Dr. Lanetta Bronté-Hall: Hi everyone. And thank you for that wonderful introduction. Sickle cell is very near and dear to me. So I do appreciate the invitation. Today, we'll discuss understanding gene therapy and addressing health disparities in sickle cell disease. So the New England Journal of Medicine in 2017, [inaudible] published a primary challenge to many patients with sickle cell disease remains a social one, being seen and treated as individuals who deserve relief and being supported rather than stigmatized in a highly charged atmosphere. When we review- and what does that really mean in terms of health disparity. So when we look at where sickle cell has been since discovered in the United States more than a hundred years ago, this graphic shows for the most part there was a very slow progression in advancements in therapies and treatment. And then you start to see more of an advanced- for nearly a hundred years, we didn't have a whole lot of advancement in sickle cell disease. And what we know about sickle cell disease, which is so exciting or at least about the sickle gene, is that it is a genetic mutation that arose about 7,300 years ago. And most mutations that occur really result in deleterious outcome. The sickle gene is actually a survival gene. So by itself, there is immunity against malaria. However, two genes together we know, has some serious consequences. When we also assess some of the funding related to sickle cell disease, as we know, sickle cell is now a part of mandatory newborn screening.

Of all of the newborn diseases that are screened for at birth, sickle cell is the most common. When we compare sickle cell to another genetic disorders, cystic fibrosis, where there are about 70,000 individuals in the US with cystic fibrosis and about a hundred thousand with sickle cell disease in the US, you can clearly see the disparity in NIH funding and foundation funding and the amount per person that is there to care for an individual with either of these diseases. We look at sickle cell disease and we see about, you know, $700 per person to care for an individual and compare that to cystic fibrosis, it's about $8,500, big difference, big, big difference. Survival in sickle cell has really changed. It used to be that children rarely live to be age 18 and the most common cause of death with infection. Because of penicillin prophylaxis and

pneumococcal vaccine, it really has reduced the rate of invasive pneumococcal infections by 90%, which was why the props one and props two clinical trials with penicillin prophylaxis were stopped early, and the institution of newborn screening and penicillin prophylaxis. So greater than 98% of children with sickle cell disease now live until adulthood. So excellent, excellent public health outcome there, but what are the causes of death now? So we now see acute chest syndrome and multiorgan failure in both children and adults. We also see a disparity in ED admissions and hospitalizations by age, meaning that when the baby is born with sickle cell disease, they're in a wonderful system of care. And we see that here where you see a mirroring of ED visits and hospitalizations.

So we kind of look at this as that ED visit was an appropriate ED visit because there was a hospitalization associated with that. And you don't see an erratic pattern of the child just going only to the ER and really not being assessed very well for any ongoing, long-term complications. When we hit age 15, that transition period, which we all know so well and many difficulties arise, children just kind of want to be free of the disease and are tired of going to many hospitalizations, and you start to see this pattern unfold of where [inaudible] have a lot of ED visits and then you also see the erratic pattern of the hospitalization. So it really begins at age 15 as they're transitioning. And what we now know, what the current data is showing that we've done such a great job of getting these children beyond the age of 18 with penicillin prophylaxis. Now, because of the lack of adult providers, we're now seeing greater than 50% of patients with sickle cell disease are dying before the age of 45 years old. And this is a trajectory that we want to change. We're trying to change that with treatment. What new FDA approved drugs are now available for sickle cell disease, where we didn't have anything for over a hundred years and now we have three drugs that we have in the market that are FDA approved for sickle cell disease. And now I'll just briefly go over those. This slide highlights that sickle cell disease is a chronic and complex disease and trying to manage a disease in an acute care setting, where we saw that erratic pattern of ER visits and hospital admissions will not lead to good outcomes for this patient population.

And the complications are just so many, acute complications on top of chronic complications. There are various exacerbations over and over again.
But there are many acute and chronic complications and so we definitely need better solutions and better management and a better system of care for these patients who constantly still experience pain, which is the hallmark of sickle cell disease. There are many different types of pain. And so we want to, you know, make sure that we are assessing the pain appropriately, but pain starts very early as you know, and the VOC or the vaso-occlusive episodes or this pain can last anywhere from three to nine days. Pain management primarily involves acetaminophen, some NSAIDs, opiods, IV hydration. But now we have these FDA approved drugs- hydroxyurea has been out there for a while since 1988. We have slow uptake for various reasons. Patients report, you know, it's a chemotherapy drug, they don't want to take that, they want to have children. So we only have about anywhere from 10% to maybe 20% uptake of hydroxyurea nationwide. We also now have L-glutamine, crizanlizumab, and voxelotor. Those are the three drugs that were recently approved by the FDA. And these drugs work in various aspects of anti- of targets within the capillaries and within the red blood cell. So they're anti-sickling agents, anti-inflammatory agents, anti-oxidants, but this whole system of this highly charged inflammatory system leads to a great deal of pain for these patients.

