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Hot Topics in Blood-based Cancer Screening: Key Information on Multi-Cancer Early Detection from 2023 Spring Oncology Meetings

Announcer:
Welcome to CME on ReachMD. This activity entitled, Hot Topics in Blood-Based Cancer Screening: Key Information on Multi-Cancer Early Detection from 2023 Spring Oncology Meetings is provided by Integritas Communications and jointly provided by Global Education Group and Integritas Communications, and is supported by an educational grant from GRAIL. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

[CHAPTER 1]

Dr. Westgate:
Hi, and welcome to this program about multi-cancer early detection tests, or MCEDs. I'm going to give you information about MCEDs, their role in primary care, and we'll discuss the most recent presented data from ASCO, AACR, and NCCN research conferences with my colleague, Dr. Ethan Schram, I'm Dr. Candace Westgate, an OB/GYN and Cancer Prevention and Early Detection Specialist. I'm the Medical Director for the AHEAD Programs helping you and your patients stay ahead of cancer, a population-based program that helps to prevent and catch cancers early for our organization, Adventist Health. I'm also the Chief of Staff at St. Helena Hospital.

Our first topic of discussion is going to be the current status of cancer screening. So currently, cancer is the second leading cause of death within the United States; 40% of Americans will be diagnosed with cancer in their lifetimes, and more than 600,000 lives are estimated to be lost to cancer in 2023. Overall, 5-year survival rates with any malignancy is around 68.7% from data looking at 2013 to 2019. Five-year relative survival rates is about 3 times higher for tumors detected at a localized stage than when the detection is at a distant stage, or known as metastatic disease.

Currently, we have 5 cancer screenings that are routinely recommended by the United States Preventive Task Force, or USPSTF. Breast cancer and cervical cancer screening for women, colorectal cancer screening for both sexes, lung cancer screening for both sexes, and prostate cancer screening for men. These guidelines have changed recently, with the breast cancer guidelines being decreased down to the age of 40. But USPSTF still recommends it on a biannual screening. So for breast cancer screening, USPSTF recommended mammograms start at the age of 50 and be biannually; however, recently these guidelines have now been dropped to age 40 biannually. The USPSTF currently recommends against screening asymptomatic individuals for cancers like ovarian, pancreatic, testicular, and thyroid cancers. However, these cancers are estimated to account for about 11% of all cancer deaths in 2023.

We know that cancer screening works because of the importance of early detection. And here's just some examples of where breast cancer and lung cancer have reduced the age-adjusted mortality rates were looking at data between 2011 and 2020. So there was an annual decrease of 1.3% with breast cancers, and 4.1% with lung cancers as a result of screening. Since its peak in 1989, when it came to breast cancer screenings, female screenings resulted in 20% reduction in overall mortality. And when we look at the lung cancer space, early diagnosis decreases mortality rates at 10 years by 39%, compared to those individuals with lung cancer that had no intervention. And this was startling statistics for me when I took a look at this. So only 25% of diagnosed cancers are detected through current recommended screenings, with 57% of cancers do not have routine screening recommendations or more modalities. So there's a huge unmet need here when it comes to cancer screening and early detection.

There are limitations to our current cancer screening guidelines. These screening recommendations are for an individual to be tested for one organ cancer at a time. Some populations do not benefit from current guideline recommendations because they are not included in the guidelines. For example, the mortality rate among adults less than the age of 50 with colorectal cancer has increased by 1.2% annually. And I think this has also been the reason why recent guidelines for USPSTF have been to decrease that screening risk to start screening age to start at age 45 instead of age 50. And 65% of Americans over the age of 21 are not up to date on at least one of their routine cancer screenings and we know the harm that COVID has done to these statistics as well.

MCED testing has the promise to detect cancers not assessed by traditional screening modalities. One modeling analysis, quantified for each target population, the rate of incidence and mortality due to cancers other than the one being that they were being screened for. So in each of the populations, other cancer screening incidence rates were significantly higher than the single cancer with guideline-recommended screenings. For example, in those individuals in the study, 13 cervical cancers were diagnosed by conventional screening, but those individuals were 35 times more likely to have another cancer that would have been missed. And in the individuals with colorectal cancer, 90 cancers were diagnosed in that cohort via screening. But there was a 12 times increased risk of those individuals having another cancer, and that would have been missed if they'd only been screened for colon cancer at that time.

What about the cost effectiveness of a multi-cancer early detection test? So modeling that was done by Hackshaw et al, it showed the significant decrease in cost associated with working up a cancer when we add MCED testing to our current cancer screenings. So just with current cancer screenings, the total diagnostic cost was around $16 billion. Whereas, when MCED was added to that, the cost decreased by 80% to around $3 billion. So what this looks like per cancer, and the cost per cancer, is that by adding an MCED test to our current cancer screening guidelines, the cost of the workup is decreased by 92%, with the per-cancer cost of $7,000 versus $89,000. An MCED ordered during a preventative care exam could have detected up to an additional 11% of breast cancers cases and up to 58% of unscreened cancers that are the leading cause of cancer deaths.

