

MMRF Patient Webinar – Minimal Residual Disease

July 14, 2023

Transcript

Mary DeRome (MMRF): Hello and welcome to the MMRF Patient Webinar Series, brought to you by the Multiple Myeloma Research Foundation. I'm Mary DeRome, senior Director of Medical Communications and Education at the MMRF. All of us at the MMRF appreciate your making time today to participate in our MMRF Patient webinar. With us today, we have two myeloma experts who will be describing the role of minimal residual disease (MRD) testing in management of myeloma now and in the future. Dr. Benjamin Derman is assistant professor of hematology-oncology and director of the Multiple Myeloma Clinic and Tumor Board at the University of Chicago. Dr. Rafael Fonseca serves as Goetz Family Professor of Cancer, professor of medicine, consultant in the Division of Hematology-Oncology, and the interim executive director of the Mayo Clinic Comprehensive Cancer Center, and the Director for Innovation and Transformative Relationships at the Mayo Clinic in Arizona.

So now, let's get started with our first speaker, Dr. Benjamin Derman.

Benjamin Derman, MD: Thanks so much, Mary. I really appreciate that, and it's really an honor to share with Dr. Fonseca this presentation. We're going to be talking all about MRD. That's why we're all here, right? So, let's get right into it and talk about the principles of MRD testing. So, when we think about how we approach this, as a clinician and probably as a patient as well, what are the goals of myeloma therapy? Well, crudely, what we're trying to do is reduce the amount of disease that we detect in the body, and we can do that in a couple of different ways. One way, the traditional way, has been to measure the proteins that the myeloma cells make. Because myeloma cells are plasma cells that make antibodies, and these antibodies are proteins that we can measure in the blood. Many of you who are patients who are undergoing monitoring for therapy are probably very familiar with something called the M spike or light chains that we follow. And that's a really nice way to see how the disease is responding, but we can go beyond that. We can go under the surface, so to speak, and talk about the elimination of myeloma cells at the level of the bone marrow. And we can do that using what we call minimal residual disease testing, or some people call it measurable residual disease testing or MRD testing. And that's what we're going to be focusing on today.

We have other things that are obviously very important to patients and to us as clinicians, which include improving quality of life, prolonging the time before the disease comes back, and ultimately prolonging overall survival. And we'll talk a little bit about how MRD can help with these things as well. So, as I just mentioned, when we talk about measuring response to therapy, the conventional way that we've done it for many, many years has been what you see on the left side of the screen. Partial response is a more than 50% response. A very good partial response is a greater than 90% reduction

in the proteins that we can measure. And then we have these deeper responses, a complete response and a stringent complete response. And essentially, what this means is that when you do blood work, and even when you do a bone marrow biopsy using some less sensitive techniques, we can't really detect any myeloma. But then we have the concept of MRD negativity, which refers to the absence of low levels of cancer cells using sophisticated techniques.

The flip side, MRD positive, would be the presence of small amounts of myeloma cells that are left over. When we refer to this, we're really talking about disease that's only detectable by these more sophisticated methods. And I'll get into that in just a little bit. But right now, with our current capabilities, which are fairly good, I would say very good, the most sensitive MRD tests can detect at least 1 myeloma cell out of about a million cells. The best that we can do right now is take between 3 to 10 million cells from the bone marrow, and we can pick out a cluster of myeloma cells from there.

Why should we even measure MRD? Well, it's this concept of, we used to clink our champagne glasses when we had a patient who would get to a complete response or a stringent complete response because we really couldn't detect any disease. But yet, some of these patients would still experience disease relapse. And we know now why that was, because there were low levels of myeloma cells that remained and were ultimately responsible for the disease progression. So, when we layer MRD on top of this, what we get from that is a better understanding of how much disease is left over and how to figure out what does that mean and how that can help us in terms of care of the patient at the bedside.

MRD is measured right now in the bone marrow through two different techniques. The first is flow cytometry, and flow cytometry is looking at markers that are on the surfaces of the myeloma cell that we know are particular to the myeloma cells. And so, you don't need any baseline samples, you don't need anything special. What you need is good equipment, a good pathologist who's going to be able to review this, and that's essentially what we can do with flow cytometry. Next-generation sequencing (NGS) refers to analysing the DNA of the myeloma cells at the beginning, before we even start treatment, and then essentially creating a myeloma fingerprint that we can track over time. And we can put the sample through the "myeloma criminal database" to figure out if that fingerprint is present later down the line. And these are the bone marrow biopsy techniques; we'll talk a little bit about what other techniques are going on right now as well. To mirror the phrasing around NGS, we now have something called next-generation flow cytometry, and these are the most sensitive techniques that have been validated thus far. And so, let's break it down to exactly what are the pluses and minuses here.

Next-generation sequencing primarily is going to be performed centrally by a third-party company. Next-generation flow cytometry does require substantial investment in equipment and pathologists to be able to interpret these results. But that's really the main limitation there. So, it can be done at your local centres if need be.

