Concurrent Session B

Research Updates on Colorectal Cancer Risk

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
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
What role does the gut microbiome play?

**Gut microbiota functions**

- **Modulation of host physiology**
  - Digestion of food
  - Gut motility
  - Gut immune regulation
  - Protection of intestinal epithelial cell integrity
  - Body energy homeostasis

- **Metabolic function**
  - Neurotransmitters and other metabolites synthesis
  - Antimicrobial peptide secretion
  - Production of vitamins
  - Amino acid biosynthesis

- **Metabolism**
  - Dietary components
  - Branched-chain and aromatic amino acids
  - Drugs
  - Xenobiotics

- **Regulation of Gut-Brain axis**
  - Establish a bi-directional communication of gut-brain-microbiota axis
  - Interact with gut-based effector systems and visceral afferent pathways
  - Promote metabolic benefits via gut-brain neural circuits

What impacts the gut microbiome?
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

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
Fusobacterium in colorectal cancer


Fusobacterium in colorectal cancer

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
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

# Microbiome and treatment response: immunotherapy

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

<table>
<thead>
<tr>
<th>Publication</th>
<th>Cancer type</th>
<th>ATB window</th>
<th>Outcome</th>
<th>P-values</th>
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</thead>
<tbody>
<tr>
<td>Routy, Science 2018</td>
<td>NSCLC n=140, RCC n=67, UC n=32</td>
<td>2 months PRE or 1 month POST</td>
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<td>0.017</td>
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<tr>
<td>Rubio, JASLC 2018</td>
<td>NSCLC n=168</td>
<td>2 months PRE or 1 month POST</td>
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<tr>
<td>Kadarthiba, Anticancer Res 2017</td>
<td>NSCLC n=74</td>
<td>3 months PRE</td>
<td></td>
<td>0.026</td>
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<tr>
<td>Oulamine, JASLC 2018</td>
<td>NSCLC n=72</td>
<td>2 months PRE or 1 month POST</td>
<td></td>
<td>0.072</td>
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<tr>
<td>Labani, ASCO GI 2018</td>
<td>RCC n=14</td>
<td>2 months PRE or 1 month POST</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Guti, JASLC 2018</td>
<td>NSCLC n=157</td>
<td>2 months PRE or 1 month POST</td>
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<td>0.026</td>
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<tr>
<td>Derosa, Annals 2018</td>
<td>NSCLC n=349, RCC n=121</td>
<td>1 month PRE</td>
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<tr>
<td>Brief, Oncology Immunology 2018</td>
<td>Melanoma n=74, CTLA-4 with chemo-therapy, CTLA-4 alone, anti-PD-1</td>
<td>30 days PRE</td>
<td></td>
<td>0.03</td>
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<tr>
<td>Do, ASCO 2018</td>
<td>NSCLC n=109</td>
<td>1 month PRE or 1 month POST</td>
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<td>0.004</td>
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<tr>
<td>Huemer, Oncotarget 2018</td>
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<tr>
<td>Tinsley, ASCO 2018</td>
<td>Melanoma n=301, NSCLC n=38, RCC n=46</td>
<td>14 days PRE or 42 days POST</td>
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<td>0.04</td>
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<tr>
<td>Ahmed, Oncology Immunology 2018</td>
<td>Various cancers n=69</td>
<td>14 days PRE or 2 weeks POST</td>
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<td>0.012</td>
</tr>
</tbody>
</table>

NSCLC, non-small-cell lung cancer; RCC, renal cell cancer; UC, urothelial cancer; ATB, antitumor biologic; 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 IC use.
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

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

Probiotics affect microbiome

Torres Maravilla, et al. Role of gut microbiota and probiotics in colorectal cancer. Microorganisms. 2021
The Gut Microbiome & Colorectal Cancer

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. difficile 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
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 strategies

It's complicated and we still have a lot to learn!
Thank you!
Questions or Comments?
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
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>
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<tr>
<td>Participants</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>Volunteers</td>
<td>22,000</td>
<td>68,000</td>
<td>77,000</td>
<td>25,000</td>
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<tr>
<td>With blood (or DNA)</td>
<td>n/a</td>
<td>n/a</td>
<td>40,000 (70,000)</td>
<td>297,000</td>
</tr>
</tbody>
</table>

* Tumor tissue for selected cancer types collected


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

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 throughout 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 it 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
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- )
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

Population Science

- Principal Investigators
- Data Analysts
- Study Management
- Biospecimen
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
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Division of Gastroenterology & Hepatology
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University of Colorado Anschutz Medical 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

