Speakers:
Gary Schiller, MD
Erin P. Demakos, RN, CCRN

Audrey Hassan: Hello, everybody. I'm Audrey from the MDS Foundation. My colleague, Janice, is also here. She's (inaudible). We're going to start the (inaudible) shortly. We're very fortunate that we have Dr. Gary Schiller from UCLA as our guest speaker and Erin Demakos from our Nurse Leadership Board from Mount Sinai in New York City. I want to thank our sponsors, (inaudible 0:29), Novartis and Celgene. I also want to make a brief announcement that immediately following this program, it's an optional education opportunity specific to iron overload and that will be in the room that's adjacent to this room. So, I'll give you more information on that shortly and I just wanted to also let you know that Monday is (inaudible 0:54) Disease Day. It's a day that was developed by (inaudible1:00) and today we're doing something unusual. We're having one on a patient program and, obviously, this one today (inaudible) California. The sign-up sheet (inaudible). There is one going on in Tampa. We want to do that (inaudible 1:19) and on Monday I am also (inaudible) for other nonprofit (inaudible) get together. I'm going to the (inaudible) on Monday and we're doing a very MDS specific awareness day there. I'm hoping to draw a lot of (inaudible). So, thank you for coming.

(General chat 1:41: - 7:11)

Gary Schiller, MD: Hi. I'm Gary Schiller. I'm the Chief of the Hematologic Malignancy Stem Cell Transplant Unit at UCLA. We have a combined unit where our doctors take care of patients with various diseases of the blood and bone marrow as well as do bone marrow transplant. So unlike a lot of institutions, we don't have a separate unit. We like to think that we like to treat based on disease and if one day a better technology comes up than bone marrow transplant our doctors will be there to do it because they're disease focused and today we're going to talk about something that is not exactly a disease. We're going to talk about myelodysplasia which is a syndrome and we don't have to stick with these slides at any point. You can just raise your hand and we'll depart from it. This is a little bit different from a talk that I might give for doctors. So it should be, I think, a little less formal.

Myelodysplasia is a syndrome and as my own doctor likes to tell me about a syndrome that I have, a syndrome means that it is not a single pathologic entity. It is several or many entities that are held together by the nature of their presentation and so it's not one pathophysiology that's going on, but several and I think we're going to try to make that clear by looking at two very different kinds of patients who have certain things in common but whose diseases are biologically very distinct and yet the billing code as established for Center for Medicare Services is the same one – myelodysplasia.

So, the first is an 86 year old gentleman with a six year history of anemia characterized by big red cells, macrocytic and now he's referred because his hemoglobin has fallen from 10. The

normal is 13 and above to eight and he need transfusion support. His physical exam is not particularly interesting and his blood counts show a good white count, a good platelet count, anemia with the red cells slightly on the large side, the bone marrow shows a sideroblasts which are immature red blood cells where iron is distributed like in a circle around the nucleus that's distinctly abnormal and his chromosomes in the marrow show loss of the Y chromosome in two cells, 18 cells are normal. This is very common in older men. It may happen even without myelodysplasia. It just is a characteristic loss of Y chromosome that occurs with age.

The other is a guy, also a male, but he's 53 and he's only had a one month history, not a six year history of anemia and he doesn't just have anemia. All of his cells are decreased. So if you look at the blood count, his white count is low compared to this guy. The normal, by the way, is about 4,000 or 3,900 to about 8,000. His hemoglobin is low, even lower than this man. His platelet count is low, much lower than the other guy and his bone marrow shows very immature cells, blasts, and he has an extra chromosome, eight, in 11 cells, nine cells are normal.

What keeps these two patients together in a clinical practice? Well, they both have anemia, but that's about where it ends. Otherwise, they're markedly different. This guy untreated will die in six weeks to three months. This guy if untreated could go years. Unfair, isn't it? The 86 year old will go for years. The 53 year old if you don't treat him is gone in a few weeks or a month because he doesn't have white cells adequate to fight infection and his platelets are dropping and he can die from hemorrhage. So, they're both called myelodysplasia, but they are very, very different in terms of their prognosis and the way they present and so therefore we have to come up with a definition. This is an old definition that I wrote with a resident oh, more than 10 years ago, but I think it's a good definition still and myelodysplasia is a disorder of blood production that is due to one or a few abnormal clones in the marrow and I'll explain that in a moment and these abnormal clones do not effectively produce blood. This is the fancy way of saying not effectively producing white cells, red cells and platelets. People wonder why we use jargon. Well, we use jargon because these two words say what took me 12 words to describe to you. So, that's why we use jargon. Low blood counts, that's called cytopenias, various abnormal chromosomes that we don't see and a variable tendency to evolve to leukemia.

So, let's step back a minute and talk about what is the normal bone marrow. I have a lot of analogies. I got patients here in the audience. They've heard them all and that's because if I weren't a doctor I love studying foreign languages. So if you speak a lot of foreign languages, you have to think of ways to remember stuff and so I like to think of tools. The bone marrow is like a garden that contains lawn and many different kinds of plants. It is a stable garden. It is generally not overtaken by weeds. It is a productive garden and its stability maintains from about the age of six till the end of life. Let me tell you my grandmother at age 100 a few weeks before she died had normal blood counts the same as they were probably 90 years before. That's normal bone marrow production. A heterogeneous garden of grass and plants and trees and trees that bear fruit and the fruit, some of the fruits are red cells that carry oxygen, 100 different kinds of white cells that fight infection and platelets that clot the blood. In myelodysplasia the garden is

overtaken by a weed. The weed is homogeneous, not heterogeneous. The weed is one type of weed. It takes over the garden. It impairs the production of fruit and depending on the aggressiveness of the weed and depending on the type of weed, that's the clinical difference between the old patient who will live a long time with his disease and the younger guy, the 53 year old, that will live very short time with his disease, but both are different from leukemia because in overt leukemia there is only weeds. There is no remnant of grass or trees or flowers or fruit. So, that is like the end manifestation of myelodysplasia, but the elderly patient that I showed you will never develop a weed overgrown garden. It will never get to that point in his lifetime. This guy, the weeds are rapidly progressing. So, there's a fundamental difference and we need to identify what different weeds are in the garden because that'll help us determine treatment. Although you can challenge me on that in a moment, but that's at least the way we think today that if we can determine the biology of the weed we can determine what kind of therapy to give.

Now, how does this happen? A lot of arguments about this. There's no question that some injury to the DNA will promote growth of weeds – radiation exposure, chemical exposure could have been decades before, but I wonder very hard to prove whether there's something about the soil that is inductive or conductive toward the growth of the weed and nobody has really been able to identify this well, but I'll give you a tantalizing example why I'm not completely out of my mind to tell you that the soil could have something to do with this. Every once in a while, very uncommon, very, very uncommon, but nature gives us sometimes uncommon events to help us understand the common. So, once in a long while we do a bone marrow transplant on somebody for disease X. It doesn't have to be myelodysplasia and the patient develops leukemia, but the leukemia is in the donor cells. How do I know this? You have a woman who receives a bone marrow transplant from a man. Her chromosomes in the bone marrow and blood are all male. She develops leukemia and the chromosomes of the leukemia are male. You go back to the male donor, her brother. He doesn't have leukemia. You find in his donor cells some cells that have been genetically damaged by radiation or chemicals. You follow him for the next 30 years and he never develops leukemia. She goes on and dies of leukemia in XY cells, in male cells. So, what that tells me is that the male donor had already some substrate of DNA damage, but it never manifest in him, but there was something about her that was conducive to the growth of the clone or the weeds, the cells derived from the single abnormal parent and this has been shown now several times. Now, there are not hundreds of these cases otherwise we wouldn't be able to do bone marrow transplant. Worldwide there are about 25,000 or 30,000 bone marrow transplants from donor to recipient, another 25,000 are what we call atalogous where the patient is his own donor. So, the 25,000 or 30,000 that are done every year there can't be more than 10 or 20 that this happens to, but the fact that it happens makes me tell you that there's more than just some exposure damage to DNA. There must be something about the patient that is conducive to the growth of the clone, but we don't know and so we don't know how to go after it.

What about the DNA damage of the clone? Oh, there are many things that distinguish the weed from normal grass and normal plants. The weed ages quickly. It doesn't have an enzyme

telomeres that will help the DNA repair properly. That's interesting, isn't it? If the clone ages quickly then it can develop more genetic mutations over its life because it's aging faster than normal bone marrow. The way that it expresses DNA which I'm going to go into in a moment is distinctly different from the normal and there are many things that are called epigenetic changes.

Now, let's talk about epigenetics because that's very important to therapy. Epigenetics is a word that comes from Nazi medicine, the doctors of the Third Reich were very interested in genes. They attributed all sorts of behavior to ethnic groups that justified their elimination of ethnic undesirables and they had all sorts of concepts about how genes are turned on and off. Most of the concepts were bullshit and there was not science and it was just abuse. However, some of their concepts were interesting and they came up with this idea of epigenetics which today is very hot, but in the 1920s and 30s was just theoretical. I have white hair here on my temples. Twenty years ago I didn't have white hair on my temples. Did the cells of the hair follicles lose the gene to make the black pigment? No. They just silenced the gene. So, the idea is that in the course of life our cells turn on and off gene expression which translates to protein and we don't know how those things happen. Some of them are very obvious. A young man begins to make testosterone, his cells start making hair around his mustache and then his beard and finally his chest. A woman makes estrogen. Her cells turn on, make breast tissue. So, those things we understand, but a lot of things we don't understand. How come a cell in the bone marrow can become a neutrophil to fight infection or that same cell could become a platelet to clot the blood or a red cell. It must mean that genes are being turned on and off in some pattern that we don't understand. Here, take a look at the mustard plant that my wife works on. If the genes are turned on and off in the correct way this is what the petal looks like. If there's something the matter with the way the genes are turned on and off, these proteins that turn on genes are dysregulated, look how disturbed the petal formation is. It doesn't look normal. So, apparently this is going on in myelodysplasia as well. There is abnormal turning on and off of genes. Now, there are probably many ways that genes are turned on and off. One way is methylation. You can methylate certain residues that'll turn on or off the genes and that's a target of two drugs that I bet people in this room use all the time, Azacitidine and Decitabine. These are not chemotherapeutic drugs. These do not kill cells by damaging DNA. What they do is they turn on and off methylation in a very gross way, not at all scientific, not at all targeted. They just kind of generically turn on and off genes and for 40 percent of patients with myelodysplasia that makes their blood counts get better. Kind of miraculous. Who would have thought? We don't know why, but we do know vaguely that the drugs are turning on and off gene expression indiscriminately and for whatever reason that might take an abnormal clone and either make the clone mature or kill the weed one way or the other.

Now, here are some of the chromosomal abnormalities that some of you in the room have that describe your family of bad cells, the clone. There are all different kinds and we know retrospectively that they confer favorable or unfavorable prognosis. We didn't know this 20 years ago. We had to take registries of hundreds of patients with myelodysplasia and say what happens to the seven percent of patients that have a 17P mutation in their clone? Well, they do

badly. They either die of leukemia or their blood counts deteriorate quickly. What about if they have just a loss of the Y chromosome like that man had, the first older man? Well, it turns out they do fine and they live a long time. So, those things were determined retrospectively by large registries, but this begins to make some sense out of a very complicated otherwise difficult to understand set of diseases. So, I no longer say patient has weeds in the garden. I can say patient has weeds characterized by a chromosome 11 mutation and that gives me a much clearer understanding of what is likely statistically, not for the individual, but what is likely to happen to that person and I will alter my therapy accordingly.