Now moving on to our next area of focus, and this is going to be the science behind MCED testing. What we know about MCED testing is that it is a liquid biopsy, it's not invasive, it can characterize across all tumor stages, it can produce real-time information for diagnosis, it can also monitor potential treatment responses, whereas traditional tissue biopsies are usually invasive, only possible if the tumor is visible and accessible. It can be costly, tricky, and potentially painful to the patient, and only provides detailed information about cancers at that site and at the time of the biopsy. So cell-free DNA testing is the basis of this new noninvasive screening modality. Cellular material, including cell-free DNA and proteins go into the bloodstream via apoptosis, necrosis, and secretions. Many types of cell-free DNA anomalies can be measured and characterized in these kinds of assays. Looking at multiple different things like copy number alterations, point mutations, rearrangements, and methylation changes.

DNA methylation is the mainstay of these tumor biomarkers. Cancers associated with epigenetic changes, i.e., DNA methylation, that can alter not only the 3-dimensional conformation of the genome, but protein DNA interactions and different expressive patterns. So changes in DNA methylation patterns can contribute to tumor organogenesis or progression. It can be identified and characterized by next generation sequencing as well as with the help of machine learning.

I now want to take just 2 minutes to remind us all about sensitivity, specificity, and positive and negative predictive values. Yes, this is going to be taking you all the way back to college and your statistics class, so I apologize for that. But I think it's very important that we take a few minutes to do this because of the new era that we find ourselves in with multi-cancer early detection, and the differences based on the single cancer screenings that we have currently.

So sensitivity is the testability to detect a true positive sample. And specificity is the testability to detect a true negative. So for example, if the sensitivity is 98%, this would produce 2 false negative results for every 100 samples from patients that have cancer. If the specificity is 98%, this would result in 2 false positive signals for every 100 samples from patients that did not have cancer. The positive predictive value assesses for the utility of the test in clinical practice, and measured as the percentage of all the positive samples that are true positive. And the negative predictive value is the percentage of all the negative samples that truly are negative or don't have cancer.

So when we're looking at this, it's really important to understand how our paradigm is shifting. So with a multi-cancer test that is looking at multiple cancers, not just a single cancer, the importance is to focus on the test positive predictive value, and the test specificity, versus the current cancer screenings that we have now, where we're mainly focused on sensitivity of those tests. And so there's a significant amount of false positives that come out of our current cancer screenings. Additional criteria to consider for cancer screening would be the ability for a multi-cancer early detection test to localize the site of the tumor, so that we can minimize imaging needed, as well as the ability to minimize over-detection and overtreatment of indolent cancers; we want to avoid unnecessary workups and treatments for non life-threatening tumors.

Now, let's talk about some of the tests that are under development currently, and the science behind them. So the first test I'm going to

talk about is the DETECT-A study that has resulted in a test called CancerSEEK. So it's the first prospective interventional study of an MCED test, using the earliest version of this CancerSEEK. It analyzed methylated patterns of around 18 different genes as well as protein biomarkers, and it's able to screen for 8 cancers. If a cancer signal is found, then the next step is to confirm this with a whole-body PET/CT scan. What this test showed us that out of 10,000 women with no prior cancer history, 96 cancers were identified in this study, 26 of them were found from the multi-cancer early detection test, 24 of them were found from standard-of-care screening, and 46 were found from other reasons as a result of, for example, diagnostic initiated because the patient had symptoms.

So the proof of concept for the study in regards to 26 different cancers that were detected, showed a positive predictive value of around 40.6%, and a specificity of around 99.6%. The test also gives us different sensitivities, looking at all cancer types, versus cancers with recommended screening guidelines, versus those that did not. And those sensitivities ranged from 23 to 31%. And what the study showed was that multi-cancer blood testing along with PET/CT imaging can safely be incorporated into routine clinical workflow, in some cases, leading to surgery with the intent to cure. So this further validation of CancerSEEK that is currently undergoing, there's a prospective observational study called the ASCEND study involving subjects with known or suspected cancer, versus subjects with no evidence of cancer. And another study that is currently undergoing is the DETECT-ASCEND 2 study. CancerSEEK received breakthrough device designation from the U.S. Food and Drug Administration for the detection of genetic mutations and proteins associated with pancreatic and ovarian cancer in 2019.

So the Galleri test is the only current commercially available multi-cancer early detection blood test. It screws for over 50 different cancers, looking at over 100,000 methylated regions and utilizing machine learning. The validation studies for Galleri are called the Circulating Cell-free Genome Atlas study, or CCGA. There were three parts to the study. The initial part identified the highest performing assays for further development. Part 2 was then taking that highest performer which was the methylation-based assay and selecting and training the machine learning for the validation process. And then part 3 was the large-scale clinical validation. The CCGA studies were prospective case-control observational study for part 3, that looked at over 15,000 participants. It evaluated genome-wide cell-free DNA sequencing, as well as machine learning that localized a large number of cancer types with specificity high enough to support general population-based screening. It's a blood-based biopsy, from patients with newly diagnosed but untreated cancers and those with no known cancers.

