Andrea Dwyer:

Thank you on behalf of Fight CRC for joining today. I'm Andi Dwyer with University of Colorado Cancer Center, Colorado School of Public Health Advisor to Fight Colorectal Cancer. And we're super delighted to continue the discussion related to early age onset research and really building off a number of the themes and strategies that came from our meeting recently with Vanderbilt University as well as the NCI in a collaboration to talk about where we're going with direction for early age onset.

So at that December meeting, we shared a lot of perspective about the opportunities for understanding etiology, biology exposures and what does that possible complement for looking at strategies for research moving forward. So we had part one with Dr. Follamay and Josh Stem sharing some perspective based on the different types of interventions, risk stratification strategies. And then today we're turning on a TED again, much like we did in December to talk about that cross point in terms of looking at the biology exposure, etiology and where might we see the direction for research and even some of the shared opportunities with some of the themes that were discussed at the meeting and also in part one with Dr. May and Dr. Dem.

So I'm delighted to turn it over to my colleagues and friends, Dr. Caitlin Murphy and Dr. Cathy Eng who will be sharing the perspective as the folks who were the panelists, or excuse me, were the facilitators for the meeting and get the fun and dubious task of really synthesizing what was really come in terms of the themes from that meeting and thinking about that continued discussion as well.

So Caitlin from the University of Texas and then Dr. Eng from University of Vanderbilt. Dr. Eng, who is a board member for Fight CRC, and I think Cathy Wood is this your third Fight CRC webinar this week. So doing a lot of great work for the org. And Dr. Murphy as well, who's always really a fantastic collaborator, scientist in the work. So ladies, I will have you share a little more of your background as we get ready. I'll punt to you and before I get ready to go, Carly has put together or put in the chat the link for part one and any other details that we want to share today. Be watching for the chat.

There will be time for Q&A at the end, but all throughout the session as you have questions, please make sure that you are going ahead in real time, adding those in so we're keeping track of those questions and we can move quickly and efficiently through the Q&A session as well. So as we get started though, we will ask a couple of poll questions. So we would like to know from the audience today which one best describes you, as a patient, survivor, caregiver, blood relative, policy professional researcher, physician.

Tell us who you are in joining today. We'd love to get those responses. And I think Carly, we have one more after this and then we'll turn it over to Murphy and Dr. Eng. All right, Carly, how are we doing? We are good to go? All right, cool. So a little less than half per researchers, policy professionals, people who identify as survivors, about 10% caregivers, patients, about half of the group, as well as people who identify as clinicians. So great. And Carly, remind we have one more or are we set to rock? One more, research priorities.

If you are joining the organization as a researcher or someone who's interested in a specific area of research priority, let us know what you think in terms of order of priority, in terms of where we should be concentrating our expertise and our work. Gut microbiome, life course exposure, novel biomarkers, treatment of metastatic disease, early detection. And Carly, I believe we can denote which area of priority. So play with that poll a little. We can't hear as hosts and panelists vote, but we'd love to know the rating and ranking in order and we'll get that feedback real-time as well.

How are we doing?

Carly:

The answers are still filtering in, so I'll give it one more minute.

Andrea Dwyer:

Great. And I want to say thank you for Dr. Carly King, who's recently finished her PhD, who's joined the Fight CRC research team, and is going to be moderating and facilitating some of the questions, but today helping really make sure that the nuts and bolts of the webinar are working famously. But we're delighted to have Dr. King joining us as a Fight CRC, one of the research team members. So thank you Carly, and congratulations on your recent achievements.

And interesting. You want to interpret this for us Carly because I can't remember... There we go. There's the... So in terms of looking at the need from critical to not an immediate need, it really looks like we have a... Hold on. Sorry. Carly, you want to read through this really quickly [inaudible 00:05:23]

Carly:

It looks like early detection, 90% of the people who voted voted that that was the most critical. And there's just a variety of answers here. We'll have to take a deeper dive into this. Let me look at this throughout the course, then maybe we can bring it back up during the discussion.

Andrea Dwyer:

Great. And we'll continue to get a pulse check from everyone. I know that we don't have a ton of people on today, but we're going to be continuing to do a pulse check based on where people think priority and interests are when we have a captive audience. So with that, I'm going to turn it over to Dr. Murphy to kick us off, I believe. Caitlin?

Caitlin Murphy :

Can you all hear me okay?

Andrea Dwyer:

Yes.

Caitlin Murphy :

Perfect. Here we go. Well, hi everyone from Texas, we're excited to welcome you today. And I just want to start by quickly orienting us to the motivation for our session at the December meeting, again focused on the biology and etiology of early onset colorectal cancer. It's really no secret to anyone here that rates of early onset colorectal cancer are increasing in the US and worldwide. And in this figure you can see that the increasing incidence rates have manifested as shifts in risk across generations or birth cohorts.

