James M. Rossetti, MD
Jayshree Shah, APN-C, RN, MSN, BSN, BS

?: … is moderator and Dr. Rossetti is our physician moderator from Western Pennsylvania Cancer Institute. Welcome everyone and I hope you find this helpful and thank you all for coming.

Jayshree Shah: I just want to say thank you for taking out a Saturday morning to join us today. We're going to be sharing a lot of important information regarding MDS. The basics, the nuts and bolts of it along with Dr. Rossetti answering questions from you as patients and caregivers. I just wanted to let you know if you can or request, if you have cell phones, can you just put them on vibrate for us? The bathrooms are on the right hand side around the corner and feel free to stretch, get up, whatever you need in between. There is water and coffee and stuff in the back. We'll have Dr. Rossetti go first and then I'll speak on my topic of quality of life issues and then we'll take a lunch and then we'll finish up with more questions and talking amongst each other. I'm going to have Dr. Rossetti take over.

James Rossetti, MD: Can I do it without the… everyone can hear? Alright. Thank you. These are I find very good events and it's funny I did my first one several years ago and I was very impressed with how much information, how much you all know about these diseases. So, when Dr. (inaudible 1:38) who's a good friend of mine from Hopkins and I did one two years ago, we really put a lot of scientific information in and we found actually that the patients prefer that. So, I do have a lot of slides that we use as clinicians to help guide your care, but ultimately it's you as the patient and what your goals are, your quality of life and variety of other things that come into play when we decide on the treatment strategy for you. I do want to leave time for questions. Just a couple of introductory remarks though. At West Penn, we're fortunate to be an MDS Center of Excellence which is why we (inaudible 2:14).

Jayshree Shah: (inaudible 2:18) we're recording.

James Rossetti, MD: Oh, you're recording.

Jayshree Shah: Yes. We're just recording the patient forum or we'll at least put it on the website because people want to (inaudible 2:29) things that we (inaudible) to share or learn from.

James Rossetti, MD: Okay. I will wear it. Does that work? I thought I was allowed enough. Anyhow, we are an MDS Center of Excellence which is something that we are very proud of. It's the status that it gives us obviously a lot of referrals, but to get to that point to get that status, it does require research, it requires clinicians who are really specialized in this particular area of illness and it's something we're proud of. Joan Lasko is here. She was a big part of why we're an MDS Center of Excellence. She's no longer practicing with us, but many of you (inaudible 3:20). Joan worked with Dr. Richard Shaddock. Who remembers Dr. Shaddock? I know there's a few hands in this room that do. Dr. Shaddock is… I was joking yesterday during an MDS talk that he's sort of a grandfather. I hate to say that though because if he hears me he'd be upset, but he really was at the cutting edge of defining what this disease and group of diseases even is and I was fortunate to train under him and we were fortunate to continue with the MDS Center of Excellence status at West Penn Hospital and,

again, I want to thank Joan for her contribution to all of that over the years. It's wonderful to meet up with an old friend and colleague. I also brought with me today Valerie Demarco who's the physician assistant in our practice and if any of you and some of you are patients, if any of you end up seeing us, you'll get to know Val really well and you'll be very pleased with her. She's excellent.

So, let's get started and then we'll go to questions and you can see the subtitle of the talk is "Improving Marrow Function Quality of Life" and very importantly in bold print "Survival." Why is that important? Up until 2004, there was very little we could do outside of bone marrow transplantation to alter the natural history of this group of disorders. If people were going to go on to leukemia, they were going to go onto leukemia which is one of the concerns, of course, with MDS and there was nothing we could do to alter that and very, very few patients at that point in time were ever able to even get to transplant because of the risk associated with it. A lot of that's changed, but very importantly our treatment strategies are now impacting survival. What that means for us as primary care physicians are now recognizing even mildly low blood counts and sending patients to us earlier and earlier because we can do something about this group of diseases. So at the end of the day, you'll see a lot of statistics, some good and some not so good, but at the end often day, I want you to leave with the take home message of hope. That's what today is about. We're really making great strides in enhancing survival while helping the blood counts, i.e. marrow function and very importantly improving your quality of life, keeping you out of the hospital, limiting transfusion needs, limiting infection, etc., etc.

So, this is sort of one of those when I was your age type of slides and I just want to… I show it for its historical context into reiterate what I said about change and transition in Myelodysplastic Syndromes. A cancer treatment with a (inaudible 6:03) book in 1987, that's a pretty well-known and respected book in our field, had less than one page dedicated to the Myelodysplastic Syndrome and it wasn't an issue of neglect. It was that we really didn't know a whole lot about what MDS was and, again, we could do very little to even change the disease. So, not a lot and you can see just moving forward about a decade in the year book of hematology, two pages. So, not a whole lot of change there, but if you go from the mid 90s forward when we really started to understand the biology of these diseases, what drives the diseases, why everybody with MDS is different, why some people have high grade disease and low grade disease and this chromosome or that chromosome all more on that in a minute. You can see there was sort of a rapid jump to the point where in 2002, we actually had it in a textbook entirely dedicated to just this group of disorders and now there's multiple textbooks being produced as we learn more and more about these diseases. So again, it's all a matter of hope.

This group of disorders was first described in the 1900s. At the time in the year 1900, it wasn't known that this was MDS. It didn't have that name yet, but there were a group of older individuals who had large cells. Their cells were too big and when they passed and autopsies were done they found that the bone marrow as full of what they thought at the time was puss and in fact it was white cells, excess white cells, and so it really was about the same time that we started to understand acute leukemia that that group of disorders came into play, but as a unique clonal entity whether or not it ever goes on to acute leukemia, that wasn't really described until 1982 and most of us remember the '80s for parachute pants and big hair. That's where MDS really was taking off. So 1982, we

understood what these diseases really were, but again limited understanding as to the biology of the disease and as with any other disease that we treat the biology always dictates the treatment. When we understand on a molecular basis, on a genetic basis why these diseases occur we can then start to develop treatment strategies targeted against those particular areas. Now the incidence of the US is on the rise. Ten years ago when I started doing a lot of speaking on MDS, the incidence and that's the number of new cases annually, the incidence in the US was only about 7,000 cases per year. Most experts anticipate that this number is going to go up to about 50,000 sometime in the next few years. That's a big concern, of course. Now on a positive side, most of the patients we diagnose today have low grade disease. Again, people are in tune with the fact that low blood counts is not normal for any age and they're sending patients to us earlier and earlier allowing us to find people like yourselves at lower risk categories where we can start to do something to change the disease pace and we're going to talk about all that in great detail.

The question becomes why is this number rising? Well, one, is very obvious. In our great country, we live longer than many other nations and in most industrialized nations the average survival has gone up and we know that this tends to be a disease of older individuals, a group of diseases of older individuals and so as people live longer, we see diseases that affect the aged population more and more, of course. The problem is the incidence of these groups of disorders in people who are older is plateauing a little bit and we're seeing a subtle rise in the incidence in younger and younger people, 30, 40 years of age .The youngest person I ever saw was 18 and I know my colleagues at the children's hospital treat juvenile type Myelodysplastic Syndromes as well which may have a genetic component, but the reality is we have to acknowledge the fact that in our industrialized world we are exposed to things that we probably shouldn't be and so environmental exposure becomes important as well and very, very importantly another reason is that us people are outliving other cancers. Some of you may have heard or have what we call treatment related myelodysplasia. Treatment related myelodysplasia usually follows treatment for something else like breast cancer or sometimes even colon cancer or lung cancer, etc. In transplantation, a lot of the drugs that we use can lead to the development of MDS sometimes 10 years later. So, people are outliving other malignancies, but sometimes this is the end result is MDS and it tends to behave a little more aggressively and why we tend to be aggressive back and oftentimes take patients how have that particular and see the transplant.

Now people are living longer and longer with MDS to be sure and that's the take home message. Really the take home message on this slide is we're seeing more and more of it, we're finding it earlier and people are living longer.

So, this is what we see when somebody's diagnosed with MDS. Usually, the tip-off is low blood count. Sometimes the tip-off is only that the cells are too big. What we may have heard from your doctor macrocytosis. Your MCV some of you may see on your CBC is high. That means the cells are too big. One of the things that we worry about is a problem with the DNA or the early development of the cells when the cells are too big and in fact we start looking for MDS after we exclude other things and raise your hand if you like a bone marrow biopsy. Nobody likes a bone marrow biopsy. I always say if you can figure out a way to diagnose MDS without a bone marrow, you will be an exceedingly wealthy individual and have a whole lot of friends, but a bone marrow is necessary. It's

not only necessary to make the diagnosis, but it's necessary to utilize in our prognostic models and the prognostic models are what ultimately what dictates what type of treatment we employ.

