FAQs on Multiple Myeloma Precursor Conditions

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Transcript

Mary DeRome (MMRF): Welcome, and thank you for joining us for today's session. I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation. I am joined by Dr. Ola Landgren and Mr. Dennis Verducci from the University of Miami Sylvester Comprehensive Cancer Center in Miami, Florida, and Lonni McDonough, a patient from Boise, Idaho. They will answer some of the frequently asked questions we receive from patients and caregivers about the precursor conditions monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM).

Many individuals in our audience who have multiple myeloma often wonder if they had previous signs or symptoms that were a clue of MGUS or SMM. Some have asked whether pruritus or neuropathy are potential symptoms. Dr. Landgren, how do most people find out that they have one of these myeloma precursor conditions? Do patients experience any specific symptoms?

Ola Landgren, MD, PhD: Typically, the precursor conditions of myeloma do not come with symptoms. Monoclonal gammopathy is very common in the general population. In people who are 40 years or older, you can probably find it in about 2% or 3%. Most people are completely unaware that they have it.

Having a protein in the blood does not impact any organ systems, at least not in those low concentrations that these conditions have. SMM is when the disease is between the earlier stage MGUS and multiple myeloma. To emphasize, this was proposed based on a case series of only 6 cases, about 40 years ago, so in 1980. It was proposed that maybe this was a separate entity, and that has become established. I predict that it will probably go away and we will go more towards MGUS and multiple myeloma. But there could still be cases in the SMM category when we cannot really determine which of the two categories these individuals are in.

But for now, the standard-of-care is to talk about MGUS, SMM, and multiple myeloma. SMM is usually asymptomatic. But some cases lean more towards myeloma and patients have symptoms although they don't fulfill the diagnostic criteria for myeloma such as pain or recurrent infections.

Mary DeRome (MMRF): After a long time, finally MGUS and SMM seem to be getting the research attention that they deserve. This is a rapidly developing field.

Dennis, do we know what causes MGUS or SMM? Many patients ask whether previous radiation treatments for a different cancer or other conditions such as Bell's palsy, sarcoidosis, or light chain amyloidosis are related to having the precursor conditions?

Dennis Verducci, MSN, RN, NP-BC, OCN: Unfortunately, we don't know what causes these precursor conditions or myeloma. But we have identified some environmental factors that increase the risk of developing precursor disease.

Dr. Landgren did a study that was published in the *JAMA Oncology* in 2015 where he looked at the use of Agent Orange in veterans. The study showed an increased risk in veterans who sprayed Agent Orange as opposed to those who did not. So, Agent Orange is a risk factor. Additionally, when Dr. Landgren and I were at Memorial Sloan Kettering in New York, we did a study that looked at the correlation between exposure to aerosolized dust and toxins from burning jet fuel in first responders and clean-up crew at the 9/11 site and MGUS. The results showed they had an increased incidence of MGUS.

Are other conditions such as Bell's palsy, sarcoidosis, or light chain amyloidosis related to multiple myeloma precursor conditions? In the years I have been a nurse practitioner, the cases of amyloidosis that I have seen have had underlying MGUS.

I'm sure there are rare cases where patients do not overexpress light chains in the blood but do have some evidence of amyloid somewhere, whether it is in the gut, heart, bone marrow, or other tissue such as the kidneys. But in my experience, the patients had an underlying diagnosis of MGUS as well.

Mary DeRome (MMRF): A patient asked us on a recent webinar regarding the other conditions such as sarcoidosis and Bell's palsy, and the faculty that was present talked about how the immune system can be really affected by multiple myeloma. Sometimes you can have these autoimmune like reactions with multiple myeloma, which is what these sorts of diseases are, especially sarcoidosis.

Dennis Verducci, MSN, RN, NP-BC, OCN: Yes.

Mary DeRome (MMRF): Dr. Landgren, Dennis mentioned the studies that you have done around the 9/11 site, and you've published a number of papers on them. Can you elaborate a little bit more about your study and findings?

Ola Landgren, MD, PhD: Well, you're referring to the individuals exposed to the World Trade Center disaster. We did a study a few years back where we looked at the onset of different types of cancers in the first responders. It looked like there were more myeloma cases than you normally would see. But because myeloma is still a rare cancer that happens in about six individuals per 100,000

person years, it’s not easy to know whether an increase is due to randomness or if it’s due to a true biological increase. So, if you have, for example, nine cases or ten cases, that's more than six cases. But it's just a few more cases. So how do you really know? You must do a study that includes a lot of people with a long follow-up. That makes it more complicated to study.

