MMRF Patient Webinar Series – Learn Your Labs

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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 Multiple Myeloma Research Foundation.

We have with us today two myeloma experts who will be describing the tests used to manage myeloma as well as the importance of these tests and their clinical potential benefits. Dr. Craig Cole serves as Director of Clinical Cancer Research at the Michigan State University Karmanos Cancer Institute. Dr. Cole's focus is on hematology and multiple myeloma, and he has worked extensively with patient advocacy groups across the spectrum to empower, educate, and bring equitable care to all myeloma patients.

Dr. Joshua Richter is an associate professor of medicine, hematology, and oncology in the myeloma division at the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai and the Director of Myeloma at the Blavatnik Family, Chelsea Medical Center at Mount Sinai. He has been published in numerous oncology journals and has an interest in immunotherapy, multifunctional antibodies, and precision medicine. Now let's get started with our first speaker, Dr. Craig Cole.

Craig Cole, MD: Thank you, Mary. And thanks to the MMRF for setting up this meeting. It's so empowering for patients to be able to understand their blood tests. Myeloma, unlike lung cancer or colon cancer, where the disease is monitored by CT scans and MRIs, is monitored by blood tests, which gives patients an advantage because they can follow their disease in real time.

But to be empowered to know when to worry, and especially to know when to celebrate, it's good to know what your blood tests actually mean. So that's what we're going to talk about today. One question that I get from my family, my friends, and that I talk to my patients about is exactly what is a blood cancer and, specifically, what is myeloma, which does require just a little bit of knowledge about anatomy and biology. So, inside the bones, the hollow part is called the bone marrow. And the bone marrow, that squishy stuff that people throw away, if you look really close, is actually a very complex organ full of lots of different types of cells. It is the blood factory, and inside the blood factory, there are the bone marrow stem cells that go on to create the red blood cells, white blood cells, and the platelets that we all know and love.

There are also the lymphocytes that live inside the bone marrow. They’re hatched in the bone marrow, and they migrate to and from the lymph nodes, and their big function is to fight infection. They get their education in the thymus gland in some cases, and they are specialists in fighting infection and hand-to-hand combat. There are also the plasma

cells, and the plasma cells are permanent residents of the bone marrow. If the lymphocytes and the white blood cells are the infantry, the artillery are the plasma cells. They create antibody proteins, which then are fired from the plasma cells and destroy infection from afar. Just like any other cell in the body, if those stem cells become cancerous, we call that leukemia, and those leukemia cells are unable to make the red blood cells and white blood cells and platelets, and they proliferate without differentiating into the different components of the blood. So, the blood counts go very low and people can be very sick with leukemia.

If the lymph cells become cancerous, we call that lymphoma, and those lymphocytes can populate inside the bone marrow, but especially they begin to grow out of control inside the lymph glands causing lymph gland enlargement. And so, lymphomas are usually diagnosed by biopsies of the lymph glands. Myeloma is different, because if those plasma cells become mutated and malignant, we call that multiple myeloma, and those cells will grow and proliferate inside the bone marrow and then begin to fire off antibodies from the bone marrow in excessive numbers. That’s the M protein, and that's how we can detect myeloma initially, by doing blood tests.

We can also detect myeloma by some of the key features that are the hallmark of the disease. And we use a “CRAB” mnemonic to remind us of those key features, those myeloma-defining events that we see with multiple myeloma. Those plasma cells can wear away at the bone, releasing calcium in the blood, causing high levels of calcium (hypercalcemia). That's what the “C” stands for. The “R” stands for “renal,” or kidney, function. Those antibodies and light chains that are produced by the myeloma cells can get trapped in the kidney, causing decreased kidney function because the filter doesn't work because it's clogged up full of protein. When those plasma cells take over the bone marrow, they destroy the normal red blood cell production inside the bone marrow. So, the red blood count drops. We call that anemia; that's the “A.” And those plasma cells, when they run out of room inside the bone marrow, they'll then travel to the long bones, take up shop there, and cause bone damage, thinning of the bones that we call lytic lesions. So, the CRAB mnemonic helps us remember the different clinical features of multiple myeloma.

One of the top symptoms that people present with are weakness, fatigue, and infection from those low blood counts because of the marrow takeover. Weakness and confusion can occur with decreased kidney function. And of course, bone pain can occur with the bone damage that those plasma cells cause; those weaken the bone and cause those lytic lesions. But about 10% to 20% of newly diagnosed patients won't have any symptoms. And sometimes if they don't have any symptoms, some of those patients are said to have smoldering myeloma.

