## WELCOME AND INTRODUCTION

***Lizette Figueroa-Rivera, MA***


Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Tomer Mark for sharing his time and expertise with us today. We have over 2,200 people participating in today's program from across the United States, Canada, and India. We would like to acknowledge and thank Bristol Myers Squibb, Genentech & Biogen, GlaxoSmithKline, and Takeda Oncology for support of this program.

Before we begin, Cynthia, a myeloma patient and advocate, as well as LLS volunteer, will make some welcoming remarks.

***Cynthia Sims***

Hello, my name is Cynthia Loyal Sims, and I'd like to welcome all the patients, caregivers, and healthcare professionals attending this program today. My journey with cancer began in 2015. While on my summer vacation in Florida, I began experiencing back pain so severe that I had to be in a wheelchair for the rest of the trip. When I returned home, I immediately went to see my doctor who referred me to an oncologist. After several tests, I would receive the devastating news that I had multiple myeloma. Chemotherapy and radiation soon followed, along with the horrible side effects, sleepless nights, countless blood transfusions, but I was not going to let cancer defeat me. I recalled a quote, "Cancer is a word not a symptom," and I thought, okay, I've got this, and I felt spiritually strong.

In 2016, I underwent an autologous bone marrow transplant that used my own stem cells, then immediately extended or entered into an immunotherapy clinical trial. It was an extremely difficult time, and the experience gave me a new meaning to the word sick.

When I was initially diagnosed, I was told that life expectancy for my type of cancer was only two years. Thankfully, since the transplant and the trial, I am doing much better. And as of today, I've been in remission for nearly three years. My faith has been a vital part of my physical and mental healing. I'm so grateful to my family, friends, and doctors who saved my life. I am also thankful to The Leukemia & Lymphoma Society for funding one of the treatments that helped save me and for providing a valuable support system.

Now I work to help others and give them hope. I volunteer for LLS in various ways, including their Myeloma Link program that aims to create awareness and improve access to education and treatment for myeloma to the African American community.

As Dr. Mark will mention in this presentation, the incidence in African Americans is almost twice as high as in Caucasians. Knowledge is so critical. So like you, I am looking forward to hearing Dr. Mark provide this update on treatment options for myeloma patients. Every day that I survive is a blessing and a victory. So, remember, if you ever feel that you've come to the end of your rope, remember to tie a knot and hang on.

***Lizette Figueroa-Rivera, MA***

Thank you so much, Cynthia, for sharing your story with us. I know many of our listeners can relate to you and your cancer journey.

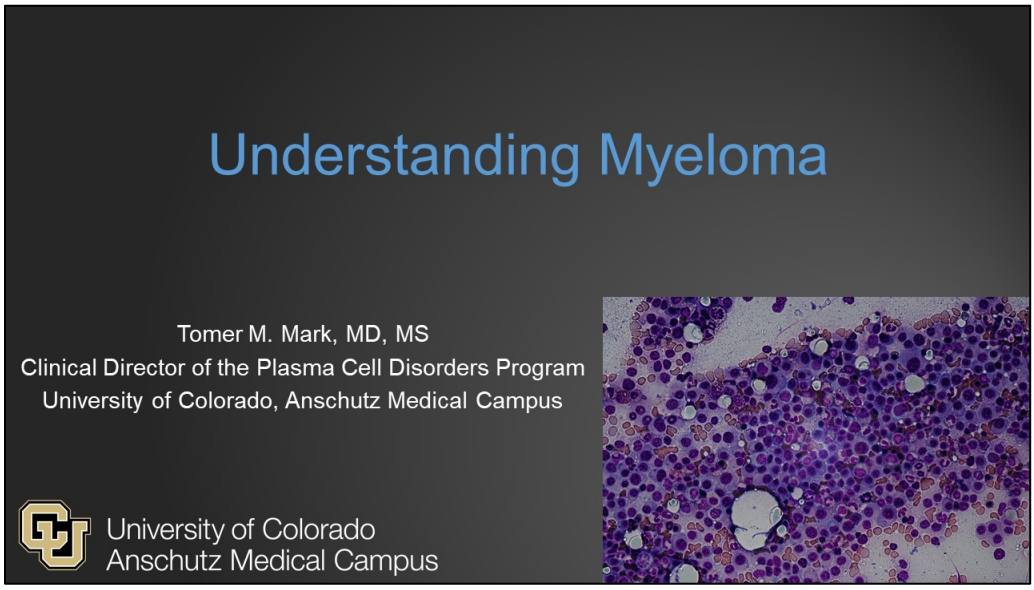
## PRESENTATION

***Lizette Figueroa-Rivera, MA***

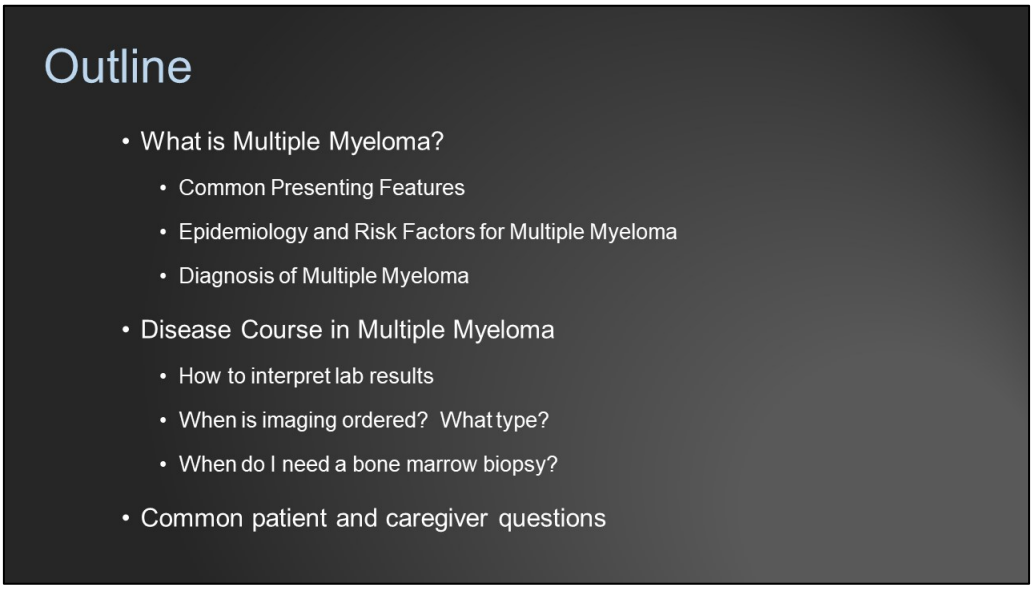
I'm now pleased to introduce Dr. Tomer Mark, Associate Professor of Medicine at the University of Colorado, Anschutz Medical Campus in Aurora, Colorado. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Mark, I'm now privileged to turn the program over to you.


***Tomer M. Mark, MD***

Thank you. These are my disclosures.




And I first want to start off by thanking The Leukemia & Lymphoma Society for giving me the opportunity to talk to you all and help you understand multiple myeloma, what it is, the philosophy of treatment, and also things that you can do to make your myeloma journey more comfortable. I work at University of Colorado in Aurora, and I wanted to point out that at the bottom right-hand corner of the slide over here, there's a bone marrow sample taken from one of my patients that shows involvement with myeloma.



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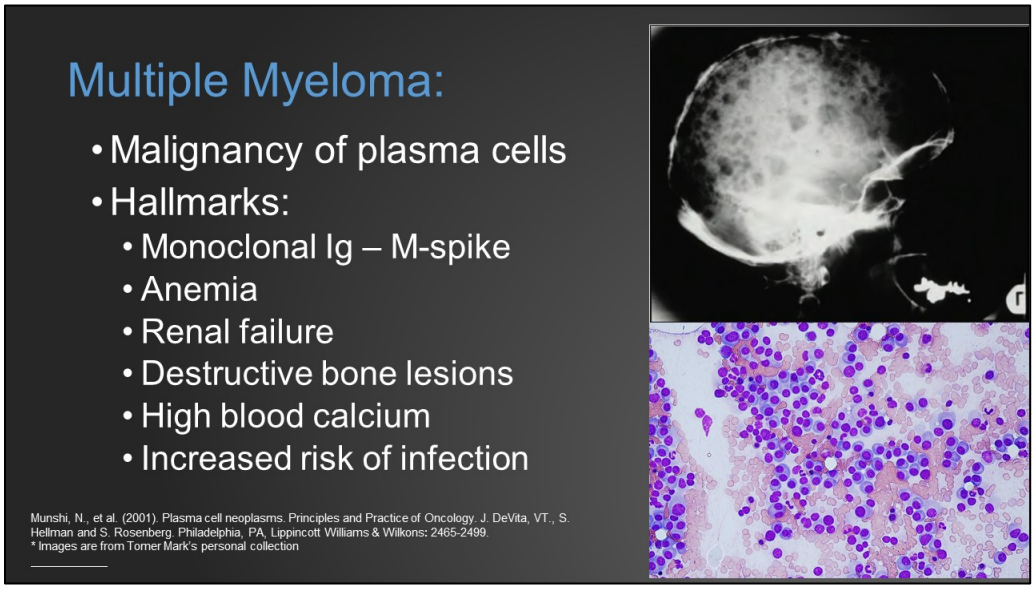
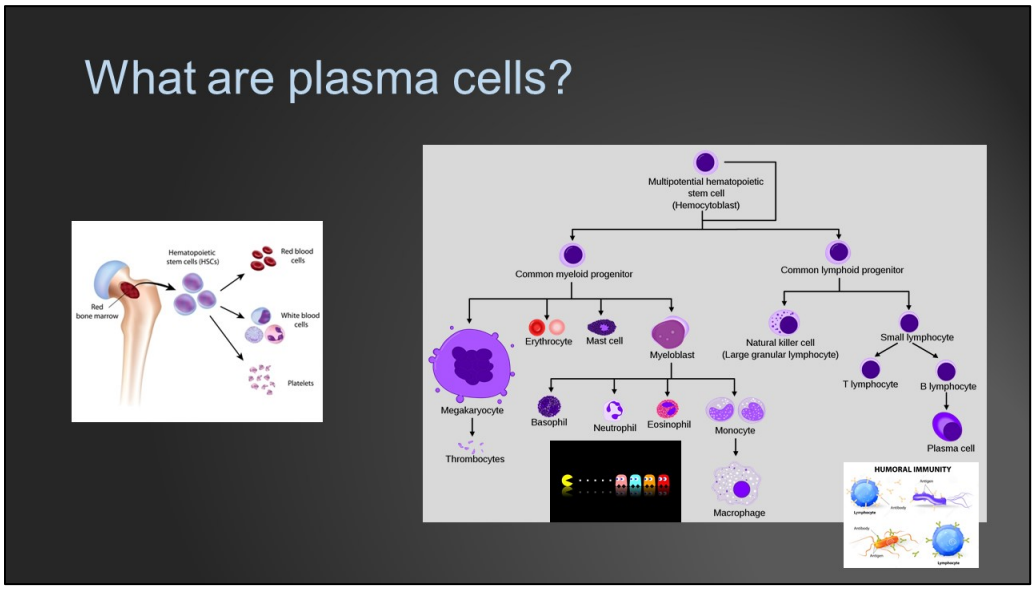
So, here's the outline for the talk. I won't spend too much time on this, but we'll go through what is myeloma, what's the disease course, and then there are common patient and caregiver questions that I'd like to go through.




So, multiple myeloma is a malignancy of a cell called the plasma cell, and the hallmarks of the disease are this protein called monoclonal immunoglobulin or M spike, anemia, renal or kidney failure, destructive bone lesions, high blood calcium, and increased risk of infection.

In the upper right-hand corner, you can see a picture of a skull from a patient with myeloma, and you can see these punched out lesions that sort of look like swiss cheese that are the lytic lesions that we describe that go with this disease. And then below that is another marrow picture with an infiltration of cells that look sort of like sunny-side up eggs, and those are the myeloma cells. There are slightly

different sizes and shapes, but you can see that in most of them the nucleus, the round purple dot is moved off to one side of the cell, and that's pretty typical of a plasma cell.



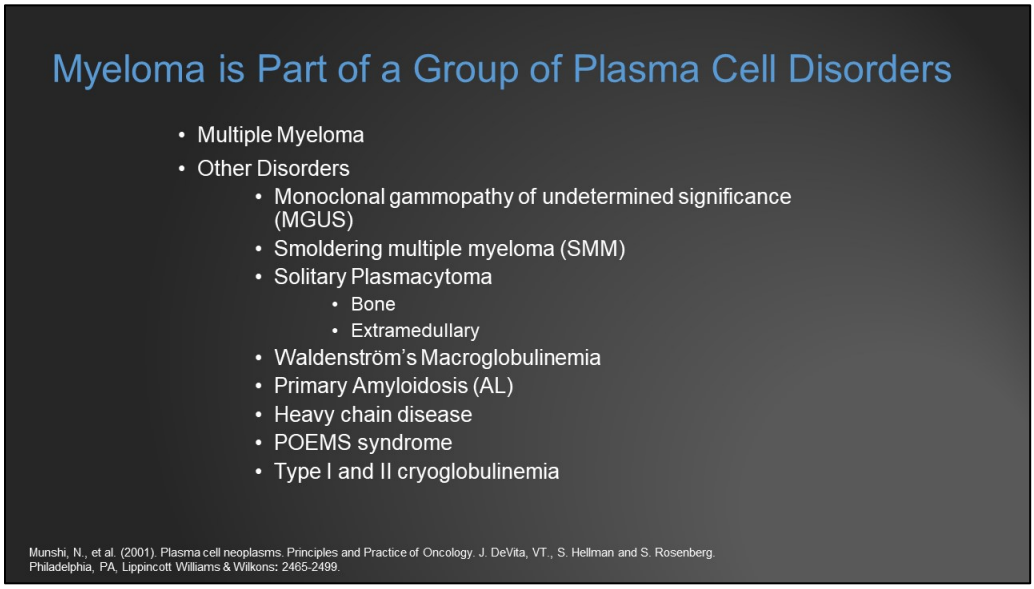

So, what are plasma cells? All of the elements in our bloodstream come from the bone marrow and more particularly these hematopoietic stem cells, HSCs. From these hematopoietic stem cells, you get red cells, white cells, and also platelets. And if you go on the right-hand side of this slide over here, you get this sort of family tree. And on this half of the tree over here, that's called the myeloid theories; and from there you get red cells, over here erythrocytes, megakaryocytes which leads to platelet production, and then other cells like neutrophils, eosinophils, and macrophages.

On this side of the family tree, this is called the innate immune system. This is the immune system that's been present since the dawn of time. Amoeba have this kind of immunity. And I put this picture of Pacman down below because this immunity is pretty dumb. If there's something foreign in your bloodstream, some particle, or virus, bacteria, these cells will just chomp those foreign bits up like Pacman in the video game without any sort of rhyme or reason.

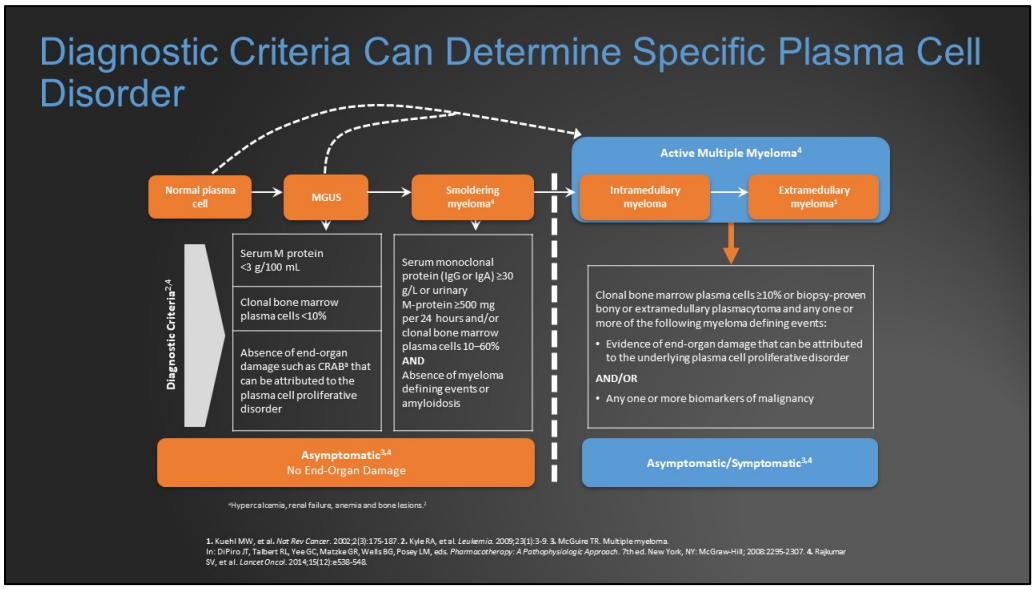
This brings us to this part of the tree. This is the humoral immune system or adaptive immune system that comes form lymphocytes. And some of these lymphocytes are T cells over here. Others are B cells over here, and these are important in certain infections. Certainly, if you don't have T cells, that's a major manifestation of HIV. B cells can lead to lymphomas. But at the very bottom over here you can see is the plasma cell. The plasma cell's the most differentiated, the most mature type of lymphocyte, and it is the job of the plasma cell to make antibody. Antibodies are also called immunoglobulins, and these are proteins that are generated as part of our defense against foreign invaders.

So, if a bug comes into our body, what happens is that the B cells and the T cells recognize that bug as foreign, they talk to each other, and they may generate these plasma cells that will produce an immunoglobulin or an antibody that is specific for that bacteria or virus. It will coat the foreign particle, and then your body will get rid of that foreign invader very efficiently.

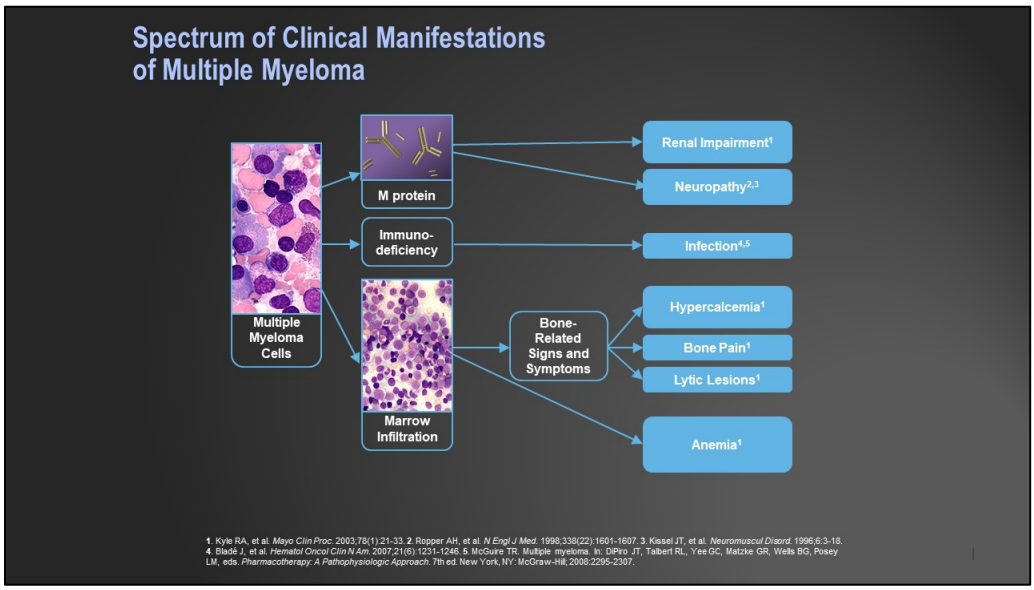
As you can probably surmise, the innate immune system is instant. It turns on right away. It turns off right away, whereas the humoral immune system with antibodies is relatively slower because you need time to generate those antibodies. The advantage of the humoral immune system, of course, is memory, such that you don't get reinfected with the same thing over and over and over again. And this is the principle behind vaccinations.




I'd like to remind you that myeloma is just one of a group of plasma cell disorders. The most common type of plasma cell disorder is MGUS (monoclonal gammopathy of undetermined significance) over here. In between MGUS and myeloma is this entity called smoldering myeloma, and then there's other more rare forms of plasma cell disorders listed below.

