Speakers:
Deborah Murray
Stuart Goldberg, MD
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Deborah Murray: Hi, everyone. I'm Deborah Murray from the MDS Foundation. I know I've talked to just about everybody in here, but I just wanted to mention though the bathrooms are out the door past that reception desk to the right, not that far and the meeting, as you know, will be recorded. So if everyone could just grab the mic and pass it to… it should be one in every area. Just pass it to the person that's going to be doing the talking, asking questions and things like that and, of course, you know the breakfast is back there. Jayshree is here, the nurse, and the doctor should be here soon.

Okay, everybody. Welcome. Thank you for coming, too. Thank you very much and if you have any questions, just let me know and if we have any extra material, you're welcome to it.

Dr. Goldberg should be here in a minute and you just hit that button. Some of them sound like they're already on. Just pass it back and forth to one another. If you need anything, let me know. I'll be right out here and maybe right back in the room. Okay?

Stuart Goldberg, MD: I'd like to welcome you to the John Theurer Cancer Center and on behalf of the (inaudible 8:42) I'd like to welcome you to (inaudible 8:45) patient forum. Try to keep this a little informal, so if you have questions, just sort of broad questions and they can last to the end, that's fine, but if you have something (inaudible 8:55) you have the answer right then feel free to interrupt me.

So, I've had the pleasure of working here at John Theurer for about 17 years now. First as (inaudible 9:06) transplant doctor and then in the division of leukemia, taking care of patients with myelodysplasia and so we're going to talk a little about what is Myelodysplastic Syndromes and some of the new therapies and really sort of set the stage as to where we are. The good news is that they have made a lot of progress as I started here about 17 years ago. The bad news is there hasn't been a lot of progress in the last 10 years. So, we saw a flurry of activity about 10 – 15 years ago and then it sort of halted and we're sort of in that phase right now where there is a lot of experimental therapies being given, but nothing really is sort of jumped out as our next wave. So hopefully, some of the new genetic revolution that we're starting to see that's coming across all of oncology will pay off for patients with myelodysplasia and I try to hit some of the things that we're doing in fits there and new in MDS.

So to start with before you talk about MDS, you really got to talk about what is the (inaudible 10:07) because Myelodysplastic Syndrome is a group of diseases that affect the blood production and so when you see your doctors and you get those printouts every day, they always hand and expect that you sort of know what they are. I'm going to remember that one has three cellular elements and then plasma. So if you left some blood sitting on a table or sitting in a tube, it'll settle to the bottom and you'll see some thick stuff at the bottom, the red stuff and then a little bit

of layer of white cells and platelets above that. So, we have the red cells which carry the energy and the oxygen and that's measured in hemoglobin, but if you look at your (inaudible 10:45) you'll see the word HTV or hemoglobin. A normal healthy man has about 14 pints of blood which would be hemoglobin about 14. A healthy woman has a hemoglobin of about 10 or about 10 (inaudible 11:00) on the hemoglobin scale. Then there's a whole bunch of other things they talk about with the red cells on that sheet but really pay attention to the hemoglobin because it tells you how many pints of blood and why do you care about that, well what does the red cells do? Red cells are the trucks that go to the lungs. They pick up the oxygen and then they take it to the muscles. If the muscles get fed you have energy, you can move around. If the muscles don't get fed, if you're tired, you feel weak (inaudible 11:27). Now, there's other reasons why we get tired and (inaudible 11:31) to bed and that might be if you have lousy lungs because if you can't get the air in you can't (inaudible 11:38) and if you don't have a good heart, you can't push those trucks around. So in order for the legs and the muscles in the legs to be fed, you have to have good lungs, blood to pick up the oxygen and then a heart to push it around. If all three things are working then your energy level can be okay. If anyone is broken then you can have the same effect and unfortunately some of our patients with myelodysplasia because myelodysplasia tends to hit older individuals, may have problems with their lungs and their blood, heart and their blood, and that compounds the issue.

In addition to the red cells, we have white cells and white cells their job is to fight infection. That's the immune system and that's the key to when you're getting infections over and over again and then there are platelets and the platelets, their job is to stop you from bleeding. Now, they're only half of the clotting system. The other half is the clear stuff that goes above the blood. That's called the plasma and the best way to think of platelets and plasma are the platelets are the bricks and the plasma is the glue. So if you have a cut, I'm going to have those little bricks, those little platelets fill in the holes, but then after a while they'll fall out so you need to the plasma then to sort of seal it up. In patients who have hemophilia, they're missing the plasma and that's why they get big bleeds, bit joints like knee bleeds that are big and are swollen whereas patients with myelodysplasia have problems with the platelets and platelets are not being able to seal up the holes and that's why the classic bleeding for patients with myelodysplasia are a little tiny dots called petechia. Those are the bruises that you see in your legs because they're little tiny bleeds. So, there're very different kinds of bleeding, but this is all the blood elements and all this blood is made in your bone marrow. So if you think about what a dog bone looks like that's what your bones look like. They're hard on the outside, they're hard on the inside and there's a red core just like in a dog bone that red core is called the marrow and that's where the factories are that make the reds, the whites and the platelets. Now when we were little, we made in all our bones, but by the time we become adults, we make them mostly in our back thighs and the iliac crest that top part of your back thigh which is where the doctors stick their needles and a little bit here in the sternum and all the other bones are unfortunately are not scarred and can't be used. So, that's' the blood elements.

So, what is myelodysplasia or Myelodysplastic Syndromes? Well, it's a group of diseases where the bone marrow factories have become damaged and no longer produce blood. So, think of it as that the damage to those factories and if you damage the factors then what happens? You don't make blood, you don't make red cells, you don't make white cells and you don't make platelets and part of the problem with MDS is it can be very, very heterogenous. There are some people that just don't make reds because the red factories are broken, but their white factories and platelet factories are perfectly normal and there are other people that have broken platelet factories, but their red factories and their white factories are normal. So, this disease can show up in a number of different forms and it can change over time. Most commonly people will have the red factories, the energy factories being the ones broken first and then over time the other factories will start to disintegrate and what you can see at the bottom is what we also don't want to see and the old name for MDS was preleukemia. We got rid of that because most people don't develop leukemia, but what can happen to about 15 – 20 percent of individuals is the white factor as it degenerates can turn truly cancerous and become like a weed in a garden where it just… all of a sudden it grows out of control and destroys all its neighbors.

So, you have plants that are dying and now you may have a few weeds and if it's just a few weeds in the side, who cares? The plants will still be dominating and it depends on how fast they slow down, but if the weeds take over then it doesn't matter how good the plants are. So sometimes we'll have patients who have myelodysplasia who their path are slowly drifting down and then all of a sudden it looks like they went off a cliff and what happened? Well, all of a sudden one of the white cell factories became a leukemia cell and took over the whole field all at once. That doesn't happen to most individuals, but it is one of the things that we see in myelodysplasia.

So, probably until your doctors told you that you were involved or your loved one was involved you probably never heard of the term myelodysplasia. It's not one of those sexy diseases that they have big walks for and… because it is pretty rare disease, but it is a common disease actually as people get older. So, we used to think of it as a very rare disease, but now as we look more and more we're see actually there are more people who are getting this disease as we sort of look for them and so this is a study that I did… Well, this is one of the studies that we did here at Hackensack about a decade ago that looked at how common is MDS really in the United States and what we did was we went to at the end of the day you get a bill. So, we went to Medicare and said to Medicare how many times did you get a bill for somebody that had MDS? One way to find out just add up the bills and it turns out that the bills… what the government thought was 10,000 cases a year when you start looking at how many times they were being billed, it's probably in the order of 40, 50, even 60,000 patients brand new per year. Put that in perspective breast cancer is about 180,000. So maybe a third as common as breast cancer. So, it's not one of the most common cancers, but it's probably not as rare as people have heard and so what we saw is the incidence about a third or quarter of breast cancer about as common as non-Hodgkin's lymphoma, some of the diseases that maybe people have heard of and so I know that you probably talk to your friends that I have myelodysplasia and they sort of look at you because

they never heard of it, but it actually is a disease that is something that most hematologists, most blood doctors and most cancer doctors have heard of because it is actually a fairly common disease.

The next question is who gets this disease? And so when we look at the epidemiology we see who gets the disease. It is a disease of the elderly. As people get older, we see much more. We rarely see this disease in people under the age of 50, even under age of 60 it's pretty uncommon. When we see it in young individuals, we can see it sometimes in children first when they're born because it's some genetic abnormality, but when we see it in younger individuals we almost see it in combination with a chemical or a poison or something that would have damaged their bone marrow. We have a famous patient right now across the river, Robin Roberts, who's on TV and she got myelodysplasia from chemotherapy that she got years ago for breast cancer. So, we see people get chemotherapy. We see them on purpose get a poison and then three to five years later, we see the damage to that out to the bone marrow.

Now, in many of our individuals they have in patients that haven't seen a chemotherapy drug, but what they have is they've been working in the industries that have gasolines, they've been working with (inaudible 19:09) in the painting industry and the printing industry. Here in New Jersey we have that toxic gunk called the New Jersey Turnpike and as you drive there you start to get all the nice odors and you know that if you lived around there and working with all those chemicals then those chemicals over time could cause damage and it's usually not a one-time, oh, I painted the house. It's people who are in the painting industry that are getting exposed to these agents year after year and month after month, those type of long term exposures. Little tiny exposures that over time accumulate that damage to DNA, damage to the genes that make the blood damage the factories and that leads to myelodysplasia. We also see that it does run a little bit in families. We see that smoking… or we know smoking damages a lot of things. We think of the damage to the lungs and the heart and the cause of lung cancer, but it also can damage the bone marrow itself and cause it and solvents as we talked about.

Interestingly… Go ahead and have your glass of red wine because it's good for your heart, but it also it seems that red wine has been associated with a decrease in the risk of myelodysplasia. I don't know why, but that's just one of the things that has come out in public studies. So, that's a good thing.

Q1: (inaudible 20:27)

Stuart Goldberg, MD: Unfortunately, it won't improve disease. It actually may make the platelets go down and could actually cause you to have more trouble with the disease. So, I don't say that you can't have any glasses of wine and things like that, but it's actually… small doses of alcohol given for (inaudible 20:46) period of time will actually suppress the bone marrow. So actually, it can make the blood counts go down. When you stop drinking actually you see a rebound in the blood counts come up. It's very common as a fellow we used to get calls on the weekends for

just go to the veteran's hospital. I worked at a veterans' hospital on weekends and we would get called to the (inaudible 21:06) with low blood counts. That's because were binge drinking on Friday and the counts were really low on Saturday and we started drag our feet and said I don't want to see them today, I want to see them today. By Monday when we walked in the blood counts were normal. It was an easy consult saying… counsel, patients been cured. Call us next week.

So how do we go about making the diagnosis of myelodysplasia? Well usually what triggers it is the family doctors when they're doing a routine blood count or because somebody's feeling tired or weak or because they're bleeding. They do a regular old fashioned blood count. They look at the blood counts and they see the blood counts are low. You have low red. You have low white and the white platelet and then they send you to a hematologist and the hematologist then says, "Well, I take out the vitamin deficiencies. So, they're not iron deficient and they're not B12 deficient and not folate acid deficient. So, it's not something I can easily correct. Let's take a look at the bone marrow. Let's look at the actual factories," and that's why they do the bone marrow biopsy where they stick a needle into your hip. Usually in the hip, sometimes a little in the sternum and take a look at the actual factories and what they need to see is dysplasia. Dysplasia means change. So, they have to see that the factories now look abnormal. You can't make a diagnosis of MDS unless you literally see the actual factories looking abnormal and it's supposed to be at least 10 percent of the factories look a little abnormal. That's how we make the definition. So, we look under the microscope and we'll see this is red cell factories. This is what they actually look like and I will tell you that these are ugly looking red cell factories. Typically, this type of (inaudible 22:40) right here would be the right size, maybe the (inaudible 22:43) these are all different shapes. They're all different densities of how the staining is. This a person who looks under the microscope all the time and say these are ugly looking red cell factories. If you break your factory you're going to have lower red blood counts and that's myelodysplasia. So, there's how you make the diagnosis.

