FAQs on Understanding Your Labs

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Transcript

**Mary DeRome (MMRF):** Welcome and thank you for joining us for today’s session of Frequently Asked Questions on Understanding Your Labs. I’m Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation. Today, I am joined by Dr. Hans Lee and nurse practitioner Becca Lu from MD Anderson Cancer Center in Houston, Texas and Lauren Eaves, who is a myeloma patient living in Houston, Texas.

Patients and caregivers have a lot of questions about all of the lab tests that are used in the diagnosis and management of multiple myeloma, so let’s take a stab at answering some of these questions with our panel today. Myeloma patients will be familiar with having bone marrow biopsies but may not be familiar with what doctors can learn from them. So, my first question is to you, Dr. Lee. Among the various cytogenetic and genomic analyses that are done on a patient’s myeloma DNA, for example, fluorescence in situ hybridization, or FISH, karyotyping, and genomic sequencing, what is important for patients to know and how do they put the results from this testing into context?

**Hans Lee, MD:** Thanks so much, Mary, for the invitation to join on this chat, and I thank all the patients who are joining live on this livestream as well. You bring up some really, really important questions about why the bone marrow biopsy is important to perform at baseline, besides just showing that there are myeloma cells. Basically, what’s really important for the bone marrow biopsy, in addition to showing myeloma cells, is to perform certain genetic testing known as FISH, as you referred to earlier. Essentially, what the FISH testing does is to look for certain common genetic abnormalities that might be present in patients’ myeloma cells. This can be important for informing prognosis, but also, in some cases, can help dictate which treatment approaches we may take.

To get a little more specific, there are certain chromosome abnormalities that we would consider high risk. High-risk myeloma refers to myeloma that responds fairly well to therapy but has a higher chance of coming back earlier, or having an earlier recurrence; essentially, it’s a more aggressive type of myeloma. There are certain genetic abnormalities, such as something called deletion of 17p, which is loss of part of your chromosome number 17 on your myeloma cells. Sometimes there’s extra material on chromosome number 1. Sometimes there’s extra material on chromosome number 1. Sometimes there’s what we call translocation, an exchange of material between different chromosomes, sometimes between chromosomes number 4 and number 14, which is written as (4;14), and translocation (14;16). These are considered more aggressive or high-risk myeloma markers. That would help inform, on one hand, prognosis, but on
another hand, we may also approach treatment a little more aggressively in such patients, maybe do a more aggressive maintenance regimen.

The other thing that’s really important to establish in the bone marrow is certain mutations that can inform which treatments might work better. There’s a drug called venetoclax (Venclexta) that’s an oral pill. And we’ve learned over the last several years that there are certain translocations, translocation (11;14) specifically, that predict response to this oral pill. So, it’s nice to know at baseline, up front, whether you might be a candidate for some additional therapies such as venetoclax later on. It’s not something we really use in the beginning, but later on, it’s good to know.

Mary DeRome (MMRF): Lauren, since your myeloma diagnosis, when did you learn that you had a 1q amplification, and how did you come to understand what that means?

Lauren Eaves: I had a FISH analysis done at diagnosis as part of my bone marrow labs, and my initial diagnosis was done by a general practitioner, and he didn’t really have the specialist information to provide a lot of explanation. I just read the lab report that came to me, and it came with the notification that there was a 1q amplification and a note that said it’s an indicator of poor prognosis, which of course piqued my interest, and so it was a lot of self-education. I got on the internet and started digging, and I’ll use this opportunity to plug MMRF and HealthTree for the tremendous amount of resources that are available. So much that I’ve done has been self-taught. The nurse navigators, the peer program, there’s so much. It’s a remarkable amount of time and energy that the community puts into these knowledge transfers. If you’re like me, and you didn’t have that immediate access to a myeloma specialist, there’s a tremendous amount of information out there. When I had the meaningful conversations about the 1q amplification, there were two decision points. One was for a transplant decision, which I was dead set against, and ultimately ended up doing very reluctantly, but that’s when the 1q amplification/high-risk discussion came in. And then for maintenance as well and determining what kind of therapy would be the best fit for the high-risk marker.

Mary DeRome (MMRF): Yes. That makes perfect sense. It’s becoming more and more apparent as more research is done that there are risk-adapted therapies that can be successfully used for patients who are high risk, which is really great. About 25% of myeloma patients fall into that high-risk category, so it’s important to make sure that those patients are diagnosed as high risk as soon as possible when they’re diagnosed with myeloma so that this risk-adapted therapy can be brought into play with their care plans. Dr. Lee, which, if any, of the cytogenetic or genomic results can change over time, and how often does this DNA testing have to be repeated?
**Hans Lee, MD:** As you mentioned, Mary, it’s critical to get a baseline, so I just put the plug in that patients being newly diagnosed with myeloma, if you haven’t had the FISH testing at baseline, make sure that your doctor orders it as part of the bone marrow biopsy. Certainly, that would be a reason for me to repeat the bone marrow at baseline if it wasn’t done, because it’s really, really, critically important, but you make a great point, Mary, that genetics can change over time. The myeloma cells can adapt and evolve, depending on different treatments that they receive, and the treatments can make the myeloma cells more resistant to certain treatments. The scientific or medical word we use is clonal evolution. These cells can evolve. In terms of when I repeat a bone marrow biopsy, initially, I do repeat it a little bit more frequently just to assess response. After the initial, induction therapy, which is the three- or four-drug regimen that you will probably receive at initial diagnosis, I will probably repeat the bone marrow biopsy after four to six cycles before potentially going forward with the transplant, and then also after the transplant itself to assess response as well. But beyond that, I think it’s important to repeat a bone marrow biopsy at the time of every relapse, potentially, because that’s may inform your provider of further changes in the genetics that might explain if the myeloma has evolved, and there can be changes.

