

Speakers:

Steven D. Gore, MD

Jayshree Shah, APN-C, RN, MSN, BSN, BS

Susan Hogan, Operating Director of the MDS Foundation

**Susan Hogan:** So, I think you can hear me through the microphone. Right? And good morning and welcome again. My name is Susan Hogan. I'm Operating Director of the MDS Foundation and you also saw Deborah Murry from our office. I think you've spoken to Dee on the phone. She's with us here today. In case you're not too familiar with the Foundation, our office is located in Yardville, New Jersey, but we are worldwide. We have Centers of Excellence, global patient support groups and our Nurse Leadership Board. We are international in scope. So, we are dedicated to offering professional education, Young Investigator Awards for research and events that you're coming to today, patient advocacy events for patients and caretakers. Anyway, you saw our agenda. We have a pretty full agenda in store today. We have... Thank you, Dr. Steve Gore for being here today from Yale and we have our nurse, Jayshree Shah, from Hackensack. She drove up from Hackensack and thank you for having... for coming and joining us today and in addition today if you would like to, the date actually tomorrow is MDS World Awareness Day and this is a global recognition of the Myelodysplastic Syndromes. So, we'd like to kind of acknowledge this day. If you would like to right before lunch, we'd like to take a picture of everyone, whoever would want to, holding up the sign and we're going to stream it, we're going to Facebook it and this is our acknowledgement of the day. It's happening all over the world with the patient advocacy groups. So again, a very warm welcome and also thank you to our supporters, Novartis, Baxter and Celgene for making a day like this possible and I will now turn the agenda over to Dr. Gore.

**Steven D. Gore, MD:** Good morning, everybody. Thanks, Sue. A pleasure to be here. I didn't have to drive as far as Jayshree. I just come down from Branford which is just 10 minutes away or 15 minutes away. I encourage anybody who wants to move on down closer, but you don't have to. None of us will bite and we won't attack you. I promise.

Anyway, it's a pleasure to be here. It's been awhile since I've done one of these patient groups. As a matter of fact, Jayshree and I did one two years ago and Johns Hopkins right before I left. I was at Johns Hopkins for 26 years and came up to Yale. It'll be two years next week and it's been... I had a great life there and it's been a wonderful experience here so far. So, I'm pleased to see everybody.

I like to keep these like totally informal. So, please feel free to interrupt at any time with questions and I use slides that I use with my colleagues, use to speak to my colleagues because I never seen a virtue in having dumbed down or different slides for lay people. So, I think I'm pretty good at explaining them, but if I'm not just let me know and I don't take offense if I'm going too fast because I forget sometimes.

So, I'm going to give an overall review of Myelodysplastic Syndromes, how we apply the latest clinical data in patient care and just I like to start with an example. So, this case which is from one of my colleagues is a 59 year old homemaker who's married and lives at home with her husband and she's been anemic for at least two years that she's known about and she has required intermittent red

blood cell transfusions over the past 18 months. She's really required quite a lot of blood, 30 units of packed red cells over two years. She had been treated with Erythropoietin or Procrit, weekly shots. Many of you are familiar with that drug and had some benefit. Oh, didn't have benefit actually. She increased her transfusion requirements. So, she moved and was referred to a hematologist who made the diagnosis of a particular kind of low grade MDS that we call refractory anemia or refractory cytopenia and she's otherwise a reasonably healthy woman with some asthma and some sinus infections and a reasonable heart. She has a normalish white blood count and a normal neutrophil count. I'm sure that most of you who are patients are familiar with these numbers. Incidentally, how many of you are actually patients, let me ask? And how many of you are involved with somebody or have a family member who has... Okay. Great. Thank you. You don't have to tell me if you're abstaining that's fine, too. She's mildly anemic at about 9.8 grams and, of course, she's getting transfusions, a normal platelet count. They measured her blood levels of the kidney hormone, erythropoietin. We'll talk a little bit more about that, but that's basically the natural compound that the kidney makes to tell the bone marrow to make red blood cells and the manmade version of this is what is Procrit. Procrit is manmade human erythropoietin. So, I presume that she had not been getting Procrit when we she had this... I'm sorry, go ahead.

**Q1:** Isn't Procrit the injection.

**Steven D. Gore, MD:** Procrit is an injection, you're right, of this hormone.

**Q1:** (inaudible 5:49)

**Steven D. Gore, MD:** The goal of Procrit is to increase the red blood count. Right.

So, I'm presuming she wasn't getting Procrit when she had this serum measurement because otherwise we'd just be measuring the drug that she was given. So, let's just assume so and this level of over 500 indicates that giving her commercial or pharmaceutical Procrit or Darbepoetin, Aranesp is unlikely to help her and we'll talk more about that a little later. She had a measurement of her serum ferritin which is a measure of how much iron is in her body kind of globally and it's quite high. That's a lot of iron and as many of you may know when you get red blood cell transfusions, they have iron in them and our body is not able to dispose of iron, of extra iron. It gets stored in the body for the most part. We lose a little bit in our feces every day, but for the most part the body doesn't have any way of getting rid of iron. So, it piles up and it can actually damage tissue and that's why we worry about this a little bit. So, she had a bone marrow test which showed that she did not have a lot of these immature cells that we call blasts that you guys have all learned to be afraid of. So, she has a low grade disease, but it's causing her a lot of problems because she's requiring a lot of blood and the blood is leading to iron buildup and appropriately her chromosomes were tested. They were normal.

So if you are a bunch of docs, we would do this as a Socratic dialog, but we won't put you through that, but this is the kind of things I pose the questions because this really is, I think, how we approach patients like you or her when we see you or her. We want to know what her prognostic score is and there's two that are currently in vogue or up to date. One is the WHO based prognostic scoring system

or WPSS and one is the International Prognostic Scoring System Revised, IPSS-R, and these scores are used to give the patient some idea of what the future may hold and how worried to be in the short or long term and to help with your decision-making about your treatment. Is this patient a good candidate for treatment? How would we treat this patient if we decide that she wants to be treated and what do we expect of the particular treatment and should she receive some medication to get rid of the extra iron that she's building up to prevent complications like diabetes, pituitary problems, heart failure and liver inflammation which are the main consequences of having too much iron. So anyway, I'm not going to answer those questions about her. It was really more to kind of frame how we think about seeing new consultations, patients in consultation.

The first sort of internationally agreed upon risk scoring system was called the IPSS or International Prognostic Scoring System was published in 1997. Many doctors are still using this. Many of you may know your IPSS score. It's been kind of... there was a while where... I think it was one of the pharmaceutical companies pushing know our score as kind of a patient ed thing, but also see if you would benefit from buying their drug, to be a little cynical and the IPSS was pretty easy because most people who have had a bone marrow test which tells us how many blasts they have, blasts of immature cells. Hopefully, everyone's bone marrow was studied for chromosomes and the number of cytopenias it has to do with the degree of anemia, low neutrophil count and low platelet count and you need to say how can you have MDS and not have any of those? Well, there are certain thresholds that we count. So, you can be anemic with a hemoglobin of 12, but that won't count for this, or you could have lowish neutrophils, but they're not below 1,800 or your lowish platelets that are 120,000 that won't count. So anyway, we shouldn't be using this system anymore. So, I'm not going to spend a lot of time with it and if you're saying, "Well, gee. That's all my doctor talks about," then you got to say well Gore said that you should be using one of the update to date systems and they'll say oh that blah, blah, blah Gore. I'll take that because they shouldn't be using it anymore because we have better systems and this is why.

So, all of you need to... don't need to but when you go to talk you need to understand what a survival curve is. These are survival curves and in a survival curve, we have time on the X axis here measured in years and we have the percent of people alive or free of whatever endpoint we're measuring on this axis. So, everybody that we're measuring hopefully is alive when we start seeing them otherwise they shouldn't be on the curve. They don't count previously dead people. Not to be disrespectful to anybody. So, everybody's alive at time zero, 100 percent of people and as time goes, unfortunately, people pass away. Of course, some people are older and have other problems. Not everybody is dying of MDS and you can see that the IPSS, the old fashioned one, divided people into four risk groups – the lower risk group, Intermediate 1, Intermediate 2 and high risk group. You see that none of the curves is particularly fantastic, like I wouldn't sign up to be on any of these curves honestly, but the biggest problem really in the low risk groups... the lowest risk group, the green one, half the people are still alive at six or seven years. So, at least they don't have to worry about anything today and the biggest problem group here is this yellow line, the Intermediate 1 because while there's some people who are not doing well at all and dying early on, there is this group of people sort of if you can imagine this to be kind of two curves. So, this group of people at the end are surviving a long time. Here we go out to 20 years and they may not... if they knew they were going to live for 20 years they might not want to do something aggressive like a stem cell transplant which

might shorten their lifespan, but if I can't tell them you're at this part of the curve or you're in that part of the curve, I can't be very helpful to those patients and on the other hand these high risk patients are in trouble and that's important to know.

**Q2:** Excuse me. Should you ask your doctor what part of the curve you're on?

**Steven D. Gore, MD:** They can't tell you.

**Q2:** Oh, they can't tell.

**Steven D. Gore, MD:** So that's why we don't like that system anymore and this just shows you that everything's a little worse if you're older. Any of us who are getting older know that but the disease tends to be worse in patients over 60 than under 60.

So, here is one of the newer systems the World Health Organization based prognostic scoring system. This system requires that the pathologist who's reading the bone marrow is using the (inaudible 13:29) system. Well, you could say, "Gee, how should I know if my pathologist is up to date?" Well, the system has been the go to system for at least 12 years. (Inaudible 13:39) not again. There's a problem. So, this is how your pathologists are supposed to be reading your marrows and it should get into one of these categories and get points for that. Again, we look at the chromosomes and this is an older slide that says whether you're getting transfusions regularly or not. Now, it's based on the hemoglobin actually. So, it's a little easier to apply and this divides people into five categories – very low, very high, low, high and intermediate. This particular patient that I demonstrated as the sample case had refractory anemia, normal chromosomes and was receiving regular transfusions. So, she got zero, zero, plus one, one point low risk, but not very low. If she weren't requiring transfusions, she would be in a very low group, but we know the people who are requiring transfusions that in and of itself is a less good thing than if you didn't need transfusions and now you can see rather than that line that was so hard to interpret, if she were in this low risk group, she'd be feeling pretty good about herself. Right? About her prospects anyway and here she's in this middle group, low, and even then this is what, seven – eight years out here. She has a 50 percent chance of being alive in eight years and, again, the high risk is pretty bad. Now you can say, "Well if I'm in this red group, intermediate, it's a little bit like that other line that I showed you, but here it's again more of a, I think, more of a uniform curve. People are expiring at a certain rate and here at about seven years unlike the other intermediate group that I showed you there are very few people still alive. So, that's pretty serious.