And what the CCGA3 showed was that the specificity for detecting a cancer was 99.5%. What the study did show was that the sensitivity increased with the stage of the cancer. The overall sensitivity was 40.7% for stages I through III, and 51.9% for stages I through IV. However, a subanalysis was done looking at just a pre-populated group of cancers, which account for 2/3 rd of all the cancer deaths within the United States. There were 12 cancers that were picked up from this, and the sensitivity from that was 67%. This test also is able to provide the clinician with a cancer signal of origin. And the CCGA3 study showed an overall accuracy of cancer signal of origin in true positives of 88.7%.

The next study after the CCGA validation studies was the PATHFINDER study. And this was testing and refining the Galleri test. It was an interventional prospective study using methylated cell-free DNA to detect cancer and predict the tumor of origin. There were 2 versions of the tests that were evaluated, MCED-E, and this was eventually refined into MCED-Scr, which was then renamed now is what we know of the Galleri test. Hence, the signal detected was detected in 0.9% of the analyzed participants. And imaging was performed on over 90% of the participants who had a signal. Cancer was confirmed and 25 of the 58 patients who received a positive cancer signal showing a specificity of 99.5% and a positive predictive value of 43.1%, with an 88% accuracy in predicting signals of origin.

I'm going to pause for a moment to compare and contrast this multi-cancer early detection blood test and its positive predictive value compared to a test that we know already like the mammogram, for example. So the PPV for a mammogram is only around 45%, whereas the PPV for this multi-cancer early detection blood test was 43.1%. So the conclusion for the Galleri test is that Galleri can detect more than 50 different types of cancer in the early stages, with approximately 40% positive predictive value, as well as being able to determine with 88% accuracy the cancer signal of origin. The Galleri test was granted breakthrough device designation in 2019.

Galleri has ongoing clinical trials here in the United States, as well as in the United Kingdom. There's the STRIVE study, the SUMMIT study, PATHFINDER-2, as well as the REFLECTION study. And there's currently a study with the National Health Service in the United Kingdom, looking at about 140,000 individuals aged 50 to 77 years old. They're going to be tested and followed over a course of 2 years, and their outcomes in regards to cancer detected as well as cost savings will be determined.

The next MCED test I'd like to talk about is the development and validation of OverC this test looks at about 5 cancers, it uses deep methylation sequencing, and the studies looking at and validating this oversea test of THUNDER 1 and 2. It is a prospective observational trial to develop and validate that also seek methylation-based cell-free DNA test. It specifically targeted cancers of the lung, colon and rectum, liver, ovarian, pancreas, and esophagus. Results from this showed specificity of 99.5% in the training set and

98.3% in the validation set, and a sensitivity of 79.9% in the training set and 80.6% in the validation set. In the case control studies just looking at lung cancer, there was a 98.9% specificity and 69.1% sensitivity. OverC is currently being examined in ongoing prospective trials, PREDICT and PREVENT, and it was granted FDA breakthrough device designation in January of 2023.

PanSeer is another MCED test under development. It screens for 5 different cancers, looking at 595 different methylated regions. In the longitudinal study for validation, over 123,000 healthy participants provided plasma samples for long-term storage and were monitored for cancer occurrence over 4 years. Plasma from 605 asymptomatic individuals analyzed for cell-free DNA methylation, and 191 received a diagnosis of stomach, esophageal, colorectal, lung, or liver cancers within 4 years of their blood drawn. PanSeer detected 88% of cancers in post-diagnosis patients with a specificity of around 96%. Cancer was detected in 95% of the asymptomatic patients who later received a cancer diagnosis.

I would now like to talk more about how do we implement this in our everyday practice as clinicians? Currently, there is a lack of guidelines when it comes to these multi-cancer early detection tests. So who should be offered this kind of testing, as it is not included currently in any national guidelines or consensus recommendations? Patients who may benefit from MCED testing includes those at higher risk of cancer. So for example, those just based on age or over the age of 50, those with a family or personal history of cancer, those with the history of childhood cancers, those with known genetic mutations and cancer predisposition syndromes, or those with significant risk factors, for example, firefighters, those that have a smoking history, or liver cirrhosis, for example.

So who's not eligible for this testing? This testing has not been tested in the pediatric population, so no one under the age of 21, also pregnant patients or those with an active cancer diagnosis or treatment within the last 3 years. MCED testing should be used to complement the recommended screening approaches to identify cancers, not as a replacement for our current screening guidelines.

So here are some considerations for you, as practitioners, when you're discussing MCED testing with your patients. We know that there is advantages as well as disadvantages to this kind of testing. So the advantages include increased in early cancer detection rates, trials demonstrate improved efficiency of testing with increased positive predictive value and decreased number needed to treat compared to our current screening guidelines, screening of organ sites currently without screening modalities, this testing screens for multiple cancers at one time, and it's a less invasive procedure. However, there are some possible disadvantages.

It's currently not covered by most insurances. Having a result of no cancer signal detected does not rule out future cancer diagnosis as the sensitivity is limited. Consequential cancer is found sooner, but patients may not live longer as a result of the earlier detection. There may be some harm from unnecessary diagnostic procedures due to that 0.5% false positive rate. And overdiagnosis and overtreatment of cancers that would have otherwise never bothered that patient.

Let's talk a little bit more about where we are currently with the state of coverage for this test by insurances. It is not covered by insurance, and the only test that is currently available is the Galleri test, and it is around $949. A significant amount of work is being done at the Congress level, where a bill was introduced in 2021 and now reintroduced in March of 2023. The Medicare Multi-Cancer Early Detection Screening Coverage bill, and we're hopeful and waiting for this to get passed.

