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Poster Pearl: A 2-Biomarker Class MCED Test Delivers High Specificity and Sensitivity

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

Dr. McDonough:
This is *Project Oncology* on ReachMD, and I'm Dr. Brian McDonough. Here with me today to discuss the poster he co-authored and presented at the 2024 American Association for Cancer Research Annual Meeting, or AACR, is Dr. Frank Diehl. Dr. Diehl is the Senior Vice President of Multi-Cancer Early Detection at Exact Sciences Corporation, and his poster presented findings on the performance of a multi-biomarker class, multi-cancer early detection, or MCED, blood test. Dr. Diehl, thanks for being here today.

Dr. Diehl:
Yeah, it's great to be back and I'm happy to discuss our most recent results presented at AACR earlier this month in San Diego.

Dr. McDonough:
Before we dive into this poster, Dr. Diehl, I'd like to start with some background. Can you tell us about your previous research on a multi-biomarker class MCED test design and what the findings were?

Dr. Diehl:
Let me start with one foundational multi-biomarker class MCED publication that's relevant for this discussion today. It's by Anne Marie Lennon from the Johns Hopkins University and was published in 2020 in *Science.* The publication describes the use of an initial version of a multi-biomarker blood test that combines a mutation and protein test, and it was called CancerSEEK. The blood test was utilized in a study that's called DETECT-A. DETECT-A was the first prospective interventional study to evaluate the performance of an MCED test in an average-risk population. It enrolled about 10,000 women with no prior history of cancer aged 65 to 75, and a positive MCED test was followed by an imaging procedure to localize the tumor.

So there are three main findings that are important. One is that the MCED test doubled the number of cancers detected by screening by combining the blood test with standard-of-care screening versus just standard-of-care screening alone. Second, the MCED blood test detected cancer from multiple organs, including those organs where there's no screening option available. And lastly, in the follow-up analysis, it showed that the earlier detection through that blood test enabled treatments with curative intent. So in summary, the overall sensitivity of that test in DETECT-A was 27 percent at the 98.9 percent specificity. It's very promising. And the next step we wanted to find out is if other biomarkers could be added that would allow us to increase the sensitivity further without reducing specificity. So we took a deeper look at the two biomarker classes, mutations and protein, and there was very little overlap between these two biomarker classes except one cancer was detected by both. And so in the recent years, we have developed new biomarker assays that were added to the MCED test, specifically DNA methylation and aneuploidy was added. We showed in 2022 at ESMO and then at an ACCR Special Conference the combined performance of these four biomarkers. And we really showed that a multi-biomarker approach for MCED can improve sensitivity and has a great potential going forward.

Dr. McDonough:
That's very interesting. But what were the goals for the ASCEND 2 study and how was it designed?

Dr. Diehl:
So following the feasibility studies I just mentioned to you, there is an addition. We have a new study called ASCEND 2 that's a

development study that we're using to train and test new calling algorithms for other biomarkers. That is leading toward the MCED test Exact Sciences is going to take into clinical validation in a pivotal study. So ASCEND 2 is designed as a multicenter prospective collected case-control study of clinically characterized subjects. To date, we have enrolled over 19,000 non-cancer controls and over 5,000 cancer subjects used across 151 sites in the US and Europe. They include both males and females over the age of 50. So the goal of this study is really to allow us to train and test new biomarker algorithms and to come up with an algorithm that's generalizable in the future when we go into the clinical validation study. So in summary, we're very happy with the enrollment. It's a racially, ethnically, and geographically diverse cohort that we achieved in the enrollment.

Dr. McDonough:
So as a quick follow-up to that, can you give us some insights on the objectives for conducting this first analysis from the ASCEND 2 study and why it was so important to do this?

