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Tracking Tumor Resistance in Metastatic Breast Cancer Care

Announcer:
You're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. Here's your host, Ryan Quigley.

Ryan Quigley:
This is *On the Frontlines of Metastatic Breast Cancer* on ReachMD. I'm Ryan Quigley, and joining me to discuss strategies for tracking tumor evolution and treatment resistance in patients with breast cancer is Dr. Megan Kruse. She's an Associate Staff Member of the Department of Hematology and Medical Oncology at the Cleveland Clinic in Ohio. Dr. Kruse, welcome to the program. Thank you for doing this.

Dr. Kruse:
Thank you for having me.

Ryan Quigley:
Absolutely. So let's jump right in Dr. Kruse. First question I have for you is, how do breast tumors typically evolve under treatment pressure? And what are the most common resistance mechanisms you encounter in your practice?

Dr. Kruse:
I think when you think about tumor evolution and resistance, the key thing to remember is these cancer cells are trying to survive like anything else in life. And when they are faced with a pressure from treatment, they will try to find a way to live that is no longer requiring that specific either pathway or protein within the cancer cell itself.

So whatever part of their function we are trying to shut down, the cancer cells will try to do without. We know that some of these cancer cells can figure it out and they can go on to survive and become resistant. And some of the cancer cells are actually so sensitive to our methods of treatment that they die off entirely and we don't have to worry about them anymore. I think about this as an actively evolving process over time because we know that we are putting out the fires of only some of the cancer cells with any of our given treatments.

We talk about breast cancer as though it's one uniform diagnosis all the time with the same sensitivity to treatment. But in reality, these cancer cells are heterogeneous. They may all look a little bit different. They may all grow a little bit differently, and we have to keep that in mind, that when we're effective with one treatment, it won't last forever, and we may be inducing new survival mechanisms in the cancer cells while using effective and active treatment.

Ryan Quigley:
And now, just to build off that, why is it so important to monitor a tumor's evolution on an ongoing basis rather than waiting for clinical progression?

Dr. Kruse:
Yeah, this is an interesting question because the dogma in breast cancer management for decades has been that unless there are signs of true progression clinically, meaning a patient has symptoms and you know that there's cancer growing in a site that would cause those symptoms, or if there are spots that the cancer is growing on a scan where you can visualize that, that those are the signs that the cancer is becoming more active and that we should step in and do something different about our management. It's hard to know if intervening when you're seeing signs of resistance as early as possible with some of our newer technologies actually makes a difference in terms of long-term management for patients.

Do they actually live longer? Do they live better? Because we're trying to detect these resistance mechanisms early. I think all of our gut impressions as oncologists is that that should be true if we jump in and we put out those resistance mechanisms early, before we are faced with a larger number of cancer cells that are harder to kill. That should lead to better quality of life, less complications, and better survival for our patients. But the challenge comes when we've looked at these strategies before with potentially less sensitive technology—things like protein tumor markers in the blood or circulating tumor cells—and that intervening early just based on those markers in the absence of clinical symptoms and in the absence of radiographic changes hasn't really improved overall patient outcomes.

So I think this is a point of contention and actually a little bit of uncertainty in our world, that we hope that detecting resistance early is actually gonna lead to better outcomes, but we're actively studying that.

Ryan Quigley:
Thank you very much for that detailed breakdown, and for those just tuning in, you're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD. I'm Ryan Quigley, and I'm speaking with Dr. Megan Kruse about the importance of tracking tumor evolution in breast cancer patients.

So, Dr. Kruse, let's quickly shift gears and talk a little bit about the ways we can detect resistance. How have liquid biopsies changed the way we identify resistance earlier, and how are you using them in your own practice?

Dr. Kruse:
Liquid biopsies have been great, I think, for us as clinicians and for our patients, because it makes getting into assessment of tumor evolution and changes in tumor behavior a little bit more accessible on an everyday basis. Before we had liquid biopsies, if we wanted to try to get a sense of why a cancer was becoming resistant, we really only were able to do that by getting a tissue biopsy. If you think about why tissue biopsy would be hard for our patients, there's the inherent pain and discomfort that comes from putting a needle into a tumor site. For some of our patients, getting a tissue biopsy may not even be feasible. They may have growing tumors that are located in places of the body that are hard to get at.

And then the type of evaluation that we could do off of that sample was relatively limited. We could look for estrogen receptor, progesterone receptor, and HER2 protein, and we could do some early genomics-type assessment. But there's an inherent problem when you're only going after one site of tumor. Aside from all the normal logistic factors of it being difficult, hard on our patients, potentially hard to schedule, and the time that it takes to get results back, but you're also only biopsying one area, which may be okay if there's only one area of progression that you're seeing on your scans or that you're worried about, but when you are able to get a liquid biopsy, that, in my mind, captures more of the overall information of what's happening with all the different tumor sites in the body, because all the different metastatic sites should be shedding cancer DNA into the blood, and we're picking that up and getting that overall assessment of all the different sites putting out their unique makeup. And that's probably not as simple as I just made it sound. There are definitely areas of metastatic involvement that may or may not shed more DNA into the blood, but it certainly gets us a little bit closer to an understanding of the heterogeneity that's going on in metastatic breast cancer, and it's definitely a lot easier on our patients.

