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
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
What does the microbiome do?

WHAT DOES YOUR GUT MICROBIOME DO?

- Help to break down food and its components (e.g., fiber)
- Protects your gut from pathogenic bacteria
- Help to shape and regulate your immune system
- Produce bioactive molecules, like short-chain fatty acids to support your gut cells
- Synthesize essential vitamins (e.g., vitamin K and B group vitamins)

What Factors Impact the Gut Microbiome?


Torres Maravilla, et al. Role of gut microbiota and probiotics in colorectal cancer. Microorganisms. 2021
Gut Microbiome Varies with Age

Gut Microbiome Varies with Ethnicity

Life-course exposures with potential effects on CRC development

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
CRC: The potential impact of the microbiome

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 increased after antibiotic use in dose-dependent fashion, especially penicillins
- Prolonged antibiotic use appeared protective against rectal cancer
- Antibiotic-cancer association occurred after antibiotic exposure > 10 yrs prior to cancer diagnosis

## Factors associated with the microbiome and CRC

*a confusing landscape!*

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

Lactobacillus
Bifidobacterium
Granulicatella
Ruminococcus
Bifidobacterium
Oribacterium
Desulfovibrio
Clostridiales
Lachnospiraceae
Haemophilus
Faecalibacterium
Lactococcus
Streptococcus
Enterococcus
Actinobacteria
Lachnospiraceae
Desulfovibrio

Fusobacterium
Peptostreptococcus
Ruminococcus
Proteobacteria
Solobacterium
Corynebacterium
Parvimonas
Neisseria
Porphyromonas
Parvimonas
Alcaligenaceae
Enterobacteriaceae
Gemella
Prevotella
Bacteroides
Desulfovibrio
Oscillospira

Healthy colon
Colon cancer

a) Normal epithelium (No abnormalities)
b) Small benign growth (Polyp)
c) Large benign growth (Early adenoma)
d) Large benign growth (Late adenoma)
e) Malignant tumor (Carcinoma)

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

Prevent and conquer cancer. Together.
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 galoliticus

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 signalling, ephrin signalling, 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 signalling and TGF signalling
*Fusobacterium nucleatum*

- 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

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


A Cell line (cells on a plate)

B Colon cancer growing in a mouse

Prevent and conquer cancer. Together.
Is *Fusobacterium. nuc.* present in adenomas?

Registry Cohort A
Patients with CRC < 45 years
n = 48

Registry Cohort B
Patients with CRC ≥ 65 years
n = 48

Prospective Cohort C
Patients with untreated CRC < 45 years
n = 16

Prospective Cohort D
Patients with untreated CRC ≥ 65 years
n = 16

Prospective Cohort E
Normal controls < 45 years
n = 16

Total n = 144
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.
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
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

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

Positive effects of microbiota and probiotics in CRC
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

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.
Thank You
Thank You
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.

<table>
<thead>
<tr>
<th></th>
<th>Hammond-Horn</th>
<th>CPS-I</th>
<th>CPS-II*</th>
<th>CPS-3*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>188,000</td>
<td>1,000,000</td>
<td>1,200,000</td>
<td>304,000</td>
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<tr>
<td><strong>Volunteers</strong></td>
<td>22,000</td>
<td>68,000</td>
<td>77,000</td>
<td>25,000</td>
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<tr>
<td><strong>With blood (or DNA)</strong></td>
<td>n/a</td>
<td>n/a</td>
<td>40,000 (70,000)</td>
<td>297,000</td>
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</table>

* Tumor tissue for selected cancer types collected
**DIET & NUTRITION RESEARCH FROM CPS**

**2017**

**DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER**

- **DECREASES RISK**
  - Physical activity
  - Whole grains
  - Foods containing dietary fibre
  - Dairy products
  - Calcium supplements

- **INCREASES RISK**
  - Processed foods
  - Alcoholic drinks
  - Body fat
  - Adult alcohol
  - Red meat

**LIMITED**

- Foods containing vitamin C
- Fish
- Vitamin D
- Multivitamin supplements

**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**

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

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


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 of 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

It is best not to drink alcohol
- 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
- 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

Cancer.org | 1-800-227-2345

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WHAT’S AHEAD IN CPS

- ~2 million yrs ago: Hunter-gatherers
- ~12,000 yrs ago: Agriculture & farming
- 1950s: Convenience foods
- 1980s: Genetic engineering
- 2010s: Plant-based meat products

EVOLUTION OF FOOD
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

Cancer Prevention Study-II

Blood (n ≈ 37,000)
Buccal cell (n ≈ 70,000)
Tumor tissue collection

Deaths through 2022
Enrollment
(survey, blood, waist measure)

n ≈ 303,000

Follow-up

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

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
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
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Disclosures

Olympus America (research support)

(NCCN Colorectal Cancer Screening Panel)
(US-MTSF on Colorectal Cancer)
I wish we had more time...