One reason we know multiple myeloma is associated with MGUS is all patients who have myeloma previously had MGUS. The conversion rate of MGUS to myeloma is not known to be different in different settings. So, if there’s an increased risk of MGUS, the rate of conversion to myeloma seems to be the same. For that reason, we designed a study where we screened for MGUS in the first responders because there are more MGUS cases than there are myelomas so from a statistical point of view it could be an easier task to address.

We found a doubling of risk in the first responders. The criticisms one could raise, obviously, is that the first responders are fire fighters who put out fires all the time, so they went to many other places before the World Trade Center disaster. So, could this be because they had been exposed elsewhere? We did a follow-up study, which we published in August of 2022, that involved over 1,000 police officers and construction workers who participated in the cleanup of this disaster. Unfortunately, their blood shows the same increased risk as in the fire fighters. So, this is in my opinion mounting evidence that there is an association. We don't know yet what the carcinogen is, but exposure during the 9/11 cleanup seems to correlate with a higher incidence of MGUS in all these different groups.

Mary DeRome (MMRF): Such an interesting correlation, and then thinking about Agent Orange as well. So, this is a very active area of research trying to figure out what those triggers are. Lonni, can you tell us how you learned that you had SMM? What led you to see your doctor, and did you get a second opinion?

Lonni McDonough: I was diagnosed back in April of 2021. I wasn't really having too many symptoms. I had some fatigue, and some low red blood cell and white blood cell counts, but nothing that was too concerning to my doctor.

It wasn't until I did the DEXA scan, and it showed that I had osteoporosis, that she grew a little bit concerned. So, she decided to send me to a rheumatologist who was fantastic. He spent over 1.5 hours with me. We went through my history, he asked me a ton of questions, and we talked about bisphosphonates.

Before I left, he said, “Hey, would you mind if I run a couple more tests just to rule a few things out?” I never asked any questions like what the tests were or what he was trying to rule out. So, when he called and said, “Hey, we found some protein in your blood and in your urine and I’m going to send you to a hematologist oncologist.” I was really surprised.

So, we met with the hematologist-oncologist, and she explained that I might have multiple myeloma, which I'd never heard of before.

She ran a plethora of other tests including a bone marrow biopsy, an MRI with contrast, a skeletal survey, and a lot of tests. During the time that I was waiting for the results, I looked up everything that I could about myeloma. She called me back in and we were happy yet sad that it was SMM. But I was grateful that the doctor had spotted it early, and we were able to do something about it. But at the time, she said your numbers are such that we can start treatments on you. But I had done enough research to know that this was a very complex disease, I really did need to get a second and probably even a third opinion. We're in a small city, so we don't have any myeloma specialists here. So, I went about searching for the best and that's how we ended up consulting Dr. Landgren.

We were so happy we did because the specialists all agreed that I probably did not need to start treatments, we just needed to monitor my disease with labs every quarter to see how my disease progressed or didn't progress and how it behaved over time. So far so good.

Mary DeRome (MMRF): So, it's more like watchful waiting with you, right?

Lonni McDonough: Correct.

Mary DeRome (MMRF): Dr. Landgren, on our webinar on precursor conditions, we learned that not all patients with MGUS or SMM are the same. Some patients are more likely to progress to multiple myeloma than others. So many questions we've received from patients is them trying to understand what their personal risk of progressing is, which can be a complicated thing.

So can you summarize for us the general progression risk for both MGUS and SMM and the personal factors that might make a patient's trajectory to multiple myeloma faster or slower, such as lab values or other comorbid conditions, et cetera.

Ola Landgren, MD, PhD: I should say that many years ago, it was believed that there was no correlation between these monoclonal proteins and multiple myeloma. The person who initially discovered the monoclonal proteins was Dr. Jan Waldenström, who also has given name to Waldenström's macroglobulinemia. He did all the basic work, all the discovery work, and all the translational work. He was of the strong opinion that there was absolutely no correlation between these proteins and multiple myeloma. He said it's a benign condition.