Now, once we say okay the factories look bad then you want to give it a name. We want to say what kind of myelodysplasia and there are different factories – the red factories, the white factories, the platelet factories and depending on which factory breaks and how many of them break we can give it different types of names. So, back in the… back 20 plus years ago the so called French American British (inaudible 23:27) FAB was sort of the naming classification and the strategy that the FAB came and took was that myelodysplasia was preleukemia. So, we named it from the least aggressive to the most aggressive by how many leukemia cells the person had. So if somebody had no leukemia cells and just an ugly looking bone marrow that was called refractory anemia. If you had leukemia cells called blasts you had refractory anemia with excess blasts. If you were having a whole bunch of (inaudible 24:00) excess blasts in transition and if you crossed the magic barrier of 30 percent weeds in your garden, 30 percent blasts that's when we called it AML, acute myeloid leukemia because when you have 30 percent weeds in your garden that's when it steals enough nutrients and all the blood counts tend to crash. So, it's a very simple diagnostic naming system, but of course we make things more complicated as we

learn more and so the World Health Organization then changed the names to more reflect some of the other advances that we had in understanding the disease and also understanding what we could see under the microscope and so they took that refractory anemia and realized that there were people who just had low platelets or people who just had low whites and they made it instead of refractory anemia the low red count to refractory unilineage descending on what lineage, what cell was broken so we could now have a name for the people who just have low platelets and then we started to change when we realized that there were some people that had iron granules stuck in their bone marrow and then we call that ring sideroblast (inaudible 25:11). So, there's (inaudible 25:13) with ring sideroblasts and then we renumbered the number of blasts to refractory anemia type 1, excess blasts type 1 and excess blast 2 depending on how many leukemia cells were there and got rid of this transition in name because it was felt that actually it wasn't 30 percent weeds in the garden. It was really 20 percent weeds in the garden when things started to be more dangerous. So, it's a just a renaming of this. So when you see your reports, you'll see somewhere on the pathology report the doctor will say this looks ugly, we're going to call it MDS and then we'll give it a specific name of the type of MDS depending on what they visually see under the microscope. The reason this is important is that as you move from here down to here the aggressiveness of the disease gets worse and unfortunately the prognosis also gets worse which means that we may not be very aggressively treating the patients up here, but the people down here we're talking about serious chemotherapy drugs.

Now in addition to what we can see under the microscope, we know that if we go into those cells, they're damaged the way they look on the outside, but they're also damaged the way they look on the inside and so that gets into the genetics, the chromosomes. So as we all know we're either boys or girls. That means we either have 2 Xs or an X and a Y as the chromosomes that everybody here knows about, but every cell in your body has a whole set of codes to make you. So, there are 46 chromosomes in every cell that the sperm and the ovaries and starts sperms in the eggs. So if you look at inside the red cell factories or inside those white cell factories you pull out the damaged factory and look at the chromosome pattern in there, you may see that they've been broken or damaged and the breaks that we're seeing are consistent. There are certain breaks that happen all the time that we think that that's what gets broken. That then leads to the factory being broken. If the gene is broken then that's what leads to the whole syndrome of MDS. And so although we have a number of people having normal there are several of you that are very high. Chromosome 5, for example, tends to break in a lot of patients, the most common break and especially the long… the long arm of chromosome 5 which is called the 5Q that area tends to be very fragile in patients with myelodysplasia. So if you break that area that then tells the factories not to be able to make red cells. There are other chromosomes that can be broken. Chromosome 7, for example, is frequently broken and when 7 breaks it tells the whole bone marrow to sort of disintegrate at a very fast rate and move more quickly to leukemia. So, it's not just that there's a break, but it actually tell the factory how to break or what way it's… which way it should move and how fast the bone moves. So, the chromosomes have not only just a diagnostic property, but they make prognostic property because they actually will tell us how that person may evolve during the course of their disease.

So, once we've seen the patient and we said, "Okay. Unfortunately, that low blood count is being caused by a damaged factory," and you call it MDS, you put a fancy name on it. The next thing that we'd logically want them to do is figure out how dangerous is that person's MDS for that particular person. So, we want to put it in a risk category. Is it a high risk disease or a low risk disease because once again we're going to… it's going to change how we think about treating the patient. If somebody has a low risk disease they're not going to want to take a lot of risks in their therapy and we don't need to offer them a lot of very risky therapy because their disease is going to move slowly. On the other hand if they have a high risk features such as they had bad chromosomes, they have bad numbers of leukemia cells. Well, that disease is going to be much more aggressive and therefore you may want to talk to them about more aggressive therapies because the disease is more dangerous. So, we can do this at different levels. We can do it by just looking at the microscope or we can start getting into the genes and then to try to pull this all together over the last 20 years we developed so called scoring systems that you may have heard about and they're in the MDS Foundation's book. They're in the Leukemia Society's book. There's usually some type of scoring system and I'm going to go through that because it's important.

So, it's called the International Prognostic Scoring System or IPSS. This is the most commonly used scoring system that was developed in 1997 by Dr. Greenberg and colleagues from Stanford as a part of an international, that's the I, the International, effort. So what they did they looked at over 1,000 patients who had MDS who had not received any treatment at all. In fact when they were doing this, there weren't any really good treatments. So, all his patients that received was blood transfusions and antibiotics and they saw that some of those patients did very well and unfortunately some of those patients didn't do well and they went and pulled their charts and they said, "Had I met them on day one, was there some way to predict that this person was going to do well and this person was going to do poorly? What should I have been able to recognize that would have told me how their disease was going to move?" And what turned out was there were three simple things that if the doctor knew on day one he or she could predict the sort of the idea of how fast that person's disease was going to evolve. And the three things make sense. The first was how many leukemia cells? The more leukemia cells, the more weeds you have in your garden, the faster the whole garden is going to fall apart. The second was how many plants are damaged? The person who's just anemic, just tired, is going to live a lot longer than the person who's tired and bleeding and infected. So if all three plants are damaged, the prognosis is not as good and the third is that genes, those chromosomes. If the chromosomes are damaged well, that's going to tell us that the whole… If you damage the code, the program doesn't run as well. So and depending on where the code is broken it tells the whole thing just to break at different speeds. So a simple thing that the doctor can do when they first meet a patient to try to get an idea of where this patient's disease may head is to look at how many leukemia cells, how many factories are broken and what are the genetics and with that doing this more complicated system we could then add up the points that you get for each of those and put people in the four categories of a low risk category where people do pretty good for a long period of time and two

middle categories, Intermediate 1 and Intermediate 2, where the survival starts to drop and a high risk category. Now, people have sometimes broken these… they'll do this testing and then they'll call it low risk and high risk and generally the line is right here at the right between Intermediate 1 and Intermediate 2, but in general most doctors would say that if a patient has… after adding up the number of leukemia cells, looking at the genetics and figuring out how many blood factories are broken if you have low amounts of points you fall into a low or Intermediate 1, those are patients we'll take a more slow approach to and if people fall into higher risk categories that would be considered Intermediate 2 or high risk.

Now the problem is that although the system really revolutionized how we think about the disease and really has guided how we started our treatment, it's not so accurate on the ends. Most of the people who have high risk disease, they don't do well and they don't do well consistently. So, we add up the points and it's high risk we can tell people pretty assuredly this is a high risk disease let's be more aggressive and likewise for the most part if the score comes out very low we usually can tell if a patient, "You know what? You have a low risk disease and we can take a slow approach," but as you get into the middle it sort of becomes harder and harder to really predict and if we can't predict, we can't then advise our patients the best way of should they be slow or should they be faster in their approach to therapy. So after a decade and most people, fortunately, I will tell you show in those lower risk categories when they're first diagnosed, but over time the factories continue to disintegrate and people move from one to the other and this is showing that there is a difference in survival and rates of leukemia as you move up the score.

So one of the things that you should do when you were first diagnosed and sometimes doctors will repeat the bone marrow and if they repeat the bone marrow and rescore you to get a sense of where you are now. Now, the scoring system was developed off of treatment. It was what the natural… it was called natural history. This is how people do if they're not getting therapy. So, we don't really know how this changes once people start getting treated because, obviously, we can take a person who's got a very risky disease, give them an aggressive therapy and maybe move them to a different curve and that's, obviously, the hope is that if you treat the person and you're going to change how that disease is going to progress, but this is a simple system. It's in most of the campuses you get, some which your doctor I'm sure has done. If you don't know your score, this is how they determine what your prognosis is and that helps them decide what kind of therapies to be talking to them.

Now, can we do better? And this is where there have been some changes in the last couple years and so the IPSS has been revised or the IPSS-R and this gets much more complicated, but when the same doctors actually went back to new guys, but Dr. Greenberg the same guy from Stamford led it. When they went back they said, "Okay. What have we learned in the last decade or so that we could help refine this?" Well, some of the things that we learned was that the genetics profile that we looked at before had gotten smarter. We can actually get more genes out and we know how the genes do, there are new gene categories. So, we can start putting those into the scoring system. We can move the number of leukemia cells around. We know that age

becomes important that there are differences in survival and difference in how people follow therapy (inaudible 35:55). So they need some juggling of the system. In general, it's the same system. It's just the scores have been juggled around a little bit and now we get five categories of instead of four. We rebalanced some of the scoring weights to try to get a better fit to help us basically more refine our prognosis, so we could then once again more refine our therapies.

So now, many of the physicians who will see when they see a brand new patient will do the IPSS because we're all used to that, but they'll start looking at this more refined revised edition to sort of see if that will help move people a little bit better. It's still not great. It still misses people there are unfortunately are some people that I think are going to do well and they don't do as well as I predicted based on the score and vice versa. There are some people who I thought they're in trouble and they actually do much better in scoring systems and no scoring system is perfect. So, we're trying to continually revise that because the better we can get our prognosis, the better we can take the right therapies. What's happened over the last five years for MDS and really over the last five years for all of oncology is that the efforts that we spent in the last 10 years on the human genome project are starting to pay off. So as you know, the government spent lots and lots and lots of money trying to figure out every single gene in the human body and they spent lots of money doing this, but it's now paying off in dividends for a lot of cancers because we're now finding that these individual genes, not the whole chromosome, but let's go not to the whole thing that says make your eye, but look at your eye color and maybe blue eyes do better than brown eyes. We're getting into that very fine things and looking at specific mutations and these specific mutations are starting to guide us even beyond with the old (inaudible 37:48) chromosomes are and so these are some of the different mutations that we're seeing and how they are grouping in certain areas. There are some that are important for proliferating, for cells growing back. There's some that make them… that don't have anything to do with the speed but have to do with how they actually differentiate. Do they mature properly? Some that have to do with regulation. Does one cell talk to the next cell? So, there's different ways that these genes are grouping in patterns that we're seeing in MDS and these patterns are different than we look at colon cancer, lung cancer. So, there're different genes that are involved that are telling different cancers to move at different speeds.