The benefit of flow cytometry is that you don't need a baseline diagnostic sample. You don't need to go back into the archives and figure out if there's a sample stored for your myeloma when you were diagnosed. You can look at any point in time to see if there is a positive or a negative result. But with NGS, you do need to either have had samples stored from before or a sample that was submitted to, let's say, Adaptive Biotechnologies, to be able to pick up what that fingerprint for the myeloma cell is. In general, these techniques are highly applicable; almost all patients are able to have a sequence in NGS or a profile in NGS that can be analysed. And the main difference is probably in turnaround time, because flow can be done at your local institution and then whenever that is done, it's done. With NGS, the [longer] turnaround time is because the sample has to get sent somewhere else, and then it's processed, and then it's sent back, and the results are sent back. So, by that time, it often takes around seven days to be able to get a result.

The actual testing does not take seven days to do, as I mentioned. We can pick out one myeloma cell out of a million total cells in the bone marrow, but with flow, you need about 10 million cells to do that. Whereas with NGS, you only need about 2 to 4 million cells to be able to do that. So, there's a much bigger difference in the total amount that you need in order to get the sensitivity that you want. The last thing that is a benefit of NGS is that you can take stored frozen samples and run this test on it, whereas with flow cytometry, you really need to do it fresh. That's why we have to do it locally, for the most part. There are some exceptions to that, but that's generally the idea. So, that's a little bit of a lay the land in terms of the bone marrow techniques that we have right now in multiple myeloma.

And some have said, "Well, why can't you just do these tests in the peripheral blood?" or "Why not just do a blood test and run these same techniques?" Part of the issue is that myeloma really likes to stay in the bone marrow. It does not like to go out into the peripheral blood. And so, unlike other cancers where that is the case, in myeloma, often when we do a blood test using these same techniques to find the myeloma cells themselves, we really fall short. It's not as good as a bone marrow biopsy or aspiration.

Let's get some key terms down. When we refer to MRD positivity, it's actually not a good thing, per se. This is when myeloma cells are still detectable. MRD negativity, on the other hand, is when we cannot detect any myeloma cells. And then we can go further and call something "sustained MRD negativity," which means two MRD negative measurements that have been separated by at least one year.

And we're finding out that this has one of the most important implications for patients. It's not just getting to a point where we can't define any disease on one occasion, but actually showing that we can get there and then keep it there, that we can sustain it. Ultimately what we have to do is put this all together. We probably can't take one test at one point in time and say that's it, we have to really put together everything. So, we may have an MRD result from the bone marrow, that's one thing. But then we also have to consider the fact that in myeloma, disease can be patchy; if a needle is put one part of the bone and not another, you may find disease in the part that you looked but you

wouldn't have if you went in the other spot. And the same is true vice versa. That's why multiple measurements over time can be very helpful.

But another question that's come about is, "Well, are there other techniques that could help us find out if there's disease outside of the bone marrow too?" Because that's another issue. We refer to something called extramedullary disease. You may have heard that terminology. And what that refers to is myeloma disease that's not localized to the bone marrow. It's not something that you're going to necessarily detect when you do a bone marrow biopsy. So, a PET scan or even more sophisticated MRI techniques are able to pick up areas of myeloma. Think of them like solid masses of myeloma that exist outside of the bone marrow. And now you're going to hear more and more about peripheral blood testing, which is a little bit different than the other techniques I've mentioned, to really figure out if we can find any myeloma that might be floating around elsewhere from the bone marrow.

Now, there's a lot that's controversial on MRD, but this, I think, everyone can agree with, that patients who achieve MRD negativity while on treatment live longer than those who are MRD positive, and their disease takes longer, obviously, to come back, if it ever does come back in those cases. There have been 44 studies that were analysed as part of a study that was done in 2020 and that has shown that MRD negativity was associated with a longer progression-free survival and overall survival. And this association is true regardless of if a patient had high-risk disease coming in. If they used flow cytometry or NGS, if they looked at 100,000 cells or a million cells, it doesn't matter. And it also doesn't matter if you're talking about the newly diagnosed setting or in patients who are relapsed/refractory, even after CAR T-cell therapy. So, this is the most important thing.

And the other thing that's really important is that all of that stuff I mentioned about complete response, very good partial response, partial response, all that stuff comes out in the wash. What really matters is are you MRD negative or not. None of those other conventional methods really matter anymore. So, you can see why there's a lot of enthusiasm around MRD testing.

Where are we going? Well, I think where we're going, for sure, is this MRD-driven therapy. Can we use an MRD test to guide the decision-making that we come up with? Can an MRD-negative result allow us to de-escalate therapy? Should an MRD-positive result force us to continue therapy or even escalate therapy? Those are very controversial topics, and that's something that we're going to need more evidence to really investigate. And of course, the other thing is, let's figure out new ways to measure MRD that might not always depend on a bone marrow. I think the bone marrow is always going to be a key part of this, but can we find ways to spare some patients having to go through bone marrow biopsies each time? There's a lot of enthusiasm around that.