We're actually now working with a company where we can measure some of biomarkers, the p-selectins and the VCAM, which show the inflammation. And I tell you, it breaks your heart because all of the patients are in the critical zone. So just as we get a call from Quest about critical labs, we're now receiving calls from Functional Fluidics about the patients in these biomarkers that are all these pain biomarkers that are- they're all in the critical zone. So we're really trying to make sure that we get them on these newer medications to help with that inflammatory process. So what do we consider- how do we go about using these medications? And particularly, when we think about transplant or gene therapy- we want to consider the age, we want to consider route of delivery, and we want to consider indication. The types of therapies are disease modifying. So how can we change the course of the disease without a cure? So that

would be with hydroxyurea, crizanlizumab or Adakveo, voxelotor or Oxbryta, L-glutamine or Endari. So these are disease modifying. Then they're also curative therapy, bone marrow stem cell transplant. There can be a sibling match, haploidentical or unrelated. And then there's gene therapy. And these are conversations and options that we would like to start to present to patients and families, because they really don't look at their disease in sort of like buckets of, okay, there's therapies, there's curative therapy and then there's gene therapy. Okay. We also want to take into account the quality of life, which is typically very poor for many of our patients. We do a PHQ-9 on a daily basis if they come in and definitely on a monthly basis, and they're usually greater than five and we refer them to our in-house social worker. We have to weigh the risk and benefits of short-term, long-term risk. And then reproductive health. I mean, a lot of patients will not want to participate and be compliant with certain medications because they do want to have children. And so we have to respect that. This just discusses the recommended treatment approaches.

So I'll just let you review that on your own so we can kind of get to some of the gene therapy and discuss some of those targets of the newer medications. And this is the treatment options, hemoglobin S polymerization. Are we targeting S gene? Are we targeting vasocclusion? So some of the inflammatory biomarkers as well. Blood transfusions, the mainstay of treatment in sickle cell disease patients, again, more palliative, acute episodic. There are patients on chronic transfusion program, you know, those who've had strokes. And then there are various benefits to each of the therapies. And again, you can take your time and review those. So current curative therapies and strategies. And the patients and their families are always interested in curative therapies, particularly when they watch television and then there's 60 Minutes and Dr. Francis Collins is on and talking about gene therapy or transplant and successful outcome. We then start getting a lot of calls and patients are like, sign me up, I want to learn more about the transplant or the gene therapy. So this is a long process, a long commitment and a lot of education that really needs to go out to patients and families. But this is a very exciting time for sickle cell. I mean, we are really marching down this path of curative therapies and the strategies that work best. So we have allogeneic stem

cell transplant, where there's myeloablative regimens, reduce intensive regimens and non-myeloablative regimens where we actually have 50 clinical trials listed now in clinical trials.gov for allogenic and autologous transplant. There are 10 clinical trials. We also now have gene therapy with the lentil viral strategies where we can induce fetal hemoglobin. There's downregulation of the BCL11A globin chromatin structure. And so the goal there is to downregulate beta globin gene expression. And then we also have the gene editing, using the zinc fingers or CRISPR-Cas9. And again, that is downregulation of the BCL11 genes.

So the approaches to gene therapies- is it disease modifying versus curative like results? So kind of keep in mind that the sickle gene by itself, you know, technically is a survival gene. So if you are a carrier, if you have sickle cell trait, typically you don't have any untoward outcomes. I mean there are some complications that are associated with sickle cell trait. So we do educate patients or individuals who are carriers about trait, but when we talk about disease modifying versus cure and gene therapies, you know, the thought sort of is if a patient has a hemoglobin profile that look like a carrier status, then is that good enough? Or do we need the outcome to be hemoglobin AA? So the approach to gene therapy allows for the addition of a helpful gene so the level of production of this new hemoglobin will determine how well it changes the course of sickle cell disease. So it's disease modifying. Then there's also the gene knockdown. We're looking at that BCL11A to improve the fetal hemoglobin levels and the level of production of fetal hemoglobin, which can also determine how well it changes the course of the disease, almost like hydroxyurea that increases the fetal hemoglobin level. We are going to look at the efficacy and safety of CRISPR-Cas9 gene edited therapy to treat sickle cell disease. So again, what is the risk-benefit profile? And is this something that we can move forward with in a way that will lead to almost a standard of care in the future for sickle cell? Okay. So the lentiglobin gene therapy versus the CRISPR-Cas9 gene editing. With lentiglobin, it is insertion- lentiglobin gene is inserted randomly into the target cells. This makes a functional protein despite it's still a faulty gene, but we are concerned about insertional mutagenesis using this strategy.

