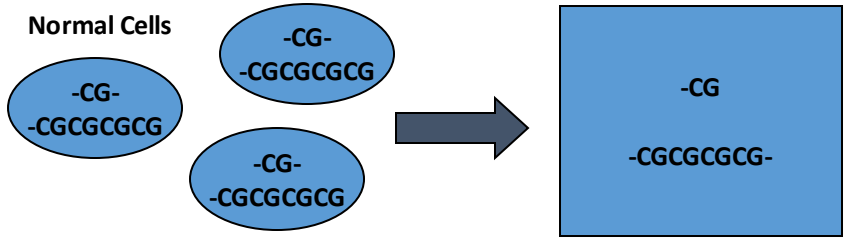
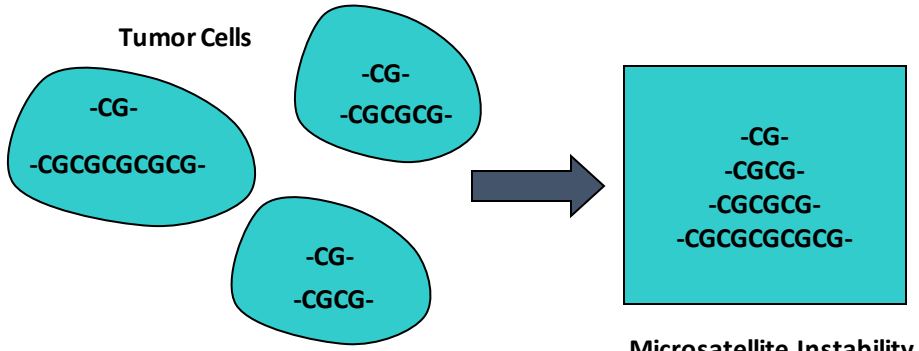
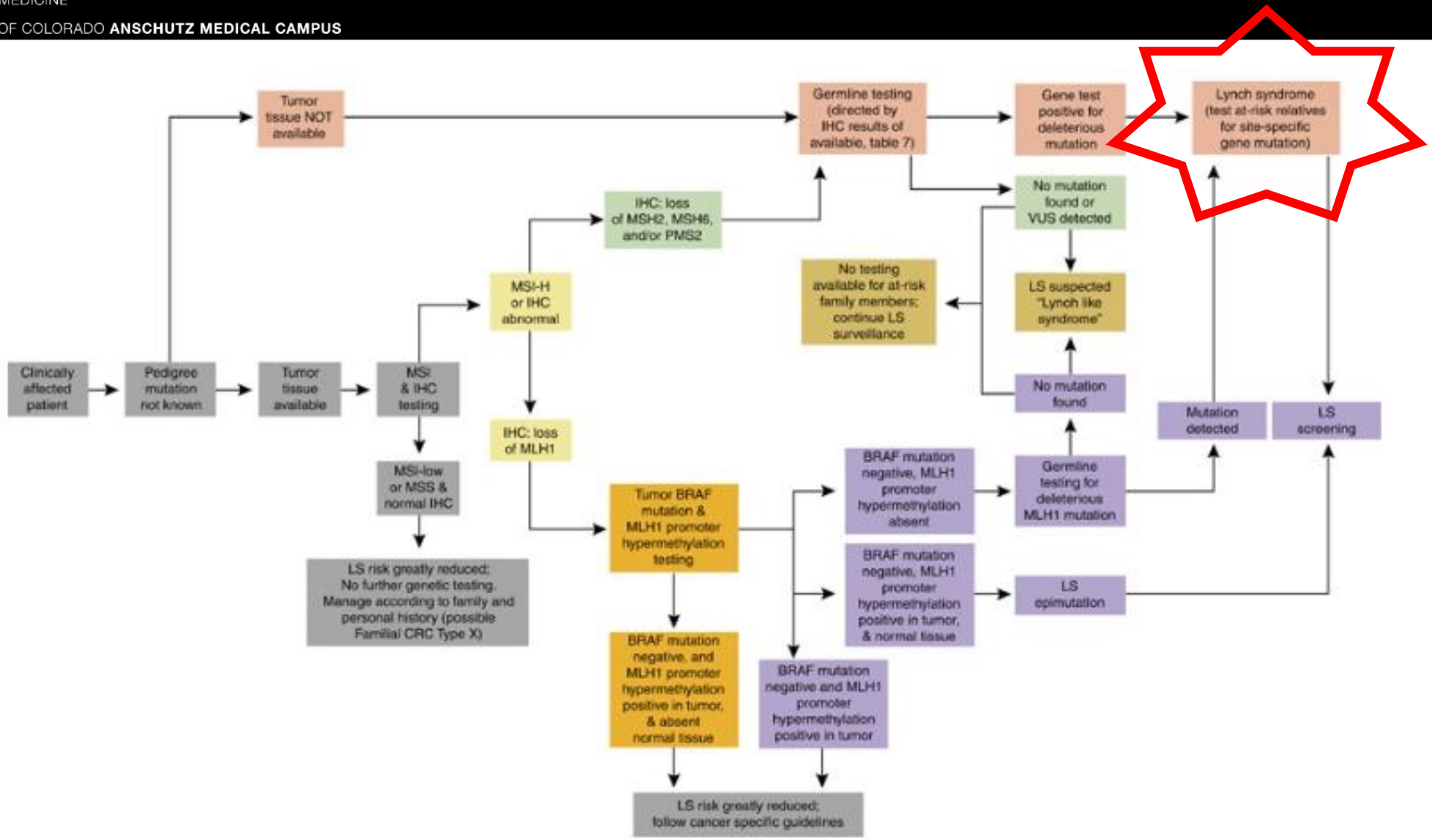