This is a very important paper from our colleagues up in the Boston area, Dr. Bahar has published about four years ago where they looked at a series of mutations in genes, individual genes, and found that there were several… several genes that even beyond the IPSS could then move your score up or down one's category. So, we will take the (inaudible 38:55) IPSS score and say, well, they fell into the Intermediate 1 category. There's four categories. They fell into Intermediate 1, but this particular gene is mutated and that should probably move them up to an Intermediate 2 and that changes… so here's how we can start now with finding our prognosis. This is tests that can be done from the peripheral blood. So, you don't have to have another bone marrow done to get these type of (inaudible 39:21). They, however, are very costly in the range of a couple thousand dollars to do these tests and so as the technology gets better and you see the cost drop, you may see these tests being done more commonly. We started to do here at

Hackensack only within the last year or so and we don't do them routine on everyone. We do them when we think we're going to… If we're sitting on that fence, do we treat the person aggressively or do we treat them in sort of more cautiously and not as aggressive. Well, these are the type of tests that will actually help us push this one way or another because they can be used to refine that prognosis. If somebody's really on the end with a high risk disease, this doesn't add very much. If they're on the low risk disease, well, once again, this doesn't meet… but we're in the middle and we're trying to decide do we go to transplant? Do we go to more aggressive chemotherapy or do we sort of take a cautious look? These are the type of tests that might help us go one way or another. In addition as we start getting smarter and learning more about what's broken in these diseases, what genes are broken, maybe down the road we can then come in with specific therapies that target those genes or that turn them on or off. So, this is where the future of oncology is and the future of treatment for MDS at the genetic level looking at the actual codes that are telling the factories to be not growing so well.

So as that as background, we've now seen the person. We said they have low blood counts. We've categorized what kind of MDS it is based on how it looks under the microscope and how it looks under the genetics and now we've also decided what their prognosis is to give us a general idea, general flavor of okay who's sitting in front of us and now we want to start saying, okay, let's time for us to act. Do we treat them in aggressive fashion? Do we take them in a nonaggressive fashion? So, we've broken our patients into the low risk disease and higher risk disease. In the low risk disease the focus is really on improving the quality of life. If your red count is low, but that's all that's low and you don't have leukemia cells and you don't have bad chromosomes. Well, that person's not going to die. (Inaudible 41:35) not that fast. Never that fast, but that person's… we're not worried about life and death, but what we are worried about is that person with the low red count is feeling lousy because they don't have any energy and so the focus there is to try to improve the red count, improve their quality. On the other hand if we have a patient with a high risk disease where they've got lots of leukemia cells, bad chromosomes, all three factors are broken. So, they're bleeding and infected and tired. Well now, they're unfortunately in jeopardy of dying. So, the focus changes from not just quality to possibly… and I put the word possibly quantity because once again we need to talk to our patients and say how much risk and how much do you want to go through to get an improvement in quantity? So quality is always in part in both parts. We want to keep quality, but the change in therapies from a scientific standpoint really does change how we approach the (inaudible 42:33) from a quality to a quantity as we start seeing that score move up.

So, the cornerstone in any treatment is supportive care and by supported care I mean if the person's tired and there're low blood counts, give them some blood. If they're bleeding, give them some platelets. If they're having infection give them some antibiotics. Nothing is special about this. That's sort of the basics, but it's something that is a cornerstone of therapy and sometimes we sort of forget the main thing that we can do to help somebody is to give them a pint of blood and make them feel better. So, this is the real cornerstone of the day to day management. However, giving pints of blood all the time is maybe not the best thing over a long

haul. We do see that there is a correlation between blood packs, the lower your hemoglobin, the more fatigue. No surprise. That was sort of expected and this is a study that we actually did here at Hackensack a number of years ago and we found the patients who received more and more blood transfusions had more heart attacks and the question is if they we're always anemic, they were always tired. Well, that always anemia not only weren't you feeding your leg muscles, you weren't feeding your heart muscle. So walking around all the time with chronic anemia is not that good for your heart. Likewise there seen potential damage to getting all that transfusions and the potential damage is that with each unit of blood there's also iron in the blood and so blood is not just something that brings oxygen. It actually carries iron with it and iron can damage the heart and damage the pancreas. It can damage the liver and it can cause other problems and so it's fairly well established now that the higher the iron levels which we measure in something called ferritin the worse the outcomes. So just getting blood all the time although it sounds like an easy fix in the long run can be some difficult also and I know that we have some people here who are on medications to try to keep that iron down. There's one called Exjade. There's another one called (inaudible 44:47). Actually we have a patient here who's actually on an international study trying to show us if that's the right thing to do also. So, that's supported care. Give the person what they need, what they're missing and then keep the iron levels under control. Give the antibiotics when they need to. It also means not giving people antibiotics all the time because then you're going to get resistant organisms. It also means not giving people growth factors, GCSM, Neupogen all the time because once again the cost of it and whether the effectiveness are worth it.

Q2: (inaudible 45:20)

Stuart Goldberg, MD: You didn't hear it… as far as… SO, there are damages to just doing supported care all the time. So, it's blood transfusions all the time because the iron levels can go up. Damages… you can become platelet refractory if you keep getting platelets for every single time the platelets are low. You can start getting resistant and infections if you start giving people antibiotics all the time. So, you want to make sure that use the supported care agents when you need to.

The next level up is to try to stimulate the bone marrow it makes more blood and using the garden example, the next logical thing is to get some fertilizer and we have natural fertilizers that are in all of our bodies that tell our body to make blood. So, how do I know how much blood to make for me? If I cut myself and bleed a pint on the floor and now instead of 14 pints of blood, I only have 13 pints because I cut myself. How do I make that extra blood? Well, my kidneys do the job. My kidneys actually figure out that last hour I only worked on 13 pints of blood whereas I usually work on 14 pints of blood and they send a signal to the bone marrow to make more blood. That fertilizer that they send is called erythropoietin or EPO. It goes by a couple different brand names. One is called Procrit. One is called Epogen. These are very common medications early on in the course of the disease and that is a natural chemical made by the kidneys that tells the bone marrow to make more blood and if you give a person who's got MDS some extra EPO,

well, it's like putting extra fertilizer down on the ground and trying to squeeze more blood out of those factories and so an early treatment for patients with myelodysplasia is they have low red counts is to give them erythropoietin and see if we can squeeze those factories to make more blood. Now in the experimental world, there are new Epogen-like medications. There's one called ACE001 which I know somebody in this room as been on that (inaudible 47:31). So, there are in the New York area there are studies looking at new what are called growth factors. I call them fertilizers that basically tell the bone marrow to make more red cells. Their natural chemicals or variations on natural chemicals. There also are (inaudible 47:52) and this is actually a predictor of who might respond. So, somebody who's got just early in the course of disease, but once the person's needing blood transfusions all the time, well, the factory is pretty much dead and you can put a lot of fertilizer on a dead factory and you're not going to wake it back up. So, these are the type of drugs that we use early in the course of the disease. There also are fertilizers for white cells, the most common one is called Filgrastim or Neupogen and there's one called Neulasta and there's one called Leukine and these are white cell fertilizers that can stimulate the white cells to produce. The concern always, however, has been the leukemia blasts are also white cells and so you don't want to use these chronically although fortunately we don't see that that accelerates leukemia, but there's always been a fear of giving those drugs too long for too (inaudible 48:41). So, we use these sparingly when a person will have infections to try to bring the white count up when we need it and there also are fertilizers for platelets. There are a couple of them. The use of the platelet fertilizers in people with MDS, however, has been somewhat fraughtless and vague because we do see some acceleration to acute leukemia with one of them and so these are…

Q3: Which one?

Stuart Goldberg, MD: A drug called Nplate or Romiplostim. When it was given as a single agent to patients with higher risk MDS moves it towards up to acceleration towards acute leukemia and the study was actually stopped by the Data Safety (inaudible 49:20). We were actually one of the centers and one of our patients actually accelerated into acute leukemia. Fortunately, it's not really acute leukemia. We stopped the fertilizer. The blasts came down, but worldwide there were some concerns that this drug may not be the safest drug for patients with MDS. There are other ones however. Eltrombopag, Promacta is the brand name that are being looked at in patients to try to bring up platelets that may now have the same effect on the white cells. So, the platelet factory issues with fertilizers have been a little more tricky, not just a little bit, a lot more tricky, but the red cell fertilizers have been something that are commonly used and actually have now been shown to improve survival because we can prevent the patients from needing blood transfusions with all the danger and so a couple years ago Medicare which pays for a lot of this actually put a ban on the use of Procrit and Epogen across all of oncology because they were worried it may accelerate cancers because it does accelerate breast cancer and colon cancer and lung cancer and they actually put a ban on it for a while and the MDS Foundation as well as the Leukemia Society and all the MDS doctors actually went back to the government and said, look, that's wrong. It actually helps our patients and there were some nice studies done mostly in

Europe that actually showed that the use of these actually improves survival. So, they're back on… there are now rules and some of you may have been caught in those rules where your doctor had you sign extra papers when used Procrit and there are rules by the feds on when you can use it, how high… how much you can use and those rules actually different for states. Just like there's a federal government (inaudible 51:02) it makes the rules but then each state can interpret it and I know that some of my patients go to Florida and back and there are different rules between Florida and what they can do during the winter… and they go there or they come back to me or often sometimes different because they're… but there are rules on how to use Erythropoietins.

Once we get beyond covering it up with a transfusion, we're stimulating the factors with a fertilizer, we then have to get into real therapies. Some of these are going to change the factory and that because real treatment of the underlying disease and so for the lower risk patient who has problem primarily with red cells the most commonly used medication is a drug called Lenalidomide also known by the brand name of Revlimid, is a knockoff of an old drug called Thalidomide which I'm sure have heard because of the Thalidomide babies in the 1950s, but it turns out Thalidomide actually when they gave it women for morning sickness and for other reasons and for nauseous… for morning sickness primarily what they saw was the red count actually went up. So somebody had the great idea well in cancer patients could we use Thalidomide to then bring up the blood counts and then sure enough it actually does bring up the blood counts a little bit, but Thalidomide also has a sedative quality. So, you brought the red counts up but they were still tired because now the drug made them tired. So, one of the drug companies played with this compound and came up with a new version, Lenalidomide, which when in clinical tests are now you can see almost 10 years ago showed that in patients with MDS who had primarily low problems with their red that it could make the red counts go up in (inaudible 52:44) or 12 percent, but patients depending on what genetics. In other words, it wasn't that it worked on every factory. It worked on the red cell factories in people that had specific chromosomes that were broken. If you have chromosome 5 broken, the most common chromosome broken, it actually worked fairly good. If you had normal chromosomes, it worked okay, but if you had other chromosomes, it didn't seem to help very much. The FDA, the government, gave the company approval to use it here in the 5Q patients based on two-thirds of the patients responding and didn't give them approval in the other diseases, but as we've had more clinical experience, we've now started using in patients who have normal chromosomes and we're starting to get to some selective not other chromosomes that are may have some benefit. It's not as high as it is in chromosome 5, but there may be a broader area of patients that can use the drug. The nice thing about Lenalidomide is it's a pill and so it's convenient for our patients and since in the low risk disease our goal is quality, we're trying to bring up the energy and not have them tied to the doctors because that defeats the quality. It actually is not a bad choice. It does have some side effects. Rashes are common. Blood clots especially in the lower… leg clots can be seen in patients in myelodysplasia. So, there are some toxicities that admittedly you should talk to your doctor this is what they recommended.

So that's principally the drug that we use for the lower risk and we'll talk about some other low risk in a second. I'm going to veer off because I actually know that there were some questions that were sent to me ahead of time. As a sort of unusual things, therapy and this is one of the more unusual therapies that sometimes is used in lower risk patients and that is called immunosuppressive therapy. There are a group of patients who have a different disease called aplastic anemia. Aplastic anemia is where the bone marrow basically dies. There's no… you stick a needle in somebody's hip and you see a hard bone and nothing in the middle and usually that's a chemical or a poison and sometimes it's a virus. Worldwide it's hepatitis where it just kills the bone marrow but the bone marrow is still there. It's just the immune system now has just died and it's not going to keep it down. If you ring off the immune system temporarily you allow that bone marrow to start growing back and then you hope immune system reboots it's not going to kill off the bone marrow again. It's sort like you can't get your computer to work. It's not working and you just shut it down. Let it start over from scratch and maybe it will come back up alright and so there are a group of patients who have lower risk myelodysplasia, not a lot of leukemia cells, but they have low blood counts across either reds alone or across the board and when you look at them they have immune other problems. They have arthritis. They have lupus. They have other immune problems and if you look at their immune system what they were born with they were born with a specific HLADR system, DR15. In other words they were born with an immune system that maybe allowed them to develop this over time and so these patients if we shut down their immune system temporarily by giving you horse serum and I really mean from Wilbur and from Mr. Ed, I mean real old fashioned horse serum. It actually turns off the immune system temporarily and then when the horse comes out of their body and the immune system reboots you hope that it can solve the problem and so this is what I would call mouse serum. The same idea. A drug called Campeth Alemtuzumab. The same idea. We temporarily turn off the immune system and allow them to work. It's fairly rare we don't use it very often, but this is when we see a younger patient with low risk disease. We check their immune system to see if they have the type of immune system where it may have been problematic and we've given them a short course of immunosuppressant type therapy. So a very weird combination. Not something that most oncologists are familiar with. This is actually one where the big centers will do these type of therapies.

