A Summary of the Fight Colorectal Cancer Working Meeting: Exploring Risk Factors and Etiology of Sporadic Early-Age Onset Colorectal Cancer

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In contrast with dramatic decreases in older populations, the incidence rates of colorectal cancer (CRC) in younger adults are rapidly increasing in the United States (Figure 1).[1] Early-age onset (EAO) CRC, defined as colon and rectal cancers diagnosed in persons <50 years of age, has nearly doubled since the early 1990s. According to Siegel et al, "compared with adults born circa 1950, those born circa 1990 have double the risk of colon cancer and quadruple the risk of rectal cancer."[1] Additionally, younger patients are often diagnosed at a later stage, when the disease is more challenging to treat, because of delays in seeking medical care and misdiagnosis. Mechanisms contributing to increasing incidence rates are poorly understood.[2]

Fight Colorectal Cancer (Fight CRC) is a national advocacy organization actively tracking trends in CRC diagnoses and prevention. Fight CRC has identified EAO as a priority to take action to help advance the research agenda and patient care for all patients with CRC and survivors of CRC. In addition, the patient and advocate community are vocal about the need for dedicated EAO CRC research and Fight CRC hosted this meeting responding to this urgent request.

Introductory Session and Framing the Issue

Fight CRC hosted a dedicated research meeting in Denver, Colorado, on February 1, 2019, to explore some of the many research priorities in EAO CRC research: risk factors and etiology of sporadic EAO CRC. Owing to increases in the incidence in those <50 years of age, this meeting was held to address the clinical and scientific issues necessary for understanding why the number of new cases of EAO CRC is on the rise and how to study underlying causes. The etiology of sporadic disease was specifically focused on because approximately 70% of EAO CRC cases are sporadic (ie, occurs among those with no family history of CRC or genetic predisposition).[3]

In the fall of 2018, Fight CRC began convening a team of experts from around the world to examine the research

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initiatives underway with the goal of hosting a working meeting on February 1, 2019. Fight CRC built on the objectives noted by previous EAO CRC focused activities to advance the work and partnerships. The objectives of the meeting included:

1. To prioritize risk factors and contextual elements to be studied;
2. To determine the means to study these priorities with existing studies and/or data repositories; and
3. To determine the means to study priorities with new studies.

At the close of the meeting, dedicated time was set to explore the perspectives of policymakers and funders. Introductory lectures and 2 general topic lectures kicked off the meeting, and the majority of the day was devoted to working group time to address the objectives.

Introductory Lectures

Dr Dennis Ahnen opened the session by defining EAO CRC and the need and interest to explore this topic as a potential research area, referencing Figure 1. Dr Ahnen is a leader in the field of CRC prevention and as a medical advisor to Fight CRC, was a champion for the meeting.

Andrea (Andi) Dwyer presented an overview and provided background information on how the working meeting came to fruition beginning with an explanation of the 2017 EAO CRC Strategy Session meeting convened by the National Colorectal Cancer Roundtable (NCCRT). Dwyer explained that the short-term action items identified by the NCCRT Strategy Session were the guiding principles for the meeting on February 1. These short-term action items for research included (1) define the landscape of on-going research, and (2) convene a group of investigators to identify key study components, study design, data sources, and funding opportunities. Dwyer noted that this short-term research recommendation from the NCCRT meeting helped to propel the work of Fight CRC and ensure the alignment of EAO initiatives in the field. The repository of the current studies, databases, and descriptive summaries of the work of attendees, which was used to prepare and inform the working meeting is available on the Fight CRC website at: https://fightcolorectalcancer.org/research/driving-research/under-50/.

Identifying the Cause of EAO CRC: How Can Epidemiology Help?

Dr Caitlin Murphy provided an overview of the epidemiology of EAO CRC, focusing on the following domains.