So, think of it like this, in terms of the peripheral blood, when you're looking at blood tests right now, which is kind of the holy grail in the MRD world for myeloma. We can

look at the cells themselves, [asking if] we can find whole circulating myeloma cells in the blood and then do something called single-cell sequencing, or some kind of bulk sequencing similar to what has been done previously with NGS in the bone marrow. The other possibility is to say, "Okay, well, we can't find the whole cells, but there is a breakdown of myeloma DNA. There are some fragments of DNA in the blood. Let's try to capture that." And then the third one, that's probably most promising, is mass spectrometry, which is a totally different way to look at it. Which is to say, "Can we figure out a much more sensitive way to detect teeny amounts of the myeloma protein in the blood?" So, you're not really reliant on the myeloma being present in the blood. Now you just want to figure out that protein. It's basically doing what we already do with a serum protein electrophoresis, the M spike, but really taking it up a notch. Or, in another way of thinking about it, lowering our threshold quite a bit. That's what we want to focus on.

So, when we talk about blood-based MRD testing, we did a trial with a certain induction regimen, transplant, and treatment following that. And what we did during this was try to figure out, "Okay, can we piece together the bone marrow testing that was already being done for MRD with peripheral blood testing using mass spectrometry?" And what we found was that in some circumstances, using mass spectrometry in the blood was able to detect disease that wasn't able to be detected in the bone marrow. And to go further, what we found is that patients who still had residual disease detected by this blood test, even when it wasn't detected in the bone marrow, those patients were more likely to have their disease come back.

What does this tell us? It tells us that the blood may give us some information that the bone marrow cannot, in some circumstances. And I think over time what we may see is this cascade, where patients may get a blood test, and if that blood test shows no disease, then maybe they do the bone marrow biopsy to really provide a comprehensive assessment. But the flip side is if the blood test is positive, perhaps that's a sign that we don't really need to do a bone marrow. We know there's still something there, but figuring out the right time to do that, the right technology to do that, that all remains to be seen. So, the summary, before I hand it back to Mary and Dr. Fonseca, is that MRD is really helping us define the deepest responses after treatment. And we have bone marrow techniques, we have techniques through PET scan or MRI, and then of course now we have blood-based MRD testing that's starting to take root. MRD negativity has typically been associated with longer progression-free survival and overall survival. And now the next frontier is figuring out whether it can be used for response-directed therapy. And I think that's going to be the really important thing to focus on as time goes on. That's probably a nice segue into Dr. Fonseca's talk. So, Mary, back to you.

Mary DeRome (MMRF): Great, thank you, Dr. Derman. That was a really great presentation. And I know I speak for many patients when I say that any kind of testing that can be done in the blood versus having to do it in the bone marrow is always preferable. It's great to see that that type of testing is really coming online with MRD as well. Now we're going to move on to Dr. Fonseca's talk, who is going to talk about achieving MRD negativity.

Rafael Fonseca, MD: Thank you very much, Mary; it's a pleasure to be with you here, and an honor to share the podium with Dr. Derman. I'd like to talk to the patients a little bit about the implications of what it means to achieve this negativity and use some examples of clinical trials that have attested to what you just heard from Dr. Derman. Before I do that, let me give you some background here. When we look at the various regimens that are currently available for induction therapy, which is the very first time a patient receives treatment, a large fraction of myeloma patients are able to become MRD negative and that, in the mind of any of us who see myeloma patients, is something that we feel good about. During my talk, I'm going to bring in a couple of concepts, and I think it's very important for you, as patients, to think about this when you have these conversations with your doctor.

The first point is before you do treatment, and then the next point is, what happens once you complete treatment, and how do you assess that by your MRD? So, before you need treatment, in my opinion, we have to do everything in our strategies possible to set the stage so that the person in front of us can achieve MRD negativity. When I choose regimens that I'm going to use for my patients, I look at data like this and I think, "Yes, this is what I would like to see my patients receive, because I know they're going to have a higher chance of becoming MRD negative."

What happens afterwards? That's a very important point. We've learned that, yes, it's better to be MRD negative, but also, we know there are some patients that were not able to achieve that negativity and yet can have very good outcomes. That's only something we know afterward. At the beginning, we don't know that. So, in our goals of treatment, we want to do everything we can to try to make the patient become negative. And I will say, like I tell my patients all the time, with your consent and in a safe way, we want to choose treatments that will make patients become MRD negative.

I'm going to show you some examples here. Many of you have heard, of course, about the DETERMINATION clinical trial from the French group that asked the question "Do we still need to do the transplant?" A very important question for everyone, particularly for patients, and much talked about in this clinical trial, because we know that it delays the time until the disease might show up again and that a patient needs treatment. But one of the things that we're doing more and more is when we see these clinical trials, we put a filter in front of our eyes that looks at who's MRD negative and who's MRD positive; then, you start seeing curves like what you see here. I presume many of you have seen curves like this, but as you know, as you move to the right, that's the passage of time. And every time the curve drops a little bit, that means that something has happened, like the disease has come back. So, the flatter the curve, the better. And what you can see here is for patients who are MRD negative, whether they get transplant early or late, the results are very good. The main difference is between those that are MRD negative and MRD positive.

