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

MCED Testing: Strategies for Mitigating the Risk of Overdiagnosis

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. Joining me to discuss how we can mitigate risks of overdiagnosis in multi-cancer early detection testing are Drs. Nima Nabavizadeh and Tom Beer. Dr. Nabavizadeh is an Associate Professor in the Department of Radiation Medicine in the School of Medicine at OHSU in Portland, Oregon. Dr. Nabavizadeh, welcome to the program.

Dr. Nabavizadeh:
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. Dr. Beer, it's great to have you with us as well.

Dr. Beer:
Great to be with you. Thank you.

Dr. McDonough:
So let's just dive right in. Starting with you, Dr. Beer, can you provide a high-level overview of the importance of cancer screening and the potential benefits and the harms that should be considered?

Dr. Beer:
So cancer screening is really foundational in the fight against cancer. We know that in combination with reductions in tobacco use and improvements in cancer treatments, cancer screening has contributed to a sustained reduction in cancer mortality over the last several decades. Cancer screening can help detect cancers early when interventions can be more effective, less toxic, and sometimes also less expensive. And in some cases, such as colorectal cancer and cervical cancer, screening can also detect pre-cancerous lesions that can be removed. And as a consequence, we can prevent the development of those cancers. As with any type of effective screening, we must strike a balance between the benefits and the potential harms of the intervention. The benefits, of course, include detecting cancers early when interventions can be more effective and the potential to reduce cancer-related mortality. Some of the potential harms include test-related complications, false positives, which subject people to unnecessary diagnostic evaluations and anxiety, and the possibility of overdiagnosis and overtreatment, meaning the diagnosis of small, slow, and indolent cancers that may not benefit from intervention.

Dr. McDonough:
And if we turn our attention to multi-cancer early detection or MCED testing, Dr. Nabavizadeh, how does it fit into the cancer screening paradigm? And are there any potential benefits and risks associated with this new technology?

Dr. Nabavizadeh:
MCED testing is a novel technology, and it really has the potential to have a significant impact on cancer screening. MCED tests are designed on the principle that all tumors have shared biologic features with a common set of cellular products that are accessible through the circulatory system. This biology allows for the detection of a cellular signature associated with many different types of

cancer. And as such, MCED tests are intended to be used and evaluated as a single integrated test, not as a panel of individual cancer screening tests like we currently have. MCEDs are able to detect the presence of multiple cancer types through the identification of multiple different biomarkers, many of which are cell-free DNA, but there's also protein biomarkers, circulating tumor cells, and other more exotic biomarkers that are being looked at.

As I mentioned, MCED tests are designed to detect multiple types of cancer all at the same time with a single blood test. And this is including cancers that currently have no recommended screening modalities. This is really important because today, only a handful of cancers have recommended screening methodologies. So MCEDs may certainly help bridge this huge gap. Due to the limited sensitivity of MCED testing, it's really going to be in a scenario where we're using it as a complimentary screening modality in addition to the screen modalities that we know have survival impacts, like mammography and colonoscopy, and this may help potentially expand the range of cancers that can be detected by screening.

One potential risk, however, that may need further consideration is the potential for overdiagnosis with MCED testing. As I mentioned, because MCED tests are designed to detect multiple cancers from a single blood draw, they're often designed to detect biomarkers that are common across multiple cancer types. Those may include very aggressive cancers and some very indolent cancers. And these tests certainly have the potential to detect these indolent cancers where they may not make an impact on a patient's quantity or quality of life.

Dr. McDonough:
With those advantages and drawbacks in mind, Dr. Beer, how can we balance all of that and optimize our approach to using these tests?

Dr. Beer:
Yeah, thank you for that question. I think at this point, it's more about optimizing our approach to designing the test. We'll be thinking about its use further down the line as we gather more data, but I think the most important features that we're thinking about is, first of all, how to balance sensitivity and specificity. So sensitivity is all about detecting cancers and detecting as many cancers as possible. And we, of course, would like that sensitivity to be as high as possible, but at the same time, specificity also needs to be high. That's what limits our false positive results and limits the exposure of patients to unnecessary diagnostic procedures and unnecessary worry and anxiety. So we're working very hard to think that balance through and capture as much sensitivity, especially for the more aggressive cancers and those cancers which we don't currently have any screening tests, while maintaining a high level of specificity and avoiding as many false positives as possible.

Now turning to the issue of overdiagnosis and overtreatment, which we have both recognized as important in screening, there are some reasons to be cautiously optimistic about that challenge, and that's because MCED tests are designed around detecting substances in the bloodstream that are secreted by cancer, often DNA, but sometimes proteins or other biomarkers. These types of biomarkers tend to be secreted in higher concentrations as cancers get more aggressive and more advanced. And so what we're seeing right now is that sensitivity of these tests for earlier-stage cancers is relatively lower than for more advanced versions of these cancers. And that leads us to think that it is less likely that we would be picking up a lot of very small and very indolent cancers.

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. Nima Nabavizadeh and Tom Beer about how we can navigate the potential for overdiagnosis with multi-cancer early detection testing.

Coming back to you Dr. Nabavizadeh, let's switch gears a bit and take a look at some of the clinical data on MCED tests from prospective trials. Starting with the PATHFINDER study, can you tell us how this was designed and what the key findings were, especially in regard to the topic of potential overdiagnosis?