So, what do we see in the bone marrow when we diagnose somebody with MDS? Typically, there's far too many cells. The bone marrow is what we call hypercellular. With each decade of our life, about 10 percent of our bone marrow gets replaced by fat like the rest of our bodies do and ultimately as we age, an 80 year old should have a cellularity in the bone marrow of about 20 percent. The rest is replaced by fat, plus or minus 10 percent. So for 80, a normal cellularity in the marrow is somewhere between 10 and 30 and a lot of times in a patient with MDS at 80 years of age, they'll have a 100 percent cellular marrow like an infant would be expected to have. Why is that? Why is the bone marrow full of cells, but the blood stream isn't? You got all these cells in the bone marrow trying to work and they're not getting into the blood and one of the reasons is they're either stuck at their early phase of development and they never get to that point of maturation to do what they're supposed to do and why do people with MDS get infections? Because they don't have functional white cells or low white cells. Why do you get transfusions of red blood cells and platelets or bleeding complications and fatigue? It's all the end result of poor maturation or early death of those cells in the bone marrow before they get into the blood stream to function. The cells in the bone marrow don't do anything. They don't function. They have to get in the blood first and then when they get in the blood in their mature phase they start to do their job and so that's why the bone marrow is usually chock full. I want to mention there's a different type of disorder we call hypocellular MDS and I mention that because some of it may have it or have a loved one who has it and that is oftentimes treated very differently with immune suppressive therapy and we can talk about that more, but this the majority of patients right here and when we look under the microscope, this is the type of thing that we see. These are very, very atypical cells. This cell here is a neutrophil. That cell is meant to fight infection. It's supposed to have lots of granules in it that have certain proteins that are released to help fight infection. The nucleus you see in side gets tied up in a knot when it is no longer useful when its job is done and then the granules in what we call the cytoplasm cell take over. In this cell here you can see it's got too many lobes to it. This is what we call hyper segmentation. Very dysplastic and you can take my word for it all the cells in this slide are dysplastic. So, MDS not only manifests with low blood counts, but as the name implies dysplastic or dysplasia means the cells look atypical. The morphology what the cell is supposed to look like doesn't look normal. Now, I share this slide for that reason for educational purposes, but I also share it for the reason that most of the time when we diagnose MDS we don't' see it this obvious. Most people come and oftentimes the pathologist will tell us you may have… this patient may have MDS and so we have to work with our pathologist. We have to work with our cytogenetic folks in the lab, our flow cytometry folks and very importantly what's happening to you clinically as the patient as we put all that information together to help make the diagnosis correctly and then from there we can go into prognostics and what your risk of leukemia is, what your risk of developing other blood count abnormalities, etc. is.

This guy here I share with you just to show you what a ring sideroblast is and what this suggests in patients with MDS is that there's a functional iron deficiency. You have lots and lots of iron in your bone marrow sometimes even before you start getting transfused, but the iron is not being utilized.

It's just sitting in a certain cellular compartment in the cell and not being effective and there's things we can do to help alter that as well. So, that's MDS under the microscope.

This slide really serves as the basis for the rest of the talk. This is why we now have treatment for people with MDS and I don't expect any of you here to remember this and quite honestly there's a lot of people, experts, in the world who know a whole lot more about these different pathways than I ever will, but the reality is our understanding of the genetics of this disease has allowed us to develop treatment strategies that are giving you all hope, making you feel better, live longer and reach certain milestones in life that I know are important and I think that really does become as we talk a little bit more about treatment, really, really important as an aside. While I'm thinking of it, I think it's really important that you communicate to your physician whoever it is what your goals are in both the short term and in the long term. I have had people with aggressive disease who have said my goal is to see the birth of my first granddaughter in two months. I've had a gentlemen with low grade disease, but very low platelets who had just retired. His goal in life was to mountain bike into the sunset and with 1,000 platelets, mountain biking is not a good idea and so it really affected his quality of life and I think it's important for you to share those types of things and don't minimize them to your physician because it helps us to develop a good strategy for you in your treatment.

I do want to note one thing that's interesting and it's this one right here what we call epigenetics. Epigenetics in cancer suggests that the DNA itself is actually fully intact and normal. The old understanding of cancer, the cancer models, you go to the doctor and say, "Doc, why do I have cancer? Why do I have a malignant disease?" and the answer typically was something like this. Our bodies have an immune mechanism by which they destroy atypical cells every day. For whatever reason, yours didn't and the DNA became damaged and that damaged DNA cell became a copy of itself to get another copy, another copy, another copy and became a so-called cancer. That's not always the case in cancer. What we've understood now especially in diseases of the bone marrow is there's something called epigenetics where the DNA is completely normal, but the way the DNA is expressing itself is hampered and so certain proteins can't be produced. The cells can't mature appropriately. So rather than just fire away or as Dr. Shaddock always used to say man the torpedoes. Rather than do that and kill everything in the wake of the cancer as well, we want to employ strategies that get inside the DNA of the cell and tell the cell to grow up. That's our goal. At the end of the day if you feel better and your cells are maturing, you're not going to need transfusions, you're not going to need to see us as frequently and be hospitalized, etc. So, that's a real, real important development and many of our treatment strategies, in fact, target that particular pathway.

Most of you know that the risk of MDS is twofold. One is a complication of a low blood count whether it be infection from a low white count, bleeding from low platelets, fatigue, heart disease, etc. from low hemoglobin. The other risk is that risk of progressing to acute leukemia and as an MDS physician our primary goal, one of our primary goals is to prevent this from occurring because we know when acute leukemia evolves from MDS it tends to be very, very aggressive and is more difficult to treat. So knowing where you fall in the risk models helps us to determine how important this is to prevent versus how important is it on this side just to get your blood counts better because you're probably not going to get leukemia anyway and that's what all the models today are helping, but again in this paradigm, in this balance, talk to your doctors, talk to your PAs, talk to your nurse

practitioners, your nurses, your MA. Express to them what's important to you in the short and in the long term.

Various classification systems and I'm just going to blast through these. Again for historical context. The FAB classification, French American British looks at two things – the blast count in the marrow and how relates to survival and it's very crude estimate. The problem with these categorization tools is within each category we know sometimes there can be a 10 or sometimes even 20 month difference in overall survival. So, they're really poor tools, early ones. As we developed further, we have better models that look at the DNA. Cytogenetics is very important and I would encourage you to at least have an understand as to what it means to have a DNA abnormality if your physician finds one and know from your clinician is that a high risk abnormality or a low risk abnormality. Does it increase my risk of leukemia or does it actually make my risk of leukemia lower because that's the most important thing at the end of the day is what your DNA is and I want to show you that here in just a minute.

So, our newer models, I share this with you. This is how work with you to help you understand what is likely or unlikely to happen with your disease and there's a couple of caveats with this and the caveats are that it's not always accurate. We know in MDS still today with his model which is still the most widely used model for prognosis in myelodysplastic syndromes that in about 25 percent of the patients who we say have low grade disease probably actually have a slightly higher grade disease and 10 or 15 percent of patients who we say have high grade disease actually have low grade disease and, again, that's important. What is your risk of leukemia becomes one of the most important questions we ask when we decide what treatment to use, which I'll show you in just a minute. So, this tool is what we tend to use and at the end of the day we can sit down with you and say if you don't get treated, this is likely to be your survival in these kinds of numbers. Now importantly, our new risk models actually… again, the importance of cytogenetics I just note here. If you don't know your cytogenetics or your physician hasn't tested for cytogenetics, which nowadays is almost done universally, but every so often we get somebody whose cytogenetics maybe just didn't get sent. Maybe the tube never got to the lab. It becomes really, really important or we're not going to actually stage your disease. So, we now have the R-IPSS which looks at other tools as well and what ultimately happens is we start to really, really show a separation in patients with low grade disease, low intermediate diseases, high risk disease, very high risk disease and we can better estimate your risk of leukemia and your risk of dying from a complication of the disease which, again, comes into play when we start to treat. So we don't do a perfect job with our prognostic models. One of the questions that was asked by one of you, I was looking at them this morning was about the accuracy of diagnosis and the accuracy of prognosis and we're not perfect. We're not perfect. That's where your relationship with your clinician becomes really, really important in terms of following up especially early on in the diagnosis to follow what we call the pace of your disease. Is the disease behaving differently even though we think you're low risk, are we seeing the counts change more dramatically than we would have otherwise expected. That's why it becomes important and why we make you get all these blood tests over and over and over again. Some people monthly, some people weekly, some people two or three times a week depending on transfusions. It really does in that regard the power is in your hands to make sure you can get those tests and if you have

difficulty doing it, getting to the lab or getting blood draws, express that as well, so we can help you to make sure that those things are done. It really becomes important.

Now, I want to mention some new developments and some things that we find very exciting and, again, very important as it relates to overall outcomes is the development of testing for certain molecular abnormality and there was a recent paper in the *New England Journal of Medicine*, which as you know is really a worldwide recognized publication that demonstrated if you have any one of these molecular mutations in a low risk patient then your risk moves one category higher and we're starting to test for this and it's not done universally. In high risk patients who we already know are high risk probably not that much needed, but in low risk patients it does become important and if you have that added concern or something's not right or you and your physician are saying, "You're low risk, but your counts are changing and you feel poorly. Why is that? Why are you acting like a high risk patient?" This is one tool that your physician might be able to employ and it's a simple blood test. Does not have to be done off the bone marrow much to your delight. So, it can just be drawn. Now, some of these mutations may actually predict for response and this is, again, I share some statistics with you. When you talk about an 82 percent response rate in a patient with high grade myelodysplasia that's a big number. Very, very few treatments are going to get you an 82 percent, but with the molecular mutation, this one in particular, we're finding in a small series that certain patients might respond better. If you have the mutation, your response to Azacitidine might be as high, or Vidaza, you might know that as, as high as 82 percent. So, though it's not necessarily the standard of care, this is where we're moving. We learn more and more information. These molecular mutations may not only tell us the risk of your disease, but also which treatment you might respond best to.

I want to mention a little bit about what was difficult for us in the MDS community in terms of educating the primary community and even our fellow oncologists. Treating MDS seriously even for a low grade patients is really important and having that constant interaction with your clinician, I think, is really necessary because of this. If you look at the IPSS score and the median survival and you compare it to lung cancer, the risk associated… again, untreated. I don't share these numbers to scare anybody. I share them… It was really difficult for us to get even hematologists sometimes to understand don't take these disorders lightly especially now that we have things we can to change these numbers. Now, these numbers again, are in an untreated patient and we have all sorts of things to do now that are dramatically improving upon these numbers, but don't take it lightly because if you compare lung cancer which sounds awful. Right? Lung cancer is never good. They do better, lung cancer patient, and so our physicians, your physicians need to take you seriously especially as it relates to symptoms.

