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Advancing Relapse Prediction in Pediatric AML Through Genomic MRD

Announcer:
You're listening to *On the Frontlines of AML and ALL* on ReachMD. And now, here's your host, Ryan Quigley.

Ryan Quigley:
This is *On the Frontlines of AML and ALL* on ReachMD. I'm Ryan Quigley, and today, I'm joined by Dr. Amanda Winters to discuss a potential avenue for improving relapse prediction in pediatric acute myeloid leukemia, or AML. Dr. Winters is an Associate Professor of Pediatric Oncology and Bone Marrow Transplantation at the University of Colorado Anschutz School of Medicine.

Dr. Winters, thank you so much for being here today.

Dr. Winters:
My pleasure. Thanks for the invitation.

Ryan Quigley:
To start us off here, I want to start with some background, Dr. Winters. Why is predicting relapse in pediatric AML still so difficult, even with all these advancements in treatment that we've been seeing?

Dr. Winters:
I think we have made a lot of improvements in risk stratification, both with better understanding the genetic causes of AML and how that impacts therapy response. And we do have some sensitive tests for leftover leukemia cells that persist after chemotherapy. But even with these tools, there's still about 30 percent of patients who relapse without any prior warning that clinicians can have. Those tests are based on changes in protein expression, and those proteins may change over the course of therapy. That's one problem that we see sometimes with those tests. There's also limits to the sensitivity of those tests and a lot of the biology of leukemia that we're still in the process of understanding. So I think those are the current limitations.

Ryan Quigley:
Thank you for that. Now, I know that your team has been exploring a new way to predict relapse. Can you walk us through the core idea behind this research and what makes it different from traditional approaches?

Dr. Winters:
The basic premise is that while protein expression is a byproduct of the leukemia process, the genetic mutations are what actually caused the leukemia to happen in the first place. And therefore, in many cases, these are more stable than the protein expression over time, particularly in the pediatric and adolescent population. So, we think being able to measure these AML mutations on an ultra-sensitive level will be better than the protein-based methods to detect residual disease. And the genomics technologies are advancing every day, so we hope that this will enable us to improve the sensitivity.

Ryan Quigley:
Now, let's talk about the observational study that you'll be overseeing, which, as I understand it, will be testing pediatric AML samples using both the genetic method and the protein-based method to see which is more accurate. Can you explain how the study's designed and what you're hoping to learn by comparing these approaches?

Dr. Winters:
So, the study, right now, is meant to be observational only. The whole point is to test whether the genetic method is better, and that question hasn't been fully answered yet in pediatric AML, so it wouldn't be fair to change people's therapy based on our results until we

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know for sure that it's better or not. But basically, patients and parents would consent to allow us to bank extra bone marrow and blood samples both before and after that individual patient goes through bone marrow transplant. And these are at times when the samples would be collected anyway for clinical testing, so there wouldn't be any extra procedures or pain or risk incurred in participating in the study.

The protein-based MRD we do as part of the standard clinical practice. And for the study, we would record those results, but then, those extra samples that we bank, we would use to measure the genetic MRD and compare the two for sensitivity. We'll be using the clinical standard, but then using our experimental therapy at the same time, and then following those patients for outcomes like whether they relapse after transplant and see which is more predictive.

Ryan Quigley:
For those just joining us, this is *On the Frontlines of AML and ALL* on ReachMD. I'm Ryan Quigley, and I'm speaking with Dr. Amanda Winters about her research on relapse prediction in pediatric AML.

So, Dr. Winters, let's say that the genetic test proves to be better or at least equal to the protein-based test. How could that change the way we think about remission and risk in pediatric AML?

Dr. Winters:
If we see what we expect to see, which is that the genetic tests would be better, then hopefully that lowers the proportion of patients with AML where we're surprised as clinicians by relapse happening. Ideally, if we can see low levels of leukemia with more accuracy, then there are preemptive interventions that we can take in a lot of cases to try to prevent relapse from happening at all, and those include giving boosts of immune cells from the transplant donor. There are some targeted therapies that are available and maintenance chemo, and that would be something that we could use if we can better predict relapse with these new tests.

But even if the genetic test is just equal to the protein test, I think there are some advantages to genetic MRD that the protein-based test doesn't have. Most targeted therapies for AML currently are actually based on the genetics of the leukemia, so confirming those, either the same genetics or finding new mutations, could help us inform what the best options are for those patients. Also, the genetic MRD test allows potential use of less invasive monitoring, like cell-free DNA, so there might come a point at which we wouldn't even need to do bone marrows at all to follow these patients.

If we can better predict relapse with the genetic MRD, there's a possibility that we can even select patients with no detectable disease for less therapy or omit some of the toxic components of therapy. Deescalation of therapy has been a big movement in ALL, but really hasn't been something that we have had as an option in AML in the past, at least not in the vast majority of kids. If anything, we're taking more and more of them to transplant earlier. And transplant is one of the most toxic components of therapy for these kids. So, it would be great if we would be able to find the right group of patients for whom we can actually avoid transplant with all those side effects.

Ryan Quigley:
And finally, Dr. Winters, what are the biggest barriers to something like this becoming a part of routine pediatric AML care, and how do you see us getting past those challenges?

Dr. Winters:
One is that AML is such a rare disease in the pediatric and adolescent population. It really does take consortia like the Children's Oncology Group or equivalent groups around the world to get the statistical power to prove something is better. We are lucky that this study's being supported infrastructure-wise through the Cellular Therapy for AML Task Force, which is a subgroup of the Children's Oncology Group. So, we have eight large centers around the US and Canada that will enroll patients and ship their samples to Colorado for the genetic MRD testing.

But once we complete the study, I think in moving genetic MRD forward into clinical use, there would be regulatory considerations, validation, bioinformatics, and pipelines that would have to be built from the ground up, basically on a larger scale. And we'd have to decide whether we would end up as a reference lab of sorts for multiple centers, or whether we would want to give people blueprints to recreate the workflow that we have at multiple sites, which would be a good problem for us to have if we have the clinical motivation to do it. But I think there are a bunch of steps ahead of us in changing the paradigm.

Ryan Quigley:
And that's a great comment for us to think about as we come to the end of today's program. I want to thank my guest, Dr. Amanda Winters, for joining me to discuss how we can better predict relapse in pediatric acute myeloid leukemia, or AML.

Dr. Winters, thank you so much for doing this. I really appreciate you coming on the program.

Dr. Winters:

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Thank you for having me.

Announcer:
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