Normal Microsatellites



Microsatellite Instability



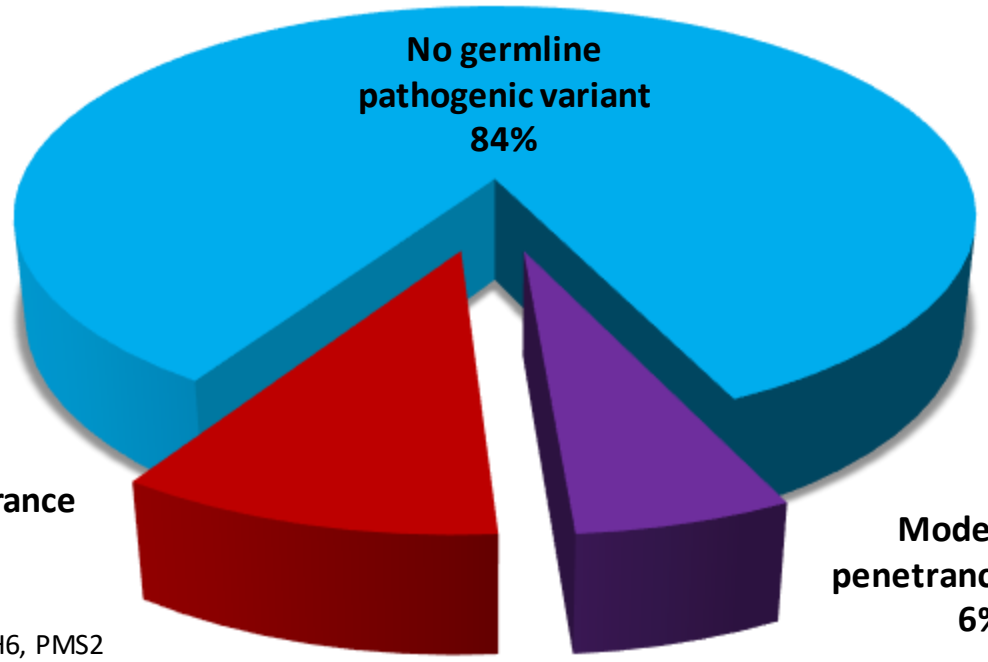
Lynch Syndrome: US-MSTF 2014.

