Understanding Multiple Myeloma: Types of Diagnostic Tests and Frequency

Myeloma presents itself differently in each patient. In order to understand your Myeloma and monitor it, you need to know which are the tests available and how often you have to get tested. No single test or study is adequate to tell the whole story. A myeloma patient needs to undergo numerous tests for more accurate diagnosis. Only when the results of all the different tests are put together do we get a complete picture. Our experienced myeloma panel is talking to Dr. Joseph Mikhael about understanding your myeloma, types of diagnostic tests and their frequency.

Full Transcript:

Priya Menon : Good evening, everyone! Welcome to CureTalks' 93rd episode. I am Priya Menon, Scientific Media Editor at CureTalks, joining you from India. Multiple myeloma is a popular topic on CureTalks; and today, we have Dr. Joseph Mikhael with us to talk about understanding your myeloma diagnostic tests and results. Dr. Mikhael is Hematologist/Oncologist at the Mayo Clinic in Arizona where he researches, teaches, and treats multiple myeloma and related conditions. My co-host of the evening is Gary Petersen. Gary is Editor of myelomasurvival.com and a myeloma survivor and advocate. Our myeloma panel consists of myeloma survivors and advocates, Jack Aiello, Cynthia Chmielewski, and Matt Goldman. I extend a warm welcome to everyone. Myeloma presents itself differently in each patient. In order to understand your myeloma and monitor it, you need to know which are the tests available and how often you have to get tested. No single test or study is adequate to tell the whole story. A myeloma patient needs to undergo numerous tests for more accurate diagnosis, and only when the results of all the different tests are put together do we get a complete picture. In the coming hour, our experienced myeloma panel will be talking with Dr. Joseph Mikhael about understanding your myeloma, types of diagnostic tests, and their frequency. Before I hand over to Gary, I would like to remind our listeners that towards the end of the talk, we will be answering questions sent in via email. Over to you, Gary.

Gary Petersen : Yes. Thank you very much. I appreciate this opportunity as always, Priya, for you bringing this forum to us and the myeloma patient community. Dr. Mikhael is an Associate Professor of Medicine, Allergic Medicine, at Mayo Clinic where he is also the Associate Chair – Education, Department of Medicine. He is also the Deputy Director of Education, Mayo Clinic Cancer Center, and Associate Dean of the Mayo School of Graduate Medicine Education. Dr. Mikhael received his medical degree from the University of Ottawa in Canada and has completed an internal medicine residency there as well. Then, he completed his hematology residency and chief residency at the University of Toronto as well as a multiple myeloma fellowship at Princess Margaret Hospital. Dr. Mikhael holds professional memberships in the American Society of Hematology, Association of Faculties of Medicine of Canada and Canadian Medical Association and The Royal College of Physicians and Surgeons of Canada among others. Dr. Mikhael has several editorial positions at the American Society of Hematology and has written numerous abstracts and articles and peer review publications, 78 of which are listed on his bio for Mayo Clinic. So, doctor, thank you so much for…, for coming here. You happen to be _____(AUDIO BREAK)_____ that has probably some of the…, the breadth of skill that is…, is not available any place else in the world as in the Mayo Clinic system and…, and you obviously have helped to create that along with Dr. Fonseca, Dr. Rajkumar, Kumar…, Dr. Kumar, and…, and also Chanan-Khan and _____(AUDIO BREAK)_____ but to begin with, Dr. Mikhael, Mayo is one of the very first to actually publish a road map for newly diagnosed patients and relapsed patients based on a risk adaptive approach related to treatment or mSMART is what you call it and I noticed in many of your publications, you have been an integral part of putting that together and I can tell you that _____(AUDIO BREAK)_____ that this is the world's myeloma patient community work, where some…, where an organization has laid out their expertise in such an understanding way to help everybody who…, who is, you

know, avails themselves of this information and its based on testing to determine what's the best consensus approach to treatment and if you could…, might be able to tell us why this testing is important, what tests are important, and the frequency of those tests for newly diagnosed patients, high and low risk, relapsed refractory patients, and also non-secretors which is kind of a difficult one and any…, any other subset that you might find.

Dr. Joseph Mikhael : Well, thank you very much. Its a genuine pleasure to be part of this outstanding session, and I am…, I am grateful for the opportunity to do so. I…, I think the way…, the best way to approach this is initially to lay a background that, as you mentioned and Priya mentioned in her opening remarks, multiple myeloma, I like to say, sometimes is appropriately called multiple because its not a single disease as it were, meaning every patient is quite unique. You know, every disease has a spectrum, but I would argue that multiple myeloma has one of the widest spectrums of any cancer that we have and so, it really emphasizes the point of appropriate diagnosis; and when we mean appropriate diagnosis, we both mean a timely one and an accurate one; and so, when patients are initially diagnosed with multiple myeloma, its critical that we understand the full nature of their myeloma and the reason for that and the…, the rationale behind the mSMART guidelines was to be very practical but to also identify that there are patients who have what we might call higher risk myeloma and patients who have lower risk myeloma, meaning patients have myeloma that seems to grow much more quickly and that grows much more slowly and as a result, we would want to intervene differently in a patient who has a much more rapidly growing disease than that who has a slower…, slower growing disease and to help that…, make that distinction, we have come to realize that its not just, if you will, the volume of the disease but the pace of the disease, meaning its not just the size of the tumor as it were but the underpinnings of the tumor and the simplest way I would lay out what tests need to be done is I put them in categories. Category number 1, we need appropriate blood tests; category number 2, we need radiological tests; and category number 3, we need specialized tests out of the bone marrow. So, for the basic blood tests and I know we don't want to spend too much time on the very simple basics here, but people need basic blood counts. The…, the three key cells that get generated from one's blood, what…, what I jokingly sometimes call the white, red, and rose. You know, we need the white cells, the red cells, and the rose cells or the platelets. Secondly, within the blood work, we need the chemistry. We need to understand some of the kidney function, their calcium level. Now, these are the…, the blood tests that define the damage that unfortunately myeloma can cause to the kidney and to other organs in the body and then the third aspect of the blood tests are the ones that are often not done particularly well and I would want our patients and others listening to make sure they capture this carefully, are the myeloma-specific blood tests, so we know that myeloma is a disease of the plasma cell. The plasma cell is a cell that makes normal proteins in our blood that would normally fight off infections, but unfortunately, when the plasma cells become abnormal, they make abnormal proteins and we measure those through various tests and the critical two tests are what's called the serum protein electrophoresis, where we…, we measure the normal and abnormal proteins in the blood and we can quantify the abnormal component, sometimes called the M component or the M spike, because when we do it in the lab, it looks like a little spike of protein on the plate and that M spike becomes critical because that's the measure of the disease. Its like measuring perhaps someone's lung…, lung cancer on a…, on an x-ray. We see and we take out the ruler and say, "Oh, its 10 cm long," and as we treat it, we see it shrink.