Some of this relates to the treatment that is chosen, of course; that's important. Some of this also may relate to the cards you are dealt: the biology, the type of myeloma you

have. But once more, if I can, I'm always going to try to do things that are more likely to achieve MRD negativity. Many of you may be on maintenance therapy or have gotten maintenance therapy in the past. And this is one study from Dr. Alonso I want to highlight. At the beginning of maintenance, 37 patients were MRD negative, but that went up to 72 after the patients completed maintenance. So even with maintenance, the level of response can improve. And this is one of the reasons why we think maintenance helps patients.

We doctors will use a lot of terms, and we'll talk about "maintenance" and "consolidation," which is just semantics. It just means more treatment. And what it means is, if there is residual disease, in general, more of a good treatment is better. We want to make sure we get rid of as many of those cells as possible. Dr. Pawlyn, from the United Kingdom, has published a particular study. It's a little bit complicated. Suffice it to say they used multiple combinations [of drugs], and then the patients went through stem cell transplant. After the transplant, by the flip of a coin, half of the patients got lenalidomide (Revlimid) and half of the patients went into observation.

Those patients that got the maintenance did better. They were 50% less likely at a given point to experience recurrence of the disease. But all of this really becomes notable as we start looking into this MRD negativity. And what Dr. Pawlyn found was a benefit of longer maintenance for those patients that remained MRD positive. So, if you are MRD positive, we're more likely to think about longer duration of maintenance.

Now a question that is not answered yet, but I think is a very pertinent question and one I hope will be answered in the near future is, if someone were to be MRD negative, as you've heard already from Dr. Derman, maybe we can stop maintenance earlier, but perhaps in the future, maybe we won't even have to do maintenance, because the incremental benefit, or the incremental ability to control the disease, will be less if you're MRD negative. Dr. Derman himself has published this particular study that looks at patients who have been on at least one year of maintenance, where those patients that are negative can discontinue that maintenance and those patients that are positive by either MRD or PET scan will continue on maintenance. And he and I were talking before this meeting; I say it's close to 85% of patients that at one year will still remain without progression, even after they stop maintenance.

And this is very, very important when you look at data in the United States, what we call real-world evidence. So, you ask, what's really happening in the world with maintenance? Most patients do not go beyond two years of maintenance. Often we discontinue maintenance because of some side effects; that would be fatigue, sometimes diarrhea, there are multiple reasons. But I really hope that we will have even more data to be able to say this is one more factor. Now, MRD negativity, I think, will ultimately lead to the notion that we have the ability to treat for a shorter [amount of time]. And as Dr. Derman puts it, there in the slide, discontinuation may have significant cost savings, and that's not only in dollars, that may be in toxicity and inconvenience, and in our ideal world, patients would get a more limited duration of that therapy.

Now, one of my other colleagues, Dr. Costa, developed a clinical trial that is called the MASTER clinical trial. They're going to be measuring MRD on a number of occasions. And once a patient is determined to be MRD negative on two consecutive occasions ("MRD sure"), they just stop therapy. And this is very, very exciting. This is one of the most talked about and one of the most innovative clinical trials we have. I hope this is one of the ones that will pave the way towards very limited [maintenance], or even at some point in the near future, not even having to use maintenance. That's kind of where we are moving. And there's a number of clinical trials. I won't walk you through all the details, but just know that when we talk about phase 3 trials, this is the highest level of evidence. [The phase 3 DRAMMATIC study and the phase 3 OPTIMUM study] are two trials where patients are being assessed for discontinuation of therapy based on MRD.

Now I will share a spectrum of how people use MRD. I think we actually can already make clinical decisions with MRD. I use it routinely; we do it in all of our patients, we do it on their bone marrows, and I think it's just informs our clinical practice. I don't think MRD needs to be treated in any exceptional way. It is just one more test. As an example of this, I make reference always to things like the free light chain. When the free light chain test, which many of you are familiar with, first came to be used in the clinic, it was dramatic how it changed our ability to understand the myeloma. We never required all these tests, but we use it routinely now to make the best decisions at the bedside.

And of course, we would like to get to the point that some of this information ultimately is approved and accepted by the regulatory authorities here in the United States, the FDA, because if we could finally have them buy into the concept that MRD is a very good end point, that means the time to develop drugs would be greatly shortened. A consequence of that would be earlier access to drugs, and it would even argue for cheaper development for those drugs. So, we really want to see more and more of this being incorporated into the regulatory process.

If you're wondering, as you listen to all this, "When should I have MRD testing or maybe talk to my doctor about this?", as you know, we have two main groups of patients, patients that will go through the stem cell transplant and patients that don't go through the stem cell transplant. So, the bottom part [of this slide] is the null transplant (no transplant), and the top part is stem cell transplant. Most commonly we test for MRD after the transplant, or after that first phase of treatment in those who are not going to go through the stem cell transplant. This, of course, this is the decision you have to make with your physicians. In our particular case here at Mayo Clinic, if you're MRD negative, we will continue to measure that.

