LEUKEMIA & LYMPHOMA SOCIETY®

# THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

***Episode: 'Mission To Complete Remission: Utilizing MRD Testing In Blood Cancer'***

## Description:

Testing for minimal or measurable residual disease (MRD) in blood cancer has transformed the way we look at remission and treatment planning.

In this episode, we speak to Dr. Adriana Rossi of Mt. Sinai Hospital in New York about how MRD testing is being utilized for blood cancer patients. Join us as we explore minimal/measurable residual disease (MRD) testing for blood cancer and its role in guiding treatment decisions and predicting relapse and prognosis.

## Transcript:

**Elissa:** Welcome to *The Bloodline with LLS*. I'm Elissa.

**Lizette:** And I'm Lizette. Thank you so much for joining us on this episode.

**Elissa:** Today, we will be speaking to Dr. Adriana Rossi, an Assistant Professor of Medicine in Hematology and Oncology and Co-Director of CAR T and Stem Cell Transplant at the Center of Excellence for Multiple Myeloma at Mt. Sinai Hospital in New York.

Dr. Rossi has extensive experience treating patients with myeloma and related diseases and has special expertise in cellular therapy.

Welcome, Dr. Rossi.

**Adriana Rossi, MD:** Thank you so much. I'm so happy to be here.

**Elissa:** So, our podcast today is on Minimal or Measurable Residual Disease (MRD). Could you share with our listeners what that is?

**Dr. Rossi:** Absolutely, and I'm glad you've already opened the definition because it is such a common point of confusion. Historically, it was known as minimal residual disease because it was used in (acute lymphoblastic) leukemia, which is considered a curable illness. And so, if you could detect any cells left, that was residual disease. If you could not, then we would label it as a cure.

In myeloma we've taken a similar test and, again, this is fairly recent in the field because until not so long ago we couldn't even get remissions let alone complete remissions. Over the last few years, the definition of what a complete remission is paired by our technology and ability to detect those cells. So, in myeloma the more correct term would be measurable residual disease because it's limited by our ability to detect.

So, when we started doing MRD testing in myeloma, we could detect down to a level of $10^{th}$ to the -3. ($10^{-3}$) meaning one in a thousand cells.

As our technology has evolved and our therapies have gotten better, where our remissions are deeper and deeper, the level and the definition of MRD negativity is linked to the test that we're using, and to that depth that we're searching for.

**Elissa:** So, you just kind of described what we're looking at for measurable. What is minimal?

**Dr. Rossi:** So it's the same test, it's just called an MRD test, and there are different technologies. We started with what are called PCR (polymerase chain reaction) tests. Those aren't really used, so I think it's okay to not give them too much attention. Just know the history has evolved.

The two main methods that we use are flow cytometry, which is a way of looking at markers on the outside of the cell, and that's a very generalizable test because every

pathology department has the machine, it's part of how we analyze every biopsy, and it allows us to look for any cells that can be labeled as myeloma.

So, we look at different markers on the surface of the cell and say, "Yes, there is myeloma in the million cells," because now we've moved from a thousand down to about one in a million. And say we can still detect a cell. So measurable or detectable would be the same thing, meaning the tests that we're using is able to identify a cell.

The other test that we use that's really coming into being the preferred test is NGS, which is next generation sequencing. Sequencing tests really look at the DNA of cells, and each cell has a very specific identifier, especially myeloma cells. They make a very specific antibody, so we can use the sequence of that identifier to look for the cells.

So, the two methods have different pluses and minuses but, in general, either method that we use, if I look at a million cells, can I find any detectable cancer cells?

**Lizette:** And why is it beneficial to know if a patient is MRD negative or positive?

**Dr. Rossi:** So, in myeloma specifically, whenever we have a effective therapy, you're then in remission. And the way we monitor response or remission is by the decrease in an M spike in a blood test. Once that M spike is completely gone, you can't detect it in the blood, and you really need a bone marrow biopsy.