Broadly speaking, there are two types of genetic changes. We call these, on the one hand, primary genetic events. These are what caused the myeloma cells to convert from a normal plasma cell to a myeloma cell at baseline. These are commonly translocations involving chromosome number 4, essentially exchanging the material between chromosome 14 and other chromosomes. For instance, if a patient had translocation (11;14) at baseline, we expect that to show up later on, because that’s what we call a primary genetic event. But there are other events, such deletion of 17p or changes in chromosome number 1, that can make the myeloma more aggressive. Those changes can occur over time, and it is nice to know if those changes are present, because that can also inform prognosis, how that myeloma might behave, how it might respond to therapy with every subsequent potential relapse.

**Mary DeRome (MMRF):** Becca, what are some issues that patients may face when they’re having a bone marrow biopsy? Is it possible that you might not receive sufficient information from the testing results, or there might be a lack of appropriate cells to test after the biopsy is done?

**Becca Lu, MSN, RN, FNP-BC:** Thanks so much, Mary. We all know that bone marrow biopsies are not the most comfortable procedures. The patients will need to lie on their stomach, prone, while the proceduralist obtains samples with an aspiration needle from one side of the patient’s hip. Because this procedure can cause bleeding, and many of our patients have low platelet counts at baseline, it’s very important that the patients consult with their provider on the time frame to hold any anticoagulants, if they are on any.
First, the area of the hip is numbed with lidocaine before the proceduralist enters with the aspiration needle to draw that liquid sample. Sometimes a dry tap can occur, and this means that the proceduralist has inserted the needle and failed to obtain enough of that sample. This can interfere with diagnostic evaluation, and this can happen in myeloma, which is a pathologic condition, especially if the marrow is very packed with malignant cells. This may necessitate redirecting that needle: the proceduralist may need to go in at a different angle. They may need to withdraw the needle completely and reinsert it, which is obviously not the most comfortable thing. After redirection, the proceduralist may still be unable to aspirate enough good-quality sample. They do their best, but the sample does not yield sufficient cells. This is usually indicated in the pathology report, and so the clinician would need to interpret accordingly.

Mary DeRome (MMRF): It’s interesting, because you do hear different reactions to bone marrow biopsies, bone marrow aspirations, from different patients. We did one of these livestreams last week, and the gentleman who was a patient who was on that call described it. To him, it was kind of like nothing. It was like getting stung by a bee. That’s how he described it, so I guess it’s different for everybody, right?

Becca Lu, MSN, RN, FNP-BC: For sure.

Mary DeRome (MMRF): Dr. Lee, what about patients with precursor conditions? Should someone with smoldering myeloma or monoclonal gammopathy of undetermined significance (MGUS) have a bone marrow biopsy?

Hans Lee, MD: Another great question. I would say that any patient with suspected smoldering myeloma should get a bone marrow biopsy, because we want to quantify the percentage of plasma cells in the bone marrow. As people may know, there are criteria that define smoldering myeloma versus myeloma: 10% to 60% plasma cells in the bone marrow would be in the smoldering myeloma range, whereas greater than 60% would be in the myeloma range, and less than 10% would be in the MGUS range. So, it would be good for informing prognosis, follow-up intervals, and things like that, to get that concrete diagnosis.

Now, MGUS is a little more of a gray area, to be quite honest. MGUS is the earliest precursor state to myeloma. These are patients with an M protein level of less than 3 g/dL, plasma cells of less than 10% in the bone marrow, and the absence of any myeloma symptoms (bone disease, kidney problems, calcium issues, and anemia). There have been some studies looking at this. If a patient, for instance, has an M protein level of less than 1.5 g/dL with a normal free light chain ratio and an immunoglobulin G (IgG)-type M protein, the risk of actually having more than 10% plasma cells in the bone marrow is fairly low, about 5%. If the M protein is less than 0.5 g/dL, the risk of having more than 10% plasma cells in the bone marrow is even lower, less than 1%. I’d probably err on the side of being more conservative in my own practice. If the M protein is more than 0.5.
g/dL, I would probably still get a bone marrow biopsy. I’d probably quiz the patient on symptoms and probably be hyper vigilant. If they have a little bit of bone pain, I would really want to make sure that we’re not missing anything as it relates to myeloma. But I think in patients with M protein levels of less than 0.5 g/dL, a normal free light chain ratio, and having no symptoms whatsoever, I may omit the bone marrow biopsy in that case because the yield would be fairly low and the probability of having more than 10% bone marrow plasma would be fairly low. It’s important to talk to your doctor about that, because every case is individualized, so you can’t really put everyone in one box versus another box. One size doesn’t fit all. But it’s important to talk to your doctor about the pros and cons about doing a bone marrow biopsy, for instance, in the MGUS state.