So, let's look at some historical data here as it relates to physicians versus patients and their perceptions of the disease and where things fall. These are physicians' survey data, a lot of surveys. Over 4,000 surveys were done by physicians between 2005 and 2007 and what you see here are an average age of diagnosis of roughly 70. That holds true. That number is coming down a little bit, again, because younger and younger people are being diagnosed. Most of the patients had relatively low grade disease. The vast majority had primary not secondary or treatment related, but in the secondary category chemotherapy was really a big one. Chemotherapy for prior treatment. Why do I

share that? We know that a lot of the drugs we use to treat cancer aren't only being used to treat cancer nowadays. In rheumatology, for instance or certain pulmonary disorders, lung disorders, drugs like Cytoxan are used. Drugs like Melphalan are sometimes used for other disorders and those are drugs that can potentially lead to the development of MDS. Again, important for the physician to have that discussion with you and so if you know people who are on those types of drugs I think it's important to stress getting blood counts done relatively frequently within reason. This was the median hemoglobin, 9.1; median platelet count about 100,000; neutrophil counts were pretty good and blast counts sort of varied there, but again the bottom line is most patients had low risk disease and I think that's certainly encouraging. This looks at sort of the historical trends for the need for transfusion support. In the low group, obviously, you're going to have less transfusion dependence and that grows for both red cells and platelets as the disease continues to progress. So, that's sort of what the physician saw and reported. What about the patients and, again, there were 358 people, 46 states and these were published data. It was in keeping with low risk patients. Most people had low risk disease thankfully. A pretty even split between men and women and the average age was a little bit lower and, again, I think this number continues to creep down.

This slide, though, I think has a couple of messages. From your first abnormal blood test to the time you actually had a diagnosis of MDS was about three years. Now, there's a whole lot of reasons that that might be the case. One of them I've already told you is hard sometimes to really make this diagnosis. When I tell a patient you may have MDS, it's because I really think you have MDS and I don't have enough information otherwise to say and that warrants close follow up of counts, etc. and symptoms, but sometimes it is neglect on our end. Sometimes it's a very minor abnormality in the blood count that maybe we want to repeat three or six months later and then start to do the investigation. Again, abnormal blood counts are not normal for any given age. You might have a baseline. We may find what your normal value is, but a low blood counts is a low blood count and needs to be investigated and not always with a great degree of zeal, but it certainly can't be ignored and so the time to diagnosis is a little bit concerning.

And this is another slide I think that was concerning and that's why we're having this slide is really why we're having this type of patient forum. How doctors first describe MDS to the patient. It's a bone marrow disorder. That was the number one. It's anemia, it's a low blood count. It's a blood disorder. It's a neutropenia, low white count, thrombocytopenia. Very, very few clinicians wanted to use the word 'cancer' or 'leukemia.' Now, we know it's not acute leukemia. Is MDS a cancer? In the strict sense of the word it is. In the strict sense of the word MDS is a stem cell that's defective and becomes a clone of itself. That's all a cancer is. Unlike other cancers that spread to other organs, we don't see that with MDS. So, we don't stage it. We do the prognostic tools as I showed you earlier, but this is sometimes a matter of not wanting to scare the patient, but I think putting it in that context of hey, let's call it what it is and treat it as it is. It doesn't mean you're going to die from it. I know a generationally the C word was always one you never wanted to use. Then again, we find more and more especially in our youthful population, they wear shirts like, "Excuse my language, but we're kicking cancer's ass," and things like this. We actually… you might have seen some of the AHN ads. It's that whole thing that tell cancer ad to not fear it because we're making progress and I think that's really important, but what this slide really demonstrate is what your understanding just how varied it might be when you leave our office and patients sometimes really don't have a good idea of what this

disease is. I think with a disease like MDS in particular when patients are so varied the course of one patient versus another. This is one group of disorders I think that requires a decent first office visit, not the first one where the bone marrow is done and we're investigating – the next one to really go over that and in today's model of 15 minutes for a patient that doesn't work. So if you leave the office uncertain or you have questions, insist on a longer visit. There's nothing wrong with that and if anything else it helps us to show our administrators we can't see patients with your types of disorders in 15 minutes. It's just not fair.

Another concerning slide. How many patients actually understood their risk? You can see 13, 18, 11. Low numbers of people know what their risk is. Fifty-five percent of patients in this survey had absolutely no idea what their risk for leukemia was. That's a problem and it's not fair to you and I think it requires great tact in having that discussion about what your risk is, but you need to know what that risk is so you can help make your own plans, too, and develop strategies that are important.

Percentage of MDS physicians who never discussed with their patient life expectancy. Those are big numbers. Now in a low grade patient, we sometimes don't know. It could be 20 – 30 years and that's fair to say, too, but I think it's important. So, I want to go through a case study here and go through high and low… low and high risk disease, 58 year old male referred for evaluation of anemia. Hemoglobin had been falling from about 12.4 down to 10.7 grams MCV. I mentioned earlier macro acidic. The cells were kind of big. It was a prototypical patient with an evolving myelodysplastic syndrome, nonsmoker, doesn't drink alcohol, had some exposures, environmental exposures. Another thing you want to understand what your risks are in the workplace. There's a whole lot of lawsuits going on about that sort of thing as well, what your risk is in terms of various exposures. White count was good. Platelet count modestly low, not dangerously low. Ferritin was high. Iron levels were elevated as is the case very, very frequently with our patient and the blood smear. The look at the blood counts from the blood stream. The cells, again, were big. Platelets were slightly large. All suggestive of myelodysplasia. The bone marrow was done. Cellularity was right about where it should be for the patient. Blasts were not increased. There were a few of those so-called ring sideroblasts. All very, very suggestive of myelodysplasia and importantly this patient was found to have a deleted 5Q. Chromosome 5 has a partial deletion associated with it. So, this patient has MDS. So, how do we treat this patient? There's no absolute right answer, but I would say in this patient observation is probably the best choice initially. The patient's not transfusion dependent, not very symptomatic and appears to have very low risk disease. So, observation is reasonable. Now, you may take issue with that if we say, "Well you have this malignant process and we do nothing. It becomes important also for your physicians to understand when treatment is needed because all of the drugs we utilize have side effects and so I tend to take a less is more approach and try to minimize treatment until it's absolutely necessary. So, my feeling would be to observe this patient and that's our perspective. Do we need to treat MDS? It depends is the short answer.

The treatment goals become important. In a low risk patient, what are our goals? Improve marrow function, decrease transfusion needs, help quality of life very importantly and establish a careful monitoring program, again, with your blood count, etc. So, observation would include this. For this patient, marrow function's not that bad yet, not feeling poorly and not getting transfused. So,

observation would be reasonable and we contrast that, of course, and we'll go into this in just a minute for the high risk patient it becomes different.

Now, what about growth factors and I'll just show you some statistical tools that we utilize in determining whether or not growth factors are important. Does everybody understand what growth factors are? Procrit, Aranesp. Anybody, you know those drugs? Neupogen, Neulasta. There's white blood cell growth factors, Neupogen and Neulasta. There's red blood cell growth factors. These are hormones that tell the bone marrow to do their job better and in patients with MDS who are transfusion dependent primarily for red cells you can use Procrit, Erythropoietin. If you have a lot of transfusion requirements and I talk about this to my patients, if you're getting transfused weekly and we do what's called an erythropoietin level which is your body's own production of that hormone and find that it's very, very elevated, the likelihood of responding to growth factors is very low. I think that's good for you to know. If after two months there's no response, we want to stop the treatment rather than put you through all these unnecessary injections which, again, carry risk. On the other hand if you're not requiring a lot of transfusions and your hormone level is low, the likelihood of responding is 75 percent and it's a very reasonable thing to do. So, had this patient not had a 5Q deletion and started to require transfusions, I think growth factor support would be very, very reasonable. The good news about growth factor support is that it doesn't increase. There was a body of literature that suggested maybe it increased the risk of leukemia, it doesn't. That's never been demonstrated. So if you're worried about taking the shots because you've heard those little rumblings on maybe a blog or something, it's not true. The risk of leukemia is not heightened by these drugs. On the other hand, they don't really change the natural history of the disease either. They don't decrease the risk nor increase the risk of developing leukemia, but they do help the blood counts in people who meet these criteria. Two years have passed with our patient. He's now 60. Over the past three months he's required red blood cell transfusions approximately every two weeks in spite of getting injections. So at one point, the patient became transfusion dependent, went on EPO. Perfectly reasonable and now the transfusion needs are going up despite being on the Procrit, we'll say or Aranesp whichever one your clinician likes to utilize and so the counts are not so good. The marrow cellularity remains in the reasonable ballpark relatively normal, a little bit low. Blasts, everybody knows what those are. Those are the leukemic cells. Those are the ones if they get over 20 percent we start calling it acute leukemia. They're low. The lower that number is the better off you are and now there's an increased number of cells that have that 5Q deletion and so what do we do with this patient now? Well, that's the story of Lenalidomide or Revlimid. Wonderful drug, side effects are there. So, we have to be cautious when we use it, but it's a very, very potent drug, more potent than its predecessor Thalidomide. Remember Thalidomide all the complications with Thalidomide babies and limb malformation because it chokes off blood supply. Revlimid does the same thing, so you have to go through the program. Thankfully, most people with MDS aren't child bearing age, so it doesn't become an issue, but some are and there is the REMS program, etc. and close monitoring, but what's interesting about the development of Lenalidomide is it is far less toxic than Thalidomide in terms of the risk of blood clots. In terms of the risk of neuropathy though some people do get that numbness and tingling that neuropathic type discomfort from it. So another important thing if you're on Lenalidomide to share with your physician if you're experiencing that numbness or tingling in the hands or feet or really anywhere else, but with Lenalidomide if your physician is thinking of putting you on this agent, in patients with MDS there is a big risk of the blood counts getting worse. Eighty

percent of the people the blood counts get substantially worse in the first eight weeks of therapy. Interestingly, those are usually the patients who are responding the best, but you do have to hold the drug, sometimes use shots of Neupogen or red blood cell stimulators to help the counts get better and then go back on at a lower dose. Very effective drug, but that is a toxicity that we see. It's, again, it's a favorable toxicity, but it can be a dangerous one and so we sort of mandate with our patients and, in fact, it's in the package insert weekly blood counts, at minimum, weekly blood counts for the first eight weeks of therapy and a significant number of patients downstream will require a second dose reduction with Lenalidomide. There's a person in this room who might know that very, very well. These drugs over time the longer you stay on them can start to suppress your bone marrow function and not the blood counts aren't getting worse because the MDS is getting worse, but rather the drugs are becoming toxic to your system and you stop the drug, you wait for the bone marrow to recover. It almost always requires you to do a repeat bone marrow, so we know what's actually happening. I know you don't want to hear that but if your physician really thinks you need it even if you have to be put to sleep for it, it's probably a good idea.

