Andrea (Andi) Dwyer:

So hi everybody, I'm Andi Dwyer. I am an advisor to fight colorectal cancer with the University of Colorado Cancer Center, and I'm super excited to have Dr. Fola May and Dr. Josh Demb joining us today to continue the discussion dedicated to early age onset research and colorectal cancer. So we're super excited today as both of our experts and panelists will be talking about the current state of risk stratification, population screening, identifying barriers, opportunities, and then really thinking about from a multidisciplinary opportunity, really thinking about possible questions as it relates to the other aspects of etiology, causation, and other aspects of the early age onset question, how can we think about some great opportunities for research and really thinking about thwarting early age onset colorectal cancer moving forward? So we're going to spend some time today with both of our panelists. We'll have a few polls, and then we'll be sharing a little bit about the series.

Carli will be sharing a little bit more from our team based on programming we have in May, and then also coming up in June as well. So a quick reminder that this work is building off of a part of the work that we have been really iteratively working towards towards research question fight CRC as a research advocacy organization working on since about 2019. But today's really going to really address and really trying to put some synthesis around some work that we did with the NCI and Vanderbilt Cancer Center in December, talking about some of those same themes and continuing this discussion about how do we really continue early onset research moving forward. We will have plenty of time for discussion today. No right or wrong answers, we just really want some great discussion opportunities for collaboration and really thinking about how we're continuing to move the needle. So I will hand it over to Carli for a few questions that we have just to start some polling and getting everybody interactively engaged in today. Then I'll turn it over to Dr. Demb and Dr. May for our presentation today. So Carli, it's all you.

Carli King:

Hey everyone. You should see a poll that's asking you to please choose which best describes you. So I'll leave that up on your screen for a few seconds and then I'll let everyone know the results.

It looks like the majority of people online have responded. So we have 25% researcher, 25% physician, and then we have about 50% that's divided between patient survivor, caregivers, and blood relatives. So thank you all so much for being here and for answering the poll. And we'll share one more poll during the discussion after we hand it over to Fola and Josh. So we'll go ahead and hand it over now and we'll have another poll at the end during the discussion.

Andrea (Andi) Dwyer:

Okay, great. Josh?

Fola May:

Thank you so much everyone. I'm not Josh, but I'm Fola, but I'm going to pull up the slides so Josh can get started.

Andrea (Andi) Dwyer:

Oh, sorry about, Fola.

Fola May:

Hi everybody. Josh and I are really excited to present today and to do some recap from the meeting that we had a few months ago. Josh, can you see those slides?

Joshua Demb:

I can.

Fola May:

Okay, great.

Joshua Demb:

Thank you so much, Fola. And I'm Josh Demb. I'm a postdoctoral researcher at UC San Diego, and I had a great opportunity to work with Fola as a moderator of this session. And so what it really covered was the opportunities for under-50 risk stratification and population-based early intervention strategies. Next slide, please.

Fola May:

Okay. Yikes, okay.

Joshua Demb:

So we had three awesome talks that covered the breadth of some of the key areas that we think about when we think about risk-based screening or detection. And so we wanted to spend a bit of time just talking through the findings from each one of these, but really wanted to start with giving a recap of the landscape of how it looks right now in colorectal cancer in the United States. Next slide, please. So this is the most recent evidence coming out of the American Cancer Society in their colorectal cancer facts and figures report. And the data really show these diverging trends where adults ages 20 to 49 have an increasing incidence. We're seeing a flattening of the incidence curve where it was previously declining in adults ages 50 to 64 and a continued decline in colorectal cancer incidence in adults 65 and older.

And the mortality trends really then match what we're seeing in incidence. Though, if you look at these tables, there's slightly additional timeline, but if you look at the middle of the mortality curves, that matches up in time with what we're seeing in terms of the incidence curves where we're, again, seeing those increases in the younger population and declines are flattening of the curve in the mid to older populations. Next slide, please. What we're also seeing that was particularly interested is in our SEER data, so the National Cancer Registry data in the United States, what we're seeing is there's this greater distribution of colorectal cancer cases across different racial and ethnic groups, whereas in 1992, we saw over three quarters of cases were in adults who identified as non-Hispanic White. We're seeing this greater distribution among those who identify as Hispanic, non-Hispanic Black, non-Hispanic American Indian or Alaska Native, and non-Hispanic Asian or Pacific Islander. Next slide, please.

And so this really set the framing for the first talk in our session, which was led by Dr. Ann Zauber and Dr. Iris Lansdorp-Vogelaar, where they really wanted to contextualize colorectal cancer screening guidelines worldwide. And Dr. Zauber really set the stage in thinking about the screening guidelines by starting with the work that Dr. Winterworth did with the National Polyp study and really thinking forward about how this dictated where we ultimately got to with screening guidelines. And so what we show here on the slide is the first decision-based analysis that justified the US Preventive Services Task Force recommendation for colorectal cancer screening to begin at age 50. Next slide, please.

And really, as the access to screening evolved and the different tests became available and more widely accessible, we started expanding our thinking not just to the age at which a screening could be initiated, but then also thinking about different types of cancer screening strategies and really thinking at a population level about the potential harms and benefits and how this could be incorporated into a

broader screening program. And so in 2016, we start seeing that even though the colorectal cancer screening recommendation was to begin at age 50, we started thinking more dynamically not just about colonoscopy, but about other potential strategies that could be employed. Next slide, please.