Mary DeRome (MMRF): Right, and if a person is smoldering, then by having the bone marrow biopsy done you can actually find myeloma cells there and then do some of the DNA analysis, which might then determine that a person is actually high risk, smoldering, which would also mean that they might be eligible for certain treatments that are available on clinical trials for high-risk, smoldering patients, which is another thing that would be useful.

Hans Lee, MD: Yes, absolutely, Mary. That’s a great point you make. The same high-risk genetic markers in myeloma often really apply to smoldering myeloma as well, with a greater risk for progression. So, things like deletion 17p is a high-risk marker for either smoldering myeloma or myeloma. And it’s a great point you make, to also do the FISH testing that we talked about earlier.

Mary DeRome (MMRF): Right. We’ll talk a little bit now about minimal residual disease, or MRD, and this is being used more and more to assess treatment response in clinical trials. Dr. Lee, are there certain mutations or abnormalities that make it harder to achieve MRD negativity? I know that you were talking earlier about how important it is to get that bone marrow sample when patients are diagnosed, and that’s really an important part of MRD determination, especially if you’re using next-generation sequencing techniques, right?

Hans Lee, MD: MRD testing is a way we can look really deep into the bone marrow to look for those residual myeloma cells, and the minimum standard is to look for one abnormal myeloma cell out of 100,000 normal bone marrow cells. That’s what we call $10^{-5}$ sensitivity. I think this was probably best studied by Dr. Costa at UAB. He recently published a study called the MASTER study, and it looked at serial MRD testing in patients that received state-of-the-art induction therapy and transplant followed by additional treatment cycles. He looked at MRD rates in high-risk and standard-risk patients. Some of the take-home messages from that study did show truly comparable MRD negativity rates in standard-risk myeloma patients and high-risk myeloma patients. But what was different was what we call sustained MRD negativity. I think this really correlates to what I see in my own practice: patients with high-risk myeloma can attain MRD negativity at a single time point. But I am a little bit cautious about reading too
much into that, because what makes high risk difficult is that the myeloma can relapse or recur fairly quickly, and this is consistent with what Dr. Costa saw in his study, that the rates of what we call sustained MRD negativity (two MRD negative time points, 12 months apart) was far less in patients with two or more high-risk cytogenetic abnormalities, versus patients with zero or one cytogenetic abnormality. I think attaining sustained MRD negativity is harder in high-risk multiple myeloma. I think what was also interesting about that study was that in patients with zero or one high-risk cytogenic abnormality, the outcomes were fairly similar, and I think this is a testament to where myeloma therapy has come. Whereas, historically speaking, 15 years ago, having one high-risk cytogenic abnormality would be, obviously, an adverse prognostic marker, but because we have new treatments and novel therapies, I think these treatments are producing outcomes for some patients who have a single high-risk abnormality that are similar to those with standard-risk disease.

Mary DeRome (MMRF): Yes. There’s been so much progress made, especially recently. If anybody listening is interested in hearing more about MRD from Dr. Costa, we did one of these sessions on Facebook Live with him last week about MRD. It was Dr. Costa and also his nurse practitioner and his patient, the one who thought that the bone marrow biopsy was like a bee sting. That was a great session. We have that on our website, and anybody who wants to can listen to that recording.

Lauren, let’s talk about your MRD testing. How did you educate yourself about MRD, and what would you tell other myeloma patients about MRD based on your experience?

Lauren Eaves: Although I had a bone marrow biopsy done at diagnosis, my MRD test wasn’t run until many months later, and I educated myself about MRD in a similar way with other things before I had a specialist, just doing a lot of internet research. And by the time I really came to know about MRD and pay attention to it, I was under a specialist’s care. Of course then I said, “I need to have this MRD testing.” What I would tell people is if you didn’t get MRD at baseline for the next-generation sequencing, don’t panic. The $10^{-5}$ is still a really good indicator of residual disease. I’m kind of obsessed with my MRD. I think myeloma patients probably are. You want to know that that clone is going away. You just want it gone. And the MRD is the best indicator of that, so I started chasing my bone marrow slides, which were in South Africa, and I was able to get them. From the Adaptive Biotechnologies website, they have a really great one-page description of what they need. I contacted the lab and was able to get the slides shipped from Johannesburg to Seattle. So, if you did get that bone marrow biopsy done, there is a chance that the genetic material is still stored somewhere, and can still be analyzed for MRD, if it wasn’t done initially. I would also say, keep an eye on the science. What I was reading about MRD a year ago and what I’m reading now, there’s so much more available.
Mary DeRome (MMRF): Absolutely.

