



THE SEVENTH ANNUAL EARLY-AGE ONSET COLORECTAL CANCER SUMMIT

VIRTUAL EVENT
MAY 14–16, 2021

*Saving Lives Through Applying
Knowledge*

PREPARED BY:

Surabhi Dangi-Garimella PhD,
Principal, SDG AdvoHealth, LLC

CONTRIBUTIONS BY:

Rachel Herrmann
Colon Cancer Prevention Intern,
Colon Cancer Foundation



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AGENDA	
FRIDAY, MAY 14	
1:00 PM - 3:00 PM ET	<p>THE INAUGURAL STATE OF EAO-CRC SYMPOSIUM – THE STRUGGLE FOR SOLUTIONS</p> <p>April Barry, LCSW, Evaluation Manager for the Pennsylvania Department of Health, Bureau of Health Promotion and Risk Reduction, Division of Cancer Prevention and Control Cindy R. Borassi, Summit Co-host, President, Colon Cancer Foundation Whitney Jones, MD, Colon Cancer Prevention Project Erin Peterson, Communications Director, Colon Cancer Coalition</p> <p><i>Invitation-only symposium, co-hosted by the Colon Cancer Foundation, the Colon Cancer Coalition and the Colon Cancer Prevention Project</i></p>
3:15 PM - 4:45 PM ET	<p>SESSION I: Improving Earliest Possible Diagnosis and Treatment through Timely Recognition of the Symptoms and Signs of Sporadic Young Adult CRC</p> <p>Moderator: Whitney Jones, MD, Colon Cancer Prevention Project</p> <ul style="list-style-type: none"> • Introduction to The Topic Whitney Jones, MD • How will EAO-CRC Incidence and Mortality Rank in 2040? Lola Rahib, PhD, Director of Scientific & Clinical Affairs, Cancer Commons • How to Involve Primary Care in Improving Earliest Stage Diagnosis Len Lichtenfeld, MD, MACP, Former Deputy Chief Medical Officer, American Cancer Society; Board of Trustees, CancerCare • CRC Patient Story Lisette Caesar, EdD, Founding Principal, Mosaic Preparatory Academy • Introduction of the Echo Chamber Challenge and Clinical Alert Erin Peterson, Director of Mission & Partnerships, Colon Cancer Coalition • Q&A
6:00 PM - 7:00 PM ET	Virtual BYOB Cocktail Event and Networking
7:00 PM - 8:00 PM ET	Fireside Chat

AGENDA	
SATURDAY, MAY 15	
10:00 AM – 10:10 AM ET	OPENING REMARKS Susan Wysoki , Interim Executive Director, Paltown Development Foundation Shannon Lee-Sin , Stage IIIc Colon Cancer Survivor
10:10 AM – 10:20 AM ET	Welcome and Housekeeping Zsofia Stadler, MD , Summit Co-Chair; Clinical Director, Clinical Genetics Service, Memorial Sloan Kettering Cancer Center Cindy R. Borassi , Summit Co-Host, President, Colon Cancer Foundation
10:20 AM - 10:30 AM ET	Framing the Conversation Cindy R. Borassi , Summit Co-Host, President, Colon Cancer Foundation
10:30 AM - 11:00 AM ET	KEYNOTE: How Did This Happen? Investigating the Causes of Early-Onset Colorectal Cancers Stephen B. Gruber, MD, PhD, MPH , Vice President, City of Hope National Medical Center
11:00 AM - 12:15 PM ET	SESSION II: The Dimensions of the EAO-CRC Problem: Do We Have Accurate, Regular, Up to Date Measurement of Key Metrics Describing the Early Age Onset Colorectal Cancer Public Health Crisis Moderator: Susan Peterson, PhD, MPH <ul style="list-style-type: none"> • Update on Rising Early-onset CRC: Impact of Recent Trends on Racial Disparities Rebecca Siegel, MPH, Scientific Director, Surveillance Research, American Cancer Society • COVID's Impact on Cancer Screening – One Year Later Len Lichtenfeld, MD, MACP, Former Deputy Chief Medical Officer, American Cancer Society; Board of Trustees, CancerCare • Under 19 EAO-CRC Incidence and Mortality – How Do We Care for Our Youngest Patients? Susan Wysoki, Interim Executive Director, Paltown Development Foundation • COVID-19 Policy Update – One Year Later Phylcia L. Woods, JD, MSW, Executive Director, Cancer Policy Institute, Cancer Support Community • Q&A

AGENDA	
SATURDAY, MAY 15	
12:15 PM - 1:00 PM ET	LIVE LUNCH WITH AN EXPERT OPTION
<p>1. Hereditary Cancer Robin Dubin, MBA, Co-founder/Executive Director, AliveAndKickn Bryson Katona, MD, PhD, Director, Gastrointestinal Cancer Genetics Program and Assistant Professor of Medicine at the Hospital of the University of Pennsylvania Zsofia Stadler, MD, Clinical Director, Clinical Genetics Service, Memorial Sloan Kettering Cancer Center</p>	
<p>2. EAO-CRC Patient Advocacy Kim Newcomer, Senior Manager of Medical Advocacy & Community Engagement, Colorectal Cancer Alliance Erin Peterson, Communications Director, Colon Cancer Coalition Terry Wilcox, Executive Director, Patients Rising</p>	
<p>3. Medical Oncology – What the Future Holds for Therapies Andrea Cercek, MD, Co-Director Center for Young Onset Colorectal Cancer, Section Head Colorectal Cancer, Associate Attending Memorial Sloan Kettering Cancer Center Marios Giannakis, MD, PhD, Gastrointestinal Cancer Center, Dana-Farber Cancer Institute, Assistant Professor of Medicine, Harvard Medical School</p>	
<p>4. Surgical Advances in the Management of Colorectal Cancer Christina E. Bailey, MD, MSCI, Program Director, General Surgery Residency, Assistant Professor of Surgery, Surgical Oncology and Endocrine Surgery, Vanderbilt University School of Medicine Jose’ Perea, MD, PhD, Surgery Department Fundación Jiménez Díaz University Hospital and Research Institute, Madrid, Spain</p>	
<p>5. Epidemiology of EAO-CRC: What the BLEEP Is Going on? Rebecca Siegel, MPH, Scientific Director, Surveillance Research, American Cancer Society Robert A. Smith, PhD, Senior Vice President, Cancer Screening, American Cancer Society; Adjunct Professor of Epidemiology, Rollins School of Public Health, Emory University School of Medicine</p>	
<p>6. Novel Approaches to MMR and MSS Colorectal Cancer Cathy Eng, MD, FACP, Vanderbilt-Ingram Cancer Center, David H. Johnson, Chair in Surgical and Medical Oncology Vice-Chair, SWOG GI Committee, Institutional PI, SWOG, Professor of Medicine, Hematology and Oncology, Co-Director, GI Oncology, Co-Leader, Gastrointestinal Cancer Research Program Christopher Lieu, MD, Co-Director of GI Medical Oncology, UCHealth Cancer Care – Anschutz Medical Campus – University of Colorado Cancer Center</p>	
<p>7. Psychology of Families Dealing With Cancer – Psychosocial Support Through Treatment Hadley Maya, MSW, LCSW, Center for Young Onset Colorectal Cancer Clinical Social Worker, Memorial Sloan Kettering Cancer Center Susan Peterson, PhD, MPH, Professor of Behavioral Science, Department of Behavioral Science, Division of Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center</p>	

AGENDA	
SATURDAY, MAY 15	
1:15 PM – 2:30 PM ET	NETWORKING / BREAK / OPTIONAL VIEWING
1:15 PM – 2:30 PM ET	<p>SESSION III: Risk Assessment / Family History Ascertainment in the U.S. What Steps are Needed to Improve the Well Documented Less Than Optimal Status of this Situation?</p> <p>What is Our Best Information on the Documentation of Cancer Family History in Primary Care?</p> <p>What are the Key Elements Required for Success?</p> <p>Moderator: Zsofia Stadler, MD</p>
	<p>Screening Guidelines for CRC Screening: What are the Guidelines and How are we Actually Doing?</p> <ul style="list-style-type: none"> • CRC Population Screening and Adherence to Recommendations David Greenwald, MD, Director of Clinical Gastroenterology and Endoscopy, The Mount Sinai Hospital • Surveillance In High-risk Patients (Advanced Adenomas, Genetic Susceptibility) Bryson Katona, MD, PhD, Director, Gastrointestinal Cancer Genetics Program; Assistant Professor of Medicine at The Hospital of The University of Pennsylvania
	<p>Increasing Access to Genetic Testing: What do We Need to do to Improve the Situation?</p> <ul style="list-style-type: none"> • How to Increase Access to Genetic Testing for Lynch Syndrome Robin Dubin, MBA, Co-founder/Executive Director, AliveAndKickn • Facilitative Genetic Testing Melissa Frey, MD, Assistant Professor of Obstetrics and Gynecology, Weill Cornell Medical College • Action at the State Level: The Role of HCRA, Call to Action for EHRs and Genetic Testing Companies Whitney Jones, MD, Colon Cancer Prevention Project

AGENDA	
SUNDAY, MAY 16	
10:20 AM ET	<p>WELCOME Jordan J. Karlitz, MD, Chief Medical Officer, Director of Clinical Operations at Gastro Girl and GI On Demand Virtual Care and Telehealth Platform</p>
10:30 AM - 12:30 PM ET	<p>SESSION IV: How to Provide Timely, Effective, Quality of Life & Fertility Preserving Treatment: What Are Key Elements of Coordinated Care for Early Onset Colorectal Cancer</p> <p>Moderator: Andrea Cercek, MD, Co-Director Center for Young Onset Colorectal Cancer, Section Head Colorectal Cancer, Associate Attending Memorial Sloan Kettering Cancer Center</p> <p>Case History Presented by: Yi-Qian Nancy You, MD, MHSc, FACS, Department of Surgical Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center</p> <ul style="list-style-type: none"> • Patient Perspective Manju George, MVSc, PhD, Scientific Director, Paltown Development Foundation • Nurse Navigation Amy Hayes, BSN, RN, OCN, Nurse Navigator, Vanderbilt-Ingram Cancer Center • Genetics Zsofia Stadler, MD, Associate Professor, Clinical Director, Clinical Genetics Service, Memorial Sloan Kettering Cancer Center • Medical Oncology and New Therapeutics Cathy Eng, MD, FACP, David H. Johnson Chair in Surgical and Medical Oncology; Co-Leader, Gastrointestinal Cancer Research Program; Professor of Medicine (Hematology and Oncology); Co-Director, GI Oncology; Vice-Chair, SWOG GI Committee; Director, VICC Young Adult Cancers Initiative, Vanderbilt-Ingram Cancer Center • Radiation Oncology Harvey Mamon, MD, PhD, Associate Professor, Radiation Oncology, Harvard Medical School, Director of GI Radiation Oncology, Brigham and Women’s Hospital, Chief, Division of Gastrointestinal Radiation Oncology • Surgery Kellie L. Mathis, MD, Mayo Clinic • Financial Burden/Toxicity Hadley Maya, MSW, LCSW, Center for Young Onset Colorectal Cancer, Memorial Sloan Kettering Cancer Center • Psychosocial Needs Krista Nelson, LCSW OSW-C BCD FAOS, President of the Association of Community Cancer Centers • Pediatrics Michael Roth, MD, Associate Professor of Pediatrics, The University of Texas MD Anderson Cancer Center; Chair, AYA Oncology Discipline Committee, Children’s Oncology Group • Fertility Preservation Terri L. Woodard, MD, Associate Professor Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center • Palliative Care Janet L. Abrahm, MD, Former Chief, Division of Adult Palliative Care, Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute and Brigham and Women’s Hospital; Professor of Medicine, Harvard Medical School