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

<table>
<thead>
<tr>
<th>Gender</th>
<th>site</th>
<th>Males</th>
<th>Females</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Prostate</td>
<td>217,730</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>Lung &amp; bronchus</td>
<td>116,750</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Colon &amp; rectum</td>
<td>72,090</td>
<td>9%</td>
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<tr>
<td></td>
<td>Urinary bladder</td>
<td>52,760</td>
<td>7%</td>
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<td></td>
<td>Melanoma of the skin</td>
<td>38,870</td>
<td>5%</td>
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<tr>
<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>35,380</td>
<td>4%</td>
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<tr>
<td></td>
<td>Kidney &amp; renal pelvis</td>
<td>35,370</td>
<td>4%</td>
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<tr>
<td></td>
<td>Oral cavity &amp; pharynx</td>
<td>25,420</td>
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<td></td>
<td>Leukemia</td>
<td>24,690</td>
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<td>Pancreas</td>
<td>21,370</td>
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<td></td>
<td><strong>All sites</strong></td>
<td><strong>789,620</strong></td>
<td><strong>100%</strong></td>
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<tr>
<td></td>
<td>Breast</td>
<td>207,090</td>
<td>26%</td>
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<tr>
<td></td>
<td>Lung &amp; bronchus</td>
<td>105,770</td>
<td>14%</td>
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<tr>
<td></td>
<td>Colon &amp; rectum</td>
<td>70,480</td>
<td>10%</td>
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<td></td>
<td>Uterine corpus</td>
<td>43,470</td>
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<td></td>
<td>Thyroid</td>
<td>33,930</td>
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<tr>
<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>30,160</td>
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<tr>
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<td>Melanoma of the skin</td>
<td>29,260</td>
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<tr>
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<td>Kidney &amp; renal pelvis</td>
<td>22,870</td>
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<tr>
<td></td>
<td>Ovary</td>
<td>21,880</td>
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<tr>
<td></td>
<td>Pancreas</td>
<td>21,770</td>
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<tr>
<td></td>
<td><strong>All sites</strong></td>
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### Estimated Deaths

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<th>Females</th>
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<td></td>
<td>Lung &amp; bronchus</td>
<td>86,220</td>
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<td>Prostate</td>
<td>32,050</td>
<td>11%</td>
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<tr>
<td></td>
<td>Colon &amp; rectum</td>
<td>26,580</td>
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<tr>
<td></td>
<td>Pancreas</td>
<td>10,770</td>
<td>6%</td>
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<tr>
<td></td>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,720</td>
<td>4%</td>
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<td></td>
<td>Leukemia</td>
<td>12,660</td>
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<tr>
<td></td>
<td>Esophagus</td>
<td>11,650</td>
<td>4%</td>
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<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>10,710</td>
<td>4%</td>
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<tr>
<td></td>
<td>Urinary bladder</td>
<td>10,410</td>
<td>3%</td>
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<tr>
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<td>Kidney &amp; renal pelvis</td>
<td>8,210</td>
<td>3%</td>
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<td><strong>All sites</strong></td>
<td><strong>299,200</strong></td>
<td><strong>100%</strong></td>
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<tr>
<td></td>
<td>Lung &amp; bronchus</td>
<td>71,030</td>
<td>26%</td>
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<tr>
<td></td>
<td>Breast</td>
<td>39,840</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Colon &amp; rectum</td>
<td>24,790</td>
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<td></td>
<td>Pancreas</td>
<td>18,030</td>
<td>7%</td>
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<tr>
<td></td>
<td>Ovary</td>
<td>13,890</td>
<td>6%</td>
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<tr>
<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>9,500</td>
<td>4%</td>
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<tr>
<td></td>
<td>Leukemia</td>
<td>9,180</td>
<td>3%</td>
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<tr>
<td></td>
<td>Uterine corpus</td>
<td>7,950</td>
<td>3%</td>
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<tr>
<td></td>
<td>Multiple myeloma</td>
<td>6,190</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Brain &amp; other nervous system</td>
<td>5,720</td>
<td>2%</td>
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<tr>
<td></td>
<td><strong>All sites</strong></td>
<td><strong>270,290</strong></td>
<td><strong>100%</strong></td>
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</table>
Opportunities for Intervention