Certainly, we will do that at least on a yearly basis, sometimes in those patients that complete transplant and are still MRD positive. Again, we're waiting for [the results of] some of those trials, but until we have those results, in my particular practice, I offer those patients additional therapy and I might measure MRD again in another six months just to see if we're moving in the right direction. Now, one more point here, the various tools that you heard of for how we measure MRD are not a black box that tells you

“positive” or “negative”; it actually gives you a number. So, if I have a patient who completes transplant, and let's say he has an MRD of 500, and then I give therapy and the patient goes from 500 to 10, then I know we're moving in the right direction. I may give a little bit more of that. If, on the other hand, I have a patient who's getting [a result of] 10, but let's say three or six months later it's 500, it makes no sense to continue on the same therapy for that particular person. There's a lot of caveats and technicalities to that, but I think the principles apply.

Now, two last conceptual slides before I go to my summary. I used to say that (this is a little bit tongue in cheek) you need to come and control myeloma like Pax Romana. So, you put your best treatment forward, and you do everything you can to control every single possibility for residual myeloma cells. And I realize, again, it's much easier said from the doctor's side. As I tell my patients, I know you're driving the conversation, and it's easier said by the doctor. We have to do it safely, but we can do it. And MRD seems to me that it will determine the two boundaries of what we're going to do for myeloma therapy.

First, the depth. You already heard about various studies [showing] the deeper the response, the better. And I'm hoping it will also determine the duration of therapy. So that's why it's so important for us. On this particular slide, I put a little grey border only on the bottom and on the right. And the purpose of that is just to remind me that there are some patients that, despite not being able to achieve MRD negativity, can still do very well. Unfortunately, I don't know that until after time has gone by. I'll give you an example. And this is even more than MRD. One of the first patients that I saw when I moved to Arizona and who had a stem cell transplant in 2007, has a small residual monoclonal protein, and to this day, has not had progression of the disease after stem cell transplant, even though he keeps a small monoclonal protein. Just elaborate that further and you could say the patient was MRD positive. So, that's number one.

Point number two (and I alluded to this before, this is really, really important), yes, we want to achieve MRD negativity. That's my goal. I'm obsessed with thinking about ways in which we can make patients MRD negative, but it may be different depending on the myeloma version we're dealing with. Sometimes, unfortunately, a patient has been dealt cards of a myeloma that is far more aggressive. And for that patient, all the studies point to say, if you have not gotten that MRD negativity, don't stop, try to do more. So that may be more treatment in the European countries, not very popular here in the United States, but maybe two transplants, and if not, other treatments after transplant. And I really hope that there's a very near future where someone's MRD positive and completes a transplant, say, we do transplant, we'll get a CAR T-cell therapy or a bispecific antibody. So, that's the high-risk myeloma.

And there may be some patients that maybe do not have as aggressive myeloma, more like a myeloma that is just kind of in the background, a little bit stubborn, like hibernating myeloma, if you may. And we might be able to tolerate low levels of residual disease. This is an analogy that Dr. High taught me. It's like if you're in your house and in the basement, you hear noises and you go down and it's a mouse, you just close the door

and call the company on Monday. But if you find a tiger, you have to deal with the tiger. That's how I think about the concept of high-risk disease.

Just to summarise and to be able to go back to our Q&A, our combination therapies result in higher and higher MRD negativity rates, with the best results we have right now with the MASTER clinical trial that I showed you from Dr. Costa. We can put up to 80% of patients in MRD negativity. When we do transplant, and with some of the historic regimens, that was about 30%. So, you can see there's a huge difference in how things have improved. Now, we need better tools. We've heard about this already from Dr. Derman. And our holy grail would be to do this through blood testing. But right now, the reality is the best way to measure this remains in the bone marrow. And I think more and more we're hoping that this will drive how we make decisions in the clinic and also how the regulators might allow for additional drug development.

Lastly, one term you're going to hear is this term of “sustained MRD negativity.” What that means is that multiple times you measure MRD and you're negative. And over time, obviously, this would be the way that we will define those patients who are cured from their multiple myeloma. There's a logic behind this that must be noted, and that is, it becomes a bit of a circular argument that if you have 20 years of sustained MRD negativity, one would say, “Yes, no surprise, that's what's happening.” But what we're learning is, if you have two and three years of sustained MRD negativity, then the risk of the disease coming back goes significantly lower. And that's why we're so excited. Whenever I get one of these MRD results, say that's on a Saturday afternoon, I will pick up the phone. I call patients that I would want to know, for instance, that they are MRD negative. So, with this, I'm going to finish and join Mary and Dr. Derman in our Q&A session. Thank you.

Mary DeRome (MMRF): Thank you so much, Dr. Fonseca.

Benjamin Derman, MD: If I can interrupt, I was reviewing some of these questions and there are some themes here that I thought would be worthwhile to bring up, if that's okay. I wanted to pose this first to Dr. Fonseca, because he's published on this as well. A lot of the questions are about “how do you define MRD negativity?”. What is the threshold that you think is negative versus positive? Can you talk a little bit about the nuances there, including the dreaded “less than 1 per million” result that is hard to make sense of?