Now, the other thing I want to use these curves to show you is that these systems all look at this issue of progression AML and this is what all your doctors have scared you about and this is one of my soapbox issues because when I think of AML and when most doctors think of AML they're thinking about the disease that tends to come out of the blue, people haven't had blood problems before, often in younger people, but not exclusively, in need of serious inpatient chemotherapy usually in a short term and which is often cured either with chemotherapy alone or stem cell transplant. When we talk about AML in relation to MDS, we're talking about MDS which has gotten worse and we've been following these immature, good for nothing blast cells and they used to be three percent and then

they were six percent and then they were eight percent and then they were 12 percent and then they were 15 percent and then they were 20 percent. Oops, at 20 percent we decided to change the name to AML. It wasn't like one day you had this disease, now you have that disease. You have the same disease and it's just gotten worse and if I'm not a sophisticated doctor and I'd say, "Oh, AML. I know what to do with that. I'm going to put the patient in the hospital, give them seven days of intensive chemotherapy and knock their counts down to zero and get them into remission," but that's silly because that kind of chemotherapy doesn't work so well for patients like you and it's never cured of in a patients like you. So, we've given it a name that's going to tend to induce a knee jerk reaction in some doctors. That's why we really encourage people to be seen at least in consultation at a Center of Excellence where people will know better, but it's also not really useful because everyone is worried about do I have leukemia today? Well, I tell everybody from the first day you have leukemia because MDS is a kind of, in my opinion and I think in most people's opinion, a low grade leukemia and if we can get over the cancer yuck thing and the leukemia blech thing, we don't like those words. They're scary words and just say just like hypertension is a heart disease. You don't say, "I got heart disease. I've got high blood pressure." Nobody worries about that, but it's a kind of heart disease, cardiovascular disease. MDS is a kind of leukemia. It's low grade and it gets worse. So if we don't worry about do I have leukemia today, I think we get into a better focus about what should I be worrying about and this is not what I would worry about in particular. Am I getting worse? Sure. I want to know that. Whether it's 19 percent, 20 percent, 20 percent, 21 percent, 30 percent blasts, your body doesn't know the difference. Your body doesn't have a thermostat for that.

Okay. IPSS-R. This is... Now, the IPSS-R between you and me was started because some American investigators didn't like the idea that WPSS was designed by Italian investigators. That's my opinion because the WPSS works really great and the IPSS-R is really complicated. I can more or less do the WPSS in my head. I can't do the IPSS-R without an app. Just saying and you can see why because now there's five chromosome groups and each of the chromosome groups, I couldn't possibly remember which one is which. Okay. So, the five chromosomes groups you got to look it up. Even within the app, I need an app for the chromosomes like when I ask for the chromosomes I have to go to the question mark because I don't know, but there's more. Okay. You got chromosomes. Look, you have to know when to skip a point. So even I knew which chromosome was which, I wouldn't know if I got a zero or a .5 ... Oops, you never get a .5. Who came up with this? I don't know. Don't tell. Don't tell I said that. Don't listen.

**Q3:** Do you use this app as well?

**Steven D. Gore, MD:** I'll tell you in a sec. Blast percent, again, skip the .5s. Don't ask me why. Hemoglobin, skip the .5, oh, but platelets you can get a .5. This doesn't make any sense to me, but there you go and, again, you get five categories.

Now, here's our patient that we talked about. She has good chromosomes, not very good. She has very low blasts. She's got a low hemoglobin. She's getting transfused. She's got normal platelets and a high enough neutrophil count, low risk. They asked me if I do this. So, I calculate both in every patient and even though at five years since there have been both of these, I've had one patient where there's been disparity out of hundreds of patients. They're always exactly the same, so go figure. I do

calculate them both, but they're always exactly the same. So, the other one is easier, I think, and again here's the five curves. They look pretty similar and she, again, would be in the low, but not very low risk and just to show you an example of that by this system it would predict that 50 percent of patients on that curve are alive at five years and in this one we got 50 percent at what? Six or seven years. So, not exactly the same, but close enough for this kind of estimate because don't forget these kind of curves and numbers only apply to groups of people. They don't tell you anything about an individual person. You can't be 80 percent of anything. You're either alive or dead. You're either sick or you're not. So, anyway. I do both but I like to make fun of the other one. It's not elegant. It's not an elegant system.

So, what does this mean for me in case you don't like curves? We try to... here's where I try to get it simple. Your doctor could use simple clinical information for every blood bone marrow tests. It's going to give you some idea how long your disease is likely to remain stable and that's important for decision-making. This information, the IPSS-R, WPSS score is useful in helping to choose therapies and planning your life. So, know your score as one of the pharma companies used to say and I think in the score you should know is the IPSS-R or WPSS. The other thing which is different about this for those of you who really kind of like to get into the details is the WPSS score was designed to be calculated at any time in your disease, diagnosis, three years later, five years later. IPSS-R is really only meant to be done at diagnosis. It probably doesn't make a difference honestly. You can probably reapply it, but it's a subtle difference.

So, goals of therapy. What are the goals of therapy? They need to be individualized, I believe. We obviously want everybody to live as long they can and want to with the best quality of life. We want symptoms to be controlled. That means minimized transfusions, minimize infections, minimize bleeding, improve your blood counts and decrease the risk of getting worse, obviously, whether we call it AML or just worse MDS. Any questions about any of that so far?

**Q4:** What's the breathing?

**Steven D. Gore, MD:** The briefing.

**Q4:** You just say about breathing?

**Steven D. Gore, MD:** I didn't, but I can talk about breathing. She had asthma, the lady who I talked about, but go ahead we can talk about breathing.

**Q4:** I thought you meant the breathing... Can breathing affect your MDS? If you're short of breath is that part of the MDS?

**Steven D. Gore, MD:** Well, patients who are anemic don't have enough oxygen carrying capacity in their blood and may feel short of breath and when you're anemic your ability to exert yourself without being short of breath is diminished, but shortness of breath per se if you're not anemic is not a feature of MDS.

**Q4:** If you're anemic you can get short of breath and you could also have heart disease, heart problems. Could it be overlapped? Could it be the blood transfusion doesn't make you really feel better. Could it be something else that is making you that way?

**Steven D. Gore, MD:** Sure. There's many things that can cause shortness of breath. Obviously, lung disease, if you've got asthma or emphysema. Those patients can be short of breath without being anemic. You're right, the patients with heart failure can be short of breath and people who have those underlying diseases may have worse short of breath, worse shortness of breath if they are also anemic. In contrast if a patient with MDS is not terribly anemic, but is short of breath then investigation into why that person is short of breath is probably warranted.

**Q4:** What's the hemoglobin level for being not really (inaudible 24:47)?

**Steven D. Gore, MD:** Well, every patient is different.

**Q4:** Every patient is different.

**Steven D. Gore, MD:** Every patient is different and I have patients who tolerate a hemoglobin of six and seven, I don't know how and I have patients who need to be over 10 without being short of breath and I think one of the other problems people get into with their hematologists is hematologists often have kind of a mindset that people are going to be transfused as first sort of threshold or they have kind of standard operating procedures in their clinic where the nurses sort of automatically do stuff whereas without sort of... I see this as a negotiation between the patient and the physician. Oftentimes, I may have a patient whose hovering around seven and they tell me they're fine and say, "You're sure you're fine?" and they say, "Well, that one time I was in the hospital they got me to 10 I felt great." I said, "Why don't we keep you at 10 I mean if that's the case," but that's something you can negotiate. I think that's something that really needs to be kind of individualized.

Okay. So when I see a new patient with MDS, the overriding question I have to start with is this patient now or will this patient ever be a candidate for stem cell transplantation because that's the only thing we have which cures some patients and another thing that I warn people about is I see patients of all ages who tell me that their doctor said, "Oh, you're way too old for a stem cell transplant," and there's almost nobody who's too old anymore. I mean, 75 is kind of cutoff at some places still. I know a patient at Memorial, a patient of mine went down to Memorial and is getting transplanted at the age of 78. So, I'm not saying people should, but people in the 60s... their 60s are being told that they're too old then I think, again, their doctor is probably a little out of date. It doesn't mean that everybody should get a transplant, but I think that that's an overall way to frame our approach to therapy and then depending on whether or not they might be a candidate for transplant we look into their risk categories. This is an old slide that uses the old IPSS, but you can think of it as higher and lower risk disease if you will.

So, I'm going to talk now about patients who have higher risk disease and for the most part the treatments which are available for such patients include the drugs that are now current... mostly called hypomethylating agents. I don't really personally like that term. I call them DNA

methyltransferase inhibitors, but you guys know them as Azacitidine which is Vidaza or Dacogen which is Decitabine. So for high risk patients, we've got Azacitidine and Decitabine or clinical trials and stem cell transplants. Those are the treatments as well as supportive care, obviously, is a treatment including transfusion support and so on.

So, back about...

**Q5:** Can I ask you a question?

**Steven D. Gore, MD:** You may.

**Q5:** Thank you.

**Steven D. Gore, MD:** You're welcome.

**Q5:** My case is similar to the case you were (inaudible 27:48 – 28:59).

**Steven D. Gore, MD:** We can do that. Hold on a second. That's a great idea. Speak into the mic and get down to the tape, so they don't yell at me.

**Q5:** Thank you. So, the platelets are well within range. The white blood cell was in well within range. I don't have the issue of the deletion 5Q, yet the only drop we see is the hemoglobin level and continue to drop periodically and I use Aranesp basically for the past two months. It hasn't really helped yet I have taken couple transfusion like every, say, 22 – 23 days I have... I took so far too. So when you're talking about the Vidaza and Azatadine if the Aranesp is not helping is that the second step that you have to go to?

**Steven D. Gore, MD:** So, I'm going to ask you...

**Q5:** When I did also a biopsy, the biopsy showed less than one percent blasts.

**Steven D. Gore, MD:** Right. So, I'm going to ask you to remind me if I don't get to that. Your question falls into one we're going to be talking about the lower risk patients.

**Q5:** Right because you already... you said here if you had... if you're not a candidate for the transplant then you become... you're high-risk. It goes to Azacitidine.

**Steven D. Gore, MD:** Right, but you're a low risk whether you're a stem cell transplant candidate or not. You're in the lower risk group and we're going to go into that in a second. So, we'll cover that.

**Q5:** Okay. Thank you.

**Steven D. Gore, MD:** Thank you.



So about 12 years ago, I helped design an international study at a time that Azacitidine or Vidaza had just gotten approved in the United States to see whether the use of Azacitidine in higher risk patients actually help people live longer and we're confronted with the problem was that because the drug was approved in the United States for all patients with MDS that wasn't really what the company at that time, Pharmion, expected, but it was approved for everybody in the United States. People in the United States were not likely to want to be on a randomized trial where not everybody got the Azacitidine. So, the trial is mainly going to be done in Europe and in Europe this will surprise you all the different countries had different styles of treatment and they didn't all agree with each other and that's really surprising in Europe despite the EU. So, we had to give the physicians and patients the opportunity to follow the usual practice Italy versus Sweden, say. So some countries like Italy mostly gave just transfusion support. In France they liked this low dose chemotherapy that people don't use too many other places and in some places they liked to treat the younger patients with very intensive chemotherapies if they had acute leukemia. So, we let the physicians make that decision for the patient before they went on the study. So, in Italy, Mr. Giovanni would be told, "Look, usually if you don't go on the study we're going to give you supportive care, but if you're on the study we'll randomize you between Azacitidine and supportive care." Whereas in Sweden, they would take Olaf and give him chemotherapy, but if he were in the hospital, but if he were on the study he could be randomized between Azacitidine and intensive chemotherapy and that's how the study was done and they lumped the three alternatives together as conventional care regimens and here's the group that got Azacitidine and here's another survival curve. Remember everybody's alive at time zero and the good news that was really surprisingly good these are people with higher risk disease is that at two years twice as many people were alive who were getting Azacitidine as were getting the other regimens combined. That was very, very dramatic and the average duration of survival was 24 months versus 15 months. So, that was really an extraordinary improvement, but you're going to look at the curve and say, "Well, Steve. Yeah, that's all great, but look this curve keeps going down. This isn't curing me," and that's the trouble. This is the best drug we have and it doesn't cure people. That's why we need to continue doing research. That's why we need people to participate in good clinical trials. That's why we keep fighting. That's why the foundations need money. That's why your congress people need to support the National Institutes of Health budget, but this is the best drug we have. Good news is that in higher risk patients it doubles survival. Now, a little bit to your question is we don't know what Azacitidine does in lower risk patients. We know that it can help blood counts and I'll get into that a little bit more.