The CRISPR-Cas9 gene editing actually, there's a disruption or a correction of the gene by targeting certain sequences. And this is therapeutic gene editing called off target effect. So this is an example of gene editing with [inaudible] using the CRISPR-Cas9 and the challenge here is improving the therapeutic gene editing rate over unintended editing. So there's still some concern about insertions and deletions. So we're, you know, still sort of treading water there, but things are moving in the right direction. So here we- this is a trial using- producing fetal hemoglobin where there was a disruption in the hemoglobin repressor BCL11A. This one is again, another gene edited therapy for sickle cell disease. This is a directly- this particular strategy correcting the sickle mutation. There is a high [inaudible] efficiency and this came from a single stranded DNA donor. This is ex vivo gene edited therapy for treating sickle cell disease. This is autologous, so we isolate it from the patient, deliver the gene editing regents into- back into the cells. We remove any of the remaining cells using chemotherapy and infuse the gene edited hematopoietic cells and then a few percent of the gene edited hematopoietic cells can then regenerate the blood system. So this is just the research workflow and you can review that. So the characterization of gene edited for sickle cell disease, it gives a high level of about 39% of the sickle mutation correction, which is, you know, excellent. There's reduced sickle hemoglobin S and increased normal hemoglobin A. It's also been shown to reduce sickling overall and the detected gene corrected cells after 16 weeks of engraftment. So very promising. They're unintended genomic modifications with unforeseen side effects of gene editing, and that is what we're looking at now. There was one study in particular with [inaudible] that had to pause their research, but they are now back up and running. But we do have the small insertions and deletions.

So successful genome editing relies on the accurate quantification of the repair outcomes. The challenge here is that we fail to detect large genomic modifications and rare insertions and deletions. So we just don't know what those outcomes are going to be. And when we're having those discussions with patients about and their families about risk benefits, with sickle cells, that could be a challenge sometimes because technically, you know, you can live a long time if you're well-managed with sickle cell

disease. So do you risk gene therapy or transplant and, you know, risk having graft versus host or creating a whole another disease because you're now dealing with graft versus host. So what- you know, how do we actually weigh some of those risks-benefits? What are some of the inclusion-exclusion criteria? And oftentimes it comes down to patients needing to have severe disease, which they get a little upset when they hear that because they all say that they have severe disease, but typically not severe enough for many of them to go into some of the transplant trials that we do have. But we know that this will will change as we continue to progress with gene therapy and transplant. So again, there are various types of insertions and deletions, and we don't know the hemoglobin variance that occur. We don't know what the function is. So the research will just continue to lead us down the path to continue to refine our strategy and regimen. So we have high fidelity. So there are lots of ways to improve the genomic rearrangement between on and off target sites so that we can have outcomes that are not deleterious to patients. So then we start getting into some of the issues related to HLA match siblings donors. And this is in the myeloablative transplant. These have historically evolved conditioning. You know that it's associated with significant toxicity. And we now know that it's not necessary since the mixed donor chimerism can achieve hematologic cure of sickle cell disease.

So can we cure sickle cell disease with less intensive conditioning? So I think that was certainly be desired by many. The non-myeloablative transplant for sickle cell disease in adults, this is one that involves 122 participants. Patients do really love participating in clinical research. And so I hope that in our community here in South Florida, we are able to get more patients to participate. But those that participated in this trial were sickle-free survival and 85% of them. And they had no chronic graft versus host disease. So we didn't create a new disease for the patients to deal with. So can we use this approach to effectively cure children? So the SUN trial sickle transplant using a non-myeloablative approach. This is a prospective phase two multi-center trial, including children and young adults ages 2 to 24.99, HLA identical siblings able to donate peripheral blood stem cells, all genome types are welcomed and it leads to one clinical complication from sickle cell disease. These are disease severity eligibility for