But in 2018, this was really the beginning of when the modeling data that informed some of these recommendations started to incorporate this epidemiologic trend that was indicating the increasing incidence in adults under 50 and really started to give us an idea of what it might look like to lower the colorectal cancer screening starting age in the United States from 50 to 45. And so this was the first time in the plot you see on the bottom of our graph there is an indication that starting screening at age 45 rather than starting at age 50 could yield a potential benefit as based on the efficiency curve. And this was what informed the American Cancer Society's qualified recommendation to lower that screening starting age from 50 to 45. Next slide, please.

And ultimately, this was the inertia that drove the next steps in terms of the task force recommendations three years later, which ultimately led to the colorectal cancer screening starting age lowering to age 45, and adding onto what the American Cancer Society's recommendation did. The task force coverage of this screening in this younger age group meant that this was covered as an essential health benefit under the Affordable Care Act, which meant that for these adults, they were newly eligible and that cost sharing would be covered as part of this recommendation. And so they had access to screening for very little and most likely no cost. Next slide, please.

But with this incorporation of the younger age group, we really have to think about that balance of harms and benefits going back to what we were initially talking about in 2016, and really think about, what does it mean to incorporate the 45 to 49-year-old age group? And so we have the potential benefit of preventing colorectal cancer in the 45 to 49-year-old age group. And in that early onset age group, we know that the epidemiologic trends indicate the highest incidents in the 40 to 49-year-old age group. So identifying cases in this highest group in this younger population is very important and make sure that we're detecting these cancers as early as possible. It's also helping us identify high-risk cancers in other groups. The American Cancer Society came out several years prior recommending that non-Hispanic Black adults get screening five years earlier than the average risk screening population.

So continuing this trend of trying to identify this group before 50 and then thinking about ways that if we incorporate this group earlier, we could potentially increase screening among adults ages 50 and older and maximize that uptake later. But we have to balance this against potential unintended consequences, one of which is the diversion of resources to lower-risk populations where we really see that even though the epidemiologic trends indicated increased incidents of early onset colorectal cancer, really understanding this in an absolute context or a population-based context where some of these older age groups, whether they be in the 55 or older range, have a higher absolute incidence of cancer. And so by incorporating this younger age group, we might be unintentionally diverting these resources away. This could also, by incorporating this younger group into the population, it could lead to an extension of the screening disparities that we already see in adults ages 50 to 75. So we really need to be thinking about focused strategies to reach out to these populations.

There's also substantial resource costs that need to be considered and thinking about not just maximizing screening outtake in these populations, but really thinking about the strategy to be employed. From a research standpoint, by changing the guidelines when we did, it limited our opportunity to really measure what screening effectiveness could look like in younger adults, though there are ongoing studies to try to understand this in the early incorporation of this younger age group into the screening eligible population. And the last note here in this unintended consequences box is one that's particularly notable, which is that the actual benefits may fall short of predictions. The

modeling evidence that we've shown in the prior slides is set with the assumption that the screening population has perfect adherence to screening uptake and follow-up.

And from a population-based standpoint, this is super important for us to see what the optimal benefit might be for a colorectal cancer screening program if it's running on all cylinders. But as we know from other efforts around the United States, we're really working to make progress in this area. We're seeing that screening uptake rates are between about 60 to 70%, depending on the population. It might be lower and higher in different communities, but there really are some needs to increase that screening uptake and really think about strategies so that we can see this maximal benefit. But in the absence of everything running on all cylinders, we're falling short of those potential predictions that justified or guided that change in the recommendation to lower the screening starting age. So it leads to that question of whether risk stratification screening can be used to alleviate some of these concerns. Next slide, please.

And so when we think about these screening recommendations, we have to really think about four key questions here, thinking about who needs to be screened, what are the appropriate intervals, which methods should be employed, and then what is the appropriate agent? We've kind of addressed to a point some of the aspects of the appropriate age, but these are the major contextual questions that we need to be thinking about as we think about what goes into that recommendation for screening. But this isn't a US specific issue. We're seeing trends of increase in colorectal cancer incidence around the world.

This figure really shows some of the trends that we're seeing in other countries around the world where the red bars reflect the incidence rates in 2020 and what we estimate to be in 2040. And so what this has done in screening programs across the world is that the screening guidelines tend to vary by country ranging from as early as 40 years old to as late as 60 years old. But what we're seeing around the world indicates that there may need to be a review of global screening guidelines. Though, keeping in mind what we know currently and what we've learned from our screening programs, there might be significant challenges and implications that we need to consider. So with that, I will hand it over to Fola.

Fola May:

Perfect. Thank you, Josh. And we do have a couple more presentations from the summit that we want to summarize, but please be ready because in a few minutes we'll engage in some conversation, really talking about how we want to move the needle forward in this area of research and investigation. After that set of slides or discussions, we had a presentation from Dr. Jose Perea Garcia and Dr. Heather Hample focusing on research and implementation and risk and family history and risk stratification. So now I'll spend a few minutes summarizing their major points.

We discussed how a substantial portion of early onset diagnoses in patients with a family history of colorectal cancer or hereditary cancer could be preventable, and specifically preventable if high risk screening guidelines were followed by the majority of the population and as well as even if just the average risk screening was initiated at the right time at age 45, highlighting that it's critical to develop and implement method for collecting family history to do that first part, which is the high risk screening guidelines, but also emphasizing that we can capture even more people if we screen at the right age. So this was data from 2017 showing that 29% of early onset colorectal cancer are potentially preventable by taking better family history and also engaging in timely or earlier and more frequent screening and surveillance.

