LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Exploring Minimal/Measurable Residual Disease (MRD)'

Description:

Join us as we speak to Dr. Lori Muffly and Dr. Matthew Frank from Stanford Medicine in Stanford, CA, about the recent advancements in testing for Minimal/Measurable Residual Disease (MRD). In this episode, we delve into what MRD is, which blood cancers the testing is currently used on, and how we can utilize it to more accurately monitor patients and customize treatment. The doctors also share exciting possibilities on how MRD and other testing can benefit patients in the future.

Transcript:

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

Edith: I'm Edith.

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

Elissa: Today we will be speaking to Drs. Lori Muffly and Matthew Frank about the latest developments in the research of minimal or measurable residual disease or MRD and how it is relevant to blood cancer patients.

Dr. Muffly is an Assistant Professor of Medicine at Stanford University. Her clinical practice focuses on hematopoietic cell transplantation and CAR T-cell therapies for patients with acute leukemia. She is a clinical researcher and the principal investigator on several clinical trials and also pursues health outcomes projects related to the treatment patterns and access to care in acute leukemia.

Dr. Matthew Frank is also an Assistant Professor of Medicine in the division of Blood & Marrow Transplantation and Cellular Therapy at Stanford University. He predominantly cares for patients with high-risk lymphoma. Dr. Frank's research is focused on

developing methods to identify patients who are high risk for CAR T therapy failure and to understand why these failures occur.

Elissa: Welcome, Dr. Muffly and Dr Frank!

Dr. Lori Muffly: Thank you, Elissa. Thank you for inviting us to be with you.

Dr. Matthew Frank: It's a real pleasure to join you guys.

Elissa: Okay, so let's get started. So tell us what is MRD, and why is it relevant to blood cancer patients?

Dr. Muffly: I can tell you my perspective on the definition of MRD from a leukemia standpoint. I think the definition translates across blood cancers; but the way that we think about MRD is different in different cancer types.

So essentially in acute leukemia, the traditional measurement of residual disease after therapy, so residual leukemia, is measured by the pathologist looking at slides of the bone marrow under a microscope and counting the number of leukemia cells that they see. And so traditionally under 5% leukemia cells is termed a remission. And what we've learned over the years is that although the pathologist interpretation and the counting of leukemia cells is very, very important, there are more sensitive ways to measure persistent or residual leukemia and more sophisticated technologies that can tell us how deep is the actual remission.

And so really minimal or measurable residual disease in leukemia is essentially defined as any residual leukemia under 5% leukemia cells in the bone marrow. But that is a very wide range from very, very tiny amounts of disease in the 1 in a million range to slightly more disease that's under 5%.

Dr. Frank: The way I often explain it to my patients is that it's a technology to detect low amounts of cancer; and there's different ways of doing that. And there's different parts of the body that we check that in. So, it can be bone marrow in leukemia or in

the blood for both leukemia and lymphoma patients and other types, not acute leukemia but chronic leukemia.

A hundred years ago we detected disease by physical exam. Did you have a lump, a bump, something in there? Did we see, you look pale? Those might be the signs or symptoms of disease. Then we got x-ray technology, and you could see a mass somewhere in the body. And then we got more sophisticated with CT scans or PET scan technology, but even those are only so sensitive.

And so biopsies, patients don't like 'em, but they're important because they detect disease. And so now we've gone to even more sophisticated technologies where we can see very small minute or measurable amounts of disease. And so that really is what minimal residual disease or measurable residual disease is now our latest cutting-edge ability to detect leftover disease, leftover cancer.

Dr. Muffly: Yeah, and this has become increasingly important because I think it's intuitive or common sense that when cancer comes back after treatment, it's telling us that not every single cell was killed off by the therapy. And really what MRD is, it's the ability to see those leftover cells. And it's helping us as clinicians to understand the depth of remission after treatment. And it allows us to introduce new therapies if we think that the response to therapy is not deep enough. It allows us to predict with patients how likely they are to have their cancer grow again. So if we still detect disease on a deep level, even if, let's say, the PET scan is negative, but we still can see that there's leftover lymphoma through more sensitive assays, then we can counsel the patient that this is what we're worried about. This is what we're going to do about it. So, it's really taking blood cancer management to the next level.

Elissa: So, that our listeners can understand. When a patient is told then they're in complete remission, there could be these cancer cells that are under detectable levels.