Dr. Joseph Mikhael : Well, similarly, with the M spike. It has to be followed, but in addition to the M spike, there is another blood test called the free light chain measurements or the immunoglobulin light chain test. 20% of myeloma patients don't have an M spike at all actually of the bigger protein. Their myeloma only makes the smaller protein, what's called the light chain and so we can measure those light chains in the blood as well and the majority of myeloma patients will have both an M spike and a light chain and we have come to learn that its critical not just to measure one or the other but to measure both. They usually move in sync, but sometimes they don't, especially with relapse later on. It can be confusing.The second category of tests were the radiological ones, I won't spend much time there, but we would generally do basic plain x-rays, what's sometimes called the skeletal survey as just a baseline to see if the bone is involved, but very often we might go to something more specialized such as an MRI test or potentially even a PET scan if we want to understand the disease a bit more and I will come to that in a moment when we talk about non-secretory disease. And the third major category is the bone marrow test and this is really the foundation to

the mSMART guidelines that you had made reference to, Gary, which was that the…, this is the home of myeloma. Myeloma grows in the bone marrow. So, we measure the volume or the percentage, if you will, of those abnormal plasma cells, but its not just measuring those…, those bad cells in the bone marrow. Sometimes they call them the, you know, the bad military or police force because they are the ones that are supposed to protect you but are now not protecting you, but we go down a bit further to do what's called cytogenetic testing and those cytogenetics are absolutely critical. We usually do those through a process called FISH or fluorescent in situ hybridization. So, I tell patients make sure your doctor knows how to go FISH because we want to be able to get those FISH tests because what those do is they highlight key genes that we know are affected in myeloma. Those genes that will distinguish a high-risk patient from an intermediate-risk patient to a low-risk patient and the presence or absence of certain genes and, for time's sake, we won't go through them all. People can look at these in detail at our msmart.org website, but here we identify certain key ones. For example, what's called the p53 deletion or sometimes called 17p deletion. When someone's missing a piece of chromosome 17, that puts them in the high-risk category because that part of the gene that's missing is part of the gene that normally keeps cells in check and so if the supervisor is away, then there can be chaos and the disease can grow uncontrollably and those individuals will need to have their…, will need to have a different kind of therapy than those who by contrast may have extra copies of certain chromosomes, something we call hyperdiploidy, which puts people in the low-risk category and our suggestion is that all newly diagnosed myeloma patients need the blood test, need the x-ray, need the bone marrow with the FISH analysis because that will help us determine which category they land in and how they are initially treated. At relapse or when the disease unfortunately as we know myeloma currently is not curable, but we are getting closer to that goal, we would want those tests repeated and in particular the FISH testing repeated because the genetics of those plasma cells can change with time and someone can unfortunately move from a standard or intermediate risk category into a high-risk category. So, patients should, as they are being treated, their blood work is checked on a regular basis. They start to grow again. They should absolutely have a repeat bone marrow where the FISH testing is done. The final category you asked me about was the non-secretory patient. There is a small proportion of patients, some are around 2% to 3% of myeloma patients where these bad plasma cells in the bone marrow, they are bad and they are there, but they don't actually release the bad protein into the blood and so we can't follow them with the serum protein electrophoresis. We can't follow them with the light chain measurement. Those patients we tend to follow with PET scans or in some cases an MRI, the PET scan is…, is more an accurate measure of the disease because we can often see the disease light up as it were on the PET scan and we don't do those monthly like we would with most of the blood work, of course, because that would be a bit excessive, but we tend to do them at either four or six-month intervals depending on what treatment they have received to be able to follow their disease and we know that its a little bit more challenging. Sometimes we are able to capture their disease in their urine but more often that not if they are a true non-secretor, we have to follow through with PET scan. I hope that answers your question.

Gary Petersen : Yes, it…, it does, doctor. Thanks very much. One thing you didn't mention when, you know, something that we see quite a bit in the literature coming up is a thing called gene expression profiling and that's included in The US National Comprehensive Cancer Network and The International Myeloma Working Group guidelines and this is a newer measurement technique and is it important and what do you see for the future use of this measure?

