FAQs on Minimal Residual Disease

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Transcript

Mary DeRome (MMRF): Welcome and thank you for joining us for today's session, Frequently Asked Questions on Minimal Residual Disease. I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation. Today, I'm joined by Dr. Luciano Costa and nurse practitioner Melissa Santell from the University of Alabama in Birmingham, Alabama, and Mr. Tom Michaels, a patient from Hoover, Alabama.

Patients and caregivers submitted a lot of questions about minimal residual disease (MRD) and its role in multiple myeloma prognosis and management during our MRD webinar a few weeks ago, and our panel today is going to answer some of them that we did not get to during that broadcast. So, let's get started.

I'd like to begin our discussion focusing on first defining what constitutes MRD and what the different methods are for measuring it. Dr. Costa, can you briefly explain MRD? And what does it mean when a result comes back as MRD negative at a level of $10^{-4}$ or $10^{-5}$ or $10^{-6}$? Are those the same from a practical clinical standpoint, or is one better than the other?

Luciano Costa, MD, PhD: Thanks, Mary, for the question, and first and foremost, thanks for having us here. It's always a joy to work with you and to work with the audience for the MMRF. And thanks, Mr. Michaels, for joining us. You know this aspect of myeloma as well as any of us, from the perspective that matters the most, which is the patient's perspective. And thanks, Melissa, for joining us. Melissa has been a fantastic collaborator, helping us take care of multiple myeloma patients, and has really become an expert on the theme over the years.

So, Mary, with MRD, I think there is almost some mystical perception of it, for what it really is. But if you think of it from a very objective standpoint, it's nothing but an assessment of how much cancer there is left. I like to say that if you go back in time 20 years ago, MRD was a concept that did not exist in myeloma for two reasons. One, we didn't have the technology, and second, we didn't have the need. The responses were so inadequate and people were left with so much disease after initial therapy there was no need to look for a minimum. And now, due to the advances of therapy, it's not uncommon that the things that we usually employ to assess disease, like the amount of the M spike in the blood, for example, or in the urine are all normal. So, I tell patients, either you are okay not knowing how much disease there is and where it is going, or you have to rely on a test that is more sensitive. MRD is nothing but detecting myeloma at lower
levels than the usual blood test can do. There are different technologies. Most are based on a test called next-generation sequencing (NGS), which looks at the sample of the patient at the time of diagnosis, when the bone marrow had lots of myeloma, and identifies unique sequences of DNA that are present in the cancer. And then down the road, looks for those same sequences and quantifies how many cells have that sequence. The other test is called flow cytometry, which does not require an initial sample. It takes a patient who has been treated, takes a sample of their bone marrow, and looks at the protein profile on the surface of all the cells of the bone marrow, and spots the ones that have myeloma, the ones that are cancer. Those are not the only technologies, but the two main technologies, and they have different levels of sensitivity. Some of the early assays, that were mostly flow cytometry, detected $10^{-4}$; that means 1 cancer cell out of 10,000. Some of the optimized flow [cytometry] can detect 1 cancer cell in 100,000 ($10^{-5}$). And the NGS can detect 1 cell in a million ($10^{-6}$). The reality is, anywhere you put the bar, for people who have been given a certain treatment, the people who are below that level tend to do better than people who are above that level. Of course, there's nothing surprising about that; having less cancer is better than having more cancer. So, if you were negative to $10^{-6}$, that's usually regarded as a better thing than being negative to $10^{-5}$ or $10^{-4}$.

Mary DeRome (MMRF): Yes, I think that I've seen, in some of the more recent meetings that we've been attending, that there's actually some development in NGS, to be able to increase that level of sensitivity to $10^{-7}$, meaning, detecting 1 cell in 10 million cells. That's really sensitive stuff. It's amazing to see how this has all developed over the course of the past couple of years, such a really sensitive test to detect how much cancer is left.

Melissa, Dr. Costa described to us these two different types of tests. What test do you use most routinely when you're evaluating patients there at UAB?

Melissa Santell: We usually use the NGS test with the clonoSEQ lab, for sensitivity.

Mary DeRome (MMRF): Do you think that that test is more widely available? And is it more widely approved by insurance?

Melissa Santell: I don't think it's as widely available, yet. That may be coming. But as far as I know, we're the only ones in the state that have that test on the bone marrow, but Dr. Costa, feel free to correct me if that's not correct.