Birth cohort effect and early life exposures. EAO CRC has increased across successive birth cohorts (Figure 2),[1,4] and persons born in and after the 1960s, or Generation X, are increasingly at risk of CRC. For example, incidence was higher among 40-year-olds born in 1970 (24.4 per 100,000) compared with 40-year-olds born in 1950 (18.3 per 100,000).[5] Birth cohort effects point to exposures in early life—or exposures accumulated over the life course—that may increase risk of cancer.[6] Higher incidence rates among these birth cohorts implicate exposures increasingly prevalent during their childhood. Dr Murphy described several environmental exposures in early life that have increased since the 1960s: cesarean delivery, birth weight, breastfeeding, prenatal or perinatal antibiotics, antibiotic use in infancy and childhood, childhood obesity, food supply, and occupation. Dr Murphy suggested that examining risk factors during vulnerable windows of growth and development, such as infancy and childhood, will improve our understanding of their role in EAO CRC and identify periods of exposure conferring the greatest risk.

Greater Increases in Rectal Versus Colon Cancer. Increasing rates of rectal (vs proximal colon) cancer have largely driven increasing incidence of early-onset CRC, particularly among whites.[7] Rectal cancer increased by 80% from the early 1990s through 2015 (from 2.6 to 4.7 per 100,000),[3,5] compared with an increase of about 40% in colon cancer. Differences in incidence by anatomic subsite

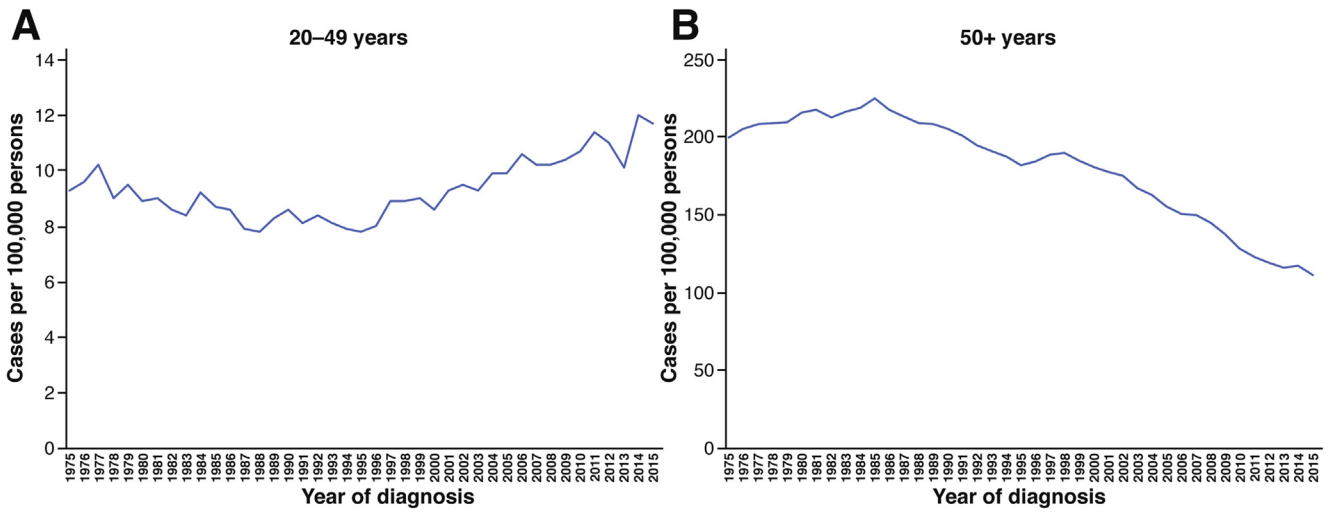

Figure 1. Incidence rates increased by 50% (from 1995 through 2015) in those ages 20–49 years and decreased by 50% (from 1985 through 2015) in those ages ≥50.[1]

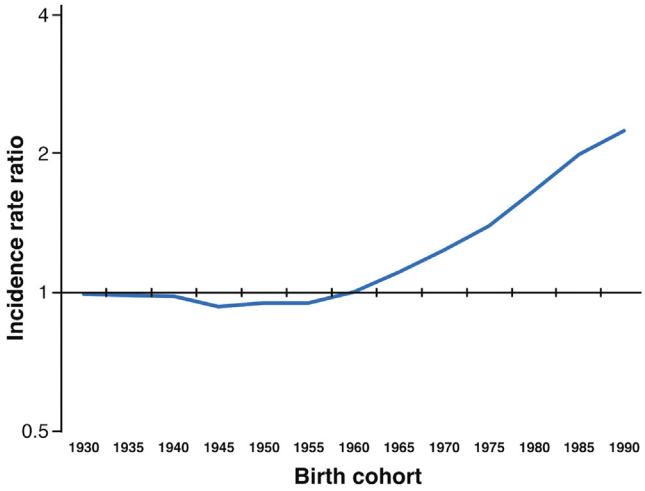

Figure 2. Incidence rate ratios by birth cohort (1930–1990).[4]