Dr. Nabavizadeh:
Yeah, happy to speak on the PATHFINDER study. So this was a prospective interventional study. This study was aimed at understanding the clinical experience of MCED testing and enrolled over 6,000 participants aged 50 and older. This was a single blood draw that was a multi-cancer early detection test with results returned to the participant. The follow-up for this study was 12 months. So for all patients, they were assessed at 12 months for any other cancers that may have been diagnosed and potentially were missed through the MCED testing.

What resulted from the PATHFINDER study was out of the nearly 6,000 participants, only 92—that's 1.4 percent—of the total study population received a signal positive result. Out of those 92 participants that had a signal positive, 35 eventually were deemed to have a cancer that was confirmed on further diagnostic workup. In that one-year follow-up, the PATHFINDER study also identified that 29 additional participants were found to have a cancer that was found on standard-of-care screening.

An additional nine on top of that were detected due to non-standard-of-care screening or symptomatic presentation of a cancer. In total, there were multiple organ systems that were identified to have a cancer on the study: 12 different organ systems and four different hematological cancer types were detected. 12 of these cancers were cancers that had no recommended screening methodologies. As far as test performance and the metrics of the test, incredibly high specificity—99 percent specificity—meaning that the true signal negative rate was quite high and really minimized the false positive rates and the unnecessary workup for patients. Overall sensitivity for cancer was 29 percent. Ultimate positive predictive value, or the percentage of patients that were ultimately found to have a cancer who had a signal positive, was 43 percent. So really one out of every two patients with a signal positive was eventually found to have a cancer. And related to the topic of potential for overdiagnosis, of the 35 cancers detected by multi-cancer early detection, 19 were solid tumors, whereas 17 were hematologic malignancies.

Dr. McDonough:
Thanks for your perspective, Dr. Nabavizadeh. And how about the DETECT-A study, Dr. Beer? What were the design and results of this trial, particularly when it came to this topic of overdiagnosis?

Dr. Beer:
So the DETECT-A study was the first large prospective study of a multi-cancer early detection test in the United States. It recruited just over 10,000 women aged 65 to 75 with no prior history of cancer between 2017 and 2019. And the initial results of the study were published in 2020. In this study, the women underwent a one-time blood draw for a MCED test, and if that test result proved a positive signal, they had an evaluation that was anchored around imaging involving IV contrast CT and PET scan imaging. These participants were at average risk of cancer and continued standard-of-care cancer screening as their primary clinicians recommended. In this study, 50 cancers were diagnosed through screening, of which 26 were diagnosed as a consequence of a MCED test and 24 additional cancers were diagnosed as a consequence of all the standard-of-care screening tests that these women took advantage of. The majority of the cancers were detected in a pre-metastatic stage, and the test sensitivity was estimated at 27 percent at a specificity of 99 percent with a positive predictive value of 19.4 percent.

Related to the topic of overdiagnosis, what we know is that amongst those 26 patients who had a MCED-detected cancer, 24 were solid tumor patients and two had hematologic malignancies. We recently looked at the diagnosis of pre-cancerous conditions in that population and found that only three participants had a pre-cancerous condition identified as a consequence of MCED testing. And in all three cases, those were relatively large pre-cancers that were recommended for surgical therapy. So it's difficult to comment about overdiagnosis, but to date, we're not seeing evidence of that in the DETECT-A study.

Dr. McDonough:
Yeah, you're kind of, Dr. Beer, getting into the next thought I was going to ask you. Based on the findings from both of those studies, I would like to ask each of you for your perspectives on how we can help mitigate the potential risk of overdiagnosis Dr. Beer, let's hear from you first.

Dr. Beer:
The primary strategy here is the design of the test, and that's what drives what kinds of cancers these tests are likely to detect. Right now, based on what we know about shedding of DNA and other biomarkers into the blood, we know that more advanced cancers and more aggressive cancers tend to shed more of these biomarkers that are the anchors of these MCED tests and small and indolent cancers tend to shed relatively little. And so that gives us some hope that overdiagnosis may not be a major feature of MCED tests, but it's going to take proper prospective studies to really examine that problem and understand the true performance of these tests in the intended-use setting.

Dr. McDonough:
And, Dr. Nabavizadeh, I'll give you the final word.

Dr. Nabavizadeh:
I really see MCED testing and the potential workup for a signal positive as a true expansion of the oncology field. We as oncologists are used to working up potential cancer signals, whether that be from an abnormal imaging result, laboratory test, or potentially with a MCED finding. I think by oncologists potentially spearheading and leading this type of workup, we may potentially be in an advantageous point to help reassure patients who may potentially have a diagnosis that is an indolent cancer for us to reassure them on an early basis as compared to somebody having this cancer diagnosis in their primary care clinic and having a lot of anxiety and worry about it to eventually meet an oncologist to identify that this cancer may not need to be treated at that time.

Dr. McDonough:
And with those strategies in mind, I want to thank my guests, Drs. Nima Nabavizadeh and Tom Beer, for joining me in this discussion on

mitigating risks of overdiagnosis in MCED testing. Dr. Nabavizadeh, Dr. Beer, it was great having both of you on the program.

Dr. Nabavizadeh:
Yes, thank you so much. It was great being here.

Dr. Beer:
Pleasure being with you today. Thank you.

Announcer:
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