AGENDA	
SUNDAY, MAY 16	
	BREAKOUT SESSIONS
1:00 PM - 2:00 PM ET	<p>1. Increasing Access to Genetic Testing: What do We Need to do to Improve the Situation?</p> <ul style="list-style-type: none"> • Introduction Candace Henley, Chief Surviving Officer, The Blue Hat Foundation • Overview of Findings: Disparities in Early-Onset Colorectal Cancer Elena M. Stoffel, MD, MPH, Director of the University of Michigan Cancer Genetics Clinic; Assistant Professor of Internal Medicine, University of Michigan Sonia Kupfer, MD, Associate Professor of Medicine, Director, Gastrointestinal Cancer Risk and Prevention Clinic, Co-Director, Comprehensive Cancer Risk and Prevention Clinic, CRC Patient and CRC Community Organizer/Advocate, University of Chicago • Patient/Caregiver Perspective Angela Caraway, MMP, President, TCMG Inc; Patient Advocate Jasmin Mejia, Member Services and Events Manager, Urban Collaborative at Arizona State University; Chair, Arizona Allies; Volunteer, Arizona Allies – Colorectal Cancer Alliance
	<p>2. Integrating Music Therapy in Cancer</p> <ul style="list-style-type: none"> • Introduction Cindy R. Borassi, Summit Co-host, President, The Colon Cancer Foundation • Presentation Joanne V. Loewy DA, LCAT, MT-BC, The Louis Armstrong Center for Music and Medicine, Icahn School of Medicine, Mount Sinai Hospital Manjeet Chadha, MD, MHA, FACR, FASTR, Department of Radiation Oncology, Icahn School of Medicine, Mount Sinai Hospital Andrew Rossetti, MMT, LCAT, MT-BC, The Louis Armstrong Center for Music and Medicine, Department of Radiation Oncology, Mount Sinai Hospital
2:25 PM - 3:30 PM ET	<p>SESSION V: What Still Needs to be Done? Challenge: Where Are We Headed and How Do We Solve This?</p> <p>Moderator: Stephen B. Gruber, MD, PhD, MPH</p> <ul style="list-style-type: none"> • Mining Electronic Health Record Data and Integration With Large-Scale Genomic Analyses: Is This Where We are Going Francisco Sanchez-Vega, PhD, Assistant Attending Computational Oncologist, Colorectal Cancer Service of the Department of Surgery, Memorial Sloan Kettering Cancer Center

AGENDA	
SUNDAY, MAY 16	CONT...
<p>2:25 PM - 3:30 PM ET</p>	<ul style="list-style-type: none"> • The Colorectal Cancer Pooling Project: What Can We Learn From This International Resource? Peter Campbell, PhD, Scientific Director, Epidemiology Research, American Cancer Society • How Are Microbiome Interactions Contributing to the rise of EAO-CRC? Cynthia Sears, MD, Professor, Johns Hopkins University School of Medicine • How Are Microbiome Interactions Contributing to the rise of EAO-CRC? Cynthia Sears, MD, Professor, Johns Hopkins University School of Medicine • Earlier Life Exposures: Maternal Obesity and Gestational Growth Caitlin Murphy, PhD, Assistant Professor, Department of Population and Data Sciences. UT Southwestern • Genomics – The European Perspective José Perea MD, PhD, Surgery Department, Fundación Jiménez Díaz University Hospital and Research Institute, Madrid, Spain • “<u>DEMETRA</u>”: <u>Diet</u> <u>obE</u>sity <u>sM</u>oking <u>E</u>pigenetics <u>geneT</u>ics <u>biomaR</u>kers <u>physical</u> <u>Act</u>ivity Giulia Martina Cavestro, MD, PhD, Director of the Postgraduate School of Gastroenterology, Gastroenterology and Gastrointestinal Endoscopy Unit, Vita-Salute San Raffaele University, San Raffaele Scientific Institute, Milan





By the year 2040
colorectal cancer is projected to be the
second leading cancer
in the 20-49 age group
and is expected to lead the ranking
for cancer-related deaths in the
20-49 age group.

OVERVIEW

The Seventh Annual Early-Age Onset Colorectal Cancer (EAO-CRC) Summit was successfully held from May 14-16, 2021. A virtual event due to the COVID-19 pandemic, the conversations at the Summit included barriers to early diagnosis, identifying the right metrics to ensure on-time screening, impact of the COVID-19 pandemic on screening rates, the vital role of genetic testing in risk assessment, and investigating the causes of EAO-CRC. A highlight this year was a case study that was presented and discussed by a diverse panel—an integrated care team—that included oncologists, surgeons, social workers, a nurse navigator, a fertility expert, and a survivor who is also a patient advocate.

While progress has been made in raising awareness around the importance of on-time screening and conversations around family health history, there remains a significant gap in our understanding of the causes of EAO-CRC. This, while knowing that the time to act is now!

Consider this: by the year 2040, colorectal cancer is projected to be the second leading cancer in the 20-49 age group and is expected to lead the ranking for cancer-related deaths in the 20-49 age group.¹



The estimated number of people under 50 years projected to be diagnosed with colon or rectal cancer in the U.S. in 2020 (12.5% of the overall incidence).*



The estimated number of people under 50 years projected to die from colon or rectal cancer in the U.S. in 2020. (6.8% of the overall mortality from colorectal cancer)*

*American Cancer Society



DAY 1

SESSION I

**Improving Earliest Possible
Diagnosis and Treatment
Through Timely Recognition
of the Symptoms and Signs
of Sporadic Young Adult CRC**

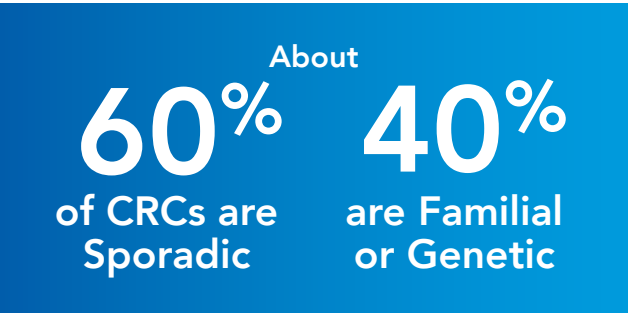
The virtual Summit was kicked off with this session, which has been identified by the colorectal cancer (CRC) research field as GAP1.

Whitney Jones, MD, Founder, Colon Cancer Prevention Project, chaired the session, along with Erin Peterson, Director of Mission and Partnerships, Colon Cancer Coalition.

Dr. Jones introduced the topic and provided perspective on the need to address the timeline of delay—often measured in months—between symptom onset and CRC diagnosis in the young adult population. The delay results from a combination of vague and infrequent symptoms, delay in making an appointment, delay in being referred for a colonoscopy. “Our goal is for those over and under 50 years to be aware of their symptoms, know their body, and know what their symptoms are to make timely appointments,” he said.

About 60% of CRCs are sporadic and 40% are familial or genetic—the symptoms have been described in detail and are well established. What remains unknown is the overarching etiology, he said, adding that we do not understand the definitive cause of early-age onset CRC (EAO-CRC) nor do we understand definitive SNP (single nucleotide polymorphism) profiles to know what our risk scores are. Additionally,

a recently published study from the Mayo Clinic in *JAMA Oncology*² has raised questions about the frequency of inherited cancers: “Is it 3-10% or 13-15%?” Dr. Jones said. Germline sequencing in nearly 3,000 patients found the pathogenic mutation rate was 13.3%—1 in 8 patients had a genetic predisposition to cancer. Interestingly, early age of cancer diagnosis (<50 years) was a predictor of pathogenic germline variants. The study also identified a 47% rate of variants of uncertain significance, which was much higher in minority populations (67%), likely because of the limited access to familial genetic information.



About
60% of CRCs are Sporadic
40% are Familial or Genetic

Shifting gears, Dr. Jones then shared his own data where he has rank-ordered U.S. states based on their CRC and EAO-CRC burden, both incidence and mortality, and found that the top 8 states for highest incidence of CRC were also the top 7 for EAO-CRC. “The hypothesis here is that underage 50 colon cancer is a significant driver of the overall rate of colorectal cancer in states with high rates of CRC burden,” he added. These states include Kentucky, Mississippi, West Virginia, Arkansas, Alabama, Louisiana, and Alaska, among others.

Encouraging the need for a complementary messaging approach to raise awareness about the need to screen for CRC, he emphasized that messaging tactics need to target the younger population and personalize the message so it can reach diverse populations, especially minorities. Dr. Jones believes that the increased risk of CRC among women is primarily because women are more diligent and proactive about preventive health compared to men, and their OB-GYN ends up being their primary care provider! Men, on the other hand, especially in the 20-50 age group, are not used to preventive health. “Men are more reactive and less proactive,” he said, which leads to gender-based disparity.

Messaging lead time and frequency are key to changing behavior, according to Dr. Jones who believes that 45 years should be the finish line for communicating the message on CRC screening and not the beginning. The “Early Messaging Package” should include identifying and evaluating symptoms, documenting family history and testing, and conversations around lifestyle modification, and it should be delivered starting in the early 20s. This would need a significant reallocation of resources from messaging among those 45 and older to messaging among those 21-45 years. The messaging does not need to wait till the research in the EAO-CRC space is completely figured out, he said, rather awareness and messaging in the younger population should be the goal over the next ten years simultaneous with understanding disease etiology.