Dr. Frank: Yeah, the medical jargon often can make it confusing for patients and their families. And I think that doctors are having to use increasingly more sophisticated language to explain what a complete remission means.

A complete remission may be as simple as just is it less than 5% of your bone marrow, as Lori was saying? But now those terms may be misleading for patients. You know, in lymphoma we often say a complete remission is, "I don't see it on a scan." But that may be misleading. It doesn't necessarily mean that they're cured, and we have to be clear about that, and so the question is can we use new technologies like these MRD tests to further refine what a complete remission means?

And so, doctors need to do a better job of communicating what they really mean by complete remission in each type of blood cancer. Is it complete remission or do we still see some cancer there? Making the term "complete remission" kind of misleading.

Dr. Muffly: Yeah, I mean now don't get us wrong. Of course, to tell a patient that they're in a complete remission is great news. And a lot of our scales and our classification systems of response to therapy still do not include MRD.

So, if your doctor says you're in a complete remission, that is cause for celebration. But then a follow-up question, if they have a blood cancer, could be, "Well, what about my MRD? Have you looked for MRD, and is there any evidence of MRD?" And I think that is where we're going as a field. It's complicated, but I don't think either one of us want to take away from a patient who's been told that they're in a complete remission how great that is.

Dr. Frank: That's absolutely right. I couldn't agree more with Lori here. I celebrate complete remissions. That's a great term to hear. Patients and their families should be excited about those terms. And what we're talking about today, a little bit is what we think the future's going to be; and so, we have to be very careful to say what we know and what we don't know regarding, these MRD or minimal residual, measurable

residual disease tests mean. But yeah, I absolutely celebrate complete remissions. Those are fantastic.

Lizette: Great, and I know that you're talking about communication and terminology; and we've all been using minimal residual disease as well as measurable residual disease. Are these terms interchangeable?

Dr. Muffly: Yeah, the thing is that the bar keeps changing for what is minimal. Right? A few years ago, if you could detect one cancer cell in a thousand normal cells in a bone marrow, that was as minimal as we could go.

Now we have assays that can detect one cancer cell in the bone marrow in a million normal cells, and so that's as low as we can go. But in five years, we may be able to do one in a billion. Who knows? We have many, many, many, many cells in our body. And so I think that the term minimal and measurable are interchangeable, but I think there's been a bit of a shift towards measurable, only because we know that even what we think is minimal today may not be minimal tomorrow.

Dr. Frank: Lori's exactly right. I think the word "minimal" can be misleading, and that's why I think the field is moving toward measurable. Minimal implies that there's not much there, but that's not much there based on current technology. We're moving toward bigger and better, and so if we can get to smaller levels to detect, that's going to help all of us.

Lizette: Just because some patients have said to us that their physicians don't test for minimal or measurable residual disease, and we've asked them to go back to their doctor and ask, and their doctors say, "Yes, we have been testing, but we haven't been using those words with you." So, we haven't actually been communicating with you that you are getting tested for MRD. So should patients know these terms so they can ask because a lot of patients are being tested but may not know.

Dr. Frank: I'm always a fan of having clear and open communication with patients and their family members. And there's a lot of different types of cancers, a lot of different types of blood cancers. Some of these tests are appropriate for certain diseases, and some are not yet ready for primetime for other diseases. So there has to be an open dialogue with the care providers and the patients and their families about what testing is going on, is it even appropriate for your disease type? There isn't yet an FDA-approved MRD test for lymphoma. There are tests that we can order and in certain contexts are appropriate and can be done, but it's not yet FDA-approved even though the field is heading that direction.

In different types of lymphoma, for example, if you have a follicular lymphoma, MRD testing can be done but is not particularly helpful. For large cell lymphoma, something like diffuse large B-cell lymphoma, I think MRD testing in certain context is appropriate. Mantle cell lymphoma, a different type of lymphoma, that also, you can order a test and is very useful; and I use that very regularly.

So the disease matters, so it's important to ask your doctor, "Do I even need MRD testing? If I do, what kind of test are you running?" And there's different types of tests, and "How will that help you? How will that help manage me as a patient?"

Elissa: So what are the different types of testing? You both work with different types of blood cancer. So, Dr. Muffly worked with leukemias and Dr. Frank with lymphomas. Could you tell us about the different tests that people are using for MRD?

Dr. Frank: I think there's three major ones; and I can highlight those. Those are cell-free DNA; circulating tumor cells in the blood, and those can be detected by what's called next-generation sequencing. It's a sequencing-based technology. The alternative one is something called flow cytometry. Those are sort of the big three.