Dr. Joseph Mikhael : Yeah, its a…, its a great question. You know, the myeloma community is still little bit divided over this. The concept here as opposed to the FISH testing that I described where we go down and look at one or two specific or, you know, several specific genes, this looks at…, at almost like what we might call a genetic signature. It looks like at a pattern of genes and part of the challenge is that there are different tests for gene expression profiling and some measure 70 genes or 80 genes or 90 genes, but they tend to look at the same kind of concept of saying, does someone have a high risk signature or a lower risk signature. One of the reasons why I didn't include it right away is they say there is still a little bit of a difference of opinion as to how valuable it is and what exactly we do with it, but it is, I think, in the near future going to become more standard practice as you mentioned, the NCCN and The International Myeloma Working Group have recommended that it be a consideration if its available to people because it does a similar kind of thing to the FISH testing, but it looks at a broader group of genes and again into a category of

higher risk or lower risk disease that might influence the specific therapy. Now, it hasn't been validated as much as some of the FISH testing in terms of specific treatments for specific genetic abnormalities, but those kinds of things we are doing now. So, I wouldn't want our…, our listeners to think, "Oh, no, I haven't had gene expression profiling, I am really missing out," but I would keep an ear to the ground for it because before too long it will probably be a more important tool in our tool box.

Gary Petersen : Well, thank you, doctor. Appreciate that, you know, that description. Dr. Morgan calls the delay in diagnosis. He is from the UAMS and previously studied…, worked in…, in England _____(AUDIO BREAK)_____ diagnosis of more than six months for symptoms to diagnosis is a scandal and…, and what he means by that is that the general practitioner doesn't seem to identify myeloma until it…, until it ends up with end-organ damage and, you know, is…, is, you know, what can general practitioners do to find it earlier before it does reach that…, that critical function? For me, for example, I don't have kidney anymore and for other people, they have got bone destruction. I know somebody else who had the problem with the stroke and so, you know, once you get to that point, you know, its…, you know, something that you live with the rest of your life. It would be nice to think that there would be something that could be done, some tests that will help us find this earlier…

Dr. Joseph Mikhael : Oh, you do…, you do highlight a very challenging question and a very important one. In order… Frankly, I.. I think talks like this help because its really a multi-fold answer. I would suggest the number 1 is just greater awareness of myeloma and I think now that we have better treatments for myeloma and patients are living with myeloma, there is a greater general awareness. The second thing is having accurate testing that can guide our general practitioners or general internists. You know, many of these individuals, they work so hard and practice and they can see, for example, a 100 patients with back pain in the next several years and not one of them will have myeloma but then the 101st does. So, how do you keep myeloma on the radar screen for all the different ways the myeloma can present with back pain or kidney trouble or low hemoglobins and I do a lot of talks for general practitioners and general internists to say, "Look, myeloma might not be the top of your differential diagnosis, but when key things are present, please keep it in the list of your thinking." So, anyone who has got a low hemoglobin or anemia and especially if they are over the age of 50 or 60 because that's more common in myeloma, it should at least be consideration and starting with that simple serum protein electrophoresis or light chain test can be helpful.

Dr. Joseph Mikhael : If someone has kidney damage that's not clearly explained by other means, if someone has thinning of the bones or a fracture that doesn't fit with their age or the trauma that they may have experienced, those tend to be the most important trigger points or if when blood work is done, there is evidence of an abnormal or excessive protein in the blood. So, I think part of it is awareness in general of myeloma, of clipping and training our internists and general practitioners to understand that at those three or four trigger points, they have to start at least considering the diagnosis and then, of course, when abnormalities are detected, to expedite a more detailed investigation usually by hematologist or hematologist-oncologist because I agree with Dr. Morgan. Its tragic when we see patients and I saw a patient today who for eight months was shuttled around to different places, trying to figure out why he was as sick as he was until the penny dropped and someone said, "Oh, maybe this person has myeloma," and sadly, he does. So, its not a simple answer, but I think raising awareness and understanding key areas to watch for with the better testing that we have now, I think, is going to help at least alleviate part of that problem.

Gary Petersen : Well, thank you, doctor, for that. I think Myeloma UK did an analysis and showed that only 3% of people in the United Kingdom have ever heard of myeloma. So, we have got a long road before us, I think, in order to accomplish that education, but hopefully we can do something here and in other ways as well. Right now, I would like to open it up to the other members of the panel and I will start with Cindy. Cindy, are you there?

Cynthia Chmielewski : – I am. Are you there? Can you hear me?

Gary Petersen : Yes. Do you have some questions for the doctor?

Cynthia Chmielewski : – I sure do. First of all, thank you. …so much for spending some time in answering the questions we have and the first question I have is that of dreaded bone marrow biopsy and no patient likes to get one, but it seems that some doctors do them more often than others and I was wondering first of all, what's your recommendation about how often or at what point in the patient's myeloma journey should they be having a bone marrow biopsy and once they have that bone marrow biopsy, I know you talked a little bit about the FISH testing, should be done with the aspirate. Are there any other tests that we should be considering; and when you are talking about the FISH testing, could you…, because as I understand that you have to like have certain targets for the FISH, like what are the main targets a doctor should be ordering the test for and if we had the biopsy and the FISH testing wasn't done and you are currently in remission, should you have another biopsy, have that done or wait until relapse? I know that was a lot of questions, but I am sure…

Dr. Joseph Mikhael : You know… That was a great question, Cindy. Thank you. So, in general, patients absolutely need a bone marrow biopsy at diagnosis. When the FISH testing is done, now most labs have set it up. The…, the physician doesn't have to ask for all the specific targets. They would just ask for the myeloma panel and there has been greater standardization amongst our pathologists to determine what are the…, the key genetic areas that we are fishing for, as it were as I mentioned earlier.