Projections of Colorectal Cancer Incidences and Deaths

To present the findings of their recently published paper in *JAMA Network Open*¹ was Lola Rahib, PhD, Director of Scientific & Clinical Affairs, Cancer Commons.

She started off by sharing projections from the American Cancer Society that estimated 149,500 diagnoses and 52,980 deaths for CRC in the U.S. in 2021, and that CRC will be the third leading cause of cancer incidence and death in the U.S. in both genders. While there has been an overall decrease in CRC incidence and mortality over the past few decades, it could be attributed to the steady increase in regular colonoscopies.³ “In the last few decades, we have seen significant decreases in both [CRC] incidence and death among people who are 65 years and older and also among people who are 50-64 years old,” Dr. Rahib pointed out, adding that the same paper by Siegel et al found that CRC incidence and mortality among those under 50 years has been growing since 2000.

Sharing findings from her team’s research that was published in *JAMA Network Open*, Dr. Rahib said that the goal of their projections of cancer incidence and death by the year 2040 can guide future research funding allocations, health care planning, and health policy efforts. The study combined demographic cancer incidence rates for the top 10 cancers from the Surveillance, Epidemiology, and End Results (SEER) program, the US Census Bureau population growth projections from 2016, and average annual changes in percentage of deaths and incidence rates.

While in 2016, the most common cancers in the U.S. across all age groups were breast, lung, CRC, and prostate cancer, by 2040, breast, melanoma, lung, and CRC will be the most common cancers. While lung cancer will remain the leading cause of cancer-related deaths overall by 2040, compared to 2016, pancreatic and liver cancer will overtake

CRC and become the second and third leading causes of cancer-related deaths.

The authors also conducted a subgroup analysis to estimate cancer incidences and deaths in adults in the 20-49 age group. “By 2040, the top four estimated cancers for both male and female combined were breast, CRC, thyroid, and kidney and renal. The top four estimated deaths in this age group were CRC, lung cancer, and brain and other central nervous system cancers,” Dr. Rahib said. “CRC is projected to surpass breast cancer by around 2030 to be the leading cause of cancer-related deaths in this age group,” she added. Dr. Rahib explained that breast cancer in the 20-49 age group is projected to see a significant drop in mortality over the next two decades, while CRC will see a slight increase. Highlighting the projected trajectory of CRC incidence and deaths, Dr. Rahib showed that while CRC incidence in the 20-49 age group is expected to nearly double between 2025 (21,930) and 2040 (40,860), mortality is projected to remain quite steady during that same period and increase just slightly from 3,620 to 3,690. By 2040, CRC will surpass thyroid cancer to be the second leading cancer in the 20-49 age group after breast cancer.

“Hopefully with the new screening guidelines, we will see less diagnoses and these numbers will be different,” Dr. Rahib said. Summing up their findings, Dr. Rahib said that her hope is to be able to see a change in the projections for EAO-CRC by:

- **Raising disease awareness**
- **Increasing research funding for EAO-CRC to understand the causes for the recent rise in EAO-CRC**
- **Developing screening programs**
- **Increasing advocacy**

The Impact of COVID-19 on Cancer Screening Rates

Leonard Lichtenfeld, MD, MACP, Former Deputy Chief Medical Officer, American Cancer Society, who is a medical oncologist by training, returned to the 2021 EAO-CRC Summit to bring to light the massive impact of the COVID-9 pandemic on cancer screening overall, including CRC screening rates. A paper published in *JAMA Oncology* found that following a nearly 80% drop in CRC screening rates in April 2020 compared with the same month in 2019, screening rates saw a recovery but remained 13.1% lower in July 2020 compared to 2019—the absolute CRC screening deficit from January to July 2020 was about 3.8 million individuals compared to the same period in 2019.⁴

Dr. Lichtenfeld pointed out that in the early months of 2020, a lot of unknowns related to the virus led to decisions in the health care field that seemed right at that moment and led to the massive drops in cancer screening rates. One of those decisions was a recommendation by the American Cancer Society to halt all cancer screenings for those with an average risk of developing that cancer. In hindsight, it is obvious that the thought that the viral infections would be overcome in a few weeks or months only reflects our limited understanding of the virus and its management at that time.

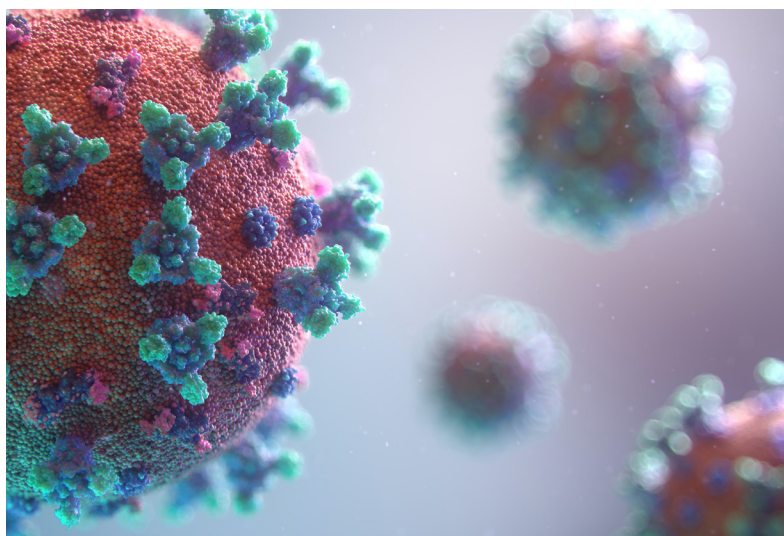
“We found ourselves in a very prolonged situation, where people were fearful or going to medical facilities even for acute conditions,” Dr. Lichtenfeld said, which, as data now suggests, has led to dramatic reductions in cancer screenings. He pointed out that while anecdotal evidence suggests that screening rates have nearly come back to normal, its early to draw definitive conclusions.

“We are now in a different year with respect to COVID-19,” Dr. Lichtenfeld continued, in that we know a lot more about the behavior of the SARS-CoV-2 virus, we have several vaccine options and patients are being vaccinated, healthcare systems have opened up and have established appropriate safety protocols. Consequently, while incidence and mortality related to the pandemic has seen a dramatic decline, “we do have to deal with the impact of this pandemic on cancer screening and early diagnosis,” he added. And as we know,

particularly with CRC, early diagnosis, both age and stage, has significant bearing on patient outcomes.

Dr. Lichtenfeld pointed out that other life changes such as job loss due to the pandemic and subsequent loss of insurance coverage would also have had an impact on screening rates, not to mention their mental health status. Infrastructure changes within the health care system itself, such as primary care practices closing down or being bought by a health system or hospital, also had an impact. The rampant use of telehealth to safely deliver remote care worked for some, but not for everyone and would also have had a bearing on screening rates. “The primary care pattern has changed, and we will have to get people back into that pattern of care,” he added, while being mindful of the fact that care is now backlogged. The *JAMA Oncology* study estimates that close to 10 million Americans are behind on their regular screening for breast cancer, CRC, and prostate cancer. “From a public health perspective, increasing the use of alternatives to colonoscopy for colorectal cancer screening may help mitigate this screening deficit,” the authors of the paper wrote in their concluding remarks.

The pandemic again underscored the social inequality in access to health care, with underserved and low-income communities being disproportionately affected by the pandemic. Dr. Lichtenfeld indicated the need to apply these learnings to improve access and health equity as society opens up and returns to normal. “We should proactively reach out to those we know need to be screened, especially those we know are at a higher risk for not coming in for screening,” he said.



CRC Patient Story

Lisette Caesar, EdD, Founding Principal, Mosaic Preparatory Academy, and a stage 2 CRC survivor, shared the story of her diagnosis at the age of 49 years. She said she initially “thought colon cancer only happened to people in their 60s,” which is a common misconception among the general population. Ms. Caesar stressed the importance of seeking a second opinion and being your own advocate after she herself was misdiagnosed with diverticulitis and told she would eventually feel better. After four months of taking antibiotics and having her condition deteriorate, she decided to consult a different physician, who ended up diagnosing her with colon cancer. This delayed diagnosis necessitated the use of chemotherapy and led to side effects such as “neuropathy in [her] fingers and [her] right leg” that she continues to live with.

Ms. Caesar’s main messages were that “colon cancer is not an older person’s disease; it is a person’s disease” and “don’t be afraid to get a second opinion.” It is up to the patient to listen to their body and speak up when they are not feeling well and to advocate for themselves or reach out for second opinions if they are not satisfied with their care. She ended her presentation by saying “it’s your body; it’s your life”, suggesting that colon cancer patients should be proactive in their care and that adults should not hesitate to get screened.

The Colorectal Cancer Echo Chamber: Breaking the Barrier or Opening Up the CRC Echo Chamber

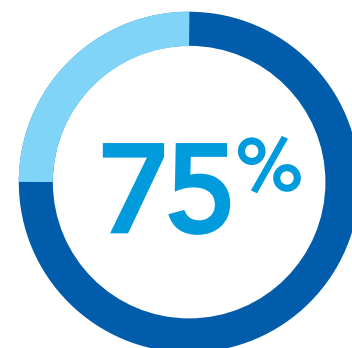
Erin Peterson, Director of Mission and Partnerships at the Colon Cancer Coalition, joined the session to speak about *The Challenge of the Echo Chamber*. She started off by identifying the constituents of the echo chamber as patients, researchers, engaged health care providers (HCPs), and advocacy groups, all of whom come together via conferences and webinars and continue conversations through social media channels and by participating at various events. “But we keep talking to ourselves and amongst ourselves about the same problem. We aren’t finding ways to reach the two important groups of people that we really need to have an impact on to solve this problem,” Ms. Peterson said, referring to the concerning rise in EAO-CRC.

The persistent issue at hand is raising awareness among the general public—the average-risk population—about the situation at hand so that we are able to make an impact. This would include the more vulnerable populations, including:

- Those with an unknown family history
- Those who are uninsured or underinsured
- Those living in rural areas
- 45–49-year-olds (this age groups makes up 75% of EAO-CRC patients)

Equally important to the process of raising awareness is reaching out to the broader health care community who man the frontlines and need to be educated about the signs and symptoms of EAO-CRC:

- Nurses
- OB/Gyns
- Primary Care
- Emergency Departments
- Urgent Cares
- Physician Assistants
- Genetic Counselors
- Pharmacists



**45–49-year-olds
makes up 75% of
EAO-CRC patients**

Breaking out of the echo chamber to be able to reach the uninformed and unengaged members of the general public as well as the health care field is the challenge in the EAO-CRC space. “How do we take the discussions from this meeting and others and share it with the general public?” Ms. Peterson said, particularly the average-risk population with an unknown family history who may see a sporadic case as well as those experiencing some of the symptoms of CRC.

