

Speakers:

Peter Greenberg, MD

Alex Aleshin, MD

Lori Muffly, MD

Mary L. Thomas, RN, MS, CNS

Audrey Hassan: Good morning, everybody. Can you hear me? I want to welcome you to our MDS Patient and Caregiver Forum today. I'm Audrey Hassan, the patient liaison with the MDS Foundation and I want to thank you all for choosing to spend your Saturday with us here today. It's an honor and a pleasure to have as our guest speakers today Dr. Peter Greenberg who is also a member of our Board of Directors, Dr. Alex Aleshin, Dr. Lori Muffly and Mary Thomas is a member of our Nurse Leadership Board at the MDS Foundation.

Just a few housekeeping rules. We are taping the forum. It'll be available up on our website after the meeting. The bathrooms are down the hall and around the corner and there are also bathrooms downstairs and across the hall if you need. Please make yourselves at home. If you need to use the restrooms it's very informational you can get up during the talk. There are also refreshments in the back. We want you to be comfortable.

So, please I'd like without further ado I'd like to get the program started for you. Please help me in welcoming Dr. Peter Greenberg.

(Applause)

Peter Greenberg, MD: Good morning, everyone.

Attendees: Good morning.

Peter Greenberg, MD: Can you hear me alright? So, maybe I need to use this. Let's see what happens. We okay now? Can you hear me now? Great. We want to welcome you today and hope this will be useful for you. We have four speakers that we'll try to put MDS into perspective. We want there also to be... we also want there to be time. We also want there to be time for questions. So, at the end of each speech there will be a time for you to answer questions, ask questions as much as possible. Can you hear me still at the back? How is it?

Attendees: It needs to be louder.

Peter Greenberg, MD: Can you hear me now? Okay.

So, as you see I'll be talking about the disease and its treatments. Following me will be Dr. Alex Aleshin. He'll talk about molecular understanding of this disease. Lori Muffly will talk about

bone marrow transplants for MDS patients and after lunch Mary Thomas will be discussing quality of life with you and, again, questions afterward will be most appreciated.

So, some of the questions that you will likely will have include these: What is MDS? What does it mean for my life? Is there a treatment for it? How should I be treated? When and why? And a lot of this relates the uncertainty that occurs in your minds and also in the minds of physicians about what's next. So, I hope to put this into some perspective.

What's the nature of this disease? It's chronic. It's heterogenous. It's not one illness. It's multiple groups of diseases. There's symptomatic blood counts that may be low called cytopenias. Patients are generally elderly. What does that mean? Usually, 10 years older than the speaker. I mean, that's one possibility, but I'll let you use your own imagination for that. Comorbid conditions. That is other illnesses can occur in people over the age of, say, 60 or 70. Potential progression to acute leukemia is the real devil and the question is why and when that will happen and what do we know about potential therapies and the impact on quality of life. So, these will be covered.

Now, as you can see here the disease as well as many other hematologic malignancies and cancers in general begin to take off at the age of 60 and 70 and so the incidence of the disease really increases markedly as we age and so what are the features that will give us some information about what's our prognosis what are things going to happen to us over the next few years. The things that we look at are clinical and molecular. Blood counts, bone marrow blasts and what are the cytogenetics. Those are the key features that we look at that help us decide this. Other features include age and a number of other features that we look at and then if you have treatment how is your response? If it's good, generally that's a positive indication. If not then the question is what's next. Molecular, Dr. Aleshen will be talking about a number of these molecular issues in much more detail, but I'll be talking about some specific mutations and the number of mutations that may occur.

We have a catalog of alphabetically named diseases that are subgroups of patients with MDS based on their bone marrow blasts. So, when your doctor gets a bone marrow he will look to see what proportion of blasts that are there. The main point is it greater or less than 10 percent and then what should we do about it and there are different names that are given to these diseases depending on what is found morphologically.

Now, as a result of the issue of how we deal with prognosis, an international group has been set up and from 11 countries, 7,000 patients and a system then developed in which one looked at bone marrow blasts greater or less than 10 percent. What are the cytogenetics? Your bone marrow chromosome. What groups where they? How abnormal where they and then how low were your blood counts and those are the key features that go into prognostic indications as well as age and so what one found is that there are five subgroups of patients with MDS depending on this. If you put all those three features together there are patients that have in the upper two

columns there very low and low risk. Patients those are lower risk in the bottom, higher risk patients and then there's intermediate and we manage patients depending on which subgroup you happen to be in for patients with lower risk the disease the main point is to try to improve your blood counts. For patients with higher risk disease and there's higher risk for potential development of acute leukemia we try to give you treatment that will modify the natural history of the disease. So, those are the things that we as physicians try to take into account when evaluating your specific stage, but in addition there are recurrent mutations, changes within the cells of your bone marrow and these can be present in a higher proportion or a lower proportion of patients, but as you can see there are many perhaps 20 possibilities that can occur of which the ones that are in bold are relatively poor prognosis. That is they're five that we look at to see if they will be additive to the features that I told you a moment ago, the clinical features of the IPSS what your subgroup is and so we look now almost routinely to see what your molecular features show, what the mutations are. In addition, there is one that has a good prognostic feature and that is this one right here the SF3B1. So, those are patients that often associated with patients that have what's called ring sideroblasts, a group of cells within your bone marrow that have a good prognosis. In addition, the number of abnormalities in the mutations also make a difference as to how you will do. So, again, these are things that we look at when we evaluate your blood cells and your bone marrow for prognosis.

Now, there have been a number of approvals for drugs for MDS over the last 10 – 20 years and as you know and many of you have been treated with some of these. Erythropoietin and Darbepoetin early evaluation, G-CSF for patients with infections and then in 2004 and 2006 these two drugs, Azacitidine and Decitabine were approved and since then there's been no major addition. So, we're talking about almost 10 years since there' been any attempt to have a drug that's been valuable to change the natural history of this disease. So, we have been looking and are still looking to see what are the best next drugs for your illness. These two drugs are called hypomethylating agents and they have potential utility for a group of patients particularly high risk patients. Lenalidomide is a drug that's very useful for a group of patients with a chromosomal abnormality called 5Q-. So, that's one subset in which a high proportion of patients may respond and we'll talk about that more in a moment. Deferasirox is a drug that is useful for iron overload patients, patients that have a lot of iron overload because of transfusions. We then can provide this drug if needed and we'll be talking about that. These two drugs here, Romiplostim and Eltrombopag these are drugs that can improve platelet counts. They're not approved for this indication as yet, but they are available and sometimes we do use them for changing platelet counts.

So, the National Comprehensive Cancer Network is an organization in which there ar consensus groups of physicians that make decisions about management for patients with all cancers in this country and so MDS the plans that have been suggested are to evaluate patients if they clinically relevant low blood counts not just are they low, but do they make a difference for you? In other words are you having an anemia that's causing fatigue, having a low white count with lots of

infections? Is your platelet counts making you susceptible to bleeding? So, it's not just low blood counts but how low they are is importance.

What's your performance status? Excellent, good or poor. That makes a difference in whether or not you can, for example, receive high intensity therapy and then the prognostic risk category and I've told you that there's lower risk and higher risk patients and for the lower risk hematologic improvement is the plan. For higher risk the plan is for trying to alter disease natural history and then are you a stem cell transplant candidate? We looked at the risk category, age, performance status and whether you have a donor and Dr. Muffy will be talking about that in great detail for one the next... not the next talk but the second talk from now.

So, what kind of treatment is there? In blue you have patients that are relatively lower risk and red, higher risk, and we have patients with 5Q-, Del 5Q. Lenalidomide I just mentioned to you is a drug that is quite useful. About 60 percent of patients will have improvement of their blood counts when they get this drug. For patients with refractory anemia and ring sideroblasts we have Erythropoietin and G-CSF. For all anemias particularly those with low EPO levels those individuals can get EPO alone. For some patients that are relatively young and have essentially low risk disease the use of immunotherapy can be useful and those individuals that lack response to these then clinical trials are suggested. Higher risk patients I've mentioned Azacitidine and Decitabine. Those drugs hypomethylating agents are the standard agents that can be used and I'll show you some evidence to suggest why that's being used in a moment and for individuals that are young enough and who are in good enough shape and have a donor transplant and so you can see that most patients are not going to be receiving transplant as of yet. However, the hope is that this will be expanded over the next few years as donor selection and the ability to deal with the complications of transplant improve.

Now, what about the use of Erythropoietin? Most of you have been treated with one or another form of Erythropoietin if you have anemia. Important to try to decide whether you should get that depends on what your baseline level of Erythropoietin is. We all make that hormone in the kidney, but if it's relatively low, if the ferritin level is okay and our risk score is relatively low we can have up to an 80 percent chance of response. However, in higher risk individuals or if the EPO level is very high the response rate is much lower. So, you can see that depending on these features that goes into the equation as to whether or not you're recommended to have treatment with an Erythropoietic substance.

Lenalidomide. So, this is a drug that is useful for patients with 5Q- and as you can see in individuals with that subgroup as I mentioned 60 percent durability of response can be quite good and is something that can be quite useful.

I've mentioned Azacitidine and Azacitidine is used for higher risk patients and in that group of patients you can see survival is much improved compared to individuals that have conventional care. As a result this drug was approved for use and is something that has been used since 2005

or '06. Decitabine has similar response rate and also is something that can be used is usually used in situations when one needs to move more quickly. It works a little bit more rapidly than Azacitidine.

Now, the molecular subgroups that I just indicated and Dr. Aleshin will be talking about this in more detail, but I mentioned SF3B1, good risk and there's a new drug that's coming out. That's called Luspatercept. It's in the midst of clinical trials, but those trials the data for which will be available probably within the next year. If positive the drug will be put on the market and be FDA approved. About 60 percent of patients with ring sideroblasts are going to have responded and are likely to respond in future. So, this will be a very valuable drug most likely that will be available within about a year for that subgroup of patients. Much less so for patients that have other forms of anemia. There are genes that are mutated in which there are splice gene modulators that are available and this is something we'll talk about a little bit more detail. P53 is a mutation that is poor risk and individuals that have this may respond to Decitabine and also a new P53 modulator. IDH2, a mutation here. There's a new drug that has become available commercially and is available for this subgroup of patients and Dr. Aleshin will talk about that in more detail and I've told you that for patients with 5Q- subtype of MDS Lenalidomide is a very useful drug.

Now, what about iron chelation? As you know individuals with getting many transfusions can have iron overload and that can cause some degree of organ dysfunction, liver, heart, pancreas, pituitary. There are a variety of changes that can occur, but it takes a large number of transfusions for them to get that way and so if patients have symptomatic anemia and further need for transfusions and this number of transfusions that are low risk or are bone marrow transplant candidates, the use of iron chelation is considered, is strongly considered and reasonable. However, there is no prospective data that say that will change natural history outcome or organ function. We use it for patients that have preexisting evidence of organ dysfunction such as cardiac (inaudible 18:11), but that's the subgroup that is mainly important. If patient's serum ferritin is over 2,500 we attempt to decrease it down to 1,000. So, the drugs that are available, Deferasirox or Deferoxamine. As you notice, I'm not using the trade names. The trade names are not up here and hopefully you (inaudible 18:33) of what the trade names are. If not raise your hand and I'll go through that with you in more detail. This is Exjade, Deferasirox. Lenalidomide is Revlimid. Azacitidine is Vidaza. Decitabine is Dacogen. So, those are the trade names, but I'm not putting them in writing.

What about future? The future, Dr. Aleshin will go into the fact that there are diagnostic, prognostic, pathogenetic and therapeutic reasons that one is going to look at the molecular mutations and the potential for them to be valuable in addition to the clinical features that I've already discussed with you.

I've told you about Luspatercept and Luspatercept is something that will likely be useful over the next few years for patients with ring sideroblasts and you're reading in the newspapers about

immune therapy for a variety of cancers. Well, in MDS that's also happening and the main point is that if you have patients that have cancer cells that will block your own immune system from working there's now antibodies that will go after these to stop the blockade and permit your T cells to work more effectively and so there are clinical trials with that including one that we're using here at Stanford to try to help responses. Splice gene mutations can occur in a substantial number of patients with MDS, acute leukemia and chronic myelomonocytic leukemia and so if one can block some of these mutations it's possible useful responses could occur and so here at Stanford in our MDS center we have a number of clinical trials that are ongoing. We've completed a trial with Exjade, with Luspatercept. We've completed a trial with both of those and we have ongoing a splice gene modulator trial that is something that are using with lower and higher risk disease and as I've mentioned the immune therapy Azacitidine plus that inhibitor is being used here and Stanford and the people that are crucial for us here for the clinical trials Evita Campbell, Mark Santos and Alex Aleshin who you'll be hearing about are doing a lot of the legwork for these trials.

Resources for you. If you need information include the MDS Foundation where you've probably seen much of the information that comes. The Aplastic Anemia and MDS Foundation has some useful information as well. The Leukemia and Lymphoma Society is here and also has a table that has lots of useful information you can get. The NCCN, you have access to that for looking at the guidelines and practice arrangements that are being used for these individuals and the Stanford MDS Center.

So, the directions to where the field is going is that we try to restructure classification and treatment. Molecular mutation characteristics, biologically activated treatments that are going on, stem cell transformation and stem cell transplantation will occur and quality of life evaluations and all of these will be covered in the subsequent talks in this session. Biology and economic situations are also being considered because certainly we need broad based forums to try to decrease costs in patients for the drugs that are there.

So, with that I want to thank you for your attention and open this up for some questions. Please. Yes?

Q1: Yes. I'd like to ask a question of iron overload. I take Exjade. Have an average ferritin of probably around 3,200 and just recently I was diagnosed with congestive heart failure and I'm wondering you mentioned the heart and the liver. Have you found in your particular practice that you do see patients from time to time where they do end up with congestive heart failure because of the iron overload?

Peter Greenberg, MD: The issue of congestive heart failure is a very important one. It's a major complication of patients with MDS, but be aware that it's also a very common abnormality in patients over the age of 60 and 65. So, it's a disease that does occur independent of MDS, number one; 2) anemia per se, long standing anemia, can cause your heart to work too hard as

well and so can contribute to congestive heart failure. So, management of congestive heart failure is very important, controlling the anemia and controlling the other potential causes for it. Now, in addition it is true that patients with iron overload may develop some degree of iron deposition in the heart and that can contribute. What hasn't been shown is that if one uses Exjade you can modify this very effectively. Logic says for us to try to do that and make a change, but as you know Mother Nature doesn't always speak the way we do as well and the language we speak is not hers. So, we use it for patients with congestive heart failure to try to decrease the problems but realize that there are other approaches that are also needed for such patients.

Q1: Well, I'm having a cardiac MRI done on Tuesday and that's what they're looking to... they're doing a study to see about the iron on my heart. So...

Peter Greenberg, MD: That's right. So, that is one of the things that one can tell whether or not there is increased iron overload that's occurring with you and certainly if that's present logic would say it's very reasonable to use Exjade to try to diminish the iron overload.

Q1: Thank you.

Peter Greenberg, MD: Okay. Yes?

Q2: Hello, Dr. Greenberg. So, for a year or maybe two years I was diagnosed with MDS, but the most recent bone biopsy came back and said there wasn't a sign of MDS. Is that something that happens very often and why?