One thing to note is that there are differences between the races with respect to how myeloma presents. Black patients usually present at a younger age than do White patients. The incidence of myeloma is twice as high among Black patients than White patients. And we know that Black patients will more likely present with hypercalcemia, kidney dysfunction, which can lead to hemodialysis, and anemia. White patients are

more likely to present with bone lesions, in part because Black patients, in general, have a higher bone density.

All active myeloma begins with MGUS, monoclonal gammopathy of uncertain significance, where there are low numbers of plasma cells in the marrow, less than 10%, and none of those myeloma-defining CRAB events. And it is very common; about 2% of the population over the age of 50 years can have an MGUS. The vast majority will never turn into myeloma, but a few of those patients could develop it, and then the plasma cells and the protein can go up. Some patients will have smoldering myeloma, where the protein is much higher: the M protein is greater than 3 g/dL or the light chains are high. The number of plasma cells in the bone marrow, which is normally 1%, can be between 10% to 60%. And again, with smoldering patients, they don't really know that they have any disease, because they have none of those symptoms or myeloma-defining events.

And then there's active myeloma, where patients know that they have problems, they feel different, the protein's much higher, the number of plasma cells can be over 60%, and they have one of the myeloma-defining events, those CRAB criteria that we talked about. Recently, we've come to the determination that if patients have high numbers of plasma cells in the marrow, over 60%, or if their free light chains, those little fragments of antibody, are very high, or if they have more than one lesion on an MRI or sensitive scan, they have a very high risk (about 80%-90%) of developing active myeloma in two years. Frequently, we will treat such patients, even though they don't have any of the CRAB criteria.

Let's talk about the labs. In order to talk about the labs, we'll talk about the antibodies that the plasma cells make. And there are three different types of antibodies that are associated with multiple myeloma. Immunoglobulin G (IgG) is most common type. All the antibodies have a main stalk and light chains hanging off of them. The light chains help the main stalk be really sticky, so it can stick to bacteria and viruses. The IgG is the main functioning antibody. The IgA is like a giant version of the IgG and is bound by a J-point linker. That antibody is usually found in the airways and in the gut. The IgM antibody is a huge protein, a pentamer of IgG proteins all linked by J-point linkers; it's usually the first on the site during an infection. Myeloma will more likely be associated with IgG than IgA; IgM myeloma is very, very rare and is usually associated with a type of lymphoma.

So, how do we detect these proteins in the blood? We'll use a test called protein electrophoresis. So if you can imagine, that's a thick gel, and you put an electrode at the front and the back of the gel, one positive, one negative, then you get the patient's plasma, put it in the gel, then you turn on the power, and it pulls that plasma, which is negatively charged, away from the negative electrode towards the positive electrode. And because that gel is thick, the proteins will segregate out by weight with the lightest protein (albumin) being at the very beginning, followed by other proteins in the alpha zone and beta zone (the vitamins, some of the carrier proteins, the coagulation proteins), and then there is a big, huge area at the other end of the gel where all the

antibodies hang out. The IgG, IgA, and IgM antibodies will all be in that gamma zone, and it gives a wide base of protein. That's what a normal protein electrophoresis looks like. However, if we have an MGUS, if we have clonal, identical plasma cells producing identically weighted antibodies, they'll all line up in a line within the gamma zone. All those proteins will just pile up from the plasma cells. And then we can measure that. And that is the monoclonal protein on the serum protein electrophoresis (SPEP) test. And that when that is graphed, the area under that curve tells us how much myeloma protein there is, which is roughly equivalent to how many myeloma cells are inside the bone marrow.

So, instead of doing bone marrow biopsies every month, we can do the SPEP test, and as we treat patients, the amount of plasma cells reduces, the amount of M protein reduces, and then you know when to celebrate: when that protein goes from 4 g down to 1 g, you know that that treatment is working to get rid of the plasma cells inside the bone marrow. Sometimes, if a plasma cell is really mutated, it'll only produce the light chains. Then when you turn on the electricity, those light chains are so light that they can wiggle all the way through the gel, and they can't be detected. And what we used to do since, 1847, was to collect 24-hour urine samples and do urine tests for the Bence-Jones Protein. If you're producing those light chains, they'll be put out in the urine, and you can detect it in the urine as a urine M spike.

Those are the two main tests that we've used for years: the SPEP test and the 24-hour urine test. Another test that we use is the quantitative immunoglobulin test, which looks at the levels of IgA, IgG, and IgM in the blood. Usually, we produce equal amounts of IgG, IgA, and IgM antibodies. However, if you have IgA myeloma, it will suppress the production of IgM and IgG and therefore reduce the function of the immune system. And this test will give us an idea of how those plasma cells are behaving. And the uninvolved immunoglobulins will be very reduced in about 91% of myeloma patients, which is a good way to be able to tell what's going on. And as we treat the IgA myeloma, then we would see the IgM and IgG antibody levels restored back to normal health.