underscore the importance of teasing apart risk factors for colon versus rectal cancer. Specifically, risk factors more strongly associated with rectal cancer and increasing in prevalence likely play a role. Studies examining risks separately suggest that family history, obesity, and smoking may have different effects on risk. For example, family history seems to be more strongly associated with colon cancer than with rectal cancer.[8] Other well-established risk factors, such as dietary intake of calcium and folate, decrease risk of colon cancer but have no association with rectal cancer risk.

Persistent Disparities by Race/Ethnicity. Incidence rates of early-onset CRC have not increased uniformly across racial and ethnic groups. Rates remain higher among non-Hispanic blacks (29.4 per 100,000) compared with non-Hispanic whites (23.3 per 100,000) among those age 40–49 years in 2000–2015.[5] Among Hispanics, rates have increased by about 15% per year in the youngest age group (20–29 years) since the mid-2000s.[9] Racial and ethnic differences in the distribution of risk factors may explain some of these disparities and provide additional insight into the mechanisms of EAO disease. For example, blacks have experienced a more constant exposure to type II diabetes[10] and childhood obesity[11] compared with the marked increases in exposure that have only recently occurred among whites. Dr Murphy emphasized that, as the demographic landscape of the United States continues to evolve, monitoring changes in the relative presence or absence of risk factors by race/ethnicity will be critical to our understanding of EAO CRC.

Next Steps. Dr Murphy concluded by summarizing how patterns of incidence, together with temporal trends in risk factors, provide etiologic clues for understanding mechanisms of EAO CRC. To advance our understanding of EAO CRC, Dr Murphy suggested future studies must carefully consider how effects of risk factors may differ by anatomic subsite and race/ethnicity, as well as when and how risk factors are measured. Specifically, she described 5 priorities for future research: (1) exposures increasingly prevalent after the 1960s, (2) how exposure to established risk factors across the life course (eg, obesity in childhood) may influence risk, (3) risk factors more strongly associated with rectal versus colon cancer, (4) differences in exposures and risk factors by race/ethnicity, and (5) how exposures may interact with family history and/or hereditary syndromes to contribute to an earlier age at onset.

What We Know and Do Not Know: The Genetic and Epigenetic Features of EAO CRC

Dr Clement Richard (Rick) Boland provided an overview of the genetic and epigenetic features of EAO CRC and began by suggesting tumors occurring in younger adults may be biologically different from CRC that occurs at an older age.

Genetic Landscape of EAO CRC. Germline mutation testing of >1000 unselected patients with CRC suggests about 10% of patients (across all ages) have a germline mutation in a cancer-related gene.[12] Similar testing of EAO CRC revealed that about 16% of younger patients have a germline mutation in a cancer-related gene and one-half of these are mutations in genes associated with the Lynch syndrome.[13] This finding was confirmed in a later study that showed 20% of young patients harbor germline mutations, and 10% of tumors had deficient DNA mismatch repair (dMMR).[14] In a cohort of younger patients (age <35 years) selected from a genetic counseling clinic, 35% had germline mutations[15]; dMMR is also more common among this younger age group.[16] Based on these findings, Dr Boland suggested that there is a germline basis for no more than 20% of EAO CRC and the other 80% are either etiologically similar to sporadic CRC occurring in older adults and represent one end of a Gaussian distribution, or they contain some proportion of tumors driven by other factors.