Some of the ideas she shared were:

- Make the symptoms easier to talk about and less stigmatized
- Make the conversations less scary and ensure the message clarifies that the symptoms are manageable
- Reach out to the 45-49 years age group about the various modalities of CRC screening

Stool-based screening may be a convenient option to be able to reach the 22 million people in this age group, rather than a colonoscopy

- Develop out-of-the-box public health awareness campaigns to reach the younger target audience
- Engage doctors via meetings like the EAO-CRC Summit and urge them to speak with their colleagues at their clinic or health care system about the rise in EAO-CRC

Ms. Peterson highlighted key questions that are vital to seeing progress in the EAO-CRC space:

1. Are conversations inclusive of all affected communities?
2. Where can we intervene and educate young adults?
3. How can we reach unengaged HCPs?
4. How can engaged HCPs reach 45-49-year-olds for screening?
5. How can HCPs reach younger patients about family history and on-time screening?
6. How do we discuss symptom awareness and on-time screening with those at average risk?



DAY 2

OPENING REMARKS

The opening remarks on the second day of the EAO-CRC Summit were led by Susan Wysoki, Interim Executive Director of the Paltown Development Foundation. With reference to her own daughter passing from CRC, Ms. Wysoki drew alarm about how CRC is becoming a pediatric cancer. Citing the *JAMA Network Open* article¹ that projects CRC will be the number one cause of cancer-related mortality in the 20-49 age group, Ms. Wysoki said, “If two out of three patients diagnosed under 50 will have late-stage disease, we are seeing that late-stage diagnosis in three out of three under-20 year-olds.”

Challenging the researchers and treating physicians to think beyond the known risk factors—alcohol, tobacco, obesity, sedentary lifestyle—she pointed out that these definitely are not the drivers of CRC among the 10 and 11-year-olds being diagnosed. One significant risk factor, however, are aggregate environmental exposures that can lead to an accumulation of harmful chemicals in the body. “We know there are distinct molecular and genomic differences in EAO-CRC, which are even more pronounced across different races,” Ms. Wysoki said, and clinicians should pay attention to the symptoms that a patient presents with and not dismiss them based on an age bias.

EAO-CRC Survivor Story: Misdiagnosis, Lack of Diagnosis, and Adverse Outcomes

Shannon Lee-Sin bravely shared her harrowing experience as a Stage IIIc EAO-CRC survivor.

Her symptoms began in high school when she woke up every morning with abdominal pain. Her pediatrician diagnosed her as having an ulcer. When she learned in her biology class that blood in the stool could be a sign of cancer, she brushed it off thinking she was too young to have a disease that only inflicts those 50 years and older. Her symptoms of abdominal pain and diarrhea persisted through college, but she was diagnosed with gastroenteritis. A severe incidence of bloody stools took her back to the clinic, to be diagnosed as having hemorrhoids just based on her symptoms, without a physical exam.

Ms. Lee-Sin continued to experience periodic symptoms and consulted nearly 20 different physicians—pediatrician, gynecologist, reproductive specialist, emergency room (ER) physicians, and a general practitioner. but was never given a CT scan or referred to a gastroenterologist. “Without fail, all of them misdiagnosed me without proper exams or scans,” she asserted.

Repeated ER visits led to the providers thinking the symptoms that Ms. Lee-Sin was experiencing were in her head. “I began to think so, too,” she added.

After another severe incidence of blood loss resulting in severe anemia and a subsequent misdiagnosis of endometriosis and polycystic ovarian syndrome, she was determined to get to the root cause of her symptoms but couldn’t see a doctor because she was uninsured and unqualified for Medicaid. Two consecutive ER visits finally resulted in a CT scan that showed a big cyst in her abdomen. “This was 2011—more than 10 years after I first started experiencing symptoms as a teenager and went to my pediatrician.” A subsequent 10 hour-long surgery led to Ms. Lee-Sin being diagnosed with stage III c colon cancer and had an ostomy.

She went through chemotherapy, and after a year and a half, decided to get an ostomy-reversal out of fear of not being accepted or finding love. In addition to physical and emotional exhaustion from her symptoms, eventual diagnosis, and treatment, she also suffers from financial toxicity. However, Ms. Lee-Sin overcame all the challenges to have a successful career in architecture in addition to being a strong patient advocate.

“I am no longer ashamed of my disease and the stigma it carries. I am no longer scared of sharing my experiences because it can help others. Self-advocacy has saved my life and it continues to keep me alive,” she said. “I will be a 10-year survivor in October at age 39, and I am still below the recommended screening age for CRC,” she concluded.

“

*I am no longer ashamed of my disease and the stigma it carries.
I am no longer scared of sharing my experiences
because it can help others. Self-advocacy has saved
my life and it continues to keep me alive.*

Shannon Lee-Sin, Stage IIIc EAO-CRC Survivor

KEYNOTE ADDRESS

How Did This Happen? Investigating the Causes of Early-Onset Colorectal Cancer

The Keynote address at the 7th Annual EAO-CRC symposium was delivered by Stephen B. Gruber, MD, PhD, MPH, Vice President, City of Hope National Medical Center. During his talk, Dr. Gruber explored the current trends, changes in incidence of EAO-CRC, and evaluated the factors that may contribute to the rising trend of EAO-CRC.

Using the EAO-CRC trends in LA county between 1988-2011 as a reference point, he said that while the risk of CRC in young adults increases with age, there was an uptick in the incidence of CRC among the younger population—both males and females—during that time period being studied. “What we are seeing is an increase in colon cancer over time. In both males and females, the rates had increased quite substantially,” he said. While risk is very low under the age of 15 years, it is higher with increasing age, and it has been rising over the period between the 1980s and 2020s.

“We also know that age-adjusted CRC incidence differs based on race and ethnicity,” Dr. Gruber said. Young-adult data from LA county for the period between 1988-2011 showed that while the rates differ across ethnicities—with the highest incidence seen among Vietnamese populations, followed by black, Korean, and non-Hispanic whites—incidence rates among males are generally higher than among females. “This is also true globally with a slightly higher incidence among males,” he said, adding that there is a disproportionate burden across ethnicities.

Dr. Gruber pointed out that while the overall national rate of CRC incidence (for all ages) has been declining for both males and females, this decline is not shared by young adults. National data based on SEER 9 registries show that the incidence rates for EAO-CRC have in fact been rising since 1995 among those under 50 years for both genders.

Going back to data from LA county (1988-2014), Dr. Gruber showed that only a third of CRC diagnosed in young adults in the 15-39 age group was at a localized stage. Based on age, their data showed that survival for the youngest age group was always lower:

- 1-year survival: 77.6% (15-24 years), 85.6% (25-34), 87% (35-39)
- 3-year survival: 56.3% (15-24), 67.4% (25-34), 69.3% (35-39)
- 5-year survival: 50.7% (15-24), 59.8% (25-34), 61.8% (35-39)

Some of the factors that have been associated with the lower survival in the 15-39 age group overall include a lower socioeconomic status.

1988-2011 EAO-CRC data from LA county:

1-YEAR SURVIVAL

77.6% (15-24 years)

85.6% (25-34)

87% (35-39)

3-YEAR SURVIVAL

56.3% (15-24)

67.4% (25-34)

69.3% (35-39)

5-YEAR SURVIVAL

50.7% (15-24)

59.8% (25-34)

61.8% (35-39)

KEYNOTE ADDRESS, CONT...

EAO-CRC Risk Factors: Looking Beyond Genetics

Dr. Gruber cited a recent review published in *Nature Reviews Clinical Oncology*, which pointed to Western dietary habits, obesity, physical inactivity, and antibiotic use during early prenatal and adolescent age as being responsible for increased risk of EAO-CRC.⁵ He stated emphatically, however, that despite continued research into EAO-CRC, the underlying causes remain unknown. The review paper shared a framework of potential risk factors, which include:

PRENATAL EXPOSURES

- Caesarian delivery
- Term of birth
- Birth weight
- Maternal lifestyle, diet, disease, and medications

INFANCY EXPOSURES

- Breastfeeding
- Antibiotic use
- Growth and developmental factors
- Maternal lifestyle, diet, disease, and medications

CHILDHOOD THROUGH ADOLESCENCE EXPOSURES

- Lifestyle
 - Diet
 - Supplement use
 - Exercise
 - Smoking
 - Alcohol
 - Medication
 - Sleep habit
 - Bowel habit
- Chronic Diseases
 - Diabetes
 - Inflammatory bowel disease
 - Obesity

By examining biospecimens throughout a person's life, the authors of the review propose investigating the interaction between germline genetics and the microbiome to better understand risk factors responsible for the uptick in EAO-CRC. Another perspective in *Nature Reviews Cancer* offered a more holistic framework that considers individual factors, environmental factors, as well as systemic and institutional policies as influencing EAO-CRC development.⁶

Germline Genetic Syndromes

Dr. Gruber then dived into what we know about the role of germline genetics in CRC development. These include autosomal dominant syndromes, such as FAP, Lynch, Li-Fraumeni etc. and autosomal recessive syndromes such as MutYH.

Germline alterations in the *TP53* gene have also been exhaustively studied as risk factors for EAO-CRC. A 2015 study by Yurgelun et al published in *JAMA Oncology* evaluated data on 457 EAO-CRC patients (40 or younger) recruited to the global Colon Cancer Family Registry. Biospecimens were collected from probands and families CRC registry.⁷ While 9% of patients had germline mismatch repair mutations and 1.1% had

biallelic MutYH mutations, 1.3% of the patients had germline *TP53* mutations and none of the probands had clinical histories that would qualify them for *TP53* testing. “Nothing in their families would have suggested that [these patients] would have met criteria for Li-Fraumeni syndrome,” Dr. Gruber said.

He also shared data from a single-center genetic testing and counseling study that was conducted among EAO-CRC patients (<35 years) at M.D. Anderson Cancer Center, which found similar trends in terms of low percentages of attributable mutations/syndromes. “Much of what we see is not easily explained by Mendelian cancer genetics,” Dr. Gruber said, adding, “Population genetics is unlikely to explain the expanded rise of EAO-CRC that we are seeing in such a short period.”