**Q6:** What about (inaudible 33:23 – 33:28).

**Steven D. Gore, MD:** We'll talk about Revlimid.

So, what does this mean for me? For high risk patients, 5-Azacitidine doubles the numbers of patients who are alive at two years compared to other common treatment strategies, but unfortunately no patients are cured.

So, we wanted to know... Well, we knew from Azacitidine from our experience over the years was that about half the people who got Azacitidine, maybe a little less than half, had improved blood counts. So of the people who are getting transfusions, half of them become transfusion independent.

Of the people who have low platelets about a third or quarter get normal platelet counts or something like that? Neutrophil's harder to improve, but sometimes you get also and we said well what about this other half of the patients who are coming into my office, they're getting Azacitidine seven days a month. We're still transfusing them. Their bone marrow looks exactly the same. They think they're doing better. I don't know. I feel it's certainly a big hassle for them to be coming getting the shots and transfusions. Should we be continuing or not because, obviously, if they're surviving longer than they would without Azacitidine want to continue. If we're just making their life miserable, we want to stop and do something else. So, we analyzed those data in a complicated statistical fashion and we compared the patients who had achieved any kind of improvement in their blood counts versus those who did not. Actually, it's not versus those who did not. I lied. This is... Everybody in this curve has achieved improvement in at least one of their blood lines. Either their hemoglobin, platelets, neutrophils or all the above, any of the above in either of the two arms. So, these are people who that's why it starts in six months. These are people who after six months on their comparator arm had some improvement and these are people who on the Aza arm had improvement because we had to compare apples to apples, improved patients and you can see that people who got Aza and improved survived longer, considerably longer, much better than the patients on the other arm who also improved. So we know that for people who improve, Aza is improving their survival comparing to people who got other treatments and improved also, but in patients whose best response in six months was just stable compared to patients in the other arm who were also stable there's not a bit of difference. Now, are these the same patients? Is Aza making some patients stable who otherwise wouldn't be? That we don't know, but we don't know that if after six months the best you could say is that you're stable, we just don't know if the Azacitidine is helping you or not. Certainly not like we do if your blood counts are improving, definitely it's helping you live longer. If your blood counts are stable, we can't tell you.

So, what does that mean? If your blood counts have improved while on Azacitidine, any of your blood counts, it's likely that the Azacitidine is helping you live longer and we believe that such patients should remain on Azacitidine as long as it seems to be helping. Some doctors say, "Oh, look. You got a great response. Let's give you a break." That's a big mistake because when people come off of Azacitidine within a few months their blood counts have gotten bad again and for reasons we don't understand they don't tend to respond the second time, but if we keep you on it it seems to maintain the response and so that's why I keep you on it. Now, on the other hand if after six or more cycles of Aza, remember this is given once a month, that's a cycle. A cycle is one month or so, 28 days. If after six months or more the cycles of Azacitidine your situation is stable. We don't know whether it's, in fact, making you live longer and so whether to stay on it or not is something you're going to have to discuss with your doctor. How bad do you think my disease was? Do you think it looks like it slowed it down? Obviously, we all come in with a bias about that. We like to think we're helping patients. So, bring the salt. How is it affecting you? Some people go through Azacitidine like it's nobody's business. They go to work. Other patients it's a major hassle. They come in in ambulances. We have to weigh the quality of life as well in that case.

Now, I want to talk just for a second about the group of patients who didn't used to be called AML, but now are who have 20 to 30 percent blasts. So, these are patients who have MDS with 20 to 30 percent blasts. They now fall into the category of AML with MDS related changes. They were

included in the Azacitidine study and you can see that for these patients, this subset of patients with a lot of blasts, Azacitidine was also better than the comparators. These patients are also in the other curve. So, this is why I say I don't like this AML thing because doctors see AML and they say, "Oh, I've got to change my treatment paradigm," but in fact the same rules apply to these 20 to 30 percent blast patients that they do better with Azacitidine. So, that's just kind of a sidebar.

What does this mean? Patients with 20 to 30 percent bone marrow blasts technically have AML, but I call them VVBMDS, very, very, very bad MDS can benefit and the outcomes are probably better with Azacitidine than with other chemotherapy that keeps them in the hospital for a long time.

Now, those of you who are getting Dacogen or have heard about Dacogen or have heard about Dacogen said what's up? Are you like a shill for Celgene that makes Azacitidine? Like what's wrong with Dacogen? Why don't you ever talk about Dacogen, Decitabine? And the reason that I don't recommend Decitabine although there's probably nothing wrong with it is that early in the day Decitabine was studied at a pretty toxic schedule that required going into the hospital and it was studied in two studies that were similar to the other comparative study of Azacitidine where half the people got it and half the people got standard of care and there was no statistical improvement in survival for the Dacogen. Now you could see that these people, you know, the curves look a little different, but statistically they're about the same and you can see the improvement in average survival is much less than with Azacitidine, but this was a toxic regimen compared to the Aza. So, I don't think the patients probably got enough drug. Also in the Azacitidine trials people didn't have to stop the drug. They could just keep getting it. Whereas in the Decitabine trial, nobody got more than eight cycles. So, I think patients were undertreated and that's why it didn't show a big difference, but the schedule and dose of Decitabine that we now use which is different than this has never been studied in a randomized trial. So, we don't know if it improves survival or not. Now, it may be just the same, but when I'm looking at a patient and they say, "Oh, should I get Azacitidine or Decitabine? I've got high risk MDS." I said, "Well, all I can tell you is that we know that Azacitidine improves survival and we don't know that about Decitabine." So, why would you do Decitabine? I mean, why would you? I don't know. It doesn't make any sense. Nothing wrong with it, but we just don't it improves survival. Why not pick the one that we know improves survival. That's how I look at it. So, that's why I don't talk about Decitabine, but if you're on it and you're doing well you should live and be well, nothing wrong with it, but that's just what I say.

Now, the thing that frustrates doctors and patients about Azacitidine is that it takes a long time to know if it's working and this is from Dr. Silverman who's at Mount Sinai. Also from our international study, we looked at how long it takes to see improvement either a complete response or just an improvement in blood counts and half the people who shows some improvement in blood counts do so within two cycles of treatment. That's nice, but even after six cycles only about 87 percent of those patients who were going to ultimately respond had shown a response. So, you might say, "Well, Gore. Why are you telling me to stop after six cycles because I might be one of these good guys that creeps along?" Like I say, this is an individual decision, but I'll say, "Well, 90 percent or 90 percent what kind of a gambler are you? Are you going to go to Las Vegas and put something on 10 percent of the horse or whatever?" I don't know anything about gambling. I don't gamble, but and for some people they say, "Look. I got nothing better to choose right now. I don't want a

transplant,” blah, blah, blah, “I’ll take my chance and give it the 12 months. I’m feeling fine.” Nothing wrong with that, but most of the responses happen within six cycles and we know that if you’re having a response, it’s improving survival just to repeat that and to best response average is four cycles, but you could see for best response, again, pretty much out to a year.

Here’s just an example of one of my patients from Johns Hopkins. These are her platelet counts on an Azacitidine based regimen and these are her neutrophil counts and you can see why does she keep going up and down? That’s because she’s getting platelet transfusions and this is her fourth cycle of drug. You can see she’s still getting platelet transfusions. Here’s her fifth cycle of drugs still getting platelet transfusions. Here’s her sixth cycle of drugs. Oops, all of a sudden her platelets spike up and she’s in the normal range. So, it took her six cycles to normalize her platelets. Yup?

**Q7:** What’s a cycle?

**Steven D. Gore, MD:** A month. Twenty-eight days. So, seven days of treatment and then usually three weeks off.

**Q8:** How does the platelets going out of the donor affect it?

**Steven D. Gore, MD:** It doesn’t. These are just... we’re giving her platelet transfusions when we gets too low to protect her from bleeding.

**Q8:** My daughter’s was diagnosed (inaudible 43:27) and she’s being getting the platelet transfusions.

**Steven D. Gore, MD:** Right. So, platelets we could talk about supportive care and the platelets are just there to prevent bleeding. They don’t affect the disease. It doesn’t affect the underlying disease. It’s like a band aid to stop bleeding. Like when you cut yourself the band aid doesn’t stop the tissue damage, but it keeps the lid on. Similarly, giving platelets doesn’t change what’s happening in the bone marrow, but it gives her enough platelets to...

**Q8:** And you were talking about why they prescribed for MDS. She just... They’re not giving her anything for it.

**Steven D. Gore, MD:** Okay. Well again, I’d like to keep individual questions about individual patients maybe to the end except as I understand that everybody’s most concerned about themselves and we’ll talk about that. When I go through everything, we haven’t covered particular topics, please... Do we have anything for people to write down their questions for themselves so they don’t forget?

**Jayshree Shah:** There’s going to be (inaudible 44:38) because we have such a nice small group just to kind of go over maybe everybody (inaudible 44:44) tell us a little bit about your case or if you’re a caregiver and then we can go through each question that you guys may have and try to answer them or refer to you accordingly.

**Steven D. Gore, MD:** So hold your questions, but there was another one over there I thought. A question? No.

**Jayshree Shah:** Did you have a comment, miss?

**Steven D. Gore, MD:** Okay. So similarly, thank you very much for that... and similarly on this patient, the same patient I'm talking about her neutrophils, you could see here's the normal range. She's below the normal range. Fifth cycle of Aza, sixth cycle, seventh cycle, eighth cycle. After really her ninth cycle she gets a little bit into the normal range and kind of stays there. So, that's just how long it takes for Aza to work.

So, what does these data mean? It takes a long time to respond to either Aza or Decitabine and improvement of blood counts may take up to a year.