The type of M protein is detected by the immunofixation. Every time we do SPEP, we have to do the immunofixation. And it sounds like just what it is: it fixes the type of protein into telling us if it's IgG, IgM, or IgA. One important point is that 17% of myeloma patients will only produce light chains. So, we have to check the SPEP and some type of test for light chains. And again, since 1847, we've been doing urine tests.

Dr. Henry Bence Jones was really the pioneer in finding the monoclonal protein inside the urine. But, as you can imagine, collecting your urine for 24 hours is difficult. During holidays, it gets in the way when you have to pee in a bucket for 24 hours to collect that urine. So, a really wonderful test came about in the mid-2000s, the free light chain assay. It is superior in how convenient it is without having to collect the urine, and it's actually a better test. How that test works is that there's a little hidden surface in the corner of those light chains that the plasma doesn't usually see.

But if there are free circulating light chains, a surface is exposed, and you can count that exposed surface to know exactly how many light chains there are. And you can count how many kappa, which is one type of light chain, and how many lambda, the other type of light chain. And if you have lots of kappa light chains, you have kappa light chain myeloma. If you have lots of lambda, you've got lambda light chain myeloma. And the ratio between kappa and lambda will be abnormal. Let me show you how that works. So normally, me sitting here in my office, I am making equal amounts of kappa and lambda light chains, and these are just light chains that are falling off my normal antibodies. So, this is what's falling off my IgG, IgA, and IgM antibodies as I'm just sitting here, and the ratio between kappa and lambda is 1:1.

If I have inflammation, so, if I have a cold or I get stung by a bee, my kappa and lambda will both increase, because I'm producing more antibodies and there are more kappa and lambda falling off those antibodies. But still, they both go up and the ratio is basically around 1:1 (kappa is always lagging a little bit behind lambda). However, if I have kappa light chain multiple myeloma, my kappa will be really high. And we talked about how the uninvolved proteins are decreased. In this case, the uninvolved light chain, lambda, is pushed down and is at a very low level, and then the ratio is greater than 100:1. There's way more kappa than lambda. And again, with treatment, the kappa goes down, because this is an indirect way to measure the number of plasma cells, and the lambda goes back up to normal, and your immune system is restored with the ratio between the kappa and lambda being 1:1.

So, it is important to know about the SPEP, the immunofixation, the light chains, and the M protein in order to follow the disease. Again, most patients will have an IgG or IgA type of myeloma. And for about 80% of patients, we use the M protein and that SPEP and immunofixation to follow it. But again, 15% to 20% will only produce those light chains. And so we use a free light chain test and, in some cases, a 24-hour urine test will do that. And in about 1% to 3% of patients, the plasma cells will become so mutated that they won't produce any antibody. And those are what we call nonsecretory patients; the plasma cells are so mutated that they can't produce any protein. And for that, we use bone marrow biopsies, PET scans, and an emerging technology called mass spectrometry, which can detect even those tiny amounts of protein being produced by those mutated plasma cells.

Another test that we use, purely for staging purposes, is the beta-2 microglobulin test. The M protein can be different from patient to patient; you can have two patients that have equal amounts of myeloma in their bone marrow but have very different M proteins. The beta-2 microglobulins are these little hairs that are on top of the myeloma cells, and they are shed into the blood and excreted by the kidney. So, they are these tiny little proteins that are pretty consistent from myeloma to myeloma. And what we can do is measure how much beta-2 microglobulin is floating in the blood, which gives us a way to measure how many plasma cells are in the marrow and to see if there's kidney damage because of the myeloma. And the higher the beta-2 microglobulin level, the more plasma cells we know are there, and it can help us in the staging process.

The complete blood count (CBC), measures the red blood cells, white blood cells, and platelets made by those normal stem cells inside the bone marrow. The comprehensive panel is a very important test. It helps to measure the levels of calcium, creatinine (a measure of kidney function), liver function, and bone status (the alkaline phosphatase helps us tell about the bones and about the liver). So, the CBC and the comprehensive panel are two tests that we regularly check for patients that are newly diagnosed and on therapy. The beta-2 microglobulin test that we talked about is a test that's only used for staging purposes. It gives us an idea of how many myeloma cells there are and what the kidney function is. And the lactate dehydrogenase (LDH) test is not a cholesterol test. LDH is a chemical that's released by plasma cells when they're reproducing quickly.

Then there are the main tests: the SPEP tells us how much myeloma is present in about 80% of patients. Immunofixation tells us what type of protein is being produced by those myeloma cells. And the free light chain assay is for 15% to 20% of patients and tells us how much myeloma there is in patients that only produce light chains. The urine protein electrophoresis is used to detect whether those Bence-Jones proteins, those light chains, are being produced in the urine. And the 24-hour urine analysis for Bence-Jones proteinuria tells us how much myeloma there is, and we use it for research purposes. We use it every once in a while. I still order it a few times for my patients, but I don't use it as a test that I regularly follow, because it's a hassle to collect your urine for 24 hours once a month.