So, we often teach using the image of an iceberg, the visible part is just the blood test. Once that's melted away, there's still a lot that could be going on under the visible level, but we need a biopsy for that.

And sometimes you actually will have myeloma that is taking up a lot of the marrow and not taking the time to make a protein to find in the blood. Other times you can't find any cells, but when you submit that special test, you're still MRD positive or negative.

And so, these are just different depths of response, and we aim to have the deepest response possible because that tends to translate into the longest remission possible. And so, trying to get to an MRD negative state is your best response, which should translate to a longer response. And that's seen in a lot of our studies. Whenever we use MRD testing in clinical trials, and you can separate out the population of patients who are able to reach MRD negative and those who are not, the ones who are still MRD positive, or have detectable disease, tend to relapse sooner and need another line of treatment sooner.

**Elissa:** That's really interesting. So, I was diagnosed with AML back in 2016, and I know things have changed a lot. And back then, I don't think MRD was used at all or as much for AML. And so, my doctor had explained to me that, yes, you're in complete remission, but there might be cells under the detectable levels. So, is that really what we're getting at with the MRD testing, is we're looking for under what biopsy would be able to catch?

**Dr. Rossi:** Yep. And, again, the technologies have changed a lot. I think the very first publication with MRD was at the turn of the century, but this was just a research tool, a lab tool. It wasn't until 2013 that I think it was first tried in a clinical setting and, again, is like five different times it was used. Now we're up in the thousands of papers published every year. And that ramp up in just that 10-year span from it doesn't exist to it's our gold standard and it's what we aim for, highlights how the field is changing so quickly. We're able to get the deeper remissions and we have the technology to then go after and detect that depth of remission.

**Lizette:** Yeah, so with the advancements, I know that MRD used to be considered an endpoint in trials or we didn't know if it was an endpoint in trials. It's used in more than clinical trials at this point, correct?

**Dr. Rossi:** Right. So that's, again, highlights the match of science and art that go into medicine. So, we've been in debates with Federal agencies for years in trying to

establish endpoints because, again, not that long ago, at the turn of the century, we pretty much would quote patients could probably expect to live with myeloma for about three years. So, we actually used overall survival as our gold standard for clinical trials because, unfortunately, in just a couple years we would lose a lot of our patients.

That has completely changed time and time again, where overall survival is reaching 10-20 years. And so, we started using what we call PFS (progression-free survival), time to progression, and then that would take a year or two. But now people are staying in remission for 5 to 7 to 10 years, so PFS is no longer a good gold point. So, we were trying to use response. Is overall response enough? Well, MRD is so much better.

And so absolutely, it is not the primary endpoint of clinical trials, but it is a secondary or exploratory endpoint in many, many studies that we have. And as physician scientists, those of us who participate in a lot of studies and have seen, the fruits of our labor, and have the practice of evaluating for MRD with every response, I think we've definitely taken that into practice.

It is not really ready for prime time to say everybody must do it because we do realize, there is effort and cost, and it is not a test that everyone has easily available.

**Elissa:** Now let's discuss the actual testing. At what point of the treatment is the testing done?

**Dr. Rossi:** Depends on how you intend to use it. We had talked earlier about the differences in the two methodologies. So, for flow cytometry, you can use it on any sample at any time. It's one of the pros on that methodology compared to sequencing where you need to have the original sequence to compare it to.

So, if you are going to pursue an NGS, a sequencing test for MRD, the MRD sequencing has to happen on the diagnostic marrow, so the first bone marrow biopsy

where we characterize the tumor, we characterize the sequences so that we can follow them later on.

The testing itself of looking for the presence of residual disease happens when the blood tests have normalized. So, once you can't detect it in the blood anymore, we do the bone marrow to see how detectable it still is in the marrow. So, it's a confirmatory test for a complete response.