Peter Greenberg, MD: Is that... have you been treated with anything?

Q2: Pardon?

Peter Greenberg, MD: Have you been treated with anything?

Q2: Revlimid just before that biopsy.

Peter Greenberg, MD: And when you were treated was there a reason you were treated with Revlimid? In other words did you have anemia and where...

Q2: Yes.

Peter Greenberg, MD: ... told that you had a chromosomal abnormality that was present?

Q2: Yes.

Peter Greenberg, MD: Was that 5Q-?

Q2: Pardon? No, it wasn't.

Peter Greenberg, MD: And so you had some abnormalities and anemia and you were treated with Revlimid.

Q2: Yes.

Peter Greenberg, MD: Okay. Well, that's useful and when we use treatments of one kind or another certainly we can diminish the number of blasts that are there and change the degree of dysplasia. However, whether or not you have MDS or not really requires review, not just of your marrow morphology, but as you'll hear from Dr. Aleshin mutations to know. Be that as it may the fact that your marrow and your blood counts are normal. It's terrific. So, occasionally one can get...

Q2: They're not normal.

Peter Greenberg, MD: They're not normal.

Q2: So, I'm not diagnosed with aplastic anemia. Red cell aplasia. Excuse me.

Peter Greenberg, MD: So, you are still anemic.

Q2: Yes.

Peter Greenberg, MD: Is that right? Well, certainly your MDS is not gone and when we really need to evaluate what the cause of your persistent anemia is. Are you still taking Revlimid?

Q2: No.

Peter Greenberg, MD: Alright. So, that again as I mentioned it's very good for patients with 5Q-. For those individuals that don't have that it is not so effective and other treatments really are necessary. Have you been treated with EPO, with Procrit, things of that nature?

Q2: No because I had high numbers in those things.

Peter Greenberg, MD: So, in individuals with very high levels of EPO and who don't respond other therapies are needed including potentially Azacitidine. So, I wouldn't use the term that you no longer have MDS, but you have an anemia that started with MDS that needs further evaluation.

Q2: Thank you.

Peter Greenberg, MD: Yeah. Yes?

Q3: (inaudible 27:18) how often do you have a patient (inaudible) that has a (inaudible) because for my (inaudible) she has a very low platelets like around 60. So, she's really afraid of taking the Exjade, but the ferritin of 1,200 right now. So we're like in dilemma if the side effect of Exjade is really (inaudible).

Peter Greenberg, MD: Well, you mentioned that her ferritin is about 1,000, but what about the number of transfusions that she's had. Do you know?

Q3: Right now it's getting better. It used to be every two weeks, two packs of ROBCs.

Peter Greenberg, MD: For how long has that been going on?

Q3: It's been like a year already.

Peter Greenberg, MD: Okay. So, that means for a year if she's had four units a month, do you think? Is that roughly what's happened?

Q3: Probably.

Peter Greenberg, MD: So, she's had perhaps up to 40. So, if she's that number of transfusions the potential for giving her Exjade is reasonable. The main side effect of Exjade is kidney problems not so much bleeding. So, kidney problems can become problem. You need to be monitored very carefully. Usually it doesn't cause problems with bleeding. So, it may be her platelets per se are the things that are causing this rather than the Exjade or she may have some bleeding lesions somewhere that's causing a problem. So, that needs to be looked at.

Q3: Okay. Thank you, doctor.

Peter Greenberg, MD: Yes, in the back? Yeah.

Q4: Yes. I've got MDS with ring sideroblasts and I also have hematomachrosis (sp? 29:03). I'm looking to do a stem cell transplant. I see that having dental work is recommended before that, but I'm already starting my... I've already finished my first round of chemo with Azacitidine. Now, my platelets are still good and I just have one cytopenia which is red blood cells at this point. Now, should I get my dental work done now before the rest of my counts presumably fall with the two more rounds of chemotherapy I've been scheduled to do presumably before a stem cell transplant at the beginning of the year here or should I just leave it as is?

Peter Greenberg, MD: Well, certainly prior to transplant you having dental work done effectively is a good idea. So, anytime between now and then would be very reasonable.

Q4: As long as my counts and my platelets, are good?

Peter Greenberg, MD: Yes.

Q4: Okay. Thank you.

Peter Greenberg, MD: Yes?

Q5: When do you start monitoring the iron level when the patient get too many transfusions?

Peter Greenberg, MD: Right. When patients have received anywhere from 20 to 40 total units of transfusions by definition they're already iron overloaded. You don't need to even measure the ferritin, but you can measure it. So, at that point in time we begin that and as I mentioned whether or not to treat patients depends on whether they have preexisting heart disease, whether they may be transplant candidates, whether they're low risk and they're going to continue to receive many transfusions. So, that's generally the plan for use of Exjade.

Q5: So, there is no symptom when you have...?

Peter Greenberg, MD: No, you don't necessarily have any symptoms from iron overload. That's true.

Q6: Hi, Dr. Greenberg. I'm two years post BMT, bone marrow transplant, and my question I had these atrial contractions, ventricle contractions, palpitations. This was years before the BMT, but now it seems like I've been having frequent contractions, palpitations, and I think it's related to the iron overload. I'm getting phlebotomies and my ferritin level has been dropping. It's, I think, about 1,256 now, but it seems like my palpitations have been increasing. Do you think it's related to this iron overload my heart palpitations? That's my question.

Peter Greenberg, MD: One question would be did you have many transfusions prior to your transplant?

Q6: Yes. I had about maybe about 15 transfusions.

Peter Greenberg, MD: Fifteen?

Q6: Yeah. I was up to 3,200, a level, ferritin.

Peter Greenberg, MD: Yes. As I mentioned the ferritin level is less important than the total number of transfusions. So, it's not clear that you've had a huge number of red cells to give you adequate iron overload. As mentioned before, MRIs to look at your heart for iron is one way to evaluate that. However, more importantly there is no problem with you getting iron chelation treatment, but more importantly you need to have your cardiologist spend a lot of time with you on medication for management of your cardiac dysfunction.

Q6: Okay. Yeah. I'm getting phlebotomies now. I'm down to 1,256. So, you advise just continue with the phlebotomies?

Peter Greenberg, MD: Phlebotomies are reasonable as long as your hemoglobin holds up okay, but I...

Q6: It is.

Peter Greenberg, MD: I think most importantly is be sure that your cardiologist is in tune with what is going on.

Q6: Okay. I haven't seen a cardio... she thinks it's minor. I went through all that. The cardiograms, I mean, the echocardiogram test and she advises just continue with the beta blockers. I don't know if that's... but do you think it's serious the palpitations? That's my last question.

Peter Greenberg, MD: Well, that's the question for your cardiologist not for me at this (inaudible 33:46).

Q6: Okay.

Peter Greenberg, MD: Okay. One more question maybe one or two questions. Yes, sir?

Q7: Hi. I had number 68 blood transfusion yesterday. My ferritin seems to jump all over the place. It was as high as 5,200 and then down to 3,200 and then up to 4,800 and I've stopped right now taking Exjade because I've been just started on Revl... and this all came about two years ago. I've been dealing with carcinoid cancer for many years and I went to the PRRT program and all of a sudden I had MDS. So, I'm dealing with two different things here and I just am curious about the number of your ferritin is that high is there a certain limit that you see it go to when all of a sudden other things start to happen or what? I'm getting around pretty good. I'm operating at a hemoglobin of six to 6.5 for the last couple of years and getting around pretty good but it's always in the back of my mind where is this ferritin going?

Peter Greenberg, MD: Right. Well, the ferritin levels that you mention are quite variable. They can occur as increased in anybody with any inflammation or infection but more importantly they

can change with transfusions themselves. So, depending on how close you get the level drawn after your transfusions that level can jump. So, as soon as you get a transfusion it'll jump up and then several weeks later it may decrease. So, we don't necessarily use that as the marker. As I mentioned it's the total number that's important and if you've had that number certainly you have some degree of iron overload whether it's playing a role in changing your outcome or your organ function is another question and so that's something that one needs to evaluate. Your heart, liver, pancreas to see and if it's there then it's reasonable to do something with Exjade. Now, there's no contraindication to using that when you're getting Revlimid. Revlimid, the side effects are drop in blood counts. So, you're dropping a platelet count and a white count. As long as that's monitored carefully that's okay. There's nothing that says you shouldn't necessarily get the Exjade during that time. It's your kidney function that's most important. Okay?

Q7: Thank you.

Peter Greenberg, MD: Perhaps one more question. Yes?

Q8: At what point do you recommend that a person gets a blood transfusion?

Peter Greenberg, MD: Okay. That's a complicated question. You might think it's simple in that a lot of it depends on the hospital itself. They have guidelines as to what level they will accept a transfusion. Some hospitals will say a hemoglobin of nine, some say eight, some say seven. What we use here is when people are symptomatic. So, I don't use a number and so in patients that have cardiopulmonary disease they may be symptomatic at 9 ½ or even 10 so that at that point in time we'll say patients are symptomatic. Give it to them there and as mentioned long term anemias can cause cardiac dysfunction. So, I think that one would try to keep people functional at a level that fits them. As people age then they need a higher level. At higher altitude they may need a higher level. So, each individual I think needs to determine where's he symptomatic, notify his physician and the physician then should have some degree of ability to respond to that.

Q8: What symptoms in particular are you...?

Peter Greenberg, MD: Fatigue. Severe fatigue is really it, disband fatigue, shortness of breath. Yes.

Q8: Thank you.

Q9: Related to that what about for platelets? When do you decide that... related to that question (inaudible 37:56) platelets?

Peter Greenberg, MD: We don't transfuse for platelet. Platelet, if platelets are below 10,000 those are... that's usually a place where we consider transfusions. Less than 20,000 if there's

bleeding we will consider transfusions. So, that's not hard or fast, but it's certainly important. Those issues are very important to try to determine as to when people will get transfusions. Yeah?

Q10: I was diagnosed with the 5Q and I was on Revlimid for about three months and then I had an allergic reaction to it, a swelling and a rash, and my counts had were good then. They came back into the normal range, but anyway they took me off of the Revlimid and for about a year and a half to eight months, a year and eight months, my counts have been stable. Now, my question is when my counts start dropping again and to a certain point, say 10, can I start the Revlimid again even though I did show a reaction to it?

Peter Greenberg, MD: Yes. That's not... that's a common... not a common problem, but it's something that happens not infrequently and so in situations like that occasionally what we'll use is steroids, Prednisone, to try to diminish the allergic reaction that can occur with Revlimid and that's something that you should be able to restart as long as it's covered well with the immunosuppressant (inaudible 39:37).

Q10: So, it could bring them back up again for a second time.

Peter Greenberg, MD: That's right. Yeah.

Q10: Good to know. Thank you.

Peter Greenberg, MD: Okay. Perhaps one last question.

Q11: Yeah, Doctor, my wife has a diagnosis of MDS years ago and she's just... she's not been receiving any medications and she's been mildly anemic and now the latest lab reports we got just two days ago suddenly show a sudden drop in the hematocrit, hemoglobin and the red blood cell count. The lowest it's been in over two years. So, I just wondered what action should we be taking.

Peter Greenberg, MD: What are the numbers? What's the number of the hemoglobin?

Q11: The hemoglobin is 10.8.

Peter Greenberg, MD: And what about the other blood counts are okay?

Q11: 3.32 is the red blood cells.

Peter Greenberg, MD: And what about her white count and platelet count?

Q11: Well, the platelet count (inaudible 40:47) is 204.

Peter Greenberg, MD: Okay. So, a hemoglobin of 10 that begins to indicate that she may become symptomatic below 10. Many people are. It's not hazardous, but it's something that should be evaluated. Right at this point then what should happen is her blood should be drawn to see what her serum erythropoietin level is. If it's relatively low and she becomes symptomatic she could start on Procrit on some erythropoietic stimulating agent. So, that's a standard approach. Your physician should just respond to your query about what to do for that hemoglobin of 10 and generally this is what would be done. It shows some change in the illness. It's possible the patient would need a repeat bone marrow soon as well to here to see what's going on.

Okay. There'll be time for questions further after each of the talks and at the end of the day as well. So, I'd like to now move on and introduce Dr. Alex Aleshin, a fellow in hematology here who's doing some great work in the clinic with clinical trials and evaluation of mutations in MDS. So, Alex, please.

(Applause)

Audrey Hassan: And I just want to remind everybody that if you have a question just raise your hand. It's being audio recorded, so we want to make sure that your questions are being heard. Thank you.

Alex Aleshin, MD: Can everyone hear me? No? Alrighty. Alright. Let's give this another try? How's that coming through in the back? Good? Alrighty.

Well, first of all thank you, Dr. Greenberg, for that introduction and thank you all for being here today on this Saturday morning. Today, I wanted to spend a little time talking about some of the molecular advances in MDS and how they're starting to change how we not only look at the disease but how we're starting to change management based on some of these mutations we're finding.

So, these are the topics I want us to cover today. So, before we kind of delve into the actual nitty gritty details I want to review exactly what are genomics and if we look back to our biology days in high school we can see that each cell has a genome and that genome is composed of chromosomes and the chromosomes are basically collections of genes and we have 46 chromosomes, 23 from mom and 23 from dad. Each chromosome is composed of a number of genes and in total there's around 20,000 genes that we all have and each gene actually is then further composed of nucleotides and these are the A, C, T, and Gs which actually make up our genetic code. Deviations also known as mutations and there's a few kind of mutations that can occur all through this genetic code and sometimes cause the genes to function improperly either turning on a gene when it should be off or turning off a gene when it should be on and we think that that's really the fundamental basis of most malignancy, MDS being not excluded. So, even

though we've known this now for quite a while, a few decades, it's only recently that this become clinically actionable and just like there's been a rise in super computing power of going from these large mainframes to minicomputers and now personal computers that can do what these computers used to do in a fraction of the time and cost there's been the same type of explosion in genetic sequencing technology. So, while in the '60s and '70s gel base sequencing would take weeks to sometimes months or even longer to sequence just one gene with the event of Sanger sequencing in the '80s and '90s that time was cut down to just a few weeks and the costs started dropping into the tens of thousand dollars. Still too expensive for routine clinical use, but now just in the last decade next generation sequencing which we'll spend a little time talking more about later has really cut down the cost to the point now that multiple genes can be sequenced for a cost in the few thousand of dollar range usually in the now range of just a few days to sometimes weeks and this is really allowed us to bring this knowledge into the clinic and this is an fairly impressive graph. You can see this is Moore's Law. This is the classical law that says how computing power increases with time and below this you can see that actually sequencing costs have dropped faster than Moore's Law and, again, this is really opened up sequencing into the clinic. So, while the first human genome took over 10 years and over \$1 billion to sequence currently an entire genome can be sequenced for a range in cost of a few thousand dollars and the shortest just a few weeks and so with this increase in technological sequencing capacity we've had an extreme exposing in the number of genomic discoveries both in cancer as well as noncancerous state and MDS has been no exception and we've definitely benefit in the MDS community from all of these sequencing discoveries.