Dr. Joseph Mikhael : Now, in terms of the frequency of repeating them, you know, thankfully, the majority of patients with myeloma do have an abnormality in the blood test that we can follow because as you even said after start, you know, bone marrow tests aren't what you are going to do on Friday night for fun. They are little bit dreaded and so we wouldn't want to necessarily do them every month. I would normally do the second bone marrow at usually one of two places. One, if the disease has responded and is now growing again and there is evidence of relapse, I want a new picture of where we are. Secondly, if someone has been treated and we want to confirm the depth of their response, it looks like they might be in a complete remission and that may or may not influence if they are going to get more treatment, whether that's after a bone marrow transplant or just with chemotherapy. We may want to get a fuller picture even though the blood tests tell us a lot, the bone marrow is really the definitive kind. I do think sometimes I see a lot of people getting maybe extra bone marrows than they really need, but it can do that. We would typically do a bone marrow test on everyone about 100 days after transplant. The third most common time to do a bone marrow test would be if there is something that doesn't fit, that the blood counts are dropping, for example, but yet the…, the protein tests didn't go up in the way that one would expect and if we are worried that something else may have happened in the bone marrow, we know that unfortunately a certain albeit small percentage of patients with myeloma can have other problems in their bone marrow, like what we call myelodysplastic syndrome or other conditions where the bone marrow is not functioning very well.

Cynthia Chmielewski : Okay. Great! Thank you. Next question I have is about flow cytometry. I… I am hearing a lot of things about MRD negativity and next-generation flow can help determine this and I just was wondering what if you could explain a little about what flow cytometry is. What kind of information does it give you that the other testing might not give you? If you are not in a CR, is there any reason for you to get a flow cytometry test and is this something that all myeloma patients should be asking?

Dr. Joseph Mikhael : Great questions! So, flow cytometry is actually just a method whereby we literally flow cells through this little machine and based on what's on their surface, we can determine what kind of cells they are. So, we do flow cytometry for a lot of different blood cancers to determine are these abnormal or normal white blood cells or…, or platelets or…, or red blood cells, etc. In myeloma, we think of, and I think in the context that you are asking, is when someone has had treatment and their bone marrow is pretty well clean of plasma cells. There aren't very many of the myeloma cells left. We can do very specific flow cytometry testing to see, are…, are there little bits of disease yet that…, that aren't easily measured in the blood, what you mentioned is a minimal residual disease, and there's different ways of doing it. There's two primary ways of doing it. One is through flow cytometry and the other is through what's called deep sequencing. Right now, again, even we just met at The International Myeloma Community last week in Rome to discuss how we are going to roll this out because there is still lots of different ways of doing it and we…, we haven't quite come to a common currency on it, but we are coming very close to it, that detecting

the presence of ongoing disease even though the disease appears to be in a complete remission by the blood test and the bone marrow, this MRD or minimal residual disease testing may be of value because it may cause us to treat a patient longer or to give them more and more therapy. So, again, for the listeners, we are not rushing out everybody and telling them, go to your doctor and get flow cytometry minimal residual disease testing, but it is something that will before long be quite likely a bigger part of how we evaluate the disease.

Cynthia Chmielewski : Okay. Great! Now, talking about the precision medicine, I am hearing a lot about sequential medicine and sequencing and sequencing of tumors and sequencing of your whole genome, how does that relate to the diagnostic test that we should be having for myeloma? Should you be having this deep sequencing or a whole genome sequencing done or not at this point or next-generation or it is gene expression profile, are they all kind of related?

Dr. Joseph Mikhael : Why, you have got all the tough questions tonight for me, hey. These are…, these are important. This is where we are looking. So, when you talk about precision medicine or personalized medicine or individualized medicine or someone is getting their whole genome tested, this is something that even just a few years ago would have cost a 100,000 dollars or more and is now getting cheaper and cheaper literally by the minute. Its probably cheaper now than it was when we started the teleconference, but it is something that we are frankly not recommending for all of our patients right away because we are still not sure what to do with all of that information. There are hyperspecialized areas like we have here in Mayo Clinic where we are understanding this and we are doing it more broadly in individuals with and without cancers to help understand their whole, if you will, genetic signature, their genetic patterns that might indicate certain diseases more likely to occur than others. For the myeloma patient's listing right now, again I have said this a couple of times, but its something that I want them to sort of have an ear to the ground on that. We are not immediately rushing out to have everyone have their whole genome sequenced or absolutely everyone getting gene expression profiling on their plasma cells and their bone marrow but something that will likely be a significant part of what we do in the future to understand not just myeloma but all diseases and how they interact in someone's genetic signature.

Cynthia Chmielewski : Okay. Another question I think its a little bit easier is about the role of the PET CT scan in the myeloma patient. How often should one be done? Is it something that should be done periodically to compare to future tests? When should we have these testing? When should we have the PET CT scan done?

Dr. Joseph Mikhael : Yeah. So, the…, you know, the PET CT scan is…, is…, is something that is allowable now in myeloma and there are some centers that are doing it on everybody at diagnosis. I would suggest its not always necessary if someone has easily measurable disease otherwise. The challenge is, of course, how frequently does it need to be done. If someone is a non-secretory patient, as I mentioned before, where we can't measure their disease by any other means, then that's pretty important. We tend to follow it somewhere around. Its…, its sometimes as often as every three months but more likely closer to every six months, but, you know, for any one of these tests, you always have to ask yourself, is the result of the test going to change my management? We all kind of want to know what's going on with the disease, but if its not going to change what you do right away, if we say, we are going to give you these three months of treatment, then…, then we don't want to do the testing too often because none of these tests are perfect and, of course, they cost and some of them come with some risk and some of them bare radiation, but in general, a PET scan can be helpful in capturing the accurate diagnosis at the start and…, and maybe occasionally being done later if we are following a patient that way but not routinely done in the majority of myeloma patients on a regular basis.