So, Lenalidomide was proven. This is just the schema of the trial that was done and 67 percent of patients who have a 5Q deletion will become transfusion independent with the drug Lenalidomide and also patients without 5Q. This is not a drug sponsored program, so I can say that. We do use Rev, Lenalidomide in non5Q patients, in patients who have normal DNA. Usually if they're not a good candidate for growth factors, etc., but we're learning more and more about where to use these drugs.

So, the patient was started on Lenalidomide 10 milligrams daily for 21 of 28 days. I usually go a continuous with no interruption and I oftentimes in older folks will start at 5 milligrams. That's not unreasonable and watch the blood counts, became transfusion independent within two months and the hemoglobin was maintained. A little bit of fatigue relatively asymptomatic so was doing well. So, what should we do now? Well, continuing Lenalidomide, the same dose and schedule is reasonable. Some people would say go to a maintenance. I don't know that there's really good evidence for that right now, but if you were experiencing any toxicity with the drug, I think it would be reasonable to lower it and continue Lenalidomide therapy until complete cytogenetic response and then stop. Why do I put that in there? Most of the treatments we use in MDS, you don't stop unless you're progressing or having toxicity. That's the right answer. Any drug for MDS that modifies the disease, you tend not to stop or the disease reemerges. These aren't curative treatments. They maintain the disease. If you have toxicity, of course, you stop. If you're progressing, of course, you stop.

So in low grade disease, how do we optimize therapy? It is a malignancy. We've talked about that. It's, again, a take home message, but it's one that we have great hope for. Patients now being seen with low risk disease thankfully the diagnosis is really a clinical one. It's not just the bone marrow as I said earlier because it's usually not that obvious. The IPSS becomes very important or the revised IPSS and we have a host of treatment options available in lower risk patient that include growth factors, sometimes observation, sometimes antibiotics, Lenalidomide, combined growth factors. What about Vidaza? Most people who think of Vidaza think that's going to be used for high risk patients. Well for low risk patients who aren't responding to other treatments, but still have really low blood counts, Vidaza becomes an option there as well and as many of you know there's an oral Azacitidine in clinical trials now and I think we'll all be really happy when that becomes available.

So, let's just shift to the high risk patients and then we'll close for questions. In the high risk category, marrow function becomes important. Now usually most patients with high risk disease are going to have more than one blood cell abnormality. Maybe it's their whites, their reds and their platelets are all low. Maybe we're starting to see those leukemic cells in the bloodstream, etc. We want to decrease the risk of transformation as I suggested earlier. That becomes a real focus of therapy. Do whatever we can to prevent this from becoming acute leukemia. So, definitive therapy maybe consider transplant if you're a candidate for transplant or maybe Vidaza to improve survival. Many people ask questions about the use of leukemic chemotherapy for these diseases and there's no evidence that leukemic induction therapy we call it is effective in MDS. Sometimes we use it if patients have failed multiple lines of treatment to try something maybe to get them to transplant, but there's really no evidence that aggressive chemotherapy does a whole lot in this disease and so I share that just in case you were entertaining that idea. In certain circumstances it's reasonable. If anybody is facing that situation, please feel free to come up and talk to me afterward or during the questions. Transplant is becoming increasingly an option. This number 10 years ago only five percent or less of patients were ever transplant candidates. Why? People tend to be older with the disease, oftentimes have other illnesses that preclude transplant. Maybe you don't have a good donor available. The number now is closer to 15 or 20 percent of patients with MDS are transplant candidate because of something we call reduced intensity transplant. That is less aggressive transplantation. That means we're going to suppress your immune system to allow the new cells from the donor to grow in your body and not be rejected and immunologically cure the disease. That's the goal of reduced intensity transplant and in fact there was just a recent publication that demonstrated in people over the age of 65 with MDS and acute leukemia, a reduced intensity transplant is as good as a more aggressive transplant. So if you're thinking about that, it's a very reasonable thing to do and having a discussion with your physician about it. The blast count becomes important in the bone marrow. If it's high, you want to do something to get it down to do this type of transplant, but it's an option and the data today is suggesting it's just as good as the old aggressive types that are really tough to tolerate and which is why most people with MDS can't go through that. So, we're doing better.

Another aside that I want to just mention to you as it relates to progress in MDS and all of the disease we treat with transplant. As of today whether you have a sibling or an unrelated donor, the outcomes are the same. Ten years ago that wasn't the same. Unrelated donors even if they were perfectly matched by the tools that were accurate then did 15 percent worse than patients who had a sibling donor. So if you're older and thinking of a transplant and the physician says only if you have a matched sibling, in MDS it doesn't seem to matter. If you can find a good unrelated donor, it's just as good and so that's also an important development I think. It's important especially for young people to know where their disease is and if they're a transplant to candidate to know if we transplant low risk patients, we're actually going to harm you. So if you have low grade disease and you're transplant age and your physician thinks you're a transplant candidate what I do and there's someone in this room who knows this probably all too well is what we call surveillance marrows because when you go from the low risk to the high risk that's when we want to do the transplant. That's where we maximize the benefit right between low risk and high risk, but not leukemia. We want to catch it at that flip and sometimes the only way to know when that flip occurs is by looking at the

bone marrow. So again, if your physician says I think it's important for you to have marrows every six months, it's probably a good idea to do that so we know when to transplant.

I'm going to flip through these. Let's go back to our case study.

Four years since the patient was diagnosed with low risk refractory cytopenia multilineage dysplasia, you've all heard some of these terms. Two months after starting Lenalidomide became transfusion independent, remained so for 14 months. Pretty good response. Now, hemoglobin is 6.8. White blood cell count's 4.8, the platelets down to 34 approaching transfusion need and he's developing some neuropathy related probably to the Rev. A bone marrow is done. Cellularity is still on the low side, but reasonable and the blasts are now going up and the patient now has in addition to the 5Q, a 7Q deletion. That's a high risk one. Now, this patient has gone from low risk to high risk. This is a real story. This is an actual case. How would you treat this patient now? Continue transfusion therapy with iron chelation to maintain the ferritin at a low end. We can talk about iron overload and the risks associated with that and I'll just mention to you why is iron unloading important. Iron overload is a very insidious process and so for a low risk patient who's likely to be alive a long time who's sitting with a ferritin at 1,000 or 1,500 the risk of that iron getting into any organ in the body, but primarily the liver and the heart muscle starts to mount and that's where getting rid of with drugs like Exjade you've heard of to get rid of the iron in those patients becomes important and interestingly if you go into transplant with a high iron level that can be increase the risk associated with transplant. So in low risk patients, I think it's really important to get that iron down through a variety of different mechanisms. Do we do auto transplant in MDS? No, we don't. It's a stem cell defect. An auto transplant is utilizing your own stem cells. We'd only be collecting malignant stem cells, damaged stem cells. So, should we increase the dose of Lenalidomide? There's really no evidence in high risk patients that Lenalidomide is useful outside of combination therapy. There are trials continuing to look at this with some encouraging data, but the right answer in my mind would be 5-Azacitidine or Vidaza and that's because this is the only drug that is now available to us to change the natural history and improve survival. It decreases the risk of leukemia and it increases survival for patients with high risk disease. So, the patient was, in fact, started on Azacitidine for six months.