So, how does this relate to MDS and what can sequencing and understanding of the genomics of MDS do for our patients? Well, historically hematology oncology has been really an imperfect art. So, while in many disease states response rates for various medicines have been fairly high and oncology across the board the response rates to any individual therapies fairly low. So, for things like Azacitidine or Decitabine the response rates are not 100 percent. We know that many patients who are treated with those therapies respond for a short amount of time, don't respond at all or have a suboptimal response and because of that what we frequently do in MDS and many other malignancies is this kind of step wise approach to treatment. We try one therapy. If it works, great, but if it doesn't then we move onto therapy B, etc. and etc. and while this works there is a problem. Using therapies that are ineffective is not only costly, but it can take up time and there are side effects that can be associated with these therapies. So, if we could predict early which therapy is going to work for which patient that would really be the end goal and because of this we're more and more starting to think about precision or personalized medicine and this is really a subtype of medicine in oncology where we're trying to identify the right therapy and the right kind of prognosis for each individual patient. So, historically we've been looking at diagnoses in a histologic or morphologic manner. So, these cells look this way and we're going to group them as an MDS, for example, of ring sideroblasts. More and more we're now adding molecular classifications to these pathological ones. So now we're saying you have MDS with ring sideroblasts and a mutation and that mutation frequently for this subtype of disease is

SF3B1, for example. So, really the mutational status is helping to refine the diagnosis and starting to early on now to actually change management in some cases.

So, before we actually dive into the mutations it's really good to kind of break down the mutations into two big subcategories. One of them are somatic mutations and the other ones are germ line mutations. Somatic mutations are kind of these wear and tear mutations. They happen in all of our cells with age and usually are accelerated by toxins like pollution and tobacco smoke. These mutations are not inherited. So, there's no chance of passing these onto our children while germ line mutations are inherited mutations that are frequently passed down from generation to generation and can increase in rare instances risks for diseases such as MDS. Somatic mutations by far the more important mutations for MDS and we'll spend the bulk of our time talking about them.

So, again, with all of the sequencing power we really have a better picture of what mutations are important in MDS and this is just a small list of the mutations that are important, but the main ones that we look at clinically. So, the mutational landscape as you can see is composed of five or six main types of mutations. There are these proliferative mutations and these are mutations that make MDS cells grow and divide a little bit faster and some of these mutations are associated with more aggressive forms of MDS or are associated with MDS turning into a leukemia. As you can imagine if a mutation gives the MDS also proliferative advantage it can divide quicker it can become a more aggressive disease. Furthermore there are these epigenetic mutations and these are mutations that are...

Q12: Can you speak up please?

Alex Aleshin, MD: Of course. The epigenetic mutations are probably the more common mutations found in MDS and these mutations basically cause the MDS cells not to be able to regulate turning on and turnoff their DNA. Additionally, there are mutations that are involved in differentiation and these are mutations that allow the cells to basically become healthy red blood cells, platelets or neutrophils and so that mutation is present that process can occur and because of that sometimes the blood counts can be low. Furthermore there are mutations in RNA splicing and these are mutations that don't allow normal DNA to make normal proteins and there's a lot of interest as we'll discuss later in developing therapies to address some of these genetic defects. Furthermore, we're now beginning to realize that all these mutations are not the same. So, even though we need mutations to cause a cancer, some of these mutations don't necessarily increase the risk that this cancer will progress, but some of them do and the ones in blue are the ones that have been associated with a slightly worse prognosis for the MDS. So, again, knowing that information can help refine and better kind of let us know just what is the risk that the MDS will change over time? Again, I don't want to you actually look at any of the specifics here, but again we're now realizing that the same mutations we saw previously are associated with subtypes of MDS. So, MDS with ring sideroblasts has a set of mutations. MDS with excess blasts, for

example, has another set of mutations and this has really helped us now to begin to see MDS as a molecular disease.

So, what may we do sometimes in clinic and you may have heard of these panel tests and these are some of the tests done by companies like GenOptics, GenPath, Foundation One. These are panels of genes that are important in MDS the same genes we looked at previously in the slide that we can now test in parallel. So, before we would test one gene at a time. If it was abnormal we'd stop and then if it was not we'd test maybe another gene, but now we can just test many, many genes at one time and this is a panel test that many of us will order for some of our patients especially if we think it's going to be clinically useful. These panels typically now are taking between two to three weeks to come back and this used to be in the order of months. So, this is getting much quicker now.

So, what can some of these genetic panels and what kind of understanding of the mutations in MDS help us with? Well, right now these can help support or refine a diagnosis. It can also help with risk stratification basically knowing which MDS is going to be likely to progress and which is not. We can also identify potential therapeutic targets. For example, these IDH2 mutations which are involved in differentiation and metabolism now have drugs associated with those which are truly personalized therapies that really attack just the cells, just the MDS cells that have those specific mutations and then more importantly we think in the future we can use these panels to monitor disease over time. How do the mutations change over time or in response to therapy and can we use that in addition to the blood counts and symptoms to see who's really responding, who's not and should we be able to be able to pick up changes that may herald progression earlier. So, for the first category, supporting or refining the diagnosis I think frequently sometimes we see patients whose diagnosis is very suggestive of MDS, but there may be extraneous circumstances that makes that diagnosis harder to make. For example, an autoimmune disease there can be evidence of dysplasia in the bone marrow as well as cytopenias and in situations like that mutational status may be helpful to establish a diagnosis of MDS and we think right now it's not necessary to build the mutations to diagnosis the MDS state, but can be helpful to, again, support a diagnosis when the diagnosis sometimes in doubt. As you can see, MDS is frequently associated with mutations. However, states that are not MDS frequently don't have mutations in them. So, again, mutational analysis in cases where the diagnosis is uncertain can be helpful.

Furthermore, risk stratification right now is the primary use for mutational analysis in MDS. There are two types of mutations, mutations that are prognostic and mutations that are predictive. Prognostic mutations basically help us differentiate the prognosis of MDS on top of what's suggested by some of the standard prognostic features that Dr. Greenberg has discussed. For example, if you have an SF3B1 mutation we know that in a low risk MDS patient this confers a further increase in prognosis. So, these patients do even better while if it's not mutated well, then there's no change in the prognosis. However, we're also really interested in finding and characterizing predictive mutations. A classical example here is deletion 5Q. So, if a deletion 5Q

is present we know that more likely than not Revlimid will work. However, if this mutation is not present Revlimid can still work, but it's less likely to work. So, again, this is an example of a predictive mutation.

So, again, this is just basically kind of driving home the points that, for example, the SF3B1 mutation is associated with a much better prognosis while certain mutations like ASXL1 are associated with a slightly worse prognosis and the more mutations we have this is going from a no mutations to three or more mutations. The more mutations we have the prognosis drops slightly as well because as you can imagine the more mutationally complex the cancer is the more likely it's going to be resistant to therapy and more likely it is to evolve and this is shown here in the data.

The last thing I wanted to discuss is disease monitoring. So, right now we're really monitoring disease by the degree of cytopenias and by the changes in the bone marrow over time. However, there is emerging research that the molecular signature can also be used to look at disease and see how it changes and this is an example of one patient where this was done and you can see that over time and in response to various therapies the proportion of mutations, changes and new mutations evolve and some of these new mutations appear to be associated with the disease progression. So, again, even though this is something we're not routinely doing, we think in the future with more data this is something we can start doing and this is in a way you can think of as almost a liquid biopsy, a biopsy of the blood that can be used to track the disease over time.

So, how can we use some of this for treatment selection purposes? I think Dr. Greenberg did a great job overviewing some of the novel therapies in MDS, but again I just want to highlight that for MDS states with splices or mutations there's a new therapy that we're looking at here at Stanford in clinical trials that, again, addresses that specific mutation and the thinking here, again, this is a personalized therapy that's only attacking the mutated cells and hopefully having less toxicity in the normal healthy cells. SF3B1 mutated cancers, again, this is frequently associated with ring sideroblasts appear to benefit from Luspatercept and these trials are now finishing up and we're waiting for some of these readouts soon. Deletion 5Q is associated with sensitivity to Lenalidomide as we discussed previously and there's actually many more examples of other mutations that may have potential therapeutic implications and this is being more and more looked at now in clinical trials.

Also I wanted to spend a few minutes talking about hereditary MDS. So, again, just kind of refresh somatic mutations, not inherited germ line mutations are inherited. In genomics we say that all cancer is genetic, but only 10 percent is inherited. In MDS this number is actually much lower. So, this 10 percent is across the board for all cancer types and MDS we think the number of inherited MDS states is actually much lower than 10 percent maybe even lower than five percent and the kind of states that may predispose somebody to MDS are some of these familial MDS AML syndromes, some inherited bone marrow failure syndromes and then some familial cancers predisposition syndromes which are usually associated with other cancers as well. Again,

these are diagnoses that are very rare, but we're beginning to look for some of these if the right symptoms are present in our patients and actually starting to test for these as well. So, people as me all the time doctor, should I be tested for an inherited MDS state? And these are kind of the criteria that... these are the benefits of the testing because right now maybe 20 years ago knowing if something was an inherited MDS state not much could be done, but now we think the benefits of testing may allow us to modify cancer surveillance for some of these cancer states. We can suggest risk reductive measures for other risks associated with some of these inherited states, clarify some familial risks, offer guidance in settings like a bone marrow transplant where knowing if there's a very rare inherited bone marrow state may change the therapy as well as identify other family members that may be at risk.

So, what are some of these red flags that if are present sometimes may suggest discussing with your physician about possible testing? Again, these are not deterministic, but if, again, any of these are familiar to you it may be worth discussing with your physician if testing for heredity MDS state makes sense.

And then I just want to close off on some of the future directions in our field. So, more and more in addition to doing pathological and some clinical tests, we're beginning integrate molecular testing in our clinical workflow and this is now allowing us not only to refine prognosis but more and more to select the right therapy for the right patient and more importantly right now at least it's allowing us to look for right clinical trials that are enrolling based on specific mutations and hopefully from all of the clinical trial knowledge this will then flow into developing new therapies that can be used clinically.

And with that I kind of want to finish and I'll be able to take questions at this time. Thank you.

(Applause)

Q13: You were talking about mutations and I have MDS and I have two cytopenias. I have a blast count around 10 percent give and take. My specialist has suggested a BMT and yet I believe she did the full (inaudible 1:02:51) of gene mutation, the panel, and she said that she saw no mutations. So, what I'm wondering is if you could provide a brief explanation if there are no mutations why are my blasts behaving badly?

Alex Aleshin, MD: Right. I think that's a great question. So, currently we're only testing for between 50 to sometimes 100 genes and we know that there's 20,000 genes in the human genome. So, right now we're only testing for kind of the hot spot regions of the most likely mutated genes, but we know that there are many, many MDS states that have mutations outside of the genes we're testing and we're kind of beginning to expand the range of genes tested, but again that requires more and more research to identify the very rare variance and if we look across all cancer states the mutation rate of MDS is one of the lowest for all cancers. On average it's around one mutation per mega base. For example, something like melanoma, the mutation

rate is 10 to 100 times higher. So, MDS typically has fewer mutations than other cancers. In many patients we identify only one or even sometimes zero mutations. So, that's completely normal.

Q13: So, then I just finish up and make sure I got it if I paraphrase. So, they didn't see any mutations, but that was simply because they only looked at a small slice of the 20,000 or whatever it is and so in effect the luck of the draw was bad luck for me. They didn't find the one that was mutated and maybe even if they did I don't know what it would tell them.

Alex Aleshin, MD: I mean, I think it's in a way fairly... I would say it's risk neutral. So, again, I think the mutations that may be implicating your MDS have not been well described and we don't know their therapeutic or prognostic implications. So, I would just leave it at that.

Q13: Okay. Thank you.

Q14: Is there a standard of care now for the mutations that are tested for or is that hospital dependent/provider dependent?

Alex Aleshin, MD: That's a great question. So, we think that some of the very, very common the ones with the really big circles really are a fairly standard of care. So, all major molecular panels will include those. Some of the more rare ones with the smaller circles and especially if they're not associated with any kind of specific therapeutics or strong prognostic implications some panels don't include those right now, but clearly the trend has been to do larger and larger panels, but we have to always balance that because more knowledge if it's not well researched is not better knowledge necessarily, because again we find a mutation that's not been super well described frequently as clinicians we don't know what to do with it. So, we're constantly always balancing this expansion of panels with kind of our expanding clinical and research knowledge of what these mutations mean.

Q15: My question is once a patient has a somatic mutation I presume that they'll always have that or do you ever see when you follow disease progression that a mutation is not detected?

Alex Aleshin, MD: Yes. So, we're now beginning to see that therapy monitoring can occur with some of these panels. Again, this is not ready for clinical use, but in some of the research papers it seems that some of these mutations can go down in response to therapy and disappear or new ones can evolve. So, again, there's definitely flux in these somatic mutations because, again, these are cancer specific mutations. So, there's less cancer there should be less mutations.

Q15: Could I ask does the test that you use amplify the genes that you're looking for or are you just looking for the base like number of copies that a patient might have. So, could it just be a detection problem when you're not seeing...?

Alex Aleshin, MD: Right. For sure. So, we only can look for mutations above a certain point in the blood or the bone marrow. We think the mutations that we may miss at very low levels may not be as important. It seems that mutations that are at high levels are the ones that really matter most and we all have mutations that are present in very, very low levels that probably are not clinically significant. So, we think the current testing is set up to detect, again, the mutations that are most likely to be clinically beneficial to know about.

Q15: Thank you.

Q16: Doctor, may I ask for my mom's FISH panel analysis it says here 7Q 31 deletion. It's positive 20.18 percent. How's the prognosis and what's the usual treatment for...?

Alex Aleshin, MD: So, I think, again, cytogenetics and mutations are slightly different. So, cytogenetics are where we traditionally use to assign prognosis and that's part of the IPSS and the IPSS-R criteria. So, remember the chromosomes and that's what the cytogenetics look at are those building blocks composed of many genes. Mutations are actually smaller kind of mutations in the DNA within the chromosome. So, what you're describing is a common cytogenic abnormality in MDS that is used as part of the IPSS-R criteria.

Q16: It's not like, for example, you are positive for a 5Q 31 deletion. Revlimid is the treatment of choice.

Alex Aleshin, MD: Right. That's the cytogenic.

Q16: But for her case do we have a treatment of choice?

Alex Aleshin, MD: So, for that mutation it's prognostic, but it's not predictive. So, there's not necessarily a therapy we'd use just for that mutation, but again we would use that knowledge in part of our larger prognostic guidelines to then assign a prognosis and treat her on that, but I would say just knowing that by itself I wouldn't be able to make a treatment recommendation. We have to look at the whole picture.

Q17: Hi. I have a question. I'm over here. I listen to a "TED Talk." These are always dangerous things for physicians I imagine and it was a person who was talking about open sourcing molecules in hopes that these open source molecules could eventually make gene therapy and it was a researcher at Dana Farber Cancer Institute and I'm sorry I don't remember his name, but one of the questions I have this particular "TED Talk" was on originally aired in 2015 and repeated this summer and one of the questions I have is when is there going to be a new therapy? Is it if you're in a mild state of MDS would it be worth putting off wondering about these gene therapy because his new molecules were talking about rebuilding cells so that they looked normal. So, they took blasts and made them look like what they should look like. I'm just curious

about that and I don't know if this is the appropriate time to ask that question, but I thought you might have more information. Thank you.