But Dr. Robert Kyle, a clinician from Mayo Clinic, had collected a lot of patient records. He had seen some patients who developed myeloma, so he wasn't sure. But Dr. Waldenström had done all the work in the laboratory and developed all

the assays with Dr. Laurel who was a chemist. With these two different schools of thought, Dr. Kyle collected a few hundred charts from individuals with monoclonal gammopathy and he found there were a few people who did progress. But to not offend anyone, he said of course we don't know, let's call it undetermined. So that's why he proposed MGUS. Over time, the Mayo Clinic continued to collect patient records that showed on average the conversion rate was about 1% in their series. Other groups have also collected series including Dr. Waldenström's group after he had passed away. It has been published and in their hands, the conversion rate is only 0.5%.

I think the differences could be that in a referral center such as the Mayo Clinic, probably people who have a higher risk than what you see in the general population go there. So, what is the true conversion rate? I don't think anyone really knows. But somewhere in that range. We also talked about SMM, and I was intentionally trying to be a little bit provocative when I said I'm not sure that it really exists. In the case series published in 1980 proposing this new terminology, none of the patients had progressed and the longest was followed for I think 16 years. The paper said that one cannot progress. It was written by Dr. Bob Kyle, but he continued to collect series and he proved himself wrong. He published the findings many years later that showed in 300 cases the conversion rate was more in the range of about 50% after having followed people for about 5 years.

There are other groups that have continued to collect cases, for example, the group in Spain has collected cases. We collected cases at Memorial Sloan Kettering, the NIH has, and many other groups as well. I think very importantly, none of these models talk about an individual's risk. They talk about the group risk. All the different models put people in low-, intermediate-, and high-risk based on different factors. But what is extremely important to remember is that in the low-risk group their risk of conversion to SMM might be 25%, in the high-risk group 75%, and in the intermediate group 50%. That tells us that there are people who progress in all the groups and there are people who don't progress in all the groups too. So, you can be high-risk and not progress, and you can unfortunately be low-risk and still progress.

This is true for all these different models. What is currently not available is an individual test like a pregnancy test. So, if you tested women and told them that they have a probability of becoming pregnant, no one would really use those tests. You would like to know if you are pregnant or not.

You could say that women are more likely to be pregnant than men and that is true and that is similar to the current MGUS and SMM models. But the pregnancy test for conversion doesn't exist. We have launched a study called the TRANSFORMM study where we are using whole genome sequencing and we welcome patients to come and be tested here. It is still a study, so we don't have the results. But that's the only option right now.

Mary DeRome (MMRF): So, what about some personal factors that may identify people as being at a higher risk of progressing from MGUS to SMM?

Ola Landgren, MD, PhD: Again, we are talking about groups of risk. So, for people who are in the group of lower risk, they would typically have lower concentrations of monoclonal protein, fewer plasma cells if a biopsy is done, and lower amounts of the free light chains. Other factors as well, like quantity of the immunoglobulins, if they're low or normal, could increase the risk.

All these models provide information for groups of people. So, within the group, people could go either way. But on average, the different groups have different probabilities. Lastly, one can look at these models and criticize them, but currently, they are the best we have. If you follow a person over time and the marker stays stable, then that is probably the best practical measure of stable precursor disease that we currently have. If the M protein goes up, if the light chains go up, if the quantity of immunoglobulins go down over time, those are probably markers of change or progression. But what we are trying to do is to develop genomic tests that can give the answer right away. Currently, we don't have those tests available.

Mary DeRome (MMRF): Dennis, once a diagnosis of MGUS or SMM has been established, how often are patients followed for these markers? Most importantly, patients want to know what tests to expect and if bone marrow biopsy is always part of the routine follow-up. When is more frequent follow-up necessary? Are there patients for whom testing and follow-up is no longer needed?

Dennis Verducci, MSN, RN, NP-BC, OCN: For MGUS patients the guidelines would tell you to check labs in about 6 to 12 months. For our patients who are newly diagnosed, we tend to check labs every 6 months at least 2 times. If everything is stable in that timeframe, we're very comfortable going to annual follow-ups with bloodwork. Patients with SMM have a higher burden of disease, so the guidelines would say to check labs every 3 months. So, about 4 times a year. That's pretty much what we follow.