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
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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>
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<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th></th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>217,730</td>
<td>28%</td>
<td>Breast</td>
<td>207,090</td>
<td>26%</td>
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<td>Lung &amp; bronchus</td>
<td>116,750</td>
<td>15%</td>
<td>Lung &amp; bronchus</td>
<td>105,770</td>
<td>14%</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>72,090</td>
<td>9%</td>
<td>Colon &amp; rectum</td>
<td>70,480</td>
<td>10%</td>
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<td>Urinary bladder</td>
<td>52,760</td>
<td>7%</td>
<td>Uterine corpus</td>
<td>43,470</td>
<td>6%</td>
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<td>Melanoma of the skin</td>
<td>38,870</td>
<td>5%</td>
<td>Thyroid</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,380</td>
<td>4%</td>
<td>Non-Hodgkin lymphoma</td>
<td>30,150</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>35,370</td>
<td>4%</td>
<td>Melanoma of the skin</td>
<td>29,260</td>
<td>4%</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,420</td>
<td>3%</td>
<td>Kidney &amp; renal pelvis</td>
<td>22,870</td>
<td>3%</td>
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<tr>
<td>Leukemia</td>
<td>24,690</td>
<td>3%</td>
<td>Ovary</td>
<td>21,880</td>
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<tr>
<td>Pancreas</td>
<td>21,370</td>
<td>3%</td>
<td>Pancreas</td>
<td>21,770</td>
<td>3%</td>
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<tr>
<td>All sites</td>
<td>789,620</td>
<td>100%</td>
<td>All sites</td>
<td>739,940</td>
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### Estimated Deaths

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<tr>
<td>Lung &amp; bronchus</td>
<td>66,220</td>
<td>29%</td>
<td>Lung &amp; bronchus</td>
<td>71,090</td>
<td>26%</td>
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<tr>
<td>Prostate</td>
<td>32,050</td>
<td>11%</td>
<td>Breast</td>
<td>39,840</td>
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<td>Colon &amp; rectum</td>
<td>26,580</td>
<td>9%</td>
<td>Colon &amp; rectum</td>
<td>24,790</td>
<td>9%</td>
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<tr>
<td>Pancreas</td>
<td>10,770</td>
<td>6%</td>
<td>Pancreas</td>
<td>18,030</td>
<td>7%</td>
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<td>Liver &amp; intrahepatic bile duct</td>
<td>12,720</td>
<td>4%</td>
<td>Ovary</td>
<td>13,890</td>
<td>6%</td>
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<td>Leukemia</td>
<td>12,660</td>
<td>4%</td>
<td>Non-Hodgkin lymphoma</td>
<td>9,500</td>
<td>4%</td>
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<td>Esophagus</td>
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<td>Leukemia</td>
<td>9,180</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,710</td>
<td>4%</td>
<td>Uterine corpus</td>
<td>7,950</td>
<td>3%</td>
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<tr>
<td>Urinary bladder</td>
<td>10,410</td>
<td>3%</td>
<td>Multiple myeloma</td>
<td>6,190</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,210</td>
<td>3%</td>
<td>Brain &amp; other nervous system</td>
<td>5,720</td>
<td>2%</td>
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<td>All sites</td>
<td>259,200</td>
<td>100%</td>
<td>All sites</td>
<td>270,290</td>
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</table>
Opportunities for Intervention

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

- Polypectomy
- Extended colectomy
- 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

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Opportunities for Intervention

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Opportunities for Intervention

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

No Neoplasia

Pre-Cancer

Polypectomy

Local Cancer

Extended colectomy

Regional/ Distant Cancer

Immunotherapy

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

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

- RR Surgery
- Chemoprevention
- Diet
- Exercise
- Vaccine

62% reduction in CRC Incidence
72% reduction in CRC Mortality

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

No Neoplasia

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

- No Neoplasia

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

Immunohistochemistry for MMR Protein Loss

Abnormal Gene (MSH2) → Abnormal or missing MSH2 protein

Normal tissue | Tumor tissue
MSH2+ | MSH2-

Lack of MSH2 expression, negative IHC staining for MSH2 protein

PCR for Microsatellite Instability Markers

Normal Cells
- CG-
- CGCCGGCG

Normal Microsatellites
- CG-
- CGCCGGCG

Tumor Cells
- CG-
- CGCCGGCG
- CG-
- CGCG

Microsatellite Instability
- CG-
- CGCG
- CGCG
- CGCG
- CGCG
- CGCG

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

Lack of MSH2 expression, negative IHC staining for MSH2 protein

Immunohistochemistry for MMR Protein Loss

PCR for Microsatellite Instability Markers

Normal Cells

Tumor Cells

Normal Microsatellites

Microsatellite Instability

Abnormal Gene (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.
Moderate-penetrance variant 6%
- ATM
- PALB2
- Monoallelic MUTYH
- APC I1307K
- CHEK2

High-penetrance variant 10%
- MLH1, MSH2, MSH6, PMS2
- Biallelic MUTYH
- APC
- SMAD4
- BRCA1, BRCA2
- CDKN2A

No germline pathogenic variant 84%

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

- **No germline pathogenic variant** 84%

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
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