**Elissa:** Okay. Now, does the patient know that they're getting this MRD testing?

**Dr. Rossi:** Our patients definitely do. Some of them actually bring it up before we have a chance. But physicians should always, when we do a test, like if we're going to do a bone marrow biopsy, it's certainly my practice to explain what we are going to look (for). So, I am going to look for the pathology for cytogenetics, for MRD testing. What samples are we sending, why are we sending them, and what information do we expect to get back?

**Elissa:** Okay. Now you mentioned the samples. Are you getting that only from a bone marrow biopsy, or are you also getting that from just a simple blood test?

**Dr. Rossi:** So, unfortunately, for myeloma, it always is on a bone marrow. We do have investigations ongoing, but the blood tests for myeloma require about 100 times the volume, and so we can't really be taking those kinds of samples just for testing.

**Elissa:** Right.

**Dr. Rossi:** As you are, unfortunately, an expert at, leukemia cells are actually in the blood, and so MRD testing for leukemia can be done on a blood sample, which is where, again, the universality and specific differences for different disease states comes in.

**Elissa:** Okay. One thing I'm sure patients listening would like to know is if this testing is covered by insurance.

**Dr. Rossi:** It is.

**Elissa:** Good. We like to hear that.

**Dr. Rossi:** So the flow cytometry, most labs have available. The sequencing is a send out test, and that's either covered by insurance or the company will cover the difference for any patient who has a copay or anything that is difficult. I think the whole community is really vested in getting that information for every patient.

**Elissa:** Okay. And so, any diagnosis where MRD would be useful, that would be something that would be covered by insurance, including, myeloma.

**Dr. Rossi:** Right. So, myeloma and leukemia are the two biggest spaces where that's used.

**Lizette:** So, what happens when you get the results back? I know that the results mean different things in different types of blood cancers like we've mentioned.

**Dr. Rossi:** Yes. In multiple myeloma, again, so far it is still early days, and so we currently have a number of clinical trials that are working to get us the data and the evidence to direct our practice to say we can use an MRD status to either increase and intensify therapy or deescalate, so take someone off therapy. That data is not available yet, and so for now, I think it just opens the room for discussion between the physician and the patient to say you have achieved the deepest possible remission that we can, but myeloma is still considered incurable, and so there is a risk of it returning.

Should we stay the course and do continuous therapy, which is the current teaching in myeloma? The way we prolong survival and remission is by continuous therapy. Or would you like to try not being on therapy and see how long we do?

What allows that to be possible is really the fact that we now have so many great therapies for myeloma. Only five years ago, we as physicians were very nervous to

ever let myeloma come back because we had very limited tools to try to get that next remission.

Now that we have so many efficacious tools that we can use even in the relapse setting, with the immunotherapies, either CAR T or bispecific T-cell engagers. We have a lot of data in patients who've had five or more relapses that are still getting this MRD negative remission. And so, the field is changing very palpably, and if we were to have this conversation in another two years, I think we'd again have evidence to back a very different practice.

**Lizette:** Sure. I mean I've seen the advancements from the past 10-15 years in myeloma and it's been incredible with all of the new therapies as well as these new tools to help people know how their body is reacting. And I guess it does lend itself to be more of a shared decision-making model, right? So, you're having a conversation with your patients and telling them about how this test is telling them something about how treatment is going for them.

**Dr. Rossi:** So, I generally refer to an MRD negative remission as like the luxury model. Whenever I start therapy, my goal is to get to an MRD negative remission. We first get into the complete remission where the blood tests are completely normal. Then we have a biopsy, and we have the discussion like, yep, we've reached it, we're as deep as we know how to go. Or we're not quite there yet.

And at that point, I think most of us in academia weigh the presence of MRD or not with cytogenetics and other factors that we know go into risk stratification. So, someone who is at a very high risk of relapse may be seen differently. Even if you're able to achieve that MRD negative remission, you're not expected to stay there very long. The conversation would probably lean towards, let's continue pressure to maintain the remission, whereas someone who has no risk factors and is able to achieve that depth of remission, will likely stay in remission for a longer period of time before needing any further therapy.