Well not surprisingly because even though these data are really exciting and encouraging for patients, we're not caring patients at only 50 percent are improving. Many of us have spent a lot of our effort to try to make Aza or Decitabine better and I spent many years at Johns Hopkins working with drugs histone deacetylase inhibitors one of which is called Entinostat and we developed what we thought was a very exciting regimen that looked like it was really helping more people and we brought it into a national study where people got a different... a 10 day schedule of Azacitidine, a little different than standard that we had developed versus the 10 day schedule of Entinostat. We were trying to double the chance of having all three cell lines improve, red cells, white cells and platelets and the usual rate of that is 15 percent using the standard dose of Aza. So, our 10 day schedule looks like it might have worked better because it got us from 15 to 30 percent, but our combination actually the number here should be 28 percent. The combination unfortunately after a lot of work turned out not to be better at all and that's just how research goes and there's been another national trial that I participated in that looked at the standard seven day schedule of Aza alone versus Aza plus Revlimid or Lenalidomide, a combination developed by Dr. Sekeres at Cleveland Clinic which looked like the cat's pajamas versus Aza plus a similar drug to Entinostat called Vorinostat, a combination developed by Dr. Silverman down in New York that looked like fantastic and you could see overall very disappointing outcome that nothing was better than Aza. The good news is that Aza hasn't gotten any worse. Aza's still working, but we have a long way to go and we continue to forge onward with trying to make these drugs better and look for new drugs.

This slide is not meant to meant anything to you although I'm happy to explain it because it's pretty cool, but it's just to remind me that to tell you that Celgene is developing an oral version of Azacitidine. I have participated in the early studies. There are some efforts to get an oral version of Decitabine as well. There is an international study for patients with lower risk MDS who have low platelets. It's kind of a weird hole of a needle, eye of a needle, to thread to find these patients who actually kind of just barely fit, lower risk but on the verge of being higher risk if you will and this study randomizes people to get oral Azacitidine or placebo. Well you could say why would I want to do that? And that's because to get to your question before, we don't know if it's a good idea to give Azacitidine to lower risk patients and I'll probably talk more about that. We don't know if may it makes things worse in the long term. I mean, only way we know will learn that is by doing a

randomized study when we know that we could help people's blood counts with lower risk disease with Aza, but what if we're inducing mutations that's making their disease accelerate because we know at least from some what we call some retrospective data where we look post hoc that patients who are lower risk who've gotten Vidaza and then it stopped working they don't seem to be living as long as we would have expected them for lower risk disease. Now, whether that's just a bias that's why we don't know, but I worry that if we treat a lot of patients with lower risk disease with Aza some of them we may be making matters worse. I'm not saying we know if that's true. If you're on it I'm not trying to panic anybody saying that's why we need these kind of placebo control trials.

**Q9:** (inaudible 49:42)

**Steven D. Gore, MD:** Well, you know, great minds are something.

Now, what about stem cell transplant? Here's the deal. Here's another survival curve. This is a made up survival curve that was made up by Corey Cutler is a transplanter at the Dana-Farber and as you'll see from the real data it's a little bit of an optimistic curve unfortunately. So in this best of all possible world in this case 80 percent of patient are cured of transplant. Unfortunately, that's not the case, but the bad news is that people die from transplant and that's a short term death. In other words, you can have complications which cause death. So, here's the patients who were getting transplanted. Some of them die right off unfortunately and then some patients are cured. If they don't get transplanted, people don't die off as fast at the beginning. So, this group of patients right here if they gotten transplanted they might have died an early death. So, we're taking life away from patients really potentially, but these patients who are just getting Aza or just supportive care are going to die of their disease or another disease. So, this is why transplant is an attractive option, why we try to make transplant safer and more accessible to more patients because it's right now is the only thing we have to cure patients and from a very old study from 2002, we know that if we applied the old IPSS score at the time of transplant, maybe not surprisingly the lower risk patients had a better chance of being cured. Kind of makes sense. Right? High risk patients have worse disease. That's just been cured. So, why wouldn't all low risk patients want to get the transplant and be cured? Well, because of some of them would have lived quite a long time without the transplant thank you very much and the transplant killed them off. So, we don't want to be killing people off. We don't want to be taking away years of life for people. So, it's a balance.

So, where are we?

**Q10:** (inaudible 51:49)

**Steven D. Gore, MD:** No hematopoietic stem cell transplant.

**Q10:** (inaudible 51:58)

**Steven D. Gore, MD:** Hematopoietic cell transplant. FCT. You know, I've never noticed that. I've shown this slide for 10 years. Nobody's ever asked me. I have never noticed that. We borrow slides from each other. That's funny. Hematopoietic stem cell transplant.

So, are you too old or is your loved one too old because my doctor says I was too old. So, the European transplant registry back about 10 years ago almost looked at about 1,400 patients, 1,300 patients who gotten transplanted of whom almost 500 were greater than 60 and 833 got what is now called the reduced intensity transplant. For a while there they were called mini transplants. Most people over age 50 or 60 get a reduced intensity transplant. We could talk about that offline or afterwards if you want to know the differences and so here's your over 60s comparing a high dose or an old fashioned full dose transplant versus the reduced intensity. This is already 10 years out of date. So, things have gotten better we hope and I want to just focus on reduced intensity transplant greater than age 60 because most of you if you were considering transplant would be considering this kind of transplant and you're probably in that age group more or less. So, here's the nonrelapse stuff are the blues are people who are dying as a complication of transplant and you can see that in the reduced intensity about 20 to 30 percent of people unfortunately still die from transplant, but compare that to the full dose transplant where it's more like 40 percent, this is obviously better, but it's not great and the brown or reddish are patients who relapse and eventually die of their disease and you can see there's probably some more relapse here than there, but overall between relapse and death from transplant about 70 percent of patients have not been cured, if you will, don't have long term survival from the standard transplant and maybe it's 40 percent that are cured, 30 to 40 percent of reduced intensity. So, that's really the truth that we don't transplant early patients with low risk disease where it's most likely to cure people because we don't want to kill them and when we do offer transplant for people who have more advanced disease and by the way you need to get into stable disease situation before you're transplanted. Talk about that if anybody wants to. The cure rate is about 30 percent. Now, are you a glass half empty guy or glass half full guy? I'm going to say 30 percent chance of being cured. I'm going for that. That's great. Are you kidding me? I'm going to my daughter's wedding next year. Keep me alive and every single patient is different. So, patients ask me, "Well, should I get a transplant?" I said, "I can't tell you if you should get a transplant. I could tell you that you're a good candidate for transplant. I could tell you that there's nothing going against you for the transplant. I could say you have a good donor and you have a 30 percent chance of being cured. Does that look good to you? Twenty percent chance of dying. You figure it out," and of course there's research being done on transplants. So, we're hoping to make it better all the time, but I like to even if I'm offering people an experimental transplant which might make things better I still think they need to know sort of the basics of what we know which is 30 percent cure, 20 percent chance of dying a toxic death, approximately. Maybe it's 40/15, but a number you can handle on. A third of patients are going to be cured and about a fifth of patients are going to die as a complication. That's just what you got to know and you got to decide that's worth it for you or not and that's a complicated decision.

This is a really complicated slide and I don't even understand it that well, but this is a mathematical model from the Boston group, from Dr. Cutler's group, for older patients greater than 60 getting the reduced intensity transplants. Here's the survival curve for patients with lower risk disease and you could see graphically that if you don't get a transplant your survival is much better than if you got a transplant with low risk disease in this older group of patients and that's why the box, the box comes out to favor don't get a transplant if you got lower risk disease and you're over age 60. That's pretty dramatic, I think. Now, here's the bugaboo for high risk patients and this is depressing, but it's the

truth. This, again, this is a mathematical model, so maybe the real data are a little better. Maybe on a clinical trial it's a little better. Patients who are not getting transplanted and I already showed you this they just continue to die off. Patients getting transplant with a reduced intensity some of them are alive and they can say, "Steve, you said 30 percent. That's only 20 percent. Not as good as I'd like to see." So, that's just how this study came out, but again in here you can see it favors transplant and this is a quality of life measure. So, that's just how it works. That's why we don't transplant to low risk patients.

**Q11:** At Yale, (inaudible 57:25).

**Steven D. Gore, MD:** So, we're in transition because we are in the process of recruiting a new Director of Stem Cell Transplant and we have a really wonderful transplant service. I would say that we are a kind of vanilla service. So, we do kind of standard transplants that are not the most avant-garde and so we're a little on the cautious side. So, it'd be usually about 75 is the age cap more or less that we are comfortable with here currently and we do only matched donors. We don't do half matched. So if people need a more complicated or experimental transplant currently they're being referred to often Memorial or Dana Farber or Johns Hopkins. That will certainly change in the next couple years. Who gets a reduced intensity versus a full dose ablative transplant? I think we're one thing that Yale is really particularly good at is we're very patient oriented and very non-doctrinaire. So, our transplant doctors really look to try to figure out what's the very best thing for this patient. So maybe this patient is a little older than many places would do a full transplant, but they think he's really robust and for his disease a full transplant is more likely to cure him. So, they'll push him to the full transplant. On the other hand, somebody's in the full transplant age group, but has some other problems. They're going to dial back. I think a lot of transplanters are like that but I think our transplanters are particularly individualizing. So, I would say we don't have an exact cutoff. In general, I think most places 55 or 60 gets you a reduced intensity. I would say that's average.

Yup?

**Q12:** My daughter's is 37 years old and we're so confused.

**Steven D. Gore, MD:** Sure.

**Q12:** (inaudible 59:22) everything is go by age group. It's very rare and there's really... They're not giving her (inaudible 59:29) because they don't know what to do with her because she's only 37 years old.

**Steven D. Gore, MD:** So... Right. Thirty-seven is young for MDS, but there are many patients in her age group who have MDS. Is she being seen at a Center of Excellence or has she gotten the consult from a Center of Excellence? It's you. (inaudible 59:48)

**Q12:** (inaudible 59:50)



**Steven D. Gore, MD:** Oh, Dr. (inaudible 59:55). Oh, Dr. Ferma's (sp?) great. So, she's being seen by a good person, but if you don't feel like you're getting the information that you need there's lots of people in New York and New Haven and Baltimore and Boston, very close range who can give you second opinions and the Foundation could refer you. None of us is ever offended when people get a second opinion. People... What's that?

**Q12:** I was just going to ask you about second opinions.

**Steven D. Gore, MD:** Yeah. I mean, I send patients of mine go down to New York all the time for second opinion. I got no problem with that.

**Q11:** We've done two and we've gone (inaudible 1:00:30)

**Steven D. Gore, MD:** I don't want to get too much into individual questions at this point. We'll have some time afterwards offline.

Okay. So now... anything else on what I've talked about just now so far, transplant right now?

