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PROGRAM NAME

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You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Exact Sciences. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me today to discuss multi-cancer early detection are Drs. Tom Beer and Betsy O'Donnell. Dr. Beer is the Chief Medical Officer for Multi-Cancer Early Detection at Exact Sciences Corporation. He also serves as an Adjunct Professor of Medicine at the OHSU Knight Cancer Institute in Portland, Oregon. Dr. Beer, welcome to the program.

Dr. Beer:
Glad to be here.

Dr. Turck:
And not only is Dr. O'Donnell the Director of Early Detection and Prevention of Malignant Conditions at the Dana-Farber Cancer Institute, but she's also an Assistant Professor of Medicine at Harvard Medical School.

Dr. O'Donnell, it's good to have you with us as well.

Dr. O'Donnell:
Thank you. It's great to be here.

Dr. Turck:
So why don't we start by doing some level-setting. Dr. Beer, what do we need to know about the current landscape surrounding standard-of-care cancer screening?

Dr. Beer:
Well, as we all know, screening is foundational in the fight against cancer because if we detect cancer in earlier stages when it can be more treatable with fewer side effects, we can reduce morbidity and mortality related to cancer. But unfortunately, recent estimates show that only 14 percent of cancers are detected through routine screening, and so the majority of patients are diagnosed after the onset of clinical symptoms, which may require extensive evaluation to identify an underlying malignancy that is often then found at a later stage when it's more difficult to treat.

Part of the reason for this is that the USPSTF recommends screening for only four cancers: lung for high-risk patients, breast, cervical, and colorectal. This means that nearly 70 percent of incidence cancers and cancer deaths are from cancers with no recommended screening options.

Another important limitation we need to be aware of is associated with access, adherence, and equity. Even for cancers that do have guideline-recommended screening options, many patients aren't able to access them or simply don't participate in screening. And underserved populations often experience higher burden in accessing screening in addition to experiencing even higher rates of cancer and cancer mortality, further widening the gap in health disparities.

Dr. Turck:
Well, it certainly sounds like there's some key limitations we need to address. And with that background in mind, let's turn to you now, Dr. O'Donnell, and focus our attention on multi-cancer early detection tests. Can you tell us more about what these tests are?

Dr. O'Donnell:
Sure. So multi-cancer early detection tests, or MCED tests as we typically refer to them, are a new modality for screening for cancer through a single blood draw. So as Dr. Beer just explained, there are only four cancers for which we have standard screening tests for. This is an opportunity to leverage new science that we have to potentially expand our ability to detect cancer through a single blood draw.

If you think about it, it was only about two decades ago that we first sequenced a human genome. Since that time, we've been able to increase our libraries to include the genomes of different cancers. Now, we can look inside peoples' blood and detect differences between healthy and abnormal DNA. And then, we can also incorporate other biomarkers that increase our ability to potentially detect cancer at low concentrations within the blood. And the beauty of this is that it has potential to cause a major paradigm shift in how we screen for cancer.

Dr. Turck:
Based on what you just said, Dr. O'Donnell, can you expand on how MCED testing might fit into current standard-of-care screening?

Dr. O'Donnell:
Absolutely. So we don't want patients to stop doing their cancer screening. This is something intended to complement the existing screening tests.

And so where we really see the biggest potential is in that greater than 70 percent of cancers that do not have existing screening tests.

And not only do they not have tests, but it's very hard; these are not as common as cancers like colon cancer and breast cancer, so it would be very challenging to try to screen for multiple types of cancer annually for our patients. So these tests enable us to aggregate multiple cancers that may be less common into one test.

In addition to that, Dr. Beer said it earlier, for cancers that don't have screening tests available, most patients present when they have symptoms.

And so what we want is to shift when we find these cancers to earlier stages. So when patients have symptoms, they often have advanced disease and are not curable.

By having a blood test that can potentially find cancers at their earlier stages, we then open up the potential to identify and cure more patients.

And in addition, and what I think is probably the most significant, is the ability to expand access through these tests. And so, you know, there's a broad variability in terms of who currently adheres to screening guidelines, and a lot of that is dictated by equity, and access, and location. And so the beauty of a blood test, though the technology is not simple, having a blood test is relatively simple and offers broad and democratized access to screening.

Dr. Turck:
Thanks for making those important distinctions, Dr. O'Donnell. And if we switch gears a bit and examine some of the data on MCED tests, Dr. Beer, what have we learned from recent trials about their potential clinical value?

Dr. Beer:
Well, there have been two prospective interventional studies where candidate MCED tests have been evaluated in the intended use population: the PATHFINDER study and the DETECT-A study.

If we focus on the PATHFINDER study first, that was a study that examined a methylation-based multi-cancer early detection test that enrolled a little bit over 6,600 participants that were of average and of elevated risk for cancer.

This study examined a prototype MCED test and then retrospectively also evaluated an updated version of that MCED test. The study's primary focus was on evaluating the diagnostic journey that would follow the return of a positive MCED result. We also learned quite a bit about the performance of that candidate MCED test. And what the study showed is that MCED testing approximately doubled the number of cancers detected through screening with a sensitivity of 29 percent for the version one of the test and about 21 percent for the updated version at a specificity over 99 percent. It also showed the feasibility of MCED testing and provided initial evidence about the safety and other outcomes.