I will say that myeloma is a very gray area disease and there are multiple ways of doing things. So, this is also very subjective. We have patients with SMM who we've followed for many years and because their markers have been stable for so long, we're very comfortable pushing those patients' testing out to say 3 times a year. So, we check them every 4 months or even every 6 months. We don't always do bone marrow biopsies for patients with MGUS.

Again, it's very subjective, it depends on how high a burden of disease the patient has. If we do the bloodwork on a patient and we see that there's a little bit of monoclonal protein, but the patient feels well and has no associated symptoms, many times we'll defer a bone marrow biopsy. Of course, we'll

monitor them, and we'll be quick to obtain a staging bone marrow if we see the labs start to trend in the wrong way.

But it’s not something that we do automatically. For patients with a higher burden of disease, you absolutely want to do a bone marrow biopsy and any type of imaging such as a PET/CT or a whole-body MRI, which are the two gold standard tests for plasma cell disorders. When is more frequent follow-up needed? It’s very important to know that when you're following the patient’s bloodwork, you're not going to get the same labs across the board. So, we want to look at the trend of these markers.

We're looking for patterns, so we're not necessarily looking at what one data point was. We're looking at what all the data points are and how they relate to one another. If we see a trend that these markers are heading in the wrong direction consistently, then we are quick to do another bone marrow biopsy to restage them.

This is because you want to make sure that this patient is not progressing to active myeloma. If the patient is complaining of some focal pain, their back is hurting and it’s new pain that hasn't gone away, or they have some discomfort in their hip and it's unusual pain, those are the type of patients with SMM who you want to be very quick to image. Because, again, you want to rule out progression.

Mary DeRome (MMRF): Lonni, do you have high-risk SMM? How are you managing your condition? For instance, how do you coordinate your care with Dr. Landgren and Dennis over such a long distance? How often do you see your care team and what tests do you receive?

Lonni McDonough: Yes, so I am considered high-risk based on my myeloma markers. I have a high-risk cytogenetic feature. Currently, the way that we coordinate our care is that Dr. Landgren and Dennis will send me a requisition for my labs to be drawn at a hospital. They gave me the option of them working with my local hematologist oncologist. So right now, they’ll send me that requisition every 3 months, I’ll do the labs that Dennis just went through, the M-spike, immunoglobulins, light chains, and CBC. Once those lab result are back in, they’re uploaded into my chart and then we have a telehealth call, a Zoom call together.

We go through all the results, I ask all my questions, and we talk about next steps. I recently joined a clinical trial with Dr. Landgren, so in addition to that I’ll go down and see him in person once a year and we'll do an annual bone marrow biopsy, the whole-body MRI, and any additional labs that might be required. But it’s just working. It’s very easy and efficient. We just feel so grateful that we can be here in Idaho and still have access to the best care team available.

Mary DeRome (MMRF): Dr. Landgren, at what point is MGUS or SMM considered myeloma?

Ola Landgren, MD, PhD: So, there are definitions for every condition in the medical literature. Multiple myeloma is a clinical diagnosis, we currently have 7 variables that we are looking for. They are the CRAB markers, so hypocalcemia, renal failure, anemia, and bone lesions. The three additional ones are number of plasma cells, number of light chains, and also presence of focal aggregations in the bone marrow on MRI. So, we look for those variables and if they are not there, it is not multiple myeloma. The difference between MGUS and SMM in the textbook currently is how many plasma cells are in the bone marrow and also the concentration of monoclonal protein.

Mary DeRome (MMRF): Okay, so we've also received several questions regarding the effect of MGUS and SMM on bones.

Dennis, are patients' bones at risk when they have a precursor condition? Many in our audience ask about osteopenia or osteoporosis, which is one of your symptoms, Lonni, right? So, what are these conditions, and are they a direct result of MGUS or SMM?

Dennis Verducci, MSN, RN, NP-BC, OCN: No, having a precursor condition such as MGUS or SMM does not increase your risk of bone disease. There is a very large population-based screening study done in Iceland involving over 80,000 people aged 40 or older. The study showed no evidence of patients with MGUS or SMM having more bone disease than the general population.

There are also many randomized studies that have tested whether the use of bisphosphate therapy could potentially slow down the rate of progression. They all show that there is no impact on the rate of progression for patients with MGUS or SMM. One of those studies was terminated prematurely because patients had developed osteonecrosis of the jaw and/or renal failure.