Now, this is a normal blood smear. It's not complete, unfortunately, but the normal blood smear has red blood cells that all look about the same size and shape even though they're made by many different families of cells in the marrow. They end up looking the same. This is a neutrophil that fights bacterial infection. This is a platelet that clots the blood. In myelodysplasia many times patients have anemia. They don't make many red cells. That's usually the first thing to go and if they make neutrophils they look strange. This was described by the early microscopist as neutrophils with pince nez nuclei. Does anybody here know what pince nez are? Your grandparents knew very well. Those are the glasses without the side frames like Franklin Roosevelt worse. I have a pair at home, but they don't work well. I think it's great for people with old age vision like me because you don't have to open up the whole glasses. You just put them on your nose and so this is never… almost never seen in normal people, but in myelodysplasia it's seen a lot. Now, most of the time these neutrophils still fight bacterial infection even if they look weird, but I have seen some patients who make these and they cannot fight bacteria or fungus and the patients get life threatening infection. So, the abnormal appearance might have something to do with how the cell is maturing and it's not maturing in a normal appropriate way. So, its appearance becomes abnormal.

Now, this patient makes a lot of platelets. So, this patient is not likely to hemorrhage because the clone is still making platelets to clot the blood and if you look in the marrow you can see some very weird looking cells and that's where the diagnosis of myelodysplasia comes. Very 1960s old fashioned thing. You take a patient with abnormal blood counts, you do a bone marrow biopsy, the pathologist says, "Oh, I see all of these weird findings. The diagnosis is myelodysplasia," and then the pathologist is kind of done, but we're not done because we really want a little more detail than that. We really want to know more than what the cells look like. This was an old French-American-British classification based on what the cells look like. We really want to know how bad are the blood counts. That's very important to us and what are the chromosome abnormalities? That was, I think, the big change in the 1990s and then in the beginning of this century to start looking at what are the abnormal genes that are driving this weed in the garden and that has helped us develop a whole different system of assigning risk to patients and today we use something called the International Prognostic Scoring System. If you're a patient of mine, we open up Google and we type 'IPSS' or we can look at the MDS Society because they have the International Prognostic Scoring System there and I and the patient type in the numbers ourselves together and so what we do is we type in the number of

immature cells in the bone marrow. We type in the chromosome abnormalities and we type in the blood counts that were associated with the first bone marrow biopsy and this thing is sort of like an insurance form. It gives us a statistical prognosis of how likely is the patient to survive. How likely is the clone to evolve to AML, but again with a group of patients I want to emphasize that it is a statistical likelihood. It isn't 100 percent for any patient. So, you have to be a little bit careful because we're applying a statistical probability of reading the future based on the past, but it's done all the time. Twelve weeks ago I had a heart attack at our national meeting. I'm not supposed to have a heart attack. I'm a skinny guy. I never had a high LDL. I'm a runner. I don't have any risk factors at all. I can't get life insurance today no way. I mean, I have, but I don't have enough because statistically I am a high risk person now and so too that's how these things are derived, but for the individual you have to have a little bit of what I call scientific skepticism and don't necessarily accept the statistic on face value, but use them for what they can be used. If you're a 53 year old guy with a high risk MDS well maybe you should do a bone marrow transplant because the prognosis based on statistics is not so good for you. If you're an 86 year old and you have low risk myelodysplasia maybe you shouldn't do anything and just get blood transfusions because the statistics look favorable for you. Maybe what the doctor could do with his medications might be more adverse than you getting a blood transfusion every so often. So, that is kind of the unscientific way of how we assign risk.

What are these cytogenetics tell us historically? Well, that I think is even more interesting because Americans always want to have a reason for everything and I'm an American, too. So, I behave the same way. Why does Dr. Schiller get a heart attack? It doesn't make sense. So, people… the cardiologist says, "Well, you were under too much stress." Well, that doesn't tell me much because everybody's under stress. So tell me biologically what is happening here. Well, there actually is more known here than in cardiology. So, if you have a myelodysplasia with a chromosome 5 or 7 abnormality, you probably were exposed to chemotherapy in the past particularly what's the most common? A woman with branch cancer who got chemotherapy to prevent the breast cancer from recurring and four or five years later gets one of these MDSs with chromosome 5 or 7. It's fascinating. Or you had Hodgkin's disease and you had radiation 20 years ago. These are very, very stereotypical. Now, you should ask me why do those drugs or radiation produce chromosome 5 or 7 abnormality. That I don't know yet. Patients who got a certain type of chemotherapy we call topoisomerase inhibitors very often have myelodysplasia with chromosome 11 mutation. Must be where those drugs work. It must be where those drugs act on the hidden breast cancer or the hidden Hodgkin's disease and they must also hit the target in a bone marrow cell and, again, in the right person in the right soil, that thing grows.

Q1: X-rays don't have any…?

Gary Schiller, MD: Everybody asks that question. I'm not going to ask that question because I'm going to get a lot of x-rays in the future. I think that certainly CT scans and PET scans are risky. They have a lot of radiation but they're tiny in comparison to therapeutic radiation. So somebody with a lymphoma got 3,000 – 4,000 RADs of radiation to the chest. They tell me then

they're worried about the three RADs that they get with the CT scan. I think the cat's out of the bag there already. The three RADs compared to 3,000 or 4,000 can't contribute much. However, compared to zero it's some risk. Yeah. Probably. Dental radiation people ask me all the time. Well, that's even less. That's, again, rally miniscule stuff. So, you have to think statistically well why would that have contributed in this person and not in the 10,000 other people who got it? Well, they might be different.

Q2: (inaudible 31:31) environmental.

Gary Schiller, MD: Correct. We are all exposed and you are right. Environmental radiation exists. I park my car on Whitworth and I walked over here. You don't know if there's radon gas in the ground or something.

I think that that is legitimate but hard to answer and prove and, again, you can always say but it's the person's risk, the soil is different and I believe that, but I cannot prove it to you, but you know that that's true. Why does breast cancer cluster in certain families? Well, we know about BRCA1 and 2 mutation, but there could be a bunch of other mutations that we don't know yet and if all of us died at the age of 30 like Alexander the Great from an infection then none of these would come to pass because all of these DNA damaging diseases are diseases of aging and that's… well, not you. You're very young, but it's just an accumulated damage. Now, that's not intellectually satisfying either because why can a 30 year old repair a DNA damage and a 60 year old cannot? That should bother you a little bit and there's something there for a pharmaceutical company to exploit to try to develop a drug to it, but it's not going to be easy. That's going to be a very tough, tough task.

Anyhow, this is how the scoring system looks. Now, there's a much more sophisticated version of this today, a revised scoring system that also takes into account age, but basically the scores predict in an actuarial insurance company kind of way for survival, but they're not 100 percent for a given patient. So, just view it with a little bit of skepticism. Now, survival is not only based on the risk that the disease will evolve to leukemia. Survival is also dependent on how severe the blood counts are depressed. So, you can have myelodysplasia and die of opportunistic infection without ever evolving to leukemia. So, there are two competing risks here and that's something that you have to think about as well. Now, there are a whole bunch of people who develop different staging and classification systems. If I were a patient I wouldn't pay too much time looking at this. I think it's a way to get promoted in academics if you spend a lot of time in a dark room developing a staging system and a classification system. However, what I would spend some time learning about is these terms and how they impact our choice of therapy. Basically, we have I like to say and here's some revised prognostic scoring systems. This is your actuarial insurance company survival based on your risk stratification, but again this is talking about populations of patients. It's not talking about you. So, you have to view it as I say with some skepticism.

Now, I think there're basically three forms of therapy of myelodysplasia and we can argue more details, but the first is supportive, the second is remittive, the third is curative and we have to decide which is the right one for the right patient. Now, there's a lot of trouble in determining what the right therapy is for the right patient because the patients are heterogenous. In any study, you're going to have people from age… well, the youngest person we can see with MDS is probably 12 years old with an inherited defect of DNA repair like a Thankoni's (sp? 35:20) patient to 100. So, the age is heterogenous. The prognostic group is heterogenous. In some of our studies you can read that not every patient in the study has had disease fully characterized. Boy, that's frustrating to try to interpret a study where you have 100 patients, but only 80 of them had chromosome evaluation. Very frustrating to deal with and you also wonder do some of these studies include people who already have AML? That'll mess up your statistics, too. We also can't agree on what is an end point. Is an end point recovery of low blood counts, stopping transfusion need or the FDA says survival is the ultimate end point. Well, that's true, but if you wait for survival as has happened, for example in the leukemia world, you're just not going to get a drug approved.

Do you know that in AML we do not have a drug on the market that was approved after 1990. It's disgusting. In multiple myeloma, they had three drugs approved this year. They had three drugs approved last year. They have a different advocacy group. More people survive. They go and picket in front of the FDA. They say don't wait for survival to approve a drug. Approve a drug if it works on one of these other end points .So, there's a huge number of drugs available. In AML and to some degree MDS, you have to show that your treatment made a survival difference, but that might take years to show that and in the meantime nothing happens. So, it's wonderful to have so many people like you. I wish we had an audience like you in AML and we could mobilize you and become politically active because otherwise nothing is happening.

So, these are the three treatment approaches. Curative which is bone marrow transplant, remittive to get the clone to behave and supportive to keep the blood counts up. Now, today we talk about risk adapted therapy and this implies that your doctor knows something. I don't think that we know so much. I've just given away all my secrets to you. We basically try to anticipate what will happen and then make a therapeutic recommendation on that basis. First, the easy part is the people with high risk disease. These are candidates for curative therapy because you're willing to accept even a 15 or 20 percent chance of dying from the procedure because the disease is high risk and the patient will die in short order. This is actually a much bigger option than it used to be. We now transplant people even over the age of 70. We use alternative donors, half matches. So, the bone marrow transplant business has expanded. However, what do you think the outcomes are if you will transplant only high risk patients? Not so great because the disease can relapse. So even in your attempt to get rid of the weeds, if this is a high risk disease you have a high likelihood that the weed will come back. However, it is an option and it will cure a certain percentage of people whereas the other therapies will not. So, you have to decide is the disease worth the risk and that requires some prognostication which is challenging.

Supportive care is the easiest. Supportive care we just give drugs to support the patient and this could be blood transfusion or growth factors. Now, no growth factor other than the red blood cell stimulating growth factors have ever been shown to improve survival, but they might reduce infection. Thrombocytopenia, maybe Eltrombopag works. It does not have FDA approval for that use. So, we have trouble recommending it because we don't have good studies on it. However, for the anemia my mom is on Erythropoietin for year for this about 25 percent of patients get better and if you add a little bit of GCSF to the Erythropoietin you can improve the remission rates or response rates to about 40 percent. Is this better than transfusion? It depends on your perspective. Transfusion is inconvenient and is associated with iron overload which can eventually affect your heart or your liver, but it might take years for that to happen. So if you're 86 years old, transfusion is easy. You don't even have to remove the iron because it might take 10 years before you would develop iron related complications. You'd be 96. What's your statistical likelihood of making it to 96? Not so clear. So, transfusion is still an option. However, besides iron overload transfusion is inconvenient. It's probably immunosuppressive. Who knows what infections come along with it? So, if you could get away with something less most patients will do it, but it's expensive. Well actually, both are expensive. Anybody can tell me what their bills are for one or two units of blood transfusion?

Q3: Twenty-five hundred a unit.

Gary Schiller, MD: Crazy. Twenty-five hundred bucks a unit. Insanity because before my event I was going out there and donating for free. We used to say it was $750 or $1,000 a unit. So, you could see the administrative costs. So, $3,500 a unit no matter what they charge for Erythropoietin it won't be more. It'll be less. So, that's something that goes into the equation as well.