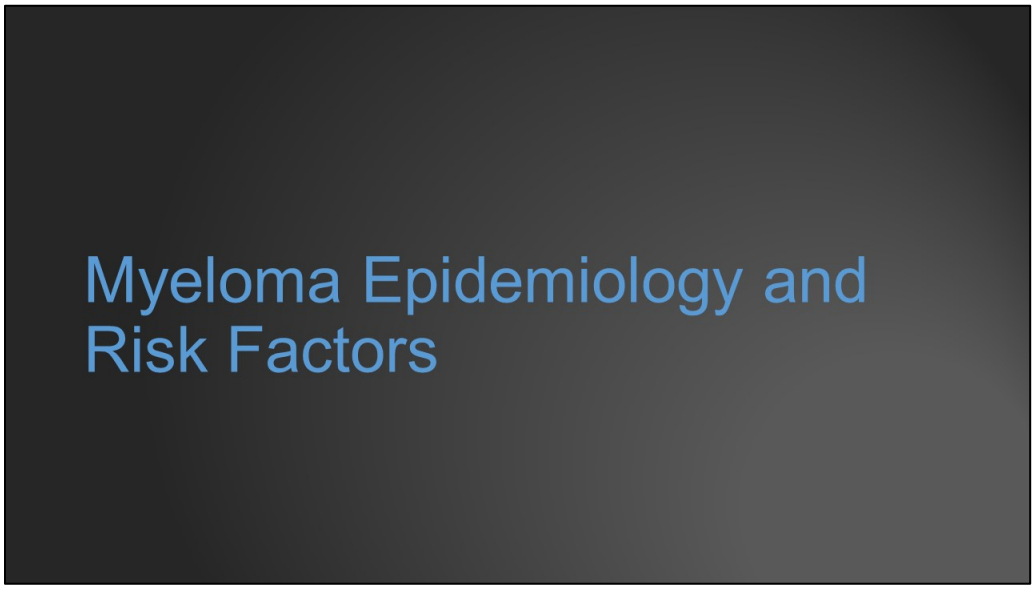


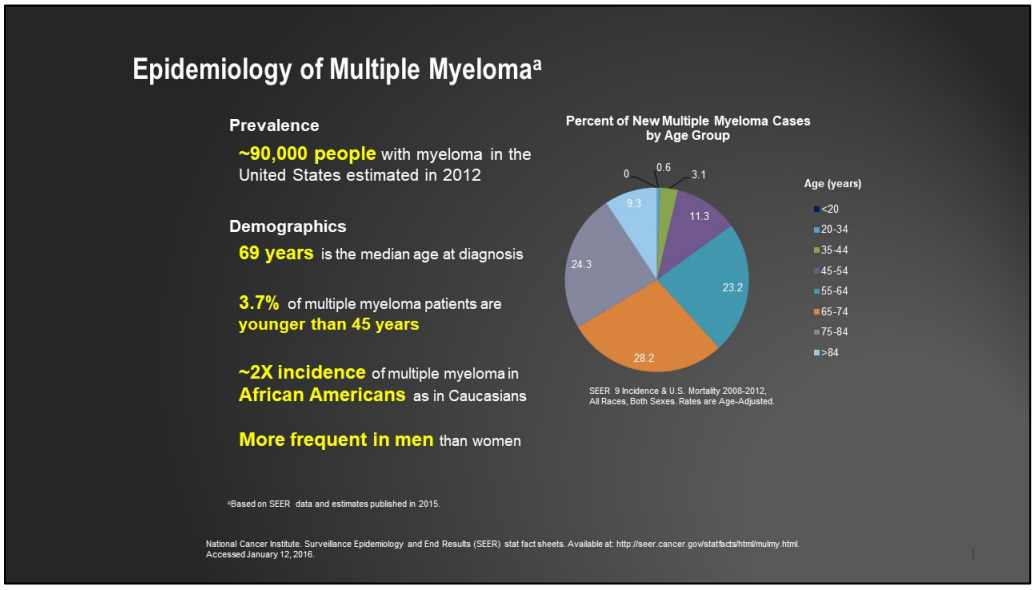
It is complicated to tell between MGUS, smoldering myeloma, and active myeloma. This is a pretty frequent consult that we get in that somebody would go for a life insurance exam or go to their primary care doctor for an annual checkup, see that the protein is elevated in the blood, and all of a sudden they wind up in my office scared to death that they may have an active malignancy like myeloma when, in fact, many of them would have MGUS or smoldering myeloma which are precursor conditions. You can see that the definitions are a bit complicated with a lot of criteria, but if you take a look at the big boxes at the bottom, you can see that MGUS and smoldering myeloma, by definition, are asymptomatic. They don't cause any damage to the body whereas active myeloma, if we let it sit and fester, it will cause damage like kidney failure or fractures.




And so, these myeloma cells, they take up space in the bone marrow, and so, over here. They take up space in the bone marrow, and they produce this M (myeloma) protein. The M protein builds up and up in the blood, eventually thickening it. And it can clog up kidneys like hair in a drain, causing renal impairment or kidney failure. This M protein can also coat nerves and cause a neuropathy which would be tingling or numbness or pain in the fingers or the toes. Neuropathy is part of the myeloma disease, not just related to treatments; and so about 10% to 15% of people can present with neuropathy as part of the myeloma.

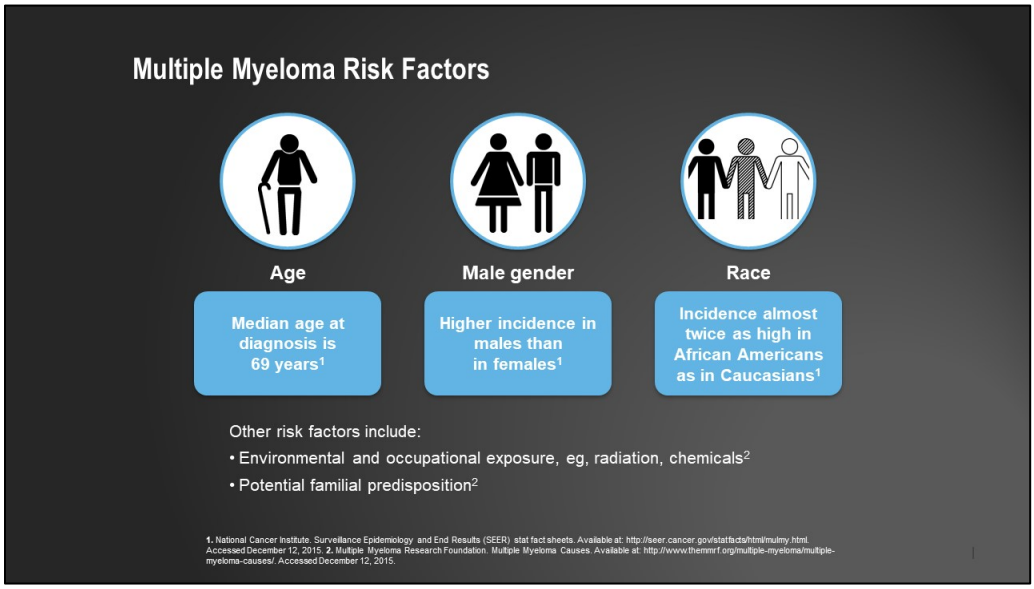
Immunodeficiency can happen because the myeloma cells are making bad antibodies. They don't do anything but cause impairment. They don't fight any infections, and so this allows other infections to come in because of the lack of good antibodies. And because these myeloma cells take up space in the marrow, it crowds out all the healthy things, and so you get leaching of calcium into your bloodstream, bone pain from these myeloma cells eating away the bone and causing fractures, lytic lesions, and then anemia because the healthy cells are crowded out, leaving no space to make healthy blood.




So, epidemiology and risk factors, where does myeloma come from? So multiple myeloma is one of only two malignancies that has actually increased in incidence in the United States. The other malignancy that is increasing is melanoma. So, about 90,000 people with myeloma in 2012; it's closer to 130,000 now. Median age is 69 to 70 years, depending on where you look. There are a good proportion of patients with myeloma that are young. I have myself, plenty of patients in their 30s with myeloma, so it really does run the gamut in terms of age. But by and far, most people are between 65 and 75.

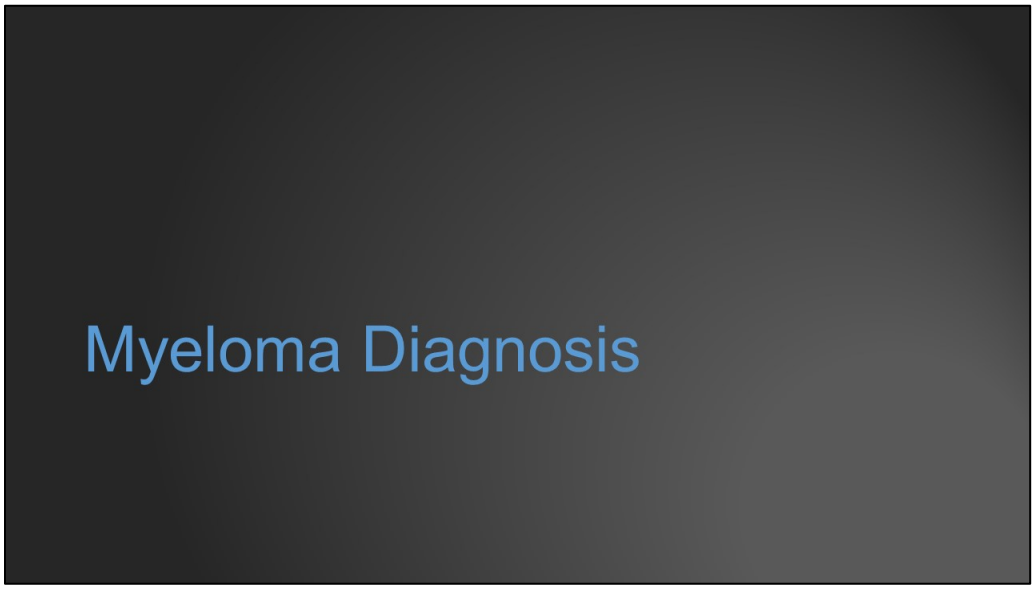
As mentioned earlier, it does occur twice as often in African Americans as in Caucasians, which certainly points to a genetic predisposition as opposed to an environmental predisposition. And it occurs twice as often in men than in women. So, again, there's a genetic or maybe hormonal predisposition there as well.

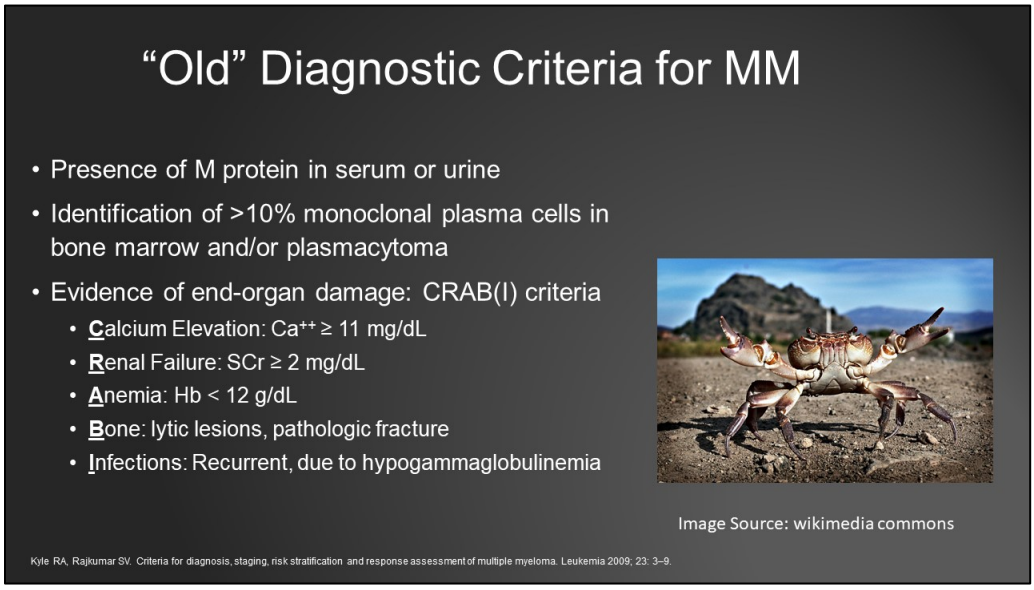



So, the major risk factors for myeloma are age, being male, being African American. I put some sort of less well-known factors here at the bottom, environmental over here. The environmental factors that we're concerned about are radiation, for instance, working in a lab with radioactive chemicals or working in a nuclear power plant. Certainly, aromatic hydrocarbons, diesel fuel, as well as pesticides, organophosphates have been associated with multiple myeloma. Agent Orange exposure or exposure to burning oil pits in Iraq have been associated with myeloma, and then exposure to wood dust and chemicals with woodworking has been associated with it.

When I was working in New York, I saw plenty of 9/11 survivors that wound up developing myeloma at an early age, in their 40s, probably because of exposure to all the dust that was kicked up by the explosions. And then just to tell you the link about insecticides and myeloma, the most common occupation associated with multiple myeloma is being a farmer.

People often ask me if there is a familial predisposition for myeloma, meaning I have myeloma. Do my children have to be tested? And the answer is that there is a slight familial predisposition. It raises your risk by approximately three-fold compared to the general population. But given that the incidence of myeloma is extremely rare, something around 20 per 100,000 people, it's not really worth screening or making people worry for a chance of 60 in 100,000. And so, in general we don't screen family members. We just tell them that there's a slightly elevated risk.

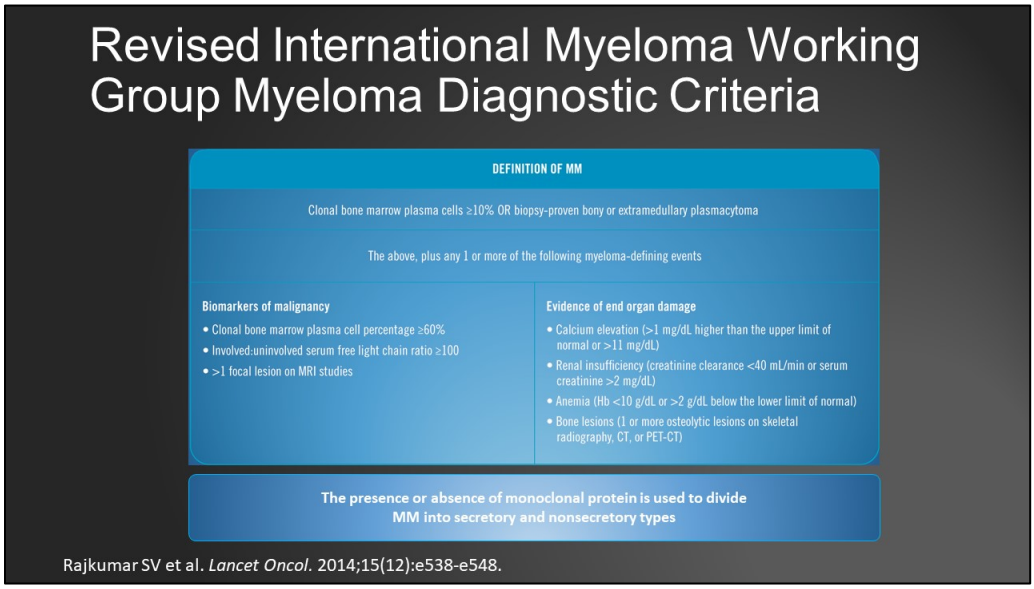



In terms of how we make the diagnosis of multiple myeloma, the way we use to make the diagnosis of myeloma is that we were looking for three things. One is the presence of an M spike in either the blood or the urine. Another is identification of more than 10% monoclonal plasma cells, meaning copies of each other, in either the bone marrow or in a tumor called the plasmacytoma. And then end organ damage as defined by this CRAB criteria over here, and that stands for calcium elevation, renal failure, anemia, bone disease, and recurrent infections.

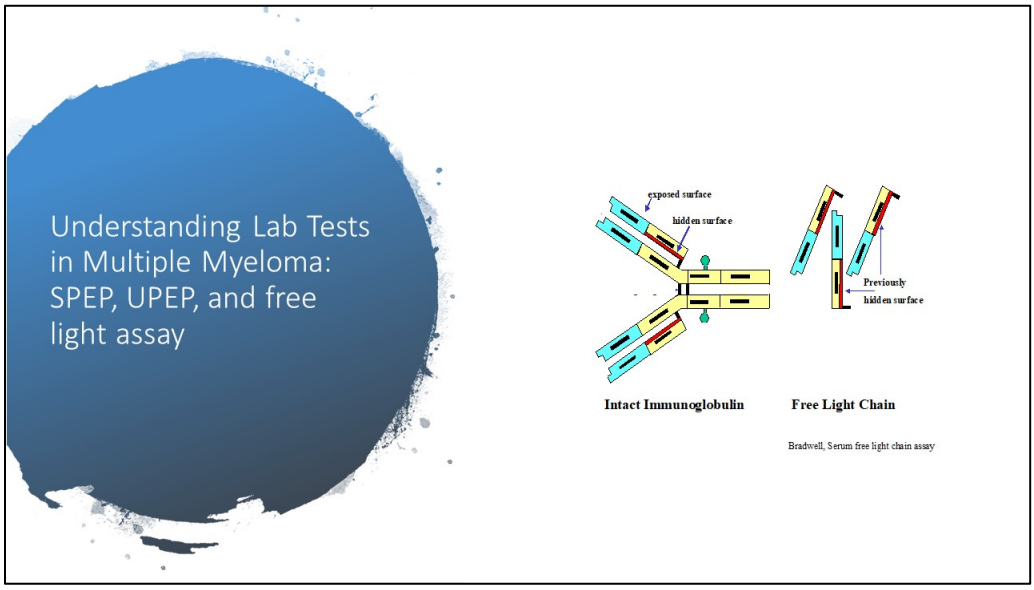
Of note, I do want to say that the anemia, you have to be pretty anemic with hemoglobin less than 12. You also have to rule out other common sources of anemia such as iron deficiency to be able to pin it on the myeloma.

The renal failure has to be relatively severe actually with about 50% kidney function because there's plenty of reasons for kidney struggling with other diseases. And I just want to say that the hypercalcemia is not that common a manifestation. People don't often present with high calcium, but if they do, it's a pretty dramatic situation. People get very confused. They get abdominal pain, cramping, severe constipation; and this is a life-threatening condition that we treat as an emergency.



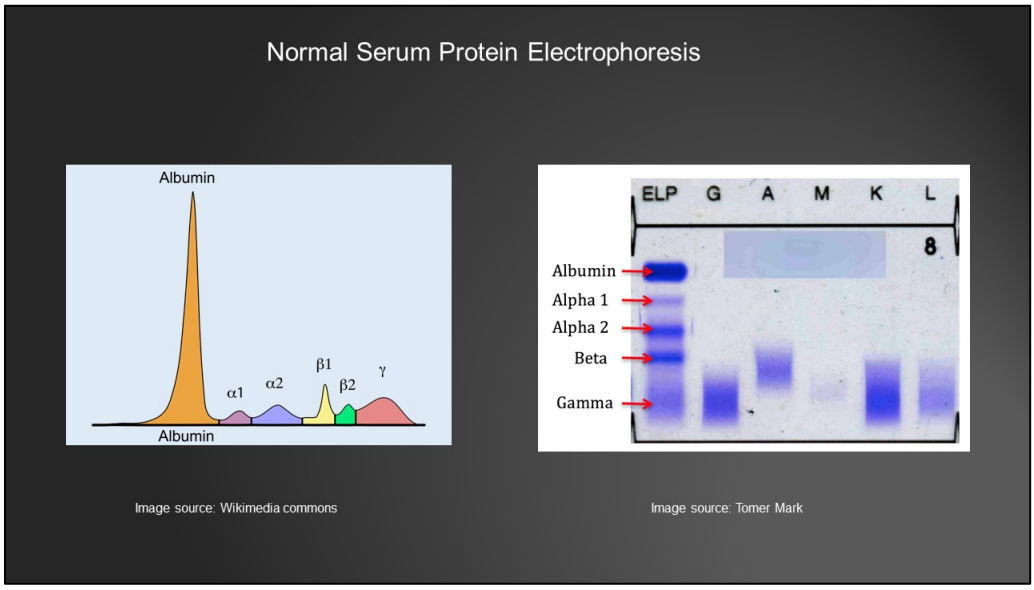

So, the International Myeloma Working Group revised the definition of multiple myeloma several years ago, such that you still need these clonal plasma cells present. However, they now define myeloma in two categories, one defined by biomarkers of malignancy, meaning that if you have more than 60% plasma cells in the marrow, if you have a free light chain ratio greater than 100, and we'll talk about free light chains later, or if you have more than one lesion on an MRI (magnetic resonance imaging), that counts as a positive biomarker malignancy, and you have myeloma no matter what – whether you're feeling sick or not.