Luciano Costa, MD, PhD: No, I think at is correct. The challenge here, Mary, is that flow cytometry, every hospital has. The challenge is that not every hospital has a flow cytometry test that has been developed, optimized, and cross-validated for MRD. Most hospitals perform what would be an MRD with a sensitivity of $10^{-4}$. And it's hard to say, "Okay, my $10^{-4}$ here is the same as a $10^{-4}$ from New York," because there is no cross-validation.
Mary DeRome (MMRF): Right, and it does depend, a little bit, on the skill of the person who’s doing the test, and the level of purity and sensitivity of the reagents that they happen to be using for the test. And that can differ from institution to institution, on that test. Whereas, the other test, the clonoSEQ test, is a kit that you receive from a company. You do the bone marrow sample and then send it back to the company, with the test, and they send you the results. So, all the results are the same for that test, across the board, for everybody who uses that test, right?

Luciano Costa, MD, PhD: Correct. And you can be confident that the results that we go and publish on the manuscript, using that test, mean the same thing as when you go to your doctor and get a test and have the same result, because it’s exactly the same platform. And I don’t mean to diminish the value of flow cytometry. You cannot overestimate the importance of the broader availability of flow cytometry, but it just so happens that NGS is the only platform that has undergone the painful steps of obtaining an FDA endorsement, the FDA clearance. Which means there’s a very robust analytical validation that ensures that the test really measures what it’s meant to measure.

Mary DeRome (MMRF): Mr. Michaels, thank you for being with us today and relaying to us some information about your patient story. It’s such a valuable thing for other patients to hear what patients go through. Can you tell us a little bit about your myeloma history, and also about your experience with MRD?

Tom Michaels: Well, the hardest part about it was getting diagnosed to start with.

Mary DeRome (MMRF): That is often the case, yes.

Tom Michaels: I was going to orthopedic surgeons and neurosurgeons and all these people, and everybody told me I had arthritis, and that took six months, but it finally was detected. I actually had signed up, before I actually saw Dr. Costa, for his clinical trial, simply because I knew that clinical trials were the best way to go and I was going to get the best treatment. And it was sort of blind luck, but it worked out very well for me, in this particular case. The first MRD I had, I saw the doctor one afternoon, and because my calcium levels were so high, he put me in the hospital that night. I went home and grabbed some stuff and came back, and the next morning or the next day, I had the first MRD test, or spinal biopsy. And the results of that were 74,000 cancer cells per million.

Mary DeRome (MMRF): Wow. And that’s not MRD negative. Of course, you hadn’t been treated, yet.
**Tom Michaels:** I guess it didn't mean a whole lot to me then. But I'm an engineer by education, so I could understand some of this and how it was going and the need for it.

**Luciano Costa, MD, PhD:** Yes, so, for context, the test that Mr. Michaels referred to is the initial bone marrow biopsy that gave us the diagnosis. But that sample is also sent to the central laboratory that does the identification of the sequence that we're going to be tracking, down the road, for MRD. And by doing that, we get this quantification that he mentioned, the 75,000 cells.

**Mary DeRome (MMRF):** So, just out of curiosity, you were on the clinical trial when you were newly diagnosed? That was your first treatment?

**Tom Michaels:** Yes, well, in July, I had a bunch of tests, obviously, in the hospital, and then within 15 days or so, I started on my chemotherapy regimen.

**Mary DeRome (MMRF):** Dr. Costa, was that a four-drug regimen, perhaps?

**Luciano Costa, MD, PhD:** Yes. Mr. Michaels, do you mind if I share your age?

**Tom Michaels:** No.

**Luciano Costa, MD, PhD:** Mr. Michaels was a very young, very driven 76-year-old, at the time. I may be off by one or two years. And I remember he was very resolute that he was not going to be okay with our shorting him for therapy because of his age. And, boy, he was so right. He enrolled in a clinical trial that has now been presented and published a few times, called the MASTER trial, that combined four drugs, which is not how people usually think about treating 77-year-old people, and adapting therapy according to MRD status.

**Mary DeRome (MMRF):** Yes, that's a really interesting trial. Dr. Costa, there's a newer concept that's known as sustained MRD. Can you talk a little bit about what sustained MRD means to a patient, and how it's measured and how that information is used?