I love the iceberg model of myeloma. I think all my patients have seen me draw this or seen me present this. It is a model to tell us how well the treatments are working. When patients walk in the door, and they have lots of myeloma, it's like the iceberg. It's obvious that they have hypercalcemia, they have lytic bone lesions and pain, and you have over a trillion myeloma cells. But as we begin treatment, the myeloma cells begin to decrease. And if the protein gets cut in half, as we call that a partial response (PR). So, the M protein goes from, let's say, 8 to 4 g/dL, that means half the myeloma protein has decreased. And that's when you don't see the iceberg anymore. It's below the waves. And so patients will feel and look pretty normal, without having lots of pain, because we've reduced the myeloma down.

We continue the treatment, and then they have a very good partial response (VGPR), where 90% of the M protein or free light chains are gone. And for some patients, they can have a complete response (complete remission; CR), where we test the protein and the M protein immunofixation is negative. That doesn't mean that there's no myeloma; there's still some myeloma, because the test has a certain sensitivity, and that means that there's still some disease there. And that's when we use minimal residual disease (MRD) testing, which is a better way and new way to detect small amounts of myeloma that the blood test can't see. And so in summary, unlike other types of cancer myeloma is diagnosed, staged, and monitored through blood tests (SPEP, free light chain, immunofixation, and quantitative immunoglobulin testing).

We do X-rays and bone marrow biopsies, which we'll talk about in a second. The blood tests allow you and your doctor to track the myeloma and also the function of the bone marrow, kidneys, liver; the CBC and comprehensive panel checks all of that, so you know when to worry, but more importantly, know when to celebrate. So, know how to read your M protein test results, because the lower the amount of myeloma, the lower the protein level gets, the M protein or free light chain. So again, you know when to celebrate that the treatment is working. So, understanding your blood work empowers you. I love it when my patients come in and they're like, “Tell me what my protein level is.” I get on my calculator, I say 90%, and then we celebrate and we have some pie and ice cream. And we know when to worry, when the protein level's going up, and then we know we need to change directions. You can cope with the diagnosis of myeloma by empowering yourself, taking charge of this disease to learn what you need to do and when to tell your family and celebrate with your family. And that's it. So, I will hand it off to my good friend Joshua Richter.

Joshua Richter, MD: Thank you to Dr. Cole for always being amazing. Just so everyone knows out there, Dr. Cole makes all these amazing slides. The entire myeloma community steals them, and he gets no credit. But I will officially thank him for supplying us all with great slides.

And with that, I will talk about the wonderful pain in the butt that is bone marrow biopsies. So, with all of these fancy new tests that Dr. Cole is talking about, including MRD and free light chains and the advances that we've had, ultimately, every now and again, we still have to do a bone marrow biopsy. We certainly do one at the time of diagnosis. And depending upon what happens throughout your treatment course, we may suggest to do another one. And there's a lot of information that we get out of the bone marrow above and beyond “Is there myeloma there or not? And if so, how much?”

One of the biggest things that we get is information about the genetics. Now, when we talk about this, we're not talking about the genetics that you got from your parents, share with siblings, or passed on to children. We're talking about abnormalities in the DNA of the cancer cells themselves. And here we send a variety of tests on the cancer cells. When we look at these chromosomes, we talk about the chromosomes as 23 pairs; we number the pairs 1, 2, 3, all the way up to 23. There are two arms of each chromosome, a long arm and a short arm, that we call P and Q. And when we talk about these abnormalities, you may hear us talk about translocations. For example, if your 11th and 14th chromosome inside the plasma cells have swapped some information, we call that an (11;14) translocation.

We often use the word “deletion.” So, if you're missing some of the material on the short arm of the 17th chromosome, we call that a 17p deletion. And sometimes there's extra material on a chromosome. So, if you have some extra material on the long arm of the first chromosome, we'll call that a 1q gain or a 1q amplification. These are the terms that we use to describe the changes in the DNA inside of the cancer cells. Now, there are a number of techniques that can be used to look at this. The first one that we use, which we don't use as much anymore, is called a karyotype. We literally crack open 20 cells

as they're dividing, spread the DNA out on a sheet and see if anything is changing (eg, translocated, deleted). But we recognize that there are millions of cells in the body, and looking at 20 doesn't really help that often.