So here I plotted the age-related acceleration and incidence for persons born in 1960s shown in this blue color, and for persons born in 1970s shown in the orange color. These birth cohorts are only separated by 10 years, but you can clearly see the shift in risk across these birth cohorts, and that remains largely unexplained. We know that increases in incidence rates or again, those shifts in risk across generations can't be explained by germline genetics, and instead, the environment is a key suspect. Our task as researchers, I think, is to identify what's happening in our environment that may contribute.

Cathy and I were really excited to organize and moderate this session, and we wanted to encourage out-of-the-box speaking by inviting speakers with expertise in the various ohms, such as the exposome, microbiome or epigenome. And in some cases, we intentionally invited speakers who had not previously

done work in colorectal cancer, but whose research can be adapted or applied for our purpose. These included Dr. Dean Jones from Emory University and who has pioneered methods to measure the exposome.

Dr. Mariana Byndloss from Vanderbilt with expertise in the microbiome. Dr. Cindy Sears from Johns Hopkins, also with expertise in the microbiome. And Dr. Kit Curtius who has expertise in computational modeling and has done some important work related to epigenetic aging and esophageal adenocarcinoma. We heard first from Dr. Jones about environmental and occupational exposures, globally termed the exposome. As a compliment to the genome, the exposome can be used to predict individual risk of disease like early onset colorectal cancer.

Dr. Jones began by reminding us that for many years we've recognized the environmental causes of cancer. He took us back to 1981 when Sir Richard Doll and Sir Richard Peto published this landmark study estimating the contribution of environmental exposures to cancer. For example, you can see in this table that, at the time, tobacco accounted for about 30% of all cancer deaths and diet accounted for about 35%. But despite having long recognized the environment as a cause of cancer, it wasn't until 25 years later that Christopher Wild, the former director of IARC, introduced the concept of the exposome.

In this 2005 editorial pictured here on the right, Dr. Wild argued that we need more sophisticated methods for measuring environmental exposures or again, the exposome, in the same way that we do for the genome. The exposome encompasses life course environmental exposures beginning in utero and is a shift from traditional approaches to measuring these exposures. It includes multiple co-occurring exposures and the interaction of these exposures with biologic responses that together are associated with health outcomes like early onset colorectal cancer.

Of course, there are many challenges to measuring the exposome. Unlike the genome, the exposome is highly variable and dynamic and evolves across the life course. Humans live a very long time and experience millions of unique exposures during their lifetime. Dr. Jones has pioneered the use of high resolution mass spectrometry methods as a new tool for measuring the exposome. As illustrated in this figure, he can capture a range of exposures in metabolites and blood or tissue samples.

Using a computational workflow, that's illustrated here on the right, he can then select mass spectral signals positively associated with the health outcome of interest, annotate these signals as metabolites or environmental chemicals, and then use network analysis to find exposome metabolome networks. Dr. Jones ended with an example of how the computational workflow, what he called exposome detective work, revealed important etiologic clues in breast cancer and can be used for a similar purpose in early onset colorectal cancer.

His laboratory used pre-diagnostic serum samples from women with and without breast cancer and identified five communities or networks of environmental chemicals and metabolites enriched in women who later developed breast cancer. And these figures, the environmental chemicals are denoted in the circles. For example, F3 and F4 here are pesticides and the metabolites are denoted in squares surrounding those chemicals. The network show us that environmental chemicals are associated with changes in amino acids.

And importantly, these amino acids are already known to impact pathways relevant to breast cancer. There may be opportunity to apply the lessons learned from this work to similarly identifying networks of environmental chemicals and metabolites enriched in early onset colorectal cancer. And I'll turn it over to Cathy now, who's going to talk about the microbiome.

Cathy:

I just want to make sure, am I advancing it or you are advancing it? Sorry, Caitlin. So I just want to reiterate, Caitlin and I are not experts in this field that we're speaking about. We're just trying to summarize what we had learned from our job as moderators for the think tank. And one of our speakers that day was the fantastic Cynthia Sears, who's done some very, very nice work looking at basically the microbiome. And really her focus also is on biofilm, which is something actually I learned quite a bit during her lecture as well as reviewing one of her papers recently.

So I know everyone wonders what's the difference between early onset patients and average age onset patients. And there's a lot of new work focused on microbiome. So Caitlin mentioned the exosome, which is very interesting, looking at basically this dynamic exposures that happen over time that may account for why patients develop colorectal carcinoma. But there's a lot of... Part of that is also our own microbiome and the impact of potentially antibiotics and other exposures that may impact how our GI tract works and how this predisposes us to colorectal carcinoma.