Dr. Gruber also touched on research that points to

coffee and caffeinated energy drinks as potential risk factors for EAO-CRC but acknowledged that these are just some of the many risk factors that have been recognized as likely causes of the rising EAO-CRC numbers.

Technological advances have now made it easier to identify genetic susceptibility using polygenic risk scores, “which can identify numerous individual loci on the human genome that contribute modest risks to EAO-CRC development.” However, have these multitude of inherited genes been meaningfully modified over the past 20 years to result in the current trends? “I think there is a greater likelihood of polyrisk than polygenic risk—physical activity, genetics, dietary effects, and other risk factors,” Dr. Gruber said, calling for a need for broader collaborations to help understand and explain the growing numbers of EAO-CRC patients.



SESSION II

The Dimensions of the EAO-CRC Problem

Under 19 EAO-CRC Incidence and Mortality—How Do We Care for Our Youngest Patients?

Susan Wysoki, Interim Executive Director of the Paltown Development Foundation, talked about whether we have an accurate picture of EAO-CRC as a public health crisis. Ms. Wysoki brings personal experience to the space as a caregiver for her daughter, Jessica, who passed away at the age of 18 years from stage 4 CRC. Since then, Ms. Wysoki has become involved with Colontown, a Paltown online community of 6,000 CRC patients and caregivers that is composed of a virtual “downtown” area surrounded by “neighborhoods” that are focused on particular aspects of CRC (i.e., early stage, caregiver, etc.).

The rising incidence of pediatric CRC cases prompted the creation of a Colontown neighborhood for young patients in 2020. Most of these cases are sporadic, and the median age is only 13 years. Contrary to what some may believe regarding risk factors for CRC, Ms. Wysoki noted that “these kids are very active. They’re typically engaged in lots of sports, and they’re not overweight, but what they do have in common is a Western diet”. Unfortunately, 95% of patients in the Colontown junior community have been diagnosed with stage 4 CRC, with similarly poor outcomes. One retrospective study found a 16% three-year survival rate among children diagnosed

with stage 4 CRC compared to a 55% three-year survival rate among adults. Besides this difference in survival rates, adult and pediatric CRC patients tend to have different disease presentations; adults typically show more T1 lesions and less peritoneal metastasis, while patients under the age of 25 years show just the opposite.

These instances of aggressive CRC in young patients is what stems Ms. Wysoki’s belief that “we need to really challenge the misconceptions that CRC is a slow disease” and that we must look for the presence of disease much earlier, by evaluating risk factors via early germline and somatic testing. Cord blood studies are currently being conducted to assess the presence of forever chemicals that bio-persist and bio-accumulate. The identification of early exposures to certain substances that could affect a person’s risk of developing CRC is incredibly important, as a study published in *JAMA Network Open* projected that CRC will remain one of the most common and deadly types of cancer in the coming years.¹ Similarly, a European study demonstrated a 7.9% annual increase in incidence rates of CRC among 20-29-year-olds between 2004 and 2016.

Ms. Wysoki noted that the increased incidence of pediatric CRC is in tandem with an increase in gut dysbiosis, inflammation, and chronic disease in children. She emphasized that pediatricians and primary care physicians must be made aware of the steady increase in CRC and intestinal issues in children, so they can respond appropriately when a child presents with symptoms.

COVID-19 Policy Update—One Year Later

Phylcia Woods, JD, MSW, Executive Director Cancer Policy Institute, Cancer Support Community, shared a policy update one year after the start of the COVID-19 pandemic and provided insight into the Biden administration’s health care priorities. The new administration has been working to promote and encourage routine cancer screenings, which have suffered a marked decrease during the pandemic, she said.

Cancer screening advocates have been urging the government to remove barriers to good health care, as the number of poor-quality health insurance plans on the Affordable Care Act (ACA) health exchange has increased. Ms. Woods mentioned that the rise in these non-comprehensive health plans “have caused a significant increase in



uninsured rates over the last few years, leaving cancer patients at risk of paying higher out-of-pocket costs and obtaining inadequate coverage.” One issue specific to cancer patients who have enrolled in an ACA exchange insurance plan is that many of the nation’s premier cancer centers are not in-network. Insurers are able to offer low premiums on the ACA exchange with the caveat of a very narrow scope of access to different providers—a potential detriment to cancer patients’ care.

Systemic issues in health care among people of low socioeconomic status as well as people of color are similar to the disparities seen among cancer patients. Ms. Woods remains optimistic, however, as she noted that President Biden has been working to improve access to health care by having a special enrollment period for health care purchases on the ACA marketplace along with tax credits to reduce premiums. Additionally, the administration announced the American Rescue Plan, which provides additional tax credits to those receiving unemployment benefits and also allocates funds to different levels of public health programs to address social determinants of health.

Regarding other efforts to expand access to health care, the expansion of Medicaid eligibility to those with a household income that is below 138% of the federal poverty level is vital. Currently, 38 states and the District of Columbia have expanded Medicaid coverage. Ms. Woods said “we are hopeful that these 12 states [that have not expanded Medicaid] will expand soon because that will allow more people to be enrolled in the

Medicaid program” and “through the American Rescue Plan, more incentives will be provided to these states if they expand the Medicaid program”. She also noted that the Medicaid expansion in all remaining states could provide coverage for up to two million Americans. The American Rescue Plan would provide significant funds for states that choose to expand Medicaid and would cover 90% of the costs for the Medicaid expansion population.⁸

Additionally, advocates have also pushed for continued access to telemedicine services after the COVID-19 pandemic has ended and to remove geographic and origin site restrictions, so people in underserved areas can communicate with doctors in larger cities. Before the COVID-19 pandemic, Medicare only provided coverage for telehealth visits for patients living outside a metropolitan area and required them to conduct the telemedicine visit at a health facility in their community (outside their home). In order for the widespread use of telemedicine in one’s home to become a reality, Ms. Woods stressed that all households need access to broadband internet, a goal of both the American Families Plan and the American Jobs Plan.

Ms. Woods ended her presentation on a positive note, remarking on President Biden’s stated commitment to cancer research by increasing funding for the NIH and his proposed creation of an Advanced Research Projects Agency for Health (ARPA-H), which would focus on research and development of treatments for diseases like cancer and Alzheimer’s.

SESSION III

Risk Assessment/Family History Ascertainment in the U.S.

Screening Guidelines for CRC Screening: What are the Guidelines and How are We Actually Doing?

David Greenwald, MD, President of the American College of Gastroenterology and Director of Clinical Gastroenterology and Endoscopy at Mount Sinai Hospital, shared an

overview of current recommendations for CRC population screening and the adherence to those recommendations along with the impact of COVID-19 on screening rates. The current goal is for 80% of people 50 years and older to be screened for CRC in every community. Dr. Greenwald remarked that “The U.S. Preventive Services Task Force, in 2016, recommended screening between ages 50 to 75 as a Grade A recommendation”. The Summit was held just prior to the release of updated guidelines from the Task

Force, lowering the screening age for average-risk adults to 45 years.

Screening rates have gone up tremendously over the past two decades (from 37.1% in 2000 to 67.3% in 2016), but there are many regional differences in screening rates around the U.S., showing that there is still much room for improvement. Dr. Greenwald pointed out that there are many good options for screening, including stool-based and direct visualization tools that can give those at average risk of CRC multiple avenues for screening.

These great strides that have been made towards screening a large percentage of the target population were largely undone during the COVID-19 pandemic. An international survey of 250 centers revealed an 83% reduction in endoscopic volume as well as fewer inpatient visits and GI procedures. Part of the reduction in

endoscopic volume can be attributed to a lack of personal protective equipment for health care providers, Dr. Greenwald ascertained.

While the impact of COVID-19 on endoscopy will not be fully understood for a long time, it has been estimated that between 18,800 cases of CRC were either missed or had a delayed diagnosis between early March and early June 2020, which may result in over 4,500 excess deaths from CRC over the next decade. Dr. Greenwald urged people to avoid postponing regular screenings, as colonoscopies remain safe, and emphasized that stool-based testing is a good option in places where access to a colonoscopy may be limited. He left us with the parting words that “we will continue to rely on our connections, our collaborations, and our comradery...despite all the barriers that have been thrown in our way, and in so doing, continue to reduce the incidence and mortality from colorectal cancer.”



We will continue to rely on our connections, our collaborations, and our comradery...despite all the barriers that have been thrown in our way, and in so doing, continue to reduce the incidence and mortality from colorectal cancer.

David Greenwald, MD

*President of the American College of Gastroenterology and
Director of Clinical Gastroenterology and Endoscopy at Mount Sinai Hospital*

Increasing Access to Genetic Testing: What do We Need to do to Improve the Situation?

Robin Dubin, co-founder and executive director of AliveAndKickn, a hereditary cancer foundation focused on Lynch Syndrome (LS), talked to the audience about the knowledge gaps surrounding LS and the importance of increasing access to genetic testing. LS is a genetic condition with a population prevalence of roughly 1 in 279 people that causes people to be predisposed to certain types of cancers such as CRC.⁹ One of the most dangerous aspects of LS is that 95% with the syndrome do not know they have it, and there is a 50% chance that the syndrome will be inherited by a person's offspring. Understanding one's

family history of cancer is a key step in making people aware of their LS status before they receive a cancer diagnosis, so they can follow LS guidelines for cancer screenings and alert family members to their potential for being a carrier for Lynch or being Lynch positive themselves.

Screening for microsatellite instability (MSI) is an important step for CRC patients, as high-frequency MSI (MSI-H) tumors can be associated with LS. This in turn can influence treatment options and may also indicate the presence of other tumors such as prostate, pancreas, and melanoma.

Ms. Dubin provided a positive perspective for LS patients with MSI-H tumors, noting that “[these patients] are exceptional responders to PD-1 inhibitors, which are immunotherapy products.” One study reported that patients with mismatch repair (MMR) deficient tumors treated with pembrolizumab (PD-1 inhibitor). showed a progression-free survival rate of 78% compared to just 11% for patients with MMR-proficient tumors.¹⁰ Impaired MMR, a type of DNA repair during replication and recombination, may cause MSI, a condition that is characterized by a predisposition to genetic mutations. Because of the remarkable response of patients with MSI-H tumors to immunotherapy, the National Comprehensive Cancer Network (NCCN) recommends that all CRC and endometrial cancer patients who display MSI tumors or a lack of MMR expression be screened for LS; however, one study showed that only 71% of National Cancer Institute-designated comprehensive cancer centers

conduct this screening on a regular basis.¹¹ That percentage drops to about 15% in community hospitals, leaving many LS patients unaware of their status and heightened predisposition to certain cancers.