hemoglobin SS or hemoglobin S beta thal 0 or hemoglobin SB or S beta plus. So again, when we talk about severity, this is the criteria that the patients often need to meet. So abnormal TCD, any infarction on brain MRI or overt strokes that you can have a chance to look at those. Here is the SUN transplant regimen. So you have your alemtuzumab, your total body irradiation, low dose and then your rejection medication there. The enrollment, we had our first patient in 2018. In March, 2020, the enrollment was positive COVID-19, and then in May, 2020, enrollment resume. So there are 28 consented patients and 24 have been transplanted. The target there is 30 and it's going to be expanded to 40. So the results on the first transplanted patients. So we have 15 that are here. The average age is 13.7, 60% males. The genome type was 80% hemoglobin SS and then 7% each for beta thal 0 plus and [inaudible. So the pre-HSCT treatment hydroxyurea, 87% were on hydroxyurea and 33% were on chronic transfusions.

The most common disease severity eligibility criteria met were greater than three episodes of pain requiring treatment with opioid or IV medication. That typically is not a challenging one to me, because again, pain is the hallmark. Hospitalization for pain or ECF on hydroxyurea, that was eight and then greater than two acute chest syndrome events, and there were six individuals with that. And then the silent strokes, there were five. The aim one was disease-free survival. So the median followup in this child was 580 days. So 291 to 1049, 73% greater than a year post-transplant had disease-free survival, so 73%. You think about some other hematologic disorders and transplant, do you have that type of survival? A greater than one year post-transplant, 73%. And then 15 out of 15, eventually with a hundred percent survival, no acute or chronic graft versus host disease. One graft rejection, return of sickle cell disease. So we now have 93% disease-free survival. So this to me is just such a selling point. If we had a child with leukemia, I mean, this would just be a great statistic to share. So hopefully, we'll be able to share this type of statistic with all children if they want it, if their parents want them to have a transplant for sickle cell and potential 93% disease-free survival. In terms of quality of life, no decline in quality of life during the transplant and improvement in quality of life one year post-transplant. So you will often hear the transplanted individual talk about just running and having more oxygen and just more life- just feeling

more lively in general. Transfusions, really big in terms of being able to reduce the need for blood transfusion. So six out of 15 or 40% of patients required no platelet transfusions. The number of platelet transfusions with the median was one. And you can see in the SUN trial, the number of platelet transfusions was literally almost nothing.

So future directions, we want to evaluate fertility, hormone levels, semen analysis, immune reconstitution studies, impact on cognition, long-term outcomes, decreased graft rejection, and expand eligibility. I think the overall goal when we, again, tie this back into healthcare disparities and looking at some of the challenges with sickle cell disease in particular, we do want to make sure that we have an opportunity to develop a system of care that embodies and embraces gene therapy and transplant therapies for sickle cell disease, which means that we really will need a system of care to do that beyond pediatrics. This is another trial, hemoglobin 206. This is just looking at a particular group in that trial in some of these outcomes. So again, we have a number of clinical trials that are now open sport. Gene transplant, this particular trial is looking at the completion of vaso-occlusive episodes, greater than six months, post lentiglobin treatment. So this is the lentiglobin gene insertions. Again, there's some randomness in this gene- in the insertion of this gene. And so we are closely monitoring this one. The patients did report a decrease in patient-reported pain intensity, and most of these clinical trials, that first aim is usually centered around the reduction of pain, because that is what the patients complained of most and pain is now the target of the FDA for sickle cell disease, although we're looking at other endpoints, clinical endpoint is going to be hard to kind of get away from that pain endpoint. So we are seeing a reduction in pain for hemoglobin 206 with the lentiglobin treatment. We also see some of the hematological parameters decrease or improve, so the reticulocyte counts, lactate dehydrogenase, indirect bilirubin- I know we don't necessarily use these biomarkers to state that a patient is actively in VOC, but we do see that these are constantly elevated in these patients. So they're either hemolyzing a lot, but whatever the reason, we do kind of want to start getting a better handle on getting these patients into a better health state. The safety profile of the post lentiglobin treatment, one patient had a non-serious grade two related neutropenic fever, but that resolved.