So, that's generally the lower risk categories. Now, if you see it's mostly focused on the low red count patients. We don't have a lot of things for whites. We use a little bit… and platelets have been our problems. So when we start to see low whites or low platelets, it often just by necessity pushes us up in our treatment algorithm (inaudible 57:17) we don't have the therapies. So what do we do for the patient who has a higher risk disease where now we see either leukemia cells, we see bad chromosomes or we have low platelets or low whites where we're having problem and we can't use the other lower risk. Well, the treatments of choice for there when we decide we need the treatment are a group of drugs called hypomethylating agents. The hypomethylating agents are the most commonly used treatments for MDS and they basically try to reverse some of the damage to the DNA and let's re-fix the codes inside so that now the factories can start producing blood again. The guidelines that we follow to sort of say who should get this are pretty

straightforward that most patients who have higher risk disease should get these therapies and I'll show you why in a minute. However, we then see these therapies bleed into some of the low risk patients if they fall into… the Procrit's are not working, the EPOs are not working or they have low whites and low platelets where we don't have the drugs. So, most of the time the doctor will think about using this therapy if we have a high risk patient, but we can use them also in the lower risk patients if that's the only thing that seems like it might work. The two most commonly used hypomethylating agents are ones that called 5-Azacitidine or the brand name is Vidaza although it's now (inaudible 58:40). They also (inaudible 58:41) and then the other one is Decitabine also known as Dacogen. Both of these medications typically have been fairly well tolerated. So when I say I'm going to give chemotherapy to people and they get really scared, these are chemotherapy drugs that are not designed to poison the bone marrow to stimulate the bone marrow. The goal of these therapies is to make quality better and even quantity better. There is no age barrier. We currently have a 90 plus year old gentlemen receiving this on a monthly base at hour center and all he does is talk to me about his garden. He doesn't ever talk to me about problems with the chemotherapy. So, these are easily tolerated medications. They have to be watched. There are toxicities. They do need to be monitored, but in general this is nonage barrier type drug and both of these drugs are covered by Medicare.

5-Azacitdine was approved based on work by Lou Silverman and colleagues across the river at Mount Sinai, so New York area actually championed the use of this therapy. By the way, Lenalidomide was championed by Dr. Raza over at Columbia. So, the New York area has been sort of a champion for developing all of these drugs and really has changed the face of how they're treating worldwide. We have a little (inaudible 1:00:00) together, sit around with all the experts in the world who actually really developed all these drugs. So, 5-Azacitidine was approved based on a study that was done most started in New York and then moved out where they showed that patients who received 5-Azacitidine actually looked like they were doing better than if they didn't get the drug, but then that lead to… not only did the blood counts get better, but if you improved the blood counts, you improve the quality. So, the quality of life went up and so by measuring fatigue, shortness of breath, physical functioning, all those numbers, the low, low numbers means that there was improvement in the quality of life by people who get the drug compared to not getting the drug. So, I've had patients who come to see me and I say I'm going to give them chemotherapy and they say, "I'm not taking chemotherapy. I'm not going to feel…" If you don't get the chemo you're going to feel worse than if you do. Now unfortunately as the disease progresses, people do feel worse and it's not the drug. It's actually the disease because the drugs actually make people in general feel better. There are side effects, however, and we do have to pay attention. So, these are the type of things the doctors worry about. We really put these drugs on the map, however, was a European study known as the AZA001 trial and this trial is usually outlined in the booklets that you get from the MDS Foundation and from Leukemia Society. In those booklets they try to stay nontechnical and they said this is the one study that has so changed the field that we'll even talk about the numbers in the chart because this was Intermediate 2 and High. Remember I had those four categories? (Inaudible 1:01:35) on this side where I said survival can be limited. So once we get into the high scores, people with

multiple factors that are broken, people with lots of lots of blasts, people with bad chromosomes. These people are at risk of dying from their disease. They took those patients and they flipped a coin and said get one of these drugs given one week a month in the office or have your doctor do the best they can without that drug which was usually transfusions and antibiotics. Sometimes it was old fashioned chemotherapy and the bottom line was that people lived longer. Survival was improved by doing the Vidaza. Not only was the survival improved, but the quality of life went up. So, we saw better survival, better quality of life, better blood counts and actually ended up being cheaper because people who aren't doing so well end up in the hospital. So, this was a homerun across the board for people who have Intermediate 2 and High risk disease so much so that this is called a category one recommendation from the NCCN. Basically, it means the lawyers can sue if you qual for this because this is so well established that this is the type of thing that there's no downside here that you need to discuss it with your patients.

Now, the question is that because I know some of the people in that room have been on these medications is that they're not miracle drugs and they also don't work very fast. You're trying to put a medication in, have it go and change the factory and the factory then start producing blood and that takes time. I usually tell my patients the first two cycles are going to feel worse. It's going to clear out the dead wood before you even have a chance to have the cells grow. The second two cycles, cycles three and four and they're given once a month. The cycles are month apart. Three and four we might have stabilization and cycle five and six… so as we get into six months in the treatment that's when you're going to start seeing the blood counts start to rise and it rises in about 60 percent of people. So, not everybody benefits and it takes a long time. So, you can see how many cycles it took to get the best response. It takes five – six months to see how people are going to do on this drug especially the first few months I have to sort of just walk you through it and say, take the medicines. I'm not going… (Inaudible 1:04:00) one of the leaders at Cleveland Clinic in the field, he actually gave a speech once and he said, "What I do is I'm an ostrich. I stick my head in the sand and I won't look at how they're doing until six months are up. Then I look at them and say it's working or not." So, time to best response can be months down the road. Likewise it's a once a day using once a day for seven days in a row was how the studies were done. Then there were a whole bunch of studies looking can you do it in five days, do you need to do the weekends and this is where oncologists will spend a lot of time because we had nothing better to do. We don't have any better drugs. So, we play with what's the best schedule.

Likewise we've now gone back and look at the genetic profiling and said maybe some of those fancy genes may predict who may respond. So, there are some of those fancier genes. For example, TET2 that may predict who might respond to Vidaza or to Aza effectively. Likewise, I said there's two hypomethylating. The other brand is called Decitabine or Dacogen and I will flip through the slides very quickly because it's the same exact story. These are given once… one week a month and continues… we see the same exact profile. The difference with Decitabine is maybe it's a little bit faster. It's a little bit also more toxic in my mind as far as peeling off blasts. So, I think that the doses we use and this is opinion now, but the doses we're currently using but

Decitabine a little bit more poisonous, so it kills off the leukemia cells and so if somebody's moving towards leukemia, I might use Decitabine to treat them. If somebody doesn't have leukemia cells and the problem is mostly blood counts then I might use the 5-Azacitdine or Vidaza. There is similar type drugs. They have slightly different how they work, how fast they are and what they are as far as how they interact with the marrow, but both of them either I think my colleagues across the river. I know one hospital uses Decitabine, another use 5-Azacitidine. These are sort of Coke versus Pepsi wars.

Q4: May I ask what you would…

Q5: (inaudible 1:06:03)

Stuart Goldberg, MD: No, both of them are IV. These are both given IV. Vidaza can also be given subcu as a little needle stick. (Inaudible) causes some irritation and bleeding.

Q6: May I ask how you would treat somebody that's been diagnosed with hairy white cell leukemia and MDS? What would you treat them?

Stuart Goldberg, MD: Well, they're different diseases. You'd have to treat them somewhat separately although the hairy cell… there's indications… some people with hairy cell don't need to be treated at all and some people actually, obviously, need to be treated the hairy cell and all of a sudden the MDS gets better. The problem is the drugs you use for hairy cell often will cause MDS. So, the hairy cell drugs can be pretty toxic. There's some newer hairy cell drugs that maybe get around that but generally you have to decide which disease is causing the problem.

Q6: That's where we are now.

Stuart Goldberg, MD: We can talk offline because it's a little more complicated.

Q6: Thank you.

Stuart Goldberg, MD: So now, we're moving what's new. Well, we have three major classes of drugs… or two major classes. We have the Lenalidomide, the (inaudible 1:07:15) drugs which we talked about for the low grade. We have the hypomethylating for the high grade. So the obvious question is two better than one? And so people have looked at combining the two or using other drugs to try to make the hypomethylators a little bit more potent and so we have research looking at combined epigenetics, drugs like the HDAC inhibitors. There's a seizure medicine called valproic (? 1:07:39) acid is being used. There's a drug called Vorinostat which is a lymphoma drug that's being used. By themselves are lousy for MDS, but in combination with a hypomethylator they may make the hypomethylator better. In other words can we do something to augment the effective good drug? Yeah.

Q7: (inaudible 1:07:59) valproic acid.

Stuart Goldberg, MD: Yup. Valproic acid is a lousy MDS drug. It's a seizure medicine, but it will stimulate the Vidaza or the Dacogen to work better.

Q7: We wanted to know… I was (inaudible 1:08:17) I read some articles that a combination of valproic acid and (inaudible 1:08:22).

Stuart Goldberg, MD: (inaudible 1:08:22). Correct. Old studies been done for a long time. Works so so. It really hasn't caught on very much in the United States, but certainly… Yeah. I mean, it's something that people have done. I think when we're grasping for straws we try a lot of different things, but it is actually one… I had that slide on here before. I took it out. I had that slide on here before. It's something that has been done before. It's not sort of the norm at this point, but for people that have no responded to these drugs, to hypomethylators, it's on the list of things that people will try.

Q7: Okay and you're also saying that valproic acid does make Vidaza…

Stuart Goldberg, MD: It makes the hypomethylators better. So, there's been a lot of interest in combining that class of medications with a Vidaza or with a Dacogen to see if it will make those drugs better.

Q7: Thank you so much.

Stuart Goldberg, MD: Sure and so the combination is two drugs better than one? There's a large US study that was just reported at the December meeting that unfortunately and when I start with unfortunately… unfortunately it did not show great benefit to two drugs versus one although the study is still immature as far as its final answer. So, we will hopefully have some more final answers by the fall of the two drug versus one idea. This is a drug that we've been playing with here. This is an oral drug. Sapacitabine. It's more for leukemia type patients. There is drug called by a company called Onconova which is an infusion and then we start getting into lots of different experimental drugs where people are trying new things. So, what I talked about was mostly the mainstays and then tweaking them and then there are drugs that are just off the board that are being tried all the time, but nothing right now as I would say personally is captivating everybody's interest. There's no hot drug. I mean, there are people who think that we may have the next great drug, but there's nothing that's really captivating the world.