Additionally, with the help of the Cancer Moonshot Initiative, President Biden did report the development plan to quickly evaluate, utilize the utility and the benefits of MCED testing. This Cancer Moonshot Initiative was reported in early 2022 with the added goals of reducing cancer death rates by half within 25 years and improving the lives of patients with cancer and cancer survivors.

The NCI is also working on this. They have a Vanguard study on multi-cancer early detection where they're evaluating MCED assays for the purpose of cancer screenings. To order an MCED test for your eligible patients, test requisition can be used via their portal or email or even a paper copy. The kit includes two 10-mL blood tubes for collection, and both tubes need at least 3 mL of blood to be injected in them. And it needs to be collected and stored in a specific test kit that protects the sample against temperature variations. The results are given to providers within 10 business days of the sample collection via an online portal or an automatic fax notification to your office directly.

If the results come back cancer signal detected, then the diagnostic evaluation will then start. As a reminder, these tests are just screening tests. So based on the cancer signal of origin that is returned, there are specific data supporting the specific tests that would be needed. For example, bloodwork versus imaging that could be used to look up that specific cancer detected.

So here are some examples for us to consider. If a cancer signal detected came back with colorectal as the site of origin, the next step would potentially be some bloodwork including a CBC, as well as imaging tests like a colonoscopy. If an ovarian cancer signal came back positive, again, there's blood work that could be considered like a CA-125, for example, and then imaging in regards to a pelvic ultrasound that could then also include, after that, an abdominal CT scan. Other cancer signals of origin could include the bowel and the liver. And for these, again, bloodwork, but ultrasounds and CT scans as well as GI referral would be the progression of the workup for these kinds of signals.

Thank you for joining us for this MCED primer. Please continue on to the next chapters, where we discuss the most recently presented data from 2023 AACR Conference, ASCO Conference, as well as NCCN.

[CHAPTER 2]

Dr. Westgate:
Welcome to Dr. Ethan Schram, Physician, Medical Oncologist from the Martin O'Neill Cancer Center, who's joining me today to cover all of the brand new data released over the last several months at the major oncology conferences, NCCN, AACR, and ASCO.

Dr. Schram:
Thank you for inviting me, Dr. Westgate.

Dr. Westgate:
So they were to meta-analysis, analyzing the accuracy and applicability of blood-based MCEDs that were presented at ASCO and AACR. And Dr. Schram, as a primary care provider, for me, when I see a meta-analysis, that makes me think, Whoa, lots of studies put together, large in number, this is going to be a real value in regards to me as a clinician and what that means, you know, in my day-to-day work. Can you talk a little bit about these meta-analysis and maybe some of the caution or hesitancy in regards to these results?

Dr. Schram:
So there was one presented at ASCO and one presented at AACR; one with 10 studies, one grouping 12 studies in aggregate. The takeaway is that there was a good correlation of the combined sensitivity and specificity of these tests with the high area under the curve. These studies were suggestion that we're getting good concordance across studies. If you look at them in aggregate, the false positive rates can be as high as 2.5%, and the false negative rate can be around 44%. Now, that might seem alarming, but if you compare these to the false positive rate for let's say mammogram, which is around 10%, and Cologuard, which you may have heard about, which is around 10%, the 2.5% actually stands out as quite good. Looking at false negative rates, the mammogram false negative rates, believe it or not, are around 20%, Cologuard is around 8%. And the false negative rate for these tests, in all stages; all stages, let me remind you, is about 44%.

Dr. Westgate:
So just to recap again, Dr. Schram, in regards to what you were saying from this chapter, so from this meta-analysis data, are you saying that the different assays are comparable with each other regarding sensitivity and specificity? And how would this translate into practice for our primary care audience?

Dr. Schram:
Well, what I would say is this; that there appears to be general concordance across the studies. But as you point out, we need to be careful interpreting meta-analyses because there could be heterogeneous populations in each of the studies that make up the meta-analysis. And so the fact that they are all arriving at similar numbers is hypothesis-generating and suggests we are on to something and that, with improvement, we can get a screening study, a multi-cancer screening study that can be useful, but I wouldn't say that these meta-analyses are validating. I think they are reaffirming that we have a signal, so to speak, and that we should continue to pursue this.

[CHAPTER 3]

Dr. Westgate:
Now, Dr. Schram, let's talk about one of the most pressing questions clinicians have about MCEDs, the real-world experience as a there's currently only one test commercially available as an LDT here in the United States.

Dr. Schram:
I think one of these posters actually was your work and so I'd like you to start off this discussion.

Dr. Westgate:
Thanks for sending that right back at me. So early real-world experience with a multi-cancer early detection test, this poster was presented in ASCO in Chicago this year. And it looked at the first 53,000 MCED tests that were delivered by physicians currently within the United States, and compared the outcomes to the PATHFINDER results, which is a previous study that was done by Galleri. So the average cancer signal detected rate for Galleri was 0.95%. And you could see the difference of 1.1% in males and 0.9% in females. And these were also comparable to the model the MCED testing performance rates and cancer incidents from SEER registry. From that 53,000 individuals screened, 72 individuals had a cancer diagnosis. What was exciting to see was the percentage that were found in earlier stages. So 33% of those 72 were in stages I and II, and 61% in stages I, II, and III.

