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Poster Pearl: Imaging-Based Localization for MCED Tests Yields Lower Diagnostic Burden

Announcer:
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Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me is Dr. Betsy O'Donnell, who co-authored a poster that was recently presented at the 2023 American Association for Cancer Research Annual Meeting and focused on evaluating the diagnostic burden of tumor localization strategies for multi-cancer early detection tests. 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 so much for the invitation. It's great to be here.

Dr. Turck:
Well let's start with some background, Dr. O'Donnell. Would you share with us the main objectives of this study and why it was important to examine this topic?

Dr. O'Donnell:
Sure. So I'm a medical oncologist, and by profession, I have been treating the blood cancer multiple myeloma for about the past decade, and we now have this new advent of blood-based tests that can potentially detect cancers in your blood. And I think that this is a really exciting scientific movement within oncology. And there are a lot of new products coming to market; some are what are called MCED tests, or multi-cancer early detection tests, and others are more focused on specific cancers. If a patient chooses to have an MCED test done, typically the results come back and say that a signal has been detected or not detected, and then the test may say Yes/No, that's it, you got to figure it out from here, or here are the potential cancers or the potential cancer that we think it is, and then a more traditional workup is embarked upon with potentially more imaging and definitely the need for a biopsy to prove this.

And so the question when we think about how does this integrate into practice is, is it more expeditious to use the tissue of origin guidance to try and localize the potential cancer or to go straight to more advanced imaging for your localization, recognizing that where tests are now, they may not be as sensitive, meaning as able to detect the cancers, and also, the positive predictive value – what it thinks the cancer might be – might not be as accurate. And so for where we are right now, we're trying to answer the question of, is it more straightforward and potentially easier for patients in terms of the diagnostic burden to go straight to imaging versus trying to make tests that localize the cancer and diagnose a tissue of origin?

Dr. Turck:
Now with that in mind, what types of procedures and outcomes for the molecular tissue of origin diagnostic resolution approach did you select?

Dr. O'Donnell:

What we did here was we looked at published research, and we came up with a model of predicting the diagnostic burden. So what we're trying to say is, if we model this out, based on the data that we have right now – tests may improve and strategies may improve – but based on what we have right now, we tried to model what the pathway would look like for imaging if it was a true positive test; so if you get that Yes back, what the number of tests would look like for a Yes test if you just used imaging versus a No test. And then for molecular tissue of origin, we looked at the tests that would be involved if it was a true positive with accurate localization, if it was a true positive but inaccurate localization, and then finally, if it was a false positive. So it was a little bit more of a complex decision tree, but basically, what we were trying to do and what we created a model for is come up with the number of diagnostic procedures that each of these different variations, I guess you would say, might entail.

Dr. Turck:
And would you describe some of the base case assumptions that went into your modeling?

Dr. O'Donnell:
So basically the assumption is that we used a mathematic formula that incorporated the positive predictive value of the current test using an estimated range for the sensitivity and the positive predictive value that came up with a number of estimated diagnostic procedures. But if we went for a case base clinically, then I think the model looked like, let's say you had a blood-based test that said you had a positive test versus a negative test, the next step would be a radiographic study, very often a CT scan just based on ease of getting, and then if there wasn't diagnostic resolution for that or more complete information was needed, then a PET scan, and then a biopsy versus if you had molecular tissue of origin, you may proceed first to a biopsy because you've been given this localizing signal, and then for some of those patients it would be accurate, for those it would be not. And so those patients would then have to go on to have imaging and that imaging would either show that there was diagnostic resolution giving a more specific signal where the biopsy should occur versus showing that this test was in fact one of the known false positives.

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 Dr. Betsy O'Donnell about the poster she authored for the 2023 AACR Annual Meeting.

So, Dr. O'Donnell, based on the analyses performed, which diagnostic resolution approach is expected to yield the lower diagnostic burden, and what are some of the key results that demonstrate that?

Dr. O'Donnell:
Sure. So our results – and again, this is based on the current existing literature that we have on the tests that have had data published thus far – would suggest that actually using image-based tissue of origin localization strategies versus molecular has a lower diagnostic burden, meaning that patients had to have fewer tests done to show what type of cancer this was, if it was a cancer.