**Lauren Eaves:** It’s really an emerging field, and it’s clearly an important data point in our myeloma labs. How best to use the information is going to evolve. I’m one of those people who gets multiple opinions, and when I had my opinions and asked about MRD, I got three different answers. Be careful what you ask for, in that sense. I think it’s pretty amazing what’s happening with it, and we’ll see over time what it means for us.

Mary DeRome (MMRF): Yes. It’s a little dicey, because there really aren’t a lot of guidelines yet published on what to do with the information, but certainly it’s a good way to tell how well patients have responded to, especially, their induction therapy, whether they’re having a transplant or not. So, it’s great for that, and there’s a lot of research being done on MRD in many, many clinical trials, including the MASTER trial, which Dr. Lee was talking about. I think that the more data we collect from patients using MRD testing, the easier it’s going to be to formulate these guidelines. I think it’s also really interesting that when we first started talking about MRD, it was always testing that was 1 cell in 10,000 ($10^{-4}$) or 1 cell in 100,000 ($10^{-5}$). Now it’s moved onto 1 cell in 1 million ($10^{-6}$) or even 1 cell in 10 million, because they’re now talking about $10^{-7}$. The testing is becoming more sensitive all the time, which is great news for our patients.

Let’s move on now to blood tests. These are a staple of multiple myeloma management, and there’s a lot that doctors can learn from them. Dr. Lee, what do patients need to know about serum free light chains? What are they? How do they impact treatment, and how do you interpret changes in those levels?

**Hans Lee, MD:** Broadly speaking, myeloma cells secrete antibodies, or the monoclonal protein (M protein). They secrete them into the blood, and this is how we track how patients are responding to therapy. If the levels are lower, we know that we’re successfully killing myeloma cells, and the patients are responding to therapy.

Broadly speaking, these immunoglobulins have two components. One is called the heavy chain, and one is called the light chain. The heavy chain can consist of, most commonly, IgG, but sometimes IgA, IgM, or IgD. The light chain component can either be a kappa ($\kappa$) or a lambda ($\lambda$) light chain. Sometimes the myeloma cells produce both light chains. Sometimes they produce one or the other. Sometimes they just produce the light chain. In someone without multiple myeloma, you should have an equal number of kappa-producing plasma cells and lambda-producing plasma cells. So, what we really look at is the ratio when someone is diagnosed with myeloma. In a patient without myeloma or in someone that’s responding well to therapy we see a normal kappa/lambda chain ratio. For the myeloma patient who is responding to therapy, essentially, that indicates that you’ve decreased the number of myeloma cells that are producing the kappa or lambda light chain that results in the abnormal ratio. It’s the ratio
that’s most important. To give you an example, if I had a recent infection, or if I’ve had some other cause of inflammation going on in my body, both my kappas and lambdas would probably be elevated if I got bloodwork, but the ratio would still be normal, because this is just a general increase in the immune system activity. But when we see skewing of the ratio, then we know that one type of plasma cell has started to grow more uncontrollably. I think it’s also important to look at the big picture. The ratio’s often dictated by the denominator, so we say, “kappa-to-lambda ratios.” For whatever reason, if the lambda is really low at a single time point, that can skew the ratio. If the kappa was 20 mg/L, for instance, and the lambda went from 4 to 2 mg/L, that would actually double the ratio. So, look at the big picture, because it’s not a reason to panic that the ratio doubled based on the decrease in the lambda light chain. If I really wanted to give general guidance, it’s that it’s really, really important to look at trends. One thing that I try not to do, and I tell patients this as well, is, don’t look at a single time point to dictate a treatment decision.

Certainly, if the ratio went up really high from one point to another, that would be concerning, but if there’s a subtle change from one time point to another, that’s not super informative. Is this a clear trend up? Then that’s a reason for concern. But sometimes it can bounce around, particularly the light chain ratio can bounce around a little, and so really look at the trends and not necessarily a single time point.

Mary DeRome (MMRF): Yes. That makes sense. Becca, let’s talk a little bit about the comprehensive metabolic panel, or CMP, and what in that panel is important for a myeloma patient to know, and why?

Becca Lu, MSN, RN, FNP-BC: Thanks, Mary. A CMP is going to look at the patient’s electrolytes, kidney function, and liver function tests, and we’ll use the CMP to assess part of the myeloma-defining criteria or CRAB criteria [CRAB is an acronym for the following group of clinical indicators of organ damage: increased calcium level, renal (kidney) failure, anemia, bone lesions; the presence of one or more of these indicators can help establish a diagnosis of multiple myeloma]. When reviewing the CMP, we want to look at the creatinine, which would tell us if the disease is impairing the kidneys or not. We’d also want to look at the calcium levels to make sure they’re normal. Bone is made of calcium, and we know that myeloma causes bone destruction, so when bone is getting broken down, that calcium is being released into the bloodstream. High levels of calcium in the bloodstream can cause many different issues, like neurological issues and cardiovascular issues. It can cause renal failure (kidney failure). So, we want to make sure that it’s okay, but the calcium level that we see on the CMP is not a true level, so the provider would need to correct this level with albumin. Albumin is a larger protein molecule in our blood that binds with calcium. We have a formula that we use to get that corrected calcium level. If the calcium levels are still high, this would warrant immediate intervention, which may include fluid hydration, calcitonin administration, or correction of that calcium
with bisphosphonate therapy, like zoledronic acid injection (Zometa) or any combination of that three.