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

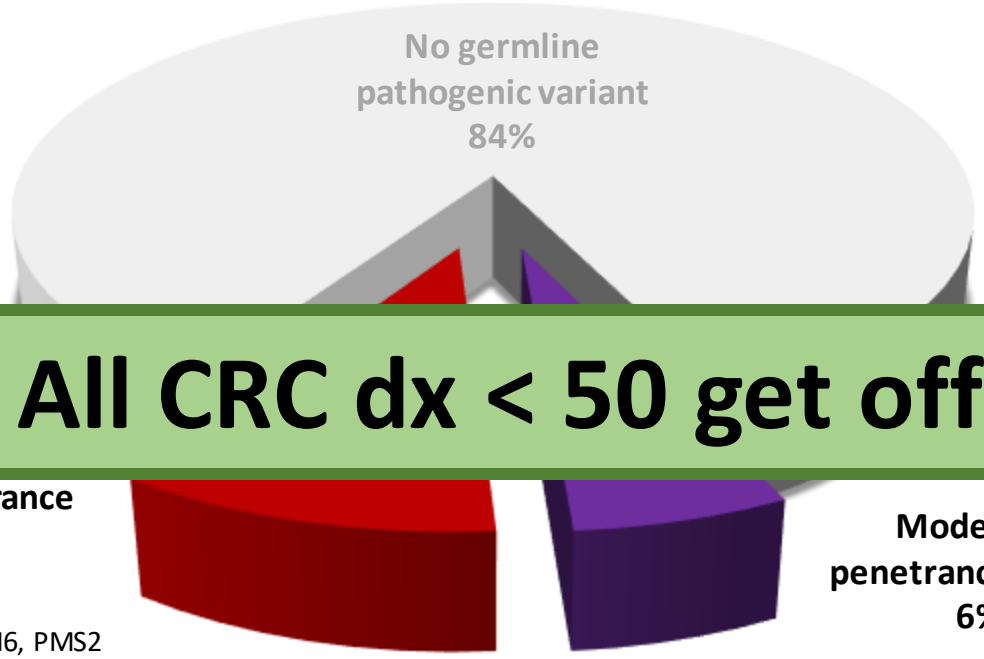
Charles Muller,* Sang Mee Lee,* William Barge,‡ Shazia M. Siddique,§ Shivali Berera,‖ Gina Wideroff,‖ Rashmi Tondon,§ Jeremy Chang,* Meaghan Peterson,* Jessica Stoll,* Bryson W. Katona,§ Daniel A. Sussman,‖ Joshua Melson,‡ and Sonia S. Kupfer*