The critical question that was discussed in a publication by Standish et al was, what proportion of early onset colorectal cancer is preventable? Getting back to this point. This study aimed to determine the proportion of early age cases that were preventable if high risk screening guidelines were followed, and if at the same time, average risk screening was started at age 45. This is a prospective cohort of people

or individuals newly diagnosed with early onset colorectal cancer in Ohio. And in this protocol, all of these individuals provided a family history and received germline multigene panels. What they found were that there were 713 patients diagnosed with early onset cancer in this cohort. Of these, there were four major groups. The large majority, so 80% and no family history and no hereditary syndrome. And it was estimated that 41% of these individuals would've been diagnosed earlier if screening was appropriately performed at age 45. So even in this group, no high risk syndromes or risk factors, we are underperforming by quite a bit.

The second group highlighted was the group of 64 individuals, about 9% of the sample that did have a family history, but no hereditary syndrome. And this had some crossover with an additional 33 people who had a family history and a hereditary syndrome. And when we looked at the data from these two groups combined, about 14% had a family history of colorectal cancer. And of these, if guidelines were followed more appropriately, 83% would've been diagnosed earlier and up to... Whoa, I'm sorry, I don't know what's going on with the slides. Let me go back to where we were. Up to 67% potentially had preventable CRC. So again, major areas for potential reduction in burden of disease. And the crossover or last group here that I want to highlight is the 7% of people who did not have a family history but did have a hereditary syndrome.

And of these, if guidelines were followed, 97% would have been diagnosed earlier. So big potential risk or disease burden reduction there. And another big group, 90% had potentially preventable CRC. So this is a smaller group, but also we're underperforming. After that lecture, we heard from Aasma Shaukat from New York about population identification, really using stool-based screening and emerging technologies and research opportunities for early onset colorectal cancer and beyond. So these are data from 2020, looking at the percentage of adults aged 50 to 75, so before the newest guidelines were implemented, fully meeting the United States Preventive Service Task Force recommendation for screening. And we looked at these data specifically by state. So first, you can notice that across the United States, there are differences in screening participation by state, where you have states in the blue colors here in the northeast, Michigan, Pennsylvania, where you've got relatively high uptake of colorectal cancer screening, really meeting the NCCRT goal of 80% in some of these states.

And then from there, you have a downward trend of uptake of screening, the lowest uptake being in the 54 to 71% range in these lighter green colored states, also including my home state of California. So we definitely see variation just regionally. We also see variation by race and ethnicity where white individuals have a higher screening rate than other individuals or other racial ethnic groups. You'll notice here that this gap between African-Americans and white individuals has closed or I'd say narrowed in recent years, although we still see significant disparities when we look at Asian individuals and Latino or Hispanic individuals. And then other areas where we have big variance is in insurance status.

So we know that individuals who are uninsured are less likely to participate in preventive health services, including colorectal cancer screening. Even people who are insured but do not have a regular health care provider or HCP, as indicated here in this box, are less likely to be screened for colorectal cancer. And then highlighting, again, as we've been focusing on in this discussion, that adults 45 to 49, which is the newest group implicated for screening, is an introduction of 21,000,000 individuals to this challenge where we already have quite a bit of variation in disparities.

So currently, the national average for meeting screening guidelines is thought to be around 59%. It really depends on whether you use self-reported data or EHR data. Nonetheless, all of these numbers are far below the NCCRT goal of 80%. As I mentioned, there are significant disparities in population adherence to guidelines across the United States, and we have improved in our implementation science to increase knowledge about the importance of colorectal cancer and screening uptake. And this has included organized screening programs, which are usually through health systems. Patient navigation, which we

know is very effective in people's screening for colorectal cancer and particularly for stool-based screening, achieving follow-up after abnormal screening. We know that offering choice of screening tests, specifically offering patients colonoscopy, but also a stool-based screening test can influence screening rates in a population of individuals. And the other thing that we're actively studying now is how the emergence of new test options will impact screening participation across our nation and worldwide.

So highlighting here that we will have an emergence of new stool-based tests. We recently saw the publication of what we're calling ColoGuard 2.0 in the New England Journal last month, but we also are going to see the emergence of blood-based screening, not yet recommended by the USPFTF, but definitely receiving some endorsement from CMS with guidance there on how to make these tests acceptable and a lot of interest in the public and the idea of getting a blood test to screen for colorectal cancer. But this does open the door to additional challenges. Josh discussed some of the challenges that we saw with lowering the screening rate, weighing those pros and cons, and we as well need to weigh the pros and cons of looking at these new screening tests as they are used more and more publicly. I'm going to close this out here by just highlighting some of the recurring themes that came up during the meeting, and that will hopefully bring us to a discussion about what we can do moving forward.

First, I want to highlight that there are significant disparities in the United States and probably globally in the adherence of colorectal cancer screening guidelines. There are also differences in screening guidelines when we look in each country in the world. We also know that identifying factors that are associated with the lack of screening in communities will provide an avenue for intervention. So when we do our implementation science, we focus on the barriers and we focus on the facilitators. We try to address those barriers through multi-level and multi-component interventions, and we try to highlight facilitators that can help increase screening participation. In the middle here, I'm highlighting that all stakeholders must be involved in collaboration at an international level. So we feel that we'll be most effective if we have help from industry advocacy organizations, doctors, researchers, patients, survivors, caretakers. It's going to take all of us working together, and that was a theme that really came out in the meeting for us to get this job done.