**Lizette:** So, it really does help in deciding maybe what the next steps are with treatment for the person.

**Dr. Rossi:** Right. So, I mentioned there are a few clinical trials underway, and these are trials mostly in the newly diagnosed space, but there are also studies in the relapse setting where the clinical trial is designed to have a fixed duration of therapy and then evaluation of response. And depending on whether you are MRD positive or negative, you would then go to a second phase of the study. And again, some studies are designed, if you're MRD negative, you continue, and if you're MRD positive, you increase treatment. Others are designed where if you're MRD positive, you continue treatment, and if you're MRD negative, you can deescalate treatment, so decrease or stop, for example, a maintenance.

So, one example would be you have your induction, your transplant. If after transplant, you are MRD negative, you don't need maintenance, you can go to observation. If you're MRD positive, you go to maintenance. On another, it may be maintenance with one drug for MRD negative, or a combination for MRD positive. And after another specified time point, we check again, and can use that dataset to pick them apart.

Other studies are designed to measure that MRD status and then continue treatment, and whenever the data is mature, we'll be able to look back and say this is appropriate again to change therapy based on this because of the outcome.

And so, there are at least five studies that I'm aware of at the moment that have these built-in decision points that are based on MRD. And so, once that data reads out, I'll be able to more confidently say yes, we can use that data to make a clinical decision.

Right now, it's not really ready for that, but many of us are tempted because of our experience to date.

**Lizette:** I know that a sense of anxiety may come over patients kind of waiting to see if they're MRD positive or negative. You mentioned that people do know that they are getting tested. How do you discuss for the patient if they are MRD positive?

**Dr. Rossi:** Yeah, I think it's similar to this concept of smoldering myeloma. So the precursor to myeloma is smoldering myeloma, where you have abnormal cells but they're not causing a problem, and so the standard is not to treat. And I think it can cause a lot more anxiety even though, as an oncologist, I would say, "Hey, you don't have cancer, this is great. It's just a risk." It can actually be a lot harder to sit with than to say, "Hey, sorry, you have myeloma but here's the plan and here's the treatment, and I can fix it."

And so, it's a similar space with the MRD positive, saying, "Look, we did pretty well, you're pretty good. You've got a lot less going on than you did before but it's still there."

I certainly have patients who are happy to have me say, "Okay, you're MRD positive, we're now going to do this." And they're very happy with that and it's not bothersome at all. Whereas others, really may feel strongly that they want more therapy to try to get to that negative state. But in my experience that has been incredibly rare.

Most patients just want to understand what does it mean, what are we doing about it? And if it comes back, what will we do about it? And I always start one therapy knowing what my next step would be. And so, as long as that's planned out, I have not found it to be a cause or a source of further anxiety.

**Lizette:** Yeah, I think it's really helpful when patients know that there's always a next step. That you're always thinking ahead, and that there is that plan, than to not know that there is a plan.

**Dr. Rossi:** Absolutely. And, again, to be reminded that an MRD positive complete remission is still pretty good.

**Lizette:** Yes.

**Dr. Rossi:** Just because we found – and many times, and the reports can read for the NGS, seven clones detected in 3,752,000 examined.

**Lizette:** Wow!

**Dr. Rossi:** So, the perspective to really appreciate how far we're looking and how detail oriented it is.

**Elissa:** That's amazing. And we've talked a lot about really how far MRD testing has come in just 10 years. And then you mentioned a couple trials already. But can you tell us a little bit more about the latest developments in MRD testing? And is there anything else on the horizon that you're particularly excited about?

**Dr. Rossi:** So yes and no. It is an evolving field and I have to say, again, when we started using MRD testing, we were very comfortable with this $10^{-4}$, as this amazing thing. So, we started at $10^{-3}$ went to $10^{-4s}$ are now generally mostly using $10^{-5}$, but the technologies are now at $10^{-6}$, and there are clinical trials reporting out to $10^{-7}$.