Mary DeRome (MMRF): Okay, another common test that patients wonder about is the serum protein electrophoresis, or the SPEP. Dr. Lee, what’s the meaning of the various components of the SPEP results, and how should patients interpret those changes?

Hans Lee, MD: As I mentioned earlier, there are different components of that immunoglobulin, the heavy chain and the light chain, and the SPEP measures the amount of the paraprotein or M protein that the myeloma cells are producing. As an overview of what the test actually is, your blood is added to a gel, and an electric current is run through the gel (electrophoresis). The different proteins in your blood will separate based on their size and charge. Different proteins in the blood have different charges, and in a patient with multiple myeloma, we’ll see a separation of the monoclonal protein in a certain part of the electrophoresis gel. That part can be quantified, and that’s known as the M spike or the M protein, and the size of that spike quantifies what the M spike number is. That’s what the SPEP measures, the amount of the paraprotein being produced by the myeloma cells. There’s another method called immunofixation. Immunofixation is not necessarily the SPEP, but it’s a “reflex” test, or a test done along with the SPEP, and it tells us the isotype, which is the type of monoclonal protein that’s being produced by the myeloma cells. As I mentioned, it sometimes will give you IgG. Sometimes it’ll be IgA or IgD. Sometimes it’ll be kappa or lambda light chains. The immunofixation, either from the urine or in the blood (serum), can tell us the types. So, SPEP quantifies the amount of M protein. Immunofixation tells us the isotype.

Mary DeRome (MMRF): Does that play any role in what therapy the patient might get at some point, or is it just one of these good-to-know things?

Hans Lee, MD: It’s more of a thing that is good to know. Once you know the isotype, then you know the markers to track, whether that be IgA, IgG, kappa or lambda ratio, et cetera, and then we know what to follow. But really, at this point, it doesn’t really have any implication on prognosis or what types of drugs we would use either for a kappa/lambda myeloma or an IgG or IgA myeloma.

One thing I will mention is that IgA-type myelomas are a little harder to detect or quantify using SPEP, and so quantitative IgA levels are probably a more accurate method for assessing response in patients with IgA myeloma. That’s one little caveat with the SPEP, that in patients with IgA, myeloma you may actually follow the IgA levels as more of an accurate assessment or response.

Mary DeRome (MMRF): How common is IgM myeloma?

Hans Lee, MD: It’s exceedingly rare. It’s pretty rare.
Mary DeRome (MMRF): That’s what I thought. You rarely hear people talking about that very much. The IgM is so different from the other immunoglobulins, a much bigger structure.

Hans Lee, MD: I probably have fewer than five in my practice, and I have probably over 1,000 patients in my own personal practice with myeloma. It’s very rare, and IgM plasma cell disorders are often a different disease, called Waldenström macroglobulinemia. True IgM myeloma is very, very rare.

Mary DeRome (MMRF): Okay. Thank you. See, I’m getting the education right now. That’s good. Becca, are these results interpreted the same regardless of the myeloma immunoglobulin isotype a patient has, for example, IgG or IgA, and how common is it for a patient to have IgD myeloma? When we did our webinar about Learn Your Labs a few months ago, there was a patient who was writing into our comments that they had IgD myeloma.

Becca Lu, MSN, RN, FNP-BC: The way we review the SPEP can change depending on the immunoglobulin isotype. As Dr. Lee mentioned, the SPEP quantifies that monoclonal protein, or the M protein, that’s present, and we want that number to decrease, and that gives us an idea if the patient’s responding to treatment. However, because immunoglobulin structures are different, it can change the way the SPEP is resulted. For instance, the IgA isotype is a two-prong structure, whereas the IgG is a single-prong structure, and because of this, the SPEP for the IgA shows as different bands on the electrophoresis. Patients may see this on their lab reports: paraprotein 1, et cetera. In these circumstances, we look at the immunofixation to ensure that all the bands on the electrophoresis are IgA isotypes, and if so, you can add them together, because it’s like adding apples to apples, to review the patient’s response to treatment. However, if the immunofixation says that the bands are different, meaning paraprotein one is IgG and paraprotein 2 is IgA, we wouldn’t add those together. It’d be like comparing apples to oranges. Those responses would need to be made separately. IgD myeloma is quite rare and has a prevalence of less than 2% of all myeloma cases, and because of this, the diagnosis might be delayed due to that lower prevalence, but we would monitor the electrophoresis and treat the patient in the same manner as other isotypes.

Mary DeRome (MMRF): Okay, let’s talk a little bit now about imaging. Dr. Lee, what’s the recommended time for a PET scan to be done, and what can a PET scan tell you?