The other part to this study was taking a look at the cancer signal of origin and the prediction, and how accurate was this test in the real-world at predicting the cancer signal of origin. And from this real-world evidence, we found a 91% accuracy rate. Whereas in the

PATHFINDER study, the prediction rate was only 84%. And from the clinical validation study, so prior to PATHFINDER, called Circulating Cell-free Genome Atlas study, it was around 89%. We did see that the cancer signal detection rate increased with age, with those significantly higher greater than age 50. We also saw in males and females that 67% and 61% of cancer signal of origins represented cancers without recommended population screenings, respectively. So what we're seeing is that real performance of Galleri is consistent with the previous large-scale clinical studies, including the cancer signal detection rate and accuracy of the prediction to help guide us as physicians with our workup.

Next, I'm going to continue and talk a little bit more about 2 different case scenarios that were discussed or case studies that are of great interest. So the first was about a HPV-mediated oropharyngeal squamous cell carcinoma diagnosed using the multi-cancer early detection blood test. So this test came back positive for head and neck on this individual, an asymptomatic 74-year-old Caucasian male.

This individual had a history in the past of chronic lymphocytic leukemia, and this was 17 years prior, as well as papillary thyroid cancer 8 years prior with no evidence of disease at that time. In regards to his other cancer screenings, this individual had had an elevated PSA level and was a nonsmoker. Bloodwork and imaging then followed this cancer signal of origin that was found. The final diagnosis of HPV-mediated squamous cell carcinoma of the oropharynx. The patient underwent surgery with staging and did not need chemotherapy or radiation, because this was caught at such an early stage.

The next one was actually a case study of a misdiagnosis. So this study showed to us that, despite high average cancer signal of origin prediction accuracy, the biological similarity among HPV-related cancers for the inner genital tract and the head and neck tract may lead to cancer signal of origin misclassification.

So that's the take-home from this; cancer signal of origin misclassification may be considered in patients with an HPV-mediated history. The use of this MCED test informed aggressive cancer workup and lead to early detection and treatment with curative intent.

Dr. Schram:
Those are both really instructive cases I think about the power and the possible pitfalls of using MCED at this point in time.

Dr. Westgate:
So Dr. Schram, I'm going add one more thing here because as a physician, myself, as I am talking to my patients in clinic, you know, when I look at tests like this, the most impactful thing for me speaking to my individual patient is actually that positive predictive value. In our real world post, I'm going to go back to that for a second, we weren't able to calculate positive predictive value yet, because there were over 300 individuals that were still going through their diagnostic evaluation, and we didn't have the data of, yep a cancer was found, or no we're considering this as a false positive right now.

So, you know, when you're looking at a test from a whole population perspective, that's where the sensitivity and specificity are really important. But, you know, boots on the ground, as physicians interacting with our patients on a daily basis, you know, what do I tell my patients when they do come back with a cancer signal of origin? Right? It's that positive predictive value of how likely are we to find a cancer for you at this stage?

So I'm excited as time progresses. And for us to continue to gather the information of those additional 300 individuals that did have a cancer signal reported to them from that real-world data to actually follow them over time, you know, for another year and see what actually are the results that we get from the continued diagnostic workup?

Dr. Schram:
Yeah. And I think it really underscores the importance of informed consent prior to any test, not just testing, like MCEDs or, in your case, Galleri, but in any test. What does a positive test mean? What does a negative test mean? So that we can manage their expectations, and reassure them, whatever the results?

Dr. Westgate:
So there wasn't another reported real-world study presented at ASCO using the THEMIS MCED platform and this is work done out of China. Can you tell us some more about the report?

Dr. Schram:
I'd be happy to. The THEMIS platform presented some interesting numbers with an N size of a little over 1,000 adults. This was a study that was done in China, in patients who are considered high risk over the age of 65. None of these patients had known cancer at the time, but they were all considered high risk for cancers that are more endemic in China, specifically esophageal cancer, colorectal cancer, hepatocellular or liver cancer, lung cancer, and gastric cancer. And the risk factors for these are H. Pylori, blood in the stool, hepatitis B virus, or history of smoking. This model, the THEMIS model, was able to determine that 58 of these individuals were found to have cancer that we might not ordinarily have been able to identify. That's about 4%. It's certainly a very interesting study, and it's a

platform that deserves further investigation.

Dr. Westgate:
Thank you for that thorough review, Dr. Schram. I wonder when we will see THEMIS making its way into commercial use? With Galleri and THEMIS real-world results, we are looking forward to what they can bring to our patients in the future.

[CHAPTER 4]

Dr. Westgate:
Let's discuss the work presented on cancer signal of origin detections and diagnostic resolutions and the clinical relevance. However, not all MCED tests in clinical development are able to report a cancer signal of origin. I'd love to hear your thoughts on this, Dr. Schram.