The needs include infrastructure development, multidisciplinary approaches, and data sharing. And we had a lot of really lively discussion about how we can engage with data from industry, from insurance plans and use those data to better understand what's happening, but also to move us forward towards interventions that are effective. Lastly, there was a big focus on future interventions and particularly tailoring those interventions to the individuals that they're meant to serve. And also particularly their exposure, their microbiome, their epigenetic age, their specific risk profile, and how we can be even more savvy in how we develop our interventions. I think this is our last formal slide before we head into discussion. And really, what we want to do right now is highlight these main takeaways, but also open the door to having a discussion about actionable items and the key to advancing CRC research, particularly as we face the emergence of new screening tests and the increase in the disease in young adults.

So specifically we ask you, what do we need to consider when evaluating screening guidelines? And this is domestically and globally. Number two, how do we accurately collect family history? Because as we've shown, that's going to have a huge role in making sure that we maximize the potential of screening guidance. Number three, how do we achieve 80% in every country, state, and neighborhood? Number four, where do stool and blood-based screening methods fit into screening guidelines? And number five, how do we integrate the microbiome, exposome, other factors to screening and risk stratification strategies? So we're hoping that in the next 30 minutes or so, we can maybe take on these questions one by one and gather some notes from our audience. Thank you very much. Andi?

Andrea (Andi) Dwyer:

Thanks. So Josh and Fola, this is awesome. And what an amazing recap for, what was that, three to four hours. So good work. And thanks, Carli, for synthesizing a lot of this as well. I wanted to say, before we get ready to go through the specific questions one by one because we really would love to have an open dialogue, Josh, Carli, I want to make sure people can come off mute, correct? We can unmute lines so we can have a discussion?

Carli King:

If someone wants to be unmuted, I can unmute them.

Andrea (Andi) Dwyer:

Okay, sounds great. So send a flag if you're interested in chatting. Let me just make sure we don't have any specific questions about any of the data that came through in the recap or otherwise, Josh and Fola, we will get jamming on the questions. I didn't see anything come through the chat, just want to make sure we're good.

Fola May:

Yeah, you can place your questions in the chat or we can help you unmute.

Andrea (Andi) Dwyer:

Okay. So I guess as we get going, Fola and Josh, are we cool with just starting to take the questions one by one? And I think it'd be awesome if you too, as we get things going, coming from the December meeting and having some times to ponder and also seeing there was that second track through the day where we did talk to your point, Fola, around the microbiome, the exposures. So when we're thinking about these questions, we are talking about I think this risk stratification, what are some of the themes? But as you mentioned, some of the other elements that are coming in. But I guess for this first question in terms of consideration for evaluating screening guidelines, you brought up some of the themes of course around differences in international, different approaches, different guidelines, but what's coming up for you two as you think about this first question, just to kick us off?

Fola May:

Yeah. And I'll start, Josh, unless you wanted to jump in [inaudible 00:27:11].

Joshua Demb:

No, no, go for it, Fola.

Fola May:

I think the big things that we have to consider, obviously age, which we focus on a lot, screening modalities. Because you look at countries like the United States where in some settings upwards 60, 80% of people are being screened by colonoscopy compared to countries like the Netherlands or parts of Europe where the majority of screening is stool-based. So the test matters and the implications for the test matter. So age, the tests, and then particularly when we're using stool-based tests, thresholds come up as important because those can vary in their implications for false negatives and false positives. And then I think the other thing that we're going to need to consider with screening guidelines, I'm really interested to see internationally how these emerging tests roll out and whether there's... I think

there will be variation regionally and who embraces the liquid biopsy or the blood-based screening tests.

Joshua Demb:

I think just to add on top of that, I think the strategy is really important. Fola noted this on one of her final slides, which was talking about the incorporation of 45 to 49-year-olds into the population. You're adding about 21,000,000 people to the screening pool. And so particularly with the US being a colonoscopy first country, strategy really matters. And I think that in the absence currently of guidelines that incorporates some of these newer emerging tests, we have to be planning and anticipatory for what it looks like to add these into the pool of eligible tests that might be available. But we really need to start thinking about the health services side of this as well, which is realistically if we want to make sure that we're maximizing screening uptake to make sure that we're maximizing the potential benefit for those who should be undergoing screening, strategy is going to matter. And I think that's where the US does need to look to what's being done globally, particularly with strategy such as incorporating stool-based tests or other potential tests that remove that resource can train away from colonoscopy for strategies.

Fola May:

I'm kind of curious what the audience thinks about what Josh just mentioned about strategy and about testing options. I mean, I think we learned a big lesson with studies like adenoma and all about choice and about how it's important to offer multiple modalities, particularly to certain patient populations. And I'm curious what the audience thinks in moving forward, how those test options will affect screening guidelines either domestically or internationally and how that will potentially impact our overall screening rate.

Andrea (Andi) Dwyer:

Awesome. So I see Samir had a question coming in right about as you were posing that. Samir, do you want to come off mute? And then if you can respond as well. And then we'll go to Whitney Jones as soon as Samir asks his questions in response and then we'll go Whitney. So off mute comes Samir.

Fola May:

And maybe, Carli, we can just unmute everybody so that they can just control their mute button. Is that possible?

Carli King:

Yes, I'll work on that while Samir [inaudible 00:30:25].

Fola May:

Okay, great. Thank you.

Carli King:

Yeah.

Fola May:

Great.