Hans Lee, MD: Imaging has really evolved in myeloma over the last ten years or so. We used to often do plain films or x-rays of the bones, something called the bone surveys, but that’s really fallen out of favor because the sensitivity for actually detecting myeloma lesions is actually not very great with x-rays compared to more advanced imaging like PET scans and MRIs. And so it’s
important to get advanced imaging, either a PET scan or MRI, on any smoldering myeloma patient, because we would really want to establish that there are no bone lesions and, truly, the patient has smoldering myeloma, and observation would be the standard of care for most patients.

On the other hand, if a patient is newly diagnosed with myeloma, even if they have other CRAB criteria (the symptoms of myeloma, eg, if they have anemia or renal [kidney] disease), it’s still very important to get a baseline PET/CT scan, because it’s really important to establish what’s present or absent at baseline. Because in the future, if you want to know what’s new or not new, if you don’t have a good baseline, then you won’t know. A PET scan’s really good for looking for small changes in the bone so it can establish where the bone lesions are. Another thing that a PET scan is helpful for is to look for something called extramedullary disease. This is where the myeloma cells escape from the bone marrow and sometimes form tumors outside the bone marrow, either next to the bone, what we call paramedullary, or true extraosseous, extramedullary disease, which are essentially soft tissue tumors in different organs. So, it’s good to establish at baseline if these are present or absent. Something that we do see later on, in patients who may have had multiple different treatment options or regimens in the past, is that the incidence of what we call extramedullary disease does increase, and so a PET scan can be informative to track these areas that need to shrink, hopefully, with different treatments.

Mary DeRome (MMRF): And isn’t the PET/CT scan now seen as part of the MRD family of tests? So, it’s one thing to take a bone marrow sample and then count the number of myeloma cells that might be in there, but you also have to have a PET/CT scan there, in addition, to really certify somebody as being MRD negative. Because they may have just put the needle into a part in the bone where there really aren’t any myeloma cells, and they could have extramedullary disease or myeloma cells growing in a different bone, in a different place.

Hans Lee, MD: Yes, you bring up a great point, Mary, and that’s the main limitation with bone marrow MRD tests, that there is the potential of a sampling error. If you happen to hit the patch of myeloma cells, your results might be MRD positive. Or if you did not hit that patch, you’re results will indicate you are MRD negative. I think it’s really important to look at all the tests: blood markers, imaging, bone marrow, and then have a collective assessment of what’s really going on. For instance, on a clinical trial, if a patient had baseline extramedullary disease (soft tissue tumors outside the bone marrow), yes, absolutely, we would need to do a repeat PET scan to confirm response, and if we see a 50% reduction, that would be a partial response. And we need complete resolution of these soft tissue tumors, via imaging, to confirm a complete response. It’s mandatory in the clinical trial setting.

Mary DeRome (MMRF): Becca, some of the patients from our previous webinar on labs were wondering if PET scans can be used to reflect the success or
failure of treatment, and if so, how long after therapy are PET scans done? We just heard Dr. Lee talk about measuring extramedullary disease with PET scans and how important that is.

**Becca Lu, MSN, RN, FNP-BC:** As Dr. Lee mentioned, if the patient’s myeloma manifests as extramedullary disease, then those PET scans are essential in determining the response of treatment, because they are more specific than other imaging modalities. If there is a target lesion at baseline, we will look for that reduction in size to be able to stage response. The current recommendation is to obtain PET/CT scans after three months or after every three to four cycles of treatment, and this is also because most insurances wouldn’t pay for the PET scan to happen sooner. There’s also a deficiency of data to support changing treatments based on earlier imaging. Thereafter, the patients can resume treatment pretty quickly. It would just take the time for the radiologist to report the images and the physician to determine if this treatment is sufficient before making the determination to proceed with the current regimen or to change it.

**Mary DeRome (MMRF):** Dr. Lee, aside from bone marrow biopsies, blood tests, and imaging, what other testing should patients be having, and how much longer will patients have to endure a bone marrow biopsy, and what’s on the horizon for that testing? I know that people talk a lot about mass spectrometry, which is a blood test and is extremely sensitive, but is not available in many places yet, so that’s kind of on the horizon.

**Hans Lee, MD:** Yes. I think that it would be great to do away with the bone marrow biopsies. As Becca mentioned earlier, it’s uncomfortable for patients. I think patients online can definitely relate to that. Lauren can probably relate to that as well. There’s definitely a lot of research going on, looking for other peripheral blood–based MRD testing. One type of test that’s being looked at is cell-free or circulating tumor DNA, essentially looking at DNA that’s shed by the myeloma cells into the blood, and trying to see if there’s absence or presence of the circulating tumor DNA that’s the signature of the myeloma cells.