Dr. Muffly: I wanted to just comment about the last question first about patients not knowing or not having MRD testing or not knowing if they have MRD testing. And I think Matt was correct that, this is a very sophisticated and complicated area of cancer

medicine right now. And I think patients that are listening to this podcast and others like it are doing the best that they can to arm themselves with the information because things are accelerating in a very positive direction quickly.

The only blood cancer right now where there is an absolute indication for MRD testing is acute lymphoblastic leukemia. Regardless of patient age, regardless of type of acute lymphoblastic leukemia, MRD is part of the treatment paradigm. That's in every guideline that you can read about this disease. So that is a blood cancer that there is no question about it that MRD must be performed.

Once we get into other areas, acute myeloid leukemia, lymphoma, there's still a lot of controversy over the role of MRD; and so, I think patients have to realize that too. I think Matt hit the nail on the head when he said, "We're really talking here about the future." This is present in the clinics, but this really is the future.

And then to answer the question about the modalities of MRD testing, right now I would say pretty much all of the MRD that we do occurs through two different, body fluids or two different ways we do MRD testing. One is through the bone marrow, and the other is through the blood.

And so within the bone marrow and blood, there's different assays that we use; and each assay, each laboratory technique has a different sensitivity of MRD detection. But typically, these tests are done through either the blood or the bone marrow.

Edith: So, since there's different types of testing, is the testing expensive? Does insurance cover it?

Dr. Muffly: Matt, what has been your experience with MRD testing in lymphoma because I can certainly speak to that in leukemia; but I'm curious since we don't actually have anything that's FDA acknowledged in lymphoma currently.

Dr. Frank: Yeah, it's hit or miss. It's been frustrating because you don't know until you've kind of asked the insurance carrier about will they cover it or not.

So, is the test expensive? Yeah. I think everything in healthcare is more expensive than we want it to be. And one of the aspects of this kind of testing is how do we manage costs in these diseases? And so I understand that there's a concern from the insurance carriers to rein in costs to a certain degree. But there are times where we just justify it to the insurance carrier, and that's the job of the doctor to say, "In this setting, this is why I want it." And we've been able to get coverage.

But this is also evolving, and, and by the time folks hear this podcast, this could be different. So, when there's not an FDA-approved indication or guideline that says this is critical for care, like Lori will probably speak about in a moment, it can be hit or miss; and this is why it's a complex conversation that needs to be had in the doctor's office.

Dr. Muffly: Yeah, I mean we have a bit of an easier time in leukemia, although it's still certainly not perfect and we still have to deal with issues of approvals and costs for sure. But because we have several techniques that have been acknowledged by the FDA that are acknowledged by Medicare, both flow cytometry and next-generation sequencing-based MRD, it has become easier and certainly available to providers across, an array of practice settings.

So in leukemia, MRD testing is available. It's commercial. Its various forms are acknowledged by the FDA. So the barriers are lower, but the cost is important. I think that is something that we as physicians, we bear some of that burden in being very thoughtful in what we order and really also in understanding how we're going to use the information that we get.

And with certain diagnoses, and I think acute lymphoblastic leukemia is a very good one because this is not a common leukemia. It's not a common cancer, particularly in adults. We really have to be very thoughtful about treating patients and understanding the disease and understanding the disease evaluation assays.

And so sometimes these are patients that need to be cared for in centers that see a lot of ALL, that really kind of know how to make sense of all of the information.

Elissa: hen is the testing done? Is it done just after induction? Is it done throughout the whole treatment?

Dr. Muffly: In leukemia, typically for centers that use MRD in both ALL and AML, MRD is evaluated after induction. Essentially, MRD is evaluated really with every bone marrow assessment that's performed, depending on, where the patient is in their disease course and what therapy is being given.

There are newer observations and interest in using MRD particularly through the blood to track or surveil for disease once therapy is complete. And I think that is also something that's very interesting and may become a common practice in the future. In lymphoma, Matt can speak to when he uses MRD as opposed to traditional CAT scans, PET scans.

Dr. Frank: Lymphoma's a lot more complicated because there's many different types of lymphoma; and so the term lymphoma really is comprising of dozens of different diseases. So, this is where it depends on what you kind of have.