Epigenetics I mentioned is a recruitment process, again, understanding the biology and why we sometimes combine Vidaza with other drugs. I want to just mention that. I've already talked to you about epigenetics, so we'll go through that… boy, that slide went weird. I'm not sure I like it or not. These were the first 92 patients, Joan actually helped put these data together that we treated with Vidaza at West Penn Hospital on the NCI's compassionate use program. Thousands of patients have now been treated with that drug. It really changed the face of how we treat MDS, but we were fortunate, again, because of Dr. Shaddock's work and Joan's to treat a whole lot of patients before the drug even got to market and we're happy about that because we have an experience that allowed us to change doses, look at alternative dosing schemas, etc., etc. One patient asked about Vidaza subcu versus IV and is there any different. There's no difference in efficacy and there's really not a whole lot of difference in the way of toxicity except if you get it under the skin, you obviously don't have a problem with ports and getting, etc., or a venous access, but some people who get it under the skin about five percent will have injection site reaction and in those patients we suggest cool or warm compresses, 10 – 15 minutes on and off a couple hours after the injection and that usually helps. If

anybody has more questions about that that's certainly fine. This was the trial that got the drug to market and, again, showed a real substantial improvement and risk reduction in leukemic transformation. Very, very importantly these what we call P values show statistical significance. If any of you in here have a statistics background, these numbers are huge, they're tiny actually, but they're huge in what they mean clinically; .0002. That means a huge number of patients felt better on the drug. What we're also understanding is there's something called cytokines that get released from the bone marrow in patients with MDS especially in high grade disease. The bone marrow is getting a constant feedback to work harder and it's trying to work, but it can't. Those cells are dying before they're supposed to and it's just this constant… what we call a cytokine storm. Patients get fever. Sometimes they start to lose weight. Sometimes they don't have an appetite. This drug seems to really blunt that effect in a significant number of patients as is demonstrated here and patients generally feel better. This is the first drug to show such an improvement in quality of life that the same study got a separate publication just for the quality of life data. It was really important to us as clinicians to know that only were we keeping people alive, but we were keeping people alive well. That obviously is our goal. For patients who have severe low platelets, there's not a lot out there. Vidaza's really a good choice as well if you've failed other options even in the setting of low grade disease. A near 50 percent response rate in those patients.

I share this slide to show that it does take time for these drugs to work. For almost every drug we use in MDS, two to three months average response time. So, don't give up too early and I always tell my patients with certain treatment especially Vidaza and its cousin drug, Dacogen or Decitabine, press on for at least three months before we call it quits unless there's toxicity or obvious progression of the disease, but otherwise it does take time. We're learning, our fellows are helping us with this. The way we utilize these drugs as is in the package insert, I would tell you with MDS drugs in general, know the package insert as it relates to toxicity and what to talk to your physician about, but don't get concerned if your physician is suggesting an alternative dosing schedule. Companies invest a whole lot of money to get a drug to market and they have to do it with one set pattern. We've had drugs in cancer therapy that got to market at this dose because of a supply issue. We knew the dose was effective. We didn't have a lot of drug available, so we had to use the lowest amount to get the right number of patients on the clinical trial to show statistical benefit so we could get the drug to market. The drug dose that's in the literature is not always the best dose and physicians can play around with it and that's where I think going to an MDS Center of Excellence becomes important because that is an issue of experience. There's not a lot of guidelines to help with that. So, our Azacitidine experience… if you've been told you have CMML, we find Azacitidine is one of the most useful drugs available and these are some of our statistics and again the AZA001 trial.

I think I'm going to close with the AZA001 trial actually and then open it to questions after I just show you a real brief treatment algorithm and the reason I want to share this with you is that your physicians don't always know best. A scary thought, but a true one. In this… and I mean that for myself, too, because if I were to… and I don't know when it transferred some of the numbers got cut off, but in this trial what happened with the randomization that's where is determined if you're going to receive this therapy or that therapy on the trial. The physician first saw the patient and after the first glance and the assessment of the disease, the physician decided which drug or which regimen the patient would be randomized against. So, you'd come in. I'd say you have high risk disease and

then I'd say I want you on this Azacitidine trial. I think it's a good trial. You're going to either get Azacitidine or I have a choice of three options as a comparator and what happened was all the physicians who saw the younger patients with the higher risk disease, a significant number of those physicians said that's a patient I want to randomize against chemotherapy because my gut feeling is that's the patient that needs chemotherapy the most, induction chemotherapy. So, the bias was you're a little bit younger, you have more aggressive disease, chemo is going to work for you. At the end of the day regardless of what your physician though was better for you, Azacitidine won out by the exact same amount. It improved overall survival an average of 10 months in very high risk patients and so sometime our biases and what we learn in med school doesn't translate with these newer treatments. Sometimes chemotherapy is not a good thing and we know that. We're trying to get away from that and get targeted therapies available to you. Combination therapies, I think are also important. Our patient, I'll just tell you, eventually started… he stabilized his counts and actually performance status was very good and so the answer what to do next would be to consider an allotransplant in that patient with curative intent and we talked a little bit about that.

So, this is the treatment algorithm that we use when you come to see us. Are you a transplant candidate? If you're a transplant candidate and you have high risk disease we try to get you to transplant and usually we start Vidaza first to help control the disease so you don't thrust into leukemia while we're finding a donor, etc. and then even post-transplant we start to utilize these. Everything got shifted. I apologize and I have a little bit of OCD. So, this is bothering me probably more than it's bothering you. Don't laugh though.

Are you not a translate candidate, you have high risk disease. I would say clinical trial should be way up at the top of the list. If you have an opportunity to get on a clinical trial, that's really good. It doesn't only help you. It helps us. It helps other patients like you. Again, a benefit of being an MDS Center of Excellence or going to a Center of Excellence, you're likely to have access to trials and the MDS Foundation certainly pushes that. There's a host of other drugs. There was an old drug I liked to call Mylotarg. It's no longer available to us. There's a company that's developing a second generation type drug which is showing promise. We're hoping to be part of the clinical trial there.

If you have low risk disease regardless if you're a transplant candidate or not, it really depends. This should all be shifted in here. You have all kinds of options as I suggested. Which cell line is low? What are your goals? How easy is it for you to get to the office? Is a pill easier than a shot? Is the insurance, unfortunately, going to dictate some of this and sometimes it does. Realities we all have to face. These drugs are not… it's not cheap. If you're a low risk patient and you are a transplant candidate, again, I'd stress the importance of surveillance marrow testing, so we know when to do the transplant.

This is a woman that we transplanted and I share this story for the sole purpose of, again, demonstrating what the goals are. This is a woman who had breast cancer and went and developed a high grade treatment related Myelodysplastic Syndrome and a good friend of mine who's a photographer got to join here for her long term goal. Her short term goal was to dance with her son at his wedding. Her long term goal was to get back into the classroom and teach her kids and this was

the first day that she got back actually in the classroom. To stress the importance of sharing what your goals are. They're important to us and we don't want to minimize them.

So, I'll close and answer any questions that you might have and I am right on time for a change.

?: (inaudible 59:10) your questions are very important and you want to make sure that we share them via (inaudible 59:17) or whatever. We need to afterwards with other people and they have the same questions. So, let me get expert (inaudible 59:26). If you can speak into the mic, I would appreciate it. (inaudible 59:30) your name.

Q1: Hi. (Attendee). I'm here representing by brother-in-law and I believe he has low level MDS, but he also has dementia and since that disease affects older people, how do medications for dementia and things like that… any concerns here?

James Rossetti, MD: In terms of interactions or the risk?

Q1: Well, I would think interactions would show up at your pharmaceutical computer. Right?

James Rossetti, MD: Yeah. You know, most of the drugs for dementia, I just want to make sure I understand the question. He has dementia and low grade MDS and is… none of the MDS drugs that we utilize really accelerate dementia thankfully. Very, very little neurotoxicity. Very few of them cross the blood brain barrier, so they don't get into the brain. If they cause any neuropathy, it's a nerve issue. It's usually out in the periphery of the body somewhere else outside of the central nervous system. It doesn't seem to be any major risk. Depending on the… I have treated patients with Vidaza who have significant dementia with high risk disease and they've done okay because they otherwise had a good quality of life and families were taking good care of them and they were happy where they were. So, it was a reasonable thing to do. I've not seen neurotoxicity. Joan, have you really seen much?

Joan: Not most recently.

James Rossetti, MD: I will tell you Vidaza when it first used in the '70s, it was used at about anywhere from 10 to 100 times the dose that we use now. It did have neurotoxicity. Some of it did cross in, but we don't use it like anymore.

Q1: He takes Procrit, the shot and I kind of wanted everyone to know that I feel so proud. We succeeded in getting the insurance to pay for the shot at home because he's 86 and it was hard… It took about two – three months.

James Rossetti, MD: Good for you. That's wonderful. It's a struggle. I mean, it really is getting people back and forth. The more we can do at home, certainly, the better. When we studied Vidaza with the NCI Compassionate Use Program, we used to let our patients do it at home and we can't now because the FDA calls it chemotherapy. So, it has to be mixed (inaudible 1:01:42) and all this

fancy stuff, but a lot of these drugs are safe at home. We need to figure out a way to have it done and paid for.

Q2: My name is (Attendee). I'm here on behalf of my wife, (Attendee), and she takes Dacogen which she takes intravenously. We were told a couple years ago that they were hopefully going to be able to come out with a pill form of Dacogen. Do we know where that stands?

James Rossetti, MD: Yes, there is development. It's further behind than the oral Vidaza to be sure. Still responding to the Dacogen well, monthly or every six weeks?

Q3: Every four weeks.

James Rossetti, MD: Yeah. It's going to be awhile before… and the problem is most of the trials if you're responding to what you're on, you can't even go on to the oral on the clinical trial. So, it's probably going to be a situation whereby you have to wait for the drug to come out and we're a ways away from these drugs being available. I mean, not a huge… not years, but definitely many months.

Q2: One other question. I know I read where MD Anderson at Houston was starting a project they called Moonshot a couple years ago where they had four diseases they were going to concentrate on one of which was myelodysplasia and what they said they felt at that time within 10 years there'd be… I don't know if it was cured, but certainly be able to control this disease. I mean, is that pie in the sky or is that something you see possible?