So the next level is something called FISH, which, even though it stands for fluorescence in situ hybridization, really is legitimately going fishing, trying to identify specific abnormalities (translocations, deletions, additions) that we know have impact in myeloma patients. And here we can literally look at two to 400 cells at a time to find these abnormalities. We look for two different parts of two different chromosomes. We tag them as green and red. And if they're separate, we know that they're in their normal spaces. For example, we looking to see whether or not the fourth chromosome and the 14th chromosome are swapping any material. If you can see that some cells have red, some have green, and some areas have green and red are right next to each other, that tells us that those chromosomes have actually swapped some material.

We can identify these with very high sensitivity in a lot of the patients. Now, what's really taken us to the next level is involving some deeper sequencing. Not just looking at the chromosomes, but looking at the genes. Are they turned on? Are they turned off? And there are some more expansive panels that exist. And there's been a lot of collaboration with the MMRF to make sure that we can not only learn from all of this, but that, when a patient walks in to the doctor and unfortunately gets diagnosed with myeloma, we have so much information that we can sit down at the phone and just type into an app, “60-year-old Black female with (4;14) myeloma. What's the best therapy?”

And that's part of the way we're trying to use some of this data from CoMMpass, to better understand, from a longitudinal standpoint, what are the optimal decisions to make, like a chess game, trying to find the perfect way to do this. But the other thing that we're looking for is what we call “actionable mutations.” Sometimes, the genetic abnormalities are there, and we know that they're good or bad, but there's nothing we can really do about it. But there are a lot of other abnormalities for which we have drugs that already exist in other diseases. So in this giant pie chart here, we can see these weird combinations of letters, and they actually each represent a genetic abnormality that we notice in patients with myeloma and for which we actually have drugs that exist in other cancers. So, you see this thing here called “FGFR3” on the left; 5% of myeloma patients have it. Well, guess what? There are FGFR3-targeted drugs in urologic cancers like bladder cancer.

PI3K-AKT has drugs approved in lymphoma. KRAS and NRAS have drugs approved in colon and lung cancer. BRAF mutations are present in almost all melanoma cases. So, the way that we've utilized this is through an amazing project called the MyDRUG Trial, where these are patients who have what we call “functionally high-risk disease,” meaning, patients who get diagnosed. And we are very excited with all of our new therapies. We expect many patients to stay in remission for years and years and years. But if you relapse sooner, and we consider that to be functionally high risk, if you relapse a lot sooner than the average patient would on a given treatment, we do a bone marrow biopsy, and we do this advanced sequencing, and we give you a base therapy

of three drugs: dexamethasone, a drug called ixazomib (Ninlaro, which is like a pill version of bortezomib), and pomalidomide (Pomalyst). And then we add a fourth drug that's custom-tailored to your abnormality.

So, if you have a RAS or RAF mutation, we give you this drug called cobimetinib (Cotellic) plus that combination. If you have the FGFR3 mutation, we use the urologic drug erdafitinib (Balversa). So, we're able to provide more personalized medicine to an individual. And some of these data have already been presented, and we're very excited as this continues to accrue.

Now, what Dr. Cole pointed out is we're able to get very deep remissions in many of our patients. And one of the ways that we have traditionally evaluated this is exactly as he said, we measure the amount of bad protein. How much has it gone down? If it has gone down 25% to 49% that is minor remission. If 50% to 89%, that is PR. VGPR is 90% to 99%. And then we start delving into the world of complete remission. And now our technology is getting so advanced, we're actually able to use what we call MRD, minimal residual disease (or, as some people call it, “measurable residual disease”) to find 1 cancer cell in a million or 1 in 10 million inside of the bone marrow.

There are actually a lot of different ways to figure this out and to find those few cells. There are two leading technologies right now. One is through the use of flow cytometry. And as we all love things that are “next generation,” like *Star Trek, the Next Generation*, we have next-generation flow (NGF), and we have sequencing that we call next-generation sequencing (NGS). These are the two main versions that you may see used at the cancer center or myeloma center where you're seen. NGF is a regular flow-based test. Flow is ubiquitous. You can send it almost anywhere, so wherever you get bone marrows done, they can send flow. And in order to look for these bad cells, you don't need a baseline sample. So, if someone is treated by me, but they don't like my jokes, and they decide to go get treated by Dr. Cole, and I decide not to send them any of the information, and Dr. Cole gives them the latest and greatest in treatment, he can send a bone marrow for NGF at any time to find it.

It can be done anywhere. There's not a 100% standardization, so there may be some differences from site to site. It's very quick to run. It says two hours here on this slide, but you have to know somebody to get it done that quick; usually, it takes a couple days. If you make some phone calls, you can get it done quickly, but it's not the most sensitive. It gets us down to about 1×10^{-5} to 1×10^{-6} in sensitivity. NGS is run by only one company, called Adaptive Biotechnologies. For this, you do need a baseline sample. So, every time I do a bone marrow biopsy to diagnose someone with myeloma, I send a primer sample, to look for a genomic sequence that we can track over time, to Adaptive.