**Luciano Costa, MD, PhD:** Yes. Achieving a deep response is important, but more important is sustaining a deep response. So, if we just take patients given the same therapy at any given point, patients who achieve MRD negativity tend to do better than patients who don't. But there are also patients who become MRD negative very transiently, and then the myeloma bounces back up, and some of that could be a variation of the test, and some of that could be the nature of the disease. So, this notion of MRD sustainability, which has been most often defined as two MRD results one year apart, has been valued as perhaps an important end point to use to compare therapies and to possibly de-escalate therapy in some patients. People debate, well, should it be one year, two years, or three years? Well, it's a balance there, right? At some point, if you say it's five
years, then it becomes a self-fulfilling prophecy. After five years, it might be negative, but I don't need a prognostic test to tell me you're going to do well. You have already done well, right? So, I think most of the field believes one year is the right balance, and I think we're going to see more and more trials develop with that end point and using that milestone to adapt therapy.

Mary DeRome (MMRF): Yes, this is such a promising technology, but there really aren't a lot of guidelines around it yet. And we certainly need more data and more studies, more trials, to be able to determine how this test can be used, potentially, to maybe stop therapy or change therapy or begin a different therapy. A lot of variables go with that, but a lot of these studies are ongoing and the MASTER trial is a pretty important part of that.

Melissa, we get a lot of questions from patients and their caregivers about MRD and transplant. What do you tell a patient who hasn't had a stem cell transplant, who either doesn't qualify for one or doesn't want to have one, about whether they can still achieve MRD negativity with treatment?

Melissa Santell: Historically, I have been a nurse practitioner that works with transplant patients, specifically, but as chimeric antigen receptor (CAR) T-cell therapy has entered the scene, I have been seeing some patients without transplant. And yes, it is possible to achieve MRD negativity without transplant, depending on patient-specific factors.

Mary DeRome (MMRF): So, patients do sometimes achieve MRD negativity just on induction therapy, right?

Melissa Santell: That is very true.

Mary DeRome (MMRF): Those are really more the lucky ones, right?

Melissa Santell: Yes, yes, we do see some patients coming into transplant already with MRD negativity.

Mary DeRome (MMRF): Right, right.

Luciano Costa, MD, PhD: Melissa, we saw a couple cases yesterday, right?

Melissa Santell: We did. One of our patients, yesterday, or actually two, had achieved one MRD-negative test prior to transplant, just with induction. They had their transplant, and their day 80 marrow again showed MRD negativity. Which was amazing. I think it's very patient-specific, but those patients were able to not go on maintenance, with continued yearly MRD testing. But they were so excited.

Mary DeRome (MMRF): I'm sure. I'm sure they were.
**Luciano Costa, MD, PhD:** And Mary, this is particularly important because there are new trials that are being done or are being launched, and we have one here at UAB, right now, that addresses this notion that, not so long ago it was almost impossible to achieve MRD negativity with just induction therapy. But now it is possible, with new therapies. And transplant is something we do very trivially and very routinely, but not everybody’s as tough as Mr. Michaels, and even for tough people like him, it is a difficult treatment. And it will be something that will be nice one day not to have to rely on transplant to achieve that level of deep response. We have a pilot study that we just completed at UAB that is essentially doing a longer induction and deferring transplant for patients who are MRD negative. And we are about to embark on the MASTER-2 trial, which will take patients who are MRD negative after induction and randomize them between receiving a transplant or managing with a transplant-free approach. And for patients who are MRD positive, we're going to try a new post-transplant therapy. The idea being that this is not just about escalating therapy, but also being able to recognize the people who are the best responders, who have more favorable disease and may be able to take one step back on their treatment.

**Mary DeRome (MMRF):** Adapting therapy in that manner certainly makes sense, and the more data that we gather about those types of incidences will be better for our patients, so, that's really interesting.

So, we just talked about this topic: a patient who becomes MRD negative before transplant, do they still need a transplant? And you're saying that maybe they do, maybe they don't, and in the trial, you're randomizing some patients, who are MRD negative after induction and randomize them between receiving a transplant or not having a transplant, and see how they do. So that will be able to answer that question, so that will be great.