By and large, this is probably not ready for prime time in terms of being on par with bone marrow MRD testing. Most studies have shown probably a one-log decrease in sensitivity, so, instead of $10^{-5}$ sensitivity that may be seen with bone marrow-based testing, probably $10^{-4}$ sensitivity with these blood-based markers. But, if successful, what would be nice about these blood-based markers is that it would eliminate that sampling error that we talked about earlier, potentially missing the spot, because the blood is circulating all over your body, so it’s representative of what’s going on in your entire body, not just a single spot in your hip. Another test that’s evolving, as you mentioned, is mass spectrometry. This is a different, chemistry technique to identify proteins that are separated by their mass-to-charge ratio, and there are certain specialized centers offering the test. The Mayo Clinic, for instance, offers mass spectrometry. This has better sensitivity detecting very small monoclonal proteins beyond what the SPEP can
detect. There have been some early data. For instance, Dr. Ben Derman did a nice study at the University of Chicago showing that MRD results determined by mass spectrometry on peripheral blood are pretty similar to MRD results determined by next-generation sequencing results found from sampling the bone marrow, which is encouraging. I think we need more data with this. There needs to be more consensus on how we would evaluate MRD using mass spectrometry, but this is a blood-based test and could be widely available in the future. I think that’s something that could be used as an adjunct to bone marrow MRD testing, imaging, and all the other testing that we already discussed.

Mary DeRome (MMRF): Yes. We had our webinar on MRD a few weeks ago, and we had Dr. Derman on that webinar, and he talked a lot about mass spectrometry, and Dr. Rafael Fonseca was also there. The two proponents of MRD testing, and they talked a lot about those things. Again, if anybody’s interested in learning more about that, we have a recording of that on our website as well.

Hans Lee, MD: I want to mention one additional point. The nice thing about mass spectrometry is that it’s able to distinguish between your therapeutic monoclonal protein and your disease-related monoclonal proteins, so as people may know, if they are on daratumumab (Darzalex), or elotuzumab (Empliciti), or any monoclonal antibody, that protein will actually show, at a very low level, on your SPEP, but mass spectrometry will be able to distinguish between your monoclonal protein that you’re receiving for treatment versus your own myeloma disease–related monoclonal protein.

Mary DeRome (MMRF): Lauren, how often are you having these various tests like blood draws, bone marrow biopsy, and imaging, and what is it that you look for in these tests when you’re discussing the results with your doctor?

Lauren Eaves: I get monthly bloodwork now, and I’m always looking at my panel. I want to know what my lymphocytes and my white blood cells and my neutrophils are doing so I can see how my immune system is, the status of what’s going on, and of course, the M spike, hoping that it’s not going anywhere, and the light chains. Those are the main things that I look for, and in MyChart, it’s really easy. You can see if something’s out of the normal range.

And if there’s something that’s popped out of normal, though some things are consistently out of normal these days, but if there’s something new that I want to talk to the doctor about, then that’s a good way to quickly get a look at things. Then there’s the annual imaging, the PET scan, CT, or the MRI. For me, I don’t do well in the MRI tube, so I personally would hope for the PET/CT. That’s just my personal preference. And then the annual bone marrow biopsy. I am one of those people who doesn’t mind so much the bone marrow biopsy. I wouldn’t call it a bee sting. That might be a little bit extreme for me, but something in between maybe. So, with me and my MRD obsession, I would do it more often, but my
doctor has told me, as we discussed, that it is just a needle in one spot, and there’s a lot more to it, so I need to try to change my thinking about it a little bit. I will make a comment about the x-ray. It’s interesting that here, x-ray is considered almost like the dark ages now, and my initial diagnosis was off an x-ray for a broken collarbone, and the orthopedic doctor knew instantly what it was from looking at the x-ray.

Mary DeRome (MMRF): Really?

Lauren Eaves: Yes.

Mary DeRome (MMRF): He just saw a lot of lesions there?

Lauren Eaves: It was just one giant lesion.

Mary DeRome (MMRF): Just one giant lesion? Wow.

Lauren Eaves: I had five broken ribs, so there was plenty for him to view.

Mary DeRome (MMRF): Wow.

Lauren Eaves: And then there was the other that said, “No, that’s not good enough. We don’t believe him. You have to go and get all these other tests.” And it was pretty definitive after all of that.

Mary DeRome (MMRF): You hear many stories from patients who go for months of testing, and diagnosis just eludes them for a long, long time. In the meantime, their myeloma is growing, and they’re getting organ damage, and it can be really serious when people have delayed diagnosis like that. So, I always like to hear the stories where people are diagnosed right away. That’s good.

Lauren Eaves: Well, I had an annual physical about ten months before that all happened, and I went back and looked at those labs, and those early indicators were showing. They were just out of range.

Mary DeRome (MMRF): Really? They were there, but nobody saw it.

Lauren Eaves: And it was kind of like, “Oh, we’ll watch and wait,” or there was just no reaction to it, and that’s really unfortunate, because I could have caught it much earlier.

Mary DeRome (MMRF): Yes.

Lauren Eaves: Hindsight.
Mary DeRome (MMRF): Yes. It’s a very common story though. Myeloma is just not that common of a cancer, and it’s not always top of mind when patients go to the doctor and say, “I’ve got this pain in my back,” or whatever, and the doctors say, “Well, you probably strained a muscle. Here, take this muscle relaxer.” Diagnosis is just not easy with this disease, because there are many symptoms that could be symptomatic of other problems, so it can be hard to diagnose, especially if you’re going to someone who’s not a specialist and doesn’t really know anything about myeloma.