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

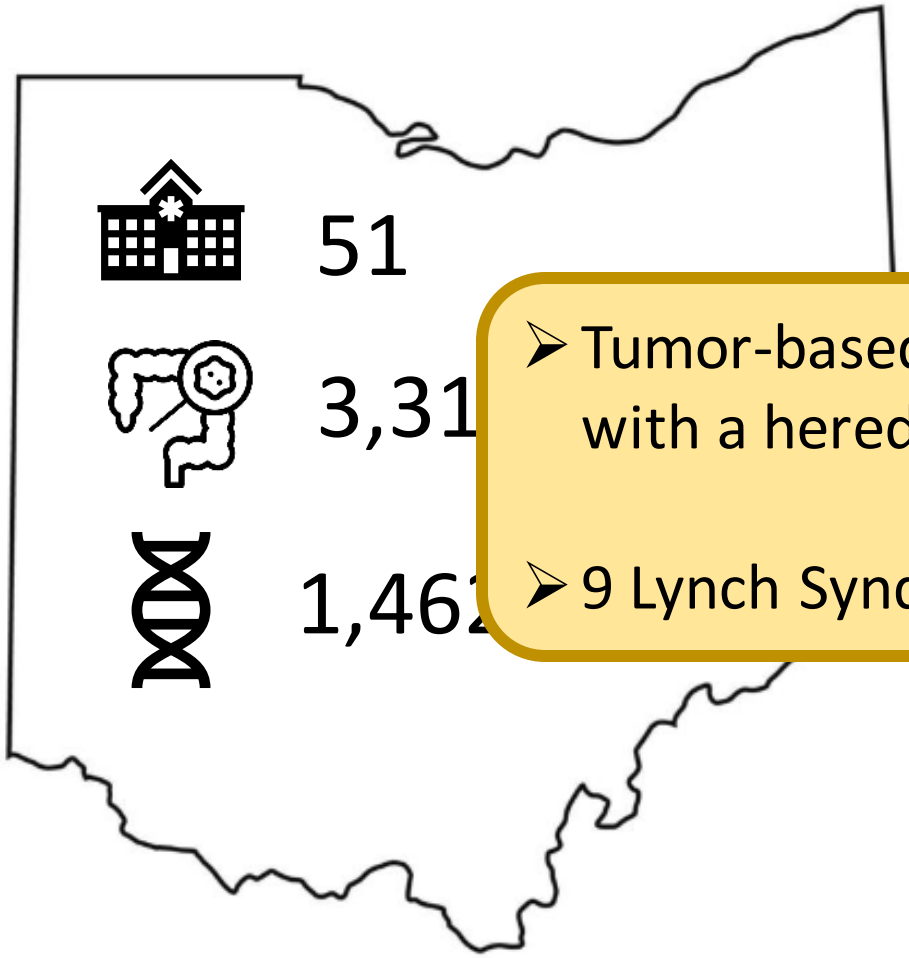
High-penetrance variant 10%

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

Moderate-penetrance variant 6%

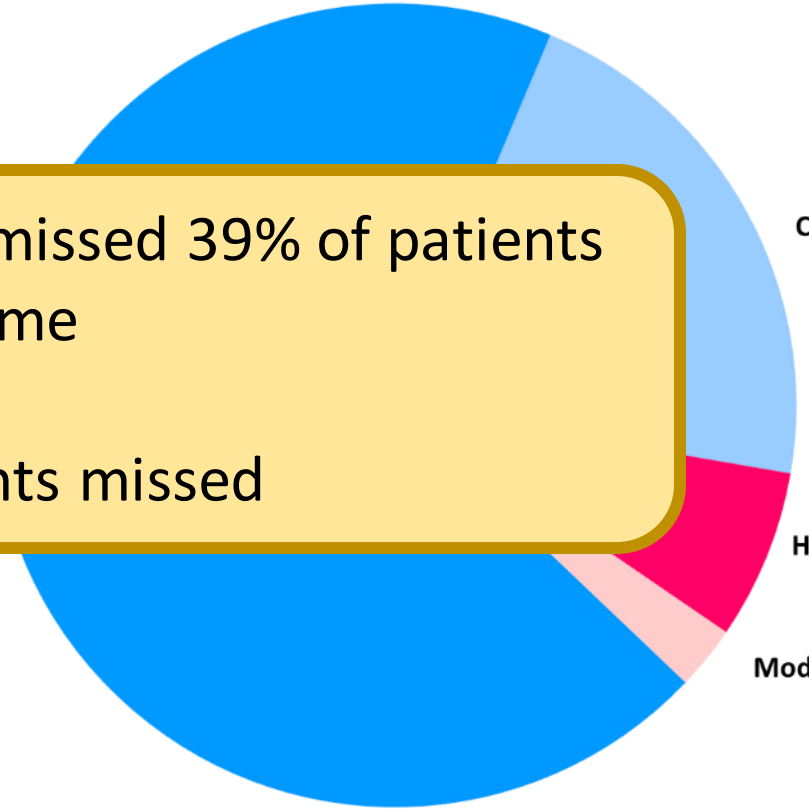
ATM
PALB2
Monoallelic MUTYH
APC I1307K
CHEK2