What about low dose chemotherapy? We don't do this very much. It doesn't work very well. Potentially toxic. Hits many dividing cells. Has not been associated with any improvement in survival. However, certain drugs like Azacitidine and Decitabine are different which we'll talk about in a moment. What about intensive chemotherapy for our young people with MDS? Again, not very effective, 50 percent of patients go into remission. The average remission is about three months and they spend a month in the hospital with it. So, this is not a great idea either. So, we don't do it very often. On the other hand… let me see… I want to get past the transplant for a second. On the other hand Azacitidine and Decitabine are very interesting therapy options. I told you they're not chemotherapy exactly. They were developed as chemotherapeutics in the 1960s and '70s, but they don't exactly work like chemo. They are not cytotoxic. They don't make cells commit suicide, but they do change the way that the DNA is read and in a large randomized trial by Lou Silverman who apparently has spoken for you guys here before compared to supportive care there was significant response rate and there was a decreased rate of evolution to AML. The survival improvements in the original study were not statistically significant however the drug was still approved and this drug is very inconvenient. It's given subcutaneously. Supposed to be seven days repeated every 28. Many of us cheat and do five days instead of seven. That's really

not the way it's approved, but it's indicated for all subtypes of MDS and it changes the growth rate of the weeds and the same is true for Decitabine. Here's the randomized trial by the way just to kind of show you. Here's some of the statistics.

Q4: Why wouldn't that fall into this category?

Gary Schiller, MD: Maybe. I'm glad you asked that. I'll tell you about Revlimid in a second. So, let me tell you the response rates compared to observation not huge, 14 – 15 percent, complete remission 5 percent, partial remission nine percent versus zero and I don't know if I have a survival curve, but the survival curve was not significantly different, but the transfusion rate was different. Decitabine similar drug originally approved for intravenous use over three hours every eight hours for three days. Nobody gives it like this in the United States. We give it daily for five days intravenously. Similar mechanism of action. This was a randomized trial. Again, compared to nothing response rate very much the same as Azacitidine versus zero. Average time to response slow. Both drugs take months to work. They're not chemotherapy. You have to be patient. The average time to response was about three months and you could see the response rates were in the similar range to what has been seen and compared to supportive care time to AML or death was better for the group getting Decitabine than for the control group.

Now, you asked about Revlimid and I have a slide on Thalidomide. This is a very interesting class of drugs, too. Thalidomide was taken by women who were pregnant for morning sickness and as a sleeping aid. It was not released in the United States. This was done outside the United States and their babies were born without fully developed arms and legs. The drug was not allowed in this country except for treatment of leprosy and then in the 1990s, a wife of a patient with myeloma begged Dr. Barlogie to give it to her husband who was dying of multiple myeloma, an immune system cancer and he thought it made no sense and her rationale was just to show you how creative people think if you give it for leprosy and leprosy is an infection with a huge immune component where people lose their nose or their digits, if it works for that can't you give it for an immune system cancer and he did and the patient rose from the bed, from his death bed. It was miraculous. It doesn't work quite that well in MDS, but it does work for some people with MDS. We are only now beginning to understand how this class of drugs, Thalidomide, Lenalidomide, Pomalidomide work. They're immunomodulators, but they change also the soil. So, remember that thing where I told you about the weeds versus the soil and for some patients particularly low risk women with chromosome five mutated myelodysplasia the drug is amazing. It's a pill. Seventy percent of the patients get better. It lasts for about two years, not forever, on average about two years. Some people short, some people longer.

Now, what about for the rest of you with myelodysplasia? It doesn't work nearly as well, but for about 25 percent of patients with lower risk MDS they will get benefit. What are the risks? Blood clots. That's the major risk of the drug. Maybe second malignancies, not sure in the myeloma group, but it's also very expensive and it doesn't have FDA approval outside of the 5Q-syndrome. So, you either will have to pay for it or somehow finagle the system to get a trial.

Q5: (inaudible 47:12).

Gary Schiller, MD: Yup. That's alright. Between $8,000 and $14,000 depending on dose, schedule and good luck. So unfortunately, all of these are very, very, very expensive. I'm sure for 5Q- patient who was getting transfusion every month the stuff is miraculous, but for the rest of you the FDA has felt that the response does not justify the approval.

Q6: It did work for a year and a half.

Gary Schiller, MD: Yup and it will for about 25 percent.

Q7: And why does it stop working?

Gary Schiller, MD: Who knows? I have a feeling that the clone evolves. That's my suspicion for all of these remittive therapies. Why does Azacitidine first of all take three or four months to work and then why does it stop working after a year or a year and a half? And I believe that there is either the clone is already heterogenous to begin with. So, even though we say that all the weeds are genetically the same there may be disparity. They may not be so exactly the same and 2) the drug puts selection pressure on the weed so that the weeds that are already intrinsically resistant will outgrow it. It's like Darwinism. You're putting a pressure on an unstable clone and it will find a way to get past the treatment. So, that's discouraging, but on the other hand the fact that we have something I have anecdotal patient and experience. I have a guy in my practice right now who was MDS already evolved to leukemia and this 85 year old man started on Decitabine. Took him six months to go into remission. It was very painful. It was a real slog. Every month he was in the hospital with another infection. The wife threatened to leave him even though they'd been married for 60 years because it was so much care involved with taking care of him and it was such an emotional stress and so on and then somehow after six months his blood counts started improving at that was three years ago and the guy is doing well. I know one day it will stop, but it's been amazing and he hasn't required transfusions. So, for these few lucky individuals maybe we need to be studying them a little more to find predictors for response. Maybe if we knew more details about the genes of his disease we would know then who are the people that would get the most mileage out of this.

Q8: (inaudible 49:51) looking any people who have stopped it were never (inaudible).

Gary Schiller, MD: Oh, yes. Yes. It's just like Lenalidomide with 5Q- syndrome. If you stop it it's like taking the beautiful woman out of Shangri-La. She will age to the age of 200 on the Eurasian steps. If you know the old 1930s move "Lost Horizon" with Robert Coleman. You cannot stop it because they're not curative.

Q8: If it stops working they go through the cycle and it stops working or you stop for a number of years then try it again.

Gary Schiller, MD: If they live long enough that you could have this treatment-free interval. In myeloma that works, but this disease is not quite as nice multiple myeloma. So, I think we just need new therapies. What that is telling me is that, again, this is not one disease. This is a bunch of different diseases. We need some more tailored approaches that perhaps are based on targets that are distinct for different people's disease.

Now how does stem cell transplant work? That's the third one in my three legged stool – supportive care, remittive care, curative therapy. Well, stem cell transplant is a sledgehammer. It's not at all discrete or targeted. What you're doing is you're trying to kill as many weeds as you can and then you're introducing a new grass that is hostile to the weed that will attempt to kill the weed if it tries to recur. Now, the analogy ends there because the bone marrow from the donor can also have trouble. It may not just recognize the bad clone. It might recognize you and it will attack your skin or your gut or your liver and that is the loose cannon that is bone marrow transplant. So, that's the risky business. It's not refined. It's not what you want. However when it works, again, if I have patients who are successful. If we select just the patients to bring to you they will say, "Oh, this thing saved my life. I was 30 years old and I had myelodysplasia and I had bone marrow transplant and now I'm 60 and it saved my life," and no question for the individuals, yes, but again we can't really predict it so well. So, it's very frustrating. So, I come to you and I'll dispense with the slides because intelligent audience. You have some good questions. I want you to ask them and I come to you sort of with a mea culpa saying that we are really not doing good enough because we haven't refined the definition enough, but I also come as an advocate and with a warning that if we refine the diagnosis enough and we have miracle drug therapy for RAS-mutated myelodysplasia we're going to have a lot of trouble getting that FDA approved because we may have 500 patients in the United States a year with that or 300 patients with it per year and how am I going to do a randomized trial of miracle drug X and prove to the FDA that they do better than if you just give transfusions or bone marrow transplant or Azacitidine or Decitabine. Statistically, you can't do it. First of all, you're not going to get every patient to sign up to such a trial and the numbers are so few that you would have trouble showing a benefit. So, we need people like you to get out there and to make trouble because that seems to work in America. Making a noise seems to make things work as witnessed by the current presidential campaign. Well, both of them are making a lot of noise.

So, let me open it up to questions for you because that's, I think, more fair and it will allow us to go off on a tangent somewhere.

Q9: I got a couple of simple questions. Does dehydration and low testosterone impact the hemoglobin count?

Gary Schiller, MD: Yes, of course because red cells are floating in a water based solution called blood. So if you decrease the water it will make it look like your red blood cell count is higher. Right? Doesn't that make sense? So take a solution of salt and water. If you remove the water the salt may even precipitate. So, it looks heavier. So if you come in with different levels of hydration, you can get a false impression that you're doing better. Now, testosterone this is an ancient thing, dates back probably to the beginning of the twentieth century. It is true that androgens stimulate red cell production a little bit. Men run higher hemoglobins than women, but it's not a very good therapy for myelodysplasia.

Q9: How much of an impact would you say… this might be an unfair question, but if you're dehydrated or you have low testosterone how much (inaudible 54:58) impact (inaudible)?

Gary Schiller, MD: It's hard to say. It would depend. If you're profoundly dehydrated, your hematocrit can go up significantly 20 – 25 percent, more 30 percent, but that's probably not what you're talking about. You're talking about today you went to get your blood count and you didn't even have a cup of coffee much less a glass of water. So, it will be a little higher .2, .3, maybe .5 higher hemoglobin than it was the day before, but not much higher.

Q9: Thank you.

Q10: How does… I had my bone marrow transplant five years ago.

Gary Schiller, MD: Congratulations.

(Applause)

Q10: And my brother was a perfect match, a 10/10 which I had to check a few times because I didn't believe because we weren't compatible on any levels…

Gary Schiller, MD: Your genes were compatible, but your personalities were not.

Q10: Yeah. Exactly. So, I was quite amazed at that, but I have some issues and one of them is the skin tightening and…

Gary Schiller, MD: That has saved your life. So, don't be too angry at it.

Q10: That's what Dr. Lill says. So, that's the one thing.

Gary Schiller, MD: That's graft versus host disease. Again, the donor not only rejected his myelodysplasia, but the donor has an ongoing argument with him and his skin.

Q10: It's just like we had our whole lives. So, the other thing I just wanted to quickly ask you was about cramping. I have from time to time in the evenings some cramping. It's not that serious, but it's… like the whole thing is annoying.

Gary Schiller, MD: Well, because the nerves are also entrapped by the scar tissue that your brother has so kindly donated to you, but again this is the blunt instrument that I told you about. It's intellectually not so satisfying because your brother's cells, obviously, recognized your myelodysplasia. Killed it. Probably forever. We don't know, but probably forever, but they also recognize your skin and they scar your skin and trap your nerves in them and you can ignore that stimuli from the nerves if you have other stuff going on, you're watching TV, you're listening to your wife complaining at your for something, whatever, but when you go to bed and those sensory things are turned off then you're suddenly very attentive to that nerve that's being entrapped there and our therapies are really not very good. I actually am working on an experimental drug right now for chronic graft versus host disease. So, I'll advertise it to you and you can come and visit us. What the bone marrow transplant field needs to do, but we've been talking about this for 20 years is dissect what cells recognize your MDS from the cells that recognize your skin and there are some skeptics who say you can't dissect them. They're the same and there are others who are more optimistic who say yes, there are different cells from your brother doing different things and we could refine this process and then there are even others who say, well, let's develop drugs that would have allowed your own immune system to reject your myelodysplasia. That's in its infancy right now, but there are drugs that will unleash your own immune system against yourself. Now, what do you think the downside of those drugs would be? There are about three right now FDA approved on the market.