In the DETECT-A study, a multi-biomarker class MCED was evaluated. It was also a prototype test evaluating DNA mutations and protein biomarkers. This study recruited over 10,000 women aged 65 to 75. And again, we saw about a doubling of the number of cancers detected through screening. Meaning that in these two studies, MCED tests used on a single occasion detected as many cancers as all standard-of-care screening tests combined that were used in the same patient population. The test detected cancers in

multiple organ types, including a number that represent cancers for which no standard-of-care screening tests are available. The sensitivity in this initial study was 27 percent at a 99 percent specificity.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Tom Beer and Betsy O'Donnell about how Multi-Cancer Early Detection tests may change the way we approach screening for cancer in our patients.

Dr. Turck:
Now, Dr. Beer, earlier you mentioned that the DETECT-A study used a multi-biomarker class test design. So can you tell us more about this approach and what was found?

Dr. Beer:
Yeah. So, you know, cancers release a variety of different substances into the blood that can be detected. And in the DETECT-A study, the candidate test evaluated DNA mutations and protein biomarkers. And what the study found is that in that setting, these two biomarker classes were complementary to one another, meaning that the results from the DNA analysis were supplemented by the results of the protein analysis to yield the cancer detection that was seen. This in turn inspired additional studies that look at different biomarker class combinations to help improve test sensitivity and reproducibility, and we hope will enable early-stage detection when treatments of curative intent are possible.

Dr. Turck:
So with that being said, let's come back to you Dr. O'Donnell. What do we need to know about these ongoing studies?

Dr. O'Donnell:
Since the initial reporting findings from the DETECT-A study, there have been multiple case control studies that have demonstrated the power to deliver added sensitivity to multi-biomarker class approach while still delivering strong specificity.

Recently, there was a large retrospective study. It was a case control study designed to train, validate, and test the performance of two different multi-biomarker tests. These tests were designed to evaluate for cancers at all stages and to try to detect up to 15 different types of cancer. There was a control arm that included non-cancer patients, and it was also enriched for individuals who had non-cancer diseases and benign tumors. In the first cohort, there were over 2,000 samples analyzed with the 3-biomarker test that included 12 types of cancer.

And then there was independent testing set that included an analysis of over 1,200 samples that used the 4-biomarker class test design. And in this latter set, the 4-biomarker included the 12 solid tumor malignancies plus 3 additional hematologic malignancies.

Dr. Turck:
And as a follow-up to that, Dr. O'Donnell, what data have been reported so far from these studies, and what implications might these findings have?

Dr. O'Donnell:
So, so far so good. What we're seeing is that in fact they are able to detect multiple types of cancer in multiple stages. I think the most important thing is the added sensitivity, so the ability to pick up cancers, has increased up to 62 percent while a 98 percent specificity is preserved. And most importantly, the sensitivity in the early stage – so stages 1 and 2 where we believe cancers are most curable – increased up to 40 percent. Again, these are preliminary reports. This is a case control study as opposed to a prospective interventional study, so these will need further evaluation. But I think what's exciting is that we are seeing an increase in sensitivity with an ability to detect cancers at earlier stages when they might be more curable.

Dr. Turck:
Now we're almost out of time for today, but given everything we've discussed, Dr. Beer, what further work is needed before we can fully utilize MCED testing?

Dr. Beer:
So while I believe that MCED testing has the potential to shift the paradigm in cancer screening, many unanswered questions need to be addressed, and these include: optimizing the test design to strike the right balance between sensitivity and specificity, establishing the optimal frequency of testing, understanding the best diagnostic resolution pathway to provide patients and providers with clear and definitive answers about their cancer status following a positive multi-cancer early detection test result, addressing patient perceptions of their MCED test result—for instance, will they continue with standard-of-care screening based on those results?—and finally, how to best implement these tests so that they're accepted and they do not exacerbate disparities, and if we're really successful, perhaps

reduce disparities in cancer screening.

In addition to addressing some of these unanswered questions, it'll be important to conduct studies that will help deliver the clinical evidence to support the broad use and accessibility of these tests. These studies could include pivotal trials for the basis of an application for FDA approval that would enable them coverage by healthcare plans and also real-world evidence programs to see how the test is accepted and learn what the best strategies for implementation might be.

Ultimately, I envision a future where multi-cancer early detection testing is used alongside recommended screening as part of routine primary care, helping to expand the range of cancers that may be detected early when treatments with curative intent are possible.

Dr. Turck:
That's a great comment for us to think on as we come to the end of today's program. And with that, I want to thank my guests, Drs. Tom Beer and Betsy O'Donnell, for helping us better understand the potential impacts of multi-cancer early detection tests. Dr. Beer, Dr. O'Donnell, it was great speaking with you both today.

Dr. Beer:
Thank you, Dr. Turck and Dr. O'Donnell, for joining me today. It's been a pleasure.

Dr. O'Donnell:
Thank you, and likewise.

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