Mr. Michaels, you educated yourself about MRD testing, and you've had several MRD tests. What would you tell other patients and caregivers who are new to MRD testing and trying to understand it? What helped you understand the implications of your MRD results?

**Tom Michaels:** Well, I'm an engineer by education; of course, that was a long time ago and I've probably forgotten about everything I know, but

**Mary DeRome (MMRF):** I doubt that.

**Tom Michaels:** I do know a little bit about logarithms like $10^{-2}$ and $10^{-6}$ and all of that. The reports I get give that information, but they also give it in terms of how many cancer cells per million, and I would hope that everybody else that does this test gets it presented in the same manner as Dr. Costa presents it to me. It's very easy to understand and see where you're going. When I signed up for the trial, I didn't know anything about it, obviously, but I got a 200-page packet showing everything that was in it and all that was going on. I did finally get into
that section and I read a little bit about it. This was five years ago. I did go online and spend a lot of time researching it, and I found that the seminars and the major players in multiple myeloma were recommending the MRD test. And I guess it really struck home after I had my transplant. I got something from the hospital saying I was cancer free, and that was just the regular test. And of course, other people that weren't on the trial or who didn't get MRD, they feel, "Now I'm home free, I don't have to worry about it." Well, it wasn't easy, but I had about six more months of treatment, and then I finally did arrive at the numbers. So, I think it's very well worth doing.

Mary DeRome (MMRF): It gives you some measure that your treatment is on the right path, right?

Tom Michaels: Yes.

Mary DeRome (MMRF): Which can be very assuring, to think that you received this treatment and now you're cancer free, at least in the near-term.

Tom Michaels: Correct.

Mary DeRome (MMRF): Great. So, initially, MRD was used to measure treatment response in clinical trials, but now it's certainly being used more and more in the real-world setting. Melissa, at UAB, is MRD testing done in patients who are not in clinical trials? And is testing available to all myeloma patients? And if it's not available to them, how would they go about getting the test done?

Melissa Santell: Yes, it is available to patients not on clinical trials; it's available to anyone. A lot of times, because it requires a bone marrow biopsy, we'll specifically use it if it affects our decision-making for treatment or maintenance.

Mary DeRome (MMRF): We talked a little bit, in our MRD webinar a few weeks ago with Dr. Costa, about whether or not MRD is used to guide treatment decisions. There are no guidelines, right now, that will guide you to what to do with MRD results for treatment decisions, because we haven't achieved that level of evidence yet. Do you think we'll ever achieve that level of evidence with this test?

Luciano Costa, MD, PhD: I think so. That is an area that I'm a little passionate about, Mary. I think it's very appropriate to say, "Okay, I want to see the highest level of evidence. I want to see that if you manage a patient with this information, they do better than if I manage a patient's disease without this information." However, that bar is very high, and I would say that bar has not been met by any diagnostic test in myeloma. Not fluorescence in situ hybridization (FISH) or cytogenetics, not image/positron emission tomography (PET) scan, not a regular bone marrow test, not simple protein measurement in the blood. So, yes, that is the ideal, that I have a randomized clinical trial with 10,000 patients showing that
managing patients with MRD outperforms managing patients without MRD. However, we use those test results all the time: we use imaging, we do bone marrow biopsies, even without MRD, and we assess how somebody responds. And we see that all the time, people make decisions, properly, based on the idea of risk. So here you are, you’ve got your transplant, you have a very good partial response (VGPR), but you have deletion 17p, so you’re considered high risk. I’m going to do a different maintenance therapy.

Now, there’s no randomized trial that shows that if I do maintenance based on FISH results, I’m going to have a better outcome than if I don’t. We just take one prognostic measure, a test, and apply it to selecting therapy. So, if we do that for FISH, if we do that for PET scan, the case to be made for MRD is even stronger, because we know very clearly how, if we’re assessing somebody, for example, post-transplant, MRD has a bigger impact on prognosis than even cytogenetics. I think there are trials being done right now that are very specific, taking patients who are MRD-positive post-transplant, comparing treatment A and treatment B. Or getting somebody with MRD negativity postinduction and doing transplant versus nontransplant. Over the years, we’re going to have, I wouldn’t say MRD-guided, I would say MRD-pivoted evidence that will help us manage patients. But that should not keep us from using that data for prognostic assessment, and it’s second nature to oncology and second nature to managing myeloma, that we use prognostic information to refine our therapies.

