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

How ctDNA and Liquid Biopsy Are Shaping Early Detection of Breast Cancer Progression

Announcer:
You're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. And now, here's your host, Ashley Baker.

Ashley Baker:
This is *On the Frontlines of Metastatic Breast Cancer* on ReachMD. I'm Ashley Baker, and joining me to discuss the role of liquid biopsy and ctDNA monitoring in early detection of metastatic progression is Dr. Nicholas McAndrew, who is a hematologist-oncologist and breast cancer specialist at UCLA Health. Dr. McAndrew, welcome to the program.

Dr. McAndrew:
Thanks so much for having me. It's a pleasure to be here.

Ashley Baker:
To start us off, Dr. McAndrew, how has the clinical utility of liquid biopsy evolved in recent years, especially for monitoring metastatic progression?

Dr. McAndrew:
I think it's important to remember that when people talk about liquid biopsy, not everyone's always talking about the same thing all the time. So you have different types of things that could be considered liquid biopsy, there are two really common uses of it in the metastatic setting. First is in a similar fashion as we use traditional protein-based tumor markers like CEA or CA15-3 or CA27-29 as a way to gauge response to therapy early on when we're changing therapies in metastatic disease. So for patients who have detectable levels of circulating tumor DNA in the bloodstream, we can detect really quick and precise changes in those levels early in treatment changes. It hasn't really changed the overall way that they're used as compared to traditional protein-based tumor markers, like the CEA or CA15-3, but when they're detected, they can certainly be more sensitive and have provided a different measure of being able to track treatment response.

What I would say has been probably even more important is in the setting of what the actual DNA is showing—a true liquid biopsy from the standpoint of what driving mutations are there in the circulating tumor DNA itself. Can we identify specific mutations that could inform treatment decisions? So these are looking in breast cancer at things like PIK3CA or Akt pathway alterations or ESR1 mutations. And so that has actually really helped us be able to use circulating tumor DNA as a way to select therapies rather than just using how many prior lines of treatment someone's been on to select our therapy or what they had previously been receiving.

Ashley Baker:
And how does ctDNA monitoring compare with traditional imaging or biomarker approaches when it comes to detecting disease progression?

Dr. McAndrew:
I would say one really important way that it has the capacity to be genuinely different is by incorporating new and evolving mutations that could arise in the course of treatment. So, for instance, the SERENA-6 trial was a revolutionary approach to how we even think about treating breast cancer, and it wouldn't have been possible without circulating tumor DNA and liquid biopsy.

So traditionally, we use how a patient's feeling and what the imaging is showing us in order to decide whether or not our treatment's working. In SERENA-6, they took patients who were on first-line aromatase inhibitor-based therapy with a CDK4/6 inhibitor, and these are all patients who did not have a baseline ESR1 mutation, and they serially monitored the blood for development of an ESR1

mutation, which basically confers resistance to aromatase inhibitors. So these are patients who did not progress on aromatase inhibitors, but they developed a mutation in the blood that was new, and that was detected on liquid biopsy.

So the study randomized patients to continue the aromatase inhibitor-based therapy or switch to an oral SERD, which is a selective estrogen receptor degrader. And switching to that oral SERD was associated with benefit across the board. There was better progression-free survival. Patients did better. They felt better. They had better patient-reported outcomes. It's a pretty new study, and we're still tracking the outcomes of it. It has not become wide clinical practice to use that approach, but it really does provide us with a framework of how we can start thinking about using this technology to guide treatment decisions in real time, even in ways that imaging can't help us do.

Ashley Baker:
Now, could you walk us through how ctDNA is currently being used to track tumor changes over time in clinical practice?

Dr. McAndrew:
It currently is being used in conjunction with next-generation sequencing performed on tissue samples from biopsies. So it's still used in conjunction with that because not all tumors release a lot of circulating tumor DNA. So it's something that is very practical. It's easy to do because it just requires a blood draw, but it doesn't always give us the answer.

However, we're constantly reassessing both of those technologies at each step along the way, so when someone does progress, we are trying to use the results of both circulating tumor DNA, but also, when feasible, a biopsy sample as well to see whether or not there are any new treatments that we're able to use.

Ashley Baker:
For those just joining us, this is *On the Frontlines of Metastatic Breast Cancer* on ReachMD. I'm Ashley Baker, and I'm speaking with Dr. McAndrew about how ctDNA and liquid biopsy are shaping early detection of metastatic progression.

So, Dr. McAndrew, how can ctDNA be used to detect minimal residual disease, and what impact could that have on long-term surveillance?