Dr. Muffly: So how do you Matt, in diffuse large B-cell lymphoma, which is the most common aggressive B-cell lymphoma, would you say that MRD is being incorporated outside of the context of CAR T-cell therapy, for example?

Dr. Frank: So I would actually say that MRD is not a standard approach yet in lymphoma for almost any lymphoma. It's not yet universally adopted by every practitioner. We're all excited about it. It's an area that I actively do research in. There are incredible groups who have shown that even after one cycle of induction initial chemotherapy for large cell lymphoma, we can figure out who's going to go on to have effective or durable remission and who's not. But that's a small number of patients. That has to get validated before it's widely adopted.

And the next question is, well, okay, so you could identify who's not going to do well; but what do you do about it? And that's the next big leap that we don't have the data back on is. So, let's say we could identify who's not going to do well. Well, what do you do about it? Those trials are now being sort of drafted and initiated.

My work in the CAR T-cell space has identified patients that even right after initiating therapy, seven days after we give the CAR therapy, we can figure out with pretty high precision who's going to go on to have a durable response and who's not. And when you combine it with PET scan technology on day 28, patients who have a partial response, there's about 60% who's going to, unfortunately, relapse and about 30 to 40 who are going to have a durable response. We find that adding minimal residual disease assessments helps identify those. The combination works well.

So, in summary what I'm trying to say is that it's an evolving science within the lymphoma sphere. There's no standard of care yet using MRD, but there are specific areas where we think we're going to be using it in the future. So, we kind of have to tell our patients stay tuned.

Lizette: And along the same line, what happens when a patient is positive for MRD?

Dr. Muffly: I'm sorry to keep hogging this about acute lymphoblastic leukemia, but I'm very passionate about that leukemia. And also, I think it's really paved the way for a lot of these discussions. And I have to say that the credit here goes heavily to the kids with leukemia and the pediatric oncologists that take care of them because this concept of MRD is an old concept for pediatric oncologists. They've been tracking MRD and using MRD in therapeutic decision-making in kids with ALL for many years. And so, we're only now catching up on the adult oncologists and the adult leukemia doctors.

But you know, the reason I bring up ALL is because we have a therapeutic that has a specific indication for MRD-positivity, and that is, I believe, the first time that the FDA has approved a drug just for measurable residual disease. And that drug is called

blinatumomab. And so, it's an interesting therapy that uses the body's own immune system to target leukemia cells.

But so, you know, in ALL when patients have residual disease, that is a very, very good option. We also use residual disease in leukemia to try to understand which patients may benefit from treatment intensification such as allogeneic stem cell transplantation. We use minimal residual disease in leukemia patients to understand which patients may benefit from treatment deintensification. So less intensive therapies for patients who achieve early deep MRD-negative responses.

And so, we have the opportunity to introduce new drugs that are targeting MRD now. We have the opportunity to escalate and de-escalate our therapies based on these responses.

Elissa: So, I imagine hearing that you're positive for MRD would be a bit stressful for a patient. What do you do as a physician to calm their anxieties and give them hope for their treatment?

Dr. Frank: So, it's important to put everyone piece of data into the larger context and to have a clear and open communication with our patients and their families. So, for some diseases, I expect patients to be MRD-positive. The goal isn't to cure them. The goal is to keep a disease at bay for many years. So, if you had something like follicular lymphoma, 80% of those patients can enjoy a very high quality of life with minimal therapy; but they still have an incurable disease without very aggressive therapy that they can live many decades with.

So those patients are expected to be MRD-positive. But for a patient with leukemia, Lori can speak to that in a moment, it's different, it means you need treatment.

The context matters, so the level of MRD also can matter. What we've noticed in a disease like mantle cell lymphoma, very low level of MRD, I don't worry a whole lot. It

might prompt an additional imaging scan, but patients can have low level MRD for many years before they have a clinical relapse or need new therapy.

There are clinical trials now incorporating MRD assessments to drive a therapy, but that's not yet standard of care. So, in mantle cell, many patients after their first round of chemotherapy, if they've gone into remission, will go through an auto transplant.

And there was a trial looking at MRD to guide when to use rituximab. It's an interesting trial concept. What we found is that we just kind of give it to everybody, and so we don't use MRD anymore. But it was an interesting trial design.

We actually did a trial at Stanford that used MRD assessment at one year as the primary endpoint of the trial because it's a good surrogate in that disease space. But the next step, which is, "Well what do I do about it?" that's still being debated within the field.