Dr. Schram:
When we talk about MCEDs, it's important to recognize that not all of them are able to produce a tissue of origin or CSO, and others are. Clinically, it's one thing to be able to find a signal, it's another to know where it's coming from. And without knowing where it's coming from, it's not much help at all. I think it's interesting from a basic science standpoint, but if you have a patient in front of you, you need to be able to tell them where this cancer is likely to be, or at least be close.

There are studies that were reported at ASCO by Eric Klein, for example, that showed that there was diagnostic resolution and achieved and about four out of five, over 80% of participants after the initial diagnostic evaluation. It reminds me a little bit of if you're missing a cell phone in your ask your friend to call the phone to find out where it is, if you don't have somebody around, you just know that you're missing your phone, and you don't know where it is. But certain tests like Galleri are able to actually tell you, where's the cancer likely to be. And that is clinically important, and I think is essential for this type of test.

There's another study from AACR, a poster presented by Dr. Oh. This was a review looking at tumor of origin prediction and MCED tests. The takeaway from this is that the accuracy of the tissue of origin prediction was quite high, again, around 80%, or 4 out of 5. Certain cancers have more accuracy than others, but they're all quite good. My point I'd like to leave you with is that an MCED that doesn't have a tissue of origin component to it, I don't think is helpful.

Dr. Westgate:
Thank you so much for that statement, Dr. Schram. I know for us in the primary care world, ordering a mammogram looking for breast cancer and then working up their breast cancer, you know, we have a place to look, right? And you know, the associated diagnostic resolution and workup, in theory, can definitely be tailored with less whole body or advanced imaging if we have that kind of signal or a clue to go and look at first. So thank you for that.

Dr. Schram:
There was a study also by Tyson that showed that advanced imaging identified the tissue cancer of origin following a positive MCED test, resulting in fewer procedures to find where that cancer was compared to just molecular testing alone. That's an interesting study, although I think it does raise the question of cost. But if you're an individual and you have a positive test, and there is question, it's possible that advanced imaging could get you to the diagnosis a little bit sooner than molecular testing alone. So that is one of the hurdles that needs to be sorted out, as we improve and develop MCEDs going forward.

Dr. Westgate:
Again, thank you, Dr. Schram, and this analysis really highlights the need for ongoing innovation in cancer detection and cancer localization as a separate part of the MCED tests. To end this chapter, can you speak about the research on clonal expansion? What is clonal expansion? And how does it play a role in regards to misdiagnosis or that false positive result?

Dr. Schram:
There's a term we use in hematology called clonal hematopoiesis of indeterminate potential. And basically, what that means is there are bone marrow cells that, for all intents and purposes, are clones of one another. And there's a subset of population that are clones and they don't necessarily become malignant at all, but we know that they live in the bone marrow. The only unfortunate part of this is that they have a methylation pattern that sometimes can be confused with a CSO signal, a cancer signal. And so, some of these tests are better than others at being able to differentiate between an aberrant signal originating from the clonal hematopoiesis, or CHIP, versus a true cancer signal.

Dr. Westgate:
Thank you, Dr. Schram. What would you say is the most important take-home message for our learners from this chapter?

Dr. Schram:
I think that correct identification of a true cancer signal and tissue of origin can reduce time to a true positive diagnosis with the hope that

this would potentially save lives, beginning with earlier diagnosis, sooner treatment, and possibly cure.

[CHAPTER 5]

Dr. Westgate:
So let's switch gears now a little bit and talk about false positives and follow-up after cancer diagnosis. I know that a few long-term outcome studies from the original DETECT-A were presented at ASCO, could you talk more about that?

Dr. Schram:
DETECT-A, it was a study that evaluated an early version of the CancerSEEK in about 9,000 women without a history of cancer. This was a study that looked at long-term follow-up of these patients. And what this showed was that half of the patients with a MCED-detected cancer were successfully treated and cancer free over 4 years after their initial MCED test. And over half the patients in remission had cancers with no standard-of-care screening, so they never would have been identified, but for this test. And all patients with stage I or stage II cancers who were treated, remained cancer free. So this, again is a proof of principle.

The second follow-up study from the DETECT-A looked at long-term outcomes of a false positive event. There were 98 false positives. I think the takeaway from this ASCO abstract was that false positives are uncommon, they represent about less than 1% of individuals tested. And for the patients where there wasn't a finding on imaging or further diagnostic, less than 1% of those few remaining, do end up having a cancer come back. So I think this is helpful and hopefully indicative of a lot of the MCED platforms that false positives are rare. And even if you get one, they're pretty easily evaluated as false positives with minimal follow-up.

Dr. Westgate:
So as a clinician that is currently ordering MCED tests, I know that it is reassuring to me and to my patients when we talk about the false positive and false negative rates associated with this kind of platform. And as these kinds of tests continue to mature and we gather more data, as well as improve our diagnostic imaging and evaluation, we really hope to continue to see that kind of high specificity with these tests so that we are not doing unnecessary workup for our patient, causing more anxiety, etc. Thank you, Dr. Schram.

[CHAPTER 6]

Dr. Westgate:
There were also some posters that looked at MCED testing in the diagnostic pathway and not just using it as its intended use currently for screening the asymptomatic individual. These posters were looking at patients with signs and symptoms preceding diagnosis, and possibly how MCEDs could help speed up the diagnostic pathway. Can you tell us more about what these posters told us?