In order to promote awareness and further research into LS, Ms. Dubin’s foundation, Alive-AndKickn, has worked to create the HEROIC Registry, a patient-centered genetic database that allows patients to share their medical information and experiences with LS. So far, 269 patients have been added to the registry, many of whom have had multiple types of cancer. Ms. Dubin was excited to announce that “since January 2018, we have had seven abstracts about the registry and the data within it accepted as posters at medical conferences... and 10 requests for enrollment for participants into a study.” Ultimately, AliveAndKickn strives to provide support for LS patients and promote awareness about the condition.

Facilitative Genetic Testing a Powerful Tool for Early Diagnosis

Melissa Frey, MD, assistant professor of Obstetrics and Gynecology, Division of Gynecologic Oncology, Weill Cornell Medicine, presented to the audience the importance of genetic testing in diagnosing CRC. Approximately 1% of the U.S. population carries a familial cancer mutation, but over 80% of those individuals are unaware of their status. Dr. Frey stressed the importance of identifying these individuals to not only provide early cancer screenings and individualized treatments, but also to facilitate cascade genetic testing to allow relatives of these identified individuals the option for genetic assessment.

A Successful Pilot: Promoting Cascade Genetic Testing

Dr. Frey noted that among the relatives at risk for a cancer-causing genetic mutation, “less than 30% undergo genetic testing.” She believes this low percentage is in part due to the fact that it involves the identified individual disclosing their cancer diagnosis to relatives as well as assisting them in getting genetic testing, all while dealing with their own diagnosis and treatment. To relieve the patient of some of this burden, Dr. Frey and her colleagues launched a pilot project that focused on clinician-facilitated cascade genetic testing. This process involved having a genetics team contact relatives of willing Weill Cornell patients who had a cancer-causing genetic mutation. The relatives were then offered genetic counseling sessions and mailed saliva test kits, which could be sent for laboratory analyses. This was followed up with a telephone consultation.

This pilot program was quite successful, as Dr. Frey reported that 60% of relatives who were contacted agreed to undergo cascade testing. Mathematical modeling done in conjunction with Memorial Sloan Kettering Cancer Center found that if all cancer patients found to have a cancer-causing genetic mutation had their relatives undergo clinician-facilitated cascade testing, it would lead to the identification of all 4 million people in the U.S. living with a germline familial cancer syndrome within 10 years.¹² Dr. Frey pointed out that it is only worthwhile identifying all of these individuals if they actually choose to undergo

the appropriate cancer surveillance and risk-reducing protocols to mediate the effects of their genetic mutations.

A 2-year follow-up of the pilot study of cascade testing showed:

- 75% of relatives who participated in the testing underwent at least one cancer screening intervention
- 14% of relatives underwent cancer risk-reducing surgery
- 44% of relatives reported that additional relatives also underwent testing (cascade of the cascade)


One issue with cascade testing is that it generally only starts when a person is diagnosed with cancer. Ideally, genetic testing should take place before a person develops cancer, so they can undergo risk-reduction strategies and initiate early screening. For this goal to become a reality, Dr. Frey highlighted the importance of collecting family cancer history. While there is consensus among the medical community that collecting family history is important, Dr. Frey noted that “some studies suggest that you need at least 30 minutes to take a really good family history and on average, providers in this country spend less than two minutes” discussing the patient’s own and familial cancer history. She suggests using health information technology (HIT) to:

- Collect personal and family history
- Identify high-risk patients
- Calculate disease risk
- Coordinate genetic testing
- Communicate results with patients
- Assist patients in sharing their test results with at-risk relatives

Ease of Access: Promoting a Web-Based Tool

Eager to use this technology in her own practice, Dr. Frey’s office launched a web-based tool (WBT) for cancer family history. This required patients to input data on the website, the WBT would then run validated cancer risk assessment models, and the final step would generate pedigree: risk assessment for cancer and risk assessment for mutations. Interestingly, Dr. Frey’s research team found that a higher percentage of patients opted to complete the WBT in the office than complete it via email. Some limitations of this WBT were that it is unable to be completed on a smartphone and participants could not provide feedback. Many patients also wanted an artificial intelligence tool to assist people in real-time if they did not understand some questions.

Ultimately, Dr. Frey is quite hopeful that genetic testing, if implemented appropriately, can be a powerful tool to identify individuals with an elevated risk of cancer and help them engage in risk-reduction strategies and early screening.



Ideally, genetic testing should take place before a person develops cancer, so they can undergo risk-reduction strategies and initiate early screening.



DAY 3

SESSION IV

**How to Provide Timely,
Effective, Quality of Life and
Fertility-Preserving Treatment:
What Are Key Elements of
Coordinated Care for Early-Onset
Colorectal Cancer?**

The highlight for the last day of the Summit was a case study discussion that provided a glimpse of what an ideal multidisciplinary EAO-CRC care team looks like.

Andrea Cercek, MD, Co-Director, Center for Young Onset Colorectal Cancer; Section Head, Colorectal Cancer; Associate Attending, Memorial Sloan Kettering Cancer Center, described the case of a 28-year-old female professional with a history of several years of chronic constipation that required her to take laxatives.

- 6 months ago, her symptoms changed: tenesmus, bowel urgency with intermittent rectal pressure, which got worse with prolonged standing
- A CT scan of her abdomen and pelvis when she presented to the ER showed a moderate amount of stool in the ascending colon, with a thick-walled appearance of the rectum, about 6 cm from the anal verge down to the anal canal/anorectal junction
- This abnormality prompted a colonoscopy, which showed a non-circumferential mass in the distal rectum to the anal verge
- A biopsy led to the diagnosis of an invasive moderately differentiated adenocarcinoma
- Medical history: A BMI of 22; father had 2-3 polyps removed a few years earlier

Manju George, MVSc, PhD, Scientific Director, Community Leader, Paltown Development Foundation, and a CRC survivor, described that this was quite typical in that on average it took about 270 days to diagnose EAO-CRC cases. "Most often, patient symptoms are dismissed as being something else," she said.

Cathy Eng, MD, FACP, Vanderbilt-Ingram Cancer Center, David H. Johnson Chair in Surgical and Medical Oncology; Vice-Chair, SWOG GI Committee, Institutional PI, SWOG; Professor of Medicine, Hematology and Oncology, Co-Director, GI Oncology, Co-Leader, Gastrointestinal Cancer Research Program, agreed with Dr. George. "This is very common in our clinics. We recognize symptoms, but it often takes about a year for the actual diagnosis," she said, adding that patients are often misdiagnosed as having hemorrhoids.

Zsofia Stadler, MD, Clinical Director, Clinical Genetics Service, Gastrointestinal Oncology; Genetic Predisposition to Cancer, Memorial Sloan Kettering Cancer Center, Cancer Risk Counseling, said that 75-80% patients in her clinic do not have a family history of CRC. "It's important to confirm that their parents have had a colonoscopy. I also like to ask them about relatives or siblings, which can help identify other family members who need to have a colonoscopy," she said.

Dr. Cercek then provided additional details on the case study. The patient's pelvic MRI showed that the tumor arose from the lateral wall at the level of the levator, distal edge of tumor was 32 cm from the anal verge, tumor abuts the internal sphincter. She was diagnosed as having clinical stage III CRC.

Harvey Mamon, MD, PhD, Associate Professor, Director of GI Radiation Oncology; Chief, Harvard Medical School, Brigham and Women's Hospital, Division of Gastrointestinal Radiation Oncology, Dana-Farber Cancer Institute, jumped in saying that sphincter preservation is unlikely in this case and that the chances of tumor recurrence are higher for distal than proximal tumors. "There'd be a neoadjuvant therapy approach. While the patient may need all three treatment modalities—surgical resection, chemotherapy, and radiation for local control—standard treatment would include an APR [abdominal perineal resection] to maximize disease control," Dr. Mamon said. He did warn about potential quality-of-life and fertility issues that would

"This is exactly the issue we face with our very young patients," Dr. Cercek said. "There's so much that comes along with treating not just the cancer but also our patient. We have to think about not just the psychosocial needs, but also fertility preservation and sexual health."

"We'd like these patients referred to us as soon as they are diagnosed," said Terri L. Woodard, MD, Associate Professor in the Department of Gynecologic Oncology and Reproductive Medicine, MD

Anderson Cancer Center, adding that ASCO guidelines also recommend the same, because it gives more time for options and to think through a lot of different things. “We encourage our patients to take a birds eye view. For example, genetic testing if there’s a mutation, or if they receive radiation, they may not be able to carry a pregnancy.”

Addressing the need for genetic testing, Dr. Stadler said that the first thing that needs to be done is MSI/MMR assessment to determine the treatment plan. “It has been shown that the colonoscopy specimen can be used for immunohistochemistry,” she said.

Those under 35 years of age have been shown to have the highest germline risk. “In our data, we found that the prevalence of mutations in the <35 was 24%, 14-15% in 35-50, and even lower among the >50,” Dr. Stadler said. “If you look at the really high-risk patients, they account for 12% for early onset and 6% in the >50 age group. A multigene panel is therefore very useful for treatment planning as well as future risk assessment,” she added.

An early referral is very important for psychosocial assessment as well. According to Krista Nelson, LCSW OSW-C, BCD, FAOSW, President, Association of Community Cancer Centers; Program Manager of Compassion, and Senior Social Worker, Providence Cancer Institute, “We need to understand where the patient is and who they are, as well as their socioeconomic status. It is important to recognize that work and family is important for young patients.” She emphasized the need to understand patient priorities and their trauma history.

Hadley Maya, MSW, LCSW, Clinical Social Worker, Center for Young Onset Colorectal Cancer, Memorial Sloan Kettering Cancer Center, agreed. “In my experience working with younger patients, colostomy affects the patient’s body image and their ability to date.” In addition to family support, “providing support and psychotherapy while adjusting to this huge life adjustment is important,” she emphasized.

Janet L. Abraham, MD, Former Chief, Division of Adult Palliative Care, Professor of Medicine, Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute

and Brigham and Women’s Hospital, Professor of Medicine, Harvard Medical School, feels that palliative care can be the neutral arbiter and help patients run through the various possible scenarios and help articulate them with their families. “If we are a part of that core team, we can help unpack the medical speak and help patients and families make those hard decisions,” Dr. Abraham explained.