So the long story short is, yes, anytime you hear you have measurable residual cancer, it's understandable to be concerned, to be scared. And that's when we want to empower our patients by having honest and open conversations about what that means in their particular situation.

Dr. Muffly: I completely agree with you, Matt. I think you hit all the high points. I mean, in acute leukemias, we don't like to sit on MRD because these cancers tend to grow. They're called acute for a reason, and if we see that there are cells there, we do worry a lot about them. In more indolent or slow-growing or chronic cancers, it's very normal to sit there with MRD. Multiple myeloma is another one. You can have low level MRD and do very well, so its context is really important.

Elissa: So, what happens if someone is MRD-negative after induction? A lot of patients think their induction, do they really have to go through consolidation afterwards? And so, if they're negative, what happens? Does the treatment change

or, if they were kind of on track for a transplant but then they're MRD-negative, is that still going to happen?

Dr. Muffly: So that's a great question, Elissa. And it's a natural question, and as someone who takes patients through bone marrow transplant, that's one that I get all the time. I think the issue here is our ability to measure the cells that give rise to leukemia at the very core, and so increasingly we believe that leukemias likely arise from a leukemic stem cell population. So, a population of cells at a very early stage have a propensity to develop leukemia.

And with my patients, I use this analogy of a garden which you may have heard. But I think of these leukemic stem cells as being a population of seeds that sort of go bad; and then they develop roots and they put down roots and then eventually the weed starts springing up.

And so really the question is when you're negative after induction, even MRD-negative, how deep into the roots and the bad seeds have we gotten? How deep have we gone, and our ability to measure, even by MRD right now, probably does not get us even close to measuring at the leukemic stem cell level.

I suspect these studies, I don't think they will be done anytime soon, that if you take populations of patients that have deep MRD-negative remission after induction and do nothing more, 100% of patients will relapse. That is my hypothesis, and they did studies like this decades ago. Of course, they didn't have MRD technologies. They just measured conventional remission; and everyone relapsed with no further therapy.

And I think until we can really clear out the disease-causing cells, the leukemia-causing cells, we will need more therapy. So, I think that's very clear.

We do use MRD to decide about transplant though, and I would say it's a little bit too challenging to make a generalization about how we use MRD because increasingly leukemia has become personalized medicine.

Elissa: Yes.

Dr. Muffly: We know very much about the cells themselves. We know about the mutations that have occurred within the leukemia cells. We have some therapies to target these mutations, and so when I see patients for consultation, I put the whole package together. Who's the patient, what's going on in their life, what's their health, what is their disease biology, what is their MRD, what's their response to therapy? And then putting that all together really helps to determine whether or not a transplant is going to be beneficial or not for them.

Dr. Frank: Yeah, I think Lori's spot on there, and I think that MRD-negative, particularly the term minimal residual disease-negative, is a little misleading in many cases. And so again, I don't think any doctor or treating provider looks at one piece of data in isolation. We need to know what kind of cancer you have. We need to know some information about the genetics of that cancer. We need to know about, there's ways of risk profiling patients beyond just MRD. So, if I have a lymphoma patient who has what's called double-hit status where they have two genetic abnormalities, after second-line chemotherapy, if they're MRD-negative, I'm still not reassured. I'm worried about that coming back.

And so, the test, as Lori was alluding to earlier in our conversation, only get down to a certain level. It's about one in a million cells. You have a lot more than a million cells in your body. And so there can still be cancers that hide out, and that's the worst part about cancer is that fear of where it's hiding out.

So again, it comes back to having that conversation with your doctor and having like what information are you using to guide my therapy? What is the situation we're in, and this is why you have to have a doctor that communicates well and is open and honest with you to communicate the information you need to make your best decision as a patient.

Elissa: I think that that's where a lot of patients may not understand that when we're starting to now talk a lot about, minimal or measurable residual disease, that if they're negative, it's just all gone. And so, I think that was a great explanation that it's not necessarily all gone. You might still have cancer cells in your body.

Dr. Frank: That's exactly right.

Dr. Muffly: Yeah.

Dr. Frank: And so, even if you're MRD negative, you still may need to have therapy. There still could be cells hiding out and you may need additional treatment, and that's why the doctor has to be very clear about that.

Edith: So, doctors, is it possible to be MRD negative and turn into MRD positive?