**Mary DeRome (MMRF):** Yes, that makes sense. I think pretty much every clinical trial that is now ongoing in myeloma utilizes MRD and gathers MRD data, in the effort to gather enough data to present this stuff to the FDA and say, “Look what we have. Can we now issue some guidelines around how to use this test and how this test can impact treatment decisions for patients?” The field has been working toward that for a long time, but as you mentioned, the bar is very high, so, apparently we’ll get there some day, but we’re just not there, yet.

**Luciano Costa, MD, PhD:** Mary, I think sometimes people confuse what is the holy grail being pursued with the FDA, which is using MRD as a surrogate for drug development. That, we don’t have yet, and it will be a while before we have it. If that were to be accomplished, we would have, for example, a trial where there’s drug A and drug B. Today, we measure progression-free survival to say A is better than B. But if we could use MRD negativity as a surrogate for progression-free survival, we would say, "A year later we do MRD on everybody, and if this group has more MRD negativity, I'm going to approve this drug." That is a very high bar, and that might be a while, if we ever get there. But again, that does not keep us from using that information to educate patients, do prognosis, and refine therapy.

**Mary DeRome (MMRF):** Yes. Do you have any feeling for how often this test is used in the community versus using it at a specialist academic medical center like UAB?
Luciano Costa, MD, PhD: I have a feeling that it is very rarely used in community practices.

Mary DeRome (MMRF): I have that feeling, too, based on some of the responses that we get from patients when they submit questions to the webinars. There are many patients who don’t know what the test is, don’t understand it, have never seen it, are asking how they can get it.

Luciano Costa, MD, PhD: Yes. It really depends on the practice being associated with a laboratory that does NGS. It's a bit tricky to set up, but once you get set up, it's an easy go. There's nothing unique there; you have to be an academic medical center to have those tests.

Mary DeRome (MMRF): Right, right.

Tom, can you tell us about your MRD testing? How often do you get testing for MRD, and what is involved with the test? And then, once you have the test done, how long does it take to get the results back?

Tom Michaels: Well, we first of all have to get the biopsy, and in fact, I just had one last week, last Wednesday, to be specific. And it's minor. You can go under anesthetics or not. I choose not to, so my dear wife doesn't have to come down and drive me back and forth. It's sort of like a bee stung you for a quick second, and then it's gone, so it's not all that difficult. As far as getting the results back, it's varied. A few times it took up to six weeks, but I think we're getting them back closer to four weeks.

Mary DeRome (MMRF): Wow, that's still a pretty long time.

Tom Michaels: Yes, as Dr. Costa will tell you, I try to negotiate with him a little bit. Now, he's the ultimate authority, so I will not go against something — I have to tell a story: When we were talking about going on maintenance lenalidomide (Revlimid), he suggested 10 mg, and I negotiated him down to 5 mg. And that was really just based on the MRD testing, and I had enough confidence that if I saw that number changing, I had an option. Whereas, if I start out at 10 mg and everything is okay, there's no way to know where I was.

Mary DeRome (MMRF): Interesting.

Tom Michaels: It's something very valuable to me. We had one occasion, and I don't know what happened, but there was a mix-up and somehow the sample was not sent off for MRD testing. So, two months later, I was back down there getting another biopsy. It's that important to me to know what that number is.

Luciano Costa, MD, PhD: I have not forgotten that.
Mary DeRome (MMRF): Wow, that’s an interesting story, and I have to say that we recorded a podcast, last week, and we were talking to a couple of patients who were relapsed/refractory, and they talked about negotiating with their care teams about their therapies. And two out of the three patients we had on that call had negotiated drug holidays with their treatment teams. I thought that was quite interesting. So, you’re not the only one who’s negotiating. This negotiation goes on.

Dr. Costa, if MRD negativity is the goal of treatment, should patients always be tested if MRD testing is available? I think I know what your answer is going to be. You’re going to say yes.

Luciano Costa, MD, PhD: I think it’s a little bit complicated. I think MRD negativity is a goal, the same way complete response is a goal or that some response is a goal. I tell patients it’s not all black-and-white. Some response is better than no response, a complete response is better than some response, and an MRD-negative response is better than a complete response. The therapies that we have now can lead to MRD negativity in many patients, sometimes most patients, but on a patient-by-patient basis, it’s important to keep in mind that it’s not like if your MRD did not become negative, it was a failure. It’s not like your treatment didn’t work. It’s not like you’re going to do poorly.