Alex Aleshin, MD: Sure. Yeah. Of course. So, I think the first question about low versus higher risk MDS. So, right now for lower risk MDS we really focus mostly on controlling the symptoms because, again, lower risk MDS you can live with lower risk MDS for a long, long time. You can possibly die with lower risk MDS for something else and not from the MDS. So, doing experimental therapies for lower risk MDS is typically something we don't do right now. We focus mostly on the modification of symptoms, treating the anemia, raising the platelets, etc. For higher risk MDS, I think that's definitely a different story and gene therapy is definitely something that's being looked at, but it's very, very, very early days because being able to effectively replace all of the mutations and all of the cells is really hard to do right now and if, again, things like gene therapy are not able to fix all the cells then the cells that are left over have a chance to come back. So, definitely something that's being looked at across the country, but I think it's very, very far away from actually being an effective treatment for many patients.

Thank you.

Q18: To follow up on that earlier discussion about mutations and then not finding any but only looking at a small portion my limited understanding leads me to believe that if my blasts aren't maturing correctly and are growing and the other part, the good parts, are reducing then something is triggering that behavior and I'm assuming that it's genetic. This is where you come in. So, if it's genetic and I get a BMT and I get new stem cells what's to stop whatever genetics it was causing the original blasts to misbehave from not retriggering the new stem cells?

Alex Aleshin, MD: Well, I think that's a great question that actually lead into Dr. Muffly's talk about the role of transplant and MDS. So, hopefully her talk will answer most of it, but yeah, I think, again, a transplant gets rid of all of the bad cells hopefully and that's why they don't come back.

Thank you, again.

(Applause)

Audrey Hassan: I just wanted to take this opportunity. There's a new research study. It's called the Journey Pro Study. They are looking for participants, those MDS patients that have chronic anemia. Vanessa is sitting outside at the reception table. During lunchtime you might want to stop by and talk to her if this is something that you're interested in participating in.

Peter Greenberg, MD: So, I wanted to introduce Dr. Lori Muffly who is one of the faculty and bone marrow transplant centers here and she's done some great work over the last few years evaluating transplant in MDS and in a number of other diseases. So, Lori, please.

(Applause)

Lori Muffly, MD: Okay. We're going to try holding the microphone because I know it's been a little bit soft in the back. So, let me know please if there's a volume issue.

So, I was tasked with talking about bone marrow transplant for MDS patients and so in this audience I do recognize a couple of our transplant patients, but I presume that most of the people here have not had a bone marrow transplant and maybe have not even met with a physician or don't plan to meet with a physician to discuss transplant. So, I thought for today it might be useful to just have a very brief overview of the basics of transplant. What is a bone marrow transplant really? It sounds scary, but I'd just like to walk you through it.

Bone marrow transplant for MDS. Some of the evidence and particularly how we decide on bone marrow transplant for MDS which is I know a conundrum for patients, but also for us physician who are trying to make these decisions. We don't take it lightly and then just reviewing a few of the innovative approaches to transplant for MDS that we're exploring here at Stanford that we're really excited about.

So, I always start with patients in the clinic by talking about what is bone marrow because sometimes we presume that our patients understand this and if you've had MDS for a long time you probably now have heard of these terminologies, but so bone marrow is the soft tissue inside of all of our bones where the blood cells are made and so we think of it like the blood cell factory where all of the white blood cells, red blood cells and platelets are made. As most of you know white blood cells are what comprise your immune system. Red blood cells help to carry energy and oxygen to our organs and platelets help to control bleeding and so the precursors for all of these cells start out in the bone marrow.

What is an allogeneic bone marrow transplant? So, this is very important because there's a couple of categories of bone marrow transplant. There's something called an autologous bone marrow transplant. This is where we use patient's own stem cells. We do not do this type of transplant for MDS. We do something called an allogeneic bone marrow transplant. So, a bone marrow transplant is also called a stem cell transplant and this can be confusing, but they are interchangeable but because what we're talking about is replacing the bone marrow stem cells. So, if you reading about this topic you may see bone marrow transplant used. You may see stem cell transplant used, but remember it's the same thing. Allogeneic means from a donor. So, autologous means from self. Allogeneic is from a donor and remember this is the type of transplant we're talking about for MDS and the majority of acute leukemias.

How do we identify a donor? So, when we're looking for a donor for this type of transplant we want to find someone who is immunologically compatible. I have patients ask me all the time about their red cell type and if they're red cell... red blood cell type is the same as their sister's

would they be a match? We're not looking at red blood cell type. We're looking at part of the genetic code of the patient's immune system and we're trying to find someone out there who is either identical in terms of that code or matched well enough that they would be compatible to receive this person's bone marrow stem cells.

And why is it called a transplant? So, it's called a transplant because we replace the recipient or patient's bone marrow with the donor's bone marrow and in doing so we replace the... we ultimately replace the red blood cells, the platelets and the white blood cells. This is a medical transplant. This is another thing I always tell patients. There's no surgery involved for the patient. So, patients are not undergoing an operation as they would with a kidney transplant. This is entirely a medical replacement of the bone marrow.

How do we perform allogeneic bone marrow transplant? Okay. So, again, no surgery. These are the broad steps of transplantation. So, step one is called conditioning or the prep and what we're doing here is we're preparing the body of the patient to accept new bone marrow stem cells. If we were to take any one of you patients with MDS and find a donor and infuse donor stem cells into you like a blood transfusion. That's how we infuse. Your body would reject those stem cells even if they were a perfect match and that is because you have an immune system. It may be weakened, but it's there and so we have to do something to deplete your immune system before we give you some else's stem cells. We can do that with chemotherapy. We can do it with radiation therapy. We can do it with some more novel therapies that we'll talk briefly about. The second step is the infusion of the donor stem cells and so I should say the first step takes about a week to 14 days. Sometimes it's done in the hospital. This chemo, radiation, whatever we're using as a prep it can be done in the hospital, it can be done as an outpatient. The second step is the actual infusion of the donor stem cells and this is done over about an hour. It's very, very similar to a blood transfusion which I believe after hearing some of the questions a lot of you have received in the past. The third step is waiting for these stem cells to engraft and engraft really means to take. So, these stem cells are primed, the donor stem cells are primed to find a patient's bone marrow to take up shop in the bone marrow to start growing. It's pretty incredible. We can infuse them and they just know exactly where to go and how to grow and so that takes about 14 to 21 days or so and this is the time period where some patients are in the hospital, some patients are outpatient. We are providing a lot of supportive care. A lot of times the patient's blood counts will be quite low from the chemotherapy or radiation therapy prep that we give. So, we are transfusing and doing things to maintain the patient, but after about 14 to 21 days we see that that white blood cell count starts to come up and if we were to look at the DNA of the white blood cells which we do we would see that for most patients it would be predominately or entirely made up of donor DNA and so that's very cool because the white cells switch over right away. The fourth step of the transplant process is preventing side effects and reevaluating the bone marrow to ensure that we've eradicated the MDS clones that MDS that was previously in the bone marrow and we do this over many, many months. So, the follow up of transplantation takes place over many months. Sometimes transplant patients are seen for years monitoring side effects and sort of taking care of the residual issues from transplantation.

How do we collect donor stem cells? This is asked almost always in my clinic and so we have two ways of collecting bone marrow stem cells from a donor. The first is called a bone marrow harvest and in this case we take donors to the operating room, we put them under anesthesia and just like a bone marrow biopsy if anyone in the room has had a bone marrow biopsy it's sort of like a bone marrow biopsy on steroids. So, we take out about a liter to a liter and a half of bone marrow from the posterior hip bone of the donor and that's why these donors are under anesthesia and as some of you may know the majority of our donors these days are unrelated volunteer donors. So, people around the world volunteer to undergo this procedure out of the goodness of their heart. The other way we collect stem cells from a donor is by using a stem cell boosting drug called G-CSF or Neupogen or Xarxio if you've heard any of those terms. So, we use high doses of this growth factor injection and this growth factor sends a signal to the donor's bone marrow stem cells to release the stem cells from the bone marrow and allow them to enter the bloodstream. We can then collect donor bone marrow stem cells right from an IV in the arm and... Okay.

So, why do we perform an allogeneic bone marrow transplant for MDS and other forms of blood cancers? And so one of the reasons is that we want to replace the recipient or patient's bone marrow with the donor's bone marrow. In doing so, we replace the red cells, the platelets and the white cells and so I think this was on my first slide and so our focus really is on the white cells and why? Because the white cells become a new immune system and this is the key to bone marrow transplant. So, immunotherapy for cancer is very hot in the news right now and I would say that bone marrow transplant is really the ultimate immunotherapy because we are entirely replacing the patient's immune system with the donor's immune system. Can be quite powerful in controlling blood cancer, but can also lead to some of the problems we see from transplantation. So, as I just said the new donor immune system can be very powerful controlling blood cancer cells and that ultimately can lead to a cure of MDS.

So, how many of these transplants do we do in this country and so in bone marrow transplant we are mandated to report everything to our national transplant agencies which is very, very useful. We keep large databases on an institutional level and then on a national and international level. This allows us to go back and look at our data and to publish our data and so we know that the number of transplantation both autologous which is where we use a patient's own stem cells which we do for diseases such myeloma and lymphoma are increasing and that allogeneic stem cell transplant back in 1980 when it first started to now has been increasing pretty dramatically in this country.

Selected diseases for which transplantation is increasing and so you see the red arrow is next to MDS and so transplantation for AML and MDS are on the rise. They together make up the largest proportion of allogeneic stem cell transplant indications. The other thing that's changing and perhaps the biggest cause for this increase in transplant numbers is the ages of patients in which we're transplanting and so this comes from our national transplant database. MDS is not

included in this, but you can see that the number of allogeneic stem cell transplants for patients under 60 has remained relatively static over the past decade, maybe slight increases, but where we see pretty dramatic growth is in transplant for patients over the age of 60 and even over the age of 70. So, 10 – 15 years ago transplanting a 60 year old MDS patient would be considered very high risk. These days that's our average age and that's kind of our bread and butter transplant and so along with colleagues from around the country, we put together and recently published a study looking more specifically at this group of patients over the age of 70 because we are increasingly seeing patients in their 70s in our clinics and we certainly got the sense that this is a population for which transplant is on the rise and so what we showed is that there has been an exponential increase in the number of transplants performed in this country for patients 70 and older. These are allogeneic bone marrow transplants and AML and MDS are the reason why. So, we are increasingly transplanting patients into their 70s and even 75 and older for these diseases.

Why is allogeneic bone marrow transplant for MDS on the rise? So, historically patients 65 and older with Medicare did not have insurance coverage for transplant for MDS and this is important because in this country Medicare sets the tone. So, if Medicare does not approve a transplant indication or a drug or something like that the private insurance companies tend to follow suit and so in 2010 along with a group of researchers and clinicians who specialize in bone marrow transplant for MDS, the Centers for Medicare and Medicaid Services established coverage for BMT for MDS through coverage with evidence development and what that means is that they would pay for allow patients with MDS to undergo transplant if they were enrolled on a national clinical trial that was developed to look at the outcomes of transplant for Medicare patients and so for a long time for up until just about a year ago all of our MDS patients over the age of 65 were getting transplant on this particular study and so our international agency developed this study comparing the goals of the study were to compare the outcomes of patients 65 and older getting transplant on this Medicare approved study to historical outcomes of allogeneic bone marrow transplant patients age 55 to 64. So, what they wanted to do was prove that patients 65 and older did just as well with transplant as patients 55 to 64 and this started in December of 2010 and so the data from this study was presented recently at one of our national meetings. The study compared the outcomes of 688 patients age 65 and older with 592 patients age 55 and 64 with MDS who underwent allogeneic bone marrow transplant from 2010 to 2014. What they found and this is not surprising to those of us that do transplant but what they found was that the survival at 100 days and two years following bone marrow transplant for MDS patients 65 and older is comparable to patients 55 to 64 and that age alone should not be a determinant when considering transplantation for patients with MDS.

So, how do we determine which MDS patients to transplant? So, Dr. Greenberg and Dr. Aleshin went through a lot of different algorithms and sort of ways that MDS is classified prognostically, predictively and these are really, really important when we're thinking about transplant because transplant is a large burden to a patient and their family. It is expensive and it's potentially has very serious toxicities and so if we took every person to transplant with MDS we would be

exposing people unnecessarily to toxicities. So, we really need to think about who really needs a transplant and so these are some tables for this is a table that is used. This comes from a consensus statement for patients with very and low risk and intermediate risk MDS by IPSS-R and so you'll see here that the first branch point is poor performance or non-fit versus good performance and fit and those are very subjective but I think there's a gestalt we have clinicians and as patients of who's fit and who's not fit. So, for fit patients if you look down the right column poor risk features and those are typically defined as Dr. Aleshin was talking about by some of these molecular categories or the need for many, many transfusions. If patients have an available donor then transplant strategy should at least be considered. That doesn't mean that the patient needs a transplant, it doesn't mean the patient will definitely get a transplant but it means it's probably worth a discussion. No poor risk features, non-transplant strategies are recommended if patients fail or their MDS progresses then it's probably times to have a discussion with the transplant doctor about transplant. This is a different algorithm. This is for patients with poor risk or very poor risk by IPSS-R and so this is patients with more aggressive MDS and so, again, we look at fit versus non-fit. In our world I would say non-fit is if patients are in a wheelchair and unable to get out of bed. They are not going to be a transplant candidate, but I think the majority of patients we see even as I mentioned up into their 70s who are performing their activities of daily living, out and about are considered fit. So, patients with a donor with... you can see here patients with a donor with either less than 10 percent marrow blasts or greater than 10 percent marrow blasts should both at least have a discussion with the transplant physician. The question always becomes do you need therapy before your transplant or not and for patients with very high blast counts it does often help to have therapy prior to your transplant.

What are the outcomes after transplantation for MDS and so this is patients' number one question and it is very, very difficult to give specifics here and so this is a generality for all comers. So, for all comers 30 to 40 percent of intermediate – high risk MDS patients will be cured following allogeneic bone marrow transplant, but some patients will have serious morbidity and mortality from the transplant process and some patients will have recurrence or progression of MDS after transplantation and so we know 30 to 40 percent is not good enough. So, we're actively working on strategies to improve that number.

How can we improve allogeneic transplantation for MDS? And so there's various points at which we think we can do better and we're trying to do better. So, one is with the first step with the prep or conditioning regimen for transplant and so altering the prep to target MDS cells is one avenue of research. With the donor stem cells engineering or optimizing donor stem cells to better recognize MDS cells to kill them and then the side effects. There's a lot of work done in this realm with transplantation. So, reducing the toxicity is critical. Additional MDS targeting post-transplant with maintenance therapies or cellular therapies.

So, I'm just going to run through a couple of the things that we're working on here at Stanford and so one is this paper comes from our group and so we have an approach to allogeneic

transplantation for older adults with MDS. An older adult means in our transplant field really as we're approaching age 70 or so and so we don't use a chemotherapy based prep at all. In fact, we don't use high dose radiation. We use a combination of something called total lymphoid irradiation with an antibody to recipient T cells in order to decrease the immune system of the patient to allow those stem cells to... the donor stem cells to come in and take. This is a very nontoxic approach. It's given as an outpatient. It takes about 14 days. Very, very, very well tolerated. The rates of transplant complications with this approach are very low and so this is something that we've pioneered that we offer to some of our patients with MDS nearing 65 – 70 plus years of age.