Rafael Fonseca, MD: Thank you, Dr. Derman. That is a great question. We have put certain thresholds at which we have decided we're going to call patients as being negative. Currently, in clinical trials and for most regulatory development processes, people are thinking about 10^{-6} . If you test 100,000 cells, and you don't find a [myeloma] cell, you're negative at 10^{-5} . I firmly believe that was a first, important step, but we're going to move forward towards deeper. There's no reason why we shouldn't use 10^{-6} or, even more, 10^{-7} . I ask our radiology colleagues, “Is there any situation where you would say, ‘I would rather have a CT scanner of lower resolution?’” And the answer is no. We always want to have better resolution, more precision. So, currently available in the

clinic, and I should say standardized, FDA-approved, and covered by Medicare, we have the clonoSEQ assay that is 10^{-6} . That's what we were using routinely.

There's a great point to that question. We have some patients that have results that are very much borderline. This probably takes a long time to explain, but I'll try to do it succinctly. When they do the DNA sequence, they get a string of letters that represent the DNA sequence that is very specific for the myeloma cells. And sometimes that sequence is so unique that if you see it again, you can with great confidence it's 0, it's 1, or it's 2. That's what allows us to say it's negative or positive. The technical term for this is the level of detection. But sometimes the sequence is so similar to natural sequences that it's very hard to tell whether it's positive or not. And that's where we go through this "below level of detection" conversation. We have some patients for whom, we'll say, the range is 0 to 1, or it is less than 1, but it's not negative. It kind of is a funny conversation. But what it means is that there's enough uncertainty that we don't know with precision whether the patient is actually negative or not. No matter what, it's still a good conversation to have. Of course, I'd rather always have a 0. But if you do have one of those "below level of detection" results, if someone is listening to those results, that is very good.

Let me just finish off that question very quickly by saying I try to use an analogy to explain it, and I tell my patients: imagine you have binoculars, and you're looking out into the forest, and you're trying to look for owls standing on trees. If you have good binoculars, you can tell whether they're owls or leaves, and you can make a confident call. If you have dirty binoculars or poor-quality binoculars, you don't know if you have owls or trees. And that's sometimes what we find with this variation in the level of detection. But thank you. And just talk to your doctor about that.

Benjamin Derman, MD: There was also a question about the utility of PET scans. And again, I'll give my comments but also ask Dr. Fonseca his thoughts, because he's published on this very recently. In the newly diagnosed setting, which spans a very large amount of time for a lot of patients, because that's anything from starting therapy, through transplant and maintenance therapy, up until any second therapy, or sometimes they never get there, because they've had such good responses, the PET scan is typically not as informative. There are situations later down the line, and even in the newly diagnosed setting as well, in rare circumstances, where a PET scan may pick something up that the bone marrow doesn't, that a blood test doesn't. And that's usually that extramedullary disease that we talked about. And so, it is possible, but I typically think of it, especially in the early years with myeloma, that it has less utility than I previously thought it had.

Rafael Fonseca, MD: Yes. Thank you for the segue. And I agree. I think that you summarised it perfectly. It's possible, but it seems to be not very common. I honestly don't know if, going into the future, we should always be doing PET scans or not. The PET scans, just for our patients in the audience, sometimes they're hard to interpret. A radiologist might say, "Well, there may be some activity here or there," and we're looking at, sometimes, tracers that would have to be the size of about a grape. And so,

when you think about a grape, that's half an inch, so it can be hard to know if a PET scan is positive or not. There's a lot of equivocation in how you read that. When it's frankly positive, there's no question. But the equivocal ones can be pretty problematic. So, I anticipate that, going into the future, PET may not be as important. I think maybe the combination of sequencing and mass spectrometry, or something like that, will be able to satisfy most of our requirements.

Mary DeRome (MMRF): Thank you for those answering those questions. That's really great. I'm going to start off with a couple of questions from patients who are asking about the use of MRD, not in the context of an academic medical center and a very experienced myeloma doctor, which you both are. One patient mentions that the local hematologist-oncologist that the patient is seeing says that MRD is still advisory data, and that stringent complete response and fluorescence in situ hybridization (FISH) are what they are using for a diagnosis and strategy. And another patient talks about wondering how MRD test results are being used by the community oncologist in their treatment decisions. I know that, from looking at the National Comprehensive Cancer Network (NCCN) guidelines that I was going through the other day, the guidelines only mentioned when to measure MRD. They don't really mention what to do with the information. So, Dr. Fonseca, what is your opinion on that?

