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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

MCED Testing: Confirming a Positive Result with Diagnostic Follow-Up

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:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and joining me to share their insights on how we can minimize the risks associated with follow-up testing after a positive multi-cancer early detection test result are Drs. Betsy O'Donnell and Tom Beer. 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, thanks for being here today.

Dr. O'Donnell:
Thank you for having me.

Dr. McDonough:
And 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:
It's such pleasure to be here today.

Dr. McDonough:
To start us off, Dr. Beer, can you give us some background on what multi-cancer early detection, or MCED, tests are and what typically happens when a patient is tested?

Dr. Beer:
Sure. So first of all, let me start with the observation that we all know that effective early detection of cancer can save lives. We've made a lot of progress in this area with screening tests for breast cancer, colorectal cancer, cervical cancer, lung cancer, and to some extent prostate cancer. But nearly 70 percent of cancer cases and 70 percent of cancer deaths occur due to cancers for which we have no guideline-recommended screening tests. That's where multi-cancer early detection tests are aiming to make a difference. These tests called MCED tests are typically blood tests. They are built around a technology that detects various different substances in the blood or biomarkers that are released from cancers and are designed to pick up a variety of cancers early with the hope that once the research confirms their utility, we can close that screening gap and extend early detection beyond the four or five cancers that we currently screen for today. Typically with a MCED test, a patient gets a blood draw. That blood draw then goes to the laboratory where it's analyzed for the cancer-related substances, and that test can return a result that suggests the presence of cancer or determines that no cancer is suspected. If a cancer is suspected, that result is not a diagnosis of cancer but requires additional procedures to determine if a cancer is present or not.

Dr. McDonough:
With that background in mind, let us turn now to Dr. O'Donnell. Should a patient get a positive MCED test result, what are the current diagnostic resolution pathways proposed for localizing and confirming that positive result?

Dr. O'Donnell: :
Well, as Dr. Beer mentioned, since MCED tests are designed to detect multiple cancers through a single blood draw, they're using

biomarkers to come up with a signal that might be suggestive of a potential cancer being present. So it's really important to understand with MCED tests that these are screening tests; they are not diagnostic tests. And so once you get this positive signal, there are a couple different ways in which that signal can read out and a workup can ensue. And so thus far, we've seen two different approaches; one is where patients might be given back a tissue of origin. So the first step is that a signal is detected or not. And then beyond that, you might see that there's a cancer site of origin or a tissue of origin suggested. It then goes on to the provider to determine what are the right tests to adjudicate that result. And in 90 percent of the cases that we've seen for the tissue of origin type test, they require advanced imaging and often some type of diagnostic procedure. If the cancer is found, then patients proceed to the appropriate oncology clinic. If cancer is not found, then there is a question of: how do you appropriately follow the patients thereafter? There is now free testing available for the one commercially available retesting, but really the question becomes: how does a provider choose to follow and to consider re-imaging in this scenario? The other modality is through imaging where patients who have, again, a binary result, a yes or a no for a signal detected, go on immediately to have advanced imaging. And in this approach, patients with a positive test would have a CT scan of the neck, chest, abdomen, and pelvis. And if there is no cancer found with this initial set of scans, then they would go on and be referred to a full body PET scan. And so if nothing were found on that PET scan, it would be felt to be a false positive. And here again, you would continue to follow the patient as deemed appropriate clinically.

Dr. McDonough:
And Dr. Beer, what are the key things to consider about these approaches, especially in regards to the potential benefits and harms to patients undergoing MCED testing?

Dr. Beer:
Well, one of the big considerations here, of course, is to minimize the test-related complications and the risks to the patient. The top priority there is to reduce the number of unnecessary or unproductive diagnostic procedures that are necessary to either identify the cancer that's present or rule out the presence of cancer. That can be accomplished through both designing tests that have a high specificity, meaning that the likelihood of a false positive result would be relatively low, and then the other goal there is to develop diagnostic strategies that are as efficient as possible that get to a definitive answer efficiently, quickly, and with as few diagnostic procedures as necessary. Another consideration from the perspective of harms is, of course, patient anxiety and all the worry that goes into going through a process like this. And again, good patient education, a strong relationship with their primary care provider, high specificity, limiting the number of false positives, and an efficient diagnostic approach that gets to an answer quickly are all strategies that we can employ to try to limit the anxiety that's associated with going through MCED testing.

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 Drs. Betsy O'Donnell and Tom Beer about minimizing the risks associated with follow-up testing after a positive MCED test result.

So now that we know more about these two diagnostic follow-up pathways, Dr. O'Donnell, let's zero in on some best practices. What have we learned from studies that may help us optimize our approach to diagnostic resolution following positive MCED test results?