Targeting of MDS stem cells. So, this figure comes from one of my colleagues in the laboratory and so we know that there's certain proteins that are expressed on stem cells and that are expressed on MDS initiating stem cells. So, the group of stem cells that then form into MDS cells and so we have antibodies now that can target these stem cells and so this is in mice and you can see that the mice that receive the antibody called SR1 the percent of MDS cells remaining after the antibody treatment goes way down. The problem with using antibodies against stem cells is that not only do you potentially kill off MDS stem cells, but you potentially kill off normal healthy stem cells. So, you have to do something to replace the patient's stem cell and that's what a transplant does and so we think that incorporating these sort of antibodies might be very powerful in MDS transplantation and so along with one of my colleagues I am going to be leading an early phase clinical trial of one of these antibodies plus this TLI-ATG low intensity conditioning that was on the previous slide for patients with MDS undergoing allogeneic bone marrow transplant and so we're very, very excited about this trial and it should be opening within the next six months or so.

This is a study that is being run through our bone marrow transplant cooperative group across the country that's been open at Stanford for about a year and we've enrolled about 35 patients and so this is for younger patients with MDS because we have a proportion of patients particularly in the transplant world that are under the age of 65 and even in their 20s, 30s and 40s and so this is looking at ways to reduce the toxicity of transplant and make transplant more tolerable especially when we give more intensive transplant to younger patients and so this is three arm trial looking at ways to reduce something called graft versus host disease and looks very, very exciting in our field and then graft versus host disease which I didn't want to get too far into today since this is an MDS crowd and probably not too deep into the transplant world, but this is one of the main toxicities that we deal with after transplant and there is a lot of research being performed to look at ways to reduce the risk of graft versus host disease and improve the treatment of graft versus host disease and so you may or may not have heard of a recent FDA drug approval for a drug called Ibrutinib. This is a drug that is approved for chronic lymphocytic leukemia so other types of cancer, but now it's also approved for something called chronic graft versus host disease. This is a drug that works on the immune cells of the body, the B cells and the T cells to decrease inflammation and so I put this up because David (inaudible 1:37:17) is one of my colleagues and

he led this study that led to that recent FDA approval of this drug. So, very exciting and we're using this in a clinic now which is also exciting.

So, in conclusion allogeneic bone marrow transplant is an immunotherapy that offers a potential for cure for intermediate-high risk MDS patients. The use of allogeneic bone marrow transplant for MDS and for older adults in particular is rising. New and innovative approaches to BMT are needed to further improve our outcomes.

Thank you very much. I'm happy to take questions.

(Applause)

Q19: What are the criteria used to decide for harvesting stem cells from a donor through a surgical versus nonsurgical?

Lori Muffly, MD: Well, it's interesting. It used to be that before I was doing this the only way to do it was harvesting in the operating room before we have the technology to mobilize peripheral blood stem cells and so once... so with 100 percent harvest and then once we figured out that we could give growth factor and collect stem cells from the blood it switched to almost 100 percent peripheral blood collection and now it's swinging back and that's because there was a very large randomized study that compared the two in the unrelated donor setting and found that the rates of chronic graft versus host disease are lower when we actually harvest from the bone marrow as opposed to when we collect from the peripheral blood. So, these days I think it's very center dependent. It's also donor dependent. So, for siblings we rarely will collect from in the operating room for siblings and it's protocol dependent because some of our clinical trials mandate that donor stem cells are collected a certain way. So, there's a whole mishmash of things going on. In my practice typically if I have a sibling we collect through the peripheral blood and if it's an unrelated donor and the patient is getting an intensive transplant we collect through the marrow.

Q20: I would like to ask I'm a bit... I think I'm going to be doing a transplant here coming up, but I'm doing Vidaza three cycles of that first and I'm just wondering how much in a bubble do I need to be post-transplant and how long would they keep you in the hospital because my house is not that clean and I can't imagine just... I mean, I can clean... have one room clean, but I just am wondering like what... how long do I need to be how isolated?

Lori Muffly, MD: So, here if you're here and every center has a different way of doing this. So, in our region the two big transplant centers are Stanford and UCSF and we do things differently. If you're having a transplant in the hospital and the entire course is in the hospital it takes about a month. The hospitalization is about a month and then the next two months we do require at Stanford that patients stay in the area and so we set up local housing. After that period of about 90 days our strong recommendation is that you're not in a bubble. We do this so that you can live

and ideally live the way that you want to live. That being said there's some definite precautions and a lot of them are very common sense precautions. For patients who are going to be home through their transplant or who are going to be discharged home who live locally is important to have your house cleaned beforehand and here at Stanford we have pretty intensive teaching and kind of a lot of nurse and social worker input on how all of those things happen and so no one enters a transplant without those sorts of questions being answered. So, if they haven't been answered and you're having your transplant here it just means that you're probably not close enough yet to transplant to having all those meeting.

Q21: Hi. Thank you for your information. I'm coming from the UCD system and I was just diagnosed maybe 60 days ago. So, I'm really here to collect information and, of course, I put the horse before the cart or whatever the saying is and I have an identical twin, so I asked my oncologist about this and she said whoa, whoa, whoa. I am your oncologist, but actually the transplant doctors are a whole different breed and we have different training, but is that a good possibility if I have to go there to use my identical twin?

Lori Muffly, MD: Well. So...

Q21: I know that's a lot. I know.

Lori Muffly, MD: I'm still stuck on the whole different breed comment because we are hematologists. So, we're the same breed.

Q21: Actually that was the quote.

Lori Muffly, MD: So, that's a difficult question. So, the problem with using an identical twin for diseases such as MDS is that you don't engage a new immune system. So, if you truly are identical and you have the same genetics all the way through then you will not have that donor immune system phenomenon that we think is so important. So, it depends on... it's hard for me to give you a blanket answer, but for a lot of times for diseases such as MDS or AML if you were to need a transplant we actually would not use the identical twin.

Q21: Okay. Thank you.

Lori Muffly, MD: But that being said every case is different and for one reason or another it may actually make sense for you depending on where your MDS is and what level and...

Q21: Yeah. We're not there yet.

Lori Muffly, MD: Yeah. That's good.

Q22: What are the age limits on an older person to get a transplant?

Lori Muffly, MD: We... I think the oldest person that we have transplanted for an allogeneic bone marrow transplant here at Stanford has been 77 or 78. We start getting a little nervous when we have referrals into the 80s although I did do that study of patients over 70 and there was, I believe, I can't remember... There was something like five to 10 patients in their 80s in that analysis. So, we definitely don't use age a discriminatory factor for this disease because MDS is predominately a disease of aging and so I think that's been our biggest breakthrough is the ability to use these therapies in all age groups.

Q23: Hi. As a low risk patient, is it possible or advantageous to see if there's a match or another way to ask that is there a risk that you wouldn't have a match so that when you become high risk it's time to have a transplant there wouldn't be one for...

Lori Muffly, MD: For a young patient?

Q23: Yeah.

Lori Muffly, MD: I do think... I don't know how Dr. Greenberg feels about this. We... I think for young people with a diagnosis of MDS it is... it's probably helpful to just do some of that homework because, obviously, when we look at these numbers of low risk and kind of timespans if you're 20 years old it's very different than if you're 75 years old and you're being told that you'll get 10 to 15 years till progression of AML, for example, and so I don't think it ever hurts to meet with a transplant doctor to get some information. We always do the initial homework to finding donors. That being said we... I can think of only very rare circumstances where we would take a low risk patient to transplant if any circumstances. So, it depends how helpful it is to you.

Q23: Thank you.

Q24: Hi. It's good to see you.

Lori Muffly, MD: You, too.

Q24: I have a question about (Attendee) had the marrow transplant from bone marrow and now they're talking about him needing a boost. Is that going to create and I've heard it it is more problematic coming from because his donor does not want to do peripheral for the boost.

Lori Muffly, MD: Oh.

Q24: So, is that going to be problematic and how long should we wait before we would do that if he's doing Neupogen and we're just trying to see if it just time?

Lori Muffly, MD: We can talk about this after, too, because we all kind of... we've been discussing you. We all know you well. So, the specifics, but I would say about the boost that is a little unusual to not have the donor give the peripheral blood mobilize themselves. That being said the only difference is that the stem cell yield from the bone marrow is lower and so it's not a better or worse it's just that we want to make sure we have... we want to make sure we have enough cells to have an engraftment and so... I mean, in some ways it doesn't really matter as long as the yield is good and I think that there comes a time where a boost makes sense and that might be where you are.

Q25: Have any studies revealed any kind of complications or risk for people donating stem cells with the use of Neupogen? Is that drug had any (inaudible 1:47:42)?

Lori Muffly, MD: In my clinic almost every week I see an unrelated volunteer donor because Stanford is a big site for volunteer donor collect (inaudible 1:47:50). Anyway we talk about this all the time with donors. Every few... so donors, a subset of donors are tracked forever and every two years data is published on donors and donor health outcomes because, obviously, that's incredibly important. We can't be taking these young healthy people and putting them through this process if something was going to happen to them. There's no signal that giving Neupogen the growth factor to these young healthy donors increases the risks of anything and some of the things they look at are autoimmune conditions, cancers and donors are compared to age matched controls across the population and so we always tell donors that's the data we have. We have absolutely no reason to believe that there's any harm that comes from the donation process. For donors that are getting collected with a bone marrow harvest I always tell them the biggest risk is anesthesia. So, it is an hour of general anesthesia.

Q25: Thanks.

Q26: This is a question that relates to the sort of the odds numbers that you quoted earlier, the 30 to 40 percent. Having read quite a bit about this as much as I could in the time I've had it seems to me that while there's a lot that's known this is a very complex situation, let's call it, and so there's actually an enormous amount that still isn't known and that what is known is not so much you understand how it works, but that you come up with a... you and the medical industry has come up with a number of treatments that prove effective across a range of time and patients. So, you try things and you say oh, this seems to work. Okay. We're going to use that and then maybe somebody comes up with a new idea or a new treatment and you try that and say oh that works even better than the other one. You don't really know exactly why it's working maybe some of the time. Some of the time you do. So, it becomes kind of a data driven/odds driven set of treatments. So, the 30 to 40 percent tell you what your odds are. You've quoted them and I assume that 30 to 40 percent is across an age range and a severity of symptoms range and I'm wondering if there are... there's sort of a being an engineer you can probably tell I'm assuming if it was me I'd be putting together a bunch of spreadsheets that showed okay in this age range and this severity range and having Paretos of all that and I'm wondering if that kind of

information is available so I can look at what my odds are and not the odds across your enormous range of people.

Lori Muffly, MD: So, being that this is Stanford we do treat a lot of engineers and so that's very common type of question that we hear and you're entirely right because I think in our business in particular even more than for maybe the hematologist, it is all about odds because there's no perfect model and we can have everything stack up perfectly in terms of donor and disease control and age and everything else and have an outcome that we're not predicting and totally vice versa where we have a patient who's not an optimal candidate who has boatloads of blasts in their marrow and a suboptimal donor and does great and so there are... it does get more specific. We have just like the IPSS-R exists, we have something called the Disease Risk Index which is broad-based. So, each disease kind of has its own factors that go into it and it's a transplant based outcomes index. We have a comorbidity index, but I've told patients that based on their own scenario the likelihood of success is five percent and I've told patients that based on their scenario the likelihood for success is 65 percent and so it does become about you and I don't know enough about you, but it is all odds based and it's very frustrating and in the end it's either 100 percent or zero percent for the individual patient. It's either going to work or it's not.

Q26: Yeah. It's binary in that sense.

Lori Muffly, MD: Yeah.

Q26: Right. I guess any of us though that are in the position or at least maybe I should just speak for myself. I look at this and granted I have a specialist that I'm working with and we talk about well what would happen if we only... if I walk away and never see anybody again. What if we take intermediate steps and not do a transplant. How does that look? Am I going to live for six months or five years or 20 years in which case why should I do anything or should I take the risk of the bone cell transplant and the associated dangers with that? So, those are the kind of things I think we're all dealing with and that's why I was asking you that question.

Lori Muffly, MD: Yeah. There are more specific risk indexes, but it does often come down to a conversation just as you said between you and your transplant doctor and sort of going through all of those scenarios and we do that all the time. It's very...

Q26: It's challenging.

Lori Muffly, MD: It's challenging for the patient and it's challenging for us, but if you have high enough risk MDS where the likelihood is that the MDS is going to cause you problems within the next year or two or progress to leukemia the discussion does become a little bit easier. The hardest discussions are for patients that have intermediate risk MDS where it really we don't know the pace of their disease and we don't know when the best time to intervene is because the problem with transplant is if you don't intervene at the right time you could miss your window

and so we have patients who decide not to come to transplant and then their disease progresses to AML and then we can't kind of get things back together.

Q26: Right. One last thing I'm hogging the mic here. I thought you referred to this while you were discussing it, but one of the things my hematologist talked about was after I came back to see him having seen the specialist he said did she give you the look test and I said look test? What's a look test? He goes well, we look at you and we... he looks pretty good. So, yeah, he looks pretty good. I think he'll do well. I'm just curious. Did you refer to that or is there anything like that?

Lori Muffly, MD: No. Well, when I mentioned fit/unfit I will say that it is unfortunately we do have all of these very well designed comorbidity indexes and ways to kind of score fitness, but it often does come down to like a look test, but I... a wheelchair that's kind of where I... the wheelchair is a big one.

Q26: How far in to the look?

Lori Muffly, MD: Well, you would be surprised.

Q26: Okay. Thank you.

Q27: Just a quick question. I just wondered are there data available that compares the low intensity preparation to high intensity and which works better at long term in terms of relapse.

Lori Muffly, MD: Yes. There are data and so for younger adults a study... and younger meaning this is a... these are all moving targets and I hate that we keep talking about age, but it's just part of the way that we do things in this field. So, for adults under the age of 60 – 65 or so there was just a study comparing randomizing acute leukemia and MDS. So, MDS often gets lumped in with AML in our field, but MDS and AML patients to high intensity prep regimens versus low intensity prep regimens and the study was stopped early for safety because the relapse rates were so much higher in the low intensity group. So, for many of our younger patients with the caveat of there's the donor issue, there's the comorbidities issue. We do recommend a full intensity transplant. For older adults it's actually the opposite. So, for older adults if you look in fact in our 70 and older analysis getting an intensive transplant was probably the... had the greatest association with inferior survival. So, for older adults we think reduced intensity conditioning is equivalent to high intensity conditioning and that's because the toxicity is lower and so when we think about survival after transplant we're balancing relapse and progression of disease of MDS against non-relapse issues. So, toxicity based deaths if that makes sense. So, yes, we tend to think for older adults we tend to use reduced intensity regimens and for younger adults we use full intensity regimens.

Q27: So, the threshold is basically 70 years old as you're using this (inaudible 1:58:05).

Lori Muffly, MD: I would say that in clinical practice the threshold for most of our clinical trials is 65 and then from a practice perspective oftentimes the threshold becomes 60 to 65, again, taking into account fitness and certain other factors.