Rafael Fonseca, MD: Thank you. It's a very important question. When you think about the average community oncologists, incredibly committed and professional individuals, the body of knowledge of oncology has exploded. It's really hard to keep up with everything that's going on. It's just a fact. There's just where we are. I would tell that person that, in fact, we already have extensive data. We have the highest level of evidence from clinical trials and the compilation of those clinical trials, as the audience heard from Dr. Derman, that tell us how MRD performs. We can ask, "Okay, what are the settings? What are the questions you can bring forward?" We might disagree on that, but this is far from an experimental test. This is a test that is well validated. I would tell you a couple of things just to show how strongly I feel about this. I devoted the first half of my professional life developing FISH. We were one of the groups that led the development of FISH testing for myeloma. And if I had to choose between doing FISH and MRD, I would spend the money doing MRD, because of how important MRD is coming into play.

The second way I would answer this would be to say, no doctor nowadays would say, "Well, no, the free light chain [test] should only be used in academic centres." No. I'm grateful everyone uses it, and we know how important it is for monitoring myeloma. So, in a kind, proper way, I would push back a little bit. I would say, "I'm just hearing this is so important." Now, it may not apply to everyone. If you have a stage of your disease where there's still an M spike you can measure and all of that, then we don't want to do MRD. But if someone has a stringent complete response, I would really want to know where we are with regard to the MRD status. I don't know, Dr. Derman, if you want to add something to that.

Benjamin Derman, MD: Yes. I am an MRD enthusiast. I know that you are as well, Dr. Fonseca, but I think that both of us don't live in la-la land. We realize that there are a lot of opponents against using it right now in the clinic, because it hasn't been shown to affect decision-making, and why should you order a test if it's not going to affect decision-making? We actually investigated this. We did a survey of clinicians, both private-practice and academic clinicians, and in the first iteration of the survey, we just said, "Hey, are you using MRD to guide decision-making?" That was it; that was all we did. And I regret that we did it that way, because we found out that only about 37% of people said that they were using it. But then I got smart, and I did another survey, and I gave specific scenarios. For example, a patient's on maintenance therapy, they have high-risk disease, and they're MRD negative: what would you do? Now they have standard-risk disease and they're MRD negative: what would you do? And if they were MRD positive, what would you do? And we found something really interesting. About 80% of clinicians would change their response about what they would recommend to patients if they were high risk versus standard risk. And about 60% of the clinicians would change their decision-making based on the MRD result. And what it told me is that a lot of clinicians, if they had that information, they are subtly influenced by it in ways that they're not necessarily familiar with. I think it's important to highlight that, because it's a little bit like a Pandora's box; once that information is out there, it's really hard to ignore it. The other thing that I would say is this: sometimes when I see a patient after transplant or after an induction therapy, if they're not going to transplant, we do a bone marrow [biopsy] because they don't have any detectable disease by other conventional methods. We do the bone marrow biopsy. I don't always know exactly what to do with that result right then and there.

I'll be perfectly honest that I'm not always sure what to do in that scenario, whether they're MRD positive or negative, because they've in general had a very nice response overall. But what it does is it helps me set the trajectory. I start creating a story for this patient. A year later, if I do another bone marrow [biopsy], I get another result. And as Dr. Fonseca said, did that number go down? Did it go up? Did it go to 0? Or were they at 0 before and after? Now I start to create a story of, "Hey, we've really kicked this myeloma's butt." Or "Hey, we're losing ground. What do we need to do differently?" Or, "There's continued progress. Just stay the course. See what happens over time." And I think that is one of the most important elements of MRD testing that I don't think is widely appreciated, especially in the community, that you may not necessarily do something with that one result right now, but it's kind of like your savings. You have to add to the savings over time in order to see the benefit. One contribution is not going to make the difference. That's my feeling on it. I think it puts patients in a hard scenario, because you're not in a position to be able to tell the physician what to do. And if they feel strongly about it, that is their prerogative too. So, I think having a respectful conversation about it is extremely important.

The last thing I was going to say is that there was a recent survey that was published of patients who had MRD testing done, or some who did not to understand what their perspectives were on MRD testing. And it doesn't surprise you that patients who got

MRD negative results felt great, and patients who got MRD positive results had some negative psychological impact. And I am really mindful of that when I'm sharing results.

So, even if you do have MRD testing, I think it's extremely important to do it with a clinician that is able to put this all into context. If I do one MRD test and it shows 5 cells per million, but I don't give the context that it was 100 a year ago, what does that mean? It's totally different than if it was 0 a year ago. Giving context to these things is extremely important.

Rafael Fonseca, MD: Thank you. The other thing that patients, I think, should be reassured of is that, at least the way we practice medicine in the United States, it's just part of the conversation. I have patients who may become MRD negative and are unsure that they want to stop maintenance, and if they're doing well, we will continue. And there are patients for whom that information may be reassuring, and if they're thinking about stopping, that may be one more factor as to how they make the decision. The other part that I would add is that sometimes we doctors tend to say, "What am I going to do differently?" And in many ways, that's a very narrow way of looking at the world. Because what doctors really think is, "How am I going to prescribe something different or do something differently?" The keyword there is actionable. But do you know what's an action? An action is explaining this to a patient. And even if you didn't change anything [about] what you prescribe, if you can have a conversation with a patient and you say, "You're MRD negative, and by the way, it's the third year," that's a conversation that is going to have a very positive hue.