“There are definite disparities in quality and access to care, from adolescent to young adults, as they move out of pediatric care and into primary care,” according to Michael Roth, MD, Associate Professor of Pediatrics, Chair, Director, Children’s Oncology Group, AYA Oncology Discipline Committee, University of Texas, MD Anderson Cancer Center, who sees 15–39-year-old cancer patients in his clinic. Considering that it is often difficult to find quality care within the community, he urged community care providers to refer their adolescent and young adult (AYA) cancer patients to AYA-specific care resources, which he described as being “vital to their health and treatment.”

Yi-Qian Nancy You, MD, MHSc, FACS, Department of Surgical Oncology, Division of Surgery, Associate Professor, Department of Clinical Cancer Prevention, MD Anderson Cancer Center, continued describing the case study at hand. “Testing the tumor for microsatellite instability is vital. Lynch and lynch-related tumors are a very small proportion [of the EAO-CRC cancers]. We have, therefore, started a universal germline testing program,” said Dr. You, adding that the patient underwent somatic testing as well.

Kellie L. Mathis, MD, Colorectal Surgery Specialist, Mayo Clinic, said that there is a need for neoadjuvant therapy, irrespective of how it is administered. “Surgery wouldn’t be an option. We’d talk to the patient about undergoing a colostomy.”

Dr. Cercek added that their Center has a formal structure to set their patients up early on with support groups, including a social worker, who informs the patient of all the available support services.

“Most younger patients are interested in talking to someone who has gone through an ostomy—a former or current patient,” shared Ms. Maya about the services available at their Center at MSKCC.

“We also have an ostomy support group that patients can attend in advance and also after they have gone through the procedure.”

The Colontown community has a subgroup (neighborhood) called Youngstown where patients have a lot of discussions about their experiences. “These groups are useful for newly diagnosed patients to get a feel for the range of experiences that other patients have experienced,” Dr. George said.

Dr. You continued describing the case, saying that the patient’s tumor genomic assay report came back with a lot of hotspot mutations.

“The patient was given a TNT [total neoadjuvant therapy] regimen,” said Dr. You, with FOLFOX for four months. The expected complications included alopecia, cytopenia, chemotherapy-induced peripheral neuropathy (CIPN), gastrointestinal issues, and hand-foot syndrome.

According to Dr. Cercek, the patient has to meet with a medical oncologist and a radiation oncologist to understand the treatment options and their sequence. “In terms of sequencing, we have moved chemotherapy and chemo-radiation into neo-adjuvant or pre-operative

setting. Early chemotherapy can help treat micro metastases and also improves tumor response and could allow non-operative management, in tandem with surgery and radiology,” she added. TNT, she said, helps with tolerance, but the sequence of treatment in TNT still stands. Giving chemotherapy-radiation upfront has shown an increased response as against chemotherapy-radiation followed by chemotherapy, with respect to pathological complete response. “In patients who have an advance tumor and where we are trying to optimize total neo-adjuvant therapy, chemotherapy-radiation followed by chemotherapy is the way to go. If the tumor is higher up, radiation may not add much to the treatment, and chemotherapy would be fine,” Dr. Cercek said.

Acknowledging that young patients typically tolerate their treatment well, Dr. Eng said that younger patients usually have few comorbidities. “It’s about communication and ensuring they have their supportive medication at home to manage their side effects. It is also important that they maintain their weight, especially if they choose surgical oncology,” she added.

Dr. Abraham emphasized the need to replenish



vitamin D deficiency in those experiencing CIPN. Risk factors for CIPN include a sedentary lifestyle, obesity, and diabetes. "There are conflicting data on oxaliplatin-induced CIPN, but duloxetine might help," she said. Dr. George said that they recommend icing for CIPN. "Almost 90% of folks have shown that they have better tolerance to CIPN with acute oxaliplatin side effects."

The other significant concern, especially among EAO-CRC patients, is treatment impact on fertility. "Sperm banking and egg banking is possible, but if the uterus cannot bear the pregnancy...this is as harrowing as the cancer diagnosis," Dr. Mamon said, emphasizing this as the main difference between younger and older patients. The other side effect is the variability in response. "Some sail through and others are often hospitalized," he said. Late effects outside of fertility include impact on bowel function, rectal function, and incontinence. Men may experience erectile dysfunction, although it might not be as frequent in younger men.

Addressing the fertility issue, Dr. Woodard said that sperm banking is a lot cheaper and is covered by insurance. "For women, we don't have that," she said. The MD Anderson Cancer Center has programs that offer fertility treatment at cheaper or subsidized cost. Additionally, the LIVESTRONG Foundation assists patients who need fertility preservation, but there are also 19 states that have passed coverage laws for infertility treatment.

Amy Hayes, BSN, RN, OCN, Nurse Navigator, Vanderbilt-Ingram Cancer Center, said while they speak with their patients about fertility preservation in the clinic, insurance coverage is often a barrier.

The conversation then veered toward other long-term effects of treatment in EAO-CRC patients. Dr. Mathis highlighted the likelihood of acute morbidity in these patients, and the risk of death. "It's hard to tease apart treatment modality impact but there's always the chance of the LAR [low anterior resection] syndrome," she said, adding that while we don't have good tools and we don't ask the right questions, patients have to face a lot of short and long-term morbidity post-surgery.

Dr. Roth described how young children with CRC who live long are faced with both physical and

psychosocial trauma. "A trauma such as cancer at 28 is hard enough and many survivors may be cured of cancer but may have trouble achieving planned life goals," he said. He believes it is vital to provide life-long support to these survivors.

Dr. You then provided the most current update on the patient. She said that the patient, who achieved a complete clinical response, is in a watch-and-wait and close surveillance period. "She is anxious, as may be expected, but she is out of psychiatry. Is this an issue that you encounter in your practice?" she asked the panel.

According to Ms. Nelson, patients are usually in a crisis mode early on, when they are newly diagnosed. "Patients often have to meet at least six specialists initially. With younger patients, they may literally be naïve to healthcare. Once they are out of their fight/flight mode, the emotional piece may actually come through" she said. There's always that fear of cancer coming back, which can lead to anxiety and depression. Her clinic uses techniques to walk them through survivorship and helping them set futuristic goals.

The ripple effects of the treatment extend beyond the patient and have an impact on their family as well. "Many of our patients have young children and they have to communicate this information to them, or they may have ageing parents that they need to inform," said Ms. Maya, who often interacts with patients' family members and caregivers. Beyond treatment, patients are also faced with logistical issues such as their finances. "Diagnosis and treatment can have a huge financial impact, so I help them assess these issues and also connect them with resources."

Ms. Nelson's center helps support kids whose parents have been diagnosed with cancer, and also connect them with other kids whose parents have been diagnosed with cancer. "We also have a drop-in day care center where parents undergoing treatment can drop their kids off during treatment, if they do not have the family support," she said.

One gap that was identified during the discussion by Dr. Abraham and Dr. Roth was caring for LGBTQ and transgender patients. "We know little about these patients, overall, and even less within the YA population," Dr. Roth said.

BREAKOUT SESSION

Understanding and Addressing Disparities in Early-Age Onset Colorectal Cancer

A breakout session during the last day of the meeting saw an interesting conversation involving a patient who is also an advocate, a caregiver who is also an educator, and a geneticist whose research interest includes CRC.

Candace Henley, Chief Surviving Officer, The Blue Hat Foundation, spoke to the financial toxicity associated with her CRC diagnosis at an early age, in addition to the communication challenges that patients experience when their care team speaks with them medical terms instead of in a language that they patients and their caregivers can fathom. Losing her livelihood left Ms. Henley and her family homeless and caused significant psychological trauma. Ms. Henley pointed out the absence of family history about her aunts and her father being diagnosed with CRC. Then there's the complication of race and racial bias. "Racial inequities are primarily responsible for the 20% higher incidence and 40% higher mortality rate [from CRC] among African Americans," she said.

Elena M. Stoffel, MD, MPH, Director of the University of Michigan Cancer Genetics Clinic; Assistant Professor of Internal Medicine, University of Michigan, agreed with Ms. Henley "Historically, CRC risk assessment was limited to the person's age, personal history of CRC and IBD [inflammatory bowel disease], as well as family history of CRC among first-degree relatives," she said.

"We now know that in addition to genetic differences, environmental factors also impact the incidence of EAO-CRC. Only 25% of young people with CRC reported having a family history of CRC, but 20% had a genetic risk factor, which was twice as high as in older-onset CRC," Dr. Stoffel explained. She emphasized the importance of genetic testing, adding that "defining the criteria that determine who is tested is vital." According to Dr. Stoffel, the following criteria are important:

- the individual's background
- provider communication with the patient
- removal of systemic constraints such as access to care and cost of care

"These factors also influence whether a person undergoes a colonoscopy, which is a key first-step to being diagnosed," she added.

CRC incidence among those under 50 years is at least two-fold higher among non-Hispanic blacks (NHBs). Mortality is significantly higher among stage 2 or stage 3 NHB EAO-CRC patients: stage 2 NHB EAO-CRC patients are 60% more likely to die of CRC compared to white EAO-CRC patients. Dr. Stoffel proposed that certain changes to our current system can help:

- Integrate CRC risk assessment into routine health maintenance for all adults
 - Symptom screen
 - Screen for family history: genetic evaluation for CRC, colorectal polyps, and other cancers

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Racial inequities are primarily responsible for the 20% higher incidence and 40% higher mortality rate [from CRC] among African Americans.

Candace Henley
Chief Surviving Officer, The Blue Hat Foundation

- Study associations between patients and tumors to inform prevention strategies
 - Modify dietary patterns/health behaviors
 - Risk stratification
- Reduce disparities in healthcare delivery
 - Increase CRC screening uptake
 - Standardize CRC treatments

An EAO-CRC survivor, Anjela Carraway, MMP, President, TCMG Inc., and a patient advocate shared the barriers that she faced that prevented her cancer to be diagnosed early and treated on time. She recollected being unable to get timely access to a primary care physician, which resulted in disease progression and misdiagnosis. It was almost a year after initial symptom recognition that Ms. Carraway was finally diagnosed with CRC, followed by treatment that included surgical resection of a portion of her sigmoidal colon and chemotherapy cycles. Her experiences led her to add a program to her Foundation to serve the needs of residents in her county in North Carolina—both patients with chronic diseases and their family members—as they face illness.