James Rossetti, MD: I don't think it's pie in the sky. The fact that we in a very short period of time really changed the survival and the risk of leukemia leads me to believe that we can control these diseases a lot better. We are starting… the other disease that we frequently treat is a disease called multiple myeloma. A host of drugs available. There's so many drugs available, we don't know how to use them. We don't know if we should sequence them or combine them, etc. Folks like MD Anderson, that's the big question. It's now that you have all these drugs available for MDS and the Cleveland Clinic's, the same types of trials. What's the best way to put them in order or to combine them? I think as we learn more about that over the next decade, we're probably going to see dramatic improvement and the other area of excitement a lot of you have heard about all the immune therapy that's being done at Penn primarily with leukemias and lymphocytic lymphomas or leukemias. That's going to start these disorders as well in immune based therapy and targeted therapy. So no, I think we're close to really controlling the disease better and better. I think cure is going to be a tough one, but to be honest with you, I'm not sure that cure matters if people are alive and living well. If we can treat it like diabetes, that's fine with me.

Q4: The one example you used was a person with low grade 5Q and then morphing into adding a higher grade form. Is that correct?

James Rossetti, MD: Yes.

Q4: How common is that?

James Rossetti, MD: It's not that common especially in patients with isolated 5Qs if they have what's in particular called the 5Q- syndrome. Very, very, very low risk. It's less than five percent of those people are going to go on to develop acute leukemia or a more aggressive form, but it can happen and now that Lenalidomide is… previously people would die of transfusions, iron overload. That was the number one cause of death in patients with that scenario previously because nothing else worked for those 5Q patients. With Lenalidomide keeping people alive longer, we're seeing it sometimes way, way, way later, but it's still relatively uncommon, but again the number is up because people are living longer with a disease they didn't live with before, but I think it's offset by the overall survival is still far better than it ever was.

Q4: So, I'll be more specific with my mom who you treat. Since she's been survived for like 12 years, would that be an indicator that she is in that very, very…? I mean, she's in a pretty good place in terms of all that.

James Rossetti, MD: It definitely is and the truth of the matter is on such the small dose that mom's on, we do monitor mom for recurrent or new cytogenetic abnormalities and, in fact, we're not seeing any of that. That is one way that we can help predict what that risk is before it happens and we've not seen any of those high risk things.

Q5: Hi. My name is (Attendee) and I do not have an MDS diagnosis, but it is something that I'm concerned about. I've had Hodgkin's… I've been treated for Hodgkin's three times over the past five years including having a stem cell transplant, etc. I've had several of the drugs that can cause it. So, I've been anemic since I finished treatment and MDS has been a concern. I had a bone marrow biopsy, but my question is and you sort of eluded to this. Is it something that can either not be evident right away in a bone marrow biopsy or I know you mentioned it takes a very… It can be missed, but I wasn't sure how closely to be looking at things and for how long…

James Rossetti, MD: So, I think usually the risk really starts to go down especially surmising what type of treatment you had and thank God it sounds like you're doing well from that perspective, the Hodgkin's. Knowing the drugs that you probably had, the risk really starts to go down at about 10 years. If you don't develop a problem within that first 10 years, it's probably not going to happen. The risk is small. It's not huge and some studies say it's five percent, some say it's 10 percent. Very importantly because even after chemotherapy and certainly after auto grafting, the cells can look dysplastic but not be MDS. Sometimes we over call it. In treatment related disease, the cytogenetics, the DNA becomes the most important tool and so if you've had a bone marrow and your physician did fish for the common abnormalities and the ones that were really concerning are 11, 5 and 7. If you do those fish… to fish for those three abnormalities and it's negative and were looking at 3-, 400 cells in that scenario and they're all clean, the likelihood of a low grade MDS that's going to emerge is pretty small, but can it happen? Of course, but it's, I think, the risk in the absence of those. Now if there is contention about the diagnosis. If your physician says I think there's MDS here, but I'm not sure. I'd feel really comfortable with a negative fish and in those patients especially with a young lady like yourself, I would consider the molecular studies. The problem with the molecular studies is you really need the diagnosis before they'll pay for it and it is expensive. So, if there is a hint and

there's enough to say it's MDS and your physician might be able to do it, but I will tell you I don't know what I would do with the information necessarily, but I would certainly follow your counts a little more frequently. There are patients who have these mutations, a small fraction, one or two percent of people who will have a mutation and never in their life get a bone marrow disorder. So, there's risk/benefits of knowing that information, I think, but it's something, I think, worth looking at. There's a trial right now that is accruing and is looking at the predictability of these in patients who might have MDS who have a low blood count, but the physician doesn't know why and doing that might… It might behoove you to wait for that trial to close and know what that data is before you go down that road. I think if you did the fish alone, that would be enough, but I can keep you abreast of that information… I'll give you my E-mail or whatever as that data becomes available from Genoptix who's the company that's running it.

Q6: I was talking to the gentleman next to me and they were in Youngstown and we're in Pittsburgh, steel making environment. You eluded a little bit to environmental factors. How much of a deal is that?

James Rossetti, MD: We see a lot of MDS in Allegheny County. It's not only one of the oldest counties in the country. Its average age goes way down in the winter months when everybody goes to Florida and follows the Pirates, but it's an aged population. So, we see more of it there, but we see a lot of MDS in these kind of industrial towns to be sure and there were just some interesting studies with cancers in some individual townships outside of Allegheny County that showed higher numbers than the national averages and that's continuing to be explored. I think that the steel and coal industry is…

Q6: The reason I was particularly interested we lived in Clairton right next to the largest coke works in the world at the time and I know I worked in there for a couple years before I went to college, too. So, it makes you wonder about your exposures to all the chemicals.

James Rossetti, MD: Sure. Most of these things can be picked up with a CBC. So if your doc… PCPs generally do them annually and that's usually enough.

Q7: (inaudible 1:11:38 – 1:11:53)

James Rossetti, MD: Sure. So, knowing how many transfusions you've had is important. Every transfusion you receive, every unit has about 250 milligrams of iron that really doesn't go anywhere. Unless you're a menstruating female, blood loss isn't normal. So, it accumulates. When you hit about 20 units of red cells, the risk of iron overload starts to really go up and when you hit 50 units it's almost universal, dangerously high ferritin levels which is the number we monitor. So if you have low risk disease and you're getting a lot of transfusions and your physician is not doing a periodic ferritin, I would encourage them to that. Again, the problem with iron overload is you're going along and you're feeling great and then you develop congestive heart failure or something because that iron has accumulated in your body over a period. It usually takes years and years for that to happen, but if you have years and years to live because your MDS is low grade, preventing it becomes an important issue. So knowing the number of transfusions is key especially for patients that move. Getting

transfusion records is always really, really hard. Val, Joan, you guys know that. It's sometimes impossible to know what a patient has received. I would encourage my MDS patients to keep a record themselves and most of them do and bring it to your physician's attention because it sometimes just slips your doc's mind.

Q7: Another question (inaudible 1:13:29 – 1:13:37) high grade type. How many times can you get that before you're considered not infected?

James Rossetti, MD: So, the question is if you're getting a lot of platelet transfusions, is there a certain threshold whereby they become less effective. The answer is unknown. It's really hard to predict when they're going to become ineffective. Women who have had multiple children oftentimes already have antibodies developed that put you at a higher risk for them becoming ineffective and the more platelets you receive… what happens is there's these proteins on the surface of the platelets that you develop antibodies to and become what we call alloimmunized and you start to destroy the platelets that you receive. If you're noticing as you're getting your platelets you're requiring more and more during any given period of time or if your physician does a post count, gives the platelets and 15 minutes later checks the platelet count and that number hasn't changed or has gone down, it's likely you've developed antibodies and might need specialized platelets and there's a simple blood test that can be done for that and then we can start to find a donor that's specifically useful for you or group of donors who would go in and donate. So it's highly variable, but it is something to be cognizant of downstream. The other risk of platelets and a lot of platelet transfusions is platelets are stored at room temperature at the blood bank which makes them susceptible to bacterial contamination. So if you get a platelet product and you starting having a fever, usually you're monitored, but even after you go home if you get a significant fever you really want to call your physician because you could have gotten infected product. Usually, you get pretty sick from it, but some patients they just have a low grade fever. So, pay attention to those types of things and transfusion medicine is safer than ever and I'll tell you like the risk of HIV is 1 in 2,000,000, HCV 1 in 1,000,000 and hepatitis C. So, those aren't big risks anymore. The bigger risks are these questions. Iron overload, less effective transfusions and the risk of bacterial infection. Those are the ones we worry about more than anything.

Q8: The Procrit shot, does that affect the fatigue? I mean should the person have less fatigue?

James Rossetti, MD: As the hemoglobin improves, yes, generally speaking. If the hemoglobin's going up but there's still a fatigue element then we start to wonder is it from the MDS. Otherwise the cytokines or is there something else going on and we pick things up… Val picks somebody up with sleep apnea a couple weeks ago. Sometimes it's not all the MDS, but you're focused on the MDS when you're in the office. So, looking for other reasons for the fatigue become important. As far as the growth factors and I don't know how long he's been on it, but generally speaking it can take up to 8 to 12 weeks to see a response.

Q8: He's been on it about 8 years… 8 to 10.

James Rossetti, MD: Well then if he's responding… Now he's fatigued and his hemoglobin is up over 10 or so it might be something else.

Q8: He's fatigued, very fatigued.

James Rossetti, MD: Do you know where the hemoglobin level has been at all?

Q8: No, I'm sorry.

James Rossetti, MD: If it's over like 10, I wouldn't expect him to be fatigued and so at that point I would ask the doctor to start looking at other causes.

Q8: He's 86. We're talking a lot of sleeping.

James Rossetti, MD: That's not normal for an 86… Now if he's got dementia, a lot of the dementia drugs do cause fatigue.

Q8: He does.

James Rossetti, MD: That could be part of it.

Q9: As my mom's getting older besides just…

James Rossetti, MD: She is.

Q9: Just we're all getting older.

James Rossetti, MD: Yeah, that's true. True, true, true.