Cynthia Chmielewski : Okay. Thank you so much for these great answers. Gary, back to you.

Gary Petersen : Yes. Thanks, Cindy…, Cindy. I appreciate it. Jack, you online? Jack Aiello?

Jack Aiello: Hear me?

Gary Petersen : Yeah. I can hear you now. Jack, your questions.

Jack Aiello: So, I have a couple on followup on your question, Gary, about mSMART. The protocol calls for patients, newly diagnosed patients who have trisomies only to get Revlimid-dex as treatment and that's a standard risk patient and my quick question is what the heck are trisomies But, my bigger question are…, is, there will be some doctors who say, wow, we think we really ought to go with a three-drug regimen, Revlimid-Velcade-dex rather than starting anybody with Rev-dex and so how do you…, are there trials that show for…, for example, for standard risk patients that Rev-dex is just as effective as Revlimid-Velcade-dex?

Dr. Joseph Mikhael : A great question! So, trisomies, as you can understand the word "tri" referring to three. It just refers to the fact that there is a subset of myeloma patients who have a third or an extra copy of certain chromosomes. They tend to be the odd numbered chromosomes – 3, 5, 7, 9, etc., and the reason why we focus on trisomies is we have known, especially from our large Mayo Clinic database that many of these patients are the ones who actually live the longest with myeloma. Now, sometimes even paradoxically, these are patients that don't often get into a complete remission. They kind of have this slow growing version of myeloma and it brings up, you know, really a fantastic question that you asked, Jack, and…, and this is one where I sometimes joke and say, "You put 10 myeloma doctors in a room and you have 12 opinions." Right? (Laughter) I mean its hard of us completely agree on everything, but there is no doubt that in general the more treatment you use, of course, there is going to be a better response. Three is always going to be better than two as long as the drugs are tolerated. Four is going to be more effective than three as long as the drugs are tolerated and we can keep using the number higher and higher. I sometimes use the analogy despite being in the Canadian pacifist here, saying, "You know, if I am going to battle, if I take all five branches of the military, I have got a really good chance of winning the battle." The question is, do I really need all five? Could I have been just as successful with four, with three, with two, and with one and our experience in many of these patients with trisomies have done very well with less treatment because, in general, I think most patients will prefer to have less drugs. There is less toxicity, meaning less side effects from it and its cheaper and it preserves options for the future. There are some studies that will soon be released, that are comparing Rd versus RVD as you said or lenalidomide-dex versus lenalidomide-bortezomib-dex. I am not going to be surprised when they, generally speaking, will show there is an advantage to the three over the two, but this is where an individualized discussion has to be had with each patient and there is really the essence of mSMART of saying, every patient has to be looked at individually. In one individual patient, I might say, "You know what, your disease is not that fast growing. You have got a trisomy. Why don't we start with just lenalidomide-dexamethasone?" I do understand the argument that we want the best for our patients, but the best doesn't necessarily mean the most. Its the most appropriate therapy for them and in some patients we might start that way, but you know what, if we are not getting the response we want, we should add bortezomib. For some, we might say, no, we need to use the three-drug combination from the very start and that's a complex situation, but its an important one and we want to highlight the point that you don't just say, everybody gets cut with the same cloth, a cookie cutter approach, and everyone gets the same regimen. We give people based on individual factors.

Jack Aiello: Just clarifying, for me actually, with respect to trisomies again, is it… Do some myeloma patients not have trisomies at all?

Dr. Joseph Mikhael : Correct. Yes.

Jack Aiello: Oh. All right. And then my other question, kind of a general question that I think a lot of people will understand, my understanding is that an MRI is better for diagnosing focal lesions rather than lytic lesions. Can you explain the difference?

Dr. Joseph Mikhael : Yes. So, what we have come to appreciate is that…, that we have just revised the correct diagnostic criteria for myeloma. We used to talk always about what you called CRAB or C-R-A-B, where someone was defined as having myeloma if they had a high calcium, if the R stands for renal insufficiency, they had kidney damage; A stands for anemia, they had a low hemoglobin; or B, they had bone disease which was usually defined by a lytic lesion. Lytic just means like a…, a thinned out piece of bone that

sometimes ends up fracturing and actually breaking the bone. We have added a few criteria to that now, saying that sometimes on MRI and even to certain degree on PET scan, the CT scan, or whole body CT scan as its sometimes called now, we can actually see that within someone's bone marrow there is a focal, which means a discrete area where it looks like the bone marrow is…, is growing a little bit out of control, the…, the bone is going to be affected because of that area. That's not only something you see on just a plain x-ray and that if you will upgrade unfortunately someone from a smoldering condition to a true active myeloma, that needs to be treated and so that's why an MRI can be quite helpful and if someone, you know, we are not sure they really have active myeloma or not, they have got this bad protein, but we are not sure if its doing any damage, we'll do an MRI to see if that person lands in the smoldering group versus the true active multiple myeloma group because that will have broad implications as to how a patient should be treated because if they have evidence of focal or discrete lesions that we see in the MRI, more than one of them, that tells us that we need to treat them as if they had true myeloma. As I sometimes say to patients, I don't have to wait for someone to be falling down the cliff to know they are in trouble if they are running towards the cliff and if we see that its coming soon, we need to do something. By contrast, there are a lot of people who just have a little bit of an abnormal protein in their blood, but they don't have true myeloma. We don't want to over treat those individuals either.

Jack Aiello: Yes. Perfect! I always appreciate your explanations and, Gary, I have another question, but I will…, but I will turn it back over to you to let other people ask.