DNA Mismatch Repair Activity. Some EAO CRCs have deficient dMMR activity, which initially suggested the role of Lynch syndrome. Multiple studies[16–21] have shown that about 15%–21% of younger patients with CRC have dMMR tumors, similar to the prevalence (15%) of dMMR across all age groups. However, the genetic basis of dMMR differs markedly between EAO CRC and later-onset CRC. There are ≥4 causes of dMMR in CRC, and these causes generally differ by age. Biallelic somatic methylation-

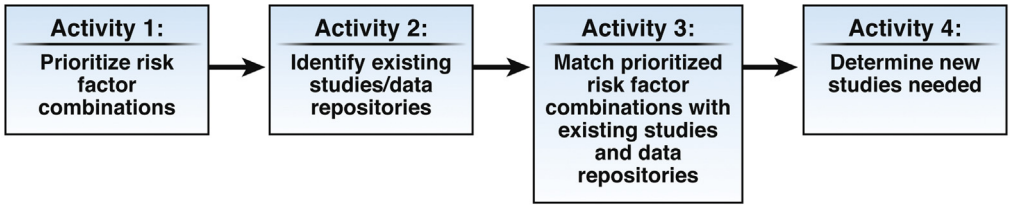

Figure 3. Structure and flow of activities at the Fight CRC EAO February 2019 working meeting.

induced silencing of the *MLH1* promoter is the most common cause in older patients and occurs in about 12% of tumors across all ages.[21] This epigenetic alteration is a reflection of a genome-wide methylation defect called the CpG island methylator phenotype (CIMP).[22] CIMP is substantially more common in older patients, not familial, and infrequent in younger patients. The remaining 3% of CRC with dMMR activity—and that are not CIMP—are either Lynch syndrome (germline mutations in dMMR genes), Lynch-like syndrome (2 somatic mutations in any DNA MMR gene), or rarely constitutional methylation of *MLH1*. Dr Boland suggested dMMR itself has different implications in younger compared with older patients.

LINE-1 Hypomethylation. A subset of EAO CRC have a substantial degree of hypomethylation at *LINE-1* sequences compared with later-onset CRC, and hypomethylation at *LINE-1* has been linked with worse clinical outcomes.[23] Importantly, *LINE-1* hypomethylation also leads to the re-expression of 3 oncogenes (*MET*, *RAB3IP*, and *CHRM3*), which may be responsible for the adverse clinical behaviors of those tumors.[24] Three groups have reported an excess of tumors that have neither dMMR activity (ie, they are microsatellite stable) plus there is no aneuploidy (ie, they also show chromosomal stability).[25–27] One group has reported homozygous deletions of the *NOMO1* gene in some cases of EAO CRC.[28]

Next Steps. Dr Boland concluded by highlighting the limitations of existing studies, including small sample size and selection bias. As a next step, he recommended a large confirmatory study, either prospective or carefully mined from publicly available databases. The analyses should include total exome or total genomic sequencing, including measures of DNA methylation and gene copy number variation. Cohorts should include patients with EAO CRC (most of whom present with symptoms) and patients with later-onset CRC, stratified by symptom-related detection and asymptomatic screen-related detection. It may help to collect fecal samples to correlate genetic and epigenetic alterations with changes in the microbiome. The genetic and microbial findings can then be correlated with tumor location, clinicopathologic features, and outcomes. Dr Boland concluded that based on his perspective, "It will be difficult to prevent this disease until we understand its biological basis."

Let the Work Begin

Attendees were assigned into 6 working groups by table (with a virtual table for online participants). Table assignments were made to ensure a mix of expertise was represented at each table in the fields of epidemiology, cancer prevention (research/clinical), molecular experts, oncology (research/clinical), basic research, and biostatistics. To ensure a patient advocacy perspective was infused in the discussion, a survivor representing EAO was assigned to each working group. To construct a productive discussion with clear outcomes, the working meeting agenda was developed into the following activities (Figure 3) with the intent that each group present $\geq$3 top priorities/combinations to the larger group, but also record all of the discussion and outcomes.

The working meeting outcomes are described in Overarching Themes and the full descriptive text from each working group can be found at Fight CRC's website at: https://fightcolorectalcancer.org/research/driving-research/under-50/.