Samir:

Hey. Hi Fola, Josh, Andi. Thank you for sponsoring this. So I think related to what Fola was talking about, Fola and I were talking last week about how do we think or how would we recommend guideline makers think about the issue of choice and increasing participation? Which we might postulate would be improved by having some of the novel tests included in the recommended list of screening tests like a blood-based test, but then this trade-off where, again, for example, for the blood-based tests, you might get substantially increased participation, but their ability to advance adenomas is lower. And I guess, the question is, what's the recommendation? How much emphasis do you put on that issue of advanced adenoma detection versus having more options that'll get more of the population screened?

Fola May:

I feel like I have a head start because I discussed this with Samir, but I think it's a really important point and I'd love for others to jump in because we definitely think there's a huge potential for activating more people into screening when we have something that is as easy as a blood test. And honestly, some people hate getting their blood drawn, so we're making a few assumptions there for people. So yes, I mean, I think Samir's point is that potentially we're going to gain more people. But we're at the loss is that when we look at the eclipse study that was released in the England Journal last month, when you look at sensitivity for advanced adenoma, it was 13%, which is a lot lower than we would see for our higher level stool-based strategies and certainly for colonoscopy. So I like Samir's question and I'd love to hear what everyone thinks is what is the appropriate trade-off? Is it okay to miss a bunch of advanced adenomas and miss the potential of preventing cancers because we're going to be recruiting more people into screening programs. Any thoughts?

Whitney Jones:

Well folks, Whitney Jones, I would think that'd be a great opportunity for modeling. I mean, that's a place where modeling could help us without having to wait the five or 10 years to see what happens in the clinical trial. We know the rates of sensitivity and specificity and pickup, so I think we could extrapolate.

Fola May:

And I think some of that work has been done, right, Samir, with some of the modeling studies that came out that have come out in the last few weeks as well?

Samir:

Yeah, I mean, just to briefly summarize, yes, there were two really good modeling studies that came out and I think the... I mean, what I took away is if we're talking about a scenario where there's going to be a lot of substitution where the blood test is going to displace some of the currently available tests, then we're probably not going to do as well in terms of colon cancer prevention and early detection. But if the new tests result in net gains in participation that are substantially higher, like you're getting 60, 70% of people to participate in a blood test when they're offered, which all this couldn't have our guess as to where it will fall, then it looks like it could be good at least from a colon cancer detection and screening perspective. So I think that the problem is, that when... Well, okay, if these go up for a guideline review within the next year, let's say, or a year and a half, it's unlikely that we will have results from head-to-head studies that give us that exact participation number and what it really looks like.

And there's a chicken or egg problem, which is it's hard to do truly unbiased studies of participation when you have one test that is Preventive Services Task Force approved and paid for and you have

another test that it might be FDA approved, but it's not guideline recommended, it's really difficult to get an unbiased estimate of how participation differs. I mean, we have to do the best we can, but I think my point is, even if we had those studies in progress, the people who are making the guidelines are going to be stuck with imperfect data and I think they're going to have to make more of a philosophy call.

And it's going to be hard, it's going to be very interesting to see how they come down it. But I think a group like Fight CRC has to decide as advocates for patients, I mean, there's... You can choose the principle potentially that increasing participation is generally going to be better or I think it's also reasonable to have a principle that you really want to get behind, be careful about tests that maybe don't offer as much potential for prevention. I mean, my leaning is more choice, more participation options, but I could see someone making an argument the other way as well.

Fola May:

Yeah, and I think... I'm scared. Samir and I talked about this at AACR last week. I think that in a perfect world, a patient or even a doctor understands the difference between a blood-based test that is primarily about early detection, and a stool-based test that has the additional gain of prevention. So my hope is that Fight CRC, other orgs, researchers, physicians, providers, can do a really good job of educating patients. Because I'm fine with the well-informed patient who understands test A is going to find polyps and cancers, test B is mostly going to find cancers. I'm fine if that patient truly understands that and picks test B. But my concern is that even at the primary care level, there might not be time, information, education, knowledge, that this is not apples and apples. That, to me, these tests are apples and oranges and that we are fundamentally considering a switch from a strategy that allowed us to prevent and early detect to a strategy that is mostly allowing us to early detect.

And when I say early detect, I'm even careful because when you look at the eclipse data, it's really stage two, three, four that it's performing best for.I think that was Dr. Jones who asked the question. I agree the modeling studies will help, but I do think we are stuck in this, see what happens in the next five to 10 years. And I think we are charged with studying it very carefully. I worry that we might see an increase in the number of cancers diagnosed because if we move away from prevention, we are going to diagnose more cancers. Now, maybe we're diagnosing them early enough to cure people, but that's still more people that saying the words, "You have cancer," to. And that is where I have a little pause and hope that it goes in the right direction.

Andrea (Andi) Dwyer:

Whitney, I know you had an additional question and it looks like Ben also has something to add. Whitney, do you want to talk a little bit about what you posted in the chat and then we'll punt to Ben?

Whitney Jones:

Sure, great. And that was a great discussion, you guys, on that. And that is the conundrum, engaging more participants but leaving some of that potential prevention on the shelf. So that's a really great discussion. One of my questions was, it seems like particularly the topics we've been on, we've talked about for quite a while, particularly how do we collect family history? That's been going on for 40 years. Certainly, we're not experts at it outside of once you get cancer, I think everybody's great at collecting family history, but how do you get an 18 or a 20 or a 30-year-old? So I think my question is, the barrier to starting educational processes earlier I think is one that's been worried about for years. People are going to get a colonoscopy too early, they might get their screening too early. But because what we're facing really between 20 and 40 is that we're not collecting family histories in a systematic fashion.