As opposed to the more older definition, which lists these CRAB criteria, they're relatively similar to what was before. And then it turns out you don't need an M protein anymore. You can have a secretory myeloma with an M protein or monoclonal protein or a nonsecretory myeloma. Be careful about calling yourself nonsecretory. It turns out that's only 1% of patients. We can usually find a protein to follow if we look hard enough.




So, I want to talk a little bit about understanding lab tests in multiple myeloma. You may hear your physician or nurse practitioner, in fact myself, throw around terms like M protein, monoclonal protein, monoclonal immunoglobulin, paraprotein; and I want to tell you that pretty much all of these mean the same thing, and I want to show you what we're talking about.

So, when we're discussing intact immunoglobulins, what we're looking at is this molecule over here with a Y shape. And you can see in this Y shape there are two longer sort of protein chains. I've highlighted them over there. And then attached to them are two shorter chains. The long chains are called heavy chains, and they have the names A, G, B, D, E, M. And then these light chains are called kappa and lambda. And so you may have already heard about these terms already. This is where it comes from. And so when we describe an immunoglobulin, we talk about the heavy chain and the light chain. IgG (immunoglobulin) kappa, IgA lambda, and that's how we follow the protein. That's how we name it.

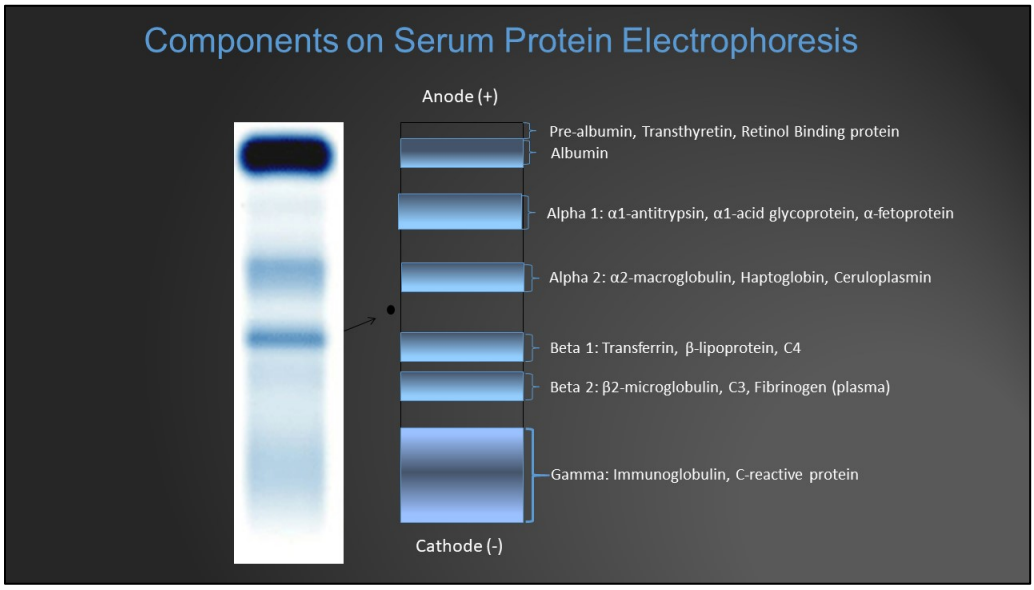



And so, this is a serum protein electrophoresis test. This is the test that is done in a person with myeloma pretty much every one to two months to see how the disease is going, whether it's responding or whether it's growing. And so, the way this test works is you get a tube of blood drawn. That blood is put into a centrifuge, and then the top part of that blood on the tube is a yellow liquid called serum. Whole cells have been removed.

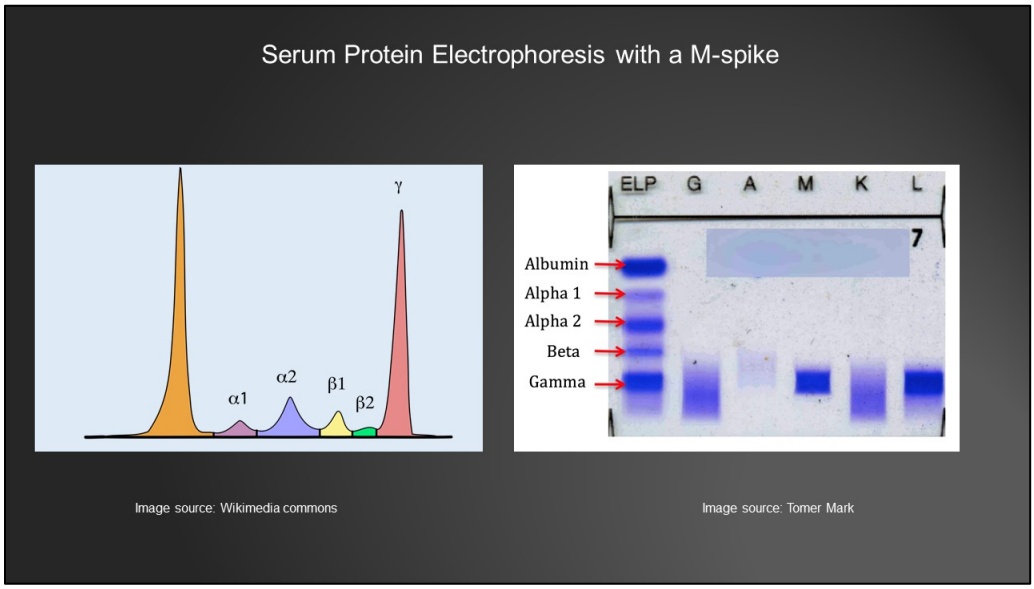
A drop of serum is placed on an agarose gel, where I put that little dot over there right in the middle. And then a current is applied to this gel such that the proteins that are present in the serum are separated by both charge and by weight. And then you can get a pattern, which I listed over here, where at the top of the gel is this protein called albumin. You get certain bands, alpha-1, alpha-2, beta, and then lastly gamma. You can look at the intensity of the band and also the sharpness of the band to determine how much protein is there, what type of protein is there. We have a lot of albumin in our bloodstream. The purpose of albumin is to keep the liquid portion of our blood inside the blood vessel rather than leaking out into our tissues and causing puffiness.

And so, because we have a lot of albumin and there's only one peak, if you put it onto this nomogram over here on the left, you can see you have a sharp, tight peak albumin and a big area under the curve over here. That's the concentration.

As you go through, you have the alpha-1 peak, the alpha-2 peak, the beta peak over here. But what we're really interested in, of course, is the gamma. In gamma, which is over here, you can see that it is smeary. It is not very focused, and that is because we have all different types and shapes of immunoglobulin molecules that float around in this gamma region. And so it's an unfocused picture because we have IgA kappas, IgG lambdas, IgMs in there. They all have similar weight and charge but all slightly differently because they can deal with all the different types of the infections out there. And because they're all different, you get a low broad hill over here with a similar area under the curve, representing the concentration of the entire gamma region.



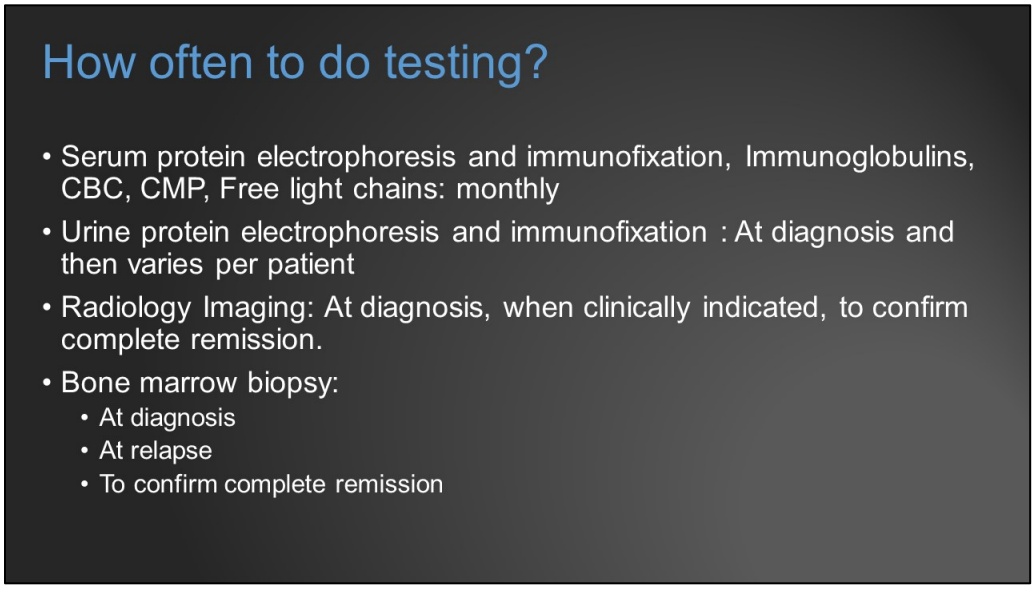

And so, again, going into the components of each band is not so important, just to remember that in this gamma region here at the bottom, that's the area that we're most concerned about with multiple myeloma.




And so, looking back at this normal serum protein electrophoresis with a big albumin peak and a low broad gamma peak over there and taking a look at a picture of someone with myeloma, you can see instantly that this gamma region over here has turned to look more like the albumin that we have seen before. And so, what that means is that instead of many types of immunoglobulins, there's one type of immunoglobulin that is predominating. And because this is a sharp peak over here, that is where the term M spike comes from. Monoclonal protein looks like a spike on this nomogram.

And we can put dyes in each area of the gel, in each lane, such that we can determine whether the protein is IgG, IgA, IgM, whether it's kappa or lambda, and you can see over here with this band that this person has an IgM lambda. That's how we tell the type of protein right there.

So, the moving of the bands across the gels, all the electrophoresis, the telling of the type of the protein is called immunofixation. They are usually run together.




So, how often to do testing? So, it's recommended to check a serum protein electrophoresis and immunofixation, the total amount of immunoglobulins, CBC, which is complete blood count, CMP (complete metabolic panel) which is electrolytes, organ functions, and free light chains monthly.

The reason for monthly is that these M proteins can hang out in your bloodstream for a very long period of time, approximately 30 days. And so, if we were to check your M protein day by day, you would see very little happening because, again, the natural half-life of the protein is measured in weeks. And so, that's why, if you check your M protein once a month and if your myeloma treatment is perfect, then you should expect that at three months that M protein should go down by 50%. Now, of course, there's a fudge factor on either end of that; but that's sort of the expected response rate – dropping your M protein by half with each month or each cycle.

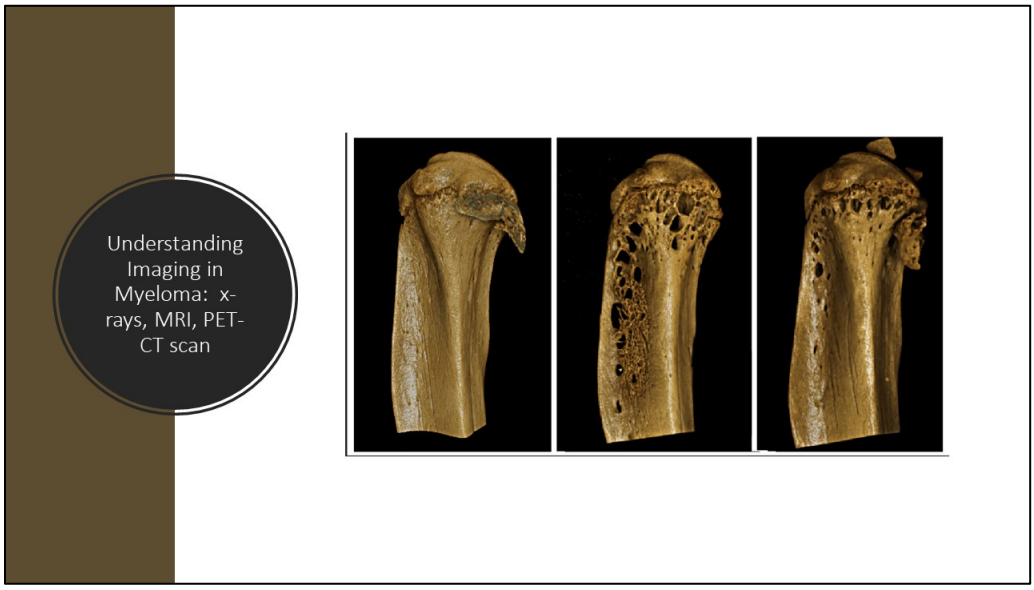
A free light chain is much more variable than an M protein. A free light chain has a half-life of four hours, and so you can tell differences between free light chains day to day. However, because they're so variable, you really need several measurements to be able to get anything with any degree of reliability.

Sometimes these free light chains, they show up only in the urine. When they're in the urine, they're called Bence-Jones protein. We do that electrophoresis and immunofixation on the urine, same just like the blood, and we can follow light chains in there as well.

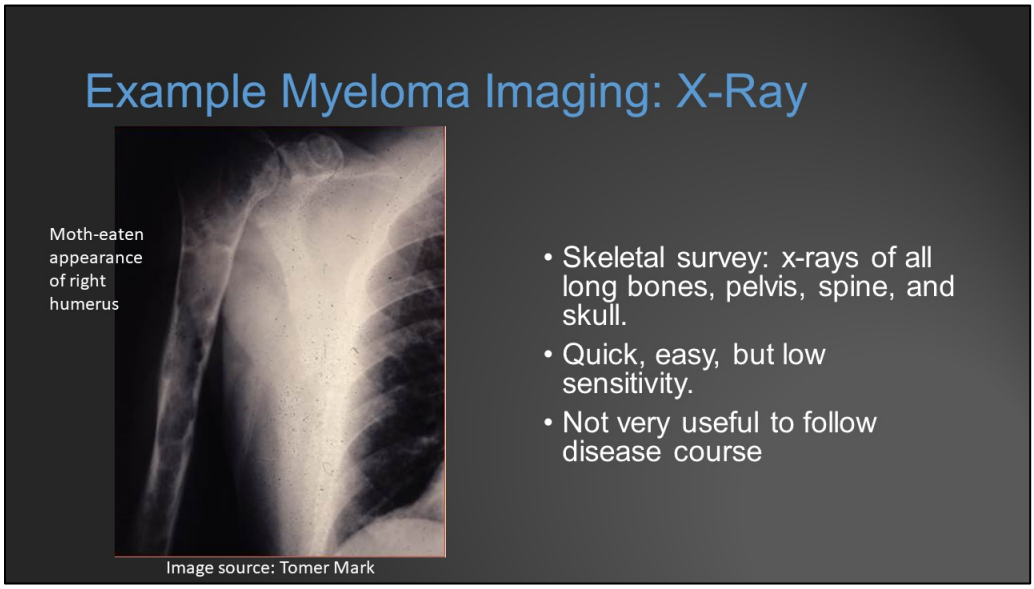
For patients that first come to me right at the beginning, I always check a 24-hour urine to see if we can measure protein in that compartment. If there is no protein there, I'd probably check a 24-hour urine once or twice a year. However, there are patients, maybe 15-20% of patients where the primary measurement of their disease is in the urine. The bloodwork is unreliable, in which case I do check a 24-hour urine every one to two months. It isn't a fun test.

How often do I need radiology imaging? How often do I need skeletal surveys, PET (positron emission tomography) scans, MRIs? Certainly, you know, at diagnosis, everybody needs skeletal imaging. We need to know where the lytic lesions are. We need to know if there's any tumors in the body. We also do it when clinically indicated. If somebody tells me that they have new back pain, new arm pain, certainly we go ahead and image to make sure that myeloma is not the cause of that pain. And then my favorite reason to do imaging, which is to confirm complete remission. If somebody's in complete remission, you should have a PET scan that shows that there's no active lesions. Of course, that's a little bit more difficult if you're using just plain x-rays because the holes that are made by the myeloma, they tend to stay there. Bones heal pretty slowly, and so you won't see that sort of dynamic change on plain x-rays. However, having an x-ray set that shows no new lesions can be used to call a complete remission as well.

How often do we do bone marrow biopsies? Obviously, at diagnosis we need a bone marrow biopsy to say whether one has myeloma or not. I find that doing biopsies at relapses are important as well because the disease can change with time. What somebody had in 2012 can be completely different in 2016, and that may prompt a change in the choice of treatments used. And then, again, you need a bone marrow biopsy to confirm complete remission. Right now, in the United States, if you want to do a test called a minimal residual disease (MRD) test, that has to be done off a bone marrow biopsy. I have a slide about minimum residual disease later on in the talk because it's becoming more and more important. However, you can take away from this that if your doc wants to do a bone marrow biopsy once a month to check your myeloma, that's not exactly the way to go.

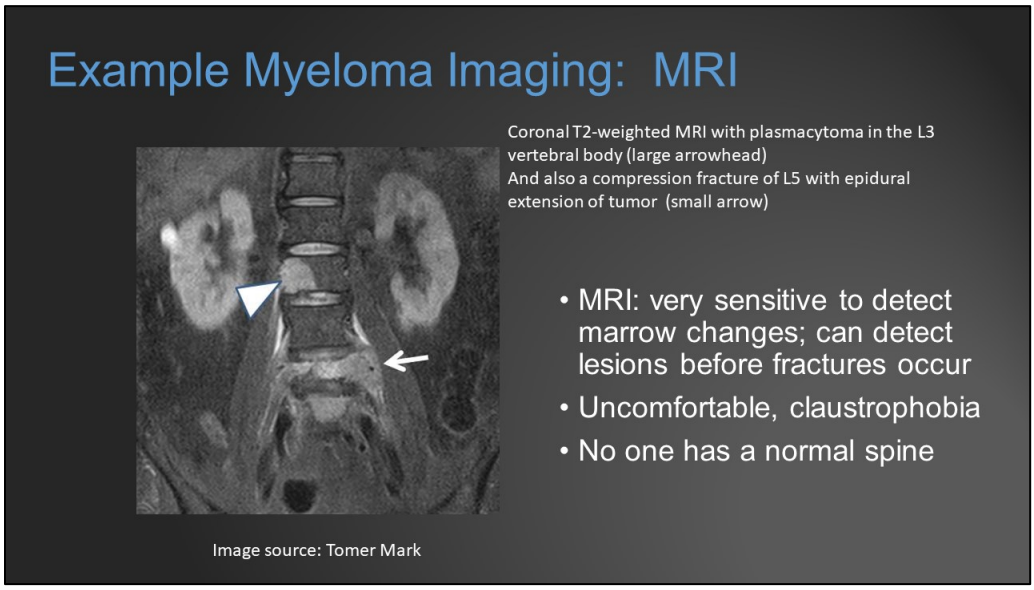



So, understanding imaging in myeloma, here is an image of an arm bone or a humerus where you can see all these little pits and holes. These are the lytic lesions that are carved out by the myeloma cells inside the bones, much like termites within a house. And even if you get rid of all the myeloma cells, the holes remain; and they tend to heal very, very slowly.




So, if we take a look at an x-ray over here, you can certainly see the moth-eaten appearance of the humerus. In certain areas the wall of the bone is paper thin. This is somebody that is going to break their arm with just minimal activity in maybe picking up a bag. And skeletal survey is the standard of care around the world in terms of determining involvement of the bone with myeloma and involves taking x-rays of all the long bones, pelvis, spine, and skull. It's very quick and easy but very low sensitivity, meaning that you need to lose 80% to 90% of the bone before you can actually see it on an x-ray. So by the time you see this lesion, it's sort of too late to do much about it. Also, because the

bones change very slowly, it is not useful to follow disease course. You won't see dynamic changes in the bone.