Q10: Infection.

Q11: Going to check none.

Gary Schiller, MD: Autoimmune disease. Correct. Some people get autoimmune colitis, autoimmune lung injury. We're just in the infancy of this, but that would deal a serious blow to bone marrow transplant, but a welcomed blow to bone marrow transplant if you could make your own immune system somehow recognize and reject this clone.

Let me go in order because I think she held hand up first and then you.

Q12: My dad is in the hospital right now with an infection and he's got a… a bone marrow biopsy and has MDS. His hemoglobin levels have been between like five and eight and he has constant infections, but they're saying they think it could be a false positive. How common is it to get a false positive?

Gary Schiller, MD: It's very common. Okay. If your definition of MDS depends on a pathologist looking for abnormal looking cells, weeds in the grass, you could make a mistake a

lot of times because it's very subjective. On the other hand if your diagnosis is bolstered by finding an abnormal chromosome or nowadays what I've been doing is I've been sending and I'm not getting paid by these people, but I've been sending bone marrow to Oregon Health Sciences University because they'll run a panel of 70 genes. Now, 70 genes compared to a million, it's still just a survey, but if you had an abnormal gene in the majority of cells that would help me make a diagnosis of myelodysplasia. A guy who's sick with infections can make the bone marrow look quite abnormal and yet not have MDS. So, I would want more information. I would agree with them. Do the bone marrow again and see what these supplemental tests would show.

Q12: So, they should do another biopsy. They couldn't get aspirations (inaudible 1:00:24).

Gary Schiller, MD: That is a problem. You need those cell… If you want to do a sophisticated not only chromosome analysis but a gene profile, you need to suck cells out of the bone marrow and send them somewhere so the lab can work on them. You give them a piece of calcified bone it's very hard for them to dissect out the cells and give you a mutational profile.

Barry had a question.

Q13: I had bone marrow… I've got low risk, 1.8, and Q5 and I was at the City of Hope and they did a match and I was 10 out of 10, but I'm 75… or will be 75.

Gary Schiller, MD: Well, you don't look 75.

Q13: Thank you, but they said…

Gary Schiller, MD: Hopefully your inside also is not 75.

Q13: Thank you, but they said I'm not a prospect anymore for bone marrow transplant.

Gary Schiller, MD: Because of your age or because you had low risk MDS?

Q13: They said all of it.

Gary Schiller, MD: Look…

Q13: I'm just transfusion dependent right now.

Gary Schiller, MD: Are you having trouble with that concept?

Q13: No.

Gary Schiller, MD: I think that's pretty good actually. It's because we're in this intermediate stage of what we know about MDS. We use risky therapy for risky disease and so the question is do you want to a therapy with minimum… the guy right behind is going to have a bone marrow transplant soon from me, so here I am saying this, but do you want to do a procedure with a minimum of 15 percent chance of killing you when you have, again, think like an insurance guy probably a 95 percent chance with low risk MDS that you're still going to be here next year and the year after and the year after that? No. If you felt that your disease was such that you had a very… a decreased risk, let's say below 50 percent that you're going to be here next year then you'll take the risk and you may turn out like this gentleman in the back with very good success. So, that's basically how we're thinking. It's not like thinking like a doctor. It's thinking more like prognosticating based on your risk.

Q13: And there's nothing really on the horizon right now as far as protocols.

Gary Schiller, MD: That's not true.

Q13: I did the Revlimid. I did the Vidaza.

Gary Schiller, MD: That's not true. There are a lot of pharmaceutical companies that are trying to develop drugs based on the genetic profile and remember when I use the word 'genetic' it's not what mom and dad gave you. It's what genes have been acquired over the course of your life based on the genetic profile of alterations in your clone and so actually we are getting pitched trials all the time, but I also told you from a regulatory point of view they'll be very hard to approve. So, you may have some miracle drug, but it may be for such a very narrow indication that a whole new strategy of trying to get drugs approved will have to be developed and I can also guarantee you with the way things are going it'll be crazy expensive.

Q13: But they'll be trials.

Gary Schiller, MD: But they are trials. There are.

Q14: It might be able to help her a little bit. My first bone marrow biopsy they had trouble getting it even out and (inaudible 1:03:33).

Gary Schiller, MD: Like her father.

Q14: But then at Stanford they did it with the drill.

Gary Schiller, MD: Well, I'm not a big fan of the drill, but I'm glad you like the drill. I don't happen to like it. I hate that noise and… but if it worked for you okay.

Q14: They got a better sample.

Gary Schiller, MD: Here's maybe somebody who maybe didn't have a good experience with the drills.

Q15: (inaudible 1:03:53) I don't even want to talk about it.

Gary Schiller, MD: I've had three bone marrow on myself for money and so I do know a little bit what it's like.

Q15: So, I have a twofold question. One of them is how often should we have a bone marrow test to see where we are?

Gary Schiller, MD: Great question. No standard. Great question. On a clinical trial sometimes they make you do it once a month. In the old Decitabine trial that we did can you believe some of those poor patients had 18 bone marrows on a monthly basis, but I say to patients outside of a clinical trial I would only do it if there's some change. Is there some change in your blood counts? Is there some reason for me to think something has changed? Is there some unexplained low white count, for example, that you never had before? So, we do it based on kind of the clinical demand.

Q15: So if you're pretty stable there is no need.

Gary Schiller, MD: Correct. There is no need to satisfy somebody's curiosity to look at your bone marrow.

Q15: So, my secondary question is so I have been on Revlimid for about five years now.

Gary Schiller, MD: Good for you.

Q15: So, can I go ahead and really charge American Express now because if it only has a five year… No…

Gary Schiller, MD: Ah-ha. You would have gotten a lot of frequent flyer miles with that.

Q15: So, I have a 5Q, obviously, and my white blood count is 1.8 to 2, but I don't have… I never get sick.

Gary Schiller, MD: And you must have more than .5 neutrophils. You have more than 500 neutrophils.

Q15: That I do.

Gary Schiller, MD: So, there you're fine.

Q15: And but so I'm getting a little nervous though with the five year prediction thing and I self-medicate myself.

Gary Schiller, MD: Oh, great.

Q15: My doctor is not happy about it. He start me at 10 milligrams. I am on 2.5 and I don't even tell hm.

Gary Schiller, MD: Oh, but that's actually… That's typical with 5Q-. People maybe sometimes can take once a week by the way is sometimes done.

Q15: And I do it every other day and it has worked great because I don't have the side effects. I mean, I have some but not. I work fulltime and I've been stable for five years. So, my question is how will I know when that runs out and do we have a secondary…?

Gary Schiller, MD: We really don't have a backup planned to Lenalidomide, but I got to tell you that the curve was not plateaued either. It does continue to drop, but you might be one of these people where you're on the tail of the curve 10 years out. So, what happens to others does not necessarily predict what happens to you. You're having a good response. Your blood counts are stable. So, I wouldn't change anything.

Q15: So, if you increased the milligrams would that…?

Gary Schiller, MD: It might that there are some… There are some people in Alan List's original *New England Journal of Medicine* publication which is where Lenalidomide was first brought out to the world who will benefit from dose escalation. You're right which, again, makes you wonder exactly what is this drug doing? Is it working on the clone? Is it working on the environment? How can it be so easy for some people to just bump in the dose and get another response?

Q15: The same thing with Vidaza.

Gary Schiller, MD: But that can also be with Azacitidine and by the way with Decitabine sometimes 10 day regimens are better than five. There are also some patients who can't tolerate those escalation because their counts go too low. So, you have to individualize it is the bottom line.

Q15: But do we have a patient who was on Revlimid or still is for 10 years?

Gary Schiller, MD: Yeah, there are, but more than that no because the trial hasn't gone on that long. It's about 10 years. That's about right, 2005, something like that.

Q16: I know a patient who has del 5Q and del 20Q. Are those individually lower risk for transformation and what about the combination of the two?

Gary Schiller, MD: That's a good question and a lot of these risk stratification things do not take into account multiple chromosomal abnormalities unless they're adverse. So, those are favorable. So, the 20Q is favorable or intermediate, but the deletion 5Q is favorable and so I being more of an optimist at work, I'm not an optimist at home, but I'm an optimist at work I would look at that like hers and I would look at that like a potential recipient of Lenalidomide and give that a try. That would make sense to me as a low risk MDS.

Q16: Thank you.

Q17: Doctor, I had MDS diagnosis back in 2006 and my complaint is about the complete blood count. Never in my life did I ever have a vitamin D3 test and when I finally insisted on one my vitamin D3 was at 20 percent on a range of 20 to 80 and my doctors put me on vitamin D3 and within six months my hemoglobin started to rise from the eight range and now it's up around the 10 range.

Gary Schiller, MD: Okay, but you're an exception. I wouldn't want the audience to walk out of here thinking that. First of all, there's at least 25 percent of Americans who are vitamin D deficient because the normal range has been elevated. It's different from what the range was three years ago. So, there are a bunch of us especially in a room like this that are vitamin D deficient. However, vitamin D has been used in clinical trials in MDS and it generally doesn't do a damn thing, but every once in a while you will have one patient who has a response and I just be careful about generalizing it because then they're going to run out Rite Aid, buy vitamin D and get vitamin D toxic because it's a lipid soluble vitamin and you can't get rid of the stuff. So for individual patient, there are also some patients by the way nobody in here who had vitamin B6. Every once in a while you'll have a patient with MDS take huge doses of B6 and they get better.

Q17: I'm also taking vitamin B6 and magnesium and folic acid and vitamin B12.

Gary Schiller, MD: I think… I give all my new low risk MDS patients, by the way for you and for you, I give them all a trial of vitamin B6, but I'm more comfortable with vitamin B6 than vitamin D because if you get…

Q18: (inaudible 1:10:32) or oral?

Gary Schiller, MD: Oral because it's not lipid soluble. It's water soluble. So if you take too much of it it goes out in your pee, but vitamin D and vitamin A, by the way you could also talk about vitamin A, very rarely works and they do accumulate. So, you got to be careful and I ask another question patients always ask me about mega dose vitamins. I always ask them how do you know that at the mega dose vitamins will only affect good cells and not act as a growth factor to your bad cells. How do you know that they're so selective that these drugs because they are drugs will only do what you want them to do and not do something you don't want them to do? So, it has been subjected to trial. You're a fortunate guy and there's something unique about your MDS that should be studied because it's obviously vitamin B sensitive.

Q17: I have another follow up question. I heard…

Gary Schiller, MD: Oh, that was a question? I thought that was a statement.

(Laughter)

Q17: My follow up question is on the test for vitamin B12, I understand the serum vitamin B12 test has a lot of false positives.

Gary Schiller, MD: It's also a lousy test in older people. I agree with you.

Q17: And now they're recommending to do the MMA test which is a urine test.

Gary Schiller, MD: We've been doing that for a long time. I've been doing the MMA and homocystine probably for 15 or 20 years. So, those are not new tests. I think those are very good especially in the older population particularly over age 80. It's very hard to interpret vitamin B12. We'll often make a mistake just like you say and that's not MDS, but it looks under the microscope back to your point, vitamin B12 deficiency can look… the bone marrow can look very much like MDS, but no chromosomal abnormalities, no gene abnormalities and so that's what really distinguishes the two.

Q17: My last point is I want to make is that I feel that we are ignoring one of the main factors that may contribute to MDS and that is diet and nutrition, food combinations, the proper food combinations and now diet.

Gary Schiller, MD: Don't you think we're just too old?