Overarching Themes: All Groups

Activity 1: Prioritize Risk Factor Combinations

Working groups were first tasked with prioritizing risk factors and other considerations for future study. A list of well-established risk factors (eg, diet, smoking), as well as other considerations such as demographics and outcomes were provided. Groups created a combination of no more than 3 factors. As shown in Figure 4, 5 major themes emerged across all groups. These included diet in childhood, weight/obesity in childhood, gut microbiota (at various ages also including childhood), antibiotic use in childhood, and gene–environment interactions. Although the majority of groups indicated the importance of studying risk factors in childhood, all acknowledged the challenges of ascertaining exposures in early life (eg, recall bias, measurement error). Attendees also noted the importance of examining etiology by race/ethnicity and geography, given possible differences in the prevalence of risk factors across demographic subgroups, and stratifying analyses by anatomic subsite and MMR deficiency, particularly for studies of diet or antibiotic use. Finally, there was consensus across groups that, in addition to studying incident CRC as the primary outcome, advanced adenomas may serve as a surrogate outcome in this population.

Activities 2 and 3: Identify Existing Studies and Data Repositories, Match Prioritized Risk Categories and Existing Studies/Data Repositories

To investigate diet and weight, primary research studies that were highlighted amongst the majority of groups included the Genetics and Epidemiology of Colorectal Cancer Consortium, National Cancer Institute (NCI) Cohort Consortium, Nurse's Health Study II, Colon Cancer Family Registry Cohort, and American Cancer Society (ACS) Cancer Prevention Study. To study both the microbiome and antibiotic exposure as a child, participants noted research studies including the Nurse's Health Study II and the National Health and Nutrition Examination Study. To study gene–environment interactions, primary existing datasets to study included Genetics and Epidemiology of Colorectal Cancer Consortium, Colon Cancer Family Registry Cohort, and the ACS Cancer Prevention Study. It is important to note that many of these studies are part of the NCI Cohort Consortium. Additional studies and databases were identified, and the full list can be found at https://fightcolorectalcancer.org/research/driving-research/under-50/. Learning more about each of these studies and the included data elements was suggested as a next step, to more deeply integrate existing work into new opportunities for research.

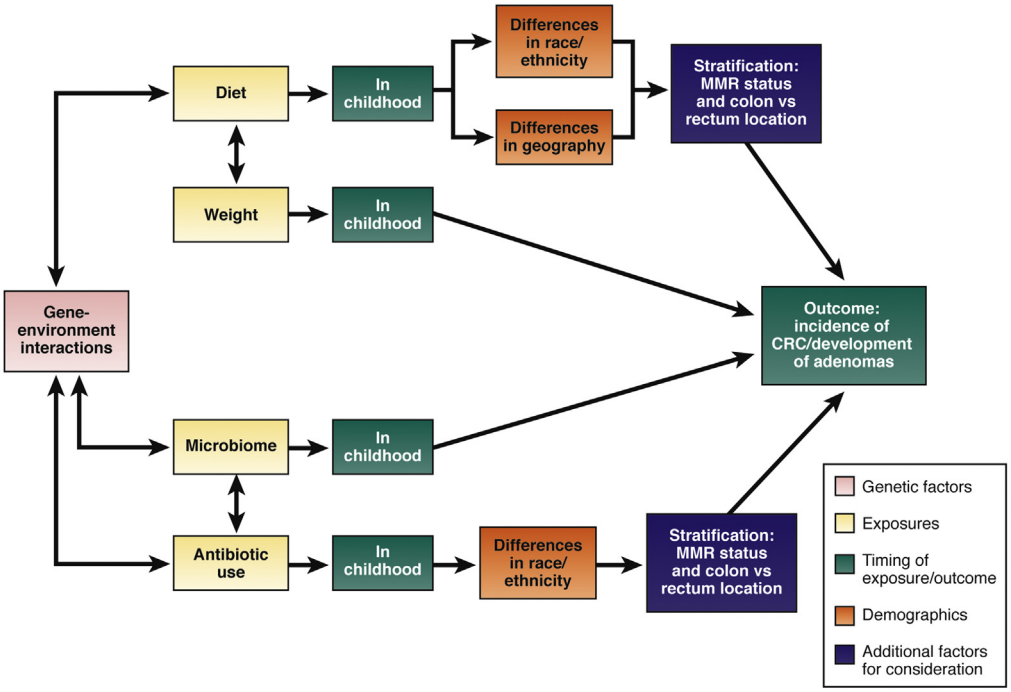

Figure 4. Major themes and risk factors of EAO CRC incidence or adenoma development, timing of exposures, and stratification of risk factor examination.