So, the next imaging modality, which would be MRI. So, on an MRI that I show over here on the left, you can see that the big arrow is pointing to a lesion taking up almost half of the vertebral body. You can see that it is light in color because on a T2-weighted MRI, water is bright. So, you can see that the kidneys light up. They're full of urine and water. Their intervertebral discs light up. But the bone marrow, the vertebral bodies are darker because they're usually filled with fat.

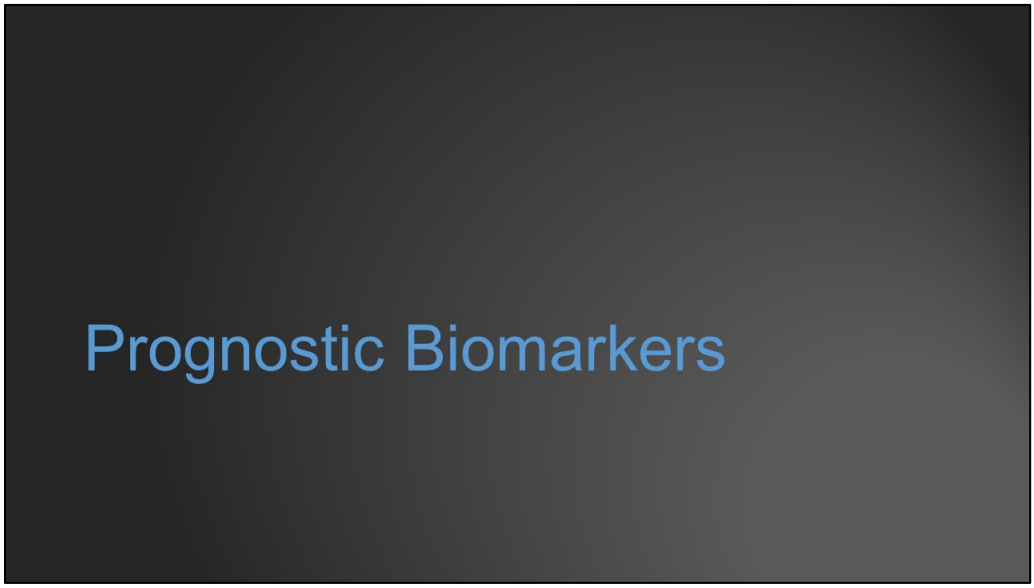
And so, in myeloma, tumor is necessarily vascular. There's lots of blood going through it, and so it becomes white on this MRI. You can see at the skinnier arrow down below that a vertebral body has been crushed. This is a compression fracture that has happened because the myeloma infiltrated and made the bone so weak it collapsed under its own weight.

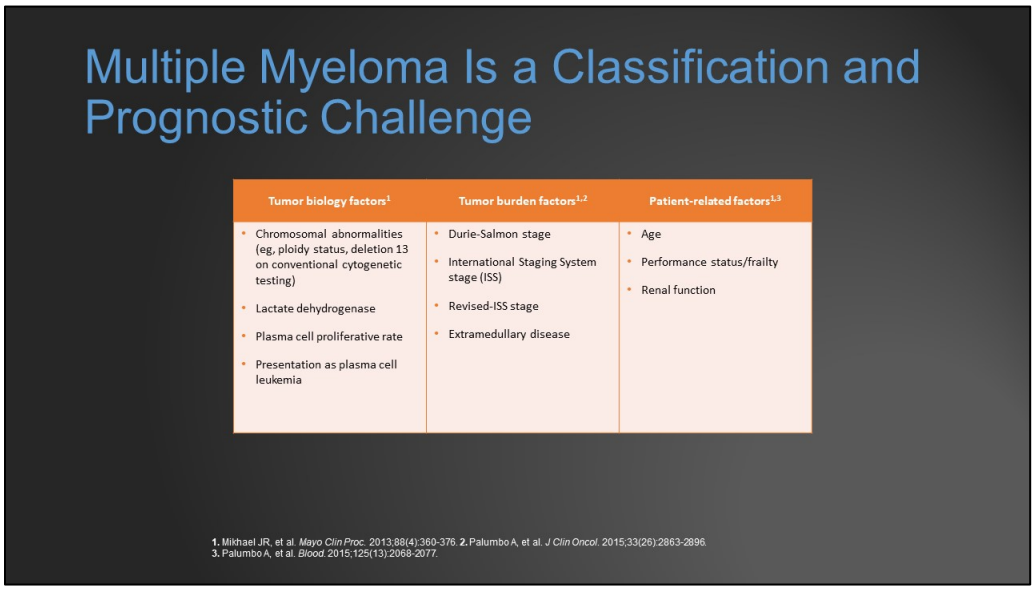
And so, MRI is a really good test. It's very sensitive to detect those marrow changes. That's that arrow up by the kidneys. That would never have been seen on a plain x-ray because, again, the architecture of the bone looks normal.

So, you can detect lesions before fractures occur. However, if any of you have had experience with MRI, you know that they are uncomfortable. Certain people do not like to be in an enclosed tube for an hour or more. There's a sense of claustrophobia, there's weird noises in there. And then most importantly, no one has a normal spine, absolutely no one. So, they're always going to find some little ditsier thing on the MRI that you may have to chase down with other test afterwards. So, take that with a grain of salt as well.

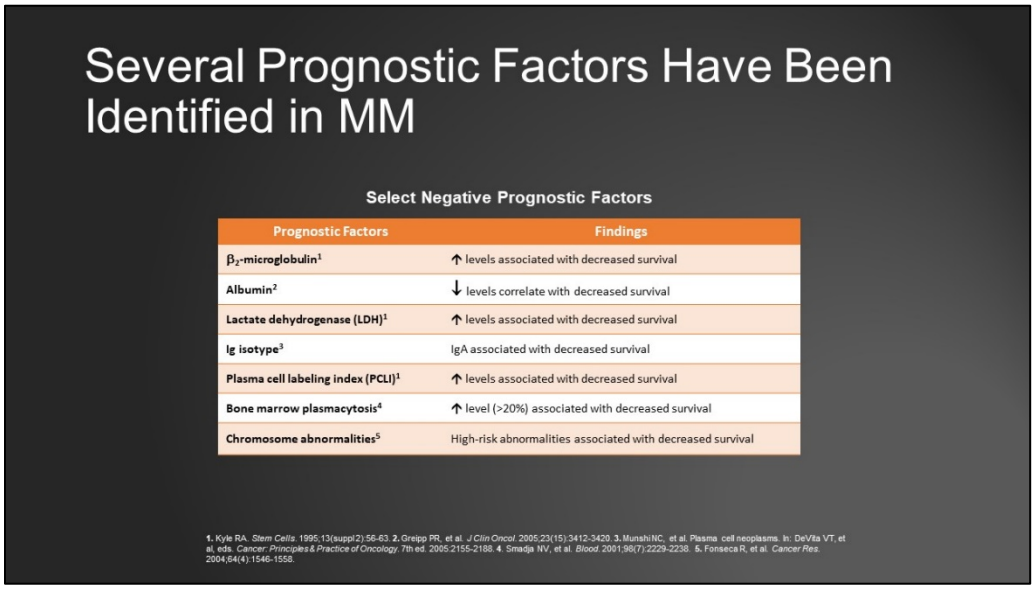

My favorite modality is PET scan, PET/CT (positron emission tomography/computerized tomography). This is because you take a look at the entire body, head to toe, so you're not only looking at bones. You're also looking at soft tissues like muscles. A PET has great sensitivity. Pretty much anything that has higher metabolic activity will take up that radioactive glucose that is injected for a PET scan. You get quick results. There is a good amount of radiation; it's about 30 x-rays' worth. And the other problem is that it is too sensitive, meaning that if you have allergies or a drippy nose, your nose will light up. If you have arthritis, like this patient does in the left knee, you can see that knee lighting up.

However, this particular patient, I did a scan for myeloma. I thought the patient was in remission; and lo and behold, where that thin arrow shows, there was one spot of myeloma in the body. And so, again, that would have been missed if we didn't do a PET scan.



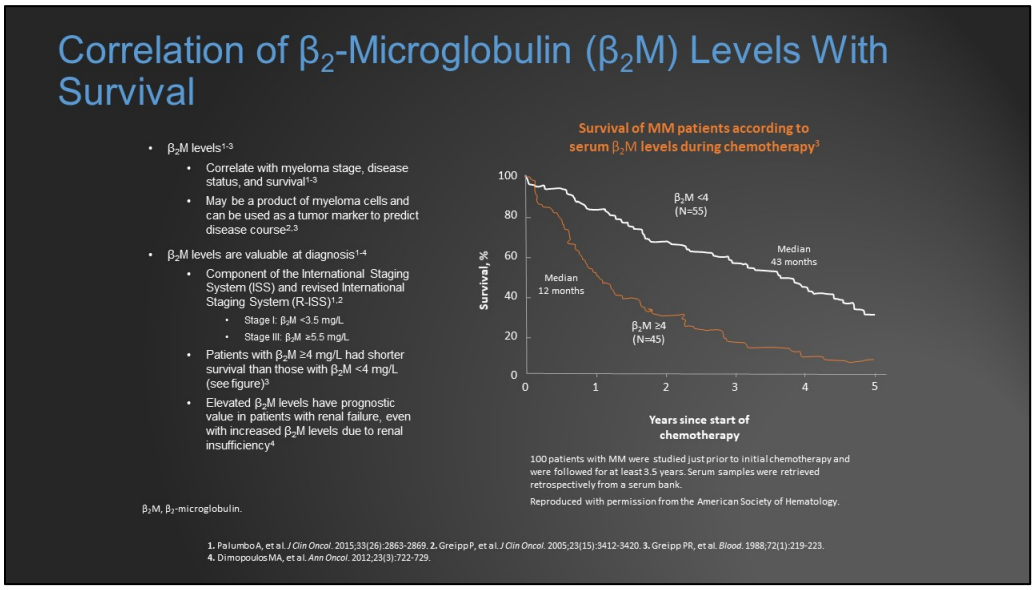



So, prognostic biomarkers, what do doctors and nurses look at to tell how well somebody's expected to do? So, here are some prognostic factors listed, and some have to deal with the tumor biology, some have to deal with how much tumor is in the body, and then the last column is patient-related factors. And so, we look at stuff like cytogenetics, a test called FISH (fluorescence in situ hybridization) or karyotype and then bloodwork like lactate dehydrogenase. That's LDH. We look at the stage of the tumor, and I'll talk about staging a little later. And also patient-related factors. One could expect a 95-year-old person who's frail not to do as well as a robust 45-year-old.

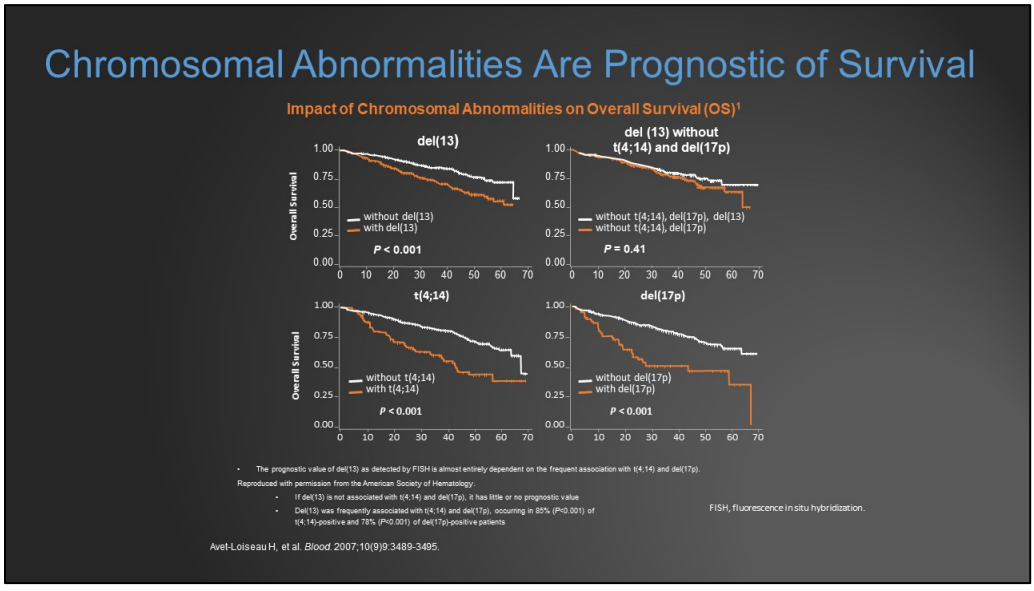



Here are these factors listed out in sort of a more table form. I'm not going to go through this for sake of time. I just want to let you know that of all the factors in this table, the one that is most important is at the top, the beta-2-microglobulin. This tells you how quickly the myeloma cells are dividing, how

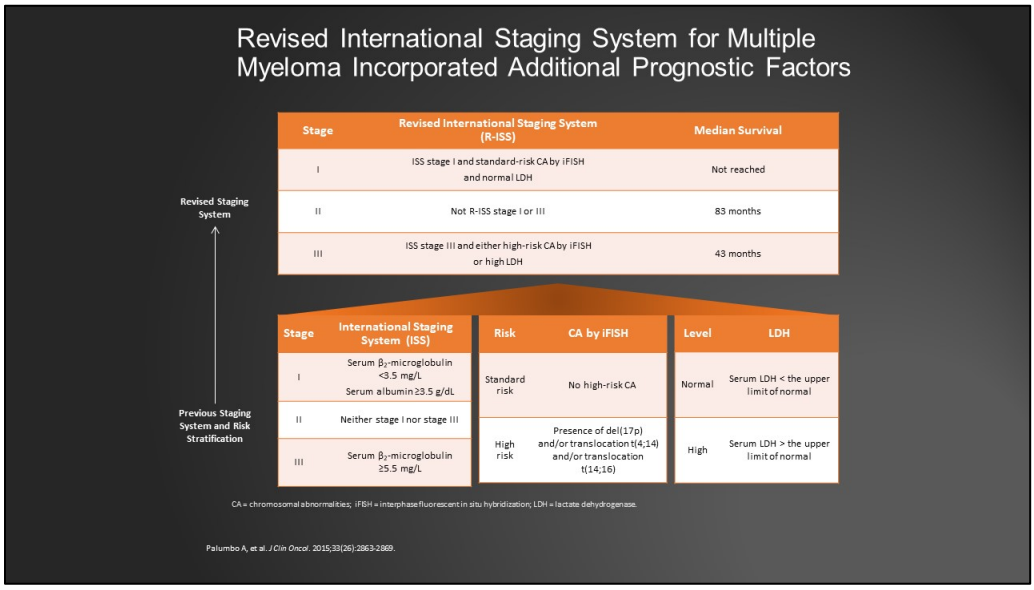
much myeloma's in the body, and how well your kidneys work all in one blood test. So, if somebody asks you what's most important, it's actually beta-2-microglobulin.



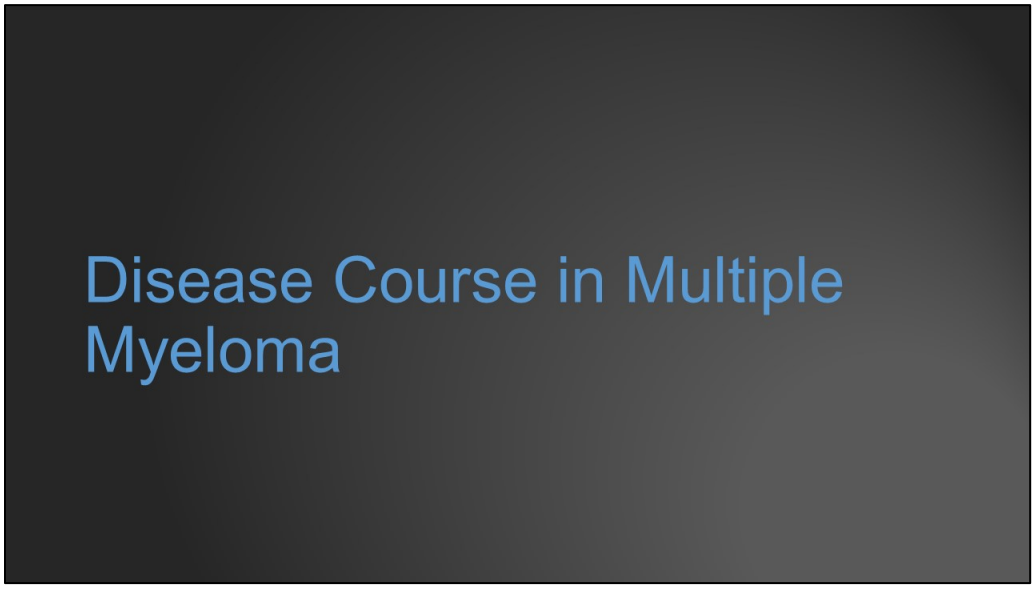

If you take a look at this graph over here, a person with a beta-2-microglobulin test of less than four has almost triple the survival of somebody who has it greater than four. So, just that one blood test can mean somebody will be expected to live three times as long as somebody else.

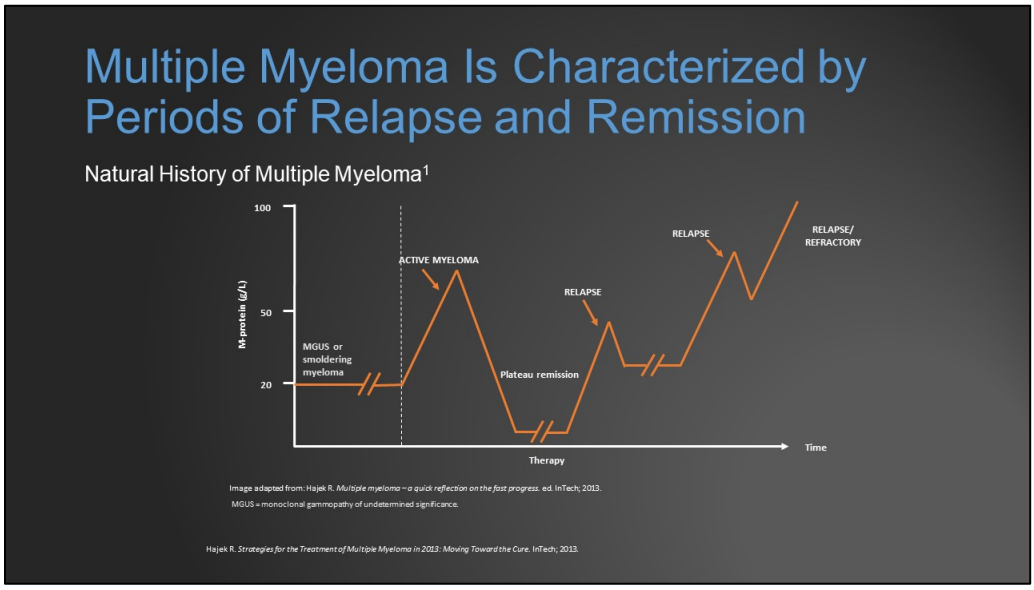



These are some graphs looking at the impact of chromosomes. They do have impact, but it depends on what the chromosome is. For instance, a deletion 13q is not as important in terms of survival impact as deletion 17. And so it's important to ask your provider about your genetic profile if you have any high-risk mutations that could affect how we would expect somebody to do.




This is the staging system that we use. As you can tell right now, it is pretty darn complicated. We take a look at the beta-2-microglobulin test, we take a look at albumin, and we also take a look at cytogenetics. That's what the CA stands for over here and LDH, that lactate dehydrogenase. We can see that if you're Stage I, we don't know what your median survival is. It is not reached. People do well with therapy and go on and on as opposed to Stage III where the average survival is 43 months. And so, you can see a wide range of outcomes, depending on staging here.