And this can be shared if you go to other facilities. And if for some reason you didn't have this done at your initial marrow biopsy, the company will help you track down your initial marrow and they can sometimes scrape off a little bit of the marrow from the slides to get your identification (ID) sample. Now, not everyone has an ID sample. About

90% to 95% of people will, but 5% to 10% of myeloma patients will not have unique sample to track over time. This takes a little bit longer, at least about a week. It costs a little bit more, but it is more sensitive, 1×10^{-6}. Now, both of these tests are being evaluated to be done in peripheral blood. They're not quite there just yet, although there are some really great data coming out. So, this still has to be done in the bone marrow.

One of the terminologies you may hear us use is “MRD positive.” Now, unfortunately, “positive” here is not generally what we want. Positive means that we found a couple of cells, even a few cells within a million or a few in 10 million. MRD negative is the deeper version. That's where we don't detect any of the bad cells. And we have a term we call “sustained MRD negativity.” If you do two bone marrows at least 12 months apart and both are negative, that's sustained MRD negativity.

And we always talk about myeloma being a movie, not a snapshot. That is the most profound thing that we can say. If you're maintaining undetectable levels, that's the deepest remission we can currently describe. But there's more to this. We don't just send MRD; it's not the one and only one test, because we recognize that sometimes with myeloma, although the cells are designed to live in our bone marrow, sometimes they don't. Sometimes they decide they're going to go live wherever they want. And we call that “extramedullary disease,” or disease outside the bone marrow. And for that, we need to incorporate imaging. There are a variety of ways that we can use imaging. These are the four most common: X-rays, MRIs, CT scans, and PET scans.

X-rays are quick and fast. And if you have a bone that's hurting or you're worried about a fracture, an X-ray is a test to get very quickly to let you know if there is a fracture in the bone or not. However, X-rays don't give us a good look at soft tissue. If you're looking at organs, if you're looking at lymph nodes, or you want to see with finer detail, you have to use an MRI, a CT scan, or a PET scan. And these tests can be anywhere from looking at one small area all the way up to your entire body. So, we put this all together: your imaging results, blood and urine tests, and the marrow results to come up with a staging prognosis and risk assessment. And here's where staging is complex, because everyone here, unfortunately, knows people that have cancer. Unfortunately, people have loved ones that have cancer. And the thing that people always say first is, “Well, what stage is it?” When most people talk about cancer in terms of stage, they refer to something called the AJCC (American Joint Committee on Cancer) staging system. This describes a tumor, how big it is, has it affected your lymph nodes, and has it spread anywhere, which we call metastases.

And this is a complex staging system that gives every cancer a stage from I, II, III, up to IV. We don't use this in myeloma, because we're different. There are actually four different staging systems. None of them go to stage IV. They all go to stage III. And probably the most commonly used one right now is the Revised International Staging System, which came about around 2015. And essentially this takes a few labs. One is albumin. Albumin is like the white of an egg. Albumin is a kind of rough estimate of your health. A high albumin is good. If you get sicker, your albumin goes down. Dr. Cole talked about the beta-2 microglobulin. This is a marker that's found on all the cancer

cells. High beta-2 means more cancer, which is less good. We want lower disease. So we basically put if you have a high albumin and a low beta-2, that puts you in the lower disease category. And we used to use those parameters for what we call the International Staging System

But as I said, in 2015, we revised that, and we added two more factors. One is called the LDH. And exactly as Dr. Cole mentioned, this is not a measure of your cholesterol. This is a measurement of how actively your tumor is turning over. LDH is everywhere. Every cell in the body has it, but the faster your disease is revving, the more of this it'll release. So high LDH means a more aggressive disease. Although, there's a lot of things that can elevate your LDH; if they put the needle in at a sharp angle and it shreds some of the red cells on the way in, even the way they draw your blood can affect it. So don't get too worried about your LDH. We also include our genetic studies. Specifically, three genetic abnormalities, a 17p deletion, a (4;14) translocation, and a (14;16) translocation. And we put that all together to find your Revised International Stage. What's most important is your genomics and really those FISH studies and genetic studies that we send.