Mary DeRome (MMRF): Yes, that makes sense. Thank you. I know, Dr. Derman, you talked extensively about NGS and next-generation flow cytometry as the main ways that MRD is measured. Are these techniques covered under health insurance?

Benjamin Derman, MD: Let's talk about NGS. The clonoSEQ assay is FDA-cleared, and if it has a designation, then Medicare will pay for it. So, for patients who are on Medicare, it's widely covered. For patients who have private insurance, there can be fees associated that might be passed along to the patient. Typically, I know from working with the company [and] a lot of patients who have done it, there's a good amount of financial assistance that can be made available to patients. And the company works hard to make sure, from an insurance standpoint, that everything is done to try to get as much of that covered [as possible]. Flow cytometry, typically, is easier in terms of coverage, because it's kind of folded in with the rest of the bone marrow biopsy. The one we have most trouble with is a PET scan. I spend a lot of time on the phone with insurance companies about PET scans, and they've really clamped down in recent years. And actually, in Medicare, for the most part, there's a cap on lifetime PET scans as well. So, you have to be mindful of that too.

Mary DeRome (MMRF): Thank you. Let's talk a little bit about thresholds for MRD. A patient is asking, if they're MRD negative at 10^{-5} , is that considered to be truly MRD negative, or do you have to be MRD negative at 10^{-6} ? Could you expound a little bit on that, Dr. Fonseca?

Rafael Fonseca, MD: Sure. If you're negative at 10^{-5} , that means it's negative. The second question is, are you still negative at 10^{-6} ? It's just at the depth that you're testing. So, if someone is negative at 10^{-5} by a test they do, let's say flow cytometry, we would say you're negative. But my answer to that would be, I would rather know if you're negative at 10^{-6} , and I know Dr. Derman and others are working to say, "Can we do a 10^{-7} ?" At some point there's going to be a ceiling for that. But no matter what, if you're listening to this or you ask that question, if you're at 10^{-5} , that's still is a very good result. We want to finish the job, is the other thing I say. We have to finish the job, but still, if that's the information I have, I'm going to be gratified in seeing what I have, even if I cannot repeat the test.

Benjamin Derman, MD: That's excellent. I agree with everything there. When you talk about 10^{-5} , that is usually what's reported right now in the literature. And most of that is because it's sometimes hard, especially for patients who are on treatment, to get enough cells to be able to get to that 10^{-6} level. You could have done everything right, and still, you just didn't get enough cells from the bone marrow to be able to make a designation of 10^{-6} . But then there are people where, if you only have 2 cells per million, that is negative at 10^{-5} , it's less than 1 in 100,000, but it is more than 1 in a million. And so that's where you are 10^{-6} positive.

Remember that it's all on a spectrum. We can't exsanguinate you guys, okay, we can't just get a billion cells! So, there's going to be a limit. And so, you just have to realize that. And eventually we're going to get to a point where, sure, we could detect disease at a lower level, but does it actually impact outcomes? Are the outcomes any different? So far, 10^{-6} is a better prognosticator than 10^{-5} , which is a better prognosticator than 10^{-4} , which is a better prognosticator than conventional testing. So far, that's held true. Will it hold true beyond that? We don't know.

Mary DeRome (MMRF): I'm going to ask one quick question. If a patient achieves MRD negativity, but then converts back to MRD positivity after a couple of years, say, on maintenance therapy, and then if they either get an increase to their treatment level or if they go on to a different treatment, can they get back to MRD negativity if they respond well to either the change in the same medication or the change in medication altogether?

Rafael Fonseca, MD: Thank you, Mary. I think the second part of the question is easier. Yes, you can become MRD negative again. What to do is less clear. We still need to understand better how we react to re-emergence of MRD, and we're collecting the data for all of that. I don't think anyone has the right answers right now. But I'll give you an example. I had a patient of mine who I treated a few years back, and the patient experienced, unfortunately, a relapse shortly after transplant. And I thought, "This patient never saw daratumumab (Darzalex)," and he was in very good shape, a young individual, so we decided to start over again.

We involved daratumumab, and he went through a second transplant. After the first transplant, he was below the level of detection, and after the second one, now, he's sustained MRD at 10^{-6} . Was that the right behaviour? We don't know. But I thought, "Such a young and capable individual. [He could receive] more treatment," [so] we went for a second chance in that particular situation. So, the answer is, yes, it can be done, but there might be some patients that could be slowly, over many years, re-emerging, and there are some patterns that are starting to be described, whether it's fast or slower, but we have very little information still.

Benjamin Derman, MD: Yes. I think looking at log-fold increases, as we say, if you add a zero to the end of it, in terms of the amount of cells per million, in between results, that's typically not a great sign. I think you're typically going to see the disease progress within a short period of time, and there are already some preliminary data that show that.

Mary DeRome (MMRF): Okay, great. So that is all the time that we have today for questions. I would like to take this opportunity to thank our amazing faculty, Dr. Benjamin Derman and Dr. Rafael Fonseca for their time and their contributions to this presentation.