Dr. O'Donnell:
Yeah, thank you for your question. So this is a really important area within the field to consider. And really Dr. Beer touched on a lot of the critical questions, you know, in terms of what is going to be the most efficient, and then also what is going to render the greatest degree of certainty, especially in those scenarios where you may have a false positive result. So there have been several studies to date. We've had two prospective studies: the DETECT-A Study and the PATHFINDER study. In addition and subsequent to that, there was a modeling study trying to get at this issue. So to begin with the PATHFINDER study, this study has a test that gives a molecular approach for when trying to adjudicate a positive MCED test. So first, there's the signal detected versus not detected, and then beyond that, there are one or two cancer sites of origin that are suggested, or CSOs.

And so when we look at the results from the PATHFINDER study, the accuracy of the CSOs for the first and second cancer potentially named are about 88 and 84 percent, respectively. And so once you have that, the question becomes, what is the next step? So 90 percent of the participants in that study who had a positive signal detected went on to require advanced imaging. And for those who had positive tests and the tissue of origin was in keeping with the malignancy diagnosed, the time to diagnostic resolution was about 57 days. For those who ultimately had false positives, it was 162 days, so almost an upwards of five months. But it is important to note that this was done during COVID.

In the DETECT-A study, an imaging-based approach was used. So here again, there was a binary result, yes or no. And from that, there was a committee that looked at each of the different cases and determined whether or not a further diagnostic workup was needed. In 101 out of 108 cases, a PET scan was recommended. And so for those who had PET scans, 62 percent of those did not require an

additional workup. For the 38 that had additional testing, about 42 percent was non-invasive and 50 percent was minimally invasive. And so another important thing that was brought up is this issue having a false positive result and the question of anxiety Dr. Beer touched on. So when you look at the long-term follow-up data from the DETECT-A study, the incident rate of cancer was quite low and in keeping with that of the SEER incident rate, suggesting that a negative PET scan in this scenario was reassuring for patients.

And so beyond that, a third study was conducted employing a predictive modeling strategy. So here, the question was really in a couple different scenarios using positive predictive value and the accuracy of the tissue origin, what was the probability that there would be less burden in terms of diagnostic resolution? And so in over 95 percent of the different scenarios, the burden was less for the imaging-based strategy; it would take a positive predictive value of 79 percent and a tissue of origin accuracy of 90 percent for that to be less burdensome than the imaging-based strategy. Currently, the positive predictive value of MCED tests are about 25 to 40 percent. It is worth noting, though, that the true positives with the molecular signal of origin is the scenario where that strategy would be the most efficient.

Dr. McDonough:
Now we've certainly covered a lot today, but before we close, I'd like to hear some final thoughts from each of you. Dr. Beer, care to start us off?

Dr. Beer:
Sure. So I think we've heard why it's so important that we continue to develop these MCED tests, striking the right balance between capturing the benefits and limiting the harms. And the primary levers that we have there is striking the correct balance between sensitivity so that we can detect as many cancers as possible, the right cancers at early enough stages to intervene and make a difference, and a high specificity to limit false positives. And getting the balance between that sensitivity and specificity right is one of the goals of MCED development programs. And the other, as Dr. O'Donnell alluded to, is the importance of an efficient and effective diagnostic strategy. So those patients who receive an abnormal result from a MCED test can get to a definitive answer and can get there quickly with as few procedures as possible.

Dr. McDonough:
Thanks, Dr. Beer. And how about you, Dr. O'Donnell? What would you like to share?

Dr. O'Donnell:
So I'm extremely excited by the potential of MCED testing. Like many disruptive technologies—and I would consider this a disruptive technology—there is tremendous opportunity, but I think we still have a lot to learn in terms of how best do we implement this. So when we think about the attributes of an MCED test that will be successful in terms of clinical implementation, I think it's important that we keep the patient front and center and that we minimize the number of procedures and help limit any potential unnecessary procedures or exposures. We have to have a fast time to diagnostic resolution. This needs to be accessible. So if we are going to have these types of tests that require any type of diagnostic odyssey that patients have access to the types of imaging tests or diagnostic tests that they need, and also we have to ensure that this is doable for the providers in a busy healthcare system that are trying to implement them. So I think these are all critical questions and specifically thinking about what the swiftest pathway is to diagnostic resolution as part of how we make the potential for something really exciting for the healthcare system a reality.

Dr. McDonough:
Those are some great comments for us to think about as we come to the end of today's program. And I want to thank my guest, Drs. Betsy O'Donnell and Tom Beer, for joining me to discuss the diagnostic pathways we can use after positive multi cancer early detection test outcomes. Dr. O'Donnell, Dr. Beer, it was great having both of you on the program.

Dr. O'Donnell:
Thank you so much. It was my pleasure.

Dr. Beer:
I really appreciate the chance to be with you today.

Announcer:
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