Switching gears is occasionally we have a patient who we think we might try to cure because up till now I've been talking about trying to make the blood counts better and prolonging survival but not curing the disease and there is a cure for this disease. The cure is something called a stem cell transplant or a bone marrow transplant, but the cure comes with a lot of price and that is these are very aggressive therapies that can hurt people. So, you have to be very selective who

you do a transplant on. It may not be on the goal for people who are frail, but age itself is not frail. This is called an allogenic transplant because you need a donor and in the old days we used to call it a bone marrow transplant because we would stick needles into the brother or sister's hip and take out the cells that way. You've all… if anybody's had bone marrow aspirate themselves for the diagnosis, we would put their brother or sister through that and we'd actually stick a needle in about 200 times to get out enough seeds and you might like… I don't mind sending my sister for that, but we would probably give her anesthesia, so she wouldn't feel it, but now it's mostly called a stem cell transplant because rather than bringing our brothers and sisters to the operating room we send them to the dialysis center or just upstairs where they sit with their arms out and the blood goes out through the machine, the machine spins around and takes what we want and gives them back their blood. Either way we have our bag of seeds whether we took it from their hip or from their blood. So, this would be bone marrow transplant or a stem cell transplant depending on where we get it from the donor. From the patient standpoint though it's lots of chemotherapy, put the seeds in and then let them grow. In other words, burn down the field, put in new seeds and wait for the new seeds to replace.

Now, what we've learned is that we don't have to burn down the field completely. So, about 10 years ago we started saying maybe we can just get a little bit less chemotherapy and do what's called a mini transplant or a reduced intensity transplant because we'd have to burn down the entire field to put the new seeds in and by doing that by giving less chemo, we allowed older individuals to tolerate the therapy. When I started doing transplants 30 years ago you had to be 20 years or less. Now, we saw that go to 40 then I saw it could go to 50 because we realized that we could give less and less chemotherapy, but the chemo I've used 30 years ago no one in this room could tolerate. It would have killed you right away, but as we've figured out that we don't need as much chemo we can get less chemo we can get the cells in and that will allow now the transplant to take.

The question is when is the right time to do it? You don't want to do it too early because the person is doing well. Why take the risk? You don't want to do it too late because then it's probably not going to work. So, trying to find the sweet spot has been a lot of interest and it looks like Intermediate 2 might be the sweet spot for many people. This is some of the survival curves and then you can see only about half the patients who go through the transplant are cured of the disease and unfortunately as we get to older individuals what we see is roughly from Europe data, the European data, one out of three… If I have three people sitting in a room and I offer them a transplant for MDS one of them will be cured and one will die because the cancer comes back and one will die because the treatment kills them. So, it's a fairly risky procedure. So, one in three and it's not a fun procedure. It's not like we do this in an outpatient. They're in the hospital. They're sick. So, it's a very thoughtful discussions as to is your disease worse enough that you need to think about it? Are you healthy enough to be able to survive it and then when we can talk about it. Now, there was a problem a couple years ago of the almighty buck and that has become less of an issue because Medicare is paying for this. It is done as part of a

national trial where the feds have set up back in the Bush administration. That gives you an idea how fast that… we're putting patients on the feds have never stopped the study.

Q8: Is that what's meant by the Demonstration Project?

Stuart Goldberg, MD: The Demonstration Project. Correct. The demonstration project was something that was set up was Medicare can't officially pay for things that aren't on their list. So, they said give us the information so we can make determination if it should be on the list and that's called the Demonstration Project, but the Demonstration Project has been going on for a decade now and it's not like there's nobody needs transplant. It's just that they have not closed the books on it. It's a loophole that the government is exploiting and they know they're exploiting it. We know we're taking advantage of it.

How about age? Age isn't the issue here. It's a performance status in the person. If they're strong enough to go in, that's what we look at. So, we have transplanted people in their late 70s. That was a question I got typed ahead of time. We have people actually… I think our oldest was 82 or 83, but he was 82 or 83 and he could bench press me. I mean, because there are some people who keep themselves in very well and shape and we didn't have any hesitation that he couldn't get through the chemotherapy portion. There are other 60 year olds I don't want to transplant because they're emphysemic, five heart attacks, (inaudible 1:15:47) had diabetes that you wouldn't touch them because you know you're going to hurt them.

So in conclusion, MDS is actually not one disease. It's a group of diseases all categorized by bone marrow that's not working. We make the diagnosis by looking and saying that the bone marrow looks ugly. We then look at the genetics inside it to see if there's any clues or anything that will help us figure out how fast it's moving. From that we can then determine the prognosis. If they have a low risk disease then we think about more supportive therapies and more quality issues what's going to make them feel better. If they have high risk disease we're going to be thinking about quantity type things and certainly the hypomethylating agents have been a big change in therapies coming out about a decade ago where they really did change the outcomes and we now have data showing that it improves the outcomes. So, those are things and then for small sets of patients we can think about transplant or immunosuppressive therapies and what's on the horizon probably will be driven by better prognostic indication from the genetics. That's where the field right now is spending its time. As far as brand new drugs out there, combinations things like that. There are lots of studies, so I do encourage people to participate in studies. We have several here. I know that across the river, obviously, in New York we have a lot… and we talk to colleagues over there, but I will tell you, frankly, there's nothing that sort of captivating the field. I mean, hopefully somebody will come up with one that sort of because when you hear the lightening one that everybody is seeking to everybody will gravitate it, but right now we're sort of in that lull again and then finally I want to give my thanks for everybody who come today and also wish you and your loved ones best wishes on all your care. Thank you.

(Applause)

Jayshree Shah: I know that you have lots of questions that were (inaudible 1:17:40) today. Feel free to raise your hand for the purpose of making sure that we don't overlap each other when speaking and then we can ask the questions of Dr. Goldberg.

Q9: One in five had the abbreviation (inaudible 1:18:00).

Stuart Goldberg, MD: So, there's a group of hospitals that got together about 15 – 20 years ago for marketing called the National Cancer Care Network and they're some of the big universities like Sloan Kettering, University of Pennsylvania, Hopkins and so they banded together for other reasons, but now what they do is every year they put out guidelines on how to treat patients. So, they publish an annual update of what in their opinion is the best therapy, but their opinion actually has taken a lot of weight. The federal government actually uses it, Medicare will use it to help make determinations of whether or not something should be paid for.

Q9: Have there been any studies in Europe and especially in France showing (inaudible 1:18:50) that there are (inaudible 1:18:53) of MDS there?

Stuart Goldberg, MD: I don't really know.

Q9: And…

Stuart Goldberg, MD: The Germans are the best ones for the incidence. They actually give us the best incidence data.

Q9: They have (inaudible 1:19:04).

Stuart Goldberg, MD: Well, they actually studied the epidemiology very well in Germany, but I don't know about the beer drinking areas versus not. It's probably in some of their publications because they actually do a lot of that kind of stuff.

Q9: (inaudible 1:19:15) question and last concern you mentioned that those who have problems with white blood cell counts their disease may more form quickly into AML.

Stuart Goldberg, MD: No.

Q9: So, then can you clarify?

Stuart Goldberg, MD: So, low white counts which are usually what we worry about. The low counts lead to you to have more trouble for the infections, but white cells are… the precursor to a white cell is a blast. So sometimes the white cells will actually become very diseased such as

white cell factories get very diseased and morph into the leukemia blasts. So, they are separate. Somebody has a low white count in of itself doesn't mean that they're more likely to move to leukemia, but it is the white cell factory that does become a leukemia cell when it decides it is going to turn into that.

Q9: Thank you.

Stuart Goldberg, MD: Yes, sir?

Q10: I have a question about the ATG. You said ATG is classified as low risk immune suppression that it empties the bone marrow and kick starts it.

Stuart Goldberg, MD: Correct. Well, it empties out the lymphocyte, the immune system part of bone marrow.

Q10: Bone marrow transplant basically does almost the same thing. Am I right or wrong?

Stuart Goldberg, MD: No. So, the… in a bone marrow transplant you basically burn down the field and replace it with somebody else's and so you have a new bone marrow and that new bone marrow when it grows it makes its own… your red cells, your white cells and your platelets and that actually new immune system, the new marrow, also can kill off any residual leukemia cells from the old bone marrow. That's in a bone marrow transplant. In ATG, all you're doing is basically you're shutting down everything and then waking up the same bone marrow itself. So if somebody has leukemia cells and you give ATG and then it shuts it down and the ATG wears off the leukemia cells will come right back. So, ATG is really used for people that have low risk who don't have leukemia cells because you are waking up the same exact immune system. You're not saving the marrow, you're not replacing.

Q10: So then bone marrow transplant would be basically with somebody that has leukemia.

Stuart Goldberg, MD: Bone marrow transplant they use… there are people who have shot bone marrow that aren't making any reds, any whites, any platelets.

Q10: That's what I was getting at. ATG would work on somebody like…

Stuart Goldberg, MD: It could. It could. If they haven't been heavily transfused, if they don't have… but they have the right immune system you can use ATG in people with very low blood counts across the board. So, you can use both of them for people who have low risk disease where they don't have a lot leukemia cells. You can use a transplant in that group, but you can also use a transplant in people who have high risk disease with leukemia cells whereas you wouldn't use the ATG on that.

Yes, ma'am?

Q11: At what point do you use Vidaza with… how do you know the last or (inaudible 1:22:30) blast over five percent. At what point would you do that and what is the purpose of the Vidaza? Is it killing off the blasts, but what are you doing to the other stem cells that you have there that are "normal?"

Stuart Goldberg, MD: Sure. So, Vidaza or Dacogen, both are hypomethylating agents are clearly the treatment of choice for people who have high risk disease. So, somebody has blasts, somebody has bad chromosomes, somebody has multiple blood counts, low red with whites, low red platelets then clearly… that's the slides I showed. That shows benefit there as far as making the blood counts get better, keeping the leukemia away and making the quality get better. So clearly, the IPSS scoring system puts you in the Intermediate 2 or high risk there's no questions those drugs. The real question is in people who have low risk disease where they don't have leukemia cells, do you then use Vidaza or Dacogen because Vidaza and Dacogen just don't kill off the bad guys, they stimulate the good guys. So if somebody has already had Procrit, already had red cell (inaudible 1:23:35) fertilizers and they're getting nowhere. If somebody has developed a low white count and low platelet counts where I don't have a fertilizer that works. That's a person where I could either just support them along with transfusions and so some people say, "Look. I'm not dying (inaudible 1:234:51). I'm just tired from the low reds. I can get going with the reds," where other people say, "Look. I don't want to keep coming to see you every week for blood transfusions. Can you stimulate my factories to make blood?" That's when we talked about using these drugs in the lower risk categories. It becomes a quality issue. Some people will find… if they're only getting blood once a month or once every two months, I'll give them transfusion. I won't bother them, but if they're coming to see me all the time for blood transfusions then I might say it's time to use a team of drug to stimulate the bone marrow and I may use that Vidaza or Dacogen which I usually reserve for my high risk patients in the lower risk patient.

Q11: Did you say that that also would help to repair the damage?

Stuart Goldberg, MD: Yes. Yes. So, Vidaza and Dacogen not do multiple things. They kill off the bad guys, they kill off the weeds, but at the same time they stimulate the plants. They actually do make the factories produce blood again.

Q11: What's the level in which you would start treating for a high ferritin level?

Stuart Goldberg, MD: For high ferritin level? So with multiple blood transfusions, the iron starts to build up in the body and there are studies that say they're around the ferritin around 1,000 that that's where we start to see damage occurring to the organs. At 2,500, that's where the NCNN, that expert panel, has said at that level we certainly see damage to the organs and they're sort of

pretty much everybody agrees at 2,500. There's controversy whether it should be dropped down 1,000.

Q11: What were the two drugs that are used to clear iron?

Stuart Goldberg, MD: Well, there's several of them. The two most common… the most common in the United States is a drug called Exjade which is powder you drink and stir and drink, but it's not so palatable. So, the same company that makes that just came out within the last two months, actually so it's right off the press with a new drug called Jadenu which is the same exact chemical, just in a pill so it doesn't have to be stirred and mixed and (inaudible 1:25:47) that.

Q12: How do you find out a way to communicate with you by way of computer or something like that?

Stuart Goldberg, MD: Ask me afterwards and I'll give you my E-mails.

Q12: Thank you.