So Cindy Sears basically mentioned that there's just at this time about two paradigms. One being focusing on a single specific species of microbiome and how that may be accounting for the development of colorectal carcinoma. But a lot of her more recent work is now focused on biofilms. And so that's a new potential risk of colon cancer carcinogenesis. And biofilm is actually something that is very interesting in fact. There's a lot of work currently, and I'll show you a slide or two specifically regarding inflammatory bowel disease and the development of C. diff.

Which is commonly seen in patients that are exposed to antibiotics and as well as the impact that having biofilm basically results in resistance and actually predispose us to developing colorectal carcinoma because it basically forms a matrix. And so here on the left basically is a single species, and yet on the right here's where the biofilm is able to develop its own kind of matrix with an ability to become very, very resistant. Next slide. So here's the idea of a single series, which was one of the original thought processes. And fusobacterium is one of the bacterium that is commonly associated as a microbiome commonly associated with colorectal carcinoma.

And basically they looked at E. coli and fusobacterium. There's basically three different microbiomes that have been identified. Fusobacterium actually has been identified more delayed in the process, more common in right-sided tumors actually, and I'll show you a slide on that as well. And then E. coli. But next slide. Here, I think this is actually quite fascinating. Here's looking at biofilms, looking specifically at sporadic colorectal carcinoma. And this is from surgical specimens within the United States and Malaysia.

And basically comparing sidedness, so right-sided tumors versus left-sided tumors. And here they notice, and this is just from a series of different publications that have been reported. That there's basically decreased barrier function with right-sided tumors resulting in this biofilm carcinogenic potential as well as having some association with APC mutation, which is very common in the development of colorectal carcinoma. So this is more common in right-sided tumors. And as many of us know, right-sided tumors also are highly associated potentially for some of our patients that have a very poor prognostic indicator relative to left-sided tumors in regards to overall survival.

Next slide. Here, this is Cindy's work again, looking at the role of C. diff, she does a lot of work again looking at the role of inflammatory bowel disease. And these patients are more predisposed to developing C. diff. And basically C. diff for many of the physicians that note that patients that have had a lot of antibiotic exposure basically are at high risk for C. diff. And this appears to result in microbiota disruption. And so there's actually a lot of ongoing work regarding C. diff in the development of colorectal carcinogenesis. Next slide.

So here, this is how... If you look at the top, this is normal mucosa. And if you look at the bottom, the development of C. diff basically results in invasion of the crypts of these deep crevices within our colonic

epithelium in which C. diff can develop and place you at risk for developing colorectal carcinoma. So these were just mouse models, but I think this was very interesting and this is a lot of ongoing work at this time. Next slide. One of the other speakers was Mariana Byndloss, who's here from Vanderbilt-Ingram Cancer Center.

And she also looks at something a little bit differently, but focusing on disruption of the microbiome and basically looking at some of the exposomes. So high-fat diets versus low-fat diets and how this may impact our microbiome resulting in dysbiosis and whether or not there's an impact with antibiotic therapy. So on the left, basically environmental exposures, once again, as I stated before, high-fat diet antibiotic is her interest. And then how this may in fact impact the development of colorectal carcinoma and obesity if you've had significant antibiotic exposure and a high-fat diet early on in development.

Next slide. So what does dysbiosis mean? It's very similar to the concept of the exposome, but we're looking at how this impacts our own microbiome to our own gut. And so once again, having a metabolic syndrome, hypertension, obesity, diabetes, prior exposure from antibiotics, some potential exposure from a previous infection, for instance, C. diff as mentioned earlier, inflammatory bowel disease. And this basically results in dysbiosis. So I think this is a very nice graphic, so that's why I kept this here. Next slide.

So it's normal to have basically an anaerobic environment for our gut in order to reduce inflammation. However, when you're exposed to antibiotics, this basically can result in anaerobic glycolysis and increased inflammation. Next slide. So Mariana has done some very nice work, and actually she just did a nice publication recently about three months ago where they looked at high fat diet, early exposure to antibiotics in young adults and young children and the risk of colorectal carcinoma.

And this is some of her ongoing work in regards to her animal models as well as what we're trying to investigate in the real life setting in our patient population and asking this type of exosome exposure to determine risk factors. There's some very interesting data regarding early antibiotic use and obesity in children, which I found very fascinating. And so I would say that a lot of this work is ongoing. Thank you.

Caitlin Murphy :

Well, we ended our session with Dr. Kit Curtius who talked to us about aging markers that may be relevant for early onset colorectal cancer. And she first described this phenomenon of epigenetic drift or epigenetic aging. The process by which DNA methylation changes simply as a function of increasing age. And when we apply this concept to carcinogenesis, epigenetic aging can provide a measure of time from initiation to invasive cancer as illustrated in this figure here. And then that raises the question of whether we can intervene earlier by identifying those who age at an accelerated rate or by using epigenetic aging as a biomarker of risk.