Q9: Besides just normal aging issues that we all have to deal with, is there anything as a caregiver, as her son, that I should be particularly aware of with regards to this MDS issue?

James Rossetti, MD: Disease related symptoms sometimes as the disease progresses even between blood counts or whatever. If the disease were to progress, things like night sweats can happen, fatigue, recurred infections or taking longer to heal from an infection. All those types of things. Poor appetite. Those things develop usually as the disease progresses, but I would just look for those types of things. The risk of second cancers in most of these disorders is slightly higher. Now, it doesn't change the current recommendations of screening. The screening should be the same, but I always tell people if you have one disorder, you are susceptible to another. Be vigilant about your screenings, your mammograms, your pap… those types of things. I think that becomes important.

Q10: After months being on…

James Rossetti, MD: I saw him and all of a sudden I heard this female voice and I'm like all tripped out. That really messed with me.

Q10: Can I go first or him?

James Rossetti, MD: No, go ahead.

Q10: Okay. After months of being on Procrit last year, my counts were only going up by a tenth of a point, so… and they weren't going above to 10. So, do you think that's ineffective for me?

James Rossetti, MD: I can tell you being your physician if I might. I think… Yeah. I think you're losing your response to it to a degree despite that we haven't seen… We've seen some evidence that there's some higher risk features, but not definitive evidence which is why I torture you with all these bone marrow and so yes, I suspect the shots are going to become less and less effective over a period of time, but the good news for you is I've been following you for so long and that's really all we've had to utilize. So, we have a lot in our arsenal still and you're certainly a potential transplant candidate at your young age. So, I promise you I'll stay on top of it.

Q11: My name is (Attendee). I'm 60 years old originally from Cleveland. I live in Las Vegas now. There's no MDS Centers of Excellence. I was diagnosed with MDS RARS last January 2014. My hemoglobin has just dropped below 10 for the first time. So, the hematologist has submitted for me to begin Procrit. I wondered from what I hear from you and from what I read, I don't think Procrit seems to be effective for a lot of people with the stage of disease I have. Whereas my hematologist, I mean, I have no problem going ahead and trying it, but he thinks it's really going to pick me up a lot and I wondered what your opinion would be on that?

James Rossetti, MD: So, the RARS population notoriously doesn't do as well with the shots. I don't mean in terms of progression, but if you've not required transfusions, I don't know what the EPO level is but… that model still applies. So, if you don't have transfusion requirements even if you had a high EPO level you still have about a 25 percent chance of responding. So, I think it's a reasonable thing to do especially if you're feeling fatigued. How do you feel?

Q11: Well, what brought me to the doctor was I'd always for 30 years done some long distance running and I could tell that as I couldn't… I knew something was wrong and because I had a heart problem, I had blood tests done annually and I would just keep the results and I always looking at the lipid panel, but what I found out looking at that 10 years' worth of blood test was that 10 years ago my hemoglobin was at 15 and it has steadily gone down to 10 and when I brought that to the hematologist's attention, he didn't mention MDS, but he immediately gave me… had me a bone marrow biopsy and the cytogenetics were okay. So, I think not that he told me, but from what I've learned, I think I have a score of zero still.

James Rossetti, MD: Good. Well, that's great news then. I think the Procrit might help you to feel better then.

Q11: And the secondary question, my hematologist seems to feel that the only symptom I should have from MDS is fatigue and things that I have a lot of problem with are restless sleeping, constipation and it seems like a slowdown in my digestive system and I did have a CT scan which was clear except FOS and I just wondered… It seems to me that if I'm oxygen starved to an extent that it would affect more than just my muscular fatigue or mental fatigue.

James Rossetti, MD: The inclination of physicians is always to attribute symptoms only to the blood count and that's… we know I mean, I know Joan knows this. She's treated hundreds of MDS patients and people have very strange symptoms sometimes that can't be explained by anything else. We're integrated creatures. I think it's… your bone marrow which is the vital organ that supplies the rest of your body is damaged and working overtime, to me it can certainly explain other symptoms. Do you have to look for other causes? Yes, of course. I mean, if you have GI issues, I'd rule out other things, but yes, MDS does weird things and we don't always understand why other to say our bone marrow is vital to every organ in our body and that cytokine activity I have learned to really respect. What I mentioned before of that constant hormone release in your body because your bone marrow is being told go, go, go, but it can't, can't, can't. Patients get wiped out. Sometimes they get night sweats. Sometimes they do get restless sleep. I have definitely seen and you start to treat and they feel better. All those things start to go away. The downside to the Procrit is it might not affect all the cytokines and all that stuff. If a lot of it's related to your low hemoglobin, they may all get better, but if you have other things and there's no other explanation sometimes saying it is the MDS and those patients sometimes we will consider something like Vidaza. Right now, I think you're far away from that from what you're telling me, but if you're really symptomatic and there's no other reason, sometimes it is the MDS. I mean, my own colleagues sometimes look at me like I have six heads because I believe that, but what else is there? Tell me what else it is.

Ma'am?

Q12: I'm (Attendee), 78. I've had MDS for three years and doing well. Why do you use Aranesp versus Procrit? What makes your decision?

James Rossetti, MD: Sometimes it's an insurance issue. The main reason that the studies went on with Aranesp over Procrit was the hope that you could give less in less injection. So, it became an issue. Procrit generally speaking needs to be given at least once a week. With Aranesp, the data suggests if you push the dose, you can extend that out to three weeks. The data is all over the board in the clinical trials, so it's not universal. My feeling is if you're getting Aranesp weekly, I tend to use Procrit. I find it to be a bit more predictable in its response rate, but if you're responding to Aranesp there's no harm. There's no evidence that one is better than the other, but from patient to patient for whatever reason some people respond to this dose or that dose or that drug or that drug and we really don't know why. My experience has been with Aranesp over Procrit. You can only extend the interval between injections. In patients who have a fair amount of disease. You can only extend it if you really push the dose and that sometimes irritates the insurance company because the idea of giving 300 every three weeks doesn't usually suffice in patients with MDS. Sometimes you have to push 500 every two or three and it becomes more costly and in that setting if you're going every week anyway, just I'd say switch to Procrit. That's what I tend to do, but the one hope was cost

savings for a lot of people. The biggest issue was can you extend the interval between injections. If it doesn't work then to me really either one is acceptable, but that's the main reason.

Q13: I had (inaudible 1:26:38) patients ask me (inaudible 1:26:40) cancer and bone marrow problem. What can I do besides the physician offering some therapy? In regards to herbs, vitamins, some alterative type of therapies. Do you any thoughts on that?

James Rossetti, MD: I do. I think real food is the easiest thing anybody can do. We all like our snacks now and then, but I think if we… My mantra has always been eat the food God made and as close to the form that He made it and I think that's useful. Avoiding processed things with chemicals that we really don't' understand what their risk is with them. As far as herbals go, turmeric is probably the one that's most commonly studied. The Indian spices have a lot of data. Dr. Raza has demonstrated that and, in fact, I think she still puts most of her patients on. So, I have patients in the post-transplant setting who I oftentimes will put on such spices and I think there's enough data there and certainly not a great deal of harm. Now, many of you may have seen that the FDA came down on some dispensers of some of these things just a few months ago saying that they had very little of what they actually said they had in their product. So, if you're going to go down that road, find somebody that's reputable and isn't emptying your pocketbook. If it doesn't smell right, if the cost seems crazy and they're making all kinds of claims don't go that route. If the cost is reasonable and their goal is to guarantee a good product, I think it's good. It's a reasonable thing to do, but anytime somebody's asking you to pay an auto ship or something and sign your insurance away, don't do it. So, I think those things are most useful and water becomes really important, too. I mean, I am a big caffeine guy, so I'm always diarizing, but I think water is important as well and avoiding… you know, really if your white count is low that's important to know, too. I don't advise… We used to… Joan probably remembers this. We had a gentleman who used to come in with gloves on and he was so nervous all the time. He's read the newspaper with gloves. You can't live in a bubble. When you have MDS or anything that affects your bone marrow, most of the infections you have are going to come from yourself. They come from your own skin or your own GI tract, but pay attention to your symptoms and report them early. Don't be afraid to irritate your physician or your PA. That's what we're here for. We'll tell you if it's important or not and avoiding people with… Flight becomes an issue. People ask me about flying all the time. If you have a really low white blood cell count and you're going on a trip and you really want to fly, ask your doc what your risk is and I do advise in that setting a mask because of that recirculated air and I've seen some nasty sinus infections. Is there a lot of scientific data to support that particular thing? No, but I do think a mask is a reasonable in that environment and if your white blood cell count is really low the only other thing I tell my patients is digging in soil is not a good idea because there's a lot of mold in soil and I'm a gardener. So, I would not want to hear that kind of news, but it's probably not a good idea until your physician does something to get your white blood cell count elevated because mold infections can be tough. Those are the kind of basics I talk about.

Ma'am?

Q14: I had the Aranesp for three years and I've had Vidaza for six months. How much longer can I take Vidaza?

James Rossetti, MD: Joan, what's the longest we ever treated?

Joan: Seven – eight years.

James Rossetti, MD: Seven plus years. As long as it's working and you're tolerating it that's how long you can take it and people go years and years. The average person that responds to Vidaza is usually on it about 18 months, but that's an average and we have many patients we treat for years and we've seen five plus many times. So, my word of caution would be if it's working don't stop it. If you travel, ideally you don't want long intervals. Six months is… six weeks rather is about the farthest I like to go once a response is achieved. Once you hit about eight weeks you start to lose the response and it's hard to get back. So if you're going to Florida or if you're going somewhere and you think there's going to be a delay, there are a network of physicians in Florida in every county that can deliver Vidaza or wherever. It's just an easy drug to get and to deliver. I would ask your physician to set that up rather than to delay it too long.