(Pause)

Matt Goldman : – Gary, are you there?

Priya Menon : Thank you, Jack. We'll… We have the next panelist. Matt, you are on. You have some questions for the doctor?

Matt Goldman : I am here. I guess we lost Gary. Thanks for your time, doctor. I… I have a couple questions. Mine are pretty simple. My first one is a two-parter. How are diagnostics different for bone-impacted patients versus kidney-impacted patients and can a person's myeloma change, you know, from being kidney to bone and is there a way or should that be tracked or can you be pretty confident that it will just stay what it is.

Dr. Joseph Mikhael : Now, those are… You might think those are simple questions, Matt, but they are great questions. You know, in terms of the diagnosis, we still do it the same way. We… You know, we try not to think of people as saying, you have got the kidney myeloma where as someone else has the bone myeloma. Really, a patient has myeloma and it may infiltrate to kidney, it may infiltrate to bone or both, and unfortunately, it can change with time, where one person can maybe don't have as much bone involvement early on and later on it can affect their bone. Later on, it can affect their kidney. You know, this is an unfortunate disease where it has the ability to evolve. Sometimes we call it clonal evolution, meaning the disease itself can be more aggressive and it can actually change a little bit with time and whereas, it appeared in one way before, it doesn't always come back to place. We have some… Initially, maybe they don't have any bone disease or any kidney disease and it happens later. So, I think its important that everyone get appropriately evaluated and monitored and the one thing in particular we want to watch for for patients with kidney involvement or potential kidney involvement are those light chains. So, I described earlier that the bad protein in myeloma is kind of this big chunky protein that's got little bit from the sides of it and those little bits on the sides of it are called light chains and those can shed and those light chains are so small that when they travel through your blood and they make it to their…, to the kidney and the kidney filters and sort of cleans all of our blood, they are small enough that they kind of get plugged into the kidney and so we…, we sometimes call this light chain disease or where these light chains can be very toxic to the kidney. So, there are times when patients who have high light chains in their blood were more nervous about their kidneys and were watching their kidneys. Sometimes the diagnosis, for example, some are going to have skyrocketing levels of light chains. Its critical, but we get those light chains down very quickly because if they circulate in the blood for too long, they are definitely going to cause kidney damage and sometimes even kidney failure.

Matt Goldman : Okay. Thanks. And related to kidneys, obviously I am kidney impacted, which is why I am asking these questions, but other than light chains, what else should a person be tracking and…, and even related to kind of living with the disease and…, and being on a renal diet, which I know Gary was on for a while as well. Are there things, markers, that we can look at that will maybe let the person relax their diet and not be overly concerned about their kidneys for a while or…, or generally should you just always stick to taking care of the kidneys?

Dr. Joseph Mikhael : Well, we all want to hug our kidneys, right, because that's such an important part of our…, of our body, you know, we want to support kidney health. You know, I think there are some basic things and the…, and most critical piece we have learned over the years, the best way to protect the kidney in a patient with myeloma is to control their myeloma because that is…, that is the key feature and some patients were able to completely reverse their kidney damage with good treatment from the myeloma, but unfortunately, as you mentioned, there are lot of people who are left with some…, some damage is permanent. By the time we get there, you know, to mop up things, there is already enough water damage, there is permanent damage to the kidney and so in that situation, you know, its hard to be very general, but there are couple of key principles. You know, things that…, that all of us want to do with kidney health, you know, I live in Arizona and its hot. I mean, today we almost broke record, I think it was 106 degrees. So, I drink a lot of water when I am down here because its hot. Hydration is an important part of our kidney projection. We don't want to make our kidneys concentrate. We want to make sure that they are very well…, very well hydrated is the word. You mentioned the renal diet and yes, there are certain aspects of the diet and I get asked all the time in myeloma, what's the best myeloma diet? Well, there really isn't. There have been some bits and pieces here and there to support one thing or another, but to be honest, it tends to be very motherhood like statements. We all should have a balanced diet, but in patients who have kidney involvement, who want to be careful of high-salt and high-protein load that can be bit more prick the kidney. Other thing that we found is very important is to beware of anything else that can hurt the kidney. Dehydration, of course, can hurt the kidney, but there are certain drugs. Sometimes when people take non-steroidal anti-inflammatories in high amounts or other drugs, that can also, certain antibiotics and so on, can affect the kidneys. So, we strongly recommend before people take drugs that they discuss them with their physician because whereas a person with a normal kidney function can take those drugs and its not going to affect them. Someone who has kidney damage, it can affect them adversely.

Matt Goldman : Okay, great! I appreciate that. That…, that's all I have.

Gary Petersen : Okay. Hey, thanks a lot, Matt. I did drop out there for a while. So, Priya, if that happens again, you can jump in again. You did a great job. You can hear me now, can you?

Priya Menon : Yeah. Yeah. Yeah. Yes, Gary.

Gary Petersen : Okay. Good. Good. All right. Let's move on _____AUDIO BREAK_____ some callers?

Priya Menon : Ah, yes, Gary. Doctor, we have a list of questions sent in by our listeners; and listeners, if you want to ask a question live right now, you can just press 1 on your keypads and let us know so that we can bring you on air. Meanwhile, we will just go through the list of questions that we have already received. The first question, Dr. Mikhael, is, there is a listener who would like to know the significance of the immunofixation test.