And our colleagues over at the Mayo Clinic maintain a website called mSMART.org. And I go to it all the time. It's got great patient information, but also keeps an up-to-date list of what we call standard-risk and high-risk genetic abnormalities. And we can see them all listed here on this slide. And these are the things that we're really looking for to figure out is your myeloma likely to behave better or worse. But we're starting to use these to come up with specific targeted drugs. For example, included under “standard risk” is translocation (11;14); we have a drug for that. And under “high risk,” translocation (4;14), we have a clinical trial right now looking at a specific drug for those patients. So really, when we talk about risk, we're trying to figure out, is your disease likely to behave better or worse? And if you take two patients, standard-risk and high-risk, and give them the same therapy, they tend to respond about the same. High-risk disease tends to come back a little bit sooner. Now, there's a little more than that, but that's kind of the 10,000-foot view over figuring out what someone's risk happens to be.

But there are other things that we factor in, above and beyond just the genetics, which are your disease features. Do you have a lot of disease or a little disease? Is it already in your blood? Normally, plasma cells, myeloma cells, live in the bone marrow and usually only a few of them circulate in the blood. But if a lot of them are circulating there, we call that plasma cell leukemia. And that's a higher-risk disease. Another disease feature is extramedullary disease. Again, myeloma normally lives in the bone marrow. And think of it like a tree. A tree has to live in the ground and the dirt, but if you saw a tree walking down the street, you'd stay out of the way of that tree. Same thing with myeloma. If your myeloma can now live outside the bone marrow, it tends to be more aggressive. So we look at that, even if the genetic studies don't show any high-risk features. We also consider patient features; we care about you. There's a difference between treating someone who has no medical problems versus someone who has multiple medical problems or even multiple cancers, which makes things more complex.

And then, ultimately, the proof is in the pudding. How do you respond to treatment? If I give you drug A and the average remission is two years and you stay in remission six months, you have high-risk disease. If you stay in remission 10 years, you have better-behaving disease. So really, it's at the end of the day, just monitoring for what happens when we actually treat.

So to summarize things, bone marrows are a pain in the butt. That's the most aggressive wording I'm allowed to use. I would use different wording, but then I would be blocked. But it's really important right now. There are ongoing studies looking to figure out if we can get all the information we need just from the blood. We're not quite there, but we're looking at it. This not only helps us know if your disease is likely behave better or worse, but we're starting to figure out which drugs we can use and really custom tailor a therapy to you as an individual based on your specific genetic abnormalities and not just give you what's en vogue that week.

Bone marrow biopsies also let us know how deep your remission is: is there any detectable disease? I have many patients who have never, ever, ever achieved MRD negativity and they will continue to live a normal life. And the reality is, deep is better when all else is equal, but all else is never equal. And there's some brilliant work being done by one of our colleagues, Dr. Bruno Paiva, to show exactly when Dr. Cole had mentioned, that all myeloma comes from an earlier state like MGUS. Normally, if you diagnose some with an MGUS, you don't do anything, you just watch it. Dr. Paiva has done some work to show that there are some people that, after you treat their myeloma, the disease that's left never goes away entirely. You can always measure it, but it’s going to behave like an MGUS, and it's just going to sit there. We’re starting to learn a lot more about, not just how much is left, but what does that look like, and whether we need to do anything about it. And again, we still need to get a total picture, and that includes blood and/or urine, bone marrow, and imaging tests like X-rays, MRIs, CT scans, and PET scans. And with that, I will turn it over to our master of ceremonies, the great Mary DeRome, herself.

Mary DeRome (MMRF): Thank you, Dr. Richter and Dr. Cole, for those great presentations. Now we're going to move on to our Q&A portion. We have a lot of questions that came in for this webinar. I'm seeing at least 60, so there's no way we're going to get to all of those, but we will answer some of the most interesting ones. Dr. Cole, here's the first question. When you are in remission, how often should labs be done? And what is the recommended time for PET scans to be done?

Craig Cole, MD: When patients are on maintenance therapy, on their baseline therapy after they have been induced, I begin to scale back the amount of times that I check. When patients are on therapy, I check it once a month. When they're on maintenance for a while a year or two, then I'll back off to every three months. And I kind of stay with every three months unless something changes. For some of the higher-risk patients, the ones that have the 17p deletion and have other adverse features, I may check them more frequently. For PET scans, I usually don't check those on a surveillance basis.

But what I will do is that if a patient begins to have a change in their M protein, if they begin to have a biochemical relapse and the protein that was at its baseline, which I was checking every three months or every couple months, begins to increase, then I'll repeat the PET scan to see if it represents a significant relapse. Because if they have new lytic lesions that are PET avid on the PET scan while I'm monitoring them, then I will talk about changing therapies. But yes, that's what I do.

Mary DeRome (MMRF): Okay. Excellent. Dr. Richter, here's an interesting question. How does treatment with daratumumab impact test results? I know that, because it's an antibody, you can see it on the electrophoresis. Can you talk a little bit about that?

Joshua Richter, MD: Sure. Daratumumab is an antibody that targets something called CD38, and CD38 is on everything.