Dr. Curtius presented several mathematical models that have been developed using epigenome-wide data and can classify fast or accelerated aging and slow aging. For example, this figure on the left shows the relationship between chronological age, here on the x-axis. And then age predicted from DNA methylation, here on the Y-axis. You can see that the two are very highly correlated, but you can also see that the model allows us to identify slow agers or those whose predicted biologic age is younger than their chronological age, and then fast agers or those whose biological age is older than their chronological age.

This mathematical model was later applied to 319 tumor and matched normal tissue from patients with breast, kidney, lung and skin cancer. And importantly, this model indicated that tumors have aged 40% faster than matched normal tissue from the same individual. In other words, tumor tissue is epigenetically older than normal tissue. And we can see this very clearly from the red circles on the

figure in the middle of your screen. Using that same model again, but this time measured in blood samples from individuals who are cancer free at the time of specimen collection.

We can see that epigenetic aging also predicts cancer incidence and mortality. And to me, the most striking finding in this figure on the right is the difference in risk associated with biologic age for individuals with a younger chronological age. So you can see in this yellow line here that younger individuals with accelerated aging have much higher risk of cancer incidence than younger individuals with decelerated or slow aging shown in this green line here. Dr. Curtius ended by sharing a study of accelerated aging and early onset colorectal cancer specifically.

And this study used tumor impaired normal tissue from 758 individuals diagnosed with colorectal cancer and then healthy normal tissues from 129 individuals without colorectal cancer. And then these individuals were further classified into three age groups. There was an early group or before age 50, intermediate or between ages 50 and 70 and older or later onset or after age 70. And for each of these three groups, the figures on this slide illustrate epigenetic aging and healthy normal tissue and impaired normal tissue.

So not too surprisingly, we can see that epigenetic aging and healthy normal tissue increases across these three age groups, but we see a different pattern in the paired normal tissue from individuals with colorectal cancer. The accelerated aging is increased in the paired normal tissue of individuals with early onset colorectal cancer, again shown here in this red color. Relative to the intermediate and older onset colorectal cancer patient shown in green and blue. This suggests that early onset colorectal cancer involves widespread and distinct epigenetic alterations, including those commonly associated with the aging colon.

If we can identify the cause of these epigenetic alterations, it may mean that we can use accelerated aging as a biomarker of risk. I'm going to turn it back to Cathy who's going to summarize the themes across the two tracks and then introduce our discussion questions.

Cathy:

Sorry. So the themes across the tracks basically are stated here. Multidimensional approaches are required to obviously understand early onset. I mean, we understand that it's not just attributed to one factor and it's likely attributed to multiple factors to account for why we're seeing early onset colorectal carcinoma. And with a focus on the exposome, metabolomics, microbiome, methylation, and genomics. And basically each panel emphasized the need for collaboration including sharing data and samples as well as greater communication amongst all researchers, clinicians, and patient advocates.

And we hope that future interventions will likely be tailored to individuals based on omics, but not necessarily one size fits all. So the key questions for discussion are what do we know and what do we not know and what do we hope to discover in the next five years and how do we integrate these findings? And are there additional opportunities to adapt methods used in other fields for our purpose? And can we better connect both bench and population scientists as well as obviously our clinicians to help lead this work? And how do we involve patients and advocates as well?

Caitlin Murphy :

We'll turn it back over to you, Andi and Carly.

Andrea Dwyer:

All right, awesome ladies, thank you so much. So I'm sorry, I just had a moment there trying to get my mic off. But I want to open it up and I think Carly, there's a way that we can go ahead and have folks

come off of mute. I don't see any specific questions that are coming up in the chat or the Q&A, let me just double check. Carly, you don't see anything either?

Carly:

Nope, there's no current questions yet, and I'll go ahead and make it so anyone that can... We have a hand raise, so I'll go ahead and put you off mute, Peter.

Andrea Dwyer:

Great.

Peter:

Yes, thank you. It was pretty interesting talk, but one of the... Recently in the last year or so, there's been a sort of notion that one of the most early changes in the DNA that long precedes cancer is the change in DNA packaging. My question would be, DNA methylation is obviously involved in this packaging, how do we know the aging is straight up aging versus the packaging of the DNA changing? Does that make sense? In other words, are these two things related?

Caitlin Murphy :

This is where the limits of my expertise become quite obvious. I wish we had Dr. Curtius, maybe she is on, I don't know, to talk more in depth about that specific question. I think it's an interesting hypothesis.