Q13: If you have a person who is low risk MDS who are the only signs of MDS is a low red blood cell count, but the person was dependent on frequent transfusions, let's say once a week or once every other week. Even the transfusions though they raise the energy never raise the hemoglobin to past 10.1. Would you ever consider in an elderly person who is unfrail stem cell transplant?

Stuart Goldberg, MD: So, the question was in a person who's in a lower risk category, they don't have a lot of leukemia cells, they don't have bad chromosomes. So, you're not worried about them dying from the disease, but their qualities of life actually may not be so good because they're needing blood transfusions all the time. Would we ever think about offering them a bone marrow transplant and the answer is yes, but it's a very difficult discussion because you're telling that person you have a one in three chance of dying from the procedure and so I have a one in three chance of being cured from this procedure and a two-third chance of dying from the disease or the procedure and so then you have to balance the risk and benefit. Is that something that that person is willing to take? Now, I will tell you I have done this and actually I have offered transplant to a younger patient thinking that wow, the person's young and even though they're fine now that disease is going to move and within the next five years or 10 years they're going to die from their disease. Why not do it now while they're healthy and young and young could be actually they're 65 and I'm not saying well, they might get in trouble when they hit 70. At 70 they might not be able to tolerate the transplant. So, you may move the age up because you said, "Look, you're healthy now you can tolerate it," but it's not a matter of what the doctor wants there. It's a matter of how much does a patient willing to put up with the risk because it is a risky procedure. I mean, I'm a transplanter. It's a risky position. Yes, sir?

Q14: What would you consider a long time is for an infusion? I'm getting infused maybe 20… every 20 days.

Stuart Goldberg, MD: You mean how often for blood transfusions before it comes onerous?

Q14: Right.

Stuart Goldberg, MD: And that's the eye of the beholder and it depends on what the goal of the therapy is. I have patients who come in once a month get their blood transfusion and they're happy with just having to see me once a month and know that's all they're going to get and I have other people say, "Look. If I have to come see you every month for a blood transfusion, I would rather see you every month to get some chemo so that I don't need to get the blood transfusions anymore," and there's no right or wrong answer there. We had that long discussion. If they're coming to see me every week, I'm usually then I start to twist and say, "Look, every week is a lot for getting blood transfusions." The human body under normal circumstances makes one pint per week. So if I were to… If my bone marrow is shut down tomorrow, I would lose about one point on the hemoglobin every week. So, that's why maybe to your question if you're getting a pint every week and you seeing that you're staying stable it's because you're getting the pint that you lose. So, you really have to stay ahead of it, but it becomes, once again, quality versus quantity versus when does that switch over and certainly for the low risk diseases where quality is the issue, quality is in the eye of the beholder. If the person says to me, "Look, I don't want to come in, see you that often, give me chemo," well then we'll do the chemo in hopes if we get the counts that they don't need to have the transfusions anymore.

Q14: I was told that I would not develop leukemia for probably 10 years.

Stuart Goldberg, MD: Right, but low risk disease that's not uncommon.

Q14: Thank you.

Stuart Goldberg, MD: Yes, ma'am?

Q15: Someone who's transfusion dependent every two weeks, two and a half weeks and suggested to do the Vidaza and at this point like it's not broken… like if you do Vidaza is that going to be anything if it doesn't work for you or…?

Stuart Goldberg, MD: Is it going to make things worse by doing it?

Q15: Is it possibly going to make things worse or if you go off it can you go back to the transfusions?

Stuart Goldberg, MD: Yes.

Q15: (inaudible 1:30:39)

Stuart Goldberg, MD: We certainly… So, the question is if you're doing okay, but the doctor things that maybe you might do better with Vidaza and should I give it a try and then if it doesn't work can I go backwards? The answer is absolutely you can go backwards. It doesn't change the outcomes. It doesn't make it worse. It's not like an old fashioned poison where you damage the body from the poisons and then you're never back to where you were.

Q16: So in other words, Vidaza won't make the disease come back more strongly if the Vidaza doesn't work. I mean for example with breast cancer, you give chemotherapy and if the chemotherapy doesn't completely knock out all the cancer cells, the residual cancer cells come back… are more aggressive.

Stuart Goldberg, MD: There's a mutation over time from the chemos. It's a harder question to answer. In general when you look at the research that's been done, people who "fail" Vidaza don't do well meaning that if their disease didn't listen to Vidaza, the disease is actually kind of bad and therefore the outcomes aren't so good, but most of those are talking about people who were treated in the later stage of disease, the high risk patients where if they didn't get Vidaza, they weren't going to be around anyway. So, the idea is once it stops working in that situation bad things happen. When you look at using Vidaza in lower risk patients, so somebody who just needing red cell transfusions and you're just going to give it a shot to see if it's going to help at all and you're not worried about the disease accelerating, it shouldn't cause… the Vidaza itself doesn't cause the damage, but the other piece of that information is remember Vidaza takes six months to work. So, you have to sort of… if you're going to do a trial of it, you got to give it a six month trial. So, it's not something that's going to work over night and you're going to say, "Oh, I did it for a month," and the worst thing to do, the absolute worst thing to do is do it for one or two months and then quit because then you've gotten all the side effects and none of the benefit because the first month or two it actually makes things worse because it's clearing out all the dead stuff. So, I've had people who start something and a month later they quit and it's like well you went through all the side effects and weren't on the drug long enough to benefit.

Q17: Just an answer to a question regarding that if the numbers go down while you're on the Vidaza does that happen or usually that doesn't happen?

Stuart Goldberg, MD: Oh, yeah. It happens all the time during the first couple of months.

Q17: If after six or seven months then if it doesn't improve then you go back to the transfusions?

Stuart Goldberg, MD: Usually after about six months I reassess to see if it's done anything good. If it's doing good then we continue. If it's not doing good in six months then we talk about stopping.

Q17: But you're basically on transfusions while you're on Vidaza.

Stuart Goldberg, MD: You can be and then if it kicks in then you hopefully don't need to be on transfusions.

Q17: What I mean if initially in the first couple months (inaudible 1:33:43).

Stuart Goldberg, MD: Right. The first couple months you're often still on transfusions.

Q17: What percentage of people react positively to the Vidaza that become transfusion independent?

Stuart Goldberg, MD: Somewhere between 40 and 60 percent depending on what other characteristics they have. So, I mean, there are people who… if it's just low red counts, they don't have a lot of blasts, things like that then it might be as high as 60 percent of people will have real benefit. Yes, sir?

Q18: Dr. Goldberg, what was the basis in the revised International Prognostic Scoring System of lowering the threshold for the neutrophil count from 1,800 down to 800 and the second part of the question is there also a qualitative factor to the white blood cell performance that impacts a patient's susceptibility to infections?

Stuart Goldberg, MD: So in general, it's been found that patients with MDS actually tolerate lower white counts much better than people with other diseases that sort of almost the people learn to adapt their immune system adapts to having a white count of 1,000 without getting infections. If I have a woman with breast cancer and I give her chemo and I drop her blood counts acutely down she's more likely to get an infection during those five days that she has a low white count before it comes back from the chemo than a person with MDS who's always running 1,000. So, I think that they felt that they could lower the threshold down without seeing… because we just clinically see people not getting trouble with infections.

Q18: So, it's just the passage of time when the initial IPSS was developed which I guess was 1997 that the experience factor suggested that 1,800 was a risk level and now 15 years later, whatever it is…

Stuart Goldberg, MD: It's probably lower before you start to really see infection problems. The incidence is probably a little… I mean, this is all the… The new IPSS was actually, once again, done with looking at, I think, an 8,000 charts where, once again, people didn't get treated and putting it through the computer and trying to figure out what levels do we start to see different cut points. One of the other thing the IPSS they have new cut points for reds and platelets, especially platelets because it used to be 100,000 yes or no. Either you have low platelets or not

and certainly a person who has a platelet count of 80,000 is low, but they're not going to bleed, but a person with 2,000 all they have to do is trip and fall they could really be in trouble. So, they put new cut points for platelets of you're a little low, you're a lot low, you're very dangerously low. So, I think that they tried to put those type of cut points and the same thing with red. They have new like yes, you get a little points for here and a lot of points for here and a tremendous amount of points if you're there. So, they're trying to revise and get it… clinically just find the right… the best (inaudible 1:36:34) points. Yes, ma'am?

Q19: Is there any information currently about diet and lifestyle and just general like if you're obese you lose weight, if you're suffering from this you be a vegetarian or…?

Stuart Goldberg, MD: Unfortunately, the dietary side…

Jayshree Shah: I was going to mention (inaudible 1:36:55) living with MDS. It actually has a nice supplement and references for you to leaf through and read upon your convenience in recommendations about nutrition and supplements and what to do and how to keep track and exercise. All of those components are in the book. It's a binder. So, (inaudible 1:37:20). The MDS Foundation (inaudible 1:37:25).

Stuart Goldberg, MD: So I mean, obviously, diet and exercise and all those things every doctor is going to say you're good and there are some tricks. I mean, we typically tell our patients one thing not to do is go on high iron diets. I mean, obviously, iron overload is an issue. So the first thing that people think of is oh, my blood counts are low. I'm going to take iron. So, they go out and they buy iron tablets which is probably the worst thing they can do for themselves. There are some complementary experimental herbalist things and the thing that has sort of caught some attention and actually some scientific basis for it would be some of the mushroom extracts. Still controversial. So, I wouldn't do this without letting your doctor know, but… I always get this wrong. Maitake mushrooms which are the ones that are sort of gnarly, they look like the tree barks, they're fairly immunosuppressive which gets into the ATG idea. If you take a mushroom and you suppress the immune system is that a lot on the blood counts to get better. So, I know that my colleagues over at Sloan Kettering in their complementary section actually had an ongoing trial of maitake mushrooms to see if they can stimulate people who primarily, once again, the low red count people who don't have problems with their whites and platelets because we don't want to suppress it and allow the leukemia clone to come up. So, it's the type of thing that if you're going to do something that's a little bizarre like that and I have patients who we have… I have one patient right now who's on lots and lots of maitake mushrooms with my approval and we're getting liver enzymes and we're doing things, but you want to let your doctor know what you're doing if you might be the type of patient that would have been in that kind of study.

Q19: Are they cooked or raw?

Stuart Goldberg, MD: Actually, it's a powder from a herbal… from like GNC type thing and you can actually buy it as a capsule.

Q20: What is your opinion about pets, Dr. Goldberg? At one time it was recommended that MDS patients not have dogs.

Stuart Goldberg, MD: In general, cats and dogs and those type… standard animals, are fine for pets. I mean, we always get nervous… As a transplanter, we always get nervous with birds because some of the bird droppings can be… can cause lung infections and certainly like we tell pregnant women they shouldn't be touching… cats… changing the litter box because of the toxoplasmosis from that, but we don't see toxo too much… I've never seen a case in an MDS patient.

Q21: Will Vidaza lower… For example, my case is red blood cell (inaudible 1:39:51) might overwhelm the other… platelets and white cells (inaudible 1:39:58)?

Stuart Goldberg, MD: The actual drug itself will lower the blood counts during the first month or two until you stabilize and then after by about third or fourth month we don't usually typically see the counts dropping from the drug. Actually, everything sort of comes up. So, that's more of a temporary side effect of the drug when you first (inaudible 1:40:13).

Q22: I was diagnosed about 10 years ago with MDS. I've been on Revlimid for eight years and I haven't had a blood transfusion in eight years. The end of December I'll start my ninth year on Revlimid. I take a pill every day. My hemoglobin as of two weeks ago was 12.5. My white count was 3.2 and I believe my platelets were 133. That's after eight years on Revlimid. It took exactly four months for it to kick in. After two months on Revlimid, I called Celgene and I wanted to know what was going on and they told me it would take approximately four months. I was on the last pill of the fourth month when notice started to change. So, there are drugs out there that can help you.