The conclusion was that there was more toxicity than benefit. Now, it is possible for patients with precursor disease such as MGUS or SMM to have a separate diagnosis of osteoporosis or osteopenia. They should be treated per the recommended guidelines for the general population.

Mary DeRome (MMRF): Dr. Landgren, what is the risk of patients with MGUS and SMM getting COVID-19 versus the general population?

Ola Landgren, MD, PhD: That's another big topic that we have been asked about many times. Of course, a lot of people worry about it. So, I think the important answer came from this Icelandic study. I'm the co-principal investigator together with Dr. Sigurdur Kristinsson in Reykjavik for this iStopMM study.

We looked for people with MGUS who had been infected with COVID-19, and we compared them with people who did not have MGUS who were infected by COVID-19 to see if there was a difference in their prognosis. There was no difference. Patients with MGUS don't have worse outcomes compared with people who don't have MGUS. We also looked at people with a higher burden of MGUS and compared them with individuals who did not have MGUS. Again, there was no difference. So, from this very large study of 80,000 people we screened in Iceland, there is no evidence that there's a higher risk of contracting the virus. There is also no evidence that the virus would act differently compared with the general population. I think that's great news. When it comes to SMM, there is less information and partly because it is much less well characterized in the literature.

Some studies suggest that maybe there is a higher risk of contracting the virus compared with the general population. But I don't know, I'm not so sure that is the definitive truth. Because a lot of these studies that have been done in people seeking medical attention, so they go to the centers. If you really want to investigate it, you must screen the population, so that you don't build in any bias. If you stand outside the supermarkets and ask people if they want to participate in the study, already you have a bias. This is because there are people who don't want to go to the supermarket, and they order food home, so people who go to the supermarket are maybe more risk-prone in general. So, every time you do a study, you will always, unfortunately, build in some form of bias.

That is still true for the SMM category, so to me, it is still an unknown. I think it boils down to what risks people are ready to take. The last thing I also want to say is that the virus has changed dramatically over the past few years. I led the program for myeloma at Memorial Sloan Kettering when we were hit by the virus in New York City. We had very many patients in the hospital with the virus. Many of our patients were very sick, and we had, sadly, people who passed away. But if I look at how the virus is impacting our patients here in Miami, I think today we have zero patients in the hospital with COVID-19 and myeloma. I think overall for the hospital, there is no increase in the rate of people with COVID-19 coming to the entire hospital. I think the virus really has slowed down. But, of course, still viruses can impact individuals. We know the flu can be bad for some people.

Mary DeRome (MMRF): Dennis, many patients with SMM and MGUS ask who they should communicate their diagnosis to in specialties outside of hematology-oncology. For example, if their primary health care provider asks for their medical history, should they tell them that they have cancer?

Dennis Verducci, MSN, RN, NP-BC, OCN: MGUS and SMM are premalignant conditions, but they are not cancer. It's always a good idea to give a thorough history to any health care professional, such as a cardiologist, rheumatologist, or nephrologist. Of course, any doctor that the patient has should always be aware

that the patient has MGUS or SMM. But I want to just reiterate that they are not cancer.

Mary DeRome (MMRF): Dr. Landgren, many patients in our audience want to know if their family members should be screened. What is the current recommendation on screening for precursor conditions or myeloma?

Ola Landgren, MD, PhD: In the general population, there is no guideline saying that screening should be conducted. In the Icelandic study that we talked about; the primary end point was to see if screening is beneficial. In a nutshell, that study has a randomization. All people in Iceland 40 years or older were invited to participate, and 80,000 agreed and had their blood drawn. By the study design and consent, about one-third of individuals were not notified but were just followed, if they had MGUS. And two-thirds of the people who were found to have it were notified. This is all per the consent people agreed to when they participated in the study.

The two-thirds were split into two groups; one group was monitored the standard way that we have been talking about and the other group was monitored a little bit more closely. The primary end point of this study is to see if screening has clinical benefit. If it shows that there is benefit, I think that would make the whole world say that screening should really be done.

If you are in a high-risk population, say we talked about the World Trade Center disaster, could you choose to do blood tests? I think it's a personal choice if you're exposed to chemicals. We have not talked about other studies that we did a couple of years ago. We looked at people who have been exposed to pesticides and found an increased risk in them as well. In fact, the rate of myeloma in the middle of the United States is about 50% higher than you see on the East and West Coast.