Q27: Thank you.

Peter Greenberg, MD: Lori, thank you... thank you for standing up to the...

(Applause)

Peter Greenberg, MD: Well, we've had a big morning and these talks I hope have been useful. It's lunch time. So, we'll meet back here at 1:00 at which time we'll begin talking about quality of life and many other questions that you still may have.

Audrey Hassan: I just wanted to interject. Thank you Dr. Greenberg. Mary Thomas just volunteered and it's up to you. She's willing to start her program at 12:30 and that'll leave more room for you guys to ask questions afterwards if you'd like. So, I wanted to see what the consensus was.

Peter Greenberg, MD: Twelve thirty okay? Let's plan on 12:30.

Audrey Hassan: Okay and there's also a back lounge. Right, Dr. Greenberg? In the back that has a big table. It might not fit everyone, but for those that want to sit at a longer... at a table and eat. I could show you where that room is. Okay. Alright. Enjoy lunch please.

Peter Greenberg, MD: See you back here at 12:30. Very good.

(Continuation)

Peter Greenberg, MD: ... a number of things for patients. Beyond our standard medical needs has been a great person in educating me in how to deal with patients many times as well. In addition, she's come down here from Santa Rosa and most of you know what's been happening with Santa Rosa. Hopefully, her home... happily her home is not that much damaged other than little more dust than she usually has. Anyhow, so I'll open it up for Mary to go ahead and start and talk about quality of life issues in MDS.

Mary L. Thomas, RN: Thank you, Peter.

(Applause)

Mary L. Thomas, RN: This is an amazing turnout and usually when Peter actually invited me to do this I was envisioning a dozen or so of us sitting around in a circle and having a conversation and then when we said over 80 people registered I thought oh, my gosh. This is going to be a lecture. How do you lecture about quality of life? So, I do have some slides, but I want to use the slides pretty much as just a focus for conversation. Now, I know this is being taped and what I'd like to do if Audrey allows me is if you have a comment or question, I'll just repeat it in the mic so that it's recorded so that we can have more of a conversation throughout this presentation rather than me just standing behind this podium and lecturing to you.

I do want to say that the content that I'm going to present stems from some of research I did quite a few years ago with the MDS Foundation where we conducted five focus groups around the country where we met with patients and I asked them to talk with me about what quality of life meant to them, how MDS impacted their quality of life and so what you'll see on the slides stems predominately from that research, but it's also going to stem from my clinical experience in having the privilege to work with individuals who have MDS for the past several years. So, I will go ahead and get started with that.

So, I'm going to start with the generic questions that I just want you to stop for a moment and think about and that is what brings quality to your life? So, just take a second and think about that and if you can try and think about that generically not specific to how MDS has impacted it, but just in general what brings quality to your life? So, let's just let you think for a second. Okay. Now, I'll show you what some people have said and then I'd like you to decide if you agree with these things or if you refute them. And so you can see some of the things that I have listed here are things that most people had said and then based on the news here I had to add this one. First of all, I am a Giants fan and given what Bochy's going through right now I figured that that was an appropriate one at least for his quality of life, but the point is that I wanted to bring from this is what's important to you may be different what's important to you. Maybe different than what's important to you and as a clinician if I don't ask you I won't know. I will make assumptions and those assumptions could be wrong. Similarly, you as the patient if you don't tell me I won't know. So, there has to be that conversation. Now, having said that I just thought I'd stop for a moment and say are there other things that came to your mind that are not on this slide that you'd like to share?

Q28: Yeah. It was a successful season for the Dodgers.

Mary L. Thomas, RN: Oh, oh, oh, oh, oh, how painful.

(Laughter)

Mary L. Thomas, RN: Touché. Touché. Very good. Alright. Yes, sir, in the back.

Q29: Feeling good.

Mary L. Thomas, RN: Feeling good. Yes. Feeling good. Yes?

Q30: Independence.

Mary L. Thomas, RN: Independence. Okay. Anything else? Yes?

Q31: Windsurfing.

Mary L. Thomas, RN: Windsurfing. Great. Oh, would I love that. Okay. Other thoughts?

Q32: Good health.

Mary L. Thomas, RN: Good health. So, you can see that each of us probably has a little bit different idea in terms of how we would define quality of life and the importance of realizing and I have to respect your opinion even though I'm sorry I'm cheering for Houston right now because what we have... what comes to our mind is going to be different than what comes to the person's mind next to us. So, it's important that we think about it but that we also make sure that we feel okay to share that with other people.

Another thing that I think is important to consider is that clearly quality of life changes over time. How we define quality of life. A small child is going to... quality of life is going to be getting the new puppy in the house versus a young adult it's probably career, establishing a relationship with someone, middle age dealing with children and those sorts of things and then, of course, as we become more seasoned in our lifespan our definitions are going to change as well. So, it's also important to think about how is our quality of life changing over time because it will in terms of what we view as important and how we would define that.

So, now is the \$50,000 question. How does MDS impact your quality of life? So, I want you to just take a second and think about that.

Q33: It takes up too much time.

Mary L. Thomas, RN: Too much time. We're going to come to that point a lot. Okay. So, from and I will get some of your immediate responses in a second, but I just wanted to show a diagram that when I did these focus groups and then kind of analyzed the conversations that we had most of what peoples' comment focused around these various what I call domains, various subparts of quality of life. So, a physical, functional, emotional, social and spiritual and oftentimes some of the comments that would fit into one of these categories sometimes they overlap. One area might be important to one individual and less important to another individual. One component may be important now and less important later. One part may be important in the past, not so important now. So, again, all of these things are in flux.

So, I'm going to start with physical well-being and this is how typically it's described as all of the symptoms that we see related to anemia, feeling fatigued, feeling short of breath, also symptoms related to therapy. If you are getting Azacitidine, for instance, and you are getting a subcutaneous injections. Do you have site reactions, skin site reactions? Do they itch? Are they painful? Those sorts of things and then an interesting one that some of the people in the focus groups shared was that it can interfere with your ability to have other conditions treated that you may have. How many of you have more than one health problem? Be honest. Okay. Many of us do. Right? MDS doesn't tend to live in amongst itself. We may have high blood pressure, we may have diabetes. Why may have osteoarthritis. We may have congestive heart failure. We often will have more than just one problem and what can happen with MDS is that because of that condition it may impede one's ability to be treated for other things such as an orthopedic surgeon may not want to do a hip replacement on someone because their blood counts are too low. Those sorts of things can be an issue for getting appropriate therapy and I will say that typically physicians tend to focus on the symptoms related to the disease, the symptoms related to therapy and those are the areas that medical world tends to think about.

In contrast and this comes to your pointing a moment is how one's ability to function is impacted by MDS and, of course, fatigue is probably the classic symptom and problem that most patients experience. Do most of you have issues related to fatigue? Yeah. Okay. And the issue is and this is a hard one, I think, for patients sometimes to help physicians appreciate, nurses to appreciate, whomever. It's not that you're tired. It's that you hit a wall and it's an oppressive feeling. It's not this pleasant, oh, I'll go to bed now. It's just you just feel burdened by the fatigue that you have and so it's the inability to do the things you used to do as well, but it also can affect your thinking. You can have cognitive fatigue. Your mind isn't as sharp as it used to be and then also a huge component that many people will describe is what I call motivational fatigue. We've got every intention of doing something, but you just can't get yourself up to actually go ahead and do it. So, there are all these different kind of components of fatigue that are an issue here and oftentimes the fatigue levels that are experienced do not well correlate with hemoglobin levels.

So, when we use hemoglobin as a surrogate we're missing the boat sometimes. So, we have to make sure that we have a good way to help convey to the clinicians who are taking care of us how the fatigue is impacting us and then, of course, alterations in preexisting roles. Are you still able to do your job? This is particularly important if you've got cognitive fatigue and you're a business person, you're a lawyer, something like that versus if you have the I'm hitting the wall kind of fatigue and you're a manual laborer you're not going to be able to do your job very well and then with that also what is your role within the family? Are you the person who has been responsible for getting the kids up and dressed and out the door and can you still do that? Are you the person who's always done the bills and the taxes and now all of a sudden your mind is fuzzy and you don't feel that you are thinking clearly enough and you're making some mistakes. You just don't have the energy to do that. All of these sorts of things come into play and then also in terms of our social roles are we able to fully engage in the activities we want to do? Are

we able to engage with our friends in ways that are meaningful and the ways we used to do them? One patient told me she used to... people will call her up and say that did you want to go to dinner or did you want to go to a play or something and she said I have to check my calendar because she would look on her calendar to see when she would like to get her next transfusion which would give her a little bit of a boost enough that she felt that she would be okay to do that versus otherwise she wouldn't be okay to do that. So, and you're nodding your head yes. You can relate to that. So, again, it's this whole impact on how fatigue and our ability to function can be severely impacted in ways that as clinicians we may not think about as carefully as we really should in terms of how it is for you living with the disease.

And this speaks to your point about how the work associated with the disease. I think many times it is astonishing if I step back and think about what we as clinicians expect of you as patients and you as family members and it just sort of becomes this sort of well, you know, come in next week and you can... and then on Tuesday you can here and there and you forget about what that impact is in terms of trying to adjust the rest of your life to accommodate what we feel is needed in terms of office visits, in terms of lab tests, in terms of transfusions, in terms of chemotherapy administration, all those kinds of things and that's when everything else is going well. We're not even talking about when you have a health problem and you need to come in urgently and so forth, but then there's also especially in not necessarily only teaching institutions, but all of a sudden you've got this plethora of healthcare providers that you don't them and they don't know you and there's always that little bit of tension until you feel that you've got a trust relationship with someone. So, even if you're just talking about MDS you've got a hematologist, you may be referred for a second opinion. Now, you're getting referred for a bone marrow transplant appointment, all of those sorts of things. Then all of a sudden now you need to meet with the staff in the infusion center where you're getting your chemotherapy or your transfusions, trying to get a sense of who these people are and how does that work and if you're in a teaching institution you may see a different doctor each time you come in and that can be very stressful for people. So, there's a lot of different healthcare providers just for your disease, but then you saw when if you have other illnesses as well that are being managed by someone else and unfortunately too many times it's the patient that ends up being the conduit between those two for information back and forth. We're doing better now. I work at the VA. We're blessed with actually the first electronic healthcare record in the country and so people can actually review people's charts, but if you are receiving your care in the community your cardiologist often may be in a completely part of town, different part of town from your hematologist's office and how well are they actually speaking with one another? So then all of a sudden the work falls on you to make sure that you convey information back and forth. So, that can be a huge problem. Another thing that we see and I was amazed at the depth of understanding from the presentations this morning all of a sudden you guys were exposed to all kinds of terms that you probably had never heard of before. Right? I mean, what is Myelodysplastic Syndrome? So, just trying to learn all of the terms that in and of itself is an immense amount of time and energy and it has nothing to do with intellect. When I take my car into the mechanic and Chuck tells me what's wrong with my car and I get home and my husband says so what did Chuck say? And I say well something to do

with the carburetor and it's not that I'm stupid. It's just that I don't really have a good understanding of how the car works. Well, most of us don't have a good understanding of how our body works let alone how our bone marrow works let alone all those genetic mutations that we may have. So, all of a sudden we're being thrust with all of this new language that we're trying to get a handle on in terms of how does this make sense to us? So, that's a lot of work that's involved and it takes a lot of time and trial and error in order to really master that and then, of course, not only the medical terminology but interpreting the lab tests. Does it make a difference if my hemoglobin is 9.2 versus 9.6? How do I interpret that? How much of a decline makes a difference? Why do I pay attention to having to do this math problem and get the actual number of neutrophils and not just the percentage of the neutrophils? All of these things are very, very complicated to try and figure out and then, of course, symptoms. A patient told me she really had a hard time when she would become short of breath. She would have to step back and say okay, now is my shortness of breath because I'm more anemic in which case I better call my hematologist and arrange for another transfusion or is my shortness of breath related to my congestive heart failure in which case I better call my cardiologist and it was the patient who was ending up having to make that determination. That's a lot of work that's involved in trying to figure all of this out to say nothing of the side effects of therapy. When is it serious enough? We all say well call. First of all, how do you call and then secondly when to call. Do you call for every little thing? Do you wait? Oh, maybe it'll go away. All of those sorts of things become an issue and complications as well. Another thing that I think we tend to give short shift to is the business of work with advocating for yourself. You are your strongest advocate. Right? Sometimes it's a family member, but it's usually you and that's an immense amount of work. You're the one that has to keep going to bat for yourself to say what about this therapy? What about that? What if I do this? What if I do that? And that is also an immense amount of work associated with that and this last one was not mentioned too much when I do the focus groups, but I think as we're seeing more and more problems with healthcare insurance in this country I would envision it being more and more of an issue. If you have Medicare, but you don't have a good supplemental coverage associated with that you may be faced phenomenal bills or I have to get clearance from my insurance agency in order to get drug X or drug Y or my insurance agency won't cover this mutation panel. It's all of those sorts of things that I think are really frustrating and cause a lot of angst for people as well.

Next is emotional well-being and I put uncertainty here because I think there's that whole business of how do you interpret life threatening illness, how do you interpret illness experience into a way that makes sense to you and it can stem from a whole slew of different things in terms of uncertainty of what this diagnosis is, what it means, how it's going to impact my life, uncertainty about my future, uncertainty about my functionality. Am I going to stay as functional as I am now? Am I going to become more and more disabled? Patients in my focus groups would say they would come into the cancer center and they would look around and see people's all different kinds of cancers, but they didn't know that they had different kinds of cancers and they would think to themselves is that going to be me? When is that going to happen to me? And so that was a major takeaway message for me of assuring people when I bring them into the

infusion center to warn them that who they see in those chairs may not at all be anything related to who they are or who they might become.

I think there's this anxiety that people typically have and I'll be curious to hear your thoughts about how you are living with anxiety and how you have come to master anxiety because I think that that's a huge issue for folks. Many patients talk about feeling very depressed and they're mourning the loss of who they were and I think, again, it speaks to how you define your quality of life to begin with and if your quality of life stemmed around being a very high functional person with a lot of physical activities or a lot of social engagements or a very prestigious position that you no longer have it's sort of like being forced to retire and you hadn't planned for it any fashion and all of a sudden what do I do with my life and who am I and how do I make sense of all of that. So, that's a large one and then, of course, another one that causes people to feel very depressed is when people say well, you know there's no cure for this disease other than bone marrow transplant. Well, yes that's true, but if you think about most medical illnesses we don't have a cure for most of them. We don't have a cure for diabetes. We don't have a cure for congestive heart failure. We don't have a cure for emphysema. We don't have a cure for high blood pressure. We can control those illnesses well and that's what we're hoping to do with MDS and to control it well so that you can live functionally, but I'm always concerned when people pick up on this lack of cure without there being this context of that's true for a lot of what we're facing in our lives, but how best to live with it and to live well with it and to feel good in the process.

Another factor that comes into play for many people is the issue of loss of control. You've been a business executive all of your life. You've whatever it happens to be you feel that you've always had the ability to control what happened and perhaps to control people below you in hierarchical setting and now all of a sudden you feel that you have no control what's going on with your body and that can be very, very distressing for folks.