**Elissa:** Wow!

**Dr. Rossi:** So, it's not that it's a completely new way to do it, but they're getting better and better. It's like a TV that got to be a flat screen, that's now HD, that's now whatever the next state is. So, it is fine tuning and we're able to get down an order of magnitude deeper and deeper each time the technology gets revamped. So, in general, the testing I don't think is going to be very different. Maybe they will.

What would excite me, but we're not there yet, again, in myeloma, is to be able to have a blood test. Having to put patients through bone marrow biopsies is really not our favorite thing. So, once there's a lot of research in that area, being able to have a blood test, I think would be a huge game changer.

And the other is just the ability to actually get these kinds of remissions. I think before the immunotherapies, we really just didn't get one in a million cells gone. Like, we could lower myeloma, but it was still at a level where we couldn't detect.

**Elissa:** Yeah. And those numbers you were talking about earlier, just so patients can really understand without busting out their calculator, so we're talking like one cell or one blast in millions?

**Dr. Rossi:** Yep, exactly,

**Elissa:** That's amazing.

**Dr. Rossi:** So, the norm seems to be to look at somewhere between 3 and 4 million cells and say, "Is there one in a million?"

**Elissa:** Wow! Okay.

**Elissa:** It's really exciting that you can get down so deep and really see. And, of course, like you mentioned that we can actually have those treatments that will get somebody that low.

**Dr. Rossi:** Exactly. And when someone gets a report that says seven in a million, like that is seven tiny little cells lost in this millions of healthy bone marrow. So, it is very important to know that an MRD positive is still very good. MRD positive CR (complete remission) is still a very good remission.

**Elissa:** That's good. Well, our final question today, on our patient podcast homepage we have a quote that says, "After diagnosis comes hope." Based on your experience working with blood cancers, myeloma, and then exciting developments in minimal and measurable residual disease, what would you say to patients and caregivers to give them hope after a diagnosis of blood cancer?

**Dr. Rossi:** In the 15 years that I've been working in the field, I have to say we've been through at least three major revolutions in the field, and each time like, no, no,

no, this is unheard of, this is amazing. And then not three to four years later, we're like, oh, no, no, that's so passé. We have this thing that is a complete revolution.

So not only the progress that we're making but the rate at which we're making it. And the almost immediate translation of the discoveries and research translating into patient outcomes is, I really have no words. It's such a wonderful space to be in and to have seen patients come with us through each of these revolutions. So, I have so many patients who've lived through them and said, "Oh, I guess there's nothing else." Six months later, but there's this one thing. And here we are seven, eight years later, looking for the next thing.

So, just the immense growth in the field fills me with hope every day.

**Elissa:** Yeah, definitely. So, thank you so much, Dr. Rossi for joining us today and telling us all about MRD testing and, really, the huge benefit it is in having for blood cancer patients, and how we can really utilize it to determine the treatment course and determine where we're going. And give them that ease that the treatment is potentially going really well for them.

So, thank you again, so much for joining us today.

**Dr. Rossi:** Absolutely. My pleasure. Thank you.

**Elissa:** And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families.

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In addition to the lounge, we could use your feedback to help us continue to provide the engaging content for all people affected by cancer. We would like to ask you to complete a brief survey that can be found in the show notes or at TheBloodline.org. This is your opportunity to provide feedback and suggested topics that will help so many people.

We would also like to know about you and how we can serve you better. The survey is completely anonymous, and no identifying information will be taken. However, if you would like to contact LLS staff, please email TheBloodline@LLS.org.

We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.

Have you or a loved one been affected by a blood cancer? LLS has many resources available to you – financial support, peer-to-peer connection, nutritional support, and more. We encourage patients and caregivers to contact our Information Specialists at 1-800-955-4572 or go to LLS.org/PatientSupport.

You can find more information on minimal or measurable residual disease in our Fact Sheets at LLS.org/Booklets.

All of these links will be found in the show notes or at TheBloodline.org. Thank you again for listening. Be sure to subscribe to *The Bloodline* so you don't miss an episode. We look forward to having you join us next time.