**Q13:** Just that maybe (inaudible 1:00:46) the difference between full and reduced.

**Steven D. Gore, MD:** Okay. We can certainly do that.

In the old days when transplant was being developed and into the old days when I was coming of age as an oncology trainee that would have been in the 1980s which is already it's now seeming like a long time ago. Like how did that happen? Wow. It's amazing. Right? Anyway, that's how you measure your days. The idea of transplant was... the thinking was the more chemo you can give to somebody for cancer the better and we would give chemo and this was true not only in blood cancers, but also in breast and lung, everything else. We would push the doses to their limit of toxicity of the chemo drugs. We felt that that's how we had to kill the resistant cells and for the drugs that we use in leukemias and MDS, the limitation of toxicity for the most part was blood count recovery. If we gave too much chemo we would fry the stem cells and people would have what's called aplastic anemia. They wouldn't recover their blood counts. So, the idea of the stem cell infusion was well if we had another source of stem cells, we could give them the highest doses we can give them, fry their stem cells. That might be good because we'd fry the cancer stem cells and give them another source of stem cells and they'd be as good as new and that was true although eventually we found that if we pushed the doses too high we would find new life threatening toxicities like we could fry the liver as well. That's what we try not to do, but if you give too much chemo for a stem cell transplant we worry about frying the liver, causing liver failure. We worry about leakiness of capillaries that cause people to drown in their fluids. On a ventilator. These are the things we avoid, try to avoid, we cause renal failure. So, there's limits. So, that was the idea and the poster child for stem cell transplantation was a different disease called chronic myeloid leukemia. That's the one that's treated with drugs like Imatinib and Gleevec that you've heard about. Everyone says oh, can I get Gleevec and other drugs like that that are dramatically changed the face of that particular disease because people used to die on average within three years from feeling fine with

CML until Imatinib came along unless they had a stem cell transplant and the stem cell transplant was mostly was killing 30 percent of young people. So, that was a big deal. So, what they found was that some people had identical twins or were identical twins and identical twins you've got a perfect donor. It's like a carbon copy of you in your sib. So, we thought that should be fantastic donor because there's no difference. You won't reject them. They won't reject you. Perfect. But very few of those patients who got those transplants were cured. They tolerated the transplant nobody's business, but they weren't cured as often as people who got transplants from a sibling donor that wasn't identical and why was that? That's because the sibling donor who wasn't identical, their cells recognize or immune cells recognize the bad guys as bad guys. That's what our immune cells are supposed to do and the immune cells would fight off the rest of the bad guys it left behind. Now unfortunately, sometimes they decide that your liver would make a tasty lunch or your skin was would be something nice to gobble on. So, that's what's called graft versus host disease where the cells that are given to you gobble up good tissues and cause you to be sick. We don't like that but that's the price you pay a little bit to have them see the bad guy bad guys come off. So, we knew that the new immune system had a very important role to play in the curative part of stem cell transplantation.

So, about 20 years ago now people started asking, "Well, is there a way to get this new immune system in the body without killing off the patient?" for older patients or patients who have kidney trouble or heart trouble who can't tolerate the big banana transplant. We call myeloablative. Myelo means bone marrow just like myelodysplasia means funny looking bone marrow. Myelodysplasia. Myeloablative. Ablative means fry. So, myeloablative transplant means fry the bone marrow, very high dose. So, they started doing what were called the nonmyeloablative, don't fry the bone marrow transplants. Little doses of treatment just enough to get the new stem cells to get a foothold in and they thought they were going to have to do booster doses... Oh, here's another story before I get to there. So, some patients who got the big banana transplant for CML relapsed anyway and doctors at the University of Pennsylvania said, "Well, let's give them a booster shot of cells from the donor. See if we could goose him up." So, they took blood cells from the donor, injected them. That was called the donor lymphocyte infusion and many of those patients went back into remission and were cured. Now, some of them got graft versus host disease, but it proved beyond a doubt that people who had relapsed after the stem cell transplant could be cured by giving them a boost of immune cells. So, this was great. This was super cool. So, they thought that they gave these nonablative donor preparative regimens, chemo regimens. They were probably going to have to do booster doses of cells to boost them up, but it turns out that didn't have to happen. Usually when people engrafted after these nonablative transplants they engrafted fully. So in a nonablative transplant you get lower doses of chemo, chemo and radiation and then you get the stem cells. The good news is you're less likely to die of liver failure. You're not going to die of liver failure. You're not going to die of draining in your fluids. You don't get any of those complications. The bad news is that we're really totally counting on the immune cells doing their job, this graft versus leukemia effect and so we're kind of asking for graft versus host disease and so people, unfortunately, do get sick. They do get graft versus host disease and some people die from that and that's why people still die and the chance of the leukemia coming back is higher with the reduced intensity but some of those patients can get booster cells. So, it gets really complicated. I don't want to get too lost in the sauce. That's kind of

the short outline is. Did I leave everybody in the back in the Bradford River or anything? We're okay?

So, we're going to talk a little bit about lower risk disease to your point and the treatments that we have for lower risk disease include growth factors like Procrit or Aranesp that many of you know about. We sometimes give drugs to reduce the immune system like antithymocyte globulin. I'm not really going to talk about that at all because I don't use it much, but I'm happy to answer questions and we sometimes use the drugs that we were talking about like Aza with the caveats that I said that I don't if we should and for some patients we got this drug Lenalidomide or Revlimid which is oral which we'll talk about.

So, growth factors, erythropoietin or Darbepoetin. These are versions of this kidney hormone. The kidney hormone what happens is you're anemic. Your kidney's got a thermostat that says 'Oh, my gosh. You're anemic,' pumps out this erythropoietin or EPO. EPO goes over to the bone marrow and says 'Okay, red cells. Let's go,' gets your hemoglobin up. The thermostat in the kidney turns off. Everything is good. Now, for some reason many patients with MDS the thermostat's not working. So, we don't know why. They're anemic and the kidney's kind of saying, 'Yeah. Here's a little bit of EPO,' but not kicking it out robustly. The people who don't kick it out robustly many of them respond to us giving you shots of EPO or Aranesp which is another version of EPO basically. It only helps the red cells for the most part and it doesn't change the course of disease. Again, it doesn't slow down the bone marrow process and this is just a scoring system that came from Dr. Hells (sp?) from Limburg in Sweden to show how to select patients, ways that we select patients who would be good candidates for this kind of approach. The main issue is what your blood EPO level. So, how your kidney is responding to your anemia. If your kidney's doing a great job and saying 'Come on, guys. Here's some EPO. Make some red cells,' and you got an EPO level of 500 even though you're anemic we can give you all the EPO or Procrit till the cows come home (inaudible 1:10:03). So in this particular study they looked at an EPO level less than 100. Some people say up to 500. If it's greater than 500, it's probably not going to work. So everybody should have their EPO level drawn if they're considering treatment with Procrit or Aranesp and also EPO works best for patients who don't need a lot of transfusions. If you're getting a lot of transfusions, it's probably not going to work. Sometimes we add another growth factor called Neupogen which is a white cell growth factor to make the Procrit work better and if you have this particular subtype of MDS called refractory anemia with ring sideroblasts it almost always requires Neupogen for it to work on your red cells, not necessarily true with Aranesp, but that's again more complicated than we need to get.

Okay. Revlimid is the son of Thalidomide or daughter of Thalidomide, Thalidomide being the drug that caused all the horrible birth defects when given during pregnancy in the 1960s, but Lenalidomide is a newer drug that we don't think does that although if you get Lenalidomide you have to sign a thing saying you're going to wear a life-size condom the rest of your life. Cover all parts of your body at all times. It's a little joke. Sorry. I tell that to all my older patients. They say, "I haven't used a condom in 70 years." Anyway. More power to you. Anyway, Lenalidomide has this peculiar feature that for patients who have a low risk MDS characterized by this particular cytogenetic abnormality loss of the long arm or Q arm of chromosome number 5, a large percentage of those patients become transfusion independent, two-thirds, and they get a whopping rise in their

hemoglobin of five and it happens really fast and it will last for a really long time. Now, there's a group of low risk patients who don't have 5Q minus who also benefit from Lenalidomide. It's only about 25 percent who become free of transfusions. Their hemoglobin rise is not as high, but it's respectable and it's also pretty fast. There's a national trial that you and others would probably be eligible for. If you're thinking about going on Lenalidomide there's a trial run by the Eastern (inaudible 1:12:29) Oncology Group which is headed by Dr. List at Moffitt in Florida that takes patients who don't have 5Q- and who are lower risk disease with anemia and randomly assigns them to get Revlimid by itself or Revlimid plus Procrit because Dr. List's research suggests that one of the ways Revlimid works is by making Procrit work better and then the group that's only getting Revlimid if they're not having a response in 16 weeks crosses over and gets Revlimid plus Procrit. So, I would encourage anybody who's got a low risk disease non5Q is thinking of getting Revlimid, we need patients for that study. All the patients on that study are getting Revlimid. Half of them are also getting Procrit. So, it's a great study to go on and we'll find out how many are really are benefitting. Now we know from a study in Europe that looked at this group, big study, I guess, placebo. They came up with the exact same 25 percent and no Procrit involved there. So, we know for non5Q, 25 percent response rate in terms of transfusion independence to Revlimid maybe with Procrit will be better. That's why the ECOG study is so important and you could see here this is looking at the erythroid response. The responders in the non5Q, you can see on average there's a pretty good response to those people who are responding getting hemoglobin into the 12 range. So, it's not bad for the people who is working, pretty well tolerated drug in general.

Skip that. Any questions about Revlimid? That's all I'm going to say really about Revlimid.

**Q14:** (inaudible 1:14:04)

**Steven D. Gore, MD:** Sure.

**Q14:** (inaudible)

**Steven D. Gore, MD:** No, I mean I see tons of patients who have been getting Procrit or Aranesp till the cows come home and they're getting transfused every month and I say, "This is not helping you," and they say, "Well, what if I stop it and I'm getting transfused twice a month?" I say, "Why don't we find out? Stop it and see because that's not like Aza. If you're responding to the Procrit and we stop it and your counts drop we can turn it right back on. Aza, that doesn't happen. So, if you're getting Procrit or Aranesp and you don't think it's working just stop it.

**Q14:** (inaudible 1:14:45)

**Steven D. Gore, MD:** Nothing you just said right.

**Q14:** (inaudible)

**Steven D. Gore, MD:** The new immune cells.

**Q15:** (inaudible)

**Steven D. Gore, MD:** Sure.

**Q15:** (inaudible)

**Steven D. Gore, MD:** Right. So the question for the people who are listening elsewhere is since we know that it takes up to six cycles or more to know if Azacitidine and Decitabine is working what about for the growth factors like Procrit? So, many of us think eight weeks or 12 weeks is an adequate trial. There is a study from Greece that show that there are patients who even 24 weeks it finally kicks in. I didn't really believe those data, but my wife who's a health economist, Amy Davidoff, and I participated did an analysis of Medicare database looking at people with MDS in the Medicare population who are getting either Aranesp or Procrit and there clearly are patients who have been getting it for a long time and stopped needing transfusions after three or four months, but not after that. So, that's kind of guidelines. Eight or 12 weeks. Here's the other bugaboo about that is that many doctors under dose Procrit and Aranesp for MDS patients. So, what doctors are used to giving for people like who are recovering from chemotherapy for lymphoma or breast cancer, it's 40,000 units a week of Procrit which is in general not enough for most MDS patients. French studies use 60,000 units a week. The national United States studies use more like 90,000 units a week. One of the national studies show that people who weren't responding to 90,000 some would respond to 150,000 a week of Procrit. For Aranesp, the usual dose for nonMDS is something like 200 every three weeks. The MDS doses are either 500 every two weeks or 300 a week. Any questions about growth factors?