- No Neoplasia
  - RR Surgery
  - Chemoprevention
  - Diet
  - Exercise
  - Vaccine

- Pre-Cancer
  - Polypectomy

- Local Cancer
  - Extended colectomy

- Regional/Distant Cancer
  - Immunotherapy
Opportunities for Intervention

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

No Neoplasia

Pre-Cancer
- Polypectomy

Local Cancer
- Extended colectomy

Regional/Distant Cancer
- Immunotherapy

Opportunities for Intervention

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

No Neoplasia → Pre-Cancer → Polypectomy → Local Cancer → Extended colectomy → Regional/Distant Cancer → Immunotherapy

Number Needed To Treat to Prevent 1 CRC = 24

Opportunities for Intervention

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

No Neoplasia

- Pre-Cancer: Polypectomy
- Local Cancer: Extended colectomy
- Regional/Distant Cancer: Immunotherapy

Non-CRC Lynch syndrome cancers per-protocol

Opportunities for Intervention

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

No Neoplasia

Pre-Cancer
Polypectomy

Local Cancer
Extended colectomy

Regional/Distant Cancer
Immunotherapy

Opportunities for Intervention

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

- Pre-Cancer
- Polypectomy
- Local Cancer
- Extended colectomy
- Regional/Distant Cancer

No Neoplasia

Standard of Care
- Colonoscopy
- Vaccine Administration

Research Blood Draw

ELIGIBILITY
- Lynch Syndrome Diagnosis
- Able to participate 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

Vilar-Sanchez et al. NCT05078866.
Bansal & Vilar-Sanchez et al. NCT05419011.
Opportunities for Intervention

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

No Neoplasia

Pre-Cancer
Polypectomy

Local Cancer
Extended colectomy

Regional/Distant Cancer
Immunotherapy

72% reduction in CRC Mortality

62% reduction in CRC Incidence

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

Opportunities for Intervention

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

No Neoplasia

Pre-Cancer
- Polypectomy

Local Cancer
- Extended colectomy

Regional/Distant Cancer
- Immunotherapy

Capturing Family Members: Cascade Testing
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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

Lynch Syndrome Diagnosis: Tumor Screening

**Abnormal Gene (MSH2)**

**Abnormal or missing MSH2 protein**

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

**Immunohistochemistry for MMR Protein Loss**

**PCR for Microsatellite Instability Markers**

**Normal Cells**

- Normal Microsatellites

**Tumor Cells**

- Microsatellite Instability

Normal tissue | Tumor tissue

MSH2+ | MSH2-
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

**Abnormal or missing MSH2 protein**

**Abnormal Gene (MSH2)**

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

---

**Immunohistochemistry for MMR Protein Loss**

**Normal Cells**

- Normal tissue
- MSH2+

**Microsatellite Instability**

**PCR for Microsatellite Instability Markers**

**Normal Microsatellites**

**Microsatellite Instability**

**Tumor Cells**

- Tumor tissue
- MSH2-
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.
No germline pathogenic variant: 84%

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

Since 2017: All CRC dx < 50 get offered MGPT

No germline pathogenic variant 84%

High-penetrance variant 10%
- MLH1, MSH2, MSH6, PMS2
- Biallelic MUTYH
- APC
- SMAD4
- BRCA1, BRCA2
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Moderate-penetrance variant 6%
- ATM
- PALB2
- Monoallelic MUTYH
- APC I1307K
- CHEK2

NCCN Genetic/Familial High-Risk Assessment: Colorectal 2017.
➢ Tumor-based screening missed 39% of patients with a hereditary syndrome

➢ 9 Lynch Syndrome patients missed
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

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

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

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIANT</th>
<th>ZYGOSITY</th>
<th>VARIANT CLASSIFICATION</th>
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<tbody>
<tr>
<td>BRIP1</td>
<td>c.3302C&gt;T (p.Pro1101Leu)</td>
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<td>Uncertain Significance</td>
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<td>c.2836C&gt;T (p.Arg946Cys)</td>
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</tr>
</tbody>
</table>

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
Thank You

nccrt.org  @NCCRTnews  #80inEveryCommunity