Q15: Question. I'm (Attendee) and I wondered does the MDS Center for Excellence accept all insurance specifically UPMC?

James Rossetti, MD: That's a… The answer is no. I mean, but I can tell you this. I don't know if you have UPMC insurance. There are certain products that we can accept. I would encourage you to call our office and this is all beyond me, believe me. I would call my office and ask to talk to Chris and she can tell you. If you have UPMC, I know the physicians there very, very well and I can tell you who I think is really good in the MDS world. Hematology and transplant is a very small community. We all work together. So, finding you a good physician there is easily done and that's a great center. They're outstanding.

Q15: And you're talking about the Hillman Cancer Center?

James Rossetti, MD: Yeah. They're very good… Finding somebody that's a bit of an expert in MDS is the real issue and they're at most big centers. The other issue is I do this not infrequently. If there is an insurance issue and you just want what we call a curbside counsel, I'm glad to review things and even communicate with the physicians there. They do it with me, I do it with them especially if there's a trial or something that they might not have available that we do or vice versa. So… and they don't care. I mean, you wouldn't hurt anybody's feelings.

Q16: About six months ago, I started developing these brown spots all over the backs of my legs. That's the only place.

James Rossetti, MD: Could you stand up and show the class? No, I'm kidding.

Q16: No. I don't think so.

James Rossetti, MD: I'm kidding. I'm kidding.

Q16: I got them on my knees, too, if you let me… Anyway, I went to a family doctor on it. He had no idea what it was. So, he sent me to a dermatologist and the dermatologist said that it was from iron and there's nothing that they could do for it and I'd always have them. Could that be from…?

James Rossetti, MD: Do you get a lot of transfusions?

Q16: Yeah. About every two weeks.

James Rossetti, MD: Do you know what your iron level is?

Q16: Iron. I think everything but iron.

James Rossetti, MD: So, if you know what your ferritin level and it's high and you have low grade disease, there are medications that you can use to help get rid of that iron if it's starting to accumulate in your skin. If they're really saying that's iron, the other thing I would want… I would be concerned about and I would ask your doctor to look at would be your heart function and your liver function because those are the two organs that get affected most frequently. So if it's depositing in your skin, there's a chance it's depositing elsewhere and I would just alert your MDS physician about that.

Q16: I have an appointment with him fairly soon.

James Rossetti, MD: So, he's not aware of the skin issue yet?

Q16: (Disagreement sound)

James Rossetti, MD: Yeah. Definitely bring that up and he'll know where to go with that or she'll know.

Q16: It's just weird. Docs completely (inaudible 1:35:02) it's just all these brown spots. They don't itch. Nothing.

Q17: (inaudible 1:35:09) a biopsy so they said (inaudible 1:35:12).

James Rossetti, MD: So, there's things you can do to get that iron down. The skin, obviously, is more cosmetic, but it may… the skin… That may fade if you start to get rid of some of that iron. It may never go away completely, but those skin color… that can start to change. It can start to get better and the big thing is knowing if the other organs are effected.

Q16: We'll ask my hematologist about it when I go in to see him in a couple weeks.

James Rossetti, MD: Good idea.

Q17: It's Dr. Leidman.

James Rossetti, MD: Oh, my goodness.

Q16: You know Dr. Leidman.

James Rossetti, MD: Oh, yeah. We trained together.

Q16: Oh, did you?

James Rossetti, MD: Yeah. He's a good guy. Joan's laughing back there.

Q16: I like him (inaudible 1:35:48)

James Rossetti, MD: Oh, we like him, too. Dr. Leid… notoriously gets very sweaty when he does his bone marrows which is funny. He doesn't sweat on the field or anything, but it's just funny because he's just… I just always remember seeing… He'd come out looking like he had just gone into battle and I'd say, "What happened in there?" "Oh, she had hard bones. That one had hard bones."

(Laughing)

James Rossetti, MD: And he's a big guy. So, I'm like, "Why are you struggling?"

Q16: Well, he did mine and it didn't hurt or…

James Rossetti, MD: He's a good doctor and we work very closely with him all the time.

Q16: Oh, do you.

Q17: He sent her up to Pittsburgh area to see somebody when it wasn't working, the Vidaza wasn't working.

James Rossetti, MD: Somebody in our group?

Q17: I don't know who we… This was a year and a half ago.

James Rossetti, MD: Which hospital? Don't say UPMC or I'm calling him right now. I won't only because they're a UPMC facility now. So, they have to.

Q16: Oh, yes.

Q17: We didn't know where it was at. So, our daughter-in-law had to take us. They (inaudible 1:36:44).

James Rossetti, MD: It's a maze. Yeah. Bring it. He'll know what to do with that.

Jayshree Shah: Dr, Rossetti, I don't know what your time is (inaudible 1:36:57) your availability is in the (inaudible 1:37:00). What I wanted to do is to go around the table and have everybody (inaudible 1:37:06) to just reintroduce themselves and how long you've had MDS, the type (inaudible 1:37:12) because we're going to be having a patient discussion. I'm trying to coordinate a lunch right after that just to get some stretching and get some food in our belly and then regroup thereafter. Do you mind if we do that and then we'll… I'll do my talk in regards to a few slides. It's going to be very quick and then the rest of the time is just us (inaudible 1:37:37) and sharing. So, do you mind if you start from there? Introduce yourself and what type of MDS you have?

Q18: My name is (Attendee) and we're from Altoona and I've been diagnosed with… I was diagnosed about three years ago.

Q19: I'm her husband, (Attendee), and you were talking about Youngstown and Pittsburgh area, she grew up in Altoona, but the last 28 years we lived in Phoenix, Arizona. They don't have coal and all that kind of stuff. So, I don't know where she picked it up at.

Q20: My name is (Attendee). I'm here on behalf of a patient that has low risk MDS.

Q21: My name is (Attendee) and I'm a caregiver for (Attendee).

Q22: And he's a great caregiver. I'm (Attendee). I've had MDS for three years and doing well on the Aranesp and chemo there also.

Q23: Hi. I'm (Attendee). I was diagnosed in 2004 and just recently I started becoming transfusion dependent and he's been a good caregiver. There for me.

Q24: I'm (Attendee). I work at West Penn with Dr. Rossetti. I'm a PA.

Q25: Hi. I'm (Attendee) and I'm (Attendee's) wife.

Q26: And I'm (Attendee), again, from Las Vegas and diagnosed with MDS RARS about a year ago.

Q27: My name's (Attendee) and I'm here for my father who is a MDS patient.

Q28: (Attendee). I'm here for her father, my brother-in-law, MDS low grade, 10 years.

Q29: (Attendee) and I'm a nurse practitioner and I'm here to listen to what everybody in the room has to say because I'm always interested in the patient, family and caregiver perspective.

Q30: I'm (Attendee). I am from Kittanning and my parents are accompanying me today and I was just coming to get information and to learn about what to do next for myself.

Q31: I'm (Attendee) and I was diagnosed yesterday and I have 5Q- syndrome and I just wanted to kind of get some more information.

Q32: (Attendee). I was diagnosed with MDS last June and here's my husband, (Attendee)

?: What therapy are you on? Are you on any therapy?

Q32: I just started Vidaza.

Q33: My name's (Attendee) and I'm a patient of Dr. Rossetti and I've had MDS 5Q since 2000. The fall of 2000 I was diagnosed and then I came with Dr. Shaddock in the fall of 2003 and I take the Lenalidomide, Revlimid, and it works for me.

Q34: I'm her son, (Attendee).

?: (inaudible 1:41:12) ask what dose (inaudible).

Q33: I had been taking five milligrams twice a week and then Dr. Rossetti because of the neuropathy. It's not bad, but it still bothersome. He changed it to 2 ½ milligrams Monday through Friday, five days a week.

Q34: I'm (Attendee). I'm here on behalf of my wife, (Attendee).

Q35: And I'm (Attendee) and I was diagnosed with MDS in 2009. I'm being treated with Dacogen and I'm doing well with it.

Q36: I'm (Attendee). I work in the pharmaceutical industry, but more recently I've gotten really involved in patient advocacy and volunteering because it makes my job feel a lot more meaningful and my life feel a lot more meaningful. So, I'm just here just to listen, observe, that's all.

?: (inaudible 1:42:06) had handed out a (inaudible) fill that out (inaudible) before you leave and hand it over to myself or Debra and it's important because, again, we run these patient forums and do (inaudible) and continue to share (inaudible) for both patient and caregivers as far as drugs and information is just by sharing, but we also get the feedback about what else can we do run the forum in a different way or the same way and thereabout. We would love some feedback if you can share that. That would be helpful. If you get a chance to fill that out now or after lunch is fine. Just give it back to me or Debra. I think lunch is ready. I would like go for lunch only because you guys have been sitting for a while here. (inaudible 1:43:58) stretching and moving around a little bit and using the restroom if you need to and (inaudible 1:44:04) return in about an hour. Lunch is on the first floor.

?: It's on the first floor in the River Room.

?: So if you took the elevators down.

?: You can take the steps or the elevators. It's on the first floor. I can't even describe it. I think it's over this way through some door and then another door.

(Laughing)

?: (inaudible 1:44:31)

?: It is called the River Room.

?: The Rivers as in Three Rivers.

?: Why don't we (inaudible 1:44:49) stretch out a little bit and then we'll regroup and we'll talk about Building Blocks thereafter. So, (inaudible 1:44:58) been sitting for a while. You can leave your stuff. Please take your purses and anything valuable. I don't want you to leave anything here that's valuable.