Dr. Schram:
The SIMPLIFY results presented at ASCO have been anticipated. This was a large-scale, observational, prospective cohort study, multi-cancer early detection test in symptomatic patients referred for cancer investigation. This found that about 6.7% of the patients were diagnosed with cancer through the standard of care. MCED detected cancer in 223 of 244, a positive predictive value of 75% and a negative predictive value of 97.6%. The sensitivity was lower in earlier stage cancers, higher and more advanced cancers, increased with age and later stages. I mentioned the cancer signal origin or tissue of origin was accurately identified in 95%. What this tells us is that this is a proof of principle really, that these tests, and this one in particular, could identify cancer in patients who were referred for a cancer workup. That's the most we can take away from this test right now, or this study.

There were two other papers that looked at patients with signs and symptoms preceding cancer, they were symptomatic. And they looked at how MCEDs could potentially use to speed up diagnosis. The first was NCCN. This was a large number of patients, over 100,000. The bottom line is that, again, this is a tool that is confirmatory, if anything, that patients with symptomatic cancer are able to be identified, in addition to traditional workups with MCED testing. I don't think we can again, take more away from the study other than that this tool is complementary, but certainly not replacing, and I'm not sure it clinically changes the lead time to a diagnosis, at least at this point in time.

There was another study that was very similar. It was retrospective observational cohort study, the median time to cancer after being referred was greater than 5 weeks. The takeaway was that there is a need for more tools for multi-cancer detection tests that could aid in the detection of multiple cancers and faster diagnostic resolution. But will that lead to clinically meaningful differences? I don't think that poster was designed, or that study was designed to sort that out. But it is additional information that I think will help refine the test going forward.

What is your takeaway? You know, as you're in the primary care setting, how do you think these tests, these MCEDs could be incorporated into primary care?

Dr. Westgate:

Thank you, Dr. Schram. That's a great question. We're at the forefront, the cutting edge of some great new innovations out there for early cancer detection. You know, we only currently have 5 cancers that we can screen for. But that only accounts for 25% of cancer deaths within the United States. And so there's a huge unmet need for us to do something differently, or, you know, integrating something different or a new test that would help us for that early cancer detection.

These last two posters that you were discussing, I think it really speaks to the possible versatility of this liquid-based testing, or these MCED tests to not only live in a space where we are screening the unaffected patient, but it can also be utilized and has the potential to be adjusted, the platform to be adjusted, and actually be utilized in potentially the symptomatic patient, as well or even in the minimal residual disease space.

[CHAPTER 7]

Dr. Westgate:
Dr. Schram, as you know, a lot of MCED research involves modeling. Let's talk about some of the modeling studies that demonstrate the various potential benefits of MCEDs.

Dr. Schram:
So let me discuss 2 reports from ASCO, both using the American Cancer Society Cancer Prevention Study, CPS-3 cohort. This was a dataset from ASCO that demonstrated that this particular MCED was able to pick up a cancer signal as early as 3 years prior to the cancers' clinical emergence. So if you look at the TPR, which is the test positive rate, at 3 years, it was 2.3%. At 2 years, it was 6%. And at 1 year, it was 15%. So that's a study that shows that this platform can detect things as early as 3 years prior to the clinical emergence of the cancer.

Another study using the same CPS-3 data provided a good benchmark for windows of early detection for different cancers. The author also suggests that long-term survival was better than the SEER data. Although I would caution everyone using SEER data for survival comparisons because SEER data is obviously retrospective, and often 4 or 5 years behind. And as we know, treatments in the last 5 to 10 years have really improved. So I think it's using survival in this study is perhaps going a bit too far. But it does validate the use of this platform for improving detection window and possibly improving survival in the future.

Dr. Westgate:
Well, this is very interesting and very exciting data that has come from these 2 abstracts. I know there was a really interesting study reported from the National Lung Screening Trial. Do you mind talking a little bit more about that one?

Dr. Schram:
I'd love to. This is a great poster by Chang et al presented at ASCO in Chicago this year. The NLST, which is the National Lung Screening Trial, was a prospective screening trial that changed the standard of care in the United States. This was a study that looked at over 53,000 patients, high risk for cancer, lung cancer specifically, ages 55 to 75, 30-pack-year history of smoking. The question was, does helical low-dose CT improve survival? And the answer that was arrived at was, yes, it does. But what is not often reported is that those lung cancers that were found represented only 1/3rd of the cancers that were detected by screening with imaging, which tells us that there is a great need for a single test that doesn't just look for one cancer, but looks for many cancers. Because once we start looking, we're finding a lot of other types of cancers. These can go missed if we don't have a single cancer screening test. And this illustrates the need for that.

Dr. Westgate:
Dr. Schram, what would you say is the main take-home points for our primary care provided listeners from this chapter?

Dr. Schram:
I think what I would say is that with new technology, any new technology, things are moving quickly. And improvements are made, sometimes incrementally, and sometimes in large steps. We've had some huge steps in the last 3 years. Ten years ago, people were really looking at circulating tumor cells. Now we're looking at cell-free DNA. And then now we're looking at methylation of that cell-free DNA. I think it's important to wait for society guidelines to make broad-brush recommendations. But I think we need to be open to becoming a little bit early adopters and not be late adopters when it comes to new technology.