Dr. Frank: So MRD is usually you're talking about a timepoint. MRD refers to when I drew that test. So, if I had a bone marrow biopsy done or if I had a blood test, it's on that day with that sample, what did we find? I think the power of MRD is that patients, unfortunately, get used to having parts of their body removed from them, having blood removed or bone marrow removed. And we don't enjoy doing that. But I think most patients would agree that a blood test is easier than a bone marrow biopsy. But even a blood test is probably easier than having to sit in a PET scanner for a couple hours. So, we're trying to move toward technologies that are easier for patients that can be done universally.

And the reason we're all excited about this is from a simple blood test, we can learn a lot about that patient. And doing serial measurements, not just one isolated one, but serial measurements, is really the power here is that it's easy to draw blood maybe once every month or once over time course than having to come in and get that bone marrow done every so often, which is much more painful, but it's the power of serial measurements over time where the MRD becomes more powerful. We can see that patient go from negative to positive.

Dr. Muffly: And both Matt and I are really excited about the idea of both in leukemia and lymphoma tracking disease through the blood rather than through bone marrow and scanners or in addition to as a supplement because, you know, we understand that if we can take very sensitive tools that can identify leukemia and lymphoma in the blood, how much better is that for the patient than having to sit through bone marrow biopsy after bone marrow biopsy. So, Matt and I both study this area, and we're both very excited about the implications that it could have for our patients to use MRD through the blood.

Elissa: I'm sure every single patient who has gotten a bone marrow biopsy would absolutely agree that they'd really rather have blood test after blood test after blood test than a bone marrow biopsy, especially since they tend to get several throughout their treatment. So that is wonderful to hear that that could be a possibility for the future.

Dr. Muffly: Yeah. Yeah. And I think it's a real possibility. Now, our pathologists taking a lymph node and looking at it under the microscope or a bone marrow sample is critical. And I don't think we're ever going to get away from that entirely, but I think this ability to serially track disease as Matt was saying, to do that from the blood I think makes a whole lot of sense. And I think that that's where we're going.

Dr. Frank: And Lori brought up a thing that I hope we actually maybe even get away from doing that biopsy actually. There are technologies in development, but my hope is not the same thing as reality. Right now, I completely agree with Lori that you absolutely need to listen to the doctor. If they say that you need a biopsy, ask why, get your information. Make sure you understand the risk and benefits of that procedure, but I agree with Lori, right now you absolutely need that biopsy. And if you need it, you need it. But there are technologies being developed using circulating tumor cells and circulating tumor DNA to get a lot of information that can guide our treatments from blood tests, what we call now a liquid biopsy. And so, there are future plans that are leading toward getting that same information that used to take a

biopsy now we can get in the bloodstream. But those are research and not ready for primetime; but the research is there, and we're excited about it.

Lizette: Yeah. It's really exciting to know what research is coming up. And I know that you alluded to in the near future that more and more physicians are utilizing MRD. Do you see in the near future MRD as an endpoint for clinical trials? I know you've started speaking about some clinical trials where MRD is utilized as the endpoint. A lot of physicians we talk to that are very enthusiastic about MRD speak about this, but I'm not sure that it's widely utilized yet.

Dr. Muffly: I'm running a clinical trial right now at Stanford where the endpoint is MRD response. It's an AML and MDS transplant trial actually that takes patients who are MRD positive, and we add a therapeutic to the transplant platform, and the primary outcome measure is MRD response. So, it's coming. I mean it's a little bit tougher in AML than in ALL in my leukemia field right now, but I really do think it's coming.

Dr. Frank: So, we had a trial in 2008 that started in 2008 and used MRD as the endpoint, so it's actually been around-

Lizette: Wow!

Dr. Frank: -for some time. But that's a very specific situation, and I think every disease is different, every situation is different, and I think we will see increasingly more and more trials, when appropriate, using MRD as the endpoint because remission isn't good enough. That term is probably not adequate in leukemias at this point, to be honest. So, yeah, it's been around for a while, and it's only going to get better. But it's very complicated, and that's why every expert has to determine what is the best endpoint for that disease in that treatment paradigm.

Dr. Muffly: When we think about how clinical trials are designed, we certainly have to think about how the FDA, sees these things. And I think as our therapeutics get

better and our assays and technologies also get better and advance, I think there will be the natural evolution that, that will be the endpoint. Using 5% blast in the bone marrow will no longer make sense.

Lizette: And I know that we've been talking a lot about lymphoma and the leukemias, which are your specialties, but do you see any movement with MRD in other blood cancers? I know you've mentioned myeloma. You just mentioned MDS, myeloproliferative neoplasms. Do you see MRD useful in those indications?