Q17: And also…

Gary Schiller, MD: That's what my boss said to me, very sympathetic boss. He said, "Well, your guarantee runs out after age 40. So no warranty. You can't take this body back." So, there was a question was right over here.

Q19: I have a question about donors. I have four siblings and I have… this is down the road for a stem cell transplant. What about children? Are they just…

Gary Schiller, MD: They are now. They are now. That's been a big change. We are doing and I think most centers are doing haplo identical transplants, half matches. This has really taken off in Latin America and pioneered really, I have to give credit to Hopkins in Baltimore for doing the most half matches. They are definitely a potential option for you.

Q19: My offspring, my children, my donors…

Gary Schiller, MD: They're likely to be half a match to you. Half the genes come from you and half from your husband. So, you can use a half match. It would be nicer to find a fully matched donor, but this is quite a good option now and most centers do them and feel comfortable with it.

Q19: And what's it called?

Gary Schiller, MD: Haplo identical. Half match… You just tell your doctor half match. You're one and you're one and that probably… I'm taking somebody else's time.

Q20: I wanted to sort of end on address the man in the back who's five years post-transplant. I'm 17 years post-transplant.

(Applause)

Q20: Unrelated donor, but got through it pretty easily looking back, but at the point I was where you are I had the same cramps and I want to say they do go away. It does get better. I still have them occasionally and now it's kind of a joke. Oh, yeah. Remember when that used to happen all the time and I remember at that age it was very difficult to cope with. Patience.

Gary Schiller, MD: Congratulations. Yes, sir?

Q21: My doctor at Cedars, Dr. Lil, Michael Lill, some people may know him. He's trying to convince me to take either Gleevec or Rituxan for the skin tightening.

Gary Schiller, MD: Yeah. For GVH, for chronic GVH.

Q21: Yeah. Exactly. So, I've been resisting all along.

Gary Schiller, MD: The jury's out on those.

Q21: So, I've been taking right now 10 milligrams of Prednisone. I've been on it for quite some time. I try to scale back on the Prednisone because I know there are some significant downsides. I've been lucky. Haven't had that many, but I've been taking it for a long time. When I cut down to like five milligrams, I do notice that the GVHD does get more active. Is there nothing that we can do… that I can do to get out from under the Prednisone?

Gary Schiller, MD: Well, I don't want to give you a personal consultation here, but since you're asking for one. Well, sure. There are steroid sparing immunosuppressant drugs. It's not surprising there… ask your friends with rheumatologic illness. My sister-in-law with ankylosing spondylitis. One milligram of Prednisone one way or the other can make or break how you feel. It's hard to understand. It's not completely logical, but it's very, very well known that just tie trading the immunosuppressive doses one way or the other can change what's going on which is this immunologic battle between your donor and you, but not withstanding, again, taking a look at you you look like a pretty healthy lucky guy. So, if you're down to five or 10 milligrams a day of Prednisone, congratulations to you. You're right to be skeptical about changing the system because you're doing so well.

I thank you all for the opportunity to talk to you. I don't want to take the next person's time up and I wish you good luck and good health. Things are getting better and they're certainly better than they were a few years ago. So, that's the point. Thanks.

(Applause)

(General chat 1:16:53- 1:18:17)

Erin Demakos: Good morning, everybody. I hope everyone's doing well. I want to thank you so much for coming out. I want to thank Dr. Schiller for a very eloquent lecture and so this is where I'm from just so you know I am a nurse. I work with Dr. Lou Silverman in New York. I did all the clinical trials on Azacitidine, Vidaza. So, I've been doing this for over 25 plus years. I like to put the plus because I don't want to keep saying higher and higher and I was sitting like you are today, but without a support group, without information, over 25 years ago when my grandfather was diagnosed with MDS. So, we had no information. I wasn't an oncology nurse at the time. I was working in open heart surgery and I've had the great fortune to work with Dr. Silverman all these years and another physician who actually just turned 91, Dr. James Holland, who really did all the pioneer work and research in the lab bringing a drug which they called an orphan drug at the time which was sitting on the shelf and studying my grandfather's bone marrow and other patients to say there is activity in MDS. It wasn't effective in (inaudible 1:19:42) leukemia, but they did all of this work and this research. So, I have worked on all of the clinical trials.

We like to talk about hope and I just want you to know that unfortunately just to touch upon it in the beginning, unfortunately every one eventually stops responding to therapy and… but there's other things that we can do. So, we do play around with dosing that you had brought up. We

have patients that have gone into remission with Azacitidine and we've re-challenged them or we've increased doses and it kind of kicks everything back in place and they start responding again, but on the horizon when we were talking about mutations, lots of things that we're learning now that we didn't know about, certain gene mutations and that we've learned and discovered. So, when he was talking about sending blood panels out we have 40 genes now that we're looking at in MDS and do you carry that specific gene and are we developing a drug specific for that gene. So, you have to think about two MDS patients are not alike. There's lots of different variables that go into play. How you respond, when you respond. So try to remember that as you're talking to other patients to say there is something different about each one of us, but there is hope. We have lots of new trials out on the market and especially that are being… that we need patients to, obviously, contribute to so we learn the science and unfortunately, yes, it's taking way too long and a lot of these trials on a global international level. We're participating in multiple studies in New York and there's a subset of a subset of an MDS patient because they might have a certain mutation, they may not have a mutation, their platelet counts might need to be below 75,000, they might need to have certain transfusion requirements. This is how the FDA has structured a lot of these trials. So, what we call eligibility criteria is very strict, but we have centers, 200 centers plus, participating in just one study so that we can try to get the accrual, get the science and information so we know where we need to go from here. So, there's lots of wonderful things on the horizon and I want you to realize that.

This is a quote from a patient that was participating in a forum such as this. They said, "As a patient, it's crucial to take responsibility and have the courage not only to ask, but also understand." So, you're getting a lot of information. You have to get your questions organized and we'll talk about that and we'll go through *The Building Blocks of Hope* today. That's my purpose here for this portion of the lecture so that kind of the fear of the unknown is removed. When you ask certain questions, it might allay some of your fears because you have some wrong information in your head and making sure that you're going to our website that is current, up to date, key opinion leaders like Dr. Schiller, like Dr. Silverman, like Dr. List. A lot of these doctors that you'll see on a lot of these references and articles have been working in the field for… dedicated their life to patients with MDS and bone marrow diseases.

So, the book is called *The Building Blocks of Hope* and it is for patients and it is a caregiver guide. It was organized with a whole group of nurses across the globe because there's definitely differences in how patients are managed and seen and clinical tests that are available to them. So, we have people from Switzerland, Germany, Italy, Spain, Australia, Japan and then a whole bunch of nurses from this nurse Mary Thomas is just right from California, Palo Alto. Sandy Curtin, big leader in the field here from Arizona. So, a bunch of the nurses got together and it was always my passion to want to do something, share stories just like you share with each other, nursing sharing stories of what's working for their patients, what's not working for their patients. So, we developed a book that we were able to update on a regular basis when important science is revealed and it's user friendly. So, it comes in different sections and we'll go through this.

We would really appreciate if possible if you do have an electronic device and you're able to complete our survey online we would hope that you're able to do that. If not there's lots of paper surveys we'd like you to complete at the end of our program today.

So as Dr. Schiller went over with us different variables in terms of when a physician decides to start treatment and where you come into play is really… You're your best person in understanding how you're feeling and what's going on. So, you got to keep track of that in some way in a diary on how you're feeling, just your symptoms. Are you short of breath? More short of breath. Separate from our clinical information like transfusion dependence and we're going to look and see are your transfusion requirements increasing and how often. That might be a sign that your disease is progressing which will then prompt the physician to say your counts are falling, you're becoming more transfusion dependent. I need to do a bone marrow biopsy and aspirate to see exactly what's going on. We're going to look at, again, like I said your blood counts and your cytopenias are they worsening. In your peripheral blood do we see the immature cells increasing or also in your bone marrow and were you now low risk and you're going into higher risk disease.

In here it is about individualized and personalized approaches for each patient. That's what we want to practice. So, we're going to look at how you're feeling in terms of your performance status. How active are you? Do you have comorbidities and are they going to complicate the choice of treatment that will prescribe to you. Do you have heart disease? Do you have hypertension? Do you have diabetes? That gets factored into the recipe so to speak in terms of what we're going to be prescribing. As Dr. Schiller went over high risk and lower risk disease. What our goals are. The cytogenetics lay a role and a very important whether or not you have good cytogenetics or bad cytogenetics. Are you a 5Q del and that's why we're going to start Revlimid in your lower risk disease and the mutations also, again, if you are not… if you're changing therap. If you were on Decitabine or Azacitidine or Lenalidomide. What is your mutations and is there a clinical trial that possible that you would fit into. Your current lifestyle. What's your support system at home? Are you available? Are you able to get to our clinic on a regular basis especially if you're going into a clinical trial? There's complicated blood draws in terms of what we're trying to learn about the drug and drug levels in your body. So, we call these pharmacoconnectic testings. It might require you to be seen in our clinic three days a week. Are you able to do that or is there an outreach in your local community that you're able to see participating local investigator as well and it's a personal choice. You basically… You're the center of everything we do, but you have a say in whether or not you want to go for a bone marrow transplant or you want to sit and you wait based on the information and the knowledge. So, we really factor all of this in.

Bone marrow transplant we talked about as being the only curative option, but it's very limited to a small subset of less than five percent of patients and age is a big thing. We are treating patients in their 90s. If they have very few comorbidities and they can tolerate it and they want to have treatment and they have a good support system, we treat our patients with Azacitidine or

Lenalidomide if that's the drug it's going to fit into their profile, but often I see this across United Sates as I'm lecturing, but also abroad there are lots of physicians that do not want to treat patients in their 80s. They just want to watch and we know that watching and waiting and just giving supportive care is doing nothing for the disease. My grandfather was an engineer. He worked for the… a Chiclet factory outside of New York in Astoria. He was working fulltime. He was 73 year of age. He was very involved in his community, but he lived in a walk up apartment and so he had to walk up five flights of stairs to get into his apartment and that's he was actually diagnosed. He was complaining of being short of breath and having to sit on the second floor stairs before he could move forward and so at that time I was literally two weeks of working with Dr. Silverman and Dr. Holland in the practice and I said, "I need you to evaluate my grandfather," and he was diagnosed at that time and it was his shortness of breath and him being just very tired and so you need to look at yourself and think about how active are you, what are some of the barriers that you're struggling with and keep a diary. Is it getting worse or is it getting better and communicate that to your nurses and your doctor so that we can help guide you treatment and decide what we're going to be doing in terms of what drugs we're going to choose, maybe we'll give you a little drug holiday, maybe we'll add something to the recipe to help you mange those side effects a little bit better.

These treatments do take time to work and so it is not a sprint. It is a marathon. It's going to take a long time. When I say a long time, we know from the science. We've been studying this data and through clinical trials for many years and we know that over 30… in the beginning we said you need at least four cycles of therapy, but what we realized when we really analyzed the data over 30 percent of patients were responding from four to six cycles. That's a large number. So now we say before a treatment is deemed not working, let's look at six treatments before we truly and any of the medications whether I'm talking about Revlimid, Decitabine or Azacitidine. The physician is going to really look at that, evaluate your bone marrow, look at your counts. Maybe it's time we do tweak. We say this is a very high risk disease patient, an older patient with comorbidities. Their disease is stable. We know also from some of the data that wasn't presented here, but knowing this work that stable disease also looks benefits patients in terms of survival and they're doing okay. If things are not getting worse and everything's okay and I'm feeling okay and I have a decent quality of life, I'm not cured, I'm not getting worse, I'll take that for right now and there are patients that we do have in our practice that are managed like that. So, it's something to think about. Your blood counts in the beginning will definitely drop and we'll go through these slides and showing you this animation. We expect that to happen and this is where you come into play in terms of so important for communicating. We're going to be doing blood counts, but you're also going to be feeling a certain way and we want to know how you're feeling so that we can help manage those side effects so that you don't give up, you don't get frustrated and you don't com off of treatment. So, be proactive.