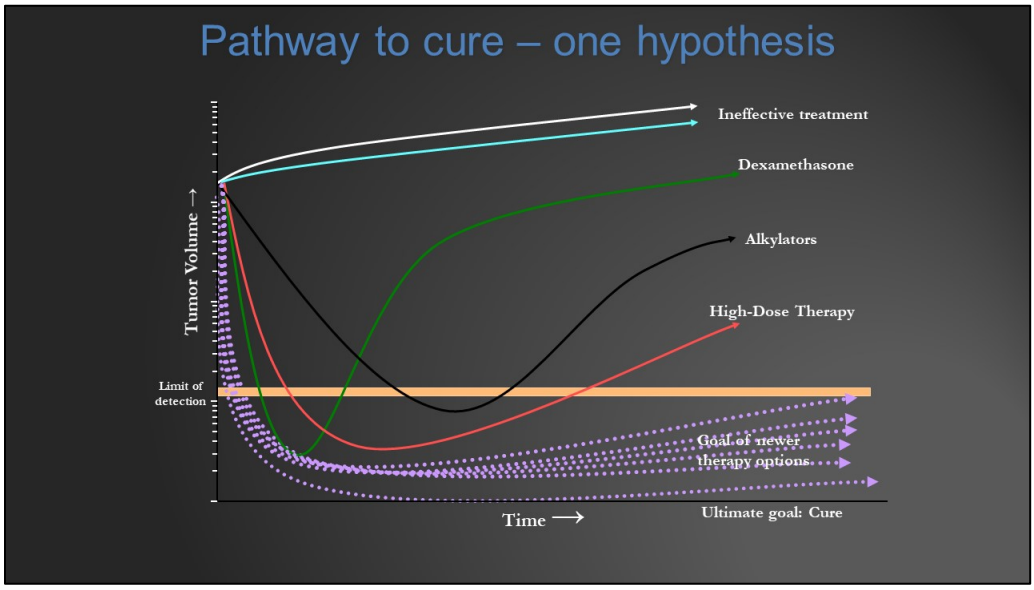

This is the most important slide that I'm going to show you today. This is the natural history of multiple myeloma. Pretty much everybody has this asymptomatic period of either MGUS or smoldering myeloma, a precursor condition much like a colon polyp is for colon cancer. And then some switch goes off and active myeloma occurs. A bone breaks. Somebody becomes anemic.

The first time we treat active myeloma is very satisfying. Pretty much everybody gets a good response, they go into some sort of plateau, a remission, and that plateau or remission can last a very, very long period of time.

However, eventually there's a relapse, and the next time you treat, you can see is not as good. You don't get as deep a response as the first time. The remission tends to be shorter as well. And as you go through third, fourth, fifth relapses, again, the responses get more poor, the remissions get shorter, until eventually the disease becomes refractory and nothing more can be done.

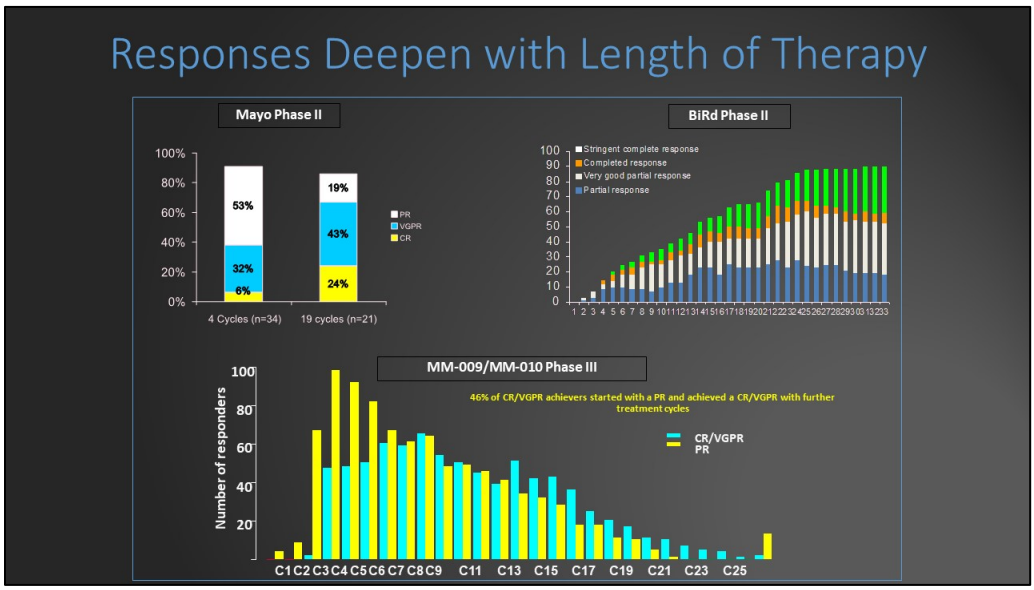
So, right now our goal is to make this period of first or second remission as long as possible. You can keep people going again for years and years. And the way to do that, of course, is to prevent relapses. And let me tell you, the most common cause for a relapse is not taking medication. It could be because the doc said, "Oh, you're in remission. You're done. You don't need anything," or "You got your six cycles of RVD (Revlimid® [lenalidomide]-Velcade® [bortezomib]-dexamethasone); you're done," and that is incorrect. It turns out that as soon as you stop therapy, even if you're in complete remission, the disease comes back. And when it comes back, it is often worse.

So, I often tell my patients that, myeloma ideally is like diabetes. You can have perfect hemoglobin A1C, perfect blood sugar control, as long as you're taking your insulin or your metformin. As soon as you stop doing that, the sugar goes crazy and you can lose your foot or have a heart attack. The same thing with myeloma. If you take your medication consistently as prescribed and continuously, you have the best chance for a good long remission and long-term outcome.

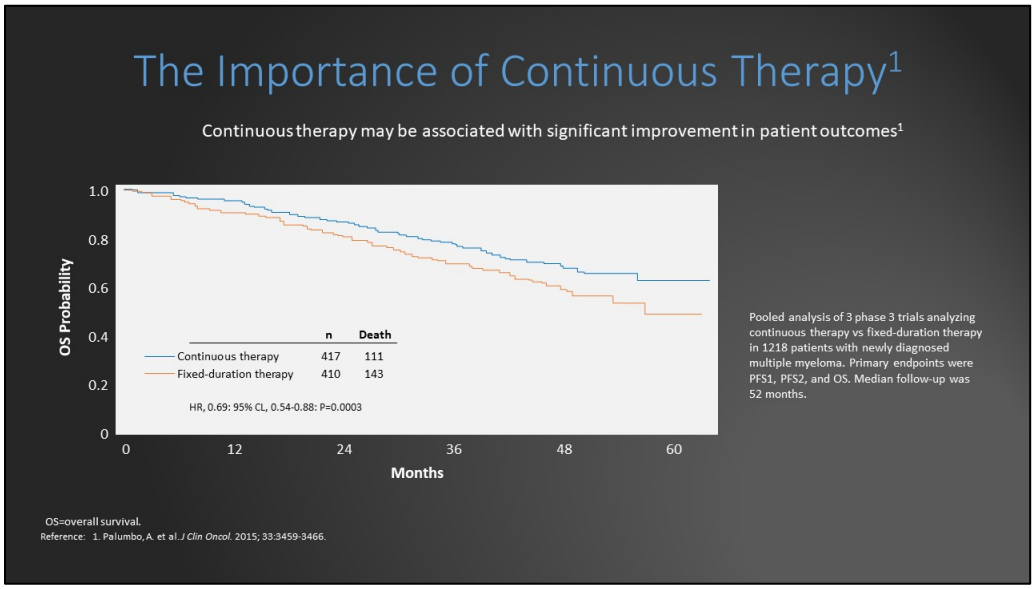



And so, when we're talking about pathways to cure, you can see on the Y axis over here, tumor volume, on the X axis over here time, that if we give ineffective treatment, for instance, what happens is that the tumor just grows, grows, grows. And maybe go through other treatments like dexamethasone, alkylating therapy, which is more like cyclophosphamide, older type of chemotherapies. And high-dose therapy, which is a stem cell transplant, you can see that you get these responses where the amount of tumor will go down, sometimes below the limit of detection but then will come back at different rates.

And so, right now our goal is to get the tumor to get down below that limit of detection and then stay there. And the way that it stays there is that we get continuous low dose therapy, called maintenance, such that the disease comes back so slowly that one would never know. And somebody winds up, just living their life with natural expectancy and dying of something else, not myeloma.

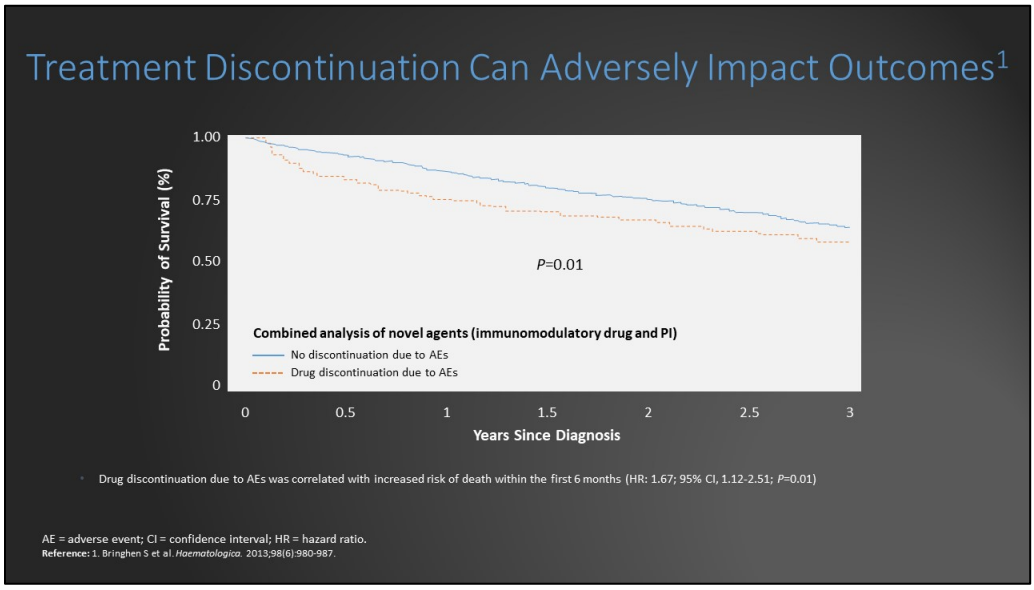


The longer you take treatment, the better the response gets. And you can see I'm showing data from several different trials showing that the percentage of patients that get to complete remission and beyond increases with longer duration of therapy.

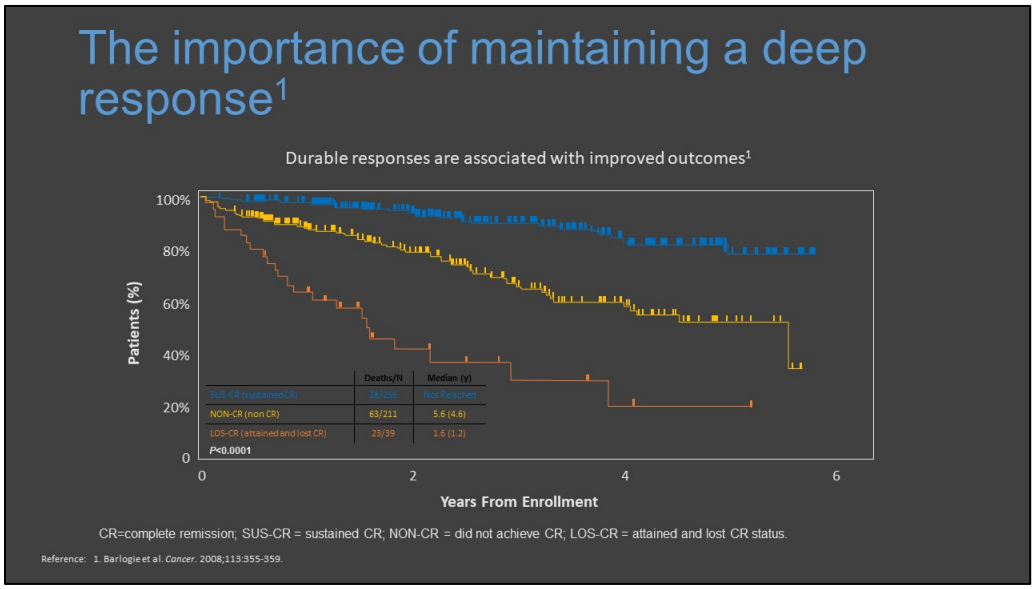



About a third of patients will not get into complete remission until after a year or more of treatment. So, it's important to be patient and to remember that you're trying to get to therapy that you can live with. If you do not give the therapy continuously, for instance, if you decide to give fixed-dose therapy which is that six or four cycles or stop, you can see that the people on the fixed-duration therapy, they do worse than the people on continuous therapy.

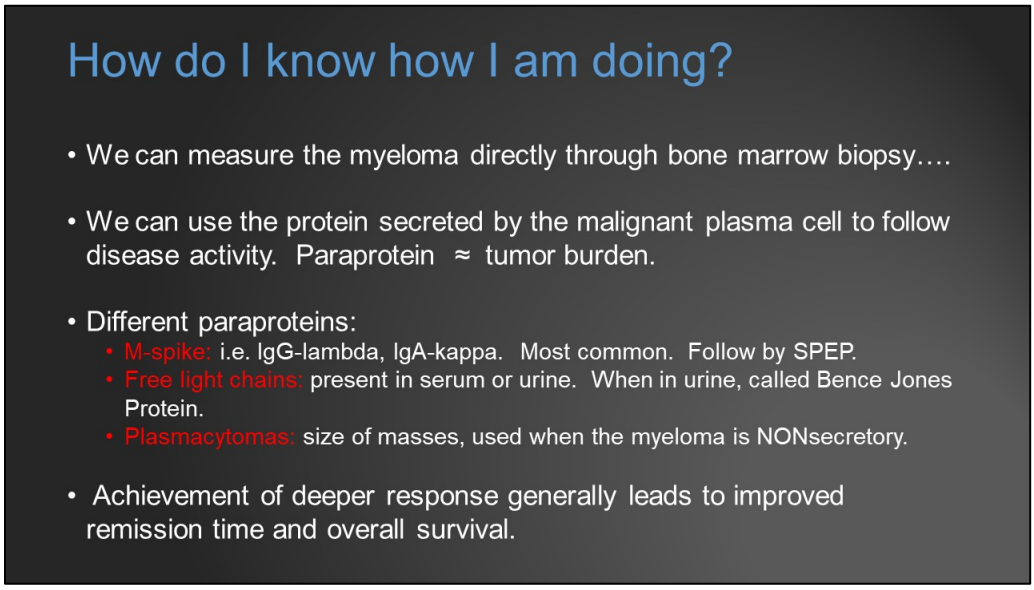
The hazard ratio here means that there's a 31% risk reduction of progression with myeloma simply by staying on the therapy.




If you discontinue treatment for any reason, it could be toxicity, be that physical or financial, again, you get worse outcomes. This is another analysis.




Even if you get into complete response, you still need that maintenance. This is data from Total Therapy III, from University of Arkansas showing that patients, this orange line, that had a CR, complete response and lost it, they do the worst as opposed to patients that get a CR and keep it or patients that never get a complete response. They've just been partial response, continued therapy. So, again, it's not just getting to complete response. It's continuing therapy to keep that complete response.

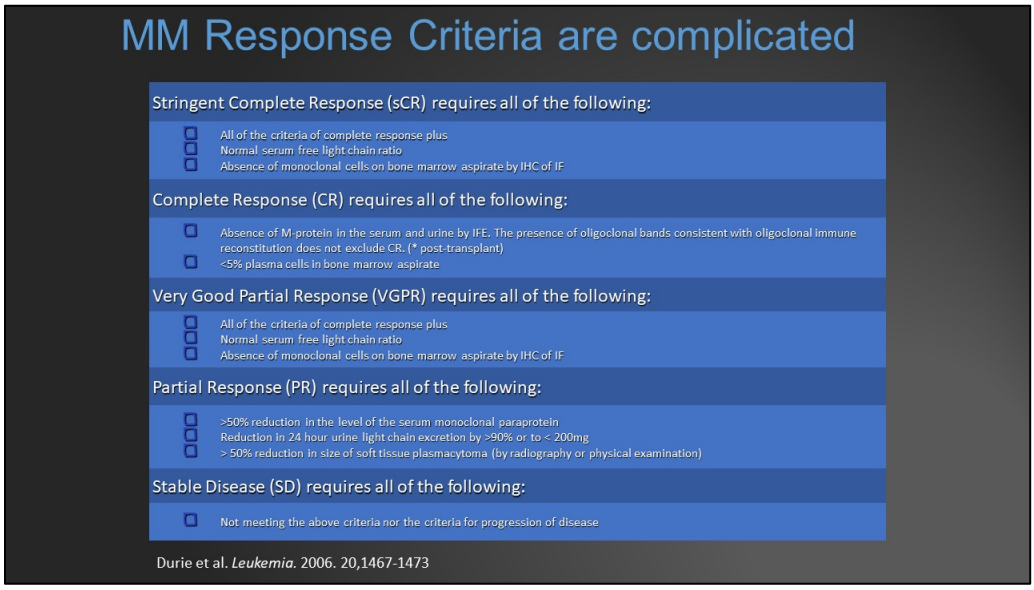



So, how do I know how I'm doing? We can measure the myeloma directly through a bone marrow biopsy. I'm pretty sure that most patients would choose not to do that month to month to see how their myeloma is doing. But what we do instead is we use the protein secreted by the myeloma, that's that M protein and also called paraprotein. And we say that's approximately equal to the tumor burden.

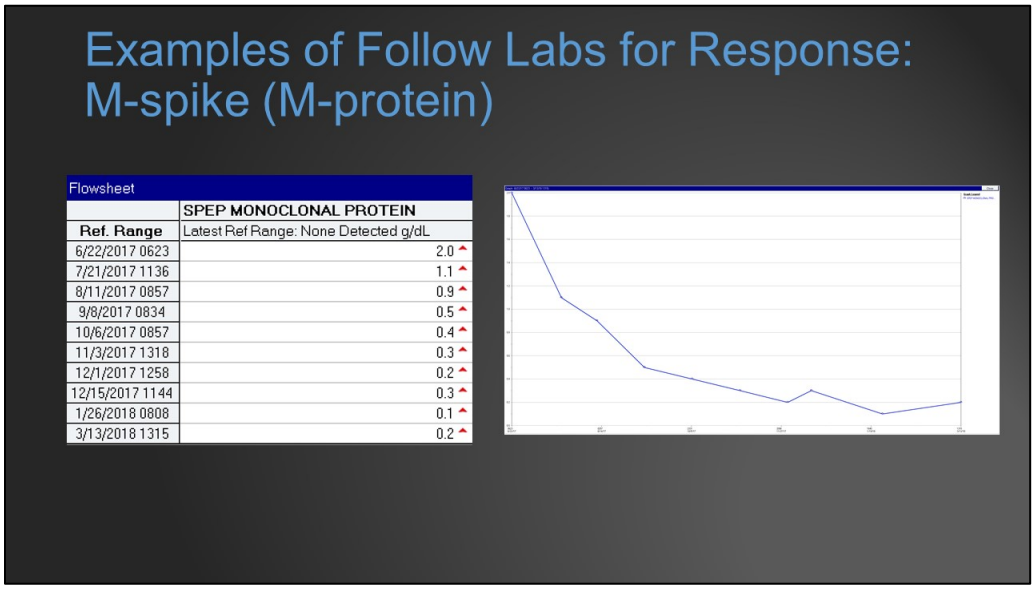
Now there are different paraproteins for different patients. No two myelomas are the same. Some patients, they make an M spike, that's an intact M protein that's IgG lambda, heavy chain and light chain, IgG kappa. This is the most common form. It's about 80% of patients. We follow this by that serum protein electrophoresis test.

About 15%, 20% of patients have only free light chains, that's either kappa or lambda, to be present in either the blood or the urine. When it's in urine, again, it's called Bence-Jones protein. And so somebody would get a free light chain test in the blood or a 24-hour urine every month to determine how they're doing.