Dr. Muffly: Yeah. So MRD is already used across various practices in myeloma, both flow based and next generation sequencing based MRD, it's a very, very hot and important area in multiple myeloma. And Matt and I just happen to not be myeloma specialists, but I can tell you it's everywhere and its controversial and its interesting topic to talk through in myeloma because myeloma in 2020 it's a very controllable cancer but not a curable one. So, it makes it even more important to try to understand the use of highly sensitive but expensive assays in a disease that we know is going to be around for a long time.

In MDS, we've had various forms of MRD for a long time. For example, if you have abnormal chromosomes that are part of your MDS clone and they stick around, that's really MRD. That's just telling us that it's still there even if we don't see overt cells that look like MDS cells. The assays that are being used for AML are also being used for MDS, different next generation sequencing based assays of gene mutations, different flow cytometry assays.

So MDS is a bit of a tricky one, but I don't think any of these MRD questions or applications are in isolation. I think this is crossing all blood cancers. I can't even think of a blood cancer where this isn't being talked about or actively studied.

Elissa: Are there any recent developments in MRD research that we haven't discussed today?

Dr. Frank: Yeah, there's a bunch. But, let me highlight one that I think I'm really excited about. So, there's technology that we developed here at Stanford, and I get the pleasure of working with some pioneering folks who have developed assays that can detect circulating cells or circulating DNA that's in the bloodstream of patients. These are particularly lymphoma patients, but this is being expanded to myeloma patients. We're working on a panel for ALL and the future's bright, but we track about 400 different mutations that are commonly occurred in a type of lymphoma. And we can detect very low levels of any of those mutations. So, we can use it just simply for MRD analysis. Do you have that mutation? Is it associated with the disease? Is it there? That's an important clinical endpoint, especially for large cell lymphoma where we use this most frequently.

But the next question is can we also learn more about the patient's risk factors? We have disease there, but can we sort out is this patient low risk or high risk? And by tracking those mutations, we can do that without a biopsy. And then we can start studying the pattern of mutations to learn about why cancers evade treatments.

So, we've done this in the CAR T-cell space where we've looked at patients who had left over, measurable residual disease, they're MRD positive; but we went one step further. Can we identify the mutation from a patient's bloodstream, not from a biopsy but the bloodstream? We were able to do that and we recognized a new mutation associated with resistance to the therapy.

Elissa: That's amazing.

Dr. Frank: All from the bloodstream.

Dr. Muffly: Matt, can you talk a little bit about what this technology is called?

Dr. Frank: Yeah. So, it's something called CAPP-Seq. It was developed by Ash Alizadeh his group at Stanford, a pioneering researcher, a great lymphoma specialist in his own right. He works with a guy named David Kurtz whose now joined the faculty

at Stanford, and there's many folks who've worked with Ash to develop this. And there's folks around the world who actually still work on this kind of approach, but it's Ash's baby. I would say that he passionately wants to make disease monitoring, disease detection easier for patients. No one likes those biopsies. No one likes fine needle biopsies, right? And so, Ash has done a great job of going one step further. Yes, we can detect the minimal residual disease, but what else can we learn from that? And these are the kind of things that we partner with great scientists and physicians to take the MRD one step further. We can now recognize a mutation in a gene that tells us you really are unlikely to respond to a therapy. We're doing two things. One is we know that now as we prepare for when we think the patient may relapse. They may have a short-lived response, but we expect to have the cancer come back, but we can prepare. We can figure out what the next line of therapy would be.

We're actually in the lab right now developing the next generation of therapy based on that MRD result. We already have a new CAR being developed to overcome that resistance. So, we're taking-

Lizette: Wow!

Dr. Frank: -that MRD analysis one step further to develop newer therapies, so it's coming full circle.

Elissa: Very exciting.

Lizette: That is exciting. I think people really appreciate when, the scariest thing is, I'm diagnosed and is it coming back? But people really appreciate that if it does come back, there's a plan. It's really helpful to know that.

Dr. Muffly: Absolutely.

Dr. Frank: And, then what should be recognized is the only way we know this is that patients have volunteered for research studies. Patients and their families should be given lots of credit. They're part of this field. Without patients sacrificing their time

and their blood, literally their blood and their bone marrow, we don't learn this. And it's a huge apparatus to run trials and so all those patients who are part of that also get credit too. But at the end of the day, it's patients who are helping other patients, which I find amazing.