Number two, we're not informing people in 20 to 40 that they're at a markedly increased risk, 200 to 400% for colorectal cancer, and these are the symptoms. Almost like going old school for any of you guys who were practicing in the '80s. Back then, we used to tell people about the symptoms of colon cancer, not how to screen for it. So somewhere along the lines, we have all the tools right now to diagnose people with family histories. We know how to do germline testing. We understand that people with symptoms should undergo immediate and urgent evaluation. None of those are barriers to us. I think the biggest barrier is that we're not starting the process early enough. And family history's tough. I'm not saying I know how to do family history, but I think if we start educating people in their 18, 20-year-old, they're going to have a lot better opportunity to understand that family history is important before they get to the 45 age or wherever.

So I think there's a real need for lead time messaging and education around these folks. And the real question to me is, how do we reach this whole group of people between 20 and 40 who are covered with insurance but don't have providers? We don't have a classic teach the doctor, teach the patient. So I really think this is going to call for us to get out of our usual comfort zone, which is to study something until we know for sure and then start messaging and educating around it. I would propose that we have all the tools right now and all the knowledge right now to start educating younger people about sporadic, which means we're going to have to educate everyone because we don't really have a clue who's going to get a sporadic cancer by definition. And then we can begin to study it concurrently in parallel rather than the classic sequence.

I know I'm a broken record on this, but I still think it needs to be said. We have the tools today, we should not wait until we have all the answers before we implement this to a younger population as well as the healthcare ecosystem that serves them. And again, that's my biggest question, what's the right way to educate people with no providers between 20 and 40 that sticks and actually does something? So that's a real question out there. I don't know how to do it. Maybe in Cali, you guys got it figured out, but we haven't gotten it completely figured out here in the southeast.

Fola May:

Yeah. Thank you for that, and I think it nicely moves us to the second and third questions on the slide on the screen. So maybe we can spend some time talking about what was mentioned, the 20 to 30-year-olds, which I think is really the third bullet, is moving us towards achieving 80% in every setting. And moving up from there, the question about family history is really about how do we collect and document it and how do we teach people? So maybe we can spend the next few minutes talking about those bullet two and bullet three. Any thoughts from the audience on either of those?

Joshua Demb:

I mean, I would just add to what Whitney said. I mean, with the efforts from national Colorectal Cancer Roundtable and such, there are resources that have been available that have been tested and validated to try to figure out how to accurately collect family history. There's both at home and also within the care system opportunities where these data could be measured. I think it's really trying to make sure that we're figuring out how to fit this appropriately into the cadence for when a patient comes to see the provider. And I think to Whitney's point, also being able to shore up that gap when the patient isn't seeing a provider and when they're not necessarily have a usual source of care or insurance.

And I think that it is a very difficult question to think about how we could expand the reach to make clear that family history is important because of what it means in terms of getting tested earlier and making sure that you're getting screened in a timely manner as it relates to colorectal cancer. And so really trying to think about wider dissemination of these resources outside of the academic circles of the

primary care circles. I think that is a really, really important point that unfortunately I wish I had the answer to, but we obviously have a lot of work to do in this area.

Fola May:

Josh, it was really interesting. I had this really interesting patient encounter, it must've been before COVID even, that changed how I think about this. And I really think fundamentally in the US at least this is a data problem and it's a data collection documentation and health system EHR problem. I was sitting with a patient who we had just diagnosed with early on, so I think he's actually around his early 50s. And we were talking to him about his care, his diagnosis, what that meant for him and his family. And on his way out of the room he said something like, "Okay, so you're going to put that in my kid's chart, right?" And I was like, "Oh yeah, that would be ideal if we had a data system or an EHR health system where once I diagnose you with family history, your brothers, sisters, and kids get that documented in the chart."

And it made my brain go wild because I was thinking, "They probably could do this in the Netherlands and other places where they've got an national screening program and connected data." But I looked at them and I was like, "No sir, actually we can't do that. It seems very easy, but we're not able to use that information to automatically populate your children and your siblings chart. Part of this is unfortunately on you to share this with your family members." And that really bleeds into the discussion we have all the time for everyone, but particularly in people of color about the stigma about rectal cancer, colon cancer, families don't talk about cancer in general in a lot of communities and particularly cancers in sensitive body parts. So it's really a double problem in that we've got a poor documentation problem and then we've got the patient stigma that precludes this conversation from happening at the dinner table.

Andrea (Andi) Dwyer:

And Whitney, I know you and I, Samir and others have had conversations full I think like you're talking about. There's a system approach, there's a tracking approach, but even then what kind of messaging and when to start those conversations and what that looks like for actionable, so that communication strategy. I'm listening with a keen ear because in June, these conversations are helping us get to June and I think our focus in the next couple of months are etiology is great to study in the context of this work. It's going to take a lot of time, a lot of resources, we're not going to stop. But I think, Whitney, you, Samir, Josh, Fola, what we're talking about is there are some immediate things that we can do sooner than later to help really think about what are research opportunities, what are implementation strategies we can learn?

Because I think there's some folks on today that are talking about implications for their family and what does this mean and how can we really stop? And so, Whitney, I think it's not falling on deaf ears that there are things we can do, it's just how are we really going to connect the pieces to get that done? And the devil's in the details, so I love how we all are sort of talking about these great opportunities, but how are we really going to make sure that hits? And I think that's really kind of the direction. I do hear several of you have talked about what is the opportunity for the research advocacy and helping catalyze the energy and what's needed within the patient community? So I will say, these are some of the things that we really are trying to think about prioritization. I don't have the answer either, but I do think there's a lot of interesting things. Whitney, I see your hand up as well.