So in the beginning, like Dr. Schiller gave us some nice slides and talking about abnormal cells and so when you present your symptoms it's usually the symptoms that drive patients in to see a physician. They're either, again, like I said fatigue and shortness of breath are very big. Fatigue a

lot of times patients will be walking around… my grandfather was tired, but he wasn't saying anything about it and he just figured, "I'm working. I walk to church. I go to church three days a week. I open up the church for people. I help some of the widows in our apartment." He was very busy and he says, "You know, I'm 73. I should be tired a little bit." So sometimes especially like in my grandfather's case and a lot of patients you could be walking around with this disease for much longer than you realize you didn't really know. So when does the clock start ticking and you look at, well, if you have low risk disease your chances of survival from this point to that point could be nine years, 10 years, 15 years, but you don't really know when you were diagnosed because you didn't really have a diagnosis made. So at the time when you start, again, your counts are dropping, your bone marrow, the seed, the soil, it's infected, bad things are happening. You're going to have counts done and even though your platelet count might say that you have a platelet count of 30,000 or 50,000 you might be bleeding like you have a platelet count of 10,000 because the percentage of the numbers whether it's a white cell or red cell or a platelet are not functioning correctly the way they need to. So, sometimes your numbers can be misleading as well, but basically this is what's happening and then we know as we implement treatment your blood counts are going to start to go down and so it's almost like a rollercoaster. We expect to see this happen. It's going to happen. You're going to start and you're going to drop and then you're going to balance back out before your next treatment. Most of these treatments are every 28 days. So, we give your bone marrow and your counts time to recover. This is the really critical time where we're going to watch you very closely, we're going to want to know how you're feeling. Again, diaries are important. Our patients are not seen weekly if they don't live in New York City. They will be seen locally. They'll get their blood counts locally. They'll be faxed into us, but we have them call us if they're not feeling great and we make them do diaries so that when they do come to see us they remember like this was the worst. My nausea was a problem, this was happening, but again this is the most challenging time for yourself and for your treatment team in the first two to three treatments and we'll go into that further with some other slides.

As the marrow recovers and the healthy blood cells start to form, you're going to start seeing subtle differences. You're going to start to feel better. Also during this time is where you're going to communicate to your family and to your grandkids this is not my best week. You got to be selfish a little bit and say I'm not available, I can't babysit, I can't do things during this time because I'm not feeling well or if the kids are not well you can't be around sick grandchildren. Is just to communicate that to your family so that we get your through that hurdle. We'll give antibiotics. It's not unusual in the beginning because your bone marrow is not working well. You might need more transfusions during that time. It doesn't mean that your disease is progressing. It's because you're getting that low in the count and we expect that and this is good and we know from data the patients that do go down and have what we call these naders (sp? 1:34:53) and do improve are the ones that are going to respond the best. It's doing what it's supposed to do. You want to knock out the bad cells and so very, very important.

As the response continues and, again, if you're keeping a diary or if you're looking at your transfusion dependency in the beginning transfusions just don't stop overnight. So, we like to make a baseline assessment and it's important to see how many transfusions you need and how often you need them in the beginning. So we look at that and when patients come in as you know, you're very focused on your blood counts. You want to know what your CBC looks like, but then you're going to say, but you know what? I feel there was something… I did a whole quality of life on these studies in the beginning. There's not too many trials. Now, there's more trials out there with quality of life. Dr. Silverman and I saw a difference in our patients before their counts actually started to rise. They had less fatigue, they had more energy, they had less dyspnea and this was part of *New England Journal of Medicine* article that was published along with the clinical trial on Azacitidine. So, keep… again, the diary is very important of how you're feeling. If you feel a little bit more energetic, a little less short of breath these are important things that we're going to manage. We're also going to look like I said with the transfusions your transfusions might lengthen. Maybe you needed transfusions every two weeks and now after two cycles you don't need a transfusion but every three and a half to four weeks. You're starting to produce normal red cells in your bone marrow so that you don't need to be getting transfused as often and eventually you can become transfusion independent with these drugs.

So, it's discouraging in the beginning, but we're going to go through *The Building Blocks of Hope* and learn how to just try to manage that. Sometimes we do very few dose modifications in our practice as it relates to Azacitidine. What we really do do is delay the therapy and this is how it was written in our clinical trials. What we do is wait a week. We wait for your counts to recover and then we'll start treatment if your counts start to go up. If we see a rise in your hemoglobin, in your platelet even though your ANC is low it's going to eventually follow. Your white count and your ANC is the last to kind of come up, but as long we know there's cells recovering then we're going to start you on your next treatment. Especially in the beginning if you have higher risk disease we want to make sure we are getting ahead of the disease instead of just kind of waiting and we've done that for many, many years. So, dose modification is kind of rare unlike Revlimid where you know and the studies patients that were started at 10 milligram were dropped to five and then 2.5. Supportive care, again, we will give you antibiotics and transfusions if you need it and, again, just realizing that we do expect this so that you do not get discouraged.

Here's just a scientific slide. This is Dr. List's from *New England Journal of Medicine*. I don't have the one from Silverman, but it was also in *New England Journal of Medicine* related to Azacitidine. So, Azacitidine, Vidaza is the same. Lenalidomide or Revlimid is the same and here's where I was just saying almost when you add 28.6 and the 7 you have over 30 percent that are responding between five and six cycles. So in the beginning when the drug was really being evaluated it was set up that if you're not responding after four cycles you come off it as we analyzed the data you could see 30 percent is a lot. So, six cycles is important and as you can see on Revlimid at least 12 weeks that you're going to see 97 percent of patients will respond by 21

weeks. So, this is where we understand how these drugs are working and why it's important to understand that you have to have patience.

Here is just an example of what we call trilineage response. Some patients will have their white cells, their red cells and their platelets. That's three cell lines that are affected. Some patients will just maybe just have a hemoglobin, monolineage, and then if you have more than… if you have two it's bilineage. So, with Azacitidine or Vidaza it's a trilineage drug effect. So, it will improve all kinds of counts, but you can see things are kind of going up and down and it's very confusing to see whether or not you're responding in the beginning. So, we expect to see this kind of pattern in the beginning. Two to three cycles, it's very, very important to just continue on. Things are going to drop and go up, but again keeping a diary of how you're feeling is very, very important.

Quickly, how many patients been received or have received or are receiving Azacitidine or Vidaza here? Did you get the subcutaneous or did you get IV?

Q22: IV.

Erin Demakos: IV. Okay. So, you didn't have to do any of the injections. In New York… So the drug was originally approved a subcutaneous injection, a little injection underneath your skin and then the FDA finally… We did a small pilot study and we were able to look at the bioavailability of the drug in your blood and then they started doing IV. Believe it or not in New York, 98 percent of our patients want to have the subcu injection. They don't want to spend any more time with this. It's almost like a Starbucks, a drive by sub cuing. They just get their subcu, stick their arm out and get a latte and go. So, they don't want to have an infusion or anything and that's fine and I understand that, but with this when this drug was approved we knew that there was definitely side effects related locally to that and so if you're getting subcutaneous injections we do give antihistamines, creams or lotions because you're going to have some itching. We do also do some oral antihistamines. So many patients have so many allergies, so they're already on Claritin or Zyrtec or Allegra and that actually helps for any of the symptoms. Cool or warm compresses, some creams and some Tylenol when they're not feeling so well. It also is what we consider a moderately… a metagenetic which is a nausea and vomiting producing drug. So, there is medication that we do give our patients to prevent that and it's usually the first couple of days and then sometimes after multiple cycles it's less and less that the patients don't really need it. So, that's important. You're going to have redness which is similar to a first degree burn. The skin will dry, peel off, but does get better over time. Cool and warm compresses help and if your platelets are low you're going to see some bruising for sure.

Some of our patients, this was presented several years ago in 2010. Dr. Platzbecker had this published, but as you know you guys all become very creative in finding different recipes to help some of the symptoms. This is an oil called primrose oil that patients did apply topically right after they received the injection. It's hard to show up here, but you could see that there's a

redness here, but then it's only a dot after they use this primrose oil. You'll read stuff like that. It has anti-inflammatory properties. Also which is very big that we've used as well and our patients have used is Manuka honey. I don't know if you guys know about Manuka honey. It's very medicinal. The Manuka honey is you can get that at a Whole Foods or anything, but it has lots of properties for blisters. I use it… My son rows for CRU so he constantly has blisters and I make up a concoction and wrap their hands and the next day they're already healing and engrafts. It's a wonderful thing as well. So, if the injection sites are irritating that's something that you might be able to try.

Here is a slide for Lenalidomide or Revlimid and you can see here over years patient that started in 2002 and out to 2011 counts are still going to kind of go up and down, but this is what we call the new normal. After a while the counts that your body has adjusted to, my grandfather walked around with a hemoglobin of six. He was 6'4" and that was my Irish side because I'm half Irish, half Italian, but he was always pasty white looking. So, being pale was kind of his normal color, but he was walking around with a hemoglobin of six. His body, obviously, got adjusted to that. Other patients so different triggers. It's different if you have heart disease, we might want to have you have a higher hemoglobin level because we want to make sure that you're getting enough oxygen to your heart. So, our criteria might have you have a higher hemoglobin. We want to transfuse you. We just don't transfuse a number. We transfuse a symptom. We transfuse you for platelets whether… if it's under 10,000 and you're bleeding and stuff for sure. If you're 12,000, 13,000 and you have no signs of bleeding and you're doing okay, we're not necessarily going to transfuse you. So again, it shows you the differences between patients and where they're going to stand, but to show you also and be reflective that you're going to see lots of up and downs and different counts and it's not so easy to just sort out and you can lose that hope and perspective that you might not be responding to treatment when in fact you are.

So, some of the strategies for Lenalidomide side effect management as you know it's an oral medication and so that you do not open these capsules. If they're broken, don't chew them. Most of the side effects are very manageable and DBTs or the blood clots are really for the higher dose in the multiple myeloma studies. You're getting a lot more Lenalidomide than patients with MDS. So, we really don't see a problem with the DBTs occurring. You're going to be watched very closely for the first eight weeks because we know that the counts are going to drop and you're just going home with a bottle of pills. So, you got to be managed. You got to make sure that you're adhering to your schedule and going in and getting your counts from your doctor or your nurse is prescribing that. Very, very important. We do, again, expect the counts to go down. We will treat you with antihistamines and, again, with steroids if you're having the rashes or any itching and, again, any side effects that you're feeling when you describe them to us. You describe them in severity, this is really uncomfortable or I can manage it and I'm fine so that we have an idea so we don't unnecessarily prescribe something that you might not need.

So, what can you do? How do you get involved in your care and that's so important. So standing up for your health. It's really being very proactive. This means being a strong self-advocate, an

empowered patient. It means taking more active role in your care to ensure you or your loved ones receive the best car and treatment available and so it's so important we want to hear from you. We want you to be involved in your care. We're not offended by all the questions. You just need to be organized when you come into the practice and make a list and we'll go through all of that and, again, it's nicely outlined in our *Building Blocks of Hope*. Asking questions and being involved in your disease and your treatment is so important. So, have very open and honest conversations with us and don't be intimidated and you might think it's a small question and it might be a very important question to us. Disclosing all of your medications. All of the herbs that you're taking, maybe the special teas that some of your family or friends like to make up. That might be impacting on your bone marrow. So, we need to really disclose everything that you're taking to us. Very, very important.