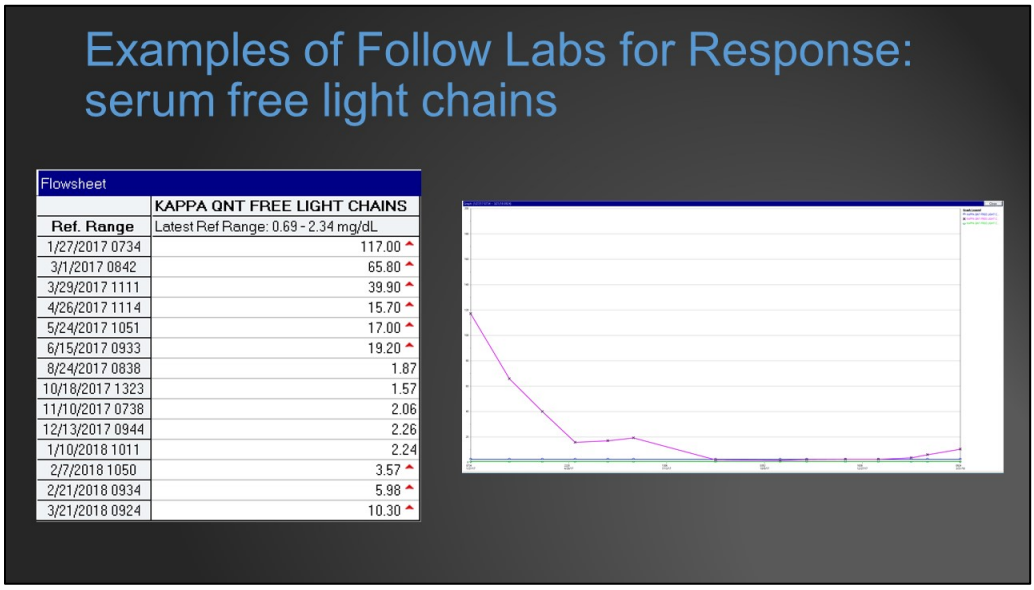
And lastly, plasmacytomas. Some patients don't make M protein or free light chains. Again, that's about 1% of people. They present as masses in the body. And in that case, the myeloma is non-secretory, and we use scans like MRIs or PET scans to determine if the tumors are shrinking or growing or gone. In general, getting a deeper response, getting rid of the most tumor leads to improved remission time and survival; and that's not surprising.



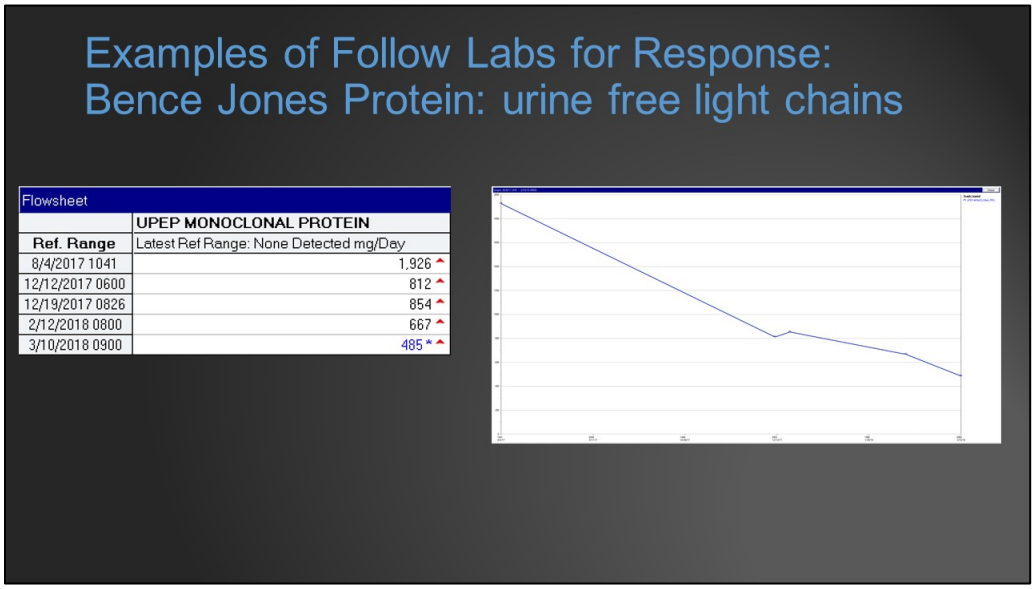

These are the response criteria for myeloma, and this is meant only to shock and awe, and that is it's extremely complicated. This is not meant to be memorized, just that there are plenty of different criteria that we use to tell how well somebody is doing.



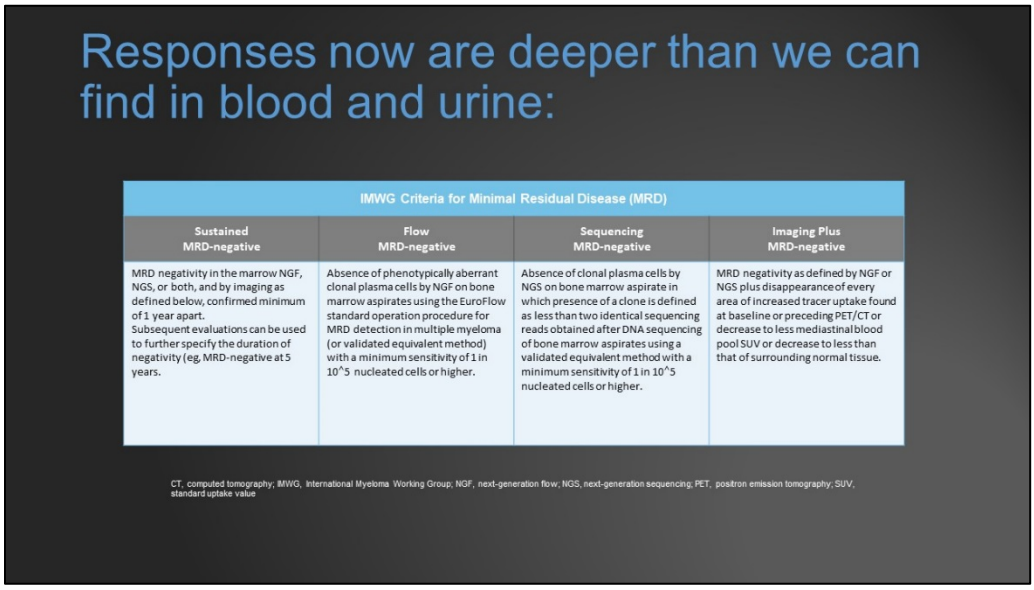

These are some examples from my own practice showing decrease of M protein over time. This is a person that started with an M spike or M protein of 2, then getting down to some sort of plateau. And if you take a look month to month to month, you actually do see that 50% decrease cycle by cycle.



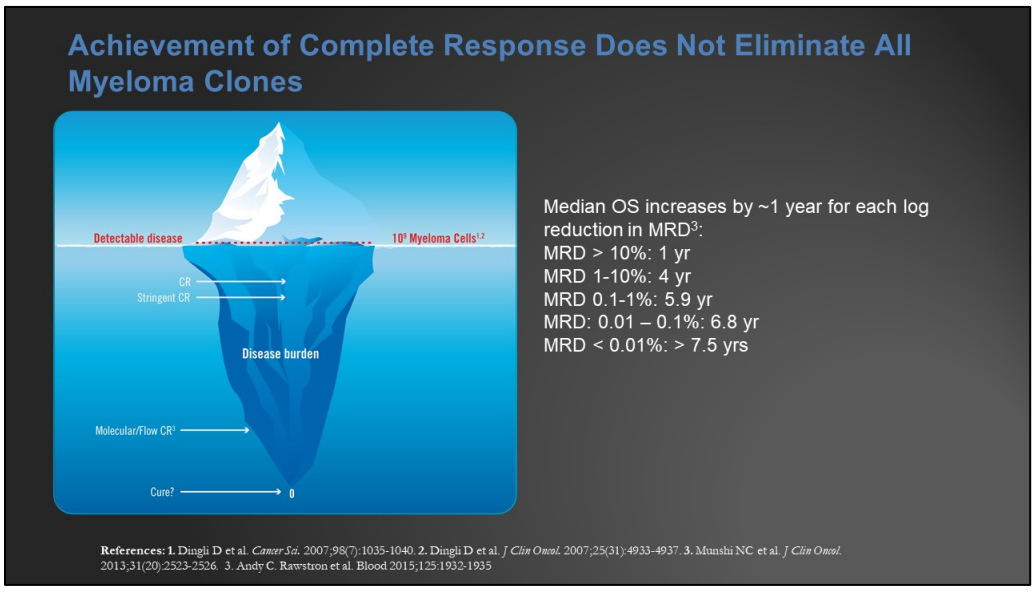

This is somebody where we only had free light chains to follow; and, again, you can see in their graph that we get these free light chains down relatively quickly and then it flattens out as any half-life curve would. At the very end, you can see that these proteins are starting to come up again, starting to tick up again. And that would indicate that we need to investigate, perhaps change treatment.




And lastly, this is following free light chain in the urine. We can see that over time that free light chain in urine, Bence-Jones protein is going down as well.

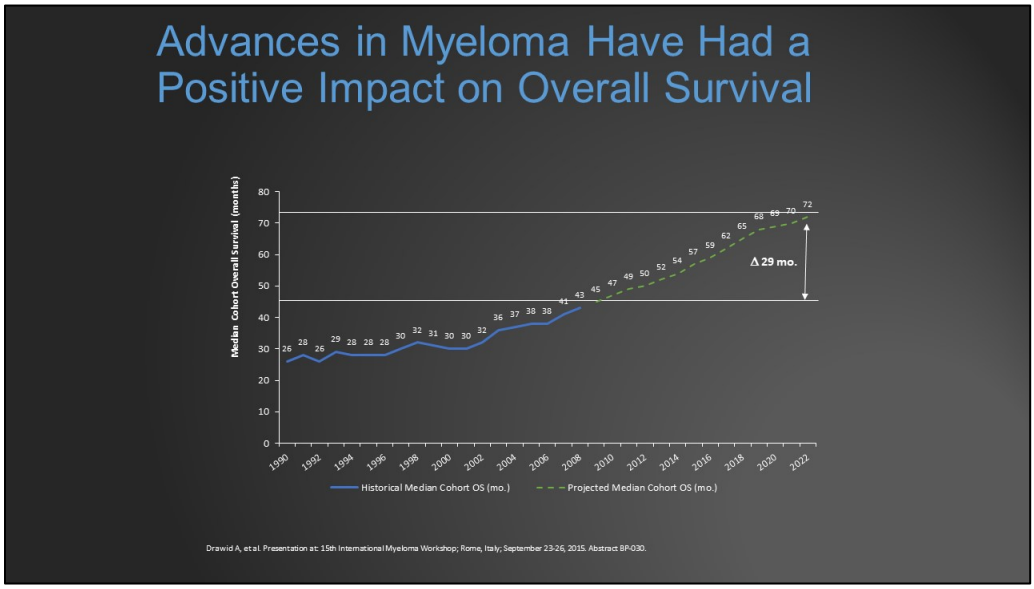



Responses are deeper than we can measure through conventional means right now, and this is what we're talking about with minimal residual disease. A lab test has a sensitivity of about 1 in 1,000 cells being positive in the bone marrow. If you do a bone marrow biopsy, the sensitivity is about 1 in 10,000 cells can be identified as a myeloma cell. If we do more advanced testing called flow cytometry or PCR (polymerase chain reaction) testing or next-generation sequencing, you can get down to the resolution of 1 in a million cells; and that has deep consequences for how well we expect somebody to do.

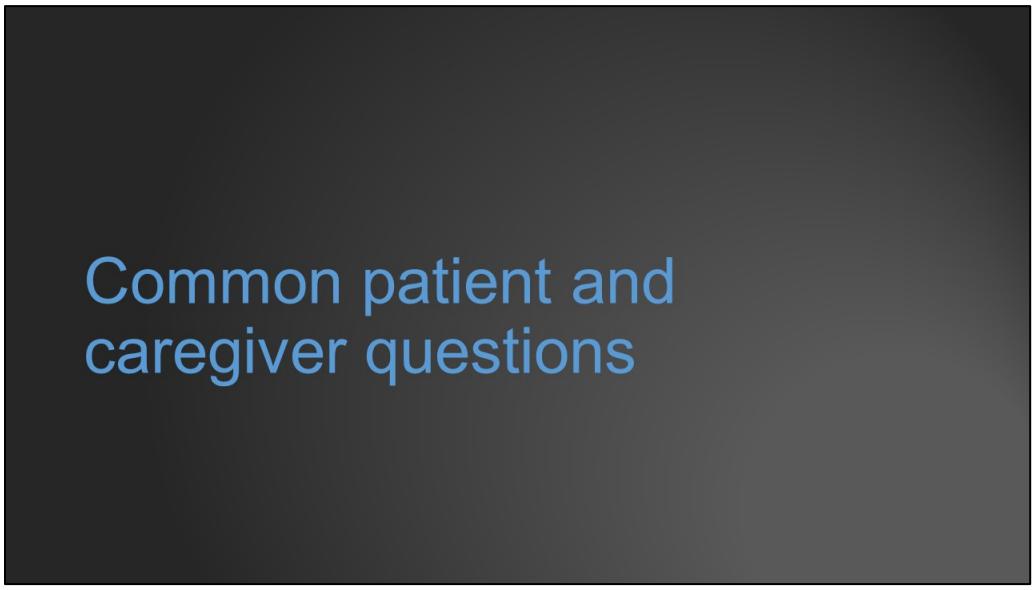


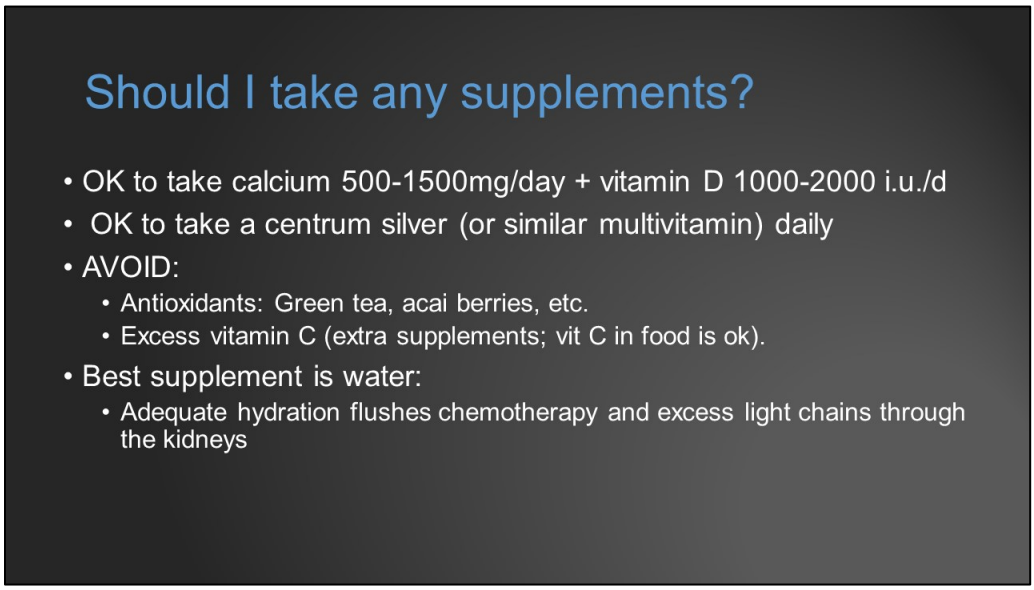

The reason is myeloma is like an iceberg. In fact, most cancers are like this in that we can only detect the top third of the disease. When people are diagnosed with myeloma, they have $10^9$ myeloma cells. So, that's about a billion cells or a gram of tumor. When people have too much myeloma to be compatible with life, that's about $10^{12}$ myeloma cells. That's about a kilogram of tumor. So, you can

see that there's three orders of magnitude, $10^9$ to $10^{12}$ from diagnosis to death. However, to get from diagnosis $10^9$ to cure, is nine orders of magnitude, so a little bit more difficult. And so, we really need to take these deep dives with molecular or flow cytometry testing from minimal residual disease because we can see that for every log reduction, you get a better overall survival, one to two more years of expected survival, depending on depth of minimal residual disease response.




Of course, you know, the survival for multiple myeloma has increased by leaps and bounds. When I went to medical school, survival was two years, maybe three years. Right now when somebody asks me how long they have to live; I tell them I don't know. Every myeloma is different, and there's certainly plenty of people with myeloma walking around 25 years after their diagnosis. And the treatments are only getting better and better.





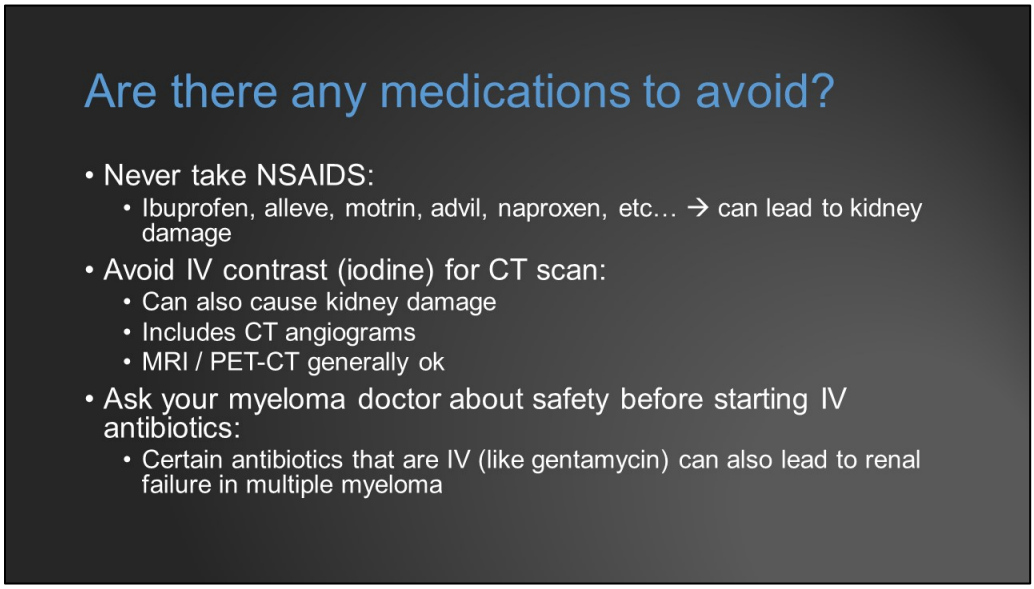

Now, lastly, I want to end with common patient and caregiver questions. "Should I take any supplements?" Well, it is okay to take calcium, 500 to 1,500 milligrams a day. Also, a vitamin D, 1,000 to 2,000 International Units a day. The reason being is that many people with myeloma, in fact most, should be on some sort of bone agent to prevent bone loss, either zoledronic acid, Zometa® or denosumab, Xgeva®. And those agents tend to suck up calcium and vitamin D. So, we want to keep those levels high so the bones can keep building up the cells.

In terms of multivitamin, Centrum Silver® is totally fine. There's not enough of any particular vitamin to cause any harm. On the other hand, do you need to take a vitamin? Not really.

You absolutely want to avoid antioxidants like green tea, acai berry. If the bottle or the package says antioxidant on it, do not take it. Antioxidants repair DNA (deoxyribonucleic acid) damage. They save the body from poisons. You do not want to take them when you're deliberately taking chemotherapy. You're deliberately poisoning these myeloma cells. You don't want to give them the poison and give them the antidote at the same time. It's been shown that green tea will neutralize the action with Velcade (bortezomib). It's been shown that cancer patients who take antioxidants will actually compromise their outcomes; they tend to die quicker because, again, it's effectively taking away the action of chemotherapy.

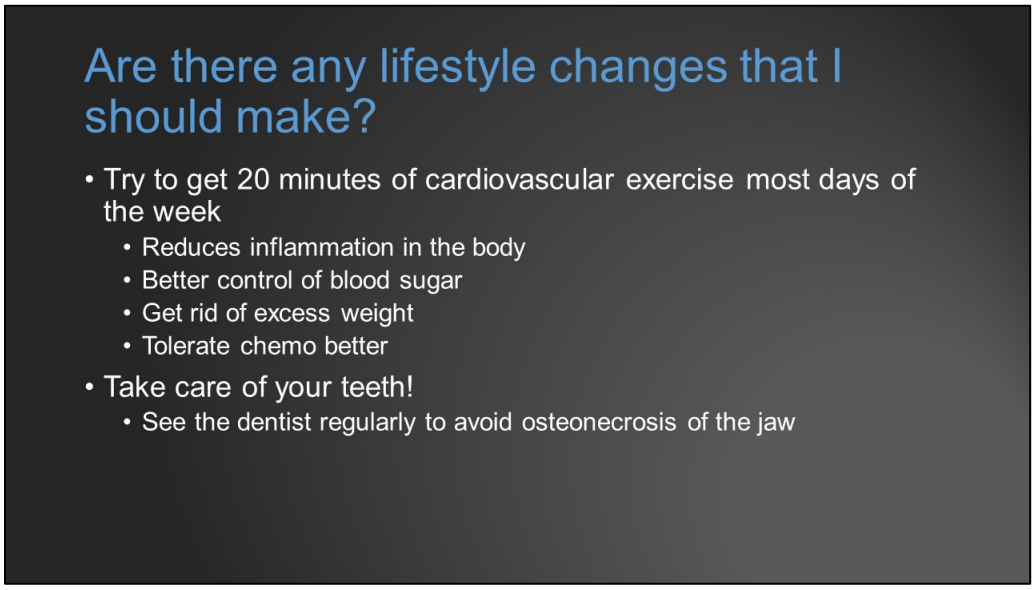
You also want to avoid excess vitamin C. Vitamin C, great for our immune system, helps you get over colds quickly; this is all true. However, myeloma is a cancer of the immune system, isn't it, and so why would you want to give something that supplements the immune system when you have a cancer of the immune system? That PET scan shows that, acid of the brain and the heart cancer eats first. It takes up that sugar first. It's the same thing with these supplements. The cancer takes it first. It's like a parasite. And so stuff that you think is helping your body may be helping your body, but it is also helping your tumor.