Activity 4: Determine New Studies Needed

Several groups indicated the need to create new studies to answer research questions. There was also a specific interest in integrating existing studies and cohorts listed in activities 2 and 3 into a new study. The majority indicated that a new prospective case-control or cohort study examining risk factors, including demographics, diet, weight, antibiotic use, and family history, would be beneficial. As a remote participant, Dr Cindy Sears, an expert in diarrheal and infectious diseases, noted potential study considerations when further studying the microbiome. These ideas can be found at https://fightcolorectalcancer.org/research/driving-research/under-50/. Additionally, groups indicated that collecting biospecimen data and samples (eg, tumor

Figure 5. Early-Age Onset Working Meeting Attendees: Denver, Colorado, February 1, 2019.

tissue, blood, DNA, serum) would be needed to complement information collected about risk factors. Starting a new cohort study completely from scratch was met with some caution given the considerable financial resources to collect data and biospecimens from birth across the life course. It was noted that collecting new data within the context of current, ongoing study parameters or launching a new prospective case-control study was more feasible.

Working Group Summaries

Fight CRC allotted time at the end of the meeting for Dr Ann Zauber to briefly explore research questions regarding CRC screening guidelines. This was in response to the change in ACS guidelines in 2018, to begin the average risk screening at 45 years (vs 50), and the impact on future guideline updates. The specific question posed was: "What empirical data does The United States Preventive Services Task Force (USPSTF) need to consider a younger age to begin screening for CRC?" Dr Zauber discussed the complexity of conducting studies to inform this effort. It is likely that some of the suggested research approaches at the meeting can help to inform guideline development, but not to the fullest extent needed. Dr Zauber shared specific ideas, which can be found at https://fightcolorectalcancer.org/research/driving-research/under-50/. This is an area for exploration in the next year.

Conclusions

The Fight CRC working group uncovered similarities between risk factors and the synthesis between groups to identify priority areas. Based on the working group and discussions, the major themes identified as key priority areas included diet, weight, the microbiome, antibiotic use, and gene–environment interactions. Each group had unique discussions regarding the relationships among risk factors and the best way to study each combination of risk factors (Table 1). However, there was strong acknowledgement that existing studies alone will not answer all questions regarding etiology of sporadic EAO CRC; therefore, many of the novel approaches should and could also be explored in future studies.

Throughout the course of the meeting, all attendees made new and meaningful connections with an expert who helped inform their research perspective on EAO CRC. Given the multidisciplinary, multi-institutional approach, all attendees reported having learned about new resources or opportunities related to the study of EAO CRC. The working meeting provided opportunities for resource sharing and collaboration amongst top experts in the field from around the world.

Even though this report describes the outcomes and proceedings of 1 meeting, attendees endorsed continued engagement with the working group participants, as well as other engaged stakeholders, to establish a prioritized research agenda for EAO CRC, which should then be promoted and activated with advocacy groups, provider organizations, funding agencies, and other potential partners.

Next Steps

Regarding the information shared in the meeting proceedings, we suggest readers consider the suggested purpose/use of the ideas developed at the meeting, which are intended for readers to:

1. Promote data sharing and the use of common data elements among institutions, research studies, and experts to be able to more comprehensively address EAO CRC cancers in larger numbers;
2. Spur investigators to consider novel EAO CRC topics noted as an important and viable avenue for research; and
3. Encourage diverse groups of stakeholders including survivors and advocates to collaborate on research ideas using intentional engagement processes similar to those deployed in this meeting.

As suggested by participants, within weeks of the meeting conclusion, Fight CRC used its research advocacy platform to engage the NCI, Centers for Disease Control and Prevention, the ACS, and policymakers to encourage exploring existing studies and data repositories. For example, longitudinal patient registries, ongoing funded cohort, or other larger-scale studies (including those outside of the cancer domain) can be used to explore hypotheses noted during the meeting, as well as for future explanation in more rigorous studies of EAO CRC, potentially also addressing limitations in biospecimen capture and genomic tumor profiling. Connecting with the NCI's Cohort Consortium is one of the priorities identified as a next step.