Set the agenda for your visit. Ask yourself what do I want to get out of this particular visit with my physician today and my nurse? And write down the top three things that you want. So if you have something focused and organized like that it helps us. Some of them might be I want Dr. Silverman to answer these three questions and then I know I have a little more time with Erin so then I can ask the nurse to help me with these. So, be organized like that. Bring that information with you and we can go over that.

Make the most out of every office visit. All current and past illnesses as well as chronic conditions you're going to have. Especially in your initial consult making sure that you disclose all of the issues that you're having whether it's arthritis, if you're having being seen by a cardiologist. We need all of this information. Your prior transfusion requirements. So again, we can look at whether or not chelation is a possibility or a necessity. Depending on how many transfusions you've had we want to look at all of these parameters. So, being a good historian very, very important, again, talking about the vitamins and the herbs and the supplements that you're taking. Very important. I wouldn't have thought about that 15 years ago, but it does… there's so many wonderful medicinal things out there. Like I said when I'm talking about Manuka honey, it's very medicinal. It's very important, but as Dr. Schiller was talking about vitamin D3 and all these other vitamins just don't take them thinking it's going to help. Just disclose it and then we can monitor you. Being in New York vitamin D levels are very low. You have a lot of sun here. We don't have a lot of sun necessarily in New York, so our vitamin D levels are usually very, very low, but it does impact on red cell production. It does impact on your thyroid. It does impact on your erythroid level. So, very important. Note symptoms, side effects that you're having and, again, and your transfusions records. Very important.

When you come to see us it's really important to really carefully listen to the dos and don'ts. This is basically your lifeline into us and your communication is essential, but if you're running a low grade fever, often our patients especially when they're going through the first couple of cycles just don't want to come in any more. They've already coming in frequently enough and they figure it's just a low grade fever. I don't have to do anything, but if your ANC and your white counts are really low and it's flu season, you're more on our watch and worry list and so

we want to hear from you and making sure that you do have a thermometer at home and you are taking your temperature because your temperature could just be a flushed face or kind of feeling a little bit unwell. You don't have to feel hot and be sweating and saying I definitely have a fever. There could be low grade things going on. So, when you're not really feeling well this is important and making sure that you show up for your appointment, make your transfusion appointments and treatment appointments appropriately.

So, we touched a little bit about balanced diet. Everything that I'm going through, again, is going to be in *The Building Blocks of Hope* in different sections, but in the MDS Foundation's website if you go and look and query all of 2015 newsletter, it's volume 21, issue two, there's a really nice section on just about diet what you can do for anemia, thrombocytopenia and so I think that… and anemia. So, very well written and basic. A well balanced diet is just important. Small frequent meals might be very helpful, but there's dense nutrient foods that are going to help. Kale and spinach and all that other stuff for your hemoglobin, but again when you go into the website and get this newsletter it's broken down in each section and also in our *Building Blocks of Hope* we touch upon that.

Important to talk about your daily activity and exercise and often patients look to us and say are you out of your mind? You want me to exercise? I am fatigued and I'm not feeling well, but it's so important and we know this from the science and all the data really important to do small little walks to build up your stamina. It helps with sleep. It helps with depression. It helps with overall well body functioning. So, definitely in New York you guys don't get snow. We get freezing weather and snow. Patients will go into different malls or different stores where they can just… they're indoors. They're away from the ice and the snow because it's very scary to think that they have very low platelet counts. They just fall, they can have major bleeding problems, but to put their sneakers on and walk around. If they want to just do it in their house it's just getting up and looking as a reminder. We're trying to test a few things and I do have the Apple watch and we're trying to think of different… just like FiLIP just different things and triggers and alerts that maybe some of these wearables like even if you have some kind of wearable on that's going to monitor your heart rate and monitor you temperature. You're feeling a little warm. We got to look at this. This is where technology is going. This is where medicine is going. So, but to really think and say okay get up and walk around every hour for 10 minutes even if it's just going to the bathroom then going into the kitchen to get a cup of tea and walking around. If you're really tired when we're talking about rest take a nap and limit it to only 30 minutes because they know that if you take more than a 30 minute nap it's going to affect your nighttime sleep.

Going into avoiding infection and bleeding. These are very important variables as well as you know that for infection if you're having an open cut or you were playing the dog or the cat and you were scratched and you have a low white count you can have a big infection. Patients can come in overnight and have their hand blown up even if they were working in the garden and they scratched themselves on the thorn bush. So, your body is not able in the beginning if you're not on a treatment that is raising your white blood cells, you won't have that ability to fight off

an infection. So, to keep your guard up on that especially, again, like I said flu season people that are sick around you. Avoid bleeding, potential issues there, but to continue to like live your life and be involved as much as you can when you're feeling good that's when you make plans with family and friends and do the things that you love doing before. It will help and, again, we'll go over *The Building Blocks of Hope*. Ask for help when needed and being an active participant in the Building Blocks.

So in *The Building Blocks of Hope* it's called book five or tab five. There's a section called My MDS Manager and it really is a wonderful tool. I'm going to… it's towards the back. It's not tabbed. Let me just pull mine out. All of this, again, is to help guide you guys and you can see that it has tracking your treatment, your profile, what were your bone marrow results, what your blood counts were, you can add pages to this. You can print it out. We are working on putting it into a digital format. It's being beta tested now with some patients, but when you go through this book you might be a new patient and you might want to just deal with understanding MDS and in this book it has embedded videos and simple ways showing you what a bone marrow biopsy is and an aspiration. It's talking about just risk categories. It's talking about different side effects, strategies to kind of manage them. Very, very important and very helpful. So, keeping track of all your information in an organized way like this little planner is you just bring that book in with you. Nurses love to see that. Doctors love to see that. There's pages that you just add to it for your notes. Like I said add your questions to that. Keep a log of all of this and just basically how you're feeling. If you changed any of your medications since your last visit or did add some herbs or something we need to know about that. If you have a transfusion that we might not know about that we didn't book for you, please make sure that that's displayed as well.

This is where we were just talking about bringing the mobile application and some of the key features in terms of just who you contact for professionals, contacts for both professionals and personals. Personnel like how do you get in touch with me, how do you get in touch with Dr. Silverman, all your trackers? You'll be able to be involved in all of this. So, let's see how this goes. I think it's in September the MDS Foundation is saying that they hope to have some more information about how that's going. It's going to require a Google account which is free, but again once you put information in there I'm sure it's going to be able to plot and track things and be nice on your iPad and we're doing more iPad related things in our own practice and a lot of doctors' practices across the United States are getting more involved in that as well. So again, this is where things are moving in terms of the field.

Another really nice website is called Lots of Helping Hands and I'm not sure if you're aware of this, but it's a help calendar and someone gets appointed to be the person to start this up and it's with their E-mail and your family and friends can get online and they can get alerts on their phone or their iPad or on their computer and you sign up. It takes just one person to start this calendar. You put the names and the E-mail addresses and the phone numbers in there. They can help organize meals and rides. If you want to… say you're even going to plan on doing something as a family and you want… you're feeling great and you want everybody just to kind

of come over and do a potluck dinner. Anything that you want in there, your doctor's appointments. It's very easy to make these changes. It's a wonderful service. A lot of our patients use this and…

Q23: (inaudible 1:57:39)

Erin Demakos: Yes. You just get it online. Here's the website – lotsahelpinghands.com. Available to everybody and it is a very wonderful tool out there. You definitely I would advise people using it. I'm using it for my mom isn't well and my mother-in-law isn't well and it's helped both of us in that because we're all over the United States and just making sure that we're helping coordinate things for them as well. So, it's a great thing. It's one place that everybody can go to.

Audrey was here and she introduced herself. If you have any questions, patients or caregivers can contact the MDS Foundation. Here's the phone number and there is Audrey's E-mail. So, let me hold that up there for a few minutes, so you can get that or without Audrey's name, there's our website mds-foundation.org. *The Building Blocks of Hope* is there. I'm going to show you a three minute video on that so that you have a better idea of what I'm talking about and how you can access it yourself from the website in case you don't know how to do that. And hope, I want you to walk away with hope. I did not have hope when my grandfather was diagnosed. There was no information out there. There was no support group and so like I said it's a noun. It describes the feeling that what you want can be had or that things will turn out for the best. As a verb it means to look forward with desire and reasonable confidence and I want you to know that there are so many clinical trials in development. So when plan A isn't working, there's a plan B and there's a plan C and you work with your physician and you know that… in *The Building Blocks of Hope* it gives you a whole list of other websites especially with the clinical trials, websites so that you can see what's being worked on in MDS, but you can look forward to hope and know that we are making major strides in the disease. It's taken longer than we would like, but we are getting there and there is good reason… I have lots of patients in our practice that have lived many years with high risk disease with us. Again, I think communication is very, very important and so I want to thank you. I want to go to this just quick three minute video. We have a little bit of time before we start lunch and then we're going to resume back here at 2:00… One. And so we have… if you want to support the MDS Foundation in any way, you can text MDS 41444 to do a little contribution. All the work and all the money that goes into that helps with support groups, pays for all kinds of wonderful things for patients and so let me just go to… do not look at my computer. I wasn't expecting to bring my computer. My desktop is like a nightmare. So, I'm at the MDS Foundation website. It says mds-foundation.org. You can see my little cursor up there. Right? So, when you go there you're going to go for Visitors and Patients and then over here is *The Building Blocks of Hope*. Hopefully, this will behave. You're going to click on there. There's lots of great information on there.

(Video)

This is a three minute video introduction of the Building Blocks of Hope program developed by Sandy Curtin and the MDS Foundation for patients and caregivers when they have MDS. At the end of this video, there will be instructions for accessing resources available to… you or someone you know has been diagnosed with MDS. Hearing the words Myelodysplastic Syndrome or MDS can be frightening. Diagnosis of MDS (inaudible 2:01:51) both long term challenges. You probably have many questions in your mind. Building Blocks of Hope program is designed to help people the information you're looking for. There are several components to the Building Blocks of Hope including printed materials, digital materials, videos, brief educational slide set, links to online resources, a number of very practical tools. All of these components are intended to provide you and your caregivers with strategies for living with MDS. The best place to start will be in our Building Blocks of Hope (inaudible 2:02:31). This will provide you with information, resources and tools to help you through your journey. This continuously updated document includes the following sections:

Understanding MDS which will give you a complete description of the process of MDS and answers to common questions,

Taking Treatment. Treatment of MDS can vary based on the type of MDS you have and how severe it is. This section will provide details about the various (inaudible 2:03:01) to treatment,

Quick Tips. Quick Tips offered in this section (inaudible) guidelines for monitoring your symptoms and reporting them to your healthcare provider when necessary;

Iron Overload. Iron overload is a possible outcome of receiving repeated red blood cell transfusions and this section answers common questions:

My MDS Plan. Understanding the diagnosis of MDS will help give your caregivers an active part in your individual treatment plan.

My MDS Plan provides several tools to (inaudible) and track and manage your journey.

The MDS Foundation. The MDS Foundation is an internationally publicly supported organization dedicated to serving the MDS patient, caregivers and the professionals that are working to improve the lives of patients living with (inaudible 2:03:53). The MDS Foundation provides a number of resources which support the Building Blocks of Hope program. You can access the handbook in a variety of ways – through our website you will

be able to answer a series of questions and download and customize (inaudible 2:04:09) view and print from your computer. You can view the complete handbook and a beautiful page turning format. This includes a search feature and thumbnail views that will (inaudible) quickly find the information you're looking for. This is also a great way to share information with others. You can also contact the MDS Foundation directly and we can mail you a binder version of the handbook. Allow yourself time to adjust to this diagnosis of MDS. Take time to explore The Building Blocks of Hope.