Dr. Diehl:
So the objective of that first data analysis was to assess the performance of two specific biomarker classes, namely methylation and protein biomarkers. We previously assessed up to four biomarker classes, and for this poster, we wanted to share the performance for just two biomarker classes. Specifically, we looked at 6,354 subjects, which means samples. And there were around 4,900 non-cancer controls and about 1,400 cancers included. The samples were split across a training set and an independent holdout set. And then the training set itself and the testing set had a similar ratio between cancers and non-cancers. There was a total of 21 tumor organ sites included in the study, and we had a mixture of high-incidence cancers. Some of them were common and rare. The goal was to reflect all of these different cancer types that we potentially would see in a screening setting. We used machine learning to develop the algorithms for the methylation and the protein biomarkers in a cross-validation approach in the training set. And then we applied two final configurations to that testing holdout set. The specificity that we were targeting was 98.5 percent and 99.0 percent.

Dr. McDonough:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Frank Diehl about the poster he co-authored and presented at the 2024 AACR Annual Meeting that focused on the use of multi-analyte MCED blood tests to assess two biomarker classes.

So, Dr. Diehl, now that we have a solid understanding of the background of the ASCEND 2 study and your first analysis from it, let's zero in on the results. What were the key findings?

Dr. Diehl:
So as I outlined, this is the result of a first analysis of the protein methylation markers, and it showed an overall sensitivity of 50.9 percent across the 21 tumor organ types that we analyzed across all four stages of cancer included in the study. We feel good about the sensitivity. The specificity we achieved in the test set was 98.5 percent. That was on target with what we tried to achieve, and it's high enough to help us limit false positive results. The sensitivity across the different stages was different, of course, right? I mean, earlier stages are harder to take than a late stage. So it ranged from 15.4 percent all the way to 85.5 percent. When we combined the sensitivity for stage one and two, which are the stages that are most relevant for a screening setting, we achieved a sensitivity of 26 percent.

We also did an analysis data cut where we took out breast and prostate cancers. We removed breast cancers because there are already very effective, recommended standard-of-care screening option modalities in place. And we also know that breast cancer, early breast cancers in particular, don't release much DNA into the circulation and are hard to detect. Similarly with prostate cancer, there are recommended screening options on an individual basis available, and the DNA shedding is also low. So that's why we excluded them; we wanted to see the performance if we took out these two tumor types. And so we achieved without breast and prostate a sensitivity of 56.8 percent.

We also looked at additional data cuts to explore the potential of MCED testing in the future, in the real world. One of them was tctake out tumors that already have a screening option like breast cancer, colorectal cancer, cervical cancer, and I mentioned prostate cancer. We kept lung cancer in because lung cancer screening is recommended for high-risk patients and also the adherence is low. So what we found in that setting is their sensitivity is about 55 percent. And lastly, and I think most importantly, is that when we look at the most aggressive cancers, I think that's where this test can potentially have the biggest impact. We just looked at the cancers with the poorest or shortest five-year survival rate, which are esophagus, liver, lung, ovary, pancreas, and stomach cancer. And what we found in this setting a sensitivity of 64 percent, which could be very meaningful.

Dr. McDonough:
Lastly, can you tell us what those results might mean for early cancer detection?

Dr. Diehl:
So let me start my answer by providing some limitations to the data I just shared. So first, the results are based on a stratified case-control study of subjects with known cancer status. So they do not come from a prospective interventional study in a screening setting where subjects usually have no symptoms. So therefore, the results do not reflect what is expected in the real world. The second limitation is that the distribution of the cancer types and stages are not fully represented of the intended-use population of such a test. We selected the type and stages for training and testing a classifier for multiple biomarker classes. So we wanted to have a representation of all stages and all of these different cancer types. And when we don't have a direct reflection of the intended-use population, the results are still valuable for the field. So we demonstrated that multi-biomarker approaches at performance, we show over and over that they can deliver a high performance. And we are continuing to analyze additional biomarker classes from this ASCEND 2 study to finalize our assay design. The two-biomarker class test results I just shared demonstrated to us that we can move forward, and we are confident to move forward into a real-world evidence study and to see how this test configuration works in the real world.

Dr. McDonough:
Well, as those final thoughts bring us to the end of today's program, I want to thank my guest, Dr. Frank Diehl, for joining me to discuss the findings from his research on multi-cancer early detection. Dr. Diehl, it was great having you on the program.

Dr. Diehl:
Thank you.

Announcer:
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