It's on a lot of your other blood tissues, so it can affect blood typing results. It turns out it can attach to red cells, and when you try to find out in the lab what blood type you have, it can interfere with that. When you do a bone marrow biopsy and you look at those plasma cells, they are typically going to show that CD38 marker. But if you're on daratumumab and you have some disease that progresses after that, if it's right after, you may not see that marker. But in the blood, you're absolutely correct, in myeloma, the disease marker that we follow is a monoclonal protein from the cancer cells, and daratumumab is also a monoclonal protein. And it turns out daratumumab is an IgG kappa protein, and that's also the most common type of myeloma. I call this a "*My Cousin Vinny*," for those people who've ever seen the movie, *My Cousin Vinny,* where they say, clearly Ralph Macchio committed the murder because you see the tire track is a model 15R. And then Joe Pesci gets up and asks, "Yeah, well, what's the most common type? Oh yeah, everyone's got 15R. Everyone makes them." If you have IgG kappa myeloma and you're getting an IgG kappa antibody drug and you see an IgG kappa in the blood, I call that a *My Cousin Vinny*. Although they do have a special test now to figure out if it's your disease or the drug, but if you have, let's say, IgA lambda myeloma, and you see IgG kappa in the blood you know it's just the daratumumab.

Mary DeRome (MMRF): Got it. Okay. Dr. Cole, how common is a PR versus a CR?

Craig Cole, MD: My goodness, I could go on for days about this. The really exciting thing about myeloma therapy in 2023 is that we're having patients go into those VGPRs, where 90% of the myeloma protein is decreased. And those CRs happen now way more often than when I had hair. When I had hair, the usual response to using the older therapies was, for PRs, about 50%. There are a lot of patients that have PRs. I would say that I did not see regular CRs until maybe 2015, maybe 2014. And now when we use these four-drug regimens, you're talking about 70% to 80% of patients having those 90% responses and CRs.

I guess the short answer is, it depends on what therapy you're getting, but the incredible evolution that we have seen just in the past 10 years has been that we're seeing more and more of those VGPRs and CRs. And now we're actually talking about MRD. When

that first came out, there were so few patients that ever reached that level. With the technology, it was like, why am I ever going to use this test? Now it's happening all the time, and the future is so bright. And I'm going to sit on my soapbox and say this, the PRs will become a thing of the past as we get better and better at treating myeloma.

Mary DeRome (MMRF): Excellent. That's a really hopeful statement. Thank you. Dr. Richter, I'm going to give you the last question, and I think this is a pretty important one. You described bone marrow biopsy as a big pain in the butt. There is one patient who wrote in and was asking about how to sedate patients and minimize pain during a bone marrow biopsy. Provide tips for how patients can ask for and have their needs met based on the pain and stress that they are experiencing from their bone marrow biopsies.

Joshua Richter, MD: I think this is a really great question, and the reality is that it differs from institution to institution. I am lucky enough to be at an institution that, for patients for whom a bone marrow biopsy, with all of the bells and whistles, is still going to be too much, we can actually do them under conscious sedation. For some patients, we do it almost like the medication you get when you have a colonoscopy, where you get a little drowsy, you wake up, and it's pretty much done.

For pain control, I think a frank discussion with your healthcare team is the way to go. There are many ways to go about preventing pain and anxiety, and in fact, it's not just giving pain medicine. Sometimes the anxiety of the procedure is the biggest pain. And taking a Valium-like drug (diazepam) or an Ativan-like drug (lorazepam) beforehand will be helpful. Make sure you have somebody who can take you home. There are some ways to use narcotics at the moment, either as pills, intravenously, or even a thing called Actiq, which is a fentanyl lollipop. Kind of a raspberry flavor, not my favorite. But that can be helpful. But there are even some nonmedication ways of doing this: listening to music, guided meditation, or even just chatting with someone in the room. There are nonpharmacologic ways of helping to improve this experience as much as possible. I think those are the main ways, but really having an upfront discussion with your care team [is important].

Mary DeRome (MMRF): Perfect.

Craig Cole, MD: In fact, we're opening a study. We actually got approached by a hand surgeon who uses virtual reality goggles. And while patients are getting bone marrow biopsies here, they're taking a tour of the International Space Station, and we're finding that there are decreases in pain and anxiety associated with the bone marrow biopsy while they're floating virtually through the International Space Station. So, at first, I was like, I don't know if we're going to do this, but patients really love it.

Mary DeRome (MMRF): Yes, that's pretty Interesting. That's amazing. Okay. Great. We're already past the top of the hour, unfortunately, so that's all the time we have today for questions. I'd like to thank our speakers, Dr. Craig Cole and Dr. Joshua Richter, for their usual amazing presentations on the Learn Your Labs topic.