Peter:

Well, the main reason I'm asking is because a lot of times... I used to work in nutrition and I understand this whole DNA aging, but it's a very nefarious topic when you're saying that you're attributing methylation patterns to aging. The correlation line definitely shows that age and changes occur and sync with each other, but if something changes in the way the DNA packaging, would that show as aging, would be the straight-up question.

And if that's the case, then we need to start looking at how DNA packaging occurs because that's the earliest thing. I mean, if the first thing a cell needs to do when it learns to do a very different task is repackage the DNA, expose different genes, et cetera, et cetera. So it's a sort of chicken and the egg. And I think this might be the egg.

Cathy:

Just based upon I think the information that we are aware of. And once again, I want to be very clear, I am not a basic scientist. I'm a clinical researcher. And what you're asking seems very... It's a great question. I don't think it's unreasonable to presume that potentially, obviously the packaging, as you stated, could be part of the impetus for development of early onset. I know there's a lot of other ongoing research that focuses just not on methylation as well. I think we're well aware of that, but I don't think we have an answer for you. I think it's a very provocative question.

Peter:

It's not necessarily an answer. It's more like I think that the people that are doing that work and it's highly specialized work and very... They need to sort of open their eyes to what the other guys are seeing. I mean, this was a paper that was in Nature about six months ago that talked about how the

packaging and this long precedes any clinical indication of cancer. It's literally the first step to the track to transformation, not to cancer yet. Far, far away from cancer.

From my point of view and what I do is I'm much more interested in something that will let me see, this will become cancer with higher probability than this group. I am looking for very early detection. So I'm looking at anything that would give me a way to pick suitable groups.

Andrea Dwyer:

I see that Matt Young's hand is up too from the NCI, and I think Carly, we can bring that on. And I don't know, Matt, if you have something that you want to do direct reply and response to Peter's questions. But Matt, anything to add?

Matt:

I think Peter's comments were interesting and clearly takes a lot more development and understanding. My comments were actually too over the whole discussion. But on the aging component, there's an interesting concept of early onset aging, which is caused by stress, changes in the microbiome, environmental things, all the things that we hear about early onset colon cancer. So it's very likely that the two could be linked and we could approach it in that kind of... And it could also be associated with other early onset cancers, not necessarily limited to early onset colon cancer.

So clearly aging is a risk factor. If you're aging earlier, you may be at risk for developing cancer earlier. So those are very interesting components and I think we should be very aware of what our aging biomarkers look like and see if we can correlate that with early onset colon cancer. The second comment was about early exposure to antibiotics. And I'm not an epidemiologist, and I don't follow this, but if I recall right, growing up, exposure to antibiotics was a whole lot more common in an earlier time period than more recently where we know the problems and the complications of being exposed to antibiotics.

So if that was actually a cause, then would we expect to see somewhat of a decline as the physicians strayed away from over-treating with the antibiotics? Those were my comments.

Andrea Dwyer:

Great. I want to keep rolling with the questions because I think Anil also had some comments and make sure to include those as well. Anil.

Anil:

Thank you. Thank you so very much. These are fascinating presentations to both Caitlin and Cathy. Fascinating presentation and making it clear to all of us. I think we recently finished our session at AACR meeting where we had invited UK Grand Challenge winners, Dr. Yin Kao and Andrew Chen from Harvard and other investigators who talked about early onset colorectal cancer. And you guys have basically nailed it. These are all the confounding factors we are looking into, the exposome and environmental factors, and we have been working on this aspect from several angles and collectively at NCI, as Matt mentioned.

We [inaudible 00:34:17] from all of our divisions. The four major divisions, Division of Cancer Control, Population Sciences, Division of Cancer Biology, and Division of Cancer Prevention. We are all collectively working together to put a framework for a workshop and subject matter experts to further explain what the state of the science is being conducted on that. And I would like to mention about

these epigenetic clocks and biological and chronological aging. They play a huge role in various racial, ethnic, disparate groups.

So we have seen... On average African-Americans, we have noticed there are three years of biological versus chronological aging difference and how to tie it up with various diverse racial ethnic population groups where incidence, mortality rates of these early onset colorectal cancer as well as other malignancies are different. So it's a fascinating field of research and we are collectively putting all the resources into it. Thank you. Thank you so very much.

Andrea Dwyer:

I think Anil, it's great to have that confirmation of really hearing similar themes in different settings to really think about some of the strategies. Because I think as Caitlin and Cathy noted, part of the idea is we've already [inaudible 00:35:55] what we know, but there's a whole lot that we need to build from to really think about some of these new strategies and ideas. And I know Caitlin, one of the questions that came up in the comments specifically, you noted also talking about that role of the environment. And that's also an area that's starting to blossom in terms of really thinking about what is that connection.