Interesting enough and curious is when I open this up for conversation if this was an issue for you many patients describe at great length the shock they had when they were diagnosed with disease and what was interesting to me was that for many of those people they had been living with this disease for five years, seven years and they still had this need to talk about the shock of receiving that diagnosis. That was very striking for me to learn about that.

And then I think, again, the whole business of what does the future hold for me.

In terms of social well-being, again, this whole business of time – time that's spent away from doing things. My son was out having hip surgery a couple weeks ago and I went with him to his orthopedic appointment and then to his physical therapy appointment and it just... being on the receiving end as opposed to on the caregiving end it's always interesting to get a sense of what it's like to sit in that waiting room and wait and wait and then to wait for them to come out and all this... the time and it's not... it is what it is, but it's time that you could be doing other things

especially if it's a time where... this is a time when I feel good and I'm wasting it sitting in this waiting room when I could be out doing something else.

The whole business of how do I plan for my future. We're all mortal. We will all die at some point in time. None of us know when that's going to be. How do I plan for that? Does living with MDS impact that in some way and if so how. When am I supposed to give my kids my inheritance? Do I do it now? Do I do it later? It's interesting to hear some people talk about those sorts of things and then the whole business of activity restrictions. I had one woman. It was just heart rendering. She said to me, "I don't know if I can hug my grandchildren because my white blood cell count is low." Ability to travel. We warn people about all of the nasties that are in the air circulation on airplanes and yet when you think about it that's our primary mode of travel from point A to point B anymore if you're beyond 100 miles or so and so how does that impact your social well-being? Talked a little bit about relinquishing roles earlier, but when you have to give something up and somebody has to take it on for you how does that impact their quality of life? How willing are they to do that? How skilled are they to be able to do those things? So, all of those factors come into play as well.

How do I continue to feel that there's something normal in my life and can my life be very normal? Is it completely abnormal? How can I move it from less normal than I want it to be to more close to the normal I want it to be? Sexuality can be a huge issue. Part of it is fatigue, part of it is anxiety, part of it is depression. All of those sorts of things come into play not only in terms of sexual activity, but just in terms of your self-concept about who you are as a sexual person and then from that also comes strained interpersonal relationships. Again, this whole business of having to redefine roles within a family or within other people's relationship with you and how does that impact your relationship with them when all of a sudden they're the ones that are stuck doing all of the housework or the bill paying or the childcare or whatever it happens to be? Are you still able to work? If you're not able to work are you okay financially and all of a sudden is this a huge burden for you or how has this impacted other people? A woman was no longer able to care for her daughter's children. All of a sudden the daughter now had to pay someone to take care of her children. She didn't have the financial resources to do that. So, it can... there's that ripple effect that we can see and then, of course, with that comes the financial strain.

In terms of spiritual well-being it was very interesting to me in not only from the focus groups but also my work with patients over the last many decades. Clearly some people have this feeling of hopelessness, but what is amazing to me is the resilience people will have especially over time when they are able to adjust to the new them and to see how it has impacted them in a very positive way and I just have listed here things that they have articulated to me over the years that I find very amazing and it just never ceases to amaze me how people can react to things and turn... the infamous is the glass half empty versus half full and how people can see a glass that looks pretty darn empty and make it very, very full because they've been able to change how

they interpret things, how they reestablish their priorities and finding meaning in this illness that they happen to have.

So, I would like to now stop. I've been talking about what I have heard other patients say. So, I want to go back to that slide just to help us remember are there other things that you think of that the MDS has or its treatment has impacted your quality of life in any of these dimensions that you'd like to share or things that you think haven't been covered from what I shared thus far.

Yes?

Q34: I think I've been functional because have a particular case which my husband can attest to. I always felt myself really independent. I've worked for years and then I got MDS. I was diagnosed with that (inaudible 2:29:38) retire and he's had to take over the times that I want to drive myself somewhere so to speak where right before I get (inaudible) lousy as all you guys know is that he has to take me and (inaudible) not have to put me in a wheelchair to take me to get to the lab work done. (inaudible) and get my blood done. So, there... the functional part (inaudible) was really hard to give up because I didn't need him to do that for me but yet I feel guilt because he's (inaudible) very active.

Q35: I can't shrink her.

Mary L. Thomas, RN: A lot of people... Thank you for bringing that up. So, what she said was she's always been a very independent person, very, very functional. Now all of a sudden she's having to rely on her husband and she was diagnosed right after retirement. Thank you very much. What a lovely retirement gift.

Q34: (inaudible 2:30:30)

Mary L. Thomas, RN: So, she's now having to rely on her husband to have to drive her where... before she would, of course, drive herself. She has to be driven to get her lab tests done. She has to be driven to get her transfusions. Her functional status can decline enough that he has to put her in a wheelchair sometimes to get her in and out of places.

Q35: I give her a little bit of (inaudible 2:30:55). Would she do that for me if I was in her shoes?

Q34: Yes.

Q35: So, that's the way I figure it. That's why I do it for her. I know she'd do it for me.

Mary L. Thomas, RN: There you go.

Q34: (inaudible 2:31:05) so true but that guilt is still there sometimes. (inaudible) give up an activity (inaudible)

Q35: I can do it again.

Mary L. Thomas, RN: So, that your point about feeling guilty I'm sure that that is something that a lot I've said. Seeing a few nods head. That is a very real feeling that people have and it's hard to let that go. I think what you are doing by sharing, but you would do that for me if the shoes was reversed. I mean, thank you, but also I think that that can help. I think there will be times, of course, in any relationship where that stress does grate on people and you want to break and you don't get a break and it becomes an issue, but if you have a solid relationship to begin with it often will wear through a little bit better than if you have a shaky relationship to begin with, of course.

Somebody else had a comment they... Yes?

Q36: I (inaudible 2:32:02) the general concept from the and I don't know if you have any comment that the medical profession in my humble opinion is really low on information regarding cost and I actually if I have to be angry and frustrated about one thing is I still don't know the cost of it and my husband we're going to have to get a lot of money. I'm a sole practitioner in my own business and I think that needs to be way more upfront (inaudible 2:32:36) we yet to have anybody sit down with a piece of paper that says aside what Azacitidine is this much money. I'm really very, very frustrated by that.

Mary L. Thomas, RN: I don't blame you. Now, I work at the VA, so I'm spared that reality because most of my patients get absolutely everything for free or... now wait, wait let me finish. There's a copay for some, but that is the direct cost of the therapy. That still doesn't take away from the cost of you having to take a day off or whatever without pay. So, there's that piece, but for those and this is where I don't want to get political here, but our insurance system is just in such a mess because what Stanford charges for Azacitidine is going to be different than what Hospital X charges for it which is going to be different than what Dr. Y charges and what insurance pays can be different from plan A versus plan B and so how one... you're shaking your head no.

Q36: I believe that the medical practitioners in the room should have some idea of the cost and that's what I find lacking. If I ask my physician how much it costs there should be some general notation about it.

Mary L. Thomas, RN: In the old days in (inaudible 2:34:00) care and (inaudible) in the old day at the VA what we would have when we would have prescriptions that needed to be renewed we would have the cost of that prescription listed and that was very, very helpful. That's gone now

and so we don't necessarily know, but it is a major challenge and please use the microphone so people can hear your response here.

Peter Greenberg, MD: Thanks. That's a great question and it's an important one. One of the problems we have is how do we modify drug company costs and what's covered. Analysis has been done of these costs. They're published so that for example, the cost of Azacitidine, Decitabine, Exjade, Lenalidomide for a year as approved by various guidelines has been published and it's known what those are and I can give you those figures. It's true though doctors don't really know about it, 1), and 2) they don't know what your insurance will cover. Usually insurance will cover most of it for patients that are on Medicare but not always, but most importantly is the cost that the drug companies charge and at the moment until there is a stakeholders meeting with everyone and that is political that is when you talk about government as well as insurance companies as well as physicians the drug companies will not modify their costs and so that's a huge issue. That's really going to take a political change for that to happen. If you want the amounts I can give those to you at some point not necessarily now and we can certainly talk about that in detail.

Mary L. Thomas, RN: But it is a moving target because what a drug company will charge in year X may be very different than what it's going to charge in year Y and how and you saw the slides from Alex on the genetic mutation stuff. We are bombarded with so much information now it's hard to keep up. Your point is a very valid one. I don't know that it should be the physician who should be able to tell you that but you should have ready access to that information when you go in. Absolutely. I fully agree with that point.

Anything else anybody else wants to share about how MDS has impacted your quality of life?

Did what you saw on these slides did that sort of ring true for you for at least some of it? Okay. Yes?

Q37: The long range plan like planning trips and buying tickets (inaudible 2:36:49) maybe I should do that because I'm not sure as what my counts will be here (inaudible). Started on a different manner, something like that. So, (inaudible) something even like remodeling a kitchen or anything like that. It does impact your planning future projects.

Mary L. Thomas, RN: Right. So, for those of you who didn't hear how it impacts your ability to plan for the future be it something like remodeling a kitchen to taking a vacation and trying to figure out will I be able to take a vacation at that time based on will my treatment be changed? Will my blood counts support it? Will my energy support it? All of those sorts of things. How do I try and plan for something in the future and the future may just be a few months let alone years, but how do I fit that in?

Anything else anyone wants to share? Yes?

Q38: Coming in from Valair today I could have got killed at least five times on the freeway easily. So, thinking about a year from now to go on vacation plan it and think you're going to go because some other thing might step up. It's not going to necessarily always be MDS. So, to control your life a year from now and say I don't think I can do that because there's a whole bunch of other things in our world today that can take you out without trying to force that in. So, in my thoughts and the way I'm living is yeah next May I'm going to do this, I'm going to do that. Yeah, you're going to put a little bit of money down maybe for a deposit or something and you might lose that but to try and keep your life going and have some sort of quality and then be worried about well, what's going to happen a year from now. That's just my thoughts.

Mary L. Thomas, RN: Did that come through adequately on the tape do you think? Oh, too bad because the way he said it was so beautiful and I'll butcher it, but the point was don't allow this disease and please let me know if I paraphrase this accurately. Don't let this disease control your life. There's something else that could take your life at any point in time and you had cited you could have been... your life could have been taken from you five times driving here from Valair today. I can relate commuting from Santa Rosa believe me. There was... I was right next to a car that was hit by a car. So, there are all those sorts of things. Two weeks ago on a Sunday I was at a winery tasting some wine and had friends over for dinner. Four hours later there was this massive firestorm. Your life can change in a split second. You just don't know and so your whole point about not allowing this to immobilize you but to move forward is very important. Not easy to do necessarily, but that's my job as a clinical nurse specialist to help you to do that if you're my patient to support from your friends and family from the rest of your healthcare team. The MDS Foundation does a great job. Jack is here from the Leukemia and Lymphoma Society. They've got some wonderful information and resources for you. So, it's very important that you try and make sure that to the extent you can you may have to redefine your life a bit but it doesn't have to control your life.

I want to close with just a couple of points and then a couple questions for you. One is managing fatigue because I know that that is by far the most frustrating symptom that many people have with this illness and I think that when you come into the hematology clinic way too much we just focus on what is your hemoglobin and will you get a transfusion or not or do we adjust your EPO level or not and that's it, but there are a lot of other things that can impact one's fatigue in addition to anemia and so there are some things that you can do that can make a huge difference. When I say exercise I do not mean that you need to join a gym. I do not mean that you need to start training for a marathon. I do mean that you need to be as mobile as you can. Our bodies are meant to be mobile. The more sedentary we are the weaker we become, our proximal... our leg muscles and our thighs just deteriorate, our lung capacity diminishes and we feel worse. We sit more we feel worse. It's a downward spiral. So, even if it's just walking to the mailbox and back even if it's just to the corner and back that can be a huge difference in terms of staying mobile and helping a little bit with that fatigue.

One of the things that we all face as we age is we lose our sense of thirst. Staying hydrated is very, very important to keeping your energy level up and if you wait until you're thirsty you're probably not going to get as much fluids in as your body really needs. So, think about how much do I really drink and I'm an avid coffee drinker. So, my coffee that I have in the morning, my four cups does not count in my fluids for the day. I have a cutoff at noon and then from then on it's water so that I make sure that I get the water that I still need in the course of the day. Come up with some strategies that work for you. For my brother-in-law I had him put out six glasses on the kitchen counter and so he would see it was one o'clock and he still had three glasses there and when you drink a glass you put one away so that by the end of the day you have an empty counter. Whatever cues you need in help yourself remember to make yourself stay hydrated because you can't rely on thirst.

A lot of people will always ask well what about nutrition? Should I be taking supplements? What kind of food should I eat? It's very frustrating but sadly there have not been enough well designed, adequately carried out studies to really help us know what is needed. What we can say is a well-balanced diet makes sense. There was 20 – 30 years ago there was this big push on what we called a neutropenic diet to make sure that there was no fresh fruits or vegetables. Everything had to be well cooked. Limit blue cheese, limit this, limit that. They have since relooked at that body of evidence and decided that it didn't... there wasn't any real substance to that evidence and it was more just an opinion at the time and it sort of carried through. So, having said that there still is a lot of common sense that you should pay attention to. So for instance if you are a lover of salads think about where that lettuce is and lettuce grows in the soil. Right? Soil is full of organisms. So, you'd want to make sure that that lettuce is washed exquisitely well before you use it. So, you wouldn't just go to a salad bar at the grocery store because you maybe if they have a little not even acquaintance with some water but likely not even that. So, you'd want to make sure that you take the lettuce home and wash it well. That sort of thing. So, thinking about what kinds of foods you're eating. Still I'm personally a little nervous about people who wanted to use the raw fish and seafood stuff because, again, how you know about those sorts of organisms but so things change over time. If you're eating a well-balanced diet that's probably all your body needs to our level of understanding right now, but you should ask your doctor has your B12 level been checked. If you're... especially if you are a vegetarian. How well are you doing on making sure you're getting the adequate supplements your body needs? Is your magnesium level okay? You can feel really crappy if your magnesium level is too low. Is your salt level okay? We're worried about salt restriction, but making sure that your sodium level is okay, too. So, making sure that those sorts of things are well balanced as well. Making sure that your thyroid function is still okay. That can certainly become an issue as we age and that can certainly be a huge impact in fatigue as well.

Yes?

Q39: How do you deal with relying on things like Boost?

Mary L. Thomas, RN: Boost? If somebody has a problem with appetite and they really are having a hard time getting food down it certainly is better than eating three bites of something and say I'm done, but to have... but if you're eating a well-balanced diet anyway you probably don't need that extra... especially the extra sugar that comes associated with the Boost, but again it's a function of getting a sense of what is someone's normal diet, how much are they eating of that normal diet and then do we need supplements as well and then that would make sense.

Q39: And how do you feel about appetite stimulants?

Mary L. Thomas, RN: Appetite stimulants. So, there are a couple one of which tends to make people a bit more prone to having blood clot disorders. So, you would definitely want to talk with your provider about starting that and see what the pros and cons are for you versus not. Some of the patients find marijuana to be a useful appetite stimulant. I'm always concerned about anything that gets inhaled into lungs. So, marijuana is included as well as tobacco from my perspective, but it's those sorts of things that you have to kind of weigh in and some of the others it's a function of you might need a much higher dose before you'd actually see an effect. So, I would definitely have a conversation with your clinician about pros and cons and which one might work best in that particular situation.