Alright. Now, we're going to move into the 21<sup>st</sup> century finally, or 22<sup>nd</sup> century and everyone's hearing about personalized medicine and mutational analysis and all that and then the last 10 years we've learned to sequence the DNA of cancer cells as well as normal cells and we found mutations in MDS patients that all of these different genes and in this study out of Japan each column and there's a gazillion of them, 800 of them, is one patient and each patient is studied and it's marked black if he or she has a mutation in that particular gene. So, you can see each patient tends to have more than one mutation. We know that and then the color tells us what kind of MDS they have and this isn't meant to be anything you take home (inaudible 1:18:14) to be impressed by how much we can do. It's really super cool, but what it does show you is that most patients like 70 percent of the patients have a mutation in one or more genes that are involved in editing RNA. RNA is the chemical that's made from DNA to tell it to make proteins, the blueprint for proteins and the RNA once it's transcribed or copied off of the DNA, so it'll use the DNA as a blueprint for the RNA and the RNA is a blueprint for the proteins you get sort of the first read of the blue print into RNA and then the cell needs to edit it to make it usable and that's called splicing. Think of spliced film. You take all the footage of your movie director takes hundreds and thousands of hours of film and edits to be a movie. The same thing here. Your cell makes lots of extra RNA and then edits it and these splicing factors that we only recently learned about are abnormal in about 70 percent of MDS patients. So, there's going to be a whole new world of drugs soon, 10 years from now anyway I think.

So, this is the area that I think is super cool. So, the other three groups involve genes which have to do with how the cell turns on and off, regulates its gene expression and this includes what we call DNA methylation and these are things that are affected by Azacitidine and Decitabine and these are all things that our drugs are working on. So, that's pretty cool and, again, the majority of patients had mutations in those as well. So, that's just kind of where we're going with this and here's a simplified version and these are the same patients from the top and the bottom. So, I would just... It doesn't really matter what you're looking at. This I just divided into two groups. A much simpler list of common genes that are commonly mutated in MDS this is from Dr. Omar Abdulwahab and Memorial Sloan Kettering and I just want to focus on red light/green light. One of the genes which is frequently mutated called ASXL1 has some negative prognostic information. So, our next generation of these prognostic scores like the IPSS-R and WPSS will probably start incorporating this mutational analysis. That's something more to know about. ASXL1 not such a great thing. SF3B1 is one of the splicing factors that does the RNA editing and that's associated with this particular MDS called MDS with ring sideroblasts and I'll tell you why that's important in a minute and TET2 has to do with DNA methylation. It may help choose patients who are good for Azacitidine. So, it's not only just prognostic and important, but it may actually help us choose drugs.

So, there's a new drug coming down the line called Luspatercept. It's being developed by Celgene and it's given intravenously and it soaks up chemicals which MDS makes too much of and which turn off red cell production and there was a phase two trial presented by Dr. Platzbecker from (inaudible 1:21:29) German. Lower risk patients who are anemic and who had high EPO levels. So, they were not likely to respond to Procrit or they had already gotten Procrit or Aranesp and hadn't responded and they treated 26 patients, actually, they've shown more patients. I just don't have an updated slide. And many of them had this ring sideroblast thing. About 40 percent had improvement in their red cells, but you can see that in patients who had ring sideroblasts it was over 50 percent that were responding and similarly we'd pick this out with this mutation that tends to be associated with ring sideroblasts, this SF3B1 mutation. So, in the upcoming phase three trial, I think you're going to be required to either have ring sideroblasts or SF3B1 mutating, but there's a phase three trial, Luspatercept... I think it's versus placebo. Do you know that? Do you know, Sue? Do you know?

**Sue Hogan:** I have not heard (inaudible 1:22:27)

**Steven D. Gore, MD:** Sotatercept.

**Sue Hogan:** Yeah. Is it SGI (inaudible)

**Steven D. Gore, MD:** No, no, no. SGI is like Decitabine. Anyway. It's a super cool drug. It's going to be very effective for a certain subset. Probably just the ring sideroblasts. If you have RARS, this is coming soon. We're going to have this opened in about four months.

P53 is a really interesting gene. It's called the gatekeeper to the genome because it protects s from the damage to our genes and it's unfortunately frequently mutated in many cancers including MDS and if you have a P53 mutation in your MDS cells, you're not going to respond to the chemo that we give for leukemia in general, but in this particular study it showed that people who had P53 mutations still

respond to Aza. So, that's good news. If you have P53, for sure don't want to get chemo, but Aza may help and I talked to you about this TET2 mutation which has to do with DNA methylation which is what Aza and Decitabine work on and this study from the Harvard group showed that the people who have TET2 mutations have a better chance of responding to Aza or Decitabine than do the people who don't have TET2 mutations although they still have a pretty good chance of responding. So, just to show you how we're using the mutations not only to get prognosis but to start to pick appropriate therapies.

**Q16:** Does this (inaudible 1:23:53) for things like (inaudible)

**Steven D. Gore, MD:** For mutational analysis? We actually have our own MDS AML panel that looks at about 30 genes or 25 genes. Sometimes they choose to send it out to Genoptix. Foundation Medicine is another one that's quite popular. There are several of them and I would hate to advocate for one. They're all pretty good I think.

So, these tests are now kind of readily available. Usually insurance will pay for them. They don't have immediate impact on therapy choice, but for those of you who are real kind of nerdy about your disease in a good way and you want to know everything about it. You can do it on blood. You don't need to do it on bone marrow.

Okay. So, I'm coming to the end. So if you're falling asleep, I'm sorry. Whenever I go to a conference in this particular room I always fall asleep. I sit in the front row and I always fall asleep. Go ahead.

**Q17:** (inaudible 1:24:44)

**Steven D. Gore, MD:** It's a super good question and hold it and get back to me. We'll do it right in a minute. Remind me. It's a super good question. Thank you.

Who should get iron chelation therapy? Remember if you're getting transfusions, you're getting too much iron and we worry it's going to hurt you. We don't know for sure it's going to hurt you. We worry about. So, here's the answer. Who should get it? We don't know, but if we wanted to give you recommendations which I'm paid to do... I'm not getting paid for this by the way. Patients who have a lifetime history of getting at least 20 units of red cells should be at least considered for iron chelation. We measure the serum ferritin. Again, that's kind of an overall picture of your iron in your body. If it's greater 1,000... if it's less than 1,000 find that worth thinking about it. If you're not still getting transfusions and the iron isn't bothering your body don't bother, but if you're still getting transfusions you're just building up more and more blood, worth thinking about and Amy and I, again, use the Medicare database... I think it was Medicare to look at the question of does the use of the oral chelating agent which is called Exjade or Deferasirox is not a new version called Jadenu. It's Deferasirox, improves survival and in the Medicare population who has MDS who's getting... who's already had at least 20 units of transfusions. So, we wanted to look at people who had at least 20 units of transfusions. So, thinking they maybe they should get chelated. If you look at people gotten any Deferasirox or not the survival is improved than the people who got any Deferasirox, but this is

not kosher because the doctors are looking at the patients and they may not be giving Deferasirox to patients who are going to die anyway who are really super sick say, “Why should I give them this expensive drug. We’re not going to be able to help them.” So, there may be... It may just be the people who don’t get the Deferasirox are sicker patients and that’s why they’re dying faster, but we did a very complicated statistical analysis which Amy could explain to you but I can’t and my colleague Amer Zeidan who’s a junior colleague here at Yale and who also works for the Foundation, wonderful guy and putting everything into the sauce, into a multivariate analysis where everything that could impact a physician’s decision to put the person on Deferasirox or not, so we could kind of get the best picture we could about it’s not just the doctor thinking the patient’s too sick. The best we could but we saw that... I’m going to blow this up for you that if you look at how long people have gotten Deferasirox compared to the people who didn’t get it patients who got 14 weeks or more of Deferasirox were living longer than patients who got no Deferasirox and it’s pretty impressive like twice... this would be like twice the survival for patients who had ongoing Deferasirox and that’s taking into account everything we possibly can. So, this is making me believe since we don’t yet have a randomized trial against placebo that for patients who’ve had at least 20 units of red cells and are still getting transfusions and they’re able to get Deferasirox they should get Deferasirox. So, I believe it now based on this data and I think if this is right it’s doubting survival. That’s as good as Azacitidine. Deferasirox is pill now, Jadenu. Jadenu is a lot easier to take than the other stuff. It’s like a fizzy tablet.

Okay. So, here’s your take home messages. You sat through a long hour. MDS remains a complicated set of diseases. You can go to all these that you want and you’ll still be confused. So, please I think the bottom line is find a doctor or a set of doctors that you’re comfortable talking to who will take the time to explain things to you who won’t just say we’re going to do this or we’re going to do that or this is what you should do. This is really needs to be a negotiated process as far as I’m concerned. I think MDS patients know better than most how they’re doing because especially the engineers with MDS they bring in their spreadsheets of their counts and everything. You know if you’re getting transfused. You know if your transfusions are going up. You know if you’ve been in the hospital for infection. You’re know (inaudible 1:29:15). You guys all know your counts. So, there’s very little I’m going to see in the bone marrow that’s going to tell me something very different than what you’re going to tell me based on how your blood counts are doing. That’s just a fact. So, it shouldn’t be that mysterious once you know your numbers and know how to follow your numbers.

Get a second opinion from a Center of Excellence. It doesn’t have to be an MDS Foundation designated Center of Excellence, but this even (inaudible 1:29:38). Know your prognostic score. Ask about your cytogenetics and mutation analysis and ask about clinical trials because there’s new drugs coming out. Some of them are better than others, but there’s lots of stuff going on and I do want to get back to the question about the ring sideroblasts. So, this is our classification system for MDS. That’s the World Health Organization Classification, actually, here and patients who have greater than 20 percent blasts in their bone marrow or in their blood are now considered to have AML with myelodysplastic related changes, what I call the VVVBMDs, very, very, very bad MDS. If they have between five and 20 percent blasts they have one of these two categories, refractory anemia with excess blasts 1 or 2 depending on the number and the number changes from year to year, but I think



it's 10 to 20 percent if I'm not mistaken is now RAB2. So now, we get to this group, 5Q- are patients with a particular disease that tends to have red cell problems only, normal platelets or high platelets and the abnormality just in chromosome 5Q. Not everybody who has an abnormality in chromosome 5Q has this particular disease. Refractory anemia or refractory cytopenia are patients who have only anemia or only low platelets or only low neutrophils just one abnormality and don't have increased blasts. The ring sideroblast thing has to do with when we stain the marrow cells for their iron content. It's a special stain called an iron stain. I don't have a picture on this slide deck, but in some patients with MDS the mitochondria which are the power houses of the cell accumulate iron and for some reason in their red cells, in their red cell precursors in their bone marrow the cells comprised of red cells the form a little ring of mitochondria filled with iron around the nucleus like all the wagon Conestoga wagons circling around the fireplace, fire pit, and those are called ring sideroblasts and for reasons that we don't entirely understand pieces with MDS have them and then refractory anemia with ring sideroblasts at least 15 percent of the red cells are these cells and the reason this is important is it goes along with this mutation in SF3B1 that I mentioned and may predict for a response to this new drug Luspatercept and these are patients who tend not to respond to Procrit by itself, but will respond to Procrit with GSF or Neupogen.