Dr. McAndrew:
I think that this is maybe one of the most exciting uses of circulating tumor DNA—this concept of somebody who has minimal residual disease. So again, this would be somebody who is otherwise considered an early-stage breast cancer patient who has finished their surgery and radiation, maybe finished chemotherapy, is on hormone-blocking therapy in the adjuvant setting, or maybe has even finished hormone-blocking therapy and is just in long-term surveillance. The concept of being able to detect some imaging occult, minimal residual disease using liquid biopsy I would hope is the future of where we're headed, but I don't think that we're there quite yet in order to really use this technology to its full potential.

The ultimate hope of using this technology is if the liquid biopsies become sensitive enough where we can actually detect the circulating tumor DNA a long time before somebody will present with metastatic disease that is detectable on imaging, if you have a long enough window there, then you can hopefully try and intervene with a new medicine that is going to try and kill those active cancer cells and prevent somebody from ever developing metastatic disease in the first place. That, if demonstrated, would completely revolutionize the way we think about treating breast cancer.

It's a perfectly valid concept in leukemia. So, for instance, in chronic myelogenous leukemia, they use the concept of minimal residual disease by detectable Philadelphia chromosome detection in the bloodstream. Now, those tests are testing a very specific gene mutation. They're highly sensitive, and so that has been a huge success story.

The challenge that we're trying to overcome right now in breast cancer is that the current tests are not quite as sensitive. Where I think the whole field is moving is trying to get more and more sensitive tests to make it so that we can have that lead time to actually intervene on that new group of cells that have presented themselves before they turn into metastatic disease. But right now, where we're at is there's very short time window between when the liquid biopsy becomes positive, when the MRD is diagnosed, and when it's not just MRD, but it's now recurrent disease.

Right now, that's on the order of a few months, and it's very challenging to even demonstrate through a clinical trial that that's now feasible. Step one is identifying it. Step two is doing something about it. And so by not having that much time in between when it presents as someone who is minimal residual disease-positive and when they have now developed imaging-based or imaging-provable metastatic disease, you just don't have that much time to really intervene in a trial.

So, currently, it's being used as a way to detect patients who potentially have metastasized earlier, and then once you've identified those patients, you would begin treatment for metastatic disease. However, in the absence of some kind of scan demonstrating that

they've developed metastatic disease, it's not recommended to act upon that information at this point because it's never been demonstrated that that's really a viable treatment approach.

Ashley Baker:
And what are some of the key limitations or considerations that clinicians should keep in mind when interpreting ctDNA results?

Dr. McAndrew:
So going back to the metastatic setting and when it's used as disease monitoring, we don't really have much evidence that in the absence of a change in the burden of disease on imaging, acting alone on ctDNA changes is better.

So, for instance, one of the most challenging scenarios is in lobular breast cancer. We have a lot of challenges quantifying the amount of disease in lobular breast cancer because it's very difficult to assess on CT scans. It spreads as sort of a web rather than as a ball, and so it's just harder to see the burden of disease in a patient with metastatic lobular disease on any kind of scan, no matter how good it is.

And so I would just caution oncologists against really burning through different treatment regimens when we're only seeing changes in the circulating tumor DNA that's not backed up by either changes in patient symptomatology or changes in what the scan is doing. I still use it as a tiebreaker, and I use as an early sense as to whether or not something is working, but I would hate to burn through lines of therapies based on just pure increases in ctDNA alone.

Ashley Baker:
Looking ahead, Dr. McAndrew, where do you see ctDNA and liquid biopsy making the biggest impact in oncology over the next few years?

Dr. McAndrew:
I think the biggest impact is helping guide our decisions in the early breast cancer setting. So if these tests get more sensitive, we can use them to really be nimble in a variety of different settings. So, for instance, in the early stage, in the neoadjuvant setting, potentially, we could use different changes in a drop in circulating tumor DNA to help us get a sense of "Hey, how much chemotherapy is really enough in the neoadjuvant setting? Do we really need to give six cycles of TCHP for someone with HER2-positive breast cancer, or if their circulating tumor DNA has dropped enough that it predicts pathologic complete response really well, can we get away with two or three?" I think that that would be a really interesting approach that would help reduce the toxicity in that setting and just improve our ability to personalize treatment decisions for patients.

And then, of course, for the majority of patients who have estrogen-positive, HER2-negative breast cancer, using circulating tumor DNA in this MRD way by saying, "Okay, somebody has minimal residual disease. We've detected that now. We have data to show us that if we act on this, it will lower their chances of ultimately developing metastatic disease," to me, that's the pot of gold at the end of the rainbow. That's really where we're going to find the best use of this technology.

Ashley Baker:
With those insights in mind, I want to thank my guest, Dr. Nicholas McAndrew, for joining me to discuss how liquid biopsy and ctDNA monitoring are helping us detect metastatic progression in breast cancer earlier. Dr. McAndrew, it was great having you on the program.

Dr. McAndrew:
Thanks for having me.

Announcer:
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