Maybe there are environmental or other factors that we don't really know. I think pesticides probably play a role. So, there is not yet a formal guideline, but I think it would make sense for some people to choose to do it at their own discretion. Lastly, we published years ago that a blood-related family member of someone with myeloma, MGUS, or SMM would have about twice as high of a risk. So, children, siblings, or parents statistically speaking have about twice the risk. We don't know why that is, and if it's because they share genetics, environment, or both. I guess relatives may want to do screening because they probably statistically are at a higher risk. But it's a personal choice right now.

Mary DeRome (MMRF): Lonni, what about your family history? Did you have any family members who had a precursor condition or multiple myeloma?

Lonni McDonough: So, like most people these days, our family has been touched by cancer. My father died of lung cancer, but to our knowledge no one

on either side of my family has had myeloma or its precursor or any blood cancer for that matter. So, I'm the first and hopefully the last.

Mary DeRome (MMRF): That's good news. My mom was diagnosed with myeloma when she was 80 years old. She passed away 5 years later but from unrelated conditions. So, she did not have an aggressive form of myeloma at all. So, I've already been screened.

People can get screened using the PROMISE study that's ongoing at the Dana-Farber Cancer Institute that's run by Dr. Irene Ghobrial. So, look it up, and you can enroll in it if you're interested in being screened whether you have a precursor condition or not. They will send you a blood kit and then you can take it to a phlebotomist and get your blood drawn, and then they send it to a lab.

I came back negative, and I have a friend who's mom was also diagnosed with myeloma, and she did the test, and she came back with just a little bit of protein in her blood. They're going to screen her in a year. But it's a good way to get screened in this ongoing study, and a great way to add your own data to this huge pool of data that is being collected on these conditions. So, I recommend it highly.

Dr. Landgren, what is the standard-of-care for patients with a precursor condition? Is there one?

Ola Landgren, MD, PhD: Currently, there is no FDA-approved medication for MGUS or SMM. So, the standard-of-care would be monitoring, so watchful waiting. We said the average conversion rate for MGUS is between 0.5% and 1% per year. To justify using treatment, is hard. Because if the therapy also has side effects, that will mean more people having problems than potentially benefitting from it. Now, the SMM numbers are slightly different. But again, I think it comes back to what we talked about a little bit earlier that we don't have that pregnancy test equivalent. If we knew who was going to progress, that would erase the question about how to manage it in the most optimal way.

I think what's going to happen is that these types of tests will come. That is where the TRANSFORMM study comes in that I mentioned we have here in Miami.

Mary DeRome (MMRF): Can you tell us a little bit about that study?

Ola Landgren, MD, PhD: So, the TRANSFORMM study was developed as an extension of a lot of work we have done previously when I was at the NIH and when I was at Sloan Kettering. We spent a lot of time doing the screening and also collaborating with the Icelandic group. So, my focus scientifically has turned from screening to trying to understand who is going to, unfortunately, progress and who is not, and how to stop the progression. So, that's where we put all our focus right now. So, this study is designed as a screening study, it's open for a

total of 1,000 individuals. We have support from large foundations like the Tow foundation among others.

People can enroll and do a bone marrow biopsy and bloodwork. The study says that the individual can come back on an annual basis for up to a maximum of 5 time points, so 5 years in a row would be the maximum. The reason the study is designed like that is because we want to look at the baseline sample to see if we can identify the genomic signature that we published last year in *Nature Communications*. We showed that with a particular signature that looks almost identical to multiple myeloma, around 95% of individuals progressed within about 2 years. So, we can identify that signature, and then offer those individuals, if they are interested, more intense monitoring or earlier intervention. There is a companion treatment protocol that we are also opening very soon.

Most importantly, we hope, of course, to see that people don't have this signature. The next question is then is if there is a risk that people without the signature could get it later. That's why we offer people to come back for testing for up to a total of 5 years. What we're trying to do is to develop a test that can identify the genetic signature for progression. That's the scope of the study. But there is also a partner test in the blood, so once the bone marrow component is hammered out, the blood is stored and we will then use that for biomarkers to correlate those two.