Dr. Joseph Mikhael : So, when I mentioned earlier, that's a great question, by the way. Thank you. What we do is what's called the serum protein electrophoresis test. So, when we look for the abnormal proteins that are in the blood, we can…, if you will drill down a little bit deeper and look a little bit more carefully into what's called the immunofixation, the immunofixation tells us a little…, gives us a little bit more detail. One, if there really is no abnormal protein left there at all. So, sometimes someone's had an abnormal protein that's going down, its going down with treatment, to prove that its gone, we do immunofixation because its…, its a more careful look at that protein. The other part of immunofixation is it tells us exactly which kind of protein it is. For some patients, they have IgG or IgA or IgM and…, and it tells us that. So, the most

common use of immunofixation in myeloma is the diagnosis the first time to determine which is the abnormal protein and then secondly, when someone has responded very well and it looks like the abnormal protein has disappeared, we give that immunofixation closer look to determine whether or not its completely disappeared which can put people into, what we call, complete remission as opposed to being near-complete remission when the immunofixation test is still positive.

Priya Menon : Thank you, doctor. We have a caller on line. Person calling in from 907-209, you are on air. Please ask your question.

Caller : Yes. Thank you very much. You know, doctor, we keep hearing about two monoclonal antibodies that are about to be approved and one, elotuzumab, I believe targets the protein CD38 on myeloma cells. Is there a test now that can determine what kind of proteins are on the surface of a person's myeloma cells so that we would know which antibiotic to use against it?

Dr. Joseph Mikhael : Fantastic question! Thank you for raising the issue of monoclonal antibodies. So, you are correct. There are actually several monoclonal antibodies that are being evaluated, two that are quite likely to be approved by the FDA in the next several months, the first is elotuzumab, as you mentioned, although its not directed against CD38. Its directed against a different marker on the surface of…, of the cell called SLAMF7, I know it sounds kind of aggressive, whereas there are two drugs that target the CD38, that are advanced in clinical testing, the CD38 monoclonal antibodies. One of them is called daratumumab and the second is called isatuximab. Trust me, it takes a while to memorize all these names. But, in answer directly to your question, we do have ways of testing. For example, I am running several clinical trials with isatuximab and for the sake of the clinical trial, you have to prove that someone is CD38 positive. Sometimes we do that by flow cytometry or different, but the reality is the overwhelming majority of myeloma patients express SLAMF7 and CD38 on the outside of their myeloma cells. So, if you know that people have that, that almost all myeloma cells have that, then there is less of a need to test everybody because you know that that they are likely to respond because almost everybody has it. So, we are not yet recommending, you know, go check the CD38 status of the disease or the SLAMF7 status of the disease or the newer ones that are coming, CD138 and the others for example. Right now, we know that these were…, were developing drugs that target surface markers that are present in at least the overwhelming majority of myeloma patients.

Priya Menon : Thank you, doctor. We have another caller on line. Person calling in from (308)381-0289, please ask your question.

Caller : Hi, Dr. Mikhael! Most of us are familiar with the free light testing. Could you please explain the value of the heavy light test and also the availability of that test in the United States?

Dr. Joseph Mikhael : Thank you for that great question. So, its a little more involved and a bit more complex, but, you know, myeloma, as I mentioned from the very start, is complicated. Its a tough enemy to follow and sometimes we can follow pretty closely with the serum protein electrophoresis. Sometimes we can follow pretty closely with the light chain test, but there are some patients where its still a challenge and for various reasons and so the heavy light can be helpful, especially in situations where there can be confusing results due to different kinds of proteins in the blood. Now, this has now been an FDA-approved modality. It is becoming more accessible. You know, again, its not something I routinely do on all of my patients. I will save it for patients where there is a little bit of a diagnostic dilemma. There is a little bit of challenge in following them. So… So, I…, I really want to reassure most people that it tends to be a very small subset of myeloma patients that can really benefit from the heavy light and that, in general, now that its been approved, its a little bit more accessible. Lot of different labs will send them into places like our Mayo medical labs because we do so many of them here, but I suspect that over this next year or so, we will see it much more commonly available to people.

Priya Menon : Thank you, doctor. We will just go forward with questions received by email. We have our next listener writing in, saying, I do not have allergies, but my labs always include tests for eosinophils. Why

are these tests done and how do eosinophils relate to multiple myeloma and what do consistently high numbers mean?

Dr. Joseph Mikhael : Thanks for a…, for a great, challenging question. So, the way I try and explain it to people is when we do that first, very first blood test that I made mention of earlier, the…, the CBC as its called or the complete blood count. We look at the…, the red, white, and the rose as they are jokingly called the red cells, the white cells, and the platelets. The white cells are composed of five subtypes of white cells. So, someone…, if someone is looking at their blood work, you look at the total white blood cell count and that total white blood cell count is made up of the five subsets, so they are what are called neutrophils, there are lymphocytes, and there are three others that are much less common of which one is the eosinophil as mentioned in the question and the eosinophils tend to be high in different states. They can be high in allergies. They can be high in certain infections. They can be high in certain leukemias and other blood diseases. Its a routine and standard test whenever we order a CBC to look at all the subclasses of white cells because that can influence very much what we do. Those first two subsets especially, the neutrophils and the lymphocytes, give us a lot of insight as to the protection that a patient has against bacterial and viral infection. Now, interestingly, there are some myeloma patients that just chronically have a slightly elevated eosinophil count. You know, its hard for me to comment on it without knowing all the specifics of this individual patient, but if someone's eosinophils are persistently very elevated, then that might warrant more testing and we can look for other things that might indicate another blood disease or…, or an infection or an allergic condition that is maybe not fully recognized, but for the average myeloma patient, we really don't see significant abnormalities in the eosinophil count. Sometimes they can even actually just be a reflection of a drug that someone is taking and someone has a very mild reaction to it, but I would…, I would say to this…, the person who asked the question, if its significantly elevated repeatedly, its probably worthwhile that your physician looks into it little bit more, but its not uncommon to have a slight elevation intermittently in myeloma.