Stuart Goldberg, MD: Yes, sir.

Q23: Doctor, did I understand you say Vidaza that if you continue on your same schedule (inaudible 1:41:25).

Stuart Goldberg, MD: The question is when you go on a hypomethylator such as 5-Azacitidine or Vidaza or Decitabine, Dacogen, will you still need blood transfusions and certainly I would tell patients that during the first month or two since it tends to make the blood counts go down a little bit during the beginning from the poisonous effects of the chemo part the number of transfusions may actually increase during those first couple of months and then depending on how the medication works if it kicks in then hopefully your own body will start making blood and you won't need transfusions as you heard somebody can be on a medication that actually

eliminate the need for transfusions. So, everyone's different, but I tell people certainly during those first couple months don't expect that the blood counts are going to get better. They actually may get worse during the first couple of months. Yes, sir?

Q24: (inaudible 1:42:21) reaction (inaudible 1:42:23).

Stuart Goldberg, MD: It's like any drug there are side effects and they have to be monitored. Certainly, we take all of these drugs… they are chemotherapy drugs. We take these drugs seriously. Revlimid has for some people been a true amazing medication. Two-thirds or more of people who have 5Q abnormality essentially can go decades and be fine and we're seeing some people who have normal cytogenetics now starting to do well. Likewise I have patients on Vidaza who are out there five or more years who have very high risk disease and we didn't predict them to be alive a year later and now five years later continue to flourish and we have a patient of mine who unfortunately he didn't come today, who's a lawyer who's been on the drug for more than five years, hasn't missed a day in court. He gets his chemo in the morning and goes back to work that same day. I mean, there are always the good ones and unfortunately there are some patients who don't respond.

Q25: Dr. Goldberg, what is your instinct about the commencement of transfusions depending on the number of hematocrit and hemoglobin. In other words you said in the beginning that 14 of pints is sort of normal. Correct?

Stuart Goldberg, MD: Right.

Q25: And so if somebody has 8.something, it means there are only eight pints in the body?

Stuart Goldberg, MD: Correct. Meaning in general, we're more guided by symptoms than by actual numbers. I mean, if a person is functioning quite well at 9 and they're not running around like they used to, but at 9 they're able to do the things they want to do and are not complaining that much then we'll let people walk around with 9. If a person is telling me, "Look, I got nine, but I can't make it across the floor," well then obviously we need to sort of talk about it. Generally, the hemoglobin in the 7s is probably not enough hemoglobin to carry oxygen to the heart. So, most of us will say that if we get… I don't care if a person walks in here and they're 6.5 and they tell me I feel absolutely normal I say well, I don't want you to be calling me from the ambulance when you're having the heart attack. So, there are certain numbers I won't let people walk around with, but anything over seven I would start talking to the patient and then we also talk to their cardiologist (inaudible 1:44:57) cardiologist said he got two stents in. If his hemoglobin drops down it's going to be a heart attack. So, there may be differences for different people, but it also depends on what your lifestyle is. My lawyer needs a very high hemoglobin because he's still working. He's running up and down the court. Whereas maybe if he's 10 years older and now for the most part sitting in his La-Z-Boy at home watching TV all day he may not need that same type of hemoglobin to have the lifestyle he wants.

Q26: My hemoglobin sometimes will drop as low as 6.8, but at 6.8 (inaudible 1:45:36 – 1:45:48).

Stuart Goldberg, MD: People get used to a low number; 6.8 gets to the point where though honestly you must have been in great shape and you're telling me about personal trainers and all. Obviously, you're in very good shape to get to tolerate 6.8, but you don't want to play too low that now all of a sudden you don't have enough hemoglobin to feed the heart. So, most doctors would say numbers in the sixes are a little bit too risky to take that.

Q26: I don't see any change (inaudible 1:46:17).

Stuart Goldberg, MD: You may not because you have enough oxygen carrying capacity from the rest of your body to be able to tolerate it. You just don't want to be caught with the first call being the bad call. It's sort of a testament to how good a shape you are that you don't have that slope where you feel worse and worse and worse, but you are getting low enough that now you're not profusing to critical organs.

Q27: Yes. I had taken Dacogen for a quite a few months and I didn't have any response to it. Would Vidaza be…?

Stuart Goldberg, MD: No.

Q27: … another formula I could try?

Stuart Goldberg, MD: It's a good question. If you don't like Coke, you don't like Pepsi. They are very, very similar drugs and that has been looked at fairly well. There's a less than 10 percent success rate when one doesn't work switching just to the other. Now with that said, what often will be done is if somebody's not doing well with one you may switch to the other, but you may try and tweak it. So, this is where people will say when we actually have a study here were people who have been on one of those drugs they didn't do well they then go on to either the same and then stop. Everybody has to go on Dacogen with the way the study is written, but everybody goes on Dacogen but they more important are going onto Vorinostat on top. So, they're getting a second drug on top to try to tweak it.

Q27: What kind of drug would use as a second drug?

Stuart Goldberg, MD: Well, that's where those experimental drugs. I mean, we're using what's called an HDAC inhibitor to try to make the Vidaza or make the Dacogen more potent, but you wouldn't just… just switching from Coke to Pepsi without making any other changes is not effective.

Q28: Is there anyone here who's on Vidaza right now?

Stuart Goldberg, MD: Yeah. There are people in this room who are on Vidaza. I know the people in here.

Q29: If we're told that the diagnosis is not fully available yet and it's between MDS and hairy white cells, they're trying to find out who's driving the bus. If it's hairy white cells is all this information not relevant to us anymore?

Stuart Goldberg, MD: The hairy cells are very specific type of leukemia that has a very specific treatment completely different than everything I've talked about and also actually one of the diseases we have one of the best outcomes with. So, I think many hematologists would say if I have a disease MDS where our outcomes… this wasn't my happy talk. We don't have the best drugs here, unfortunately, whereas with hairy cell we have very, very good drugs. So, I think that many hematologists would say well if I can't decide to why don't I try the one that I know I can cure and if that works then I got the problem fixed and if I can't… if that doesn't work then I can go into MDS world.

Q29: But you can have both illnesses.

Stuart Goldberg, MD: They're completely separate diseases.

Q29: But you can have both.

Stuart Goldberg, MD: You can have both. Yeah. Unfortunately. (Inaudible 1:49:23) but they are very, very different diseases treated completely differently, different drugs.

Q30: You don't have (inaudible 1:49:34).

Stuart Goldberg, MD: This (inaudible 1:49:41) the world. I said this is not my happy talk. We don't have the best drugs. She was asking well, should I go across the river to a better drug and the answer is no. This is what's out there, unfortunately. I mean, we have made tremendous advances. I mean, if I gave this talk in 2005 there would have been a very short talk. It would have been you have blood transfusions, you got Procrit and if you're young you can have a bone marrow transplant and then we can all go home. So I mean, there was nothing else on the board. So, the last 10 years we have made advances and these advances as you heard are translating to a small number of patients having tremendous gains, a lot of patients having small to moderate gains. So, most patients will get some gain. This is one of those diseases where I do recommend you go to a blood doctor because they can actually help you. We know that, but the gains are not been the homeruns that we want to see. They are gains. They are small increments and unfortunately my crystal ball right now is that I don't see the next big gain right in from of me. It may be there, but it's not very clear to anybody what that next gain will be. The combination studies that are just coming to fruition so far has not looked much better than just doing single

agents which I think was disappointing to us, but maybe we don't have the right combination yet because that's where we are right now and then truly we need another leap forward in experimentals, but the genetic revolution may be pointing towards that.

Q31: I didn't hear any studies on Sotatercept and are you expecting that that might be something that would be…

Stuart Goldberg, MD: So, Sotatercept is ACE001.

Q31: I'm sorry. It's a what?

Stuart Goldberg, MD: It's a red cell fertilizer essentially.

Q31: Did you mention that?

Stuart Goldberg, MD: Yeah. Very quickly in passing. So, it is one of the experimental red cell fertilizers with very… it looks very promising. We don't have it here at our center, but I know that it's available in New York City and it does… the preliminary results have been somewhat encouraging.

Q32: Is it by pill?

Q31: I'm sorry. I forgot to say outside of Hackensack. What other hospitals on the East Coast would you recommend for treatment of MDS?

Stuart Goldberg, MD: For MDS? If you wanted to go an expert center… So, the MDS Foundation has what's called their Centers of Excellence program. These are hospitals throughout the United States and throughout the world, actually, that have met certain criteria to host programs like this that do research in MDS that have expertise and certainly there are good doctors in many, many hospitals, but the centers of excellence that the MDS Foundation has put together are centers that actually decided that they want to make a real effort to study the disease, to do research and to have a full program. So, I would recommend that the first step would actually be to contact the MDS Foundation. They can then get you where the local experts in your area and they have a network of several hundred hospitals across the country, across the world actually.

Q33: In New York, it's Weill Cornell.

Stuart Goldberg, MD: There's multiple in New York. There's multiple in New Jersey. I'm sure it's in there.

Q34: What was the name of the experimental drug (inaudible 1:53:07)

Stuart Goldberg, MD: The drug she was talking was called ACE-011. The letter A, the letter C, the letter E, 011.

Q35: Is it given in pill form?

Stuart Goldberg, MD: I know that that drug is available over at Columbia University, but there are other centers. The best place to get information on which drug, experimental drugs, would be clinicaltrials.gov. That's your government… it's the government's warehouse of all clinical trials. We're required when we do a research trial, especially with experimental drugs, to register with the government and they have their website and you can put in the name of your disease and what cities you want… or what states you want to go to and it'll pop up all the research trials that are being done at those centers.

Q36: Is that being given by pill form or infusion?

Stuart Goldberg, MD: Sotatercept I believe is an infusion, IV.

Q37: I had asked you before is there a way to communicate with you…

Stuart Goldberg, MD: Well thank you very much. Let me turn this over to Jayshree.

(Applause)

Jayshree Shah: I hope that was very informative because it was informative and a refresher for me to learn from Dr. Goldberg who I worked with him in the past. I see some familiar faces here today, but there are some that I don't know and I haven't had a chance to meet. I think it would be a great opportunity just to kind of wake up a little bit from sitting down and listening. How about we introduce ourselves, if it's possible maybe where you're from and how long you've had MDS. If that's okay with you guys and what are your plans for the summer? Any cool vacations that you're planning on taking? So, let me begin with myself. My name is Jayshree. I'm a nurse practitioner here at Hackensack, John Theurer Cancer Center. I work currently in the GI division/phase one clinical trials/thoracic. So, I took care of different types of cancers along with new clinical trials that are coming about and I've been doing this for… working with MDS Foundation as a volunteer kind of like a co-speaker and teaching kind of a forum for over five – six years now and it's been really wonderful because I get to meet new people (inaudible 1:55:52) familiar faces to share updated information and to learn from each other and I've been a nurse practitioner for over 13 years and I love what I do, love sharing information with anybody and everybody and myself. I love learning and vacation-wise I have three weddings to go to this summer. So, that's going to be fun to do and a weekend trip to Niagara Falls for me. That'll be fun. Begin with you. Can you speak in the mic?

Q38: My name is (Attendee). I come from Stanhope, New Jersey which is exit 25 on Interstate 80. I was diagnosed the beginning of this year. So, I'm very newly diagnosed and I'm still sort of in that stage of where do we go next. As for the summer, my grandchildren are taking me to Disney.

Jayshree Shah: Wait. It's usually reversed. The kids are usually saying I'm going to Disney.

Q38: They were going and they called up and says please come, please come, please come. My wife and I are going to Disney.

Jayshree Shah: Very nice. You're going to go see Mickey. I would love to hear from the caregivers as well. We welcome everybody here.