Dr. Turck:
Now how might these results impact patient safety and anxiety, ordering providers, and the healthcare system as a whole?

Dr. O'Donnell:
So this is such an important question and I think this is one of the many questions for providers who are trying to think about how these will be used in practice or ask themselves. So if you're a busy provider and you rely upon schedulers and a variety of other people to help orchestrate getting testing done and prior authorizations, what our current data would suggest is that the most effective streamlined approach is to go directly to an image-guided or image-based strategy to limit the number of tests and also speed diagnostic resolution. As anybody who practices knows, it's not like you can just jump from one test to the next; you have to get the information from the first test, schedule the next test, wait for the next test, and then wait for the results of that next test to come back. So from a provider standpoint, obviously whatever is going to be the fewest steps is usually the preferred.

But from a patient's standpoint, which you brought up, I think this is incredibly important because one thing that we are studying a lot as these tests are coming of age is, how do the patients feel? What is the anxiety factor of getting a blood-based test? The positive predictive value – the accuracy – may not be 100 percent yet. There's that question of whether it's a true versus a false positive in terms of patient anxiety, but then there's also this diagnostic wait time from having a potentially positive test. And so I think the goal is obviously to mitigate that for our patients to limit the amount of time, and for patients it's not just the stress of trying to have this diagnostic odyssey; it's also the time and resources spent for patients – getting in for evaluations and undergoing invasive procedures. So I think we really want to be thoughtful about how these tests integrate and what is not only best in terms of emotional welfare, but also the logistics, the healthcare finances of all of this. We have to be really sensitive to all of those as we develop these tests so that we can come up with the right strategies for our test development.

Dr. Turck:

And are there any areas where a molecular tissue of origin diagnostic resolution is estimated to have a lower diagnostic burden than an imaging-based one?

Dr. O'Donnell:
So that's a great question. So we would need it 90 percent molecular tissue of origin accuracy, a positive predictive value of 79 percent is necessary for the molecular tissue of origin to have the same diagnostic burden as the imaging tissue of origin. So in the scenario where we could make that accurate, it would have to have a pretty high positive predictive value. We're not there yet, but I think that's an excellent goal.

Dr. Turck:
And as a follow-up to that, would you walk us through your findings regarding efficiency?

Dr. O'Donnell:
Efficiency, I think, is really characterized by the number of tests that it would require patients. So what we looked at was basically the number of procedures expected, and so for the imaging true positives, we averaged 2.75 expected procedure count. For the false positives, it was a 2.4 expected procedure count. And then going through the molecular ones, as I just mentioned, for patients who had a molecular tissue of origin that was accurate – so, identified correctly – there was 2.10 expected procedures. If it was an incorrectly localized, but there was in fact a cancer present, it was 4.4 expected procedures. And if it was a false positive with the molecular tissue of origin, there were 4.05 expected procedures to reach diagnostic resolution.

Dr. Turck:
Now before we close, Dr. O'Donnell, let's bring this all together. What key conclusions should we take away from this research and our discussion today?

Dr. O'Donnell:
Where we stand now, I think we're really at the beginning of incorporation of multi-cancer detection into our practice. I think it is an extremely exciting future. I think there are more unanswered questions than there are answered questions from a practical standpoint. What we were trying to do here is try to understand, at this point in time with the evidence that we have, is it better to have an image-guided tissue of origin strategy versus molecular? What we were able to learn from our own modeling was that at this point, it seems to favor imaging. I think there is a role for developing both. I think the future is extremely bright. I think that also it may not be as cut and dry as one or the other. I think there may be a role for a nuanced molecular tissue of origin, thinking about if there are predefined cancer risk populations. Can we use these tests specifically looking at cancers that one might expect in these populations? So I think we're really at the beginning with a lot of great potential to learn more and to better our cancer detection practices in the future.

Dr. Turck:
Well with those key takeaways in mind, I want to thank my guest, Dr. Betsy O'Donnell, for joining me to discuss her research focusing on evaluating the diagnostic burden of tumor localization strategies for multi-cancer early detection tests.

Dr. O'Donnell, it was great having you on the program today.

Dr. O'Donnell:
Thank you.

Announcer:
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