The study is open for enrollment. Any person around the world who has MGUS or SMM who wants to come here can participate in the study. We have people coming from very far away.

Mary DeRome (MMRF): Dennis, is it worthwhile for patients with SMM or MGUS to harvest their stem cells for future use if they progress to myeloma and they need to have a stem cell transplant, et cetera?

Dennis Verducci, MSN, RN, NP-BC, OCN: Collecting stem cells for precursor disease is not standard-of-care, and it’s not something that we do in our clinic.

Also, because this is not in any of the guidelines the insurance company likely won't even pay for it. So, for that reason, I would not advise patients to have collection of stem cells. It's not something that we do. So, one would collect stem cells with the premise that they will have the option to do transplant if the patient progresses to active myeloma.

However, the way we treat patients is if the patient develops active myeloma, you can collect stem cells in the middle of induction therapy. It’s not something you do when they have MGUS or SMM.

Mary DeRome (MMRF): Lonni, you mentioned that you are enrolled in Dr. Landgren’s trial, which he just described. What was your reason for enrolling? Do

you think that all patients with MGUS and SMM should be asking their doctors if they're eligible for a clinical trial? I know that there are some clinical trials open, especially in the SMM space. They seem to be particularly effective for patients who have high-risk disease.

Lonni McDonough: I think Dr. Landgren had me with the pregnancy test example. The very first time that we consulted with Dr. Landgren, he mentioned the TRANSFORMM trial. He didn't call it that at the time but explained that it was to help determine who was high-risk and who wasn't. But it was early on in my diagnosis, so the trial wasn't open yet. About a year later, I heard him speak on another forum about the TRANSFORMM trial. So, I contacted his office and we set up a meeting and he and Dennis went through the details. For my husband and I, it was a no-brainer. I knew early in the diagnosis that I wanted to be part of a trial but didn't know which one. I was keeping my options open, but I firmly believe that we need participation, and knowledge is power. Everyone's different and this is a personal journey for people. But I think that all patients should be informed and ask their doctors about trials that they might be eligible for.

If you're not into having treatments, there are all kinds of options like the one that I'm in is observation only at this point. There are amazing things happening in the field and I'm grateful to everyone who's participated and to scientists and doctors like Doctor Landgren that do this work. I knew that I wanted to be part of it.

Mary DeRome (MMRF): The myeloma community has made great strides in discovering new therapies for this disease. Things are so much further ahead than they were 10 or 15 years ago. It's all because patients have volunteered to join clinical trials, and no new drugs would be approved without patients doing that. So, thank you for volunteering.

Dr. Landgren, at our webinar last month, Dr. Sagar Lonial from Emory University spoke about ongoing research on the role of gut microbiome in precursor conditions at his center.

So, does this mean that diet and lifestyle may help prevent progression to myeloma? What are your thoughts on that?

Ola Landgren, MD, PhD: Yeah, that's an area where I think there is a lot of interest. We have an NIH grant and RO1 grant in collaboration with New York University and Dr. Gareth Morgan where we have basically a model where we believe that what we put in our mouths go into the gut and it interferes with the immune system, which maybe spills over and impacts what's going on with plasma cells in the bone marrow. So, we think that there is some stepwise process that could drive what's going on in the plasma cells. There are studies that have looked at biomarkers of immune activation when it comes to obesity, for example.

People with obesity have very high levels of immune markers, which have also been found to be elevated in people with myeloma. Some studies have shown that people with MGUS that has converted to myeloma seem to have slightly higher levels of these markers. So, all these different pieces in the puzzle have been found, but no current study has looked at all the different steps showing that what you eat impacts your weight, markers, or leads to progressive MGUS.

The RO1-funded study is investigating it and I think Emory, as you mentioned, have studies they are working on. Sloan Kettering also has Dr. Urvi Shah who is interested. She developed a study where she offered plant-based food to see if that could slow down the MGUS conversion rate. I thought that was a fun idea to pursue, to see if food could be used as medicine. That study is not yet complete. But that's what I know from the current literature and from talking to other people.

Mary DeRome (MMRF): How best can patients with MGUS or SMM cope with their diagnosis? It must be stressful knowing that one has a disease that may eventually progress to multiple myeloma. But at the same time, there's no treatment outside of a clinical trial and there is no guarantee that you are going to progress. So, everything is very uncertain.