I like to joke that everything is a gradient, but the decisions are binary. You do this or do that. But the reality is that the burden of disease is a continuous scale, and we make those thresholds. So, if our cutoff is 10 cells in a million, somebody might have 9 cells in a million and we call them MRD negative; somebody may have 11, and we call them MRD positive. We have to put the line at some place. So, collectively, yes, the goal is to develop therapies that lead more patients to have a deeper MRD-negative response. But on an individual basis, there are people who never had a complete response and can do very well for a very long period of time. So, it is always good to talk to your doctor to help contextualize that MRD test.

Mary DeRome (MMRF): Sure, sure.

Tom Michaels: Mary, if I may, just looking at my reports, like any test, there's a range or a variance. So, when I had a 4, the confidence range was 0 to 7. When I was 15, it was 3 to 23. When I was 7, it was 2 to 12. So, that number, by that error range, can change.

Mary DeRome (MMRF): Yes, that makes sense. That's interesting. I didn't know that you were given a range. I thought it was just a number, but it's actually a range of numbers. I suppose there's always error inherent in every assay.

Melissa, are there some people for whom MRD testing is not an option?
Melissa Santell: There are. Sometimes we'll send the sample to the lab, and for whatever reason they're not able to identify the dominant myeloma clone, and then those patients, we can't follow with MRD.

Mary DeRome (MMRF): Yes, that makes sense. Tom, you've had some insights on interpretation of your MRD values. How did you interpret going from 15 myeloma cells per million to 7 myeloma cells per million, which, apparently, is something that happened during the course of your therapy? Is that like having gone from positive (when you had 15) and then you were negative when you went to 7? Is that how it was interpreted?

Tom Michaels: Well, to me, it's more the trend, the slope. Obviously, if it's trending down, that's better than if it's trending up. If mine starts trending up significantly enough, then I'm sure Dr. Costa and I will be talking about what to change. Maybe I have to go back and take the 10 mg of lenalidomide rather than the 5 mg.

Mary DeRome (MMRF): More negotiation is in store.

Tom Michaels: Right.

Mary DeRome (MMRF): Dr. Costa, a lot of patients want to know about the chance of achieving MRD negativity when taking a certain regimen. Is MRD negativity achievable with any recommended treatment regimen, or is it only newer treatments that can accomplish that?

Luciano Costa, MD, PhD: Good question. For the much older therapies, we don't know, because we didn't do the MRD test, but it's highly unlikely, right? When you see, for example, triplet regimens given for induction therapy, just about 20% of patients will achieve MRD negativity. With quadruplet therapy, that almost doubles. And transplant can greatly increase the proportion of patients who go from positive to negative by anywhere from 40% to 50%. It used to be that nearly all the discussion with MRD was centered around newly diagnosed disease and transplant, because those were the only people with a chance of achieving a deep response. Well, that's no longer the case. We have, for example, now, daratumumab (Darzalex) plus Revlimid and dexamethasone, a regimen used for people who are not going to go to transplant, with which a substantial number of patients achieve MRD negativity. And we see therapies like bispecific T cell engagers or CAR T-cell therapy used in patients whose disease has been heavily pretreated, and some of them still achieve MRD negativity. But that proportion is expected to be very low for doublet regimens or melphalan (Evomela)-based therapies, as we used in the distant past.
Mary DeRome (MMRF): Melissa, can a patient who's achieved MRD negativity, but then converts back to being MRD-positive, become negative again if they are put back on a different or maybe a stronger treatment?

Melissa Santell: Yes, they can. They can achieve that again, yes.

Mary DeRome (MMRF): Dr. Costa, if a patient is MRD negative, is that all you need to know about their myeloma? Or could a patient be MRD negative but then have a positive PET scan? Or what if somebody is MRD positive but shows no M protein?

Luciano Costa, MD, PhD: Let me talk about the first circumstance, MRD negativity with finds on the PET scan. That can happen, and one of the reasons why MRD is not a perfect test is because you can have pockets of disease elsewhere that show up on the PET scan that don't show up on the bone marrow–based MRD. There is a big concordance of the two. In general, if you are PET positive, you will be MRD positive, and similarly, PET negative will be MRD negative, but there is some discordance. There are some proponents of using PET scan to complement MRD testing.