Providing the caregiver’s perspective to the panel was Jasmin Mejia, Member Services and Events Manager, Arizona State University. She was the primary caretaker of her mother who was diagnosed with stage IV CRC at 42 years. Ms. Mejia shared her mother’s frustration as a patient facing language barriers, because no one at the hospital where she was receiving her treatment spoke Spanish. Additionally, lack of health insurance led to missed doctor’s visits. Jasmin had to be the full-time caregiver to her mother at a young age, which was stressful for her. Her advice to the clinicians participating in the Summit was: “Know your community. Hold outreach events to be able to reach out to the community.”

SESSION V

How Did This Happen? Investigating the Causes of Early-Age Onset Colorectal Cancer

The final panel discussion at the meeting was moderated by Dr. Gruber, who spoke with experts from diverse backgrounds on a variety of investigational research areas, trying to understand the cause of the continued rise of EAO-CRC.

Panelists included Francisco Sanchez-Vega, PhD, Colorectal Cancer Service of the Department of Surgery, Memorial Sloan Kettering Cancer Center; Peter Campbell, PhD, Scientific Director, Epidemiology Research, American Cancer Society; Kimmie Ng, MD, MPH, Associate Professor of Medicine at Harvard Medical School, Founding Director of the Young-Onset Colorectal Cancer Center and Director of Clinical and Biospecimen Research in the Center for Gastrointestinal Oncology at Dana-Farber Cancer Institute; Cynthia Sears, MD, Professor, Johns Hopkins University School of Medicine; Caitlin Murphy, PhD, Assistant Professor, Department of Population and Data Sciences. UT Southwestern; José Perea MD, PhD;

and Giulia Martina Cavestro, MD, PhD, Director of the Postgraduate School of Gastroenterology, Gastroenterology and Gastrointestinal Endoscopy Unit, Vita-Salute San Raffaele University, San Raffaele Scientific Institute, Milan.

Dr. Gruber kicked off the conversation by posing this question to the panelists: How can machine learning and AI guide our understanding of risk factors of EAO-CRC? “There’s so much that we don’t know than what we do,” he added.

Dr. Sanchez-Vega said that there is a need to scale-up the number of patients that we use in our studies. Multidimensional integration, in his opinion, is also very important. “The field is using new models that include radiology images, using liquid biopsy data and then integrating this information with genomic analysis. We also work with whole exome and whole genome data. All of this creates incredible challenge and scaling up then becomes even more challenging.”

As for the manual effort needed for data abstraction, Dr. Sanchez-Vega said that patient data is documented in a central database. The data include detailed information on primary tumor, metastases if any, and even the site of metastasis from where the biopsy sample is collected. “We can query the database for ICD billing codes, for example. Someone could manually review the EHR [electronic health record] and NLP [natural language processing] and use automatic translation of images to abstract all this information. This could then be turned to a structured database that can then be queried by AI,” he explained.

These databases collate significantly detailed information. According to Dr. Campbell, his team has assembled 26 prospective CRC cohorts that began in the 1990s with a sufficiently lengthy follow-up time. “We do, however, have to harmonize these studies done in China, Australia, USA etc.,” he said. The patient data include blood samples up to 10-15 years prior to their cancer diagnosis, which can help identify biomarkers. “We can query things such as lifestyle changes and how they influence these biomarkers,” said Dr. Campbell.

He clarified, however, that the assumption is that risk factors for early-onset disease are similar to normal-onset disease—body-mass index,

diabetes, physical inactivity, aspirin use could all be relevant for early-onset disease. Since the molecular characterization of the two types of disease are similar, he believes that we may be looking at the same disease, just the exposures have changed. Dr. Campbell and his colleagues are currently evaluating about 96 biomarkers.

The conversation then moved onto understanding the influence of infectious disease exposure on the development of EAO-CRC. Dr. Sears and her team at Johns Hopkins are evaluating the influence of the microbiome on CRC, independent of age. “Our long-range vision is the hope that we can contribute to a diagnostic or biomarker approach to identify young-adult individuals.” She agreed with Dr. Campbell that the early-onset disease is a change in timeline, not necessarily a new disease compared to normal-onset CRC.

“We hope to go back in time and evaluate samples that date back to the 1970s,” Dr. Sears said. “We want to look at biofilms.” Previous work by her group has found that bacterial biofilms contain tumorigenic bacteria that are responsible for cancer.¹³ This phenomenon was more commonly observed in 50% of sporadic CRC. Similarly high rates were also observed in EAO-CRC. She noted that while PKS *E.coli* are very common in children even in the absence of disease, one-third of a colonoscopy population



is colonized with these bacteria. “The trick is to figure out who’s at risk, and it’s critical to integrate these exposures into the data,” she explained.

Dr. Gruber asked Dr. Sears to explain the short- and long-term impact of antibiotic overuse on gut bacteria and how it might impact risk of CRC. She cited their investigation into a large primary care dataset of over 25,000 CRC patients in the UK, with over 137,000 controls.¹⁴

“The biggest impact of antibiotic exposure was in the right colon and there was no impact on left-sided colon cancer from antibiotic exposure,” Dr. Sears explained. Interestingly, rectal cancer decreased in the population that was exposed to antibiotics. Referring to the spillover effect of unabsorbed antibiotics, she said, “My hypothesis is we do detonate gut flora, particularly the mucosal bacterial population that are important for pathogenesis. We hope the microbiome reconstitutes itself post antibiotics, but there are definitely long-lived defects that can have an impact,” Dr. Sears said explaining that there could be mucosal surface defects that evolve from the destruction of the microbial flora that could play a role in CRC.

The typical timeline for polyp development post antibiotic use is about 10 years.¹⁵ This would explain the important role of early-life antibiotic exposure on EAO-CRC development, which is an area of research interest for Dr. Murphy.

She acknowledged that longitudinal studies are quite difficult to structure and implement, as older data may be difficult to collate and often may not be documented. Also, patients may not always remember the antibiotics that they were exposed to in early childhood. So, her team identified a pregnancy cohort called the Child Health and Development Studies, which is a population-based cohort of women receiving prenatal care in the 1950s-60s.¹⁶ The study followed the offspring of those women over the past 50-60 years to identify their risk of cancer.

Some of Dr. Murphy’s findings include the in-utero exposure to the following can increase the risk of developing CRC:

- Certain anti-nausea medications
- Progestins
- Sulfa drugs

“These findings are helping us understand what was happening during those critical periods of growth and development that could help us understand what we are seeing today, 50 years later.”

Caitlin Murphy, PhD, Assistant Professor, Assistant Professor, Department of Population and Data Sciences, UT Southwestern

She then continued to address the strengths and limitations of the dataset that her research team is excavating, adding that the cohort includes data on childhood use of antibiotics and other information from the person’s early childhood that are yet to be queried. “We also have data gaps where we lack health information during adolescence, young adulthood, and mid-adulthood for some individuals,” which, Dr. Murphy acknowledged, could limit their ability to associate certain risk factors with CRC development. “However, the sample size [of the dataset] and the ability to conduct the prospective follow-up is the strength of our study.”

When asked by Dr. Gruber about the most exciting data that they are currently querying, Dr. Murphy said that she is personally convinced about the importance of early-life exposures and how we can make an impact today based on what happened in the 1960s. “For example, some of the drugs may not be currently used in patients but are persistent in the environment, and we can make an effort to limit those going forward,” she added.

From the context of the cohort’s diversity, Dr. Murphy shared that the Child Health and Development Studies cohort is racially and ethnically diverse, which she said is impressive considering that the cohort is from 60-70 years ago. “It is also socioeconomically diverse, with a third of the population at the median a third below and a third above the median income,” Dr. Murphy said, adding that this cohort presents a lot of opportunities to tap into the development of disease risks.

Dr. Gruber then brought Dr. Perea into the conversation to gain an understanding of the

diversity of the population in Spain that influences CRC development in the context of a multi-exposome approach.

“We have to separate the Spanish cohort, where we started evaluating molecular approaches to understand EAO-CRC, comparing it to normal-onset CRC and observing differences between the two. There were correlations with inflammation and metabolism,” Dr. Perea explained, speaking about their study. In addition to stool samples, his team is also working with blood and plasma samples with a long-term goal of using proteomics to integrate the data from the different samples.

“We have to bear in mind that the Spanish population is different,” Dr. Perea said. Compared to the U.S. population, for example—where obesity rates are high, and it is a known risk factor for CRC development—obesity rates among the Spanish population are not very high. Instead, their team is evaluating the rate of carbohydrate metabolism and its influence on EAO-CRC development.

Dr. Perea was then invited to comment on the CRC screening strategy in Spain, specifically the parameters that influence the screening strategy for the early-onset disease.



Dr. Perea explained that while 50 is the screening age for CRC, their understanding of EAO-CRC in the Spanish population is limited. “So, we need to identify markers that will guide our nation’s screening strategy,” especially for younger Spaniards who may be at a higher risk. He believes that liquid biopsy could be used for widespread screening, but it is currently limited by the need to find specific EAO-CRC biomarkers.

The final panelist to chime in was Dr. Cavestro, who spoke about her team’s efforts in understanding the role of dietary patterns in EAO-CRC?

“In Italy, there’s been a drop in EAO-CRC, so we could be a real control group. We lack evidence to support the role of ethnicity factors or protective microbiota, but we know that the Mediterranean diet is prime,” Dr. Cavestro said. In collaboration with 30 global centers—from Norway, Spain, Finland, Italy, USA, and Germany—they have set up a study called DEMETRA to scrutinize the role of dietary patterns on EAO-CRC development. The low numbers of EAO-CRC cases in Italy positions the Italian cohort as an ideal control group, she explained.

Considering that an individual’s dietary habits change over time, Dr. Gruber was curious about the ideal intervals to assess the diet-disease correlation.

Dr. Cavestro said that her team is evaluating dietary information for up to two years prior to diagnosis and will seek information for every year after that. She did point out, however, that patients often change their dietary habits once diagnosed.

In closing, Dr. Gruber asked the panelists that if they had the authority to invest funding dollars to better identify risk factors for EAO-CRC, how would they do it? Dr. Sears said that while it’s not a rare disease anymore, each center only has a small number of EAO-CRC patients. She’d like to see the creation of a network for those in the field to share data on EAO-CRC—a bigger dataset with parallel sample collection, which will allow us to answer the exposure question. “We need the epidemiology exposures in a sufficient population and it’s difficult to obtain in a single institution,” Dr. Sears emphasized.

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