[CHAPTER 8]

Dr. Westgate:
Now let's talk about health equity and ethics in the reality of MCED implementation. One group has already formed and started using an implementation model and presented their research at ASCO this year. Would you like to talk a little bit more about this presentation?

Dr. Schram:

I think you're the best person to speak about this, given that you are in the primary care space and you have first-hand experience developing such a program. Quite a good one.

Dr. Westgate:
Thank you, Dr. Schram. I appreciate that. This Agarwal study up at Mercy Health System, in their multistate implementation took a look at centralizing MCED testing implementation within a multistate healthcare system. So they launched in January of 2023. There are almost 4,000 referrals, led to 925 MCED tests being ordered. And what is poster showed us was that their medium time from a cancer signal test result to the patient notification was 22.8 hours, and to initial diagnostic evaluation was 3.1 days, and to a cancer diagnosis was 8.7 days. I only dream of such amazing numbers in regards to shortness of time. But I think what this presentation showed us was the ability, with careful thought prior to rolling out something new, like multi-cancer early detection and focusing on central navigation, as well as you know, nurse navigation and having pathways already created before implementing this kind of testing, we're able to do what's right by the patients and not increase their anxiety, but get them the testing and the workup that they needed in a very short amount of time.

Dr. Schram:
That's remarkable a week to diagnosis from initial screen is enviable even in traditional screening methodologies.

Dr. Westgate:
I do know that there were a few presentations about health equity. And as it relates to the use of MCEDs and the implementation into general practice. Can you shed some light on those for our learners?

Dr. Schram:
Sure. The first one was is a publication at ASCO in Chicago in June, looking at health equity challenges involving testing and evaluation and implementation of MCEDs. This was a description of the plan of the MCED Consortium, which is a -private collaboration in the U.S. and the UK, dedicated reducing the burden of cancer, but trying to figure out how we can best use these technologies equitably, and at a responsible cost. The challenge is that these tests, and any new technology generally, disproportionately increases access to the insured and higher socioeconomic groups before they make it to people who are underinsured or uninsured. And so how do we best roll these out to improve access to all? This and other health equity MCED challenges were discussed also by Leonard Fleck in another publication, abstract-only at ASCO. The argument was that it would cost Medicare billions to roll out MCED-type testing and all the downstream costs from following up on this testing, and that there was really no way to account for how to pay for this, even if MCEDs were reduced in price by 40% over the next 4 years. There's valid argument about what the cost of these tests might be. The question I think somebody needs to pose is, what's the cost of not doing this? What's the cost of not having screening tests? That would be a good kind of debate to have.

Dr. Westgate:
Thank you, Dr. Schram. And, as we know, with these kinds of new cancer screenings or new tests, it's difficult to project where the cost savings will come from, and the outcomes, especially as these MCED tests are finding cancers that we're not used to treating or taking care of, you know, at an earlier stage. So it's going to be interesting to see where this actually falls. And is the cost of this kind of testing and diagnostic going to be offset or balanced by the cost savings associated with catching a cancer at an early stage? And we know that's a lot less of a cost to our health system than, you know, catching cancer at a later stage, and the burden or the financial burden that goes along with that. So maybe there would be an even ground from that standpoint.

Dr. Schram:
Perfectly said, yes.

[CHAPTER 9]

Dr. Westgate:
Dr. Schram, let's talk about new MCEDs in development. There were many presentations on validation studies, some active clinical trials as well. Can you tell us about the presentations on MCEDs that are in current clinical trials?

Dr. Schram:
There are a few that reported but there's not a lot of data yet. The Harbinger study, Harbinger Health Assay, as reported by Gregg et al, was a study with about over 1,000 people, 621 of whom had newly diagnosed, never-before-treated cancer, 15 different types of cancer. This showed sensitivity of 82%, and 95% specificity, and it demonstrated 86% accuracy in identifying tissue of origin, breast, lung, colorectal, even in very small tumor fractions. This is also known as the CORE-HH study, and look for upcoming data on this. This is eagerly anticipated.

The next report was the Fusion Project. This is a prospective, multicenter cohort study of many different cancer screening in the

Chinese population using the PanSeer-X. I think there were over 50,000 patients in this trial, and we're looking for 2-year follow-up on that.

And then the SHIELD study which is screening for high-frequency malignant disease. It's a prospective, observational, multicenter basket study done in the United States and Europe. Its objective was to evaluate the performance of blood-based multi-cancer screening tests, Guardant base, to detect cancer and screen relevant individuals compared to the reference standard cancer screening modality.

Dr. Westgate:
That's a significant amount of information. It's exciting that all of these new MCEDs are in development and showing great promise.

Thank you so much for joining me for this conversation. I really appreciate the time that you spent with me, and all the information that you had to share about these conferences this last year.

Dr. Schram:
Thank you for inviting me.

Dr. Westgate:
Thank you for joining us for this MCED program. To access the abstracts presented here, please click on the link provided. For additional CME opportunities, clinical resources, and links to patient education materials, please visit us at exchangecme.com. And don't forget to take the post-test and fill out the CME evaluation. Thank you.

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