Lauren Eaves: Especially for younger patients. I mean, all the pain, I had just turned 50. I thought I was just getting old. I thought, “God. This is 50. What’s going to happen at 60?”

Mary DeRome (MMRF): I know, right? Becca, is there anything you tell patients about preparing for things like blood tests, bone marrow biopsy, or imaging, and what should they anticipate with this testing?

Becca Lu, MSN, RN, FNP-BC: I think one of the most important things that patients might forget is collecting the 24-hour urine collection. We typically want a 24-hour urine collection after each cycle of therapy because it helps us to determine the level of Bence-Jones protein in the urine. This is a big imposition for the patients, because many times they have to have these urine jugs in advance, and it makes it very difficult to collect urine if you're out and about.

So, I would tell patients to just grab a few extra jugs after their clinic appointment, just in case they forget the next time. And they should really discuss with their provider the appropriate time to turn in the urine, because your doctor, your nurse practitioners, are going to work with you. I would also recommend for patients to try to get their blood tests in advance of their clinic appointment so that the results can be made available, and this makes the discussions a lot more meaningful.

And for bone marrow biopsies, remember to discuss anticoagulant hold times prior to the procedure, because there are many times when patients forget to hold their anticoagulants, or if this discussion never happens, it can cause a delay in the procedure and a delay in treatment decision-making.

Mary DeRome (MMRF): Yes, that makes sense. Dr. Lee, does the frequency of the blood test, the bone marrow biopsies, and the imaging studies change during various stages of disease? For example, when patients are undergoing treatment versus when they’re in remission, and what about when a patient relapses?

Hans Lee, MD: When a patient’s first diagnosed with myeloma, we’re going to check the bloodwork, at least the myeloma labs, once a month with every cycle. We want to know if the patient’s responding with reduction in the paraprotein levels or the light chain levels with each subsequent cycle of treatment. In terms
of the timing of imaging and bone marrow biopsy, typically if a patient has a high volume of bone lesions or extramedullary disease at baseline, certainly I would want to check that after induction therapy, before the transplant, if they’re undergoing transplant, with repeat PET scan. And then, doing a bone marrow biopsy, as well, to assess response, and also potentially MRD status. And then after a transplant, I would also repeat a bone marrow biopsy to look for MRD status as well. Now, in the maintenance setting, I typically get surveillance imaging once a year, at least, and this could be a whole-body MRI or a PET scan. I think we probably favor a whole-body MRI, just because of insurance approval challenges sometimes with getting too many PET scans. But also, MRIs can sometimes show very small, subtle changes in the bones or bone marrow a little better than a PET scan, so there can be pros and cons of either test.

If, for some reason, a patient is what we call oligosecretory, which means that they don’t secrete much of the paraprotein at baseline, the bloodwork may not tell the whole story. I’ll probably do more frequent imaging for that patient, at least every six months, maybe even every three months, to monitor and track what’s going on.

And in terms of the frequency of bone marrow biopsy, I think seven or eight years ago, I was doing bone marrow biopsies less frequently in the maintenance setting because it wouldn’t really change management, to be quite honest. Because if they’re in complete remission or MRD negative, it’s not really going to change things. But I think this is going to evolve over time. I think there is a lot of ongoing studies looking at outcomes in patients who discontinue maintenance early based on MRD status and seeing how those patients do, and those trials are ongoing. I think what’s made me shift a little bit to giving more frequent bone marrow biopsies, at least maybe every year for a lot of my patients on maintenance therapy who are MRD negative, is that I do want to generate that data, for when the readouts do come out. Because I don’t want to be like, “Oh, yes, these data just came out, and they show that if you have a sustained number of negativity for X number of years, it’s just as good to stop maintenance,” but then if you don’t have that data, we can’t act right away on that. Otherwise, you have to generate that data prospectively from that time point. It doesn’t necessarily have to be on the day, annually, the bone marrow biopsy, but doing an intermittent bone marrow maintenance for MRD status I think is good to get. And then later on, when a patient relapses, getting a bone marrow biopsy at every subsequent relapse to see if there have been changes in the genetics of the myeloma would also be something we would consider as well.

Mary DeRome (MMRF): Definitely. This has been a really productive discussion. I’d like to thank my panelists, Dr. Lee and Becca Lu, and also our patient, Lauren Eaves, for their contributions today.

We did have a webinar on Learn Your Labs a few months ago and, as I mentioned, we also have a couple of pieces of information out there on MRD
testing, both a webinar and a Facebook Live, like this. Those are on our website for anybody who would like to look at those recordings and learn more about those topics.

I’d also like to thank everybody who came online to watch us.

Finally, I’d like to thank our sponsors Adaptive Biotechnologies, BMS, CURE, GSK, Janssen, Karyopharm, Regeneron, Sanofi, and Takeda Oncology.

If you have additional questions about what you heard today, please don’t hesitate to call our MMRF Patient Navigation Center at 1-888-841-6673.

Thank you.