Whitney Jones:

Yeah, I'm just going to follow up on that. So that's great and it is really a call to action because I think what we're facing here is the fact that academics doesn't venture into the unknown very often and we really do like to understand this, but we have got this roadmap to 2030 where we know this is going to be the number one cancer killer. We know this impacts about 15% of all colorectal cancer cases and growing. And so in a normal world, if you saw a threat coming six years from now, you start investing in that threat right now. And to me, that means a proportionate investment with the dollars we're spending in colorectal cancer. And this goes right to Fight CRC's sweet spot, Andrea, is we should be investing proportionally and pragmatically and proactively right now before 2030 to try to avoid it. And what we, I think, lack is that ability to get across the finish line and say, "We may not know the answer about letting folks know in their 20s and 30s, but we're going to figure it out on the way."

Otherwise, by the time we figure this out at 2030, we're going to have new technologies, we'll have multi cancer, we'll have methylation aging and everything out... I mean, our capacity for understanding is outstripping our capacity in many cases to study it, much less guideline organization's abilities to understand it. So my real issue is, is that starting early with education, understanding we're going to have to educate everyone because the nature of sporadic. Plus, who knows who has a family history of cancer until you ask them? So there's no one that we're going to be able to pare it down. It's going to have to be a broad educational piece.

And I would suggest too, since all cancers are going to be up in younger people, solid organ cancers in particular, this is maybe a really great opportunity to get with some of our other folks in the other organ systems and start talking about young colon cancer and delivering those messages early. And the gynecologist can do theirs around endometrial, et cetera, et cetera, but young cancer is coming and young colon cancer is the tip of the sword. So if we don't educate folks and we don't start delivering, let's not be shocked at 2030.

Fola May:

I agree with you completely. And I think Samir mentioned something in the chat about having a question as well, but I agree, and Samir, we'll come to you in a second, but I agree with you completely, Whitney. And I think, Andi, we should talk about ways that Fight CRC could help push forward that concept. Because it's not going to come from academics in the community because they're focusing on their health system or their local regions, but how can we have a national conversation? I'll briefly mention one unique project I saw at Howard was sending the college students home with information about colon cancer to have on their Christmas break, I think actually it's their Thanksgiving break, to have a conversation with their parents about getting screened for colorectal cancer and family history. So I think there's stuff that we can think about doing.

Andrea (Andi) Dwyer:

Yeah, for sure. And I will say this, because I think Samir's comment was to Ben who I know has been waiting in the queue for just a bit, which is funny because I said queue and I think that's a very British term because I think Ben's question is about still-based testing in the UK. But what I will say is, yeah, Whitney, I know we've been having some conversations about the messaging, how does this work? And you're right, Fola, this sort of is this opportunity, but I think there's some really interesting work we can do in communications and health behavior type stuff. So Ben, I will turn it over to you and it looks like Samir has a follow-up question. So Ben, it's all you, man.

Ben:

Thank you, yeah. So we know that a lot of the barriers for timely EEO diagnosis can occur at the primary care level and are often related to low provider suspicion. I'm curious if you have any thoughts on the recent guidance from the UK that recommends FIT screening at the primary care level for symptomatic individuals. Now, I realize there is for not necessarily aimed at the EEO population, the guidance they released, but I'm curious your thoughts on that guidance broadly and if similar guidance for those under 45 could reduce time to diagnosis or be an effective intervention at the primary care level to increase diagnoses at a timely manner.

Fola May:

So Ben, I'm actually not familiar with it. Can you just tell us a little bit more or what you do know? So is the idea that if you're under 45, I'm looking at your note, but if you're under 45 and symptomatic, you would get a FIT instead of a colonoscopy. Is that the idea here?

Ben:

Yeah, so I think the goal is to... We know that it takes a long time to get in for a colonoscopy if you're showing up to your general practitioner with stomach cramps or blood in your stool, often years for our EEO patients who are misdiagnosed for years. So I'm curious if guidance that recommends more immediate use of a FIT test when any of these symptoms appear could help reduce that time to diagnosis for some of these patients. I'm happy to share the links to the guidance that the UK released. I can drop those in the chat, just give me a second to pull those up.

Joshua Demb:

That would be great. Thank you.

Fola May:

Yeah, I guess I'm having trouble understanding it because I feel like if there's blood coming out of the rectum, do you need a FIT test? But maybe I'm missing... Maybe it's other symptoms that it's more helpful for.

Ben:

Well, I mean, I'd push back and I'd say that that is true coming from your experience in the GI community. But I think if you talk to most EEO survivors and patients, many of them are just misdiagnosed for years. They're told they have hemorrhoids, they're told they have anything else because there's such low provider suspicion, their primary care providers do not think colorectal cancer. They're told to look for horses, not zebras when they hear those hoof prints. So if we had guidance that-

Fola May:

Yeah, that's why I've always been a proponent of sending those people directly to colonoscopy. So for me, I feel like if you have rectal bleeding, a FIT test is not going to help me because I already know you have rectal bleeding and the only thing that the FIT test is going to tell me is that you have rectal bleeding. So I've always strongly felt... And we haven't done a good job, but I think in the US where we maybe have more capacity and resources, we should be sending all those patients to colonoscopy. And if you ever hear me talk, that's a huge part of what I talk about is how we miss the boat and we need to do a better job at that. I think potentially if there are other symptoms like new onset diarrhea, constipation, abdominal pain, that's not characteristic of other diagnoses, maybe in those settings a FIT

test might be helpful on the pathway to colonoscopy. But in the US, I think we're trying to convince our primary care doctors that even in that setting to go straight to colonoscopy.