Lonni, how do you deal with this diagnosis?

Lonni McDonough: First I would say that the most important thing is to have a myeloma specialist on your care team. These doctors only deal with myeloma and they're experts in this quickly evolving field. So, they're up to speed on the latest science, treatments, trials, and can really put your mind at ease so you know that you're in good hands.

Secondly, I do know personally that this diagnosis can cause a lot of worry and stress. You're constantly feeling like the other shoe is going to drop, right? However, I would just say continue to do the things that bring you joy. Don't let this diagnosis rob you of living your life to the fullest. You may be one of those people who progress, or you may not progress for many years. There's a lot of wonderful things happening in the field and the future is bright. Be present in every moment and trust and enjoy your life.

Mary DeRome (MMRF): Dennis, what advice do you give your patients who have been diagnosed with precursor conditions?

Dennis Verducci, MSN, RN, NP-BC, OCN: I think it's very important to have a very good support system at home. I would also advise patients to join support groups whether on Facebook or with MMRF or any other myeloma brand. I'm also a very big fan of 'knowledge is power', so I think the myeloma team must do a thorough job of educating the patient. I think it's important, especially at initial diagnosis to do a thorough review of the biology of the disease, and how to monitor it because most patients are going to get labs so often. Patients with

SMM will get labs pretty much every 3 months and patients with MGUS every 6 months to 12 months, I think it's very important for the clinical care team to hone in on lab interpretations with the patient because there's so many fluctuations in these labs.

I always try to drive home to my patients that they're never going to get the same number across the board. I know from a patient's perspective, and I see it all the time, that they want to hone in on lab details. A lot of times when we see these patients for follow-up, they're very upset because they think that their disease is progressing. I review with them and tell them to look at the trend of these labs, not just one data point.

One must look at the trend of these labs. I think that's very important because patients need to know this. Because if you do a good enough job of educating the patient, they can pretty much look at their own labs, and they'll know that everything is fine and then we just review with them at follow-up. But that time between them getting the labs and their follow-up with myself and Dr. Landgren can be very stressful for the patient. I think more education alleviates some of that anxiety for them.

Mary DeRome (MMRF): Dr. Landgren, I'm going to give you the last word. What advice do you give patients who are diagnosed with precursor conditions? Also, give us a little taste of what you think is going to happen in the field in 5 or 10 years.

Ola Landgren, MD, PhD: First, being diagnosed with a precursor condition is not a disease, it's a condition. So, it doesn't make the person sick, so it doesn't make the person a patient. MGUS, for example, is not a disease that makes a person sick. The same is true for SMM because most people will never progress. Most people with MGUS and SMM will never progress. That's a fact. Now, unfortunately, some individuals will progress.

The best thing is to look at the facts, monitor carefully, and work with high-quality data. Whether there's a local place that can monitor, or you have a second opinion and you work in collaboration with that second opinion and a local place, or you chose to go to a specialized center, I think high quality details and facts are very important. I often see people who have been worked up and been told that they can start chemotherapy. When you look through the details, they don't have the disease that qualifies for therapy. So, I think having a very careful workup and going to the facts is critical.

I think the field will be moving forward. I do think we will have the equivalent of the pregnancy test for myeloma not too many years away from now. They will probably eventually be blood-based tests. We don't know what the exact platforms will be, whether DNA- based, protein-based, or some other technology, but I think we will have these tests.

Also, in parallel, there are so many new drugs that are being developed for the treatment of multiple myeloma. So, a newly diagnosed patient today probably has 20 years plus overall survival on average. I think we are at a tipping point where many patients will probably have the same lifespan if they are diagnosed with myeloma versus if they had not been diagnosed with myeloma.

I was a doctor when HIV was an incurable disease in my early career. It used to be a death sentence. Today patients with HIV have the same lifespan as the general population. I think myeloma is heading very fast in that direction. So, the worst-case scenario from where we currently are would be having to get therapies.

I think the therapies are getting very good. There are more immunotherapies and I think with early detection and with the use of these new immunotherapies, we will start curing patients. I'm not going to promote that and say we are already there because we need to look at the data. But that's what I think is going to happen.

Mary DeRome (MMRF): On behalf of the MMRF, I'd like to thank Dr. Ola Landgren, Dennis Verducci, and Lonni McDonough for joining us today.