RCMD takes all these patients who are otherwise this low risk refractory cytopenia or RARS, but these patients when we look at their cells they have funny looking cells in all of their cells. So, they have funny looking platelet forming cells, they have funny looking neutrophil forming cells and that means that's the multilineage. It's the red cells and the white cells and the platelets, dysplasia is funny looking. So while their blood counts aren't so bad and they don't have increased blasts all their cells are funny looking and they tend to do worse than patients whose cells aren't all funny looking and that's why they got their own category now, RCMD.

**Q18:** (inaudible 1:33:51)

**Steven D. Gore, MD:** Refractory cytopenia. Refractory meaning it doesn't go away. Cytopenia means we don't just care about anemia anymore. It could just be your platelets that are low. It could just be your neutrophils that are low. Your hemoglobin could be normal in other words. Does that help?

**Q18:** (inaudible 1:34:10)

**Steven D. Gore, MD:** Multilineage. That means more... all the different cell lines. Dysplasia is funny looking.

**Q18:** (inaudible 1:34:22)

**Steven D. Gore, MD:** Sure. Well, it depends on what their hematologic needs are and it depends on what their score is. So, let's say you had RCMD and you're not getting transfusions and you don't have bad chromosomes. Here in this particular WPSS score you got a one. That puts you into a low risk category and that means that out of 100 patients like you in your group, 50 percent of them or 50 them are still alive at seven – eight years. Now if you're 39 years old or 29 years old that may not

sound so hotsy totsy and you may still be concerned, but if you're 80 you might say, "Well, that's not so bad." Now on the other hand if you have RCMD and you have bad chromosomes and you're receiving transfusions. Now you've got a 1, 3, 4 and now you're in a high risk category. In the high risk category 50 percent of patients are dead in two years. Now can you be followed with watchful waiting? Absolutely. Is that okay with you? I don't know. Azacitidine in that case that is a group that is known to have a survival benefit from Azacitidine if you never had it before, for example.

**Q18:** (inaudible 1:35:54)

**Steven D. Gore, MD:** I recommend not looking at anything that way. I recommend using the scoring system. The scoring system overcomes this piecemeal approach of just looking at one factor versus another. Let's look at it here well, see, here you don't get into the RARS again. So, it's kind of these more complicated things, but it's basically the same thing. If you've got low blasts which you might have with RCMD, but you got bad cytogenetics is three, you're being transfused that's 4 ½. That's what your platelets are. That's why you got to know your numbers.

More questions? Second row.

**Q19:** How often does your bone marrow (inaudible 1:36:44)

**Steven D. Gore, MD:** Highly individualized. I tend to restrict bone marrow testing to a change in clinical picture. So if I did a bone marrow test and things are kind of low grade and blood counts are doing what I expect them to do I don't necessarily intervene with another bone marrow test unless things change unless the patient's eligible for a clinical trial and they need to have a bone marrow done to determine their eligibility. On the other hand sometimes patients have more dynamic changes in their counts, things are changing faster and then it's a clinical decision.

**Q19:** (inaudible 1:37:22)

**Steven D. Gore, MD:** No, the sequencing can be done in the blood for the most part. Usually can be done in the blood, the mutational analysis can be done in the blood usually.

**Q20:** Regarding blood transfusions, how often can you have them? How should you feel? Should you feel good right away or what? Can you have too many?

**Steven D. Gore, MD:** Yeah...

**Q20:** And what's... and how long in between?

**Steven D. Gore, MD:** Every patient is different and there are patients whom we transfuse weekly, but their quality of life is not very good often. So, there's no upper limit of what can be done. People who are getting a lot of transfusions often become more resistant to transfusions. Sometimes they make antibodies to red cells and it becomes very hard to type them. They spend a long time in the transfusions suite. Oftentimes they have reactions and need medication. So, I don't think it's not

optimal for those patients. Is there any risk? The risk is iron overload and so those patients if they're going to be... if they're expected to survive for a long time should be getting a chelator probably.

**Q20:** (inaudible 1:38:53)

**Steven D. Gore, MD:** One of these anti-iron antidotes like Exjade or Jadenu, Deferasirox, but there's no absolute rules about it. We like to minimize transfusions because we don't want patients to be at risk for transfusion reactions and no blood supply is pretty safe, but not by 1,000 percent safe. So, there's (inaudible 1:39:18) of hepatitis viruses that still sneak through once in a while.

**Q21:** Is the prescribing of Procrit or Aranesp sort of a way of avoiding transfusions?

**Steven D. Gore, MD:** When it works that's the goal. It's a goal to make people feel better and to avoid transfusions. That's exactly the main goal of the growth factors.

**Q22:** What do you suggest doing first? Transfusion or the drug?

**Steven D. Gore, MD:** Well, I think you have to determine whether the patient's likely to respond to the drugs and that requires a determination of their EPO level in their blood, their erythropoietin level. If their EPO level is high, they're not going to respond to the drugs. So, outside of a clinical trial, I wouldn't waste my time and money, but if their EPO level for sure is less than 100 – 200, is less than 500 then the growth factors are worth a try and I would certainly prefer the drugs to getting red cells.

**Q22:** You prefer drugs...

**Steven D. Gore, MD:** Sure because when you get transfusions your energy level is going to go up and down depending on your hemoglobin. It's like a sine wave. So when you get transfused, you asked me how quickly you feel better. That's... Jayshree may help me with that later, but patients are all over the board. I have some patients who walk out of the transfusion suite feeling like a million bucks. A lot of people told to me it really takes a couple days before they feel better.

**Jayshree Shah:** Yeah. It's about 24 hours.

**Steven D. Gore, MD:** To really feel like it kicks in and some people never feel any different.

**Jayshree Shah:** No. (inaudible 1:40:53) other comorbidities people may have in addition to them (inaudible 1:41:00) the transfusion. So, it's (inaudible)

**Steven D. Gore, MD:** So and in contrast for people who do feel different if they're getting a growth factor and it keeps their hemoglobin at a certain level they're not getting those dips. So from a quality of life that's much better point of view, quality of life point of view. So if the growth factors work, they're awesome and they tend to work for two – three years.

**Q22:** How much should you...

**Q23:** (inaudible 1:41:28)

**Steven D. Gore, MD:** So right. So, 47 is high compared to somebody who's not anemic, but it's very low for somebody who is anemic. EPO level of 47 is very low for an anemic MDS patient and that predicts for a good response to growth factors.

**Q23:** So, it sounds like you multiply (inaudible 1:41:59)

**Steven D. Gore, MD:** No, no, no. Forty-seven is low.

**Q23:** (inaudible 1:42:06)

**Steven D. Gore, MD:** If they're not anemic? Probably zero to 10, zero to five, very low.

**Q24:** So, I see like the survival chart, but is there a chart for... I'm very low grade. I have the deletion 5Q and I have only low platelets, but...

**Steven D. Gore, MD:** Low platelets but not low red cells. Is that right? You're not anemic.

**Q24:** No, I'm not anemic.

**Steven D. Gore, MD:** So, you're backwards.

**Q24:** Good hemoglobin.

**Steven D. Gore, MD:** Your bone marrow didn't read the text book. Shame on you.

**Q24:** Basically. So is there like a chart for like low grade to high grade for how you would progress?

**Steven D. Gore, MD:** So, that's why these systems are good. So because there's so much heterogeneity in these diseases and we're not going to find a lot of people who are carbon copies of you to put together a chart for people just like you we do the best we can to give you the best information we can. So, you... if you're problem is really only platelets and they don't you have RCMD. They don't think that you have... We would call you refractory cytopenia. That's this one, zero points and 5Q is a good risk karyotype, zero. You're not getting transfusions, zero, that's a very low... That's a very low. So, that means you're in this curve. Now, everybody wants to be on this curve that nobody dies, but that's pretty good that you can watch and see if anything's getting worse I would say and very unlikely to develop the kind... the very, very, very bad MDS that sometimes called AML. Now if we went to this thing, 5Q is not the very, very best. It's good but not very good. So, we would go to get one point for cytogenetics. You probably don't have any increased blasts. Your hemoglobin's normal. How low are your platelets?

**Q24:** They range between 30 and 80. They won't go past 80.

**Steven D. Gore, MD:** So, we're probably going to have to give you a point for that. So, depending if they've been as low as 30. So, you get one two points there and your neutrophils are normal. So, two points low risk. So, here's a case where... was the other one low risk or very low? Zero, zero, zero. That was very low. That was very low. So, here's a case where I tell you they're always exactly the same. So, I lied. So, this is low risk. Again, it depends on your platelet count. On the other hand if we put you in this category, you get .5, .5 and one, 1.5. Yeah. So, that puts you in the very low risk there. So, that tells you the subtleties here. The bottom line is patients like you, the good and bad news is you have nothing to worry about right away. You're young, so we don't have experience for what happens to you in 20 years, but we don't expect anything bad in the next 10 years. So, got to be patient. Got to learn about your disease. Who knows what we're going to have new and if you haven't had an MDS gene panel it might be of interest.

**Q24:** I did.

**Steven D. Gore, MD:** You did.

**Q24:** Yeah. They did at Columbia, my second opinion. Thank you.

**Q25:** (inaudible 1:45:34)

**Steven D. Gore, MD:** In general, it doesn't. It does not.

Yes. Please. Seventh row or something.

**Q26:** I just wanted to share what happened with me. About 15 years ago my blood apparently changed. I was told I probably had multiple myeloma. Probably. Now, 10 years ago they changed it to MGUS.

**Steven D. Gore, MD:** MGUS. Okay.

**Q26:** And I have been there until recently. My platelets... the only thing I know of are my platelets are very low. They're about 30 and they've gone down a little bit and a little bit every once in a while and here I be.

**Steven D. Gore, MD:** So, MGUS doesn't... is not an MDS and doesn't cause low platelets. So, MGUS has to do with having an abnormal protein in the blood that is sometimes is seen in another disease called multiple myeloma, but MGUS means you've got the abnormal protein but don't qualify as having multiple myeloma although many patients with MGUS may eventually develop multiple myeloma, but if you have low platelets and MGUS either you do have multiple myeloma, that would be an unusual presentation or you have MGUS plus something that's causing a low platelet count.

**Q26:** Well, they're saying it's probably MDS.

**Steven D. Gore, MD:** Gotcha.

**Q26:** So, that's why I'm here.

**Steven D. Gore, MD:** Okay. Well, welcome.

**Q26:** That's where I am right at the moment.

**Steven D. Gore, MD:** It sounds like you need some information. Any questions for me? Well, I appreciate everybody's attention. Thanks for coming out on a beautiful fall day, nice and crisp and...

**Jayshree Shah:** (inaudible 1:47:48)

**Steven D. Gore, MD:** I'm probably not going to stay for lunch, but I can certainly hang around for those 15 – 20 minutes. Is it lunch time already?

**Jayshree Shah:** (inaudible 1:47:57)

**Steven D. Gore, MD:** I'll hang out. You're doing session afterwards?

**Jayshree Shah:** Yeah. I'm just right now because I just want to introduce everybody so that you have (inaudible 1:48:07) small group (inaudible) amongst ourselves.