The best supplement is water; I know it's boring, however, myeloma protein, those light chains, they do float around in your bloodstream. All those toxic byproducts of the tumor cells dying with therapy float around, all that chemotherapy is floating around. You want to flush it out of your body, and the best way to flush it is by taking in adequate water, getting it through your kidneys and into your urine rather than being stuck in there. You want to maintain that flow.



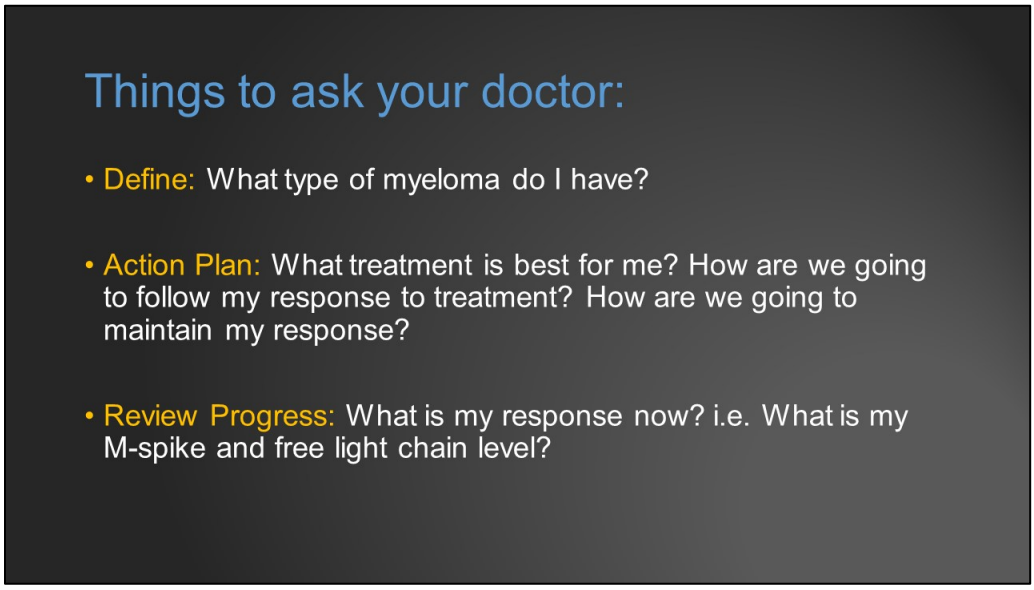

Any medications to avoid. So, I've listed some here. Most important, never take NSAIDs. That's ibuprofen, Aleve®, Motrin®, Advil®, naproxen; all of these can damage the kidneys, especially in myeloma where the kidneys are quite vulnerable. If you have pain, Tylenol® (acetaminophen) or perhaps a narcotic. There's other alternative pain medications that are used off label, but do not take Advil.

Try to avoid IV (intravenous) contrast if you can. This is the contrast used for CT scans. That also can damage your kidney. The contrast used in MRI and PET scan is generally okay. And then you want to ask your doc about safety before starting certain IV antibiotics. Certain IV antibiotics can damage your kidney, much like the NSAIDs (nonsteroidal anti-inflammatory drugs) can. A particular one is gentamicin that's used in certain places in the country. So just crosscheck with the pharmacist or the doc or the nurse to make sure that these particular medications are compatible with successful myeloma treatment.




Are there any lifestyle changes that I should make? Yes, and so, again boring but try to get exercise. Try to get some cardiovascular exercise most days of the week. It's absolutely fascinating that just doing this type of exercise reduces risk of death by almost 50%. If this was a drug, if exercise was a drug, it would be the best-selling cancer drug ever. Of course, exercise is free. Pharma is not interested in that, but I am interested in you guys doing well, so try to get this cardiovascular exercise. Now, if you can't jog or whatever, I wouldn't recommend jogging. I wouldn't recommend doing heavy weightlifting if somebody has involvement of the spine but certainly stuff like a recumbent bicycle, elliptical machine, even something like Tai Chi would be useful to get the blood flowing, get rid of the inflammation in the body, get better control of blood sugar. Again, sugar drives cancer through different mechanisms. Getting rid of that excess weight which will improve your insulin sensitivity and it will help you tolerate the chemotherapy or the immunotherapy better.

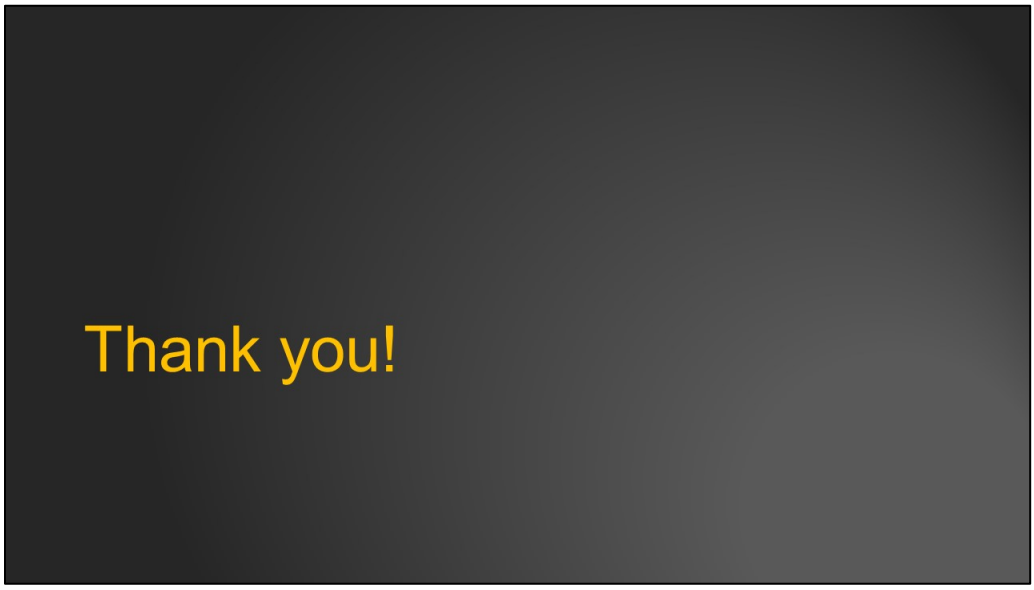
I also want to remind you take care of your teeth. The mouth is a very common source of infection, but most especially drugs like Zometa or Xgeva can cause severe damage to the teeth and jaw leading to a condition called osteonecrosis, which is essentially a nonhealing, painful ulcer in the jaw that will continually get reinfected. The risk of getting ONJ or osteonecrosis of the jaw is about one in 1,000. So, not high risk but certainly the risk is less if you have your teeth in good repair.




So, things that you should ask your doctor. Things that you should know about your myeloma. So, you need to define it. What type of myeloma do I have? Do I have IgG kappa? Do I have free lambda? Do I have nonsecretory? You want to follow these markers along with the doctor and the nurse so you're in control of knowing how you're doing and where you're going. You need to know what your action plan is. What treatment is best for me? Myeloma is not one size fits all for sure. Not everybody needs a stem cell transplant, let alone two.

How are we going to follow my response to treatment? M protein, light chains, urine. How are we going to maintain my response? And then you want to review your progress with the provider. What's my response right now? Am I in partial response, am I in complete response? What is my M spike and free light chain level?

The patients that are following their own course most closely do the best. You can't rely just on your healthcare provider, as much as we would like to, to spot everything as soon as you would be able to spot it. And so working in partnership with your nurse and doctor, taking control of your myeloma knowing exactly what's going on is only to your benefit.

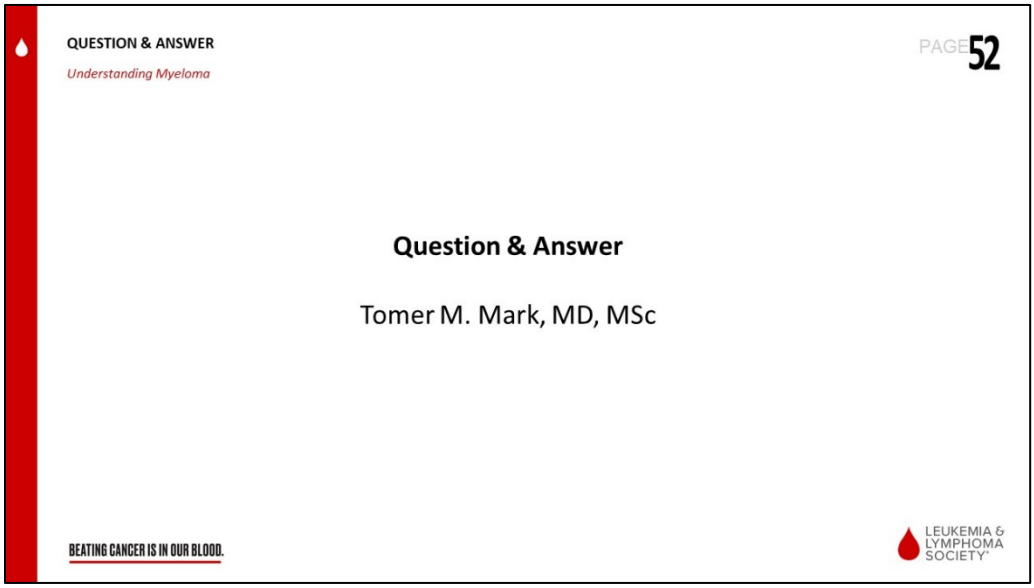



And so with that, I do want to leave enough time for Q&A. I want to say thank you to LLS and also to the audience that are here, and I'm ready to try and answer any questions you may have. Thank you.

***Lizette Figueroa-Rivera, MA***

Well thank you so much, Dr. Mark, for your very informative presentation.

## QUESTION-AND-ANSWER SESSION




***Lizette Figueroa-Rivera, MA***

Like you stated, it is time for our Question and Answer portion of our program. And for everyone's benefit, can you please keep your questions a little bit more general in nature without so many personal details so Dr. Mark can provide answers that are general.

***Lizette Figueroa-Rivera, MA***

Thank you. And, doctor, we'll start with a Web question. Steven asks, "If you've been in remission for eight years, can new cancers appear, and what are the most likely?"

***Tomer M. Mark, MD***

So, like any other medical question, the answer is, usually it depends. It depends on what the treatment was. For instance, if somebody had a stem cell transplant, a single one, then the risk of getting another malignancy, if no maintenance is used, is about 1% per year. And those malignancies tend to be bone marrow related like an acute leukemia. If Revlimid maintenance is given posttransplant, which is standard of care because it increases overall survival posttransplant, then the risk of second malignancy does come up pretty significantly to about 2% to 3%. Those malignancies, half of them are about skin cancers, squamous cells, basal cells, that you could just sort of cut off; but the other half are lymphomas, leukemias, solid tumor cancers like lung cancer.

This harkens back to what's called field theory in that if somebody has a cancer, then that tells us that their body is more prone to future cancers; that they're a target. And so for my patients in remission, I absolutely recommend that they go through skin cancer screening once every year or two, they go through their mammograms, they go through their colonoscopies because it would be a tragedy for somebody to wind up with metastatic colon cancer ten years into their myeloma remission.

***Lizette Figueroa-Rivera, MA***

Thank you, doctor. And we'll take the next question from the telephone audience please.

***Operator***

Our next call is from Shad from Montana. Shad, please state your question. Your line is now live.

***Shad from Montana***

I just wonder if Revlimid has an impact on vision, and I'm wondering about the severe abdominal pain from extended Revlimid over years.

***Tomer M. Mark, MD***

Okay, very good. If you wouldn't mind, are you taking any dexamethasone with this Revlimid?

***Shad from Montana***

No, cannot. I'm speaking on behalf of my husband. He took dexamethasone and got hiccups very badly.

***Tomer M. Mark, MD***

I see. So Revlimid per se does not cause vision changes. It's usually dexamethasone that's associated with accelerated development of cataracts. If your husband had a stem cell transplant, that also would accelerate blurry vision or cataracts. The Revlimid itself, I'm sure in some product listing there's some percentage of patients that's really low that may have blurry vision, but it is not typically associated.

As far as the abdominal pain is concerned, Revlimid can cause either diarrhea or constipation, so I'm not sure what your husband is suffering from, but it does it through a particular mechanism involving impaired recycling of bile from the gall bladder. And so your husband shouldn't have to suffer with

abdominal pain from Revlimid. If this is an issue that's coming up and making him uncomfortable, then it deserves to be worked up a little bit further in the clinic.

***Lizette Figueroa-Rivera, MA***

Thank you for the question. And our next question comes from Anna. "How long can you be in maintenance therapy with Revlimid? And does long term use, seven plus years of Revlimid, affect the bone marrow?"

***Tomer M. Mark, MD***

Great question. My record for Revlimid is 15 years of maintenance, and that's not just Revlimid. Velcade can also be given for many years. I know that Geraldine Ferraro was on Velcade for more than seven years. So, the context for the Revlimid is important. And so, if you take Revlimid outside of the context of other chemotherapy that is DNA damaging like melphalan in a stem cell transplant or cyclophosphamide, then there actually is no increased risk of another cancer no matter how long you take the Revlimid compared to the general population.

If you've had a stem cell transplant and then did Revlimid maintenance or you did an induction with cyclophosphamide, bendamustine or one of these other sorts of older chemotherapies, then there is an increased risk of using Revlimid. Again, it would increase your relative risk to the general population of about 1% to 2% per year. So, if you're on Revlimid, if you're on a maintenance, please keep up with your regular cancer surveillance screening.

***Lizette Figueroa-Rivera, MA***

Thank you. And we'll take the next question from the telephone audience please.

***Operator***

Our next call is from Joseph from Florida. Joseph, please state your question. Your line is live.

***Joseph from Florida***

I'm taking Revlimid and I'd like to know if I stop Revlimid for six months or one year and I come back start taking it again, is this okay?

***Tomer M. Mark, MD***

That's an easy one. It is not okay. The best way to set up an antibiotic resisted infection is to give a little bit of this and a little bit of that, meaning that you give the infection a chance to get used to the drug, to mutate, become resistant. Same thing with the myeloma. It's training the myeloma to become resistant to Revlimid by stopping and starting like this. And so I mean you could be lucky. You could respond to Revlimid again, but that's not a game I would recommend.

***Lizette Figueroa-Rivera, MA***

Thank you. And Sharon is asking about CAR T-cell treatment, how successful is this treatment as an option for myeloma?

***Tomer M. Mark, MD***

Well I first want to start the response by saying that CAR T[-cell therapy] for myeloma is not yet FDA (Food and Drug Administration) approved. It's still in clinical trials, although the clinical trial data is out there for the public to see. I can tell you that CAR T for myeloma, it appears to be highly effective. Between 90% to 100% response rate depending on what study you look at. I do want to say, however, that it is not curative, at least in the patients that have been tested so far, patients that have had five or more prior relapses. The duration of response is good. It's about a year of response, and a year response to a one-time treatment is pretty darn good. This is also the first generation of CAR Ts. They're only going to get better and better. And fingers crossed that we'll have CAR T FDA approved and commercially available in the spring of next year. But we're all very excited about CAR T.

***Lizette Figueroa-Rivera, MA***

Yes, thank you. And for those who are on the line that are newer to myeloma, could you just explain what CAR T-cell therapy is?

***Tomer M. Mark, MD***

Oh, I'm sorry. Yes, of course. So CAR stands for chimeric antigen receptor. T is T cell. And essentially what it is, it's extracting T cells as a type of white blood cell from a patient and then altering the DNA of that T cell such that it recognizes myeloma. Those T cells are then reproduced and grown in a vat such that there are millions and millions and millions of them. They're reinfused into the person just like a mercenary army to take out their myeloma. It's quite dramatic, quite advanced but certainly highly effective.

***Lizette Figueroa-Rivera, MA***

Thank you. And we'll take the next question from the telephone audience please.

***Operator***

Our next call is from Michelle from North Carolina. Michelle, please state your question. Your line is live.

***Michelle from North Carolina***

Okay, thank you so much for taking my question. My question is around neuropathy. I've been given, I don't know, a little bit of conflicting information. I just want to better understand the neuropathy that can come with the treatment of myeloma versus the myeloma itself, and, more importantly, how does one treat it beyond like gabapentin and duloxetine and maybe topical capsaicin? Are there other promising entities that can be explored? It affects quality of life, as you can imagine.

***Tomer M. Mark, MD***

Oh yeah, absolutely. Unfortunately, the neuropathy that's induced by certain chemotherapies and the neuropathy for myeloma can be identical. And so, if the neuropathy is due to myeloma, sometimes treating the myeloma itself will reduce the neuropathy but sometimes not. Sometimes the neuropathy from chemotherapy is permanent. We associate that more with thalidomide, but sometimes it's reversible. We associate that with Velcade. Although try saying that to a person who has neuropathy with Velcade. I mean it takes years and years to heal. Nerves grow about a millimeter a day so can you imagine a nerve coming from the base of your spinal column, all the way down your leg, all the way down to your toe tips, that would take years and years and years to heal.

I agree with you that the treatment is inadequate. Gabapentin simply dulls what's going on. It doesn't really accelerate any healing. Duloxetine sometimes helps, sometimes makes things worse, actually, in my experience. I really try to tailor the neuropathy management to the patient in such I'll ask them, "When is your neuropathy the worst?" And I would say eight times out of ten, the neuropathy is the worst when somebody's in bed trying to fall asleep. There's no other sort of stimulation out there. They're just sitting there, their feet are burning, or their feet are ice cold, and they cannot fall asleep at all. If that's the case, I do prefer giving an older agent, a tricyclic antidepressant either called amitriptyline, Elavil or nortriptyline, Pamelor™. These are drugs that are sort of similar to gabapentin in that they will dull nerve discomfort, but they also make somebody fall asleep. And so you take one of these things about an hour before you go to bed and then staying awake with your neuropathy gets much, much better.

If the neuropathy is a constant thing throughout the day, I find that, again, this is all anecdotal, I find that Lyrica® (pregabalin) works a little bit better than gabapentin. Neither drug is a panacea. And I'm fortunate enough to work in Colorado where certain substances are legal, and they also may be

helpful to control neuropathy and neuropathic pain especially. There are topical formulations of the certain Colorado substance. And in addition to that, there are compounding pharmacies that will make concoctions of topical ketamine that actually do work quite well. But these are all patches. These are all Tylenol for a fever. It doesn't address the underlying mechanism. And, unfortunately, we just haven't found a way to grow nerves more quickly.

***Lizette Figueroa-Rivera, MA***

Thank you for that question. I know that a lot of our folks were asking about neuropathy. We do have Madeline, Don, and Claudia asking about COVID and myeloma and the risk of visiting medical offices in this time of COVID.

***Tomer M. Mark, MD***

Yeah. It's a great question. So, obviously, if COVID's bad for the usual person, COVID is extra bad if you have immunocompromised state like myeloma. You won't be able to generate your own antibodies as well as somebody else without myeloma. And so COVID is much more serious, much more fatal in somebody with myeloma and going to the utmost to prevent exposure is important.