Priya Menon : Thank you, doctor. The next question is, why is magnesium tested?

Dr. Joseph Mikhael : So, when we do the second part of the blood test that I mentioned, the chemistry, one of the things we like to know from the chemistry in the blood is, what are the basic, what we call, electrolytes, like potassium and sodium and so on, because those give us a sense of the general quality of the blood that can be affected if someone has a high calcium count or has kidney failure or something and in that series of…, of less common but still relatively important chemicals in the blood that can indicate nutritional status and other challenges and one of them can be magnesium. I must say, we don't routinely order magnesium in all of our myeloma patients on a regular basis. We might do it initially when we are trying to assess someone's nutritional status and…, and making sure that their chemical system is working in general, but magnesium is not something we do routinely. We might see a little bit more of it around the time of someone going through an autologous stem cell transplant because their nutritional status tends to be affected and their gut may not be absorbing things as well and so its not surprising that some patients require supplemental magnesium, but in the regular myeloma outpatient, magnesium is not usually repeated.

Priya Menon : Thank you, doctor. The next question is, is it better to follow kappa or free light chain lab numbers or M spike numbers to monitor relapse?

Dr. Joseph Mikhael : I think the right answer there is both, to be very honest, because as I mentioned before, you know, whichever one was abnormal to begin with, you want to continue following, but we have individuals who have always been followed by an M spike, but then a relapse all of a sudden the M spike has not gone up but the light chains have. We sometimes even call that light chain escape and that's part of that evolution of the disease as I call that the clonal evolution that can sometimes happen. That can be a real challenge and…, and I know it means a fair amount of testing, but very often we want to see that change because it…, it indicates to us that the disease is re-growing again and let's say someone who is only checking the M spike and the M spike, say, "Hey, well my M spike hasn't gone up, everything should be okay," but meanwhile the light chains are climbing. Its affecting the body. It may cause damage to the kidneys and all that may have been preventable if…, if they were detected earlier. So, in general, for most

patients, when we follow them, we do that complete blood count. We do the chemistry and we are doing both the serum protein electrophoresis and light chain testing in followup, watching for potential relapse.

Priya Menon : Thank you, doctor. The next question is from a smoldering myeloma patient. The listener writes in, in my most recent lab test, my urinary protein increased significantly from a fairly stable number, while most other tests remained stable. How much of an increase or decrease in any one result should be seen as significant?

Dr. Joseph Mikhael : That's an extraordinary question, actually, and its one of the things that even on a diagnostic criteria, we are very careful to note that, you know, sometimes a single blood test can just be off, you know. Myeloma is a complex disease and sometimes someone's light chain shoots up or there is a little extra protein in the urine once or the M spike fluctuates a little bit and so that's why we tend not to make any major therapeutic decision on the basis of one single blood test, unless, of course, its a, you know, astronomically abnormal test. So, in a situation where someone's being followed for smoldering disease and all their parameters are stable, but let's think maybe there is a little bit more protein in the urine, we go back and say if there is anything unusual about the collection, did someone have something unusual happen to them, or were they sick around the time of the collection and then to validate it usually within a month we will repeat it a second time to see if its genuine because one of the ways that smoldering myeloma can, if you will, awaken into true myeloma is through protein that can be detected in the urine and usually its also detected in the blood in the form of a light chain, but there are some small subset of patients where the light chains never become abnormal in the blood but only in the urine. So, it could be just a red herring as it were or it could genuinely be a problem. So, we usually wait four weeks or so and repeat it to see if there is a consistent trend because its always the trend that's more important than a single test.

Priya Menon : Thank you, doctor. I think that's a complete list of questions that we have received so far. I think Jack has one more question for you. Jack, we have time, maybe we can…, you can ask your question.

Jack Aiello: Sure. Its more of a future question than anything else and that is, with the likelihood of antibodies like elotuzumab and daratumumab getting approved over the next six months, do you expect any of these to be incorporated in the mSMART protocol for relapsed myeloma?

Dr. Joseph Mikhael : Oh, for sure, absolutely! I mean, we are constantly updating mSMART because myeloma, thankfully, has more options than we had before, I mean we had early iterations of mSMART before we had drugs like carfilzomib and pomalidomide and now panobinostat and before long, quite likely elotuzumab, daratumumab, isatuximab, and a whole series of others that are coming. So, the short answer is yes. It will influence, you know, our guidelines and therapy…, suggested therapy for patients and that's good because we want more options for our patients. Many of these drugs when they do initially appear will quite likely appear in the heavily relapsed setting, but I can speak even specifically of the monoclonal antibodies and the CD38 monoclonal antibodies that there has been a lot of interest in bringing those even into the very early phases if not the upfront phase of treatment for myeloma. So, a lot of it will depend on how the FDA approves it and what indications are given, but ultimately we recommend it and goes to the NCCN or the mSMART guidelines, but I would definitely encourage people to keep abreast of this because I think we are entering an even more exciting era for myeloma. We are going to have more options for our patients that we hope will translate to both a better quality and quantity of life.

Jack Aiello: – Oh, that's great news. Thank you very much.

Priya Menon : Thank you, Jack. Dr. Mikhael, thank you so much for sharing all this information with us. I think this has been an hour filled with useful information for our listeners. Gary, Jack, Cindy, and Matt, thank you for your participation. This talk will be made available on CureTalks' website along with its transcript. Please visit curetalks.com for details on our upcoming talks. Thank you, everyone.

Dr. Joseph Mikhael : Thank you.

Gary Petersen : Thank you.