Ryan Quigley:
Dr. Kruse, you just mentioned how a tissue biopsy may not be the optimal approach for many patients, but on the flip side there, when is a tissue biopsy still the preferred option? And what added information does it give you?

Dr. Kruse:
Yeah, I think that's a great point, that it's not gonna be a one-size-fits-all approach when you're doing this assessment for resistance. We still need to rely on clinical factors, taking into account what treatment a patient has had before, how long they've been on their current treatment, and also where the progression is happening. And so when I think about all of those things, and I think about where tissue biopsies can still be really influential in our management, the most common situation for that right now is when we're needing to look at protein expression. And with the advent of HER2-targeting antibody drug conjugates, and especially this new state in metastatic breast cancer that we've had for a couple of years called HER2-low, or patients being defined as HER2 ultra-low, that's really information that we need to do with tissue-based assessment of a tumor and running immunohistochemistry on that tissue sample.

And then the other situation in which I really think about doing a tissue biopsy that I briefly mentioned before is if you have disease that's pretty much controlled throughout the body except for one site, because if only one site is growing, it's possible that the specific signals of resistance or biologic behavior that you have in that site may get diluted out. If you're looking at a blood-based biopsy, you don't know how well that one site of metastasis is being reflected. And so if I'm really worried that the site progression isn't making sense and I wanna go back and look at why this particular area is a problem, I might want to get tissue from that site. So I feel like I have better

assessment of what could be our most resistant or most problematic area of concern.

Ryan Quigley:
Thank you for that. And oncologists have a lot of different tools at their disposal, lots of options to consider. How do you balance the practicality and cost of serial testing with the benefits of staying ahead of resistance?

Dr. Kruse:
Yeah, this is a really great question, because just because we have all these tools that we can access doesn't mean we should be using them. We have to think about what the impact on our patients and our practices will be. This is where the routine use of liquid biopsy testing can be daunting when you think about applying this type of technology to routine assessment of patient disease response and influencing care. I think it goes back to the idea that if we're going to go down this road and use this approach, we really have to be convinced that we're improving patient outcomes. And, in my mind, what's so interesting about the data that we have out right now, particularly looking at a resistance mechanisms like ESR1 mutations that may indicate resistance to aromatase inhibitor therapy, is that we now have multiple different oral estrogen receptor targeting medications to use if we find these ESR1 mutations. The data that we have about that approach really suggests that patient quality of life—or at least decrease in the deterioration of quality of life—is better when you do this proactive monitoring approach rather than just waiting for radiographic progression.

We think about that piece of data from a variety of different angles, right? Is that because patients feel like we're watching more closely, or because they feel more empowered? Is it because we're really stepping in and preventing those very, very symptomatic type of disease progression events? And I don't think we entirely know that answer right now, but it's intriguing to think about how this type of testing can actually be informative and empowering, knowing that the flip side is that patients may actually be really stressed out by knowing that they have testing that is pending pretty frequently. If you spend time in the clinic with patients, you'll know that the phenomenon of scanxiety really is real. The patients will have very, very heightened anxiety around their scans and disease assessments. And the last thing we want to do is make that worse by doing additional testing if it's not improving quality of life or cancer control.

So it's a very nuanced discussion and decision, and I honestly approach this with all of my patients a little bit differently. I don't necessarily believe that the quality of data we have right now for proactive monitoring for these resistance mechanisms is worth it such that we should be applying this approach to everyone. And maybe future data releases will prove that to not be the case, and it will be worth it to be looking at everyone. But for now, I think it's very much an individualized discussion.

Ryan Quigley:
Before we wrap up, Dr. Kruse, do you have any final thoughts that you would like to share with our audience?

Dr. Kruse:
Sure. Thank you for giving the opportunity to discuss this. I often wonder myself, if I had this testing at my disposal for a breast cancer diagnosis, would I want it? And that's really the lens through which I talk to patients about it, because I don't think there's a correct right or wrong here. And we all have to be aware of our limitations in this space for now and keep an eye out for new data, which is why programs like this are so important.

I would also encourage my peers to think about resistance mechanisms that may be inherent in tumors and those that will evolve with the pressure of treatment like we've been talking about. You know, I focused a lot on those resistance mechanisms that come about because of treatment selection pressure, like ESR1. But there are also those mechanisms that we think about that can be in tumors from the very beginning and there, I think about something like *PIK3CA* or mutations in the PI3 kinase. And that's really influential, because we know that those types of mutations happen early on in tumor development, and so if you test early, you might find that. And now we know that for certain very aggressive types of breast cancer recurrences, targeting that particular mechanism of resistance, the *PIK3CA* mutations early on with a drug like inavolisib can be very, very helpful improving patient cancer control and also overall survival. And so I think we also have to be aware that testing once may not be enough, even though testing really, really frequently may be too much. You have to keep a pulse on what the cadence of these resistance mechanisms are and how frequently they may happen, so you can share with patients realistic expectations of what we might be hoping to find.

Ryan Quigley:
And with those key takeaways in mind, I want to thank my guest, Dr. Megan Kruse, for joining me to discuss how we can identify and address therapeutic resistance in patients with breast cancer. Dr. Kruse, it was great having you on the program. Thank you so much for this.

Dr. Kruse:
Thank you so much for having me.

Announcer:
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