Dr. Muffly: Yeah, and during COVID.

Dr. Frank: And during COVID. Yeah, exactly right.

Lizette: That's another layer, huh?

Dr. Muffly: Yeah, I think Matt, you hit on really exciting technology and really just really cool stuff that is being studied in the laboratory and I think will translate to clinical commercial application. I think one of the take-home points for me is that there's so much science happening, there's so much that we're studying, there's so many clinical trials out there. And that is our life blood. That's how we move the field forward. But MRD testing in leukemia is commercially available. We're no longer on first base anymore. We've moved on beyond that. So, there's no reason that a patient can't ask their physician what their plan is for MRD testing if they have leukemia. And I think that's a really important thing for a patient to know.

Dr. Frank: Yeah, this is incredibly complicated space, and every cancer is different. Every patient situation is different. And one of the take-home points I'd like to say is talk to your doctor. They should be communicating with you. One of the most important things is communicating with the patient to explain what MRD is, does it matter in my disease, what is the plan of what we're going to do with that data, what other data are you looking at? No patient should be in the dark about what's happening to their own body.

And if your doctor is not communicating, bring it up, like, "I need to know more." That's, that's a critical part of this. I want patients to be empowered. My favorite patients the one that ask me all the questions because that means they're really

engaged and know what they're getting themselves into. I'm confident that we're going to partner together and that we're going to be a partner getting patients through their therapy.

Dr. Muffly: Absolutely. And Matt and I both take care of patients with very, very serious versions of blood cancers. We both do cellular therapy, and our role is to shepherd patients and their families through these scary times. The patient is first and foremost and taking the time to communicate and explain the disease and the plan is just critical. So that really – no patient should feel like they're in the dark.

Dr. Frank: And I'll go one step further. Doctors are busy. We're really busy. We're always running around doing things, but that's no excuse. Your doctor needs to communicate with you. This is your life. You need to know what's happening with it.

Edith: Thank you doctors. That was very well said. On our podcast page, we have a quote, "After diagnosis comes hope." Based on the current and potential research on MRD, what would you say to blood cancer patients to give them hope of a future without relapse?

Dr. Muffly: Yeah. To patients with AML and ALL out there, I think it's one of the scariest things in the world to be told that you have this diagnosis. I can only imagine. But as someone who really does take care of the sickest and scariest leukemias, our goal is always cure. I am extraordinarily hopeful for adults with both of these diseases right now. There have been more breakthroughs, more drug approvals, more science happening in leukemia just in these last 5 years than we've seen in 50 years. And so the future is very bright.

You need to trust your team. Your care team and you are a team, and you need to ask questions and you need, as we've said, to understand what's happening with your body and what's planned. But I would say that it is time to be hopeful. We are there. We're in a good place.

Dr. Frank: I think a lot of us in this business, we see good people get sick all the time and it's not fair, but there is hope. The science is evolving quickly. It's incredibly complicated, and it could be very overwhelming. To feel overwhelmed with a new diagnosis of cancer is very normal. You know, we're talking about something that's pretty complicated. MRD testing is very complicated, but it's another tool we have to help our patients understand the disease to give them hope. It's a rapidly evolving technology.

We have to be careful not to oversell it, so I don't want to make it sound like it's the state of the art and it's, here for everything in lymphoma. But there's a lot of hope that it's going to help improve two things. One, make it easier to be monitored for your disease. We're all trying to get away from those things that hurt. We don't like patients having to come in and waste their time. Our job is to give their lives back to them. So we're hopeful for that. And then two it's going to guide how we treat patients. In some cases, it already does; and in other diseases, it will. And so, we're happy about that.

Elissa: That's great. Well, we are so excited to hear about the incredible potential of MRD testing and what it can do for the future of blood cancer treatment. So, for our listeners who would like more information about MRD, LLS recently published two new patient and caregiver resources, a Medication Resource for Blood Cancer Patients with a handy calendar to assist with adherence, and a Minimal/Measurable Residual Disease Chart, which provides a quick guide about MRD. Keep listening for how to find these resources.

And thank you so much to our guests, Dr. Muffly and Dr. Frank, for joining us today and sharing your expertise with us and our listeners.

Dr. Muffly: Our pleasure.

Dr. Frank: My pleasure.

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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. 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. 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 also find the MRD resource booklets mentioned earlier 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.