And one of the things that also makes me think in the field of public health with the work with CDC and population health, those environmental connections around as it relates to cancer prevention and control, even our agencies and Anil, Matt and many others on the phone have talked about that interconnectedness of that exposure component. Caitlin, I know you and others have submitted even grants, right? Trying to create stronger connections with really studying these environmental exposures.

Anything else you want to say about where that field is going? Any opportunities or probably what you see is some of... As we're looking at some of the questions you have here, what is this direction? What are those opportunities that we see as wins for that coupling of what haven't always been natural partnerships with environmental exposures and teams that are doing studies as well as us in the cancer world who are sometimes even really looking more from an EPI standpoint. You want to talk a little bit about what your experience has been and maybe you see as future directions?

Caitlin Murphy :

Sure. I think it's a little bit challenging because historically we've measured environmental exposures as one thing. So one by one we've examined arsenic or some other chemical, and it takes a long time to do that. And I don't think that we have the time to test environmental exposures one by one anymore. And we have the methods now where we can really do discovery based work to identify thousands of exposures that may be enriched, let's say in specimens of people with cancer versus not.

So I think there's a lot of opportunity with the technology to move away from kind of this one by one hypothesis testing, but it really means changing the paradigm of research to more discovery based work.

Andrea Dwyer:

Right, I think that's great. And I think it pairs well with Matt and then Anil even some of the things that NCI and team have really been interested in exploring.

Anil:

I think Caitlin, and you are right on the spot here, and I don't want to spill some beans here ahead of time, but we are seriously thinking about the cancer clusters and cancer alleys and what's the role of natural disasters. And so something is brewing at the NCI level. We just had a meeting yesterday and trying to explore the framework as to how we could bring in the subject matter experts and the NCI

cohort, consortia, comments where there are some data available that have been captured at the NCI level.

But how to explore the utility of those large data sets, all of us data sets and the natural disasters, tornadoes, climate change, and some of the disasters we had in Ohio and other areas, how they exacerbate early onset colorectal, as well as other malignancies. So please stay tuned. We are trying to do something about it in terms of a think tank or a workshop where we would bring in all the subject matter experts.

Andrea Dwyer:

Great. And Caitlin and Cathy, I think the question that you have is in terms of also, because I know there's a couple of patients and advocates and Carly I'd bring you in as well, is I think really in part of the work we've really been talking about that intersection of research advocacy. And Carly, I think this might be a good time for... As we're getting some additional questions and to share where Fight CRC is putting some energy in terms of research and research advocates and how it really might connect to this work.

Carly, do you want to give a little bit of perspective, and I think even what you and Fong Gallagher are hearing from research advocates, how does that really connect in today? So Carly, can I put you on the spot for a sec?

Carly:

Sure. So I know through Fight CRC, we have our research advocacy training and support program where we can help train our patients, caregivers, survivor advocates, and even just understanding the basic science and how the basic science then can translate to more clinical translational research. So I think it's really important that we get the patients and our advocates involved as early as possible.

And I know that there's a few on today, so I'm hoping that maybe they will join in the conversation. I have it so anyone can talk and explain where they see their role. I would love to hear from them specifically.

Anil:

It was a delightful experience for us to host Fong Gallagher during our AACR session, and it was very well received at the AACR, as you know, it was attended... Very much that session was just triggered a lot of interest at NCI level, the CRC center to reduce cancer health disparities, all the divisions got very excited about this aspect.

So we welcome the patient advocacy groups and we have an office. And I think at some point, Andi, we had initiated that dialogue with the Office of Advocacy at NCI with Dr. Ned Sharpless. Matt was part of that. And I think with the new leadership at the NCI, they are very much open to have another dialogue on that front.

Andrea Dwyer:

And Anil, I think that's a really good point because Fight CRC does have a strong connection with the office of the director. And so I know Patrick and Amy and that team and then also really trying to make a strong connection, which I know Dr. Eng with the new NCI director and colorectal cancer is definitely an area of passion and interest. And so as we're continuing on, I think you're right. I can't tell you how many people have shared the interest and excitement that AACR had two things.

One, and early John said panel and discussion, which I know focused a lot on what are the risk stratification, what are the opportunities for intervention, but also some of the science and basic science

that was happening. But also I think I've heard great reviews and interest about really pulling in the research advocacy and the advocate voice. And so you're exactly right. I think Fong was great, but I have to tell you in a number of settings, I've just heard that people are just excited about this interest in really fusing those worlds and having NCI and our partners around the table to continue that is going to be great.