In addition, a subset of meeting participants are now discussing with the NCI the potential for programmatic funding for novel case-control studies and connecting current research endeavors to this effort. Fight CRC will continue to explore multiple funding options with the NCI, ACS, and Centers for Disease Control and Prevention based on their research and programmatic priorities. Anjelica (Anjee) Davis, President of Fight CRC, noted that Fight CRC is able to devote money and resources to support a shared initiative with seed funding as larger funding opportunities are cultivated.

The NCCRT and others have noted additional research priorities and also the need to address clinical and public health interventions, to decrease EAO; this is an area for deliberate examination. A full manuscript from Dr Jan Lowery as the lead author will be released within the year to share more detail about the NCCRT EAO CRC Strategy Session and future directions.

Attendees of the Fight CRC EAO working meeting underscored the need to publish findings from the meeting in a peer-reviewed journal and advance the work noted in the meeting findings through a formalized working group convened by Fight CRC on a quarterly basis (independent calls/gathering and at large professional meetings).

It is the intent of Fight CRC to share the February 1 EAO CRC working meeting proceedings, striving for a unified voice and shared vision to advance the EAO CRC research

Table 1. Unique Group Summary about Risk Factors and Potential Means for Future Study

Group and Members	Key Discussion Points	Other Considerations	Suggestions for Future Study
Group 1: Heather Hampel, Dennis Ahnen, Jose Perea, Mingyang Song, Phillip Buckhaults, Jessica Martin	Critical questions: Do patients diagnosed with EAO CRC have the same mutational profile as patients diagnosed with late-onset CRC? Is EAO CRC genetically distinct? Focus on methods that allow tumors to identify cause via mutation signatures Signatures may point to mechanisms involved in EAO CRC (eg, obesity, gut microbiota); some signatures may be active in early life	Unlikely that an increase in allele frequency (and resulting phenotypes) would occur in the short, 20-year period during which incidence has increased	Sequence tumors from younger and older patients diagnosed with CRC, as well as normal colonic mucosa from a control population Identify signatures enriched in EAO CRC
Group 2: Caitlin Murphy, Swati Patel, Luis Diaz, Richard Hayes, Anil Wali, Karen Wehling	Strong birth cohort effect points to risk factors in early life (eg, medications, diet) Focus on using and linking existing data to identify risk factors of EAO CRC	Differences in how exposures are defined across existing cohort studies present challenges Consider young adulthood as a proxy time period for childhood	Ecologic studies to correlate incidence trends with medications, diet, and obesity in childhood (eg, characterize policy changes in food supply) Link existing cohort studies with cancer registry data Leverage data from national health service or integrated healthcare system
Group 3: Paul Limburg, Rebecca Siegel, Joshua Demb, Andrea Cercek, Jeff Lee, Betsy Risendal, Curt Pesmen	Environmental exposures associated with EAO CRC are likely common and pervasive, as demonstrated by global trends in incidence Given time to progress from normal to malignant, focus on exposure assessment in window spanning childhood to early adulthood Evaluate risk factors across and within race/ethnicity	Developing a prospective cohort study not feasible given the number of attendees and follow-up time required Gene–environment and epigenetic–environment interactions may improve understanding of differences in incidence by subsite	Extend evidence regarding dietary factors and antibiotic use with existing data (eg, NHANES) Generate new data by reactivating National Children's Health Study or follow-up participants from trials of childhood obesity
Group 4: Jan Lowery, Ann Zauber, Hisham Hussan, Chris Lieu, Yin Cao, Violet Kuchar	Critical questions: what is the impact on risk of early changes in or prolonged exposure to microbiota, obesity, physical activity, and diet (eg, fiber)? Has exposure to these factors change over the past 3–4 decades? Do changes in microbiota increase risk of EAO CRC independent of other factors? Must address biologic plausibility to fully elucidate the role of the microbiome in pathogenesis of EAO CRC	More research needed to causally link microbiome with CRC risk, progression, and prognosis Need tumor tissue and stool at diagnosis and multiple time points prior to diagnosis, or ascertain indirectly via proxy measures Prioritize existing data sources with ability to recontact attendees	Pool large studies with patients diagnosed with EAO CRC and precancerous polyps, as well as controls Leverage existing studies with weight and diet measurements from childhood/adolescence and updated through diagnosis Stratify analyses by familial risk or exclude high-risk patients owing to suspected genetic susceptibility