Any of you having problems with sleep? Yes?

Q40: I have a question.

Mary L. Thomas, RN: Sure.

Q40: Is it possible to take in too much protein?

Mary L. Thomas, RN: Too much protein. If you're kidneys are having problems yes. Your kidneys have to filter all that protein and a very, very high protein diet can impact your kidney function in a not good way. So, yes. There's too much of anything can be a problem including protein.

So, sleep disturbance. I just told you you need to drink all this fluids. Well, it's great. Thanks so much. Now, what's going to happen to me during the night? Right? If you're trying to get all those fluids in have a cutoff. I'm done by four o'clock in the afternoon so that I have those extra hours to try and get that out of my system before I try and go to bed and then don't have to get up quite so often during the night. Men certainly have more a problem with that than women. Women had their problems earlier in life. It's retribution time for men. Simple things though. When was the last time you had a new mattress? It's amazing and a lot of my patients say I've had it for 35 years. Well, have you considered getting a new mattress? Oh, my gosh. What a difference it made. My sister had what she redeemed restless leg syndrome. She got a new mattress. She has no problem with restless legs. I mean, sometimes it's these simple things that

we just don't think because we think well it's a medical problem we need a pill and then all of a sudden we're trying to balance taking 36 pills. Sometimes if we think about other things that we can come up with some simple solutions to things. Is the ventilation... is the temperature right in the room? Is it too hot? Is it too cold? There's been some interesting research lately on the ill effects of the blue lights from all of our electronic devices that are in our bedrooms and how can you get rid of that blue light so that your sleep patterns become a little bit more normal. So, all these little things that we can kind of consider to do and then, of course, making sure one's pain is well managed and that could be physical pain, it can be emotional pain, it can be spiritual pain making sure that that gets managed to the best it can be as well and then of course, last but not least is to improve the anemia.

So, I'm going to end by just asking some questions of you to consider. Does your spouse or other family members share your view of quality of life and is that helpful and if they share a different view of quality of life is that helpful or does that become a barrier for you?

Does your doctor understand how MDS impacts your quality of life? Why or why not? Well, they never ask. Okay. Do you tell them? It has to be a two way street. You have to be the advocate and I appreciate that that's a lot of work.

Do you use your thoughts about quality of life when you're making decisions about therapy? Now, we always say well, but it's... you come in and the doctor says oh, I think it's time... based on your counts or your last bone marrow results we should go on Azacitidine. I'm just pulling something out of the air. Well, how is that... Tell me more about that treatment, what is the work associated with that treatment, how am I going to feel during that treatment and then make those decisions about how well that impacts your quality of life in a positive or a negative way as opposed to looking at I'm treating numbers. Dr. Greenberg alluded to that earlier when he said in his practice he transfuses base on symptoms, not on numbers. I wish that were true for more clinicians.

Q41: How do we get that thought out to the hospital so they're making the decisions about a certain number?

Mary L. Thomas, RN: It's a real challenge because there been a lot of studies that have been done in acute care settings in the hospital settings and particularly in the ICU. That showed that people who were transfused with a hemoglobin level when a higher hemoglobin level did worse than if you let it down at seven. In the acute care setting you are staying in a hospital bed, you may be getting up to a bathroom and back. You're put in a wheelchair to go down to x-ray. That's it. You're not trying to live a life outside in the home. You're not trying to prepare meals. You're not trying to get to and from the doctor's office. You're not trying to still go out to dinner with someone and what sadly what has been done is with those studies we've extrapolated that from an insurance perspective usually that we shouldn't transfuse unless the hemoglobin is less than seven, eight, nine, whatever and that's where then it becomes it's not to say you can't do it

but it requires then a lot of extra work on the part of the clinicians to defend why in this particular patient you need to do that and if you think about it if we were to raise the threshold I'll just pull a number out, say 10, and we kept it at 10 we wouldn't be necessarily giving any more transfusions...

Q41: We have (inaudible 2:53:51)

Mary L. Thomas, RN: But your ability to feel better would probably be... and be able to function better might be better than if we kept it at eight which is a very common one in the community.

Q41: Well, we've been through all this because to transfuse at 8.4 and it only brings us up to 9.5 after two units...

Q42: (inaudible 2:4:12)

Mary L. Thomas, RN: Yup. Yup. Yeah and...

Q42: (inaudible 2:54:16) then you're sending out that much.

Mary L. Thomas, RN: No, it doesn't and that's I think the other... we think about it well it's and as Dr. Greenberg alluded to earlier we know that chronic anemia puts more of a strain on the heart and so I think, again, as a patient advocate to help people clinicians to appreciate that... well, what is it doing to my heart by keeping hemoglobin at 9.2 because they might not be thinking of it from that perspective. So, again, it's that sort of work that is expected of patients in order to bring that back to help remind people sometimes of those sorts of things.

Yes?

Q43: I think this is the right place to come in. I was talking about what I feel like... I go to Kaiser... Kaiser (inaudible 2:55:10) for four years and my particular transfusion center and my hematologist (inaudible) and the team (inaudible) the team. The last year has decided to put embedded with the team a psychologist and she's not like in another building. We do have to know psychologist in the building at Kaiser before I go. She's right there with the team in the clinic and I started going to her recently and of course, she's doing people who just got diagnosed in the (inaudible) for years and I really feel like just having met her and having her in my life now has helped me a little bit because I liked her immediately. She looks at you right in the eye when she talks to you and she just picks up on... I think it's fascinating and so I mean I don't know if everyone else where they go what doctor they go to. This is something new in my particular team that I work with.

Mary L. Thomas, RN: So, this woman has the luxury of having a clinical psychologist embedded in her care team at her Kaiser facility. We are fortunate at the VA. We have a clinical psychologist embedded in our team as well as the social worker, but I'm curious do others of you have access... ready access to a psychologist?

Q44: Social worker.

Mary L. Thomas, RN: Social worker. Okay. Good. Nurses that are talking with you and not just giving transfusions?

Q45: (inaudible 2:56:48)

Mary L. Thomas, RN: Okay.

Q46: Excuse me. I notice that we haven't said anything about the spiritual team.

Mary L. Thomas, RN: Yeah.

Q46: Is there a person embedded that's spiritual? I would imagine that spiritual care or a chaplain or (inaudible 2:57:02) really go into that?

Mary L. Thomas, RN: It depends on who you're dealing with. Some nurses will feel comfortable with that. Some physicians will feel comfortable with that. Others won't. Some psychologist will. Some won't. At the VA, again, we're very fortunate. We do have a chaplain staffed full time in our facility. So, we always have access to that. Some people find their own religious leader from their own church is very helpful or synagogue is very helpful. Others don't... say well, I'm not religious, but I'm spiritual and then so they don't want that conventional kind of pastoral care, but they still want to have that opportunity to talk about the spiritual thing. There are some support groups out that have sorts of things. There's a wonderful one up in Marin. I appreciate that's not convenient for a lot of people, but look around. There are venues available if you feel that those needs aren't being able to be met with your own care team and ask your care team members. As a perfectly appropriate question to say so I really feel that I have some spiritual needs that I'd like to have addressed. Who might I meet with to have that happen? And see what they say. They may not be able to do it or they may not feel comfortable doing... or they may feel that they don't have the skillset to do it, but they should be able to direct you to someone who could.

Q46: Well, thank you. I just noticed because we're living longer and stuff, but I see a lot of the palliative care stuff going on because we have hospices now and but even before that point I don't see it.

Mary L. Thomas, RN: Right. Right. Right. And the whole business of bringing palliative care in at the beginning of someone's diagnosis with a potentially life threatening illness we're not anywhere close to that and we don't have the manpower to do it for every single one. So, it still is a challenge.

Q46: Thank you.

Mary L. Thomas, RN: Yeah. A couple more questions to consider.

Think about how your MDS has impacted your life beyond the fact that you're not as young as you used to be. I think most of us it's for me it's like I see a picture of myself and oh, my God. What happened here? I don't view myself as being 62. I view myself as being 40 or sometimes even younger and so a lot of us, I think, have that issue in our heads of we're really younger than we truly are and so some of what we're experiencing is simply the impact of aging and not necessarily the disease. Other times it's the disease has certainly thrown it a bit further along.

And then thinking about the financial problems you might have and is your job currently a help versus is it a hindrance and if it's a hindrance are you financially secure such that you can leave that job? Sadly many people that's not the case and so that still is an issue for them.

And then to consider if your family and friends help versus they interfere. Does your faith help or does it interfere? And does your attitude help or does it interfere and for any of these things that it does interfere consider how you might take it and try and turn it in a way so that it's less of an interference for you.

So, last slide that I have is to decide what in your life is truly important, what truly brings quality to your life and to decide what isn't and what doesn't. Can you still do at least some of the things that really do provide quality to your life? It may not be as many as you want. That's true for many of us, but are there still some that do and are those the ones that are most important to you and to consider again how your treatment, how the illness and other health issues you may have could interfere in that regard.

Before I break for any additional questions I did want to mention this at the beginning and I forgot. (Attendee) had brought this to my attention. If any of you have gone to this in the past you know how excellent the Leukemia and Lymphoma Society sponsor a conference every January and... in San Francisco and within that conference there is a session on MDS and this year Dr. Brian Jonas from UC Davis is going to be the facilitator for the MDS session and they're also going to have a caregiver session at this event. The date is January 27th and it's going to be at the Hyatt Regency in San Francisco in Embarcadero Center from 9:00 to 2:00 and if you go on the Leukemia and Lymphoma Society website soon they will have the registration for it. It's not quite up yet, but I would really encourage you to take advantage of this excellent opportunity if you can.

Okay. With that I will ask if anyone else has any other questions that... Yes?

Q47: You were talking about nutrition that you were talking about hydration. When one has congestive heart failure as well. So, (inaudible 3:02:44) that you take a water that she needs for her anemia (inaudible).

Mary L. Thomas, RN: That's always a challenge. Are you weighing yourself regularly?

Q48: Every morning.

Mary L. Thomas, RN: Okay. So, what your weight is going to tell you how well... or how much you overdid the day before and then the other thing is that I would consider for you is making sure that you're paying attention to your sodium intake so that that's not... the chicken broth and all those kinds of things are probably not in your best interest and see... I see some very nice thin ankles so you're dealing well.

Q48: At the moment.

Mary L. Thomas, RN: At the moment and hopefully that can continue, but then that would be a good question to work with your cardiologist as well as I know I should probably get at least four or five glasses of fluid in and how well does that work for you. Good question. Any other questions? Yeah?

Q49: How do you make yourself gain weight (inaudible 3:03:44)?

Mary L. Thomas, RN: Make yourself gain weight.

Q49: Just (inaudible 3:03:50)

Mary L. Thomas, RN: So is it an appetite issue or you start to eat and then you get full very quickly or you look at the plate and you go there's no way I can eat this?

Q50: (inaudible 3:04:04) and then you say (inaudible).

Mary L. Thomas, RN: A couple of strategies that I have used that some patients have found effective but not all, of course. Give yourself a big dinner plate. Put very small amounts on the dinner plate. Rather than a small plate, big plate, little pieces and say I can get that much in. Oftentimes what happens is you see a plate of food and you go there's no way. It's too much. So, it's a quarter of a sandwich not even half a sandwich. It's just a few bite and then you need to do what my mother would call grazing. So, every hour or two hours it's just a little bit of food throughout the day as opposed to trying to eat the standard three meals. It may be six or seven

but it's very small parts at a time and then the other thing would be to make sure that what you are eating has a lot of calories and protein and then if you need to have a vitamin supplement to go along with that, but then within that something you actually enjoy eating and, again, it may only be a couple of bites but making sure that there's something of that as well and then beyond that then I would encourage you if you haven't to meet with a dietician to see if they have some additional strategies for you.

Yes?

Q51: Are there forums for more specific types of MDS? For instance in my case I'm interested in CMML.

Mary L. Thomas, RN: Are there different forums for different types of MDS? I think one of our biggest problems with MDS is we use one label for five – seven different diseases. One size fits no one and that is a major challenge that I think we find and our problem and you're particularly... I'm glad you pointed out CMML because it behaves considerably differently than other forms does. To find enough people with that particular type that you could then have a meaningful support group is a challenge. It's hard enough just to get MDS, but that is too much of a mixture of different folks. You're probably better off if... a couple suggestions I would have. One is to call the MDS Foundation and see if they have anything specific. Your local here. I'd call the local Leukemia and Lymphoma Society chapter. See if they can pair you with an individual who has CMML and get some support from that individual as well because all of the locals... people through the Leukemia and Lymphoma Society have gone through some really good training for providing support for folks, but you would want that one specific disease type. It's right here.

Q52: Excuse me. Does everybody know about the MDS forum online?

Mary L. Thomas, RN: Well, I would hope so because you're here through it, but yes that's the other point and that's what I said it's just really the MDS Foundation. So, when you go on the MDS Foundation's website there is a forum and you can certainly get some information and also support through that as well, but your point about targeting a specific subtype that's where we really struggle and I think we fall short.

Peter Greenberg, MD: One of the things that I would comment on is that the CMML is a hybrid type of disease. It's a spectrum between MDS and myeloproliferative neoplasms. There's now I mentioned earlier the NCCN, the National Comprehensive Cancer Network. There are guidelines. Those guidelines are available for patients as well as for physicians. So, for MDS there's one set. CMML is covered in there somewhat, but there is now new guidelines for myeloproliferative neoplasms that includes CMML. So, that group of diseases is now being covered at least by the NCCN and so you could certainly read there. You have access to it. You just indicate what sub disease you're interested in and CMML has similarities and dissimilarities

from MDS including some of the mutations that are present and so that set of guidelines can let you know where the disease is and what kind of treatments are suggested.

Mary L. Thomas, RN: Yes?

Q53: And for the first time (inaudible 3:08:47) society meeting this year in January. (inaudible) for myeloproliferative neoplasm which includes CMML and so hopefully there are (inaudible).

Mary L. Thomas, RN: So, for those who didn't hear. So, at the Leukemia and Lymphoma Society meeting on January 27th in addition to a breakout session devoted to MDS there will also be a breakout session devoted to myeloproliferative disorders and CMML can fit in there sometimes better than in the MDS. It kind of depends upon which flavor of CMML you have, but again to speak to your original question about support I would suggest either through the forum to see if there's someone there or through the Leukemia and Lymphoma Society.

Any other questions? Comments? Things one would like to share? Yes.

Q54: My husband has a problem when he's after chemo treatments that he doesn't have an appetite but there's a metal taste in his mouth. Is there any way we can correct that?

Mary L. Thomas, RN: Try using plastic silverware. It's the metal fork that's the problem.

Anything else? You guys have been amazing. It's been a very full day. Thank you so much for your time and attention and for your contributions to this discussion. It's a real privilege to be here and I think you. Take care.

(Applause)

Peter Greenberg, MD: Thank you. It's been a great afternoon and morning. Please keep in touch. Mary and I will be here for a little bit to answer some questions if you still have some.

Mary L. Thomas, RN: Thank you.

(Applause)