So I also just want to say Matt, Phil, Anil, the whole team and NCI have been amazing collaborators in this work, and this is something that we want to continue on as well. So it's awesome. I did scroll through and I see that Michael Holtz has his hand up as well. So Michael, we'll have you come off mute and ask a few questions and comments as well please.

Michael :

Not so much a question, but really just from the research advocate perspective. As a 12-year survivor of stage 3D rectal cancer who was diagnosed at age 43, this is a critical area of interest for me. Figuring out why this is happening, why so many younger people are being diagnosed. In the work I do on the daily, I work for a government contractor and we have a team of folks who are expert in exposure science. And so I have a huge interest both personally and professionally in understanding how exposure impacts the risk of colorectal cancer.

And it's my personal belief, and the science seems to be starting to bare that out in a big way. That it's exposure, it's the stuff that we're eating, it's all the processing and all the chemicals that we're exposed to that are increasing our risk. And how do we start framing that both to get more research done, but then also to change the policy that impacts those exposures. So there is a lot of work to do, and I see this as a member of Fight CRC's RATS team is part of why I'm particularly interested in this area of research.

Andrea Dwyer:

Absolutely. And Michael, we got a chance to hang out at the Cologuard Classic, and a couple of us met to talk about the RATS program and direction. And I think your passion and energy, definitely the type of things, and I know Cathy and others who see patients every day have questions about why is this happening and what does this look like and what does this mean for individuals and people who've already been diagnosed as well. So I do think you're right.

This is an area of passion and area of interest and why we're putting a lot of energy and really looking at that opportunity to make sure, Michael, you and others have a chance to sit on those NCI panels, share that perspective. And I think to continue to do some great advocating for policy work. Which I think even at the federal level, Yadira Caraveo has put in for some early age onset federal, for messaging, hopefully some area of research moving forward, specifically targeted working with CDC and others.

So this is an area where we want to continue to have some conversation and really think about it. So Michael, thank you for your passion and energy. And I think anyone else who's joining on the phone who wants to join in that work, Angie Molly and the Fight CRC policy team have a lot of amazing things that are really starting to move forward and even to this next legislative cycle. So that will be something. And Michael, thank you so much for all of your dedication. I want to just scroll through here.

The other thing I wanted to ask... And Caitlin and Cathy, I know on your slide, one of the questions that I'd ask Matt and Anil, I do think that whole idea of what's happening, and Anil, you touched on this on some level. But one of the things we've talked a little bit about those cross collaborations because I think Kit Curtius, some others, Dean Jones who attended this session and presented. Caitlin had helped us make some connections with folks who actually have done work in other types of cancer.

But the question is, can we apply what we've learned in some of this ideology that owns the exposures?What are some of the things that we can do, maybe coupled with other cancer types is we know early age onset disease for colorectal is happening, but it's also happening in breast and lung. So I think Matt and Phil, excuse me, Matt and Anil, Phil's on today, when the NCI is thinking about this work, and to the extent that you can share what you might be considering even across the cancer types, I mean for the people who are doing research and thinking about policy and advocacy moving forward.

Is there some specific direction in terms of really looking at collaborations amongst the different cancer disease types? What do you think their trajectory of opportunity is there?

Anil:

So Matt, you want to take a first stab? Please go ahead.

Matt:

Sure. Of course. It's always a moving target where the NCI is wanting to put money. I personally believe that working in consortiums in collaborative groups, we learn a lot more and we have more power and we're able to do more. In terms of looking for biomarkers or early signs, I don't think we have the numbers to statistically power studies looking at colon cancer or breast cancer. So I think by combining these into a large collaborative groups where multiple types of samples can be collected, where the controls will be controls for everybody, and then the cancer rates would be common for across the groups.

They would pick up colon, they would pick up breast, but this would allow us to show the statistical elements. It's really required to do any kind of power calculations in these groups. So that's one way to approach this in terms of a large group. And the other way is to work with the National Institute of Aging in terms of the aging biomarkers. And we have a working group that's going down that area, but at this time, they're more interested in the effects of cancer on aging versus the effects of aging on cancer.

And I've been working with them, but maybe the presentations we just heard about might be a good item to bring to this working group to show that early aging is a problem. Go ahead.

Anil:

Yes, yes. I think you nailed it pretty well. I think we here at NCI are trying to work among ourselves because we are siloed here as well among various divisions as I mentioned, DCCPS, DCP, DCB, DCTD. So we are working here collectively together to build on consortia. So one of our recent consortia was Medoc, we call it Medoc. We are looking at the linkage between obesity and the obesity related cancers. There are 13 different cancer types that are directly linked with the obesity challenge.