Table 1. Continued

Group and Members	Key Discussion Points	Other Considerations	Suggestions for Future Study
Group 5: Steve Waring, Rick Boland, Caleb Levell, Patrick Blatchford, Jordan Karlitz, Claire Palles	Examine temporal trends in BMI, obesity, nutrition, and dietary patterns, with focus on impact to microbiome Inflammatory markers and somatic mutations also key to generating signals for further study Emphasis on exposures in early childhood/adolescence	Account for racial disparities and differences in risk factors owing to colon vs rectal cancer Simultaneously address gaps in knowledge regarding who and when to screen	Identify large cohort studies with genotype (or tissue for genetic assays), phenotype and robust follow-up Design large multisite study to collect genetic, molecular, environmental, and other factors
Group 6 (online): Christine Molmenti, Phil Daschner, Roberto Flores, Holli Loomans	Risk factors (eg microbiome) may be directly/ indirectly affected by other risk factors; several modifiable lifestyle factors (eg, diet, alcohol, sedentary lifestyle) are likely inextricably linked Focus on multiple risk factors in the 18–30 year age group	Anatomical presentation of the cancer (eg, colon vs rectum) among younger patients	Design a large, prospective cohort study of young adults without cancer; collect and biobank blood, urine, and stool before diagnosis Existing studies (eg, American Cancer Society Cancer Prevention Study) may partially answer relevant research questions in parallel

BMI, body mass index; CRC, colorectal cancer; EAO, early-age onset; NHANES, National Health and Nutrition Examination Study.

agenda. All information from the working meeting is shared on the Fight CRC website, urging the advocate and research community to build upon the Fight CRC EAO efforts at https://fightcolorectalcancer.org/research/driving-research/under-50/.

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Conflicts of interest
The authors have made the following disclosures: C. Richard Boland has presented several lectures for Ambry Genetics. Heather Hampel is on the scientific advisory board for InVitae Genetics and Genome Medical and has stock in Genome Medical. She has performed collaborative research with Ambry Genetics, InVitae Genetics, and Myriad Genetic Laboratories, Inc. Paul Limburg serves as co-Chief Medical Officer for Exact Sciences through a contracted services agreement with Mayo Clinic. Dr Limburg and Mayo Clinic have contractual rights to receive royalties through this agreement. Cynthia L. Sears received ongoing research support from Bristol Meyers Squibb and has delivered a Merck Lecture on Microbiome and CRC. Phillip Buckhaults reports receiving a commercial research grant from Janssen Research and Development. Luis Diaz is a member of the board of directors of Personal Genome Diagnostics (PGDx) and Jounce Therapeutics. He holds equity in PapGene, PGDx and Neophore. He is a paid consultant for PGDx and Neophore. He is an uncompensated consultant for Merck but has received research support for trials from Merck. He is an inventor of multiple licensed patents related to technology for circulating tumor DNA analyses and mismatch repair deficiency for diagnosis and therapy (WO2016077553A1) from Johns Hopkins University. Some of these licenses and relationships are associated with equity or royalty payments to Luis Diaz. The terms of all these arrangements are being managed by Johns Hopkins and Memorial Sloan Kettering in accordance with their conflict of interest policies. In addition, in the past 5 years, Luis Diaz has participated as a paid consultant for Merck and for one-time engagements with Caris, Lyndra, Genocea Biosciences, Illumina, and Cell Design Labs. Jordan J. Karlitz is an Advisor, Exact Sciences, and a consultant and on the speaker's bureau of Myriad Genetics. Dennis Ahnen is on the speakers bureau for Ambrose genetics and is a scientific advisor for Cancer Prevention Pharmaceuticals.

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