I was just wondering if it would be okay if everybody just introduced themselves to share their story. So, I'll begin with myself. My name is Jayshree. I am a nurse practitioner at Hackensack University Medical Center in Jersey. It's about... just to give you a landmark. It's about 10 minutes south of George Washington Bridge. So, very close to New York City. I've been there for oh, 10 plus years now and I've done many forums, patient forums such as these and it's a great opportunity to meet you and to share information. It's nice because I go to the different sessions and I learn something new each time along with Dr. Gore sharing what clinical trials that he's possibly going to have open in the near future for MDS patients. I think it's a great opportunity to learn about you as patients and caregivers to share your story. So, that's my background. So, I'm looking forward to hearing about you.

**Q27:** (Attendee). My husband's the one who has the MDS and he was told that it was a low grade so that if you have to get it this is the kind to get it, but this is the kind, but right now we don't think so because he's undergone some transfusions and he's not felt any better.

**Jayshree Shah:** Is he being treated here or somewhere else?

**Q27:** Locally in Stamford and he wants to know about other treatments and hopefully we can get this resolved, but I see you have to know EPO and I know he does have the ring side blasters, but it's very complicated. Well, he...

**Steven D. Gore, MD:** It's not that complicated if the doctor is talking to you.

**Q27:** Well, that's part of the problem.

**Jayshree Shah:** Again, that's why you're here today to learn and coming to hear Dr. Gore speak today and he's coming from an MDS Center of Excellence is like really important because you need to find people like Dr. Gore and his team members to help kind of understand what you're dealing with and go to specialists.

**Q27:** Well, he was expecting to feel great after transfusions, but he still gets short of breath and he just had one last week and he's still short of breath.

**Steven D. Gore, MD:** Well again, we can't diagnose your husband here, but we can tell you that we can see him or he can be seen at one of the Center of Excellence in New York and it might be worthwhile.

**Q28:** Let's see. I'm over 80.

**Steven D. Gore, MD:** You look fantastic.

**Q28:** And overly committed volunteer, play squash and tennis four days a week and I've been on Aranesp for a little over a year and I don't really know whether what it's doing for me. I found it very difficult to tell, but I'm just trying... I guess I'm kind of a Lance Armstrong mode or trying to keep it so I can breathe better and obviously not be as tired.

**Steven D. Gore, MD:** Is the Aranesp helping your hemoglobin?

**Q28:** Sometimes I don't know really how to tell because when I get the complete blood counts the hemoglobin seems to stay about the same, 10.5 to 11 just enough to Medicare take care of it. Red blood cells stay at 2.9 almost.

**Steven D. Gore, MD:** (inaudible 1:52:04) We never look at the red blood cell count. The only people who look at red blood cell counts are the patients. The RBC count is not something that doctors look at except for some other diseases. It comes along on the CBC. It's not something we look at it, but was it less than 10 before you started the Aranesp or has it always been the same?]

**Q28:** It's always been about the same. Lower 10 to maybe slightly over 11, but it always creeps under so the Medicare will approve the shot every three weeks.

**Steven D. Gore, MD:** Alright. So, I look at your chart because it's never been... if it's never really shown that it's gone up from what it started at then it's probably not helping. On the other hand if it started at nine or eight and now it's 10 then you're having a great response.

**Q28:** I'll have to go back and look at it.

**Steven D. Gore, MD:** We look at the hemoglobin or the hematocrit which are the same. One is calculated from the other, but the RBC count is not something that doctors use. It's a mystery because it looks like we should, but we don't. It's for some other purpose. I know it's confusing.

**Q29:** My name is (Attendee). I'm 57 years old. I got diagnosed with this myelodysplasia basically 2 ½ months ago and I have used Aranesp for the past, I would say, seven weeks, but the problem is we started the low dose then we waited three weeks then we started high dose then we waited three weeks and then in the past three weeks I have been taking the 300 microgram every week. I live in Saratoga, New York. My doctor, the oncologist I'm seeing, started the process, but then I went for consultation at the Sloan Memorial and basically similar to the things you described I got told. The only question I had is that in fact I have a visit with the doctor on Monday, but the question he basically wanted to do the sequencing, the mutation although my first biopsy shows the genetic are normal, but he said they want to do another biopsy on this. That's why I was asking you if the biopsy can be done... the sequencing can be done via blood test or they need another biopsy.

**Steven D. Gore, MD:** So usually, I think the answer is yes and it presumes that you've got abnormal cells in your blood and if you're only problem is red cells...

**Q29:** That's right.

**Steven D. Gore, MD:** Then there's not... red cells don't give DNA. So if your only problem is with red cells then you might not find it in the blood. One strategy depending on your insurance would be dependent on the blood. If it's normal then do bone marrow, but that's probably why they're picking it up in the bone marrow. They think the problem's only in the blood then they say (inaudible 1:55:01) if the only problem is red cells.

**Q29:** It is absolutely red cells because the white... the white cells and the platelet are very normal and they haven't really fluctuated that much. I mean, the platelets are 400...

**Steven D. Gore, MD:** (inaudible 1:55:15)

**Q30:** Hi. I'm going to pass the microphone to the patient in the second, but I just wanted to ask one thing. Ring sideroblasts are different from the blasts that you talked about in terms of...

**Steven D. Gore, MD:** (inaudible 1:55:42)

**Q30:** So, the AML conversation was the other just called blasts by themselves. The ring sideroblasts...



**Steven D. Gore, MD:** Called myeloblasts actually, but we just call them blasts. They're called myeloblasts.

**Q30:** Okay and the ringed ones are the ones that have a little bit of iron in them?

**Steven D. Gore, MD:** They have abnormal iron in the certain part of the cell in a certain pattern (inaudible 1:56:04) the bone marrow (inaudible).

**Q31:** First of all, let me congratulate you. We saw you in Baltimore two years ago. You've become a little white like the rest, but you were sensational.

**Steven D. Gore, MD:** It changed naturally. I didn't have to do anything special to get there.

**Q31:** It's your crown of glory, but you were sensational today. Far superior that anything we've had. I'm over the hill, 82 years old and I had it for a period of time and now I do not take any medication. I take a lot of love. That's all.

**Steven D. Gore, MD:** Love is a good treatment. I'm sorry you didn't (inaudible 1:56:49) one of the therapies. Prayer is not bad either.

**Q32:** I told her I had spoke already about myself, but my name is (Attendee) and my husband Bob.

**Steven D. Gore, MD:** Welcome.

**Q33:** My name is (Attendee). My daughter, (Attendee), has MDS and we're just starting to learn a lot about it. It's a complicated... very complicated disease.

**Steven D. Gore, MD:** You'll like Dr. (inaudible 1:57:22) a lot.

**Q33:** He is (inaudible)

**Steven D. Gore, MD:** Lovely guy. Really and very, very smart.

**Q34:** (Attendee). I just got diagnosed in March with MDS, very low grade.

**Steven D. Gore, MD:** Well hopefully, you'll do very well.

**Q34:** Thank you.

**Q35:** My name is (Attendee) and I'm an advocate with the National Organization of Rare Diseases.

**Steven D. Gore, MD:** Oh, great. Welcome.

**Jayshree Shah:** So, as we're getting ready...

**Steven D. Gore, MD:** Another.

**Q36:** I just found out about the Centers of Excellence on the Internet and that's why we're here. Right now, (Attendee) goes to Yukon which is not a Center of Excellence. How would a patient interact with a Center of Excellence when not going to a Center of Excellence?

**Steven D. Gore, MD:** Well, that's hard, I think. Most Centers of Excellence would ask for you to come and be seen as a patient and your materials get reviewed. It usually is a bone marrow pathology will be reviewed by expert pathologist who has (inaudible 1:58:41). You would be evaluated for whether any additional testing would be (inaudible 1:58:52) for somebody who (inaudible 1:58:53) genetics done and sequencing done if it hasn't been done before. So and like I say sometimes people are on the right drug, but not always the right dose because they're seeing a very good but general (inaudible 1:59:07) why places generally go through the (inaudible 1:59:14) consultation (inaudible) unless it's somebody from that (inaudible 1:59:20)

**Q36:** One of your slides mentioned to go to a Center of Excellence for a second opinion. At what point in time would that be a good thing to do, I guess? Is there a way...?

**Steven D. Gore, MD:** What does the Foundation recommend? I would say right away.

**Q36:** Right away.

**Jayshree Shah:** You're just in time to be seen. There's a lot of material that needs to transfer over. The bone marrow biopsy, the results need to be reviewed by the Centers of Excellence hematopathologist as Dr. Gore said. So, you want to have all that information ready when you come in for the consultation. You don't want to do half of a job and come in and be like oh, you have to come back or whatever. So, you want to make sure all the data is in kind of a thing.

**Steven D. Gore, MD:** The other thing is that even (inaudible 2:00:18) in active therapy, I think it's really important to understand kind of the spectrum of the disease and where you fit and which curve applies to you and (inaudible 2:00:29) expectation for you down the road, what's in store and oftentimes if you're not at a Center of Excellence there may be clinical trials that could be very helpful to you right now that they may not know about. So, it's a lot of information... we all know what each other is doing because we're a pretty small community, Centers of Excellence (inaudible 2:00:51).

**Jayshree Shah:** And the doctors are willing to share you.

**Steven D. Gore, MD:** Oh, yeah.

**Jayshree Shah:** We're not here... Centers of Excellence are not like, "Oh, yeah. We're going to take these patients over." It's more for just a reference and resource and education just to understand

about disease a little bit more possibly and to find out is there something updated and the doctors that you guys are being taken care of can communicate either via E-mail, whatever the case may be or phone.

**Steven D. Gore, MD:** (inaudible 2:01:22) is amazing.

**Jayshree Shah:** They do. They really do.

**Steven D. Gore, MD:** (inaudible 2:01:26) low tech thing.

**Q37:** Okay. Preparing for a visit to a Center of Excellence. Do you suggest getting the patient's... all the patient's records and forwarding them or bringing them...?

**Jayshree Shah:** There should be an intake person.

**Steven D. Gore, MD:** The intake person will guide you through that, tell you what they need.

**Jayshree Shah:** Just that guidelines of what needs to be sent in first.

**Q37:** Since you are... Since Greenwich Hospital is affiliated with Yale, could a person go down there or do they come up here. They would have to come up...

**Steven D. Gore, MD:** They may (inaudible 2:02:06) come up here to be seen. We don't have any of our export MDS patient currently seeing patients. Although there is a neuro oncologist. So, that model is being explored. We are currently not exporting (inaudible 2:02:18) experts...

**Q37:** Experts to Greenwich but you do have one in West Chester.

**Jayshree Shah:** Yes. I mean, this is a Center of Excellence. I think if you go through the intake person they will guide you through what the step (inaudible 2:02:38)

**Steven D. Gore, MD:** I'm (inaudible 2:02:39)

**Jayshree Shah:** Is lunch ready? So, why don't we have some lunch, get to know each other, having food with us along with that chatting and then we will regroup and then the last hour I just have a small presentation for like literally 10 minutes just to go over some general information about what could be done or just as reminders about MDS and things you can do on a daily basis and then the rest is just for questioning and you to learn about you and assisting with any resources.