So same thing happens with diet and all that. So we have funded five sites. So I think it's publicly available at DCCPS site. And we are collectively working together from various divisions and we are managing that as a program directors as well as project scientists. And as Matt mentioned, we have a working coordinating committee with the National Institute of Aging because that is the underlying major risk factor. And it's been an ongoing effort, collective effort with National Institute of Aging.

And I would also suggest here, based on the presentation we looked at, there's a powerhouse at Vanderbilt University. So there are like-minded individuals at Vanderbilt. And similarly, they could partner with other investigators and apply for program project grants, PO1 grants, so that collectively multiples PIs from various disciplines could come together and address this early onset colorectal cancer phenomena.

Andrea Dwyer:

Excellent. Thank you. And again, I'm so delighted that we have so many of our NCI colleagues joining in all of the work as well. Cathy, let me ask you as well, I think as someone who is a clinician who helps really and has really let out one of the models for an early age onset clinic. When you're thinking about clinic, these opportunities and the direction, I mean, what do you think as a clinician for an opportunity as well as even pitfalls as we're talking about developing the research I guess in this area, anything specific that comes up as a leading clinician and oncologist in this area?

Cathy:

Sorry, can you repeat your question again? I think I missed the first part.

Andrea Dwyer:

As someone who is clinically working, and really I think to Anil's point who has... I mean you have set up one of the country's model clinics for early age onset disease as it relates to treatment and oncology. But when you think about the space of even being able to work with patients to even implement the sort of study around exposures, etiology, what do you think are some of the opportunities as well as maybe even complexities of being able to do this sort of research probably on some level retrospectively to gather information with folks? What do you think?

Cathy:

One of the big challenges is that every single institution, for the large part, there's various amazing individuals, but they're often siloed due to... They're very focused on certain aspects of research. And as stated earlier, we've got to get people out of those silos and have to do these cross-departmental collaborations, which we are trying our best to do. I think the challenges currently that we are myself as well as many others, is the fact that we've done a lot of research already.

We've seen a lot of research from our other colleagues as well, which really hasn't defined exactly what is the exact etiology to account for this. And so the research moving forward is going to be long-term research. We're not going to have immediate answers, and I think that's going to be the toughest for our patient population because they want answers now, right? They want to know why this is happening. They want to know how they can change the treatment paradigm for them to improve their overall survival. And I think that is the biggest challenge for our early onset patient population.

And so that's why I think it's extremely important to focus on education and awareness so we can hopefully diagnose these patients earlier in order to improve their overall survival and learn more from these patients. Hopefully with time, and hopefully we can have many more patients that are diagnosed early on and we can learn from these patients. But I think it's going to be a very long... It's a very large longitudinal project. I think that's where we just have to be patient. But I think we understand the urgency. Obviously there's many novel therapies that are currently being developed at this time, which don't necessarily apply to early onset.

But I think that we are trying to grasp it from multiple aspects. But I think the largest thing is that we're going to have to be a bit more patient, but really for the time being focused on education awareness so we can diagnose our patients earlier and then moving forward, myself and many other investigators as Anil stated that are really just interested in trying to figure out why this is happening, but it's not going to happen overnight. And I think that is going to be the most challenging thing, honestly.

Andrea Dwyer:

Yes, absolutely. I will say this, and I'm going to have Dr. King close us out today, and just a huge thank you to Caitlin and Cathy in terms of their expertise, willingness, I think, to help pull together a panel from a variety of disciplines and really think this through. But I do want to say, I think to the point that Dr. Eng made is that through these discussions, we will be really talking about what are opportunities for really getting people diagnosed sooner, finding earlier resolution to signs and symptoms, looking at earlier interventions.

So we can hopefully prevent as much as we can at a minimum, start earlier work-ups and downstage disease if at all possible. So I think there's a lot of areas for us to really tackle as it relates to this early onset paradigm and what's happening. And so I do think stay tuned. There's going to be a lot that will be provided in terms of opportunities as it relates to awareness, policy, research as it relates to many fronts and really thinking about how to convene and continue these sorts of discussions.

So thank you so much for the time, ladies. I really enjoyed hearing this discussion, continuing this work. Carly, I will have you close us out for today and we'll talk about some of our next steps. So Carly.

Carly:

Sure. Thank you Dr. Murphy and Dr. Eng for joining us today. And everyone else in the audience that contributed to our discussion, our collaborators, experts, and our advocates, we really appreciate you joining us. The next step would be, we're hosting our think tank on June 25th from 12 to 2 P.M. Eastern Time. And the link to register can be found on the Fight CRC website on the events calendar, or I dropped it in the chat. So please register.

And we're going to be talking about those things that we can do for more immediate impact strategies that we can have for implementation now. So that way we have work to be done now and then the more long longitudinal work that we need to be a little bit more patient for. So thank you for everyone for joining us, and we hope to see you next time.