Now, the opposite is very common. MRD testing can detect disease below the level that the protein test can do, so somebody can be in complete remission, have a negative immunofixation, and still be MRD positive. That's actually quite common. The opposite is also common, the serum protein electrophoresis (SPEP) measures the protein in the blood that the myeloma cells made, and that protein can take a long time to clear, weeks, sometimes months. So you may get to a state where the marrow is already negative, you already killed the myeloma cells to below the level that you can detect, but there is protein that was made by those cells earlier still lingering around in serum. It's always important to talk to your doctor and try to contextualize those tests.

Mary DeRome (MMRF): Interesting. I'm going to ask for some final thoughts now. Melissa, how has MRD impacted how you care for patients? How do you see it impacting myeloma care in the longer term?

Melissa Santell: It is exciting to work in the myeloma field with MRD testing. I know we talked about it before, but in certain patients, giving them time off of maintenance, if they've reached MRD-negative status, is really life changing and wonderful. And also being able to detect earlier, before they may show disease progression based on other older testing methods, that things are creeping up and we might need to change management.

Mary DeRome (MMRF): That makes sense. Tom, you're a huge advocate of MRD testing, so, what do you say to other myeloma patients you meet who may not have had MRD testing? Do you say, "Come to Dr. Costa; he'll fix you up"?
Tom Michaels: I do. In fact, I sent one of my good friends to him. She just visited with him in a seminar. But I've preached it to a lot of friends, "This is something that you need to have." And it's unfortunate, when you go online, you can type in "multiple myeloma cancer centers," and just about every hospital in the state of Alabama jumps up, but we all know well that the expertise is right here in Birmingham. And I wish everybody that has multiple myeloma would come to a national center at least once a year to get an MRD test and consult with a doctor. Get the regular treatments at home at your regular hospital, but under the direction of the myeloma specialist.

Mary DeRome (MMRF): Yes, agreed. We do preach that, certainly, from the MMRF, that being seen by a very experienced myeloma specialist who sees many myeloma patients is probably your best chance to have the best outcome for your disease. It's very, very important. And like you mentioned, you can still go to your local physician, as long as that person, and you, as part of the team, consult with a specialist once in a while, maybe yearly or something like that, or when you need to have a change in therapy.

Luciano Costa, MD, PhD: Yes, Mary, you're probably preaching to the choir with your audience, but that is so true. I tell the patients that I'm not smarter than any doctor in the community. I actually have a lot of respect for them for keeping up with so many diseases, but we have the privilege of being in a place where we can be 100% focused on one disease. And myeloma has evolved to require that. It has become very complex, with many things to consider. So, finding the myeloma expert in your area, or center of excellence as we call it, and partnering with them is the best way to go.

Mary DeRome (MMRF): For sure. Absolutely. My final question for you, Dr. Costa, is, is being MRD negative the same as being in remission? And is someone with sustained MRD negativity considered cured? That's a little bit of a loaded question.

Luciano Costa, MD, PhD: That's a good question. The term "remission" is part of our vocabulary, but it doesn't have a strict definition. We have definitions for response, you know, very good partial response, partial response, complete response, and complete response/MRD negative. Unfortunately, there is not any test, and it's a bold statement but I believe it to be true, there is not any test on any cancer that has absolute guarantee of cure. Sometimes people criticize MRD testing because, for example people may say, "Look at Joe. Joe was MRD negative and now he has relapsed. Therefore, the test is not good." But that test does not exist. For lung cancer, breast cancer, lymphoma, leukemia — there is not any single test in any single cancer that is an absolute marker of cure. We know, however, that, how most people define cure is, "Cancer is gone, I'm off therapy, I'm well in the long term, and it never comes back." That, at some point, requires elimination of disease by the best test you have. So, I say that becoming
MRD negative is not sufficient for cure, but is probably required for cure, as the years probably will show us.

**Mary DeRome (MMRF):** Agreed. That's excellent. On behalf of the MMRF, I'd like to thank our panelists today, Dr. Costa and Melissa Santell, and also Mr. Tom Michaels, for their time and telling us their stories and words of wisdom.

**Luciano Costa, MD, PhD:** Thank you so much.