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

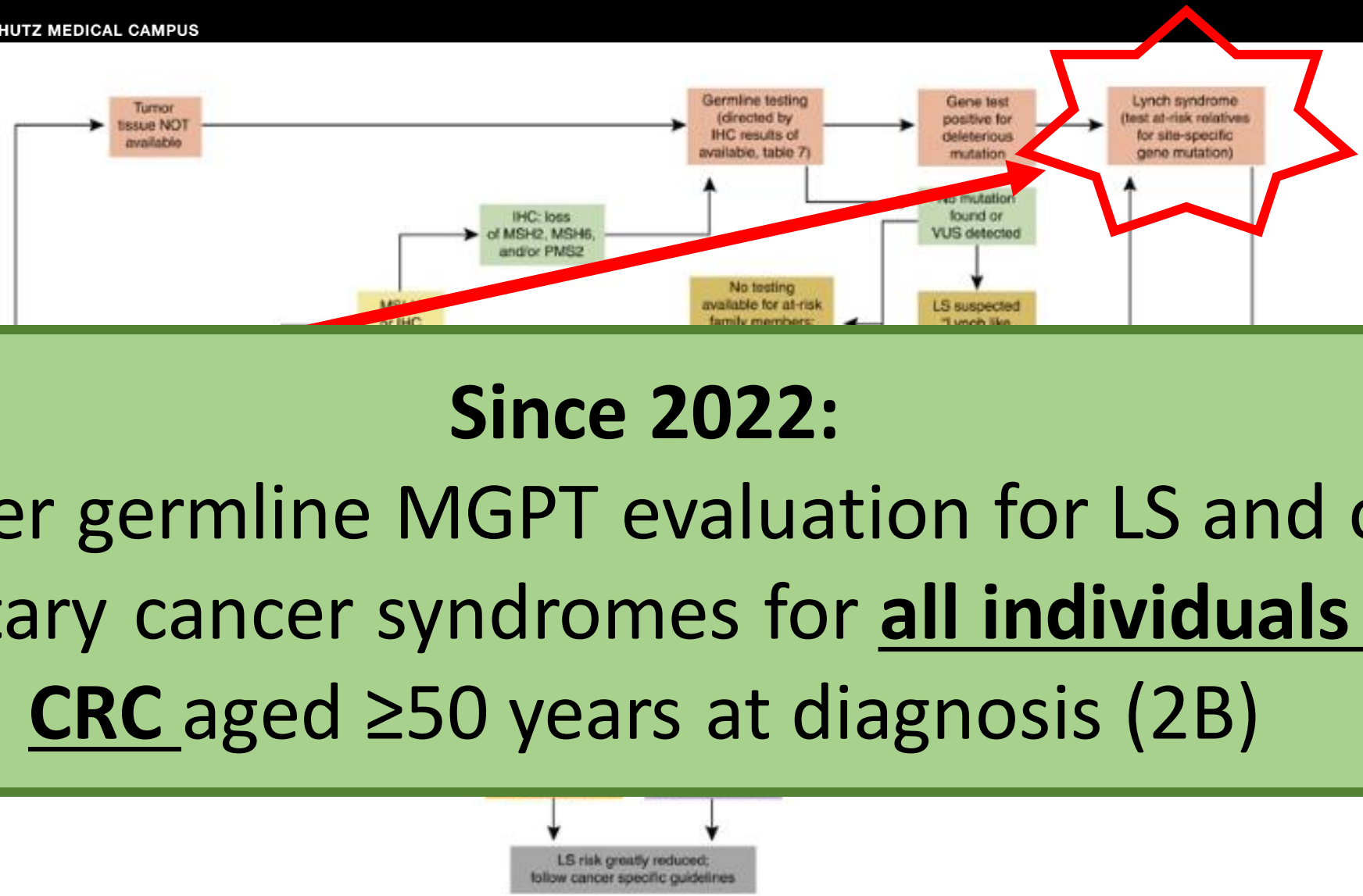


- Tumor-based screening missed 39% of patients with a hereditary syndrome
- 9 Lynch Syndrome patients missed

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.

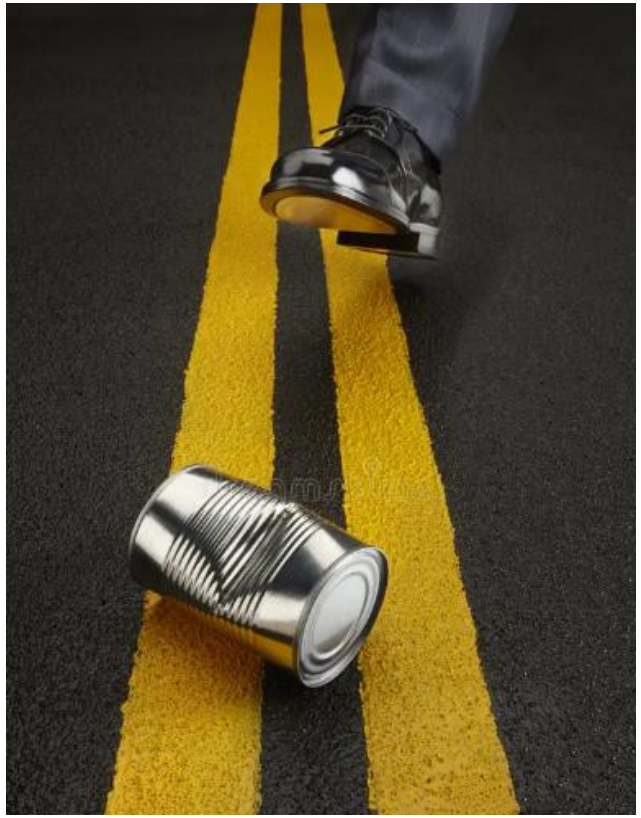
GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BRIP1	c.3302C>T (p.Pro1101Leu)	heterozygous	Uncertain Significance
DICER1	c.278G>A (p.Gly93Glu)	heterozygous	Uncertain Significance
GATA2	c.460A>G (p.Ser154Gly)	heterozygous	Uncertain Significance
MSH3	c.3382A>G (p.Met1128Val)	heterozygous	Uncertain Significance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

Swati G. Patel, MD MS

Swati.Patel@cuanschutz.edu

@swatigp

American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

Thank You

nccrt.org @NCCRTnews #80inEveryCommunity