Joshua Demb:

Samir, go ahead.

Samir:

Well, what I was going to mention, so the UK guidelines are worth looking at. They're really interesting and very much supported by data. I think you can look at them a couple ways. One is if you have a very scarce resource in terms of colonoscopy in your healthcare setting, I think what they've shown is that it's a very effective triage tool to use FIT. I think where it gets interesting for us is this issue of you're a 30-year-old person who might have minor rectal bleeding or unexplained weight loss or some other sign, abdominal pain. Abdominal pain is probably a good example. We can't be expected to send all of those patients for a colonoscopy. It's not feasible. And I think there's some room for us to do work on how do we operationalize our recommendations for primary care clinicians?

Is the recommendation end stop if you have any of these five symptoms, colonoscopy, no matter what your age, and we're comfortable with the cost implications of that and it's appropriate? Or can we offer some more refined guidance where it's not just about raising awareness? I think that still leaves the average primary clinician in the lurch, like, "What am I supposed to do? Are you telling me to send everyone with belly pain to colonoscopy or I'm supposed to use my judgment?" We're not going to get a systematic benefit to the population unless we're able to get some more clear guidance out there that optimally is data-driven. But I think there's a need for that and that addresses the needs of most people who are having early onset colon cancer where they're presenting with symptoms and where the real risk is delayed diagnosis. And so I don't think we've moved the needle on it. I don't think we're well-positioned to move the needle on that right now, how those patients get timely diagnosis.

Fola May:

And I think it'll depend on the symptom, right, Samir? So I think more vague symptoms like what you're saying, abdominal pain, it's one thing, but there are other symptoms that I truly don't understand it because it's a slam dunk to me that if you have blood in your stool, probably need a colonoscopy to figure out where it's coming from. That's just my take on it.

Joshua Demb:

I mean, I think that it's an important place to go because I think it's trying to better understand what those workup patterns look like right now and knowing what we do know about certain symptoms that should lead to some sort of workup that is guideline recommended, making sure that that's actually happening. And Samir and I talk about this a lot, the idea of closing the clinical loop and making sure that you're not disregarding colorectal cancer as part of a potential consideration, as a potential condition.

It goes to that issue of making sure that you're not misattributing the symptom, making sure that you're doing the necessary work, make sure that the symptom is attributed to a condition so that it can be resolved, whether it be the condition as a whole or so that the symptoms abate. And so I think it's much... As Fola, you said, it's much more pointed when it's something like rectal bleeding, but when you get to other ones like abdominal pain and such, and when they show up at such frequency in these younger populations, we do need to have consideration of if there's a constellation of symptoms or if

there's a workflow pattern that is achievable in practice that makes sure that these individuals are identified for whatever condition they might have, particularly if that's a cancer.

Samir:

And Fola, even what you said about your recommendation that everyone with rectal bleeding go for colonoscopy, I mean, our GI societies haven't come out consistently with that recommendation. So again, I think there's room for us to be more clear, like is that the consensus recommendation given the epidemiology and what's going on that colonoscopy end stop for rectal bleeding? Or can we update and refine and be consistent with, "Hey, under these parameters, all these people should go for colonoscopy immediately and everyone else who doesn't go for colonoscopy, we recommend X, Y, and Z and a colonoscopy if it doesn't resolve."? Think there's room there for us to advocate for more clear guidance because I think it's all over the place right now. And I think even from the average GI, you're not getting a consistent answer about what should happen.

Fola May:

And I think we need the data. So the question is, how many lives are we going to lose while we wait for the data?

Samir:

Right. No, I'm not arguing that we have to do a prospective board study to do it, but I think that at this moment, given what we have, we could make clearer recommendations.

Fola May:

Absolutely. I realize, Andi, that we are at time and I know that we've... I think we've touched on everything except for the last bullet, which speaks to how much needs to be discussed in this space and I'm just grateful for all the participation that we've had and the helpful discussion.

Andrea (Andi) Dwyer:

Yes, which we will talk quickly. Carli will bring up the quick slide, so thank you for the hands. I know there were a couple of questions and thoughts and some folks that were looking for resources as well. So Zach and Carli, I know we made a note of those, but if you like what you heard today, we're going to continue the discussion. We're going to turn it a bit on its head and talk a little bit about those exposures, maybe a bit around etiology and the like, which was track two of the December meeting. But again, I think we're starting to look at opportunities for some specific strategies, but also the fusion of the disciplines as we really start to study early onset from a variety of angles. So Carli, tell everyone what they've won for May and what we're planning for June. We'll close out today and hope that you all will spread the message about these webinars, register for the next ones and we'd love to have as much interaction. So Carli, all you and we'll close out for today. Thanks everybody.

Carli King:

Yep, in May, we'll be talking about biology and etiology. I put the link to register in the chat, so please register. And that will be May 10th at 12:00 PM Eastern time. And then in June, we'll kick off with [inaudible 01:01:25] there'll be more information to come. Hopefully during our May webinar, we'll have registration link available for that. And then we'll be really hosting those collaborative discussions and moving this work forward.

Andrea (Andi) Dwyer:

All right, so those links are in and then there will be more reminders. Josh, Fola, thank you guys so much and everyone, thank you for the wonderful contributions. I know there several of you have text me, emailed me and the like, and I will definitely follow up. Have a great morning, afternoon. And again, thank you Josh and Fola. Have a good...