We wish you the best on your journey and hope that the Building Blocks of Hope program will provide you and your caregiver's tools and strategies for living with MDS.

Erin Demakos: So, I just want to just hopefully you found that helpful and… there's also a blog on here that you can enter in and talk about with other patients and comments and answers will be posted up there. So, you should visit the website and you'll find it, I think, very, very helpful.

I would like to just open it up for questions. I know that we have a few minutes before lunch and then we're going to reconvene here if you just want to hold questions or if I can answer anything that you have right now from the nursing perspective. Yes?

Q24: I've got a stupid question.

Erin Demakos: You said you have a stupid question?

Q24: When you get to the point of getting a transfusion, I assume the drugs aren't working.

Erin Demakos: I didn't understand the question.

Q24: When you reach the point of getting a transfusion, I assumed, don't know how these drugs really work (inaudible). Get your bone marrow producing…

Erin Demakos: Okay. So when you reach the point where your body needs blood transfusions, your bone marrow is not able to produce enough red cells. Vidaza or Azacitidine helps the drug that I discussed. Are you on treatment? Okay. What are you…?

Q24: (inaudible 2:06:27) transfusions.

Erin Demakos: You don't have transfusions yet? Okay. So, if you start to need them… what are you on right now?

Q24: Some kind of (inaudible 2:06:35)

Erin Demakos: So you're on an erythropoietic stimulating thing to hopefully help. After a while when that stops to work and you become…

Q24: (inaudible 2:06:43) near that point.

Erin Demakos: Right. Then we're going to want to do a bone marrow. We're going to want to reevaluate what's happening with those immature cells in your bone marrow and take a look because maybe those… When was your last bone marrow done?

Q24: About a year ago.

Erin Demakos: About a year ago. So, at minimum we do that every year until things start to change a little bit. You would want one… It's like when you go to the doctor you get an annual checkup. So, it's definitely something that we would highly recommend you get done once a year because before things happen in your blood counts…

Q24: My question is simple. What are the other choices besides when you reach that point?

Erin Demakos: You need treatment.

Q24: When they say you have to have a transfusion that sounds to me like…

Erin Demakos: You need the transfusion. You need a blood transfusion. That's the only way that you're going to raise that up.

Q24: And if you don't take the transfusion.

Erin Demakos: You're going to have problems. You're just going to have cardiac problems. Your body needs a certain level…

Q24: So at that point, you really don't have many options.

Erin Demakos: You don't have any option and so the ESA is helping that production. After a while when it starts to not work you need to have active therapy. That's when you're going to need to either get Lenalidomide, Decitabine or Azacitidine. Those are the three drugs approved for MDS. Separate from clinical trials. Then you would have to go into a clinical trial. So, that's a whole thing. Annually, a bone marrow biopsy and aspirate is important because like I've been saying before your counts are having a problem we want to know what's happening in your bone marrow. So, if things are even getting worse it start there so if your blasts are going up that means you disease is starting to progress. We're just starting to see it in your blood, but we'll

have an answer by your bone marrow biopsy and aspirate. So, that's important to definitely have one once a year.

Q24: (inaudible 2:08:28) Are you with UCLA?

Erin Demakos: No. I'm in New York with Dr. Lou Silverman at Mt. Sinai at the Icahn School of Medicine.

Q24: There are good things (inaudible 2:08:36)

Erin Demakos: It's a very… Yeah. I've been there for over 30 years. I've been working in the field for MDS for over 28. I'm blessed. He's the nicest physician and the other doctor who's 91. He was the reason why the Azacitidine is here. They were believers then. This was like I said… It was considered an orphan drug. People gave up and put it on the shelf. They just learned how to figure it out and it's still the drug that's partnering with so many… with Lenalidomide in combination. It's Azacitidine in combination with… Azacitidine combination with a lot of these other new drugs that we know because it's so complicated. There's other things that are impacting on this disease that we say we need this other drug to be added to that recipe.

Q24: Thank you.

Erin Demakos: You're welcome.

Yes?

Q25: A question about the timing of the cycle of this drug therapy. It was all approved based on this treatment schedule, but how often do you stretch out the cycle, even tighten up the schedule based on when the patient is recovering from (inaudible 2:09:47). How much do you tinker and how common is it to not be monthly?

Erin Demakos: I know. It's interesting. The science is based on the science. So, we know that when Azacitidine was approved or Vidaza was approved it was based on the seven days. We are now open eight days a week. We were not open eight days a week up until a month ago. We were open six days a week probably about a year and a half ago at Sinai. So, patients can come in and just get their injections. Now, when you have high risk disease you have to understand the disease is bad. If we're going to want to stick to what the science is so if we weren't open and the patients had no means to get this drug locally by another doctor we would do the five days that Dr. Schiller had stated, but then the patients have to come back Monday/Tuesday. Not Tuesday/Wednesday, not Thursday/Friday. We stick to the schedule as close as we can. Once you start responding and we have patients that are on for years and they're like can I stop? And I go well, we know what happens when you stop. It's like diabetes. It's like you still need your medication. So, we just say if you want… Dr. Silverman's like I don't recommend you stopping.

If you stop the clone's going to come back, reemerge, the disease is going to come back. That's your choice. This is what's going to happen. So, we do lengthen… What Dr. Silverman will do is we'll treat every six weeks once you're in a good cruising pattern. That knocks off like two months when you think about 12 months and patients seem to be happy with that. We will tinker around. I mean, it's incredible. As I stand here, I wish I had these options for my grandfather, but we've learned enough to know safely we can give you a little bit of a break, but we're not messing with a good thing because you don't never know some of the people that you think are going to do well do bad and the ones that do bad are the ones that you thought were going to do well. So, we keep them on. We will give holiday. We will allow people… They go abroad now. Patients are going abroad and that's what's wonderful about the MDS Foundation and having this big nurse leadership board because I'm trying to work on just a Google map so that no matter where you go abroad and no matter where you go in the United States that you know there's a healthcare team of professionals knowing about MDS so that if you feel like going away with your grandkids or your family for the summer, is there somebody locally that knows MDS, knows that you can go in and get checked in and it's safe and they know what's happening because even in the United States some patients have to take a flight to go see a Center of Excellence. They don't have that professional team of people. So, we will lengthen it, but we don't do that too often and six weeks is kind of Silverman's maximum and I've been working with him forever. He rarely changes.

Q26: I had a question. Somewhere I read that one of the symptoms of MDS is anxiety and I have anxiety disorder. I've had it for years, but it seems to me if you have low hemoglobin you're not going to pull out your CO2 and get rid of it and everybody who knows me I've build up CO2 you feel anxious. Is that's what's going on or do you know? I don't even know if anyone knows.

Erin Demakos: It's just anxiety is with the whole diagnosis and it is the fear of the unknown and I think that when you have the discussions and you raise your questions with your healthcare team they can help allay some of your fears, but you might need some medication if it's interfering to such a degree to try to help some of the anxiety. Exercise helps. That's what I'm saying. You look at your diet, you look at your exercise program. You speak to other people. You might go to the MDS Foundation website and like I said look at some of these blogs that might help you. Sometimes people are very afraid to even want to know the answer. So, anxiety is common amongst everyone. It's not… It is a symptom of just having a bad diagnosis and not knowing what's going to happen next. So, you need to talk about that more.

Q26: Do doctors ever give patients those little boxes of oxygen? They don't need it.

Erin Demakos: No.

Q26: Thank you.

Q27: I've been on Erythropoietin for two years and now Medicare says I don't need it anymore and they use to pay for it.

Erin Demakos: I'm sorry.

Q27: If I stop taking it will that have any reaction?

Erin Demakos: It could and it could not. I can't… This is the government and unfortunately it's your physician is going to have to write letters and say you definitely need this, the authorization and it's very important that you have it and we're still able to get away with this, but it just depends. You have to talk to your physician or a nurse practitioner and then they can write the authorization to get the justification why you need that.

Q28: What drug was that they stopped paying?

Q27: It's the trade name is Aranesp.

Erin Demakos: And so you should be able to get it, but they have to get a justification, but more and more we're going to see that happening. That's just the reality.

Q28: Did Medicare cut it off or did you have it for a time?

Erin Demakos: He had it and Medicare said he can't have it anymore.

Q28: Why is that?

Erin Demakos: Cost cutting. I mean, that's just the reality…

Q29: We (inaudible 2:15:42) insurance companies will change year to year. They will open it up if you do get a prior authorization. So, that's what you have to… Get your doctor to write the prior authorization and the probability of them approving it is very great.

Erin Demakos: Right. Sometimes you got to pick up the phone, too.

Q29: You do. You have to be your own advocate.

Erin Demakos: You do. You got to be your own advocate .That's what this is about taking…

Q29: Just real quick. I'm (inaudible 2:16:08). I've gone through all the protocols, but I have low risk Q5 and my doc three months ago we started going to three units every three weeks and my blood pressure went up for about the first three or four days because the added units into my body.

Erin Demakos: The volume.

Q29: And with all the people that you see taking transfusions most of them take two units every other week, every two weeks?

Erin Demakos: Yes.

Q29: So, that's like the protocol in the transfusions?

Erin Demakos: It's just kind of standard with them, but it varies amongst obviously, patients. We see a lot of high risk transfusion dependent patients in our practice.

Q29: Fortunately, I'm low risk.

Erin Demakos: You're low risk. I know.

Q29: But I still need the transfusions.

Erin Demakos: So, you've had Vidaza. You've had Lenalidomide.

Q29: I've had them all. I've had… the year and a half I had the Revlimid then I want onto the Vidaza and then after about three and a half – four years I'm just totally transfusion dependent. That's for the last two years, but I feel fine when I get the blood. I have a normal life when I get the blood, but then it just… exhaustion hits and then I need more blood and I figured with the three weeks it would give me that extra week.

Erin Demakos: So not uncommon. This is with patients that it used to work. I used to feel better for a longer period of time. Now, I don't. So, it's back to looking at maybe clinical trials or getting an active therapy to get you off of transfusions.

Q29: The blood works, but I just didn't know what I was doing to my body with that extra unit of blood.

Erin Demakos: Did they give you a diuretic and making sure that you're not having problems? That's a lot of volume. Unfortunately, that's what you're on. It's just going to help your symptoms. It's not going to change anything with the disease, but that is a lot of blood and that's where you got to make the decision what…

Q29: I'm going to tell the doctor let's go to two units every other week.

Erin Demakos: And see how you do with that. Your body is going to tell you say I'm not going to be able to handle that I need...

Q29: I just didn't like my blood pressure taking a jump.

Erin Demakos: It's a lot. It's a lot on your body. Yes?

Q30: I have a (inaudible 2:18:17) RARS. I'm (inaudible) it's just recent that I was diagnosed. I don't know that much about it, but the doctor said that they're going to… they're not going to do anything but check every 90 days. Is that…

Erin Demakos: That's reasonable and so if you're feeling different though before those 90 days like if you're seeing bruising or seeing like you have a chronic sinusitis or you're just not feeling well. You know your body. You pick up the phone. They might to do another blood count, but what we call watch and wait because you're in that category right now. We're just going to watch and see how you do and if anything changes over that time then they might do a bone marrow to see deeper like something's changing. Your counts are changing. Let's see what's happening. Are you changing different course.