That being said, depending on the medical office, I know that at least where I work in my clinic, I feel safer there than I do at the grocery store. Everybody gets prescreened the day before on the telephone. Everybody gets their temperature checked. Anybody that looks sniffly is immediately isolated to a different area. And so there's a level of control in the medical clinic that you don't find in the community. Also, in the medical clinic that all of the staff are pretty diligent about wearing masks and gloves and using hand sanitizer. That may not be the case in the grocery store or in church or at your friend's house. And so, if anything, I feel a little bit more comfortable coming to the clinic if measures like what I just described are in place.

***Lizette Figueroa-Rivera, MA***

Thank you. And we'll take the next question from the telephone audience please.

***Operator***

Our next call is from Sean from Washington. Sean, please state your question. Your line is now live.

***Sean from Washington***

Yeah, hi. I'm out of a cancer program. I don't think I'll be able to get my cancer medicine Xgeva (denosumab) shots and Revlimid. My question is can I still stay healthy, cancer free taking dexamethasone 4 milligrams, five tablets once a week, my aspirin, oxycodone, calcium 600, vitamin

D every day? I started my program in September 2018. I've been cancer free for six or eight months. I have anemia. I had to get a blood transfusion and a potassium transfusion. I'm 71 years old.

***Tomer M. Mark, MD***

Yeah. Dexamethasone by itself is not a good medication to treat myeloma. The response rate is about 50%. And like I showed, I think, in an earlier slide, responses of dexamethasone are quick, but they only last about a month. And so, I certainly would urge you to try and find something to partner with that dexamethasone. It does not have to be Revlimid. But dexamethasone by itself is not okay.

***Lizette Figueroa-Rivera, MA***

Thank you. And I will give the number to our Information Resource Center where information specialists can help you in trying to find different programs to obtain your medications.

And the next question, doctor, comes from Nicholas. Nicholas is asking, "Aside from CAR T, can you provide a quick overview of other therapies that show promise and are on the horizon?"

***Tomer M. Mark, MD***

Yeah, sure. As a lot of you probably already know, it's a pretty exciting time for myeloma in that new therapies are coming fast and furious. So, some that were recently approved, one is selinexor. This is a first-in-class oral medication that is a nuclear transport inhibitor. No other drug like this on the market. It has been shown to be effective in relapsed myeloma that is refractory to everything, including daratumumab, which is pretty exciting. There are issues taking it. Being a pill, it can cause some gastrointestinal problems, however, with the proper pain medication, I have found some success with this in patients who literally had no other options. So, that's exciting.

Another drug recently approved is isatuximab. That's also called Sarclisa®. That is an alternative monoclonal antibody against the myeloma cell. It's in the same family as daratumumab but binds slightly differently. And I find that people who can't take dara (daratumumab) I can switch to this drug, so it's nice to have another option in that space.

Another drug which was just recently approved is belantamab. This is also called Blenrep® (belantamab mafoditn-lbmf). This is an intravenous drug that's given once every three weeks, and it is an antibody drug conjugate, meaning that it's an antibody that binds to the myeloma cell conjugated to a drug that's poisonous. And so, once the Blenrep attaches to the myeloma cell, it injects this poison directly to the myeloma while sparing the rest of you, at least theoretically. Blenrep has problems with the eyes. It can cause blurry vision, dry eyes, itchy eyes, and so, unfortunately, an ophthalmologist needs to be involved prior to every dose to prevent permanent eye damage. So not ideal but yet another option.

Other things in development right now include BiTEs. Those are called bispecific T-cell engagers. These work on the same principle as CAR T instead that these are off-the-shelf agents just T-cell receptors that you take off the shelf. You don't have to prepare them like a CAR T, and you can dose directly into a person to get a CAR T-like effect. The downside of this is that you need to have repeated dosing in order to keep those antibody levels up as opposed to CAR T which is sort of a one and done.

Other new drugs on the horizon, one of them is Melflufen (INN melphalan flufenamide). This is a form of melphalan that has sort of been upgraded to penetrate myeloma cells more easily. It does have pretty good activity in relapsed myeloma. There is a new immunomodulatory drug beyond Pomalyst® (pomalidomide) – it's called Iberdomide (CC-220) – that is also amazingly active in relapsed myeloma and it's great that it's oral as well.

People are now working on agents to augment the efficacy of CAR T cells. There's these class of agents called gamma secretase inhibitors that will keep the target of CAR T BCMA (B-cell maturation antigen) on top of the myeloma cell to sort of really make the myeloma cell a beacon for that CAR T to go directly there.

And this is just a few examples of what's going on.

***Lizette Figueroa-Rivera, MA***

Thank you so much for that overview. And we'll take the next question from the telephone audience please.

***Operator***

Our next call is from Valerie from New York. Valerie, please state your question. Your line is now live.

***Valerie from New York***

Well first of all, let me mention that Tomer is responsible for my survival. Do you remember me, Tomer?

***Tomer M. Mark, MD***

I'm sorry, what's your name again?

***Valerie from New York***

Valerie.

***Tomer M. Mark, MD***

Oh yeah, of course I remember you and your daughter!

***Valerie from New York***

Yes, well I arrived from the plane with a horrible situation, and I was treated by Dr. Tomer for a good two, three weeks in the hospital taking me down from a situation of 5,000 I was having a fuss. But anyway, I've been in treatment now for five years, still alive, and my question to Dr. Tomer is since he's now in Colorado, what is the news in treating what I have with the same as cannabis?

***Tomer M. Mark, MD***

Yeah, so, you know, yeah, again, working in Colorado, I would say about 80% of my patients use some form of cannabis, either the THC (tetrahydrocannabinol), the stuff that gets you high, or CBD (cannabidiol), the anti-inflammatory, or some combination of both. Eighty percent of them tell me that they use it and I suspect the other 20% are hiding something.

In terms of treatment of multiple myeloma and any other cancer the cannabinoids you can find the data if you look for it, but the data is not quality data. And so, you'll read these advertisements for CBD saying, "Has been shown to kill cancer cells." Well if you take a look at the reference, it's killing cancer cells in three mice at literally doses where you would have to take kilograms of CBD every day, so not natural situations. That being said, there may be some effects on the immune system that are modulated by CBD and THC that we are still investigating that could help in terms of fighting the cancer itself.

Myeloma, as you know, is a disease of inflammation. CBD is a pretty powerful anti-inflammatory, and so one could surmise that there may be some effect. But, first of all, the Federal government won't let us do any research on this and we're years behind other countries, especially Europe, where there's other forms of cannabis to take.

In terms of controlling symptoms, however, like low appetite, difficulty to sleep, pain, especially neuropathic pain, I find that, really, it's a fabulous product. I'm sad that it's not available to more patients, although I think the country is catching up.

Valerie, it's great to hear from you. I still think about you, and I'm glad that you're doing well.

***Lizette Figueroa-Rivera, MA***

Thank you so much, Valerie, for calling in. I'm sure Dr. Mark is very happy to hear that you are doing well. Like you said, Dr. Mark, it's great to hear from patients.

And we'll take our next question from the Web. Herman is asking, "When you mention chemotherapy, are you including Revlimid in that group? And if taking Revlimid, should I avoid taking antioxidants?"

***Tomer M. Mark, MD***

That's a great question. I mean it depends what your definition of chemotherapy is. If it's any drug that kills dividing cancer cells, then, yes, Revlimid is chemotherapy. If it's any drug that works by destroying DNA, then Revlimid is not chemotherapy. We like to think of Revlimid as an immunomodulatory drug, meaning that it does kill dividing myeloma cells, but its primary mechanism of action is altering the bone marrow environment such that it is toxic to the myeloma. The myeloma doesn't like to live there anymore, and it loses its home and then can't survive anymore. It also enhances the function of T cells.

And so with Revlimid, I don't typically describe it as chemotherapy although you'll hear it called chemotherapy all the time. And since it's given with the purpose of destroying dividing immune cells, I would recommend that you do not take antioxidants because those rescue cells that are dying. You want those cells to die.

***Lizette Figueroa-Rivera, MA***

Thank you. And we'll take the next question from the telephone audience please.

***Operator***

Your next call is from Antonio from Georgia. Antonio, please state your question. Your line is now live.

***Antonio from Georgia***

Hey, good afternoon. Thanks for taking my call. Question is I'm on dexamethasone and Pomalyst and I also do Zometa every four weeks. I'm wondering what in that combination or is there anything that causes weight gain because since I've been in treatment, I've gained almost 50 pounds and it's kind of disheartening.

***Tomer M. Mark, MD***

Well I hope to give you some heart back because you're not the only one. Lots of people gain weight with this – sometimes 50 pounds, sometimes even 100 pounds – and the source of it is the dexamethasone. Dexamethasone leads to fluid retention, it leads to fat redistribution especially around the belly/abdomen area, it also makes people very hungry and not hungry for broccoli, hungry for bad foods – potato chips, cakes, cookies, stuff like that. And you take that all together, and I can tell you pretty much anybody on steroids – prednisone, dex, Solu-Medrol® (methylprednisolone) – they will gain weight.

The advice I have for you is you have to be super careful not to take in too much sugar on the days that you take your dexamethasone. The dexamethasone will increase your blood sugar level, your insulin won't be able to catch up and then all of that extra sugar will be put into fat. And so, on those days, I know it's going to be super hard because that's the days it's most tempting, you really have to try and limit your carbs. Not a lot of white bread, not a lot of white rice, no cookies, candies, that sort of thing. And then on the other days you can lighten up a little bit. That'll help you with your weight loss.

The other thing I wanted to say is that Zometa, there was a randomized study looking at giving it every month versus every three months, and there was no difference in outcomes. So, if anything, I would reduce your Zometa dose to once every three months.

***Lizette Figueroa-Rivera, MA***

Thank you. I know that we're receiving a lot of questions about diet, about antioxidants and there's a lot of foods that have antioxidants so we're getting questions about can people eat blueberries and then we're getting other questions about…

***Tomer M. Mark, MD***

Oh yeah, I can give a blanket statement on that. Yeah. So, in general, the amount of antioxidant you get from food is very low. So please, put blueberries on your oatmeal or however you like to eat it. Just don't eat a bushel of blueberries. Some people, they'll take it to the extreme. I told you not to have vitamin C. You can have an orange; you can drink a glass of orange juice, just don't take supplements that have 7,000% daily recommended value of vitamin C. Some people will take these super supplements thinking it's helping out their cancer. So, no, I do not want anybody walking away from this talk being paranoid about how much antioxidant is in the broccoli they're eating that day. I do want them to go to the store and not buy that bottle of pomegranate juice that says antioxidant on the front.

***Lizette Figueroa-Rivera, MA***

Yeah, thank you for that clarification. And we'll take the next question from the telephone audience please.

***Operator***

Our next call is from Jeffrey from Arizona. Jeffrey, please state your question. Your line is now live.

***Jeffrey from Arizona***

Thank you for taking my call, Dr. Mark. My question is I was diagnosed earlier this year around the same time COVID came about, but I've had very, very little stamina on anything that I'm taking and I'm probably going to have a stem cell transplant in a few months. And I'm just wondering if this could help with my stamina so I could start doing things again. I really can't do very much. I mean my strength is good, but my stamina is just awful.

***Tomer M. Mark, MD***

Well, I mean I personally would do a deeper dive into why you're so tired. There's lots of reasons. I mean I would check your B12 level, I would check your thyroid level. In certain situations, I do an anemia workup. If I can't find anything on bloodwork or other sorts of tests, then I'm going to have to pin it on one of the drugs that you're taking. Certainly with dexamethasone, there's a high and then there's a crash for a few days that can leave people very winded. Revlimid can certainly make people very tired, and if you're taking it in the morning, I would recommend you take it at night instead. Velcade is associated with fatigue as well. Sometimes dose reduction is needed. But another thing is inertia. You get your diagnosis of myeloma; you may have bone pain. It may lead to not being very active, not moving around a lot. And all of a sudden, a couple of months go by and you can hardly move. Sort of like use it or lose it thing. So, sometimes it could be simply deconditioning, in which case I would prescribe physical therapy, and I would recommend to you that you're feeling tired and you're feeling crappy but please try to keep up some exercise because that really does make everything better even if you don't feel like it.

***Lizette Figueroa-Rivera, MA***

Thank you, and we have Chu Chu's asking if myeloma patients should take the flu vaccine.

***Tomer M. Mark, MD***

Oh, not only should you take it, you should take two of them. People with myeloma need two flu vaccines. It should be high dose, but any dose that you can get is fine. They should be spaced one

month apart. There was an abstract at the American Society of Hematology meeting in 2017 or 2018 that showed that after one high-dose flu vaccination a person with myeloma had about 30% immunity. After two, between 65% and 70%. So, if you're going to go and do it, get two of them. And I do recommend you do it because flu is a major killer of people with myeloma.

***Lizette Figueroa-Rivera, MA***

And also Michelle is asking if myeloma patients can take the shingles shots.

***Tomer M. Mark, MD***

The Shingrix brand that's the newer one. That does not have any live virus in it. The old shingles vaccine, varicella vaccine do not take. That is live.

***Lizette Figueroa-Rivera, MA***

Thank you. And we'll take the next question from the telephone audience please.

***Operator***

Our next call is from Tamala from South Carolina. Tamala, please state your question. Your line is now live.

***Tamala from South Carolina***

Okay. Yes. I was diagnosed with myeloma in 2010, and I celebrated ten years in August. I did the stem cell transplant, and I did Velcade and I've done Revlimid but now I'm on Darzalex® (daratumumab). And I'm noticing when I come off like several months more my steroids wear off and I'm coming down and it's lasting longer. It's lasting longer now so like it's taking me longer to get my energy back. And I'm so glad you said something like that because I go to my regular doctor – I just had chemo yesterday, but I go to my regular doctor in a month and I'm going to ask her to do that testing to see what it is, but I don't know if it's just me being on it for ten years. Well actually I was in remission for two years, so maybe I can stop. I've been on chemo probably eight years.

***Tomer M. Mark, MD***

Did you just start the Darzalex or you're a few months into it?

***Tonya from South Carolina***

I started in 2016.

***Tomer M. Mark, MD***

Oh, okay. So, this is all sort of cumulative stuff. Are you getting dexamethasone IV or by mouth prior to that?

***Tonya from South Carolina***

IV.

***Tomer M. Mark, MD***

IV. Gosh, if you've been taking it for, oh gosh, quite a while, I might try first by reducing the dose of dexamethasone that you get.

***Tonya from South Carolina***

They actually did change it because I had to have both my hips replaced and a shoulder replacement because of the dex (dexamethasone) over, the high dosage. But, it's about a 5 milligram I take now with my treatment.

***Tomer M. Mark, MD***

Oh that's pretty darn low. Yeah, again, I think I would give similar advice. This is kind of complicated, and you can have low stamina for all sorts of reasons. And so, it could be not related to myeloma or treatment at all. And so going to see the primary care doctor is a good idea. Making sure that your oncologist or nurse practitioner knows what's going on because very frequently we'll get feedback, "Oh a patient's doing okay," and we'll move on with our day, but I would encourage you to sort of speak up and let them know this a problem for you.

***Lizette Figueroa-Rivera, MA***

Thank you. Thank you for the question. And our last question today, doctor, comes from the Web asking, "How do you feel about second opinions?"

***Tomer M. Mark, MD***

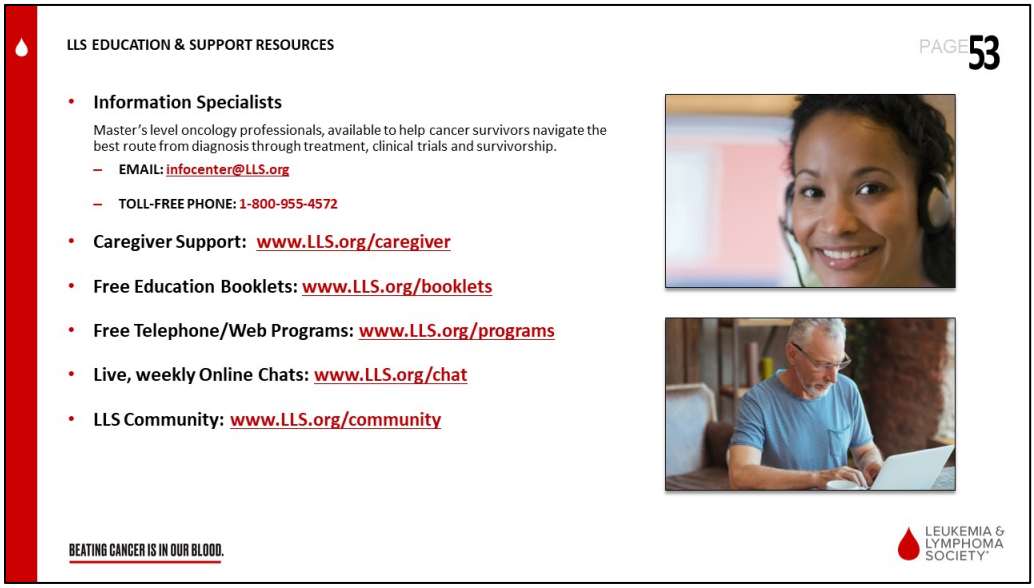
I feel fine about them. I actually encourage my patients to go seek a second opinion. I think that not everybody treats myeloma the same. Some people in some centers they have certain agendas. Everybody deserves to be seen by a myeloma expert. There's about 30 or 40 in the country. You should be able to find an expert to at least look at your chart and making sure that nothing's been missed either before starting treatment or shortly after starting treatment. Now that there's telehealth and virtual medicine, this is becoming easier and easier. So, I do highly recommend a second opinion, especially if you're getting treated by a local or community oncologist or in a community hospital that may simply not be aware of like the latest developments and options for you. And let me also add that if your oncologist is offended by you getting a second opinion, that is a red flag. You do not want an oncologist with an ego. It's about you.

***Lizette Figueroa-Rivera, MA***

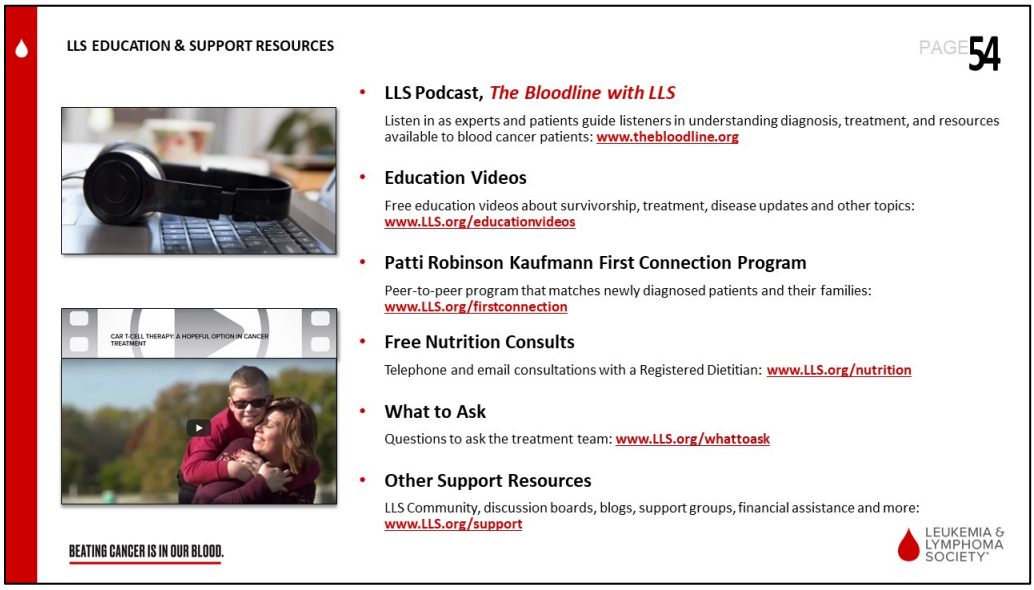
Well thank you so much, Dr. Mark.

## CLOSING REMARKS

### *Lizette Figueroa-Rivera, MA*




Thank you for answering all of these questions which we were able to get to many questions today. If we weren't able to get to your question, please call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572. And Information Specialists are available to speak with you from 9 am to 9 pm Eastern Time. Or you can reach us by email at infocenter@lls.org.




Please note that continuing education credit is not being offered for this program.

Again, we'd like to acknowledge and thank Bristol Myers Squibb, Genentech & Biogen, GlaxoSmithKline and Takeda Oncology for support of today's program.


Thank you so much, Dr. Mark, for sharing your knowledge with us today. And to all of the patients, caregivers and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Good-bye and we wish you well.