Q39: I'll speak. I'm in that category. My name is (Attendee), lived here in New Jersey and had the good fortune to be a patient of Dr. Goldberg's and Jayshree, as well, for about eight years. By the way, I'm the caregiver. My wife is the patient. She's resting today because although she was diagnosed after eight years ago, she's been on Procrit for five to six years and that has certainly helped, but her energy level and her stamina is still not the best and we have another engagement this evening, so she opted out not to come today, but as far as summer plans go it's really just someday trips down to the Jersey shore, I thank, and as of the moment that's the plan.

Jayshree Shah: Very nice. Thank you for coming. Go ahead, miss.

Q40: My name is (Attendee) and (Attendee) and I have been together for 10 years. We're both widowed and just seven years ago (inaudible 1:58:18). Six years ago he was diagnosed with the MDS and we're dealing with it and right now I just became a new grandmother for the first time on my birthday in June. That was really exciting and we've been pretty busy with that and trying to just do it all. We're doing pretty well.

Jayshree Shah: Free babysitting, huh?

Q41: My name is (Attendee). As (Attendee) indicated, I was diagnosed six years ago. I've gone through various treatments. We're at a point now where we're going to be considering Vidaza. Had a bone marrow biopsy done last week. So, we're waiting for the results of that and then we went (inaudible 1:59:07) what the next step is but right now I believe it's going to be the Vidaza. As far as summer plans, we live in Central Jersey, the shore rather and probably will be doing stuff down at the Jersey shore as much as we can. Hopefully, some short trips be on there. Thank you.

Jayshree Shah: Thank you.

Q42: Good morning. My name is (Attendee) and I'm from (inaudible 1:59:36) Jersey. I'm here with my husband, Joanne, his sisters (inaudible 1:59:40).

Q43: My name is (Attendee). I'm from Dumont, New Jersey and I have just recently in February been diagnosed with MDS and I recently started Vidaza, two months. This is my third treatment will start Monday. So, I'm hoping the numbers start going up. I did have (inaudible 2:00:02) and for summer we just hope to take day trips probably to the shore.

Jayshree Shah: Very nice.

Q43: Thank you.

Q44: I am (Attendee). My doctor is Dr. Goldberg and (inaudible 2:00:32) six years, very well. I am (inaudible 2:00:40). So, very happy with him (inaudible 2:00:48) and I'll say hello to (inaudible 2:00:51 – 2:01:07). Have a good day.

Q45: I'm a caregiver. My husband was diagnosed with MDS in 2009 and we're here to learn and we're happy to do so.

Jayshree Shah: Where are you going for the summer?

Q44: I'm going… I live in Puerto Rico.

Jayshree Shah: Puerto Rico? That's where I want to go.

Q46: So, try to take care of my husband (inaudible 2:01:48) and we talked to our doctor (inaudible 2:01:57 – 2:03:22).

Jayshree Shah: (Attendee), where are you going to vacation?

Q47: No plans and I've already spoken, so go to the next person.

Q48: I'm (Attendee). I'm from Roxbury, New Jersey. I've had MDS for about 2 ½ years now and I'm being treated up in the Denville area in the hematology group. I don't have really any plans for the summer. I'm a gardener, so I like to stay around my house and garden.

Jayshree Shah: So, what are you growing?

Q48: Well, I grow chrysanthemums and also a lot of different flowers, but I belong to the National Chrysanthemum Group. We grow exhibition chrysanthemums. So, it's kind of a hobby that I'm enjoying.

Jayshree Shah: Very nice.

Q48: Hi. My name is (Attendee). I was just diagnosed in December with MDS. I live in Allendale and I go to see Dr. (inaudible 2:04:19) and so far so good. So, this summer I've been to (inaudible 2:04:25) Martha's Vineyard for a week.

Jayshree Shah: Where are you going tomorrow?

Q48: Martha's Vineyard.

Jayshree Shah: Very nice.

Q48: It's great up there if you get a chance to go.

Jayshree Shah: One day. Definitely. Heard only good things.

Q49: Yes. My name is (Attendee). My wife was diagnosed with MDS also in 2009. I'd first like to say thank you, Dr. Goldberg and his whole team for a very, very supportive people here. For the summer, it's pretty much open this year, but I am very fortunate I have a brother-in-law who lives in St. Croix. So, I'm sure I'll be knocking on the (inaudible 2:05:08) we will be knocking on the door and I just want to say to everybody remember quality comes first in this life. Enjoy yourselves.

Q50: I agree.

Jayshree Shah: Very nice. Thank you.

Q51: My name is (Attendee) and my wife is the patient. She was diagnosed in 2004 with Dr. Goldberg and he gave her three months of Revlimid. After that nothing is happening new. She's going on. We just came back from two weeks from Norway, Sweden, Denmark just last Wednesday. So, no more big trips.

Jayshree Shah: A lot of traveling. That's great. Which one did you enjoy more?

Q51: I think Norway is very good. They cruise took around the coast. Not big cities. All the coast and just mountains. Nature is beautiful. Everybody should go to Norway. (inaudible 2:06:11)

Jayshree Shah: We missed a couple before you. Go ahead.

Q52: We're (Attendee) and (Attendee). We live in Morristown, New Jersey and (inaudible 2:06:24) and he's not on any medication or anything right now. Just watching the numbers and

vacation we're going to see our grandchildren in Phoenix for two weeks and a week at a dude ranch and then we're going to Vancouver Island. We go every summer. (Inaudible 2:06:43) Vancouver Island and we travel a lot. We just had a son go to Singapore, so we'll be visiting there, too, soon.

Jayshree Shah: You have a few trips actually planned.

Q52: And a daughter moving from the Dominican Republic to Africa. They keep us very busy. Thank you for the seminars that you give. We enjoyed them and we get so much information and hope. Thank you.

Q53: We are (Attendee) and (Attendee). I'm the patient. I was diagnosed in 1998. Started out on Prednisone and through the years I was on Revlimid, Procrit, Neupogen. I was in a clinical trial with Dr. Goldberg for Exjade which has brought the serum ferritin under control. I get transfusions every 17 days. Last weekend I had my 423rd and 424th unit and after today I'm thinking maybe Vidaza might be a way to go even though the quality of life has been fine. We go on cruises, our family's grandkids that are in California we visit several times during the year. We have a great support group. We're from central New Jersey and we have a support group that meets once a month, which is very helpful and I've seen a lot of progress over the 17 years and I've been very fortunate and I learned a great deal today and I'm glad that everybody is here today and learning and realize how much hope there is really and because when I was diagnosed in 1998 it… actually one doctor said I have less than 10 years to live. He was wrong. So, it's been 17 years and I'm doing well. Very fortunate.

Jayshree Shah: That's great.

Q54: You heard me say that I haven't had a blood transfusion in eight years. My life has been normal. I go to the gym. My wife and I go on cruises. We're going on our 18th cruise in September. We don't go away in the summer. I collect orchids and I can't leave them unattended for seven days. It's a little too much outside. I came here really to let people know there's help. There's help out there and it works. Nine years ago I came to one of these and a woman stood up and she said, "I was diagnosed with MDS and the doctor said I had six months to live." She said, "I'm standing here before you 10 years later and I've been on Revlimid." Well, I had been put on Revlimid the week before I came (inaudible 2:10:32) she made this speech and we walked out of here and (inaudible) maybe it'll work for me. Well, it has worked for me. My counts are normal. My lifestyle is just as it normally would be. I'm 77 years old…

Q55: God bless.

Q54: … and I have a lot to look forward to. I came here also to find out about ATG. It's a drug that has bothered me. It would have been my pick instead of Revlimid, but my doctor didn't like the drug and she put me on Revlimid and it worked, but I'm still thinking about ATG. I haven't

ruled it out. I still can't see the difference between ATG and a bone marrow transplant other than what the doctor said. (Inaudible 2:11:38) the bone marrow transplant will be for somebody that has leukemia. Well, 70 percent of us will not get leukemia. So, ATG to me is in the back of my mind and maybe someday I may have to use it. Good luck.

Jayshree Shah: So, I have a quick question for you, sir. You've taken 17 different cruises. Is that right?

Q54: That's correct.

Jayshree Shah: Which one has been your favorite so far besides the one you're going to soon?

Q54: We've been on cruises to Panama and I like those two the best. I mean, the Caribbean, I've been to every island. I know the backstreets. I know the restaurants in most of the places and I know where to go. So, we're going to go to New England in September. We'd been there many, many times on cruises. We're going there just to eat lobster and being on the (inaudible 2:12:37).

Jayshree Shah: Very nice. Hope you get some.

Q56: I'm glad you enjoyed the cruise to Panama. I was born and raised there and they have a lot of (inaudible 2:12:47). So, I'm sure (inaudible 2:12:50).

Q57: My name is (Attendee). I'm his wife. I think he said enough except that we've married 48 years, have 9 grandchildren and three great-grandchildren.

(Applause)

Q58: Hi. My name is (Attendee) and I'm going to be very pretentious and pompous. I'm going to try and answer your question. There's nothing like being ignorant to (inaudible 2:13:45) to answer to a question. I think the difference between the drug that you've been thinking about for so long and a stem cell transplant is that in one they tell the bone marrow to have a very nice sleep. Go to bed. Take a long, long rest and then we'll wake you up and the hope is by knocking out… by putting the bone marrow to sleep, your bone marrow to sleep, it will somehow restore itself and when it wakes up it will be normal. With the stem cell transplant, what they do is remove it. They don't put it to sleep. They remove it from you and replace it with somebody else's bone marrow but in doing that you're exposed to really serious infection that can kill you. So, that really is the difference. I think… I said I'm being very pretentious and pompous.

Q54: Well, in a bone marrow transplant you're in a hospital for 44 days. The person that donates the bone marrow is in the hospital for approximately a week. You got a 50 percent chance of it working. With the ATG, it's four days in the hospital. It's bone marrow transplant will probably cost you in excess of $1 million… Less Medicare, but the cost is in excess of $1 million. I'm

sure ATG is very expensive, but I don't think it's that expensive and they both do the same thing and they both work. The only difference I see is one could be used because you have leukemia and the other one may work if you don't have leukemia.

Stuart Goldberg, MD: They're extreme… Your description was very good, but they are very different procedures. The toxicities that we explained are extremely different. ATG less than a 5 percent chance of mortality, transplant one-third of the patients unfortunately, but they actually have very different outcomes, different success rates and they're used for different types of patients completely. They're not substitutable. There are some patients who are not appropriate for ATG. Generally people over the age of 60 do not respond to it. I'm not talking about whether they can't tolerate it. They can't respond… They won't respond to ATG. If you don't have the (inaudible 2:16:54) BR15 type which is something you were born with you won't respond to ATG. We don't have a hypocellular (inaudible 2:17:00) marrow you won't respond to ATG. So, we pick them… They're not substitutable. They're different therapies for different types of patients. Certainly if I had a choice… if both were on the board and the doctor said you could do well with both, the ATG would be much easier and actually we probably don't use the horse serum anymore. We would go to Campeth which is even easier and that's done in the outpatient room. That's a mouse serum essentially, but with that said there are different types of patients that we offer these two therapies to.

Q59: What kind of serum did you just say it was?

Stuart Goldberg, MD: It's called Campeth. It's made, I think from mice. Genetically (inaudible 2:17:47).

Q60: Were you sitting in the audience when I decided to answer his question? I didn't realize you were here. I never would have opened my mouth.

Stuart Goldberg, MD: Try to keep my ear opened.

Jayshree Shah: You didn't share what you are going to be doing for the summer.

Q60: I was too busy being pompous.

Jayshree Shah: We all want to understand what MDS is about and it's good that you're trying to translate it in your own words to explain it, but where are you going this summer? Any plans?

Q60: Staying in my apartment and find myself having hip surgery and knee surgery. So, I'm not a very happy camper.

Jayshree Shah: Rehab. So, we have lunch ready. How about we stretch ourselves a bit and chat for a little bit and then get to know each other and we regroup for questions, more questions and discussion and stuff and my little spiel about my presentation. How about like 12:40 – 12:45?