No cases of veno-occlusive liver disease, graft failure. No cases there. No vector mediated ROL or insertional oncogenesis. There was one death attributed to cardiopulmonary disease and unlikely related to lentiglobin. , This was more than 18 months post-treatment in a patient with significant baseline SCD burden. So a lot of the negative outcomes that we do have and have experienced, you know, likely has to also do with the fact that we are selecting the most severe patients. So we do have to account for that when we're doing the clinical trials. So with the lentiglobin, the trial was on hold. It was initially reported MDS diagnosis. It was revised to transfusion dependent anemia in a patient treated. So here, the patient has persistent anemia for six months after transplant and was found to have trisomy 8 in 6% of the cell. The 6% of cells scored on six-month bone marrow aspirate, but no blasts or no dysplastic cells. The PI assessed it as serious grade three ongoing and possibly related to lentiglobin for SCD. So emails went out, the child got shut down, everybody kind of freaked out. A follow-up bone marrow aspirate revealed no genetic or chromosomal abnormalities, and no evidence of myeloid neoplasm and the diagnosis was changed to transfusion-dependent anemia with investigations ongoing. So continue to watch the peer review literature if we continue this trial and look for these outcomes. The patient in group A was diagnosed with AML. This patient was treated 5.5 years ago, and we know that there are some risks to all of these studies and we'll just continue to enroll, monitor the safety profile, present the data to the data safety monitoring board and to the FDA and really continued to expand this strategy for sickle cell disease.

So in summary, for the lentiglobin and that is now back up and running, but there was complete resolution of severe vaso-occlusive episodes up to 20 for a month of followup. So it's 24 months, you know, two years, a good timeframe for patients to be pain-free probably. So there was complete resolution of vaso-occlusive episodes after stabilization of the hemoglobin A expression. Again, that was up to 24 months. Improvement in patient reported pain intensity sustained over 24 months. Median total hemoglobin consistently greater than 11 grams. So patients, you know, constantly complained about low hemoglobin, feeling tired. So we have here an opportunity to

consistently have a hemoglobin greater than 11. Near pancellular expression of hemoglobin A greater than six months post lentiglobin with an average of 90% of the red blood cells containing hemoglobin A greater than 18 months post-treatment. The key markers of hemolysis approaching near normal levels, post lentiglobin treatment and the safety profile post lentiglobin for sickle cell disease remained generally consistent with the risk of autologous stem cell transplant, myeloablative single agents [inaudible] conditioning and underlying sickle cell disease. ARU1801, this is another trial that demonstrated meaningful clinical benefit for patients with severe sickle cell disease using reduced intensity conditioning. So ARU1801 is an investigational gene therapy to induce the expression of novel hemoglobin F. We love the hemoglobin F. No serious adverse events related to ARU180 or chemotherapy have been reported so far. Long-term engraftment for up to 36 months without the use of myeloablative chemotherapy, which is excellent.

Clinically meaningful long-term reductions in disease burden was observed with ARU1801, significant reduction of vaso-occlusive episodes, process improvements correlated with improved efficacy and patient three, so greater than 37% total hemoglobin F with higher hemoglobin up-to-date, near pancellular hemoglobin F distribution and no vaso-occlusive episodes through 12 months post-treatment. The momentum study is a phase one, two trial of ARU180 utilizing reduced intensity conditioning in patients with severe sickle cell disease. So kind of more of the same type of picture but gives you just a full, comprehensive view of the sponsors that are now available in this space, not only in the drug therapy sections but also for gene therapy. So there is a lot of interest at the highest level of our government in our research institutions, National Institutes of Health to really find a cure for sickle cell disease. We- here at the foundation- we are a local organization in Hollywood, Florida, started out- I started out at one of the local safety net hospitals here and created a sickle cell program that really flip the patients from inpatient to an outpatient setting for their pain management. But the biggest part of that is getting them engaged in the clinical research process and getting them into a system of care. And we are seeing a lot of changes where patients haven't been to the hospital in three years. They're able to

try these new therapies that the FDA has now approved. It takes a lot of patience on our end, but we are starting to see a lot of good outcomes. This last slide just shows some of the patients that we helped, our services and contact information. And so now we can move towards some questions.

Okay. Are you able to provide information on sickle cell sickling? Is it [inaudible] sports and those with sickle cell trait? Yes. We can provide that. We also do testing on our students who are carriers. Many of them come in with dark urine. So we do test it for myoglobin versus blood in the urine. And then we educate them about hydration and really pacing themselves in sports. But yes, we can have some information for you sent to you for that. You mentioned a low nationwide utilization of hydroxyurea. Should high hydroxyurea utilization a public health priority, and what does an effective medication adherence program look like? So, yes, there's very low uptake of hydroxyurea and many reasons why the NIH has had a huge push, a whole national initiative on hydroxyurea. We even try to encourage primary care physicians to take care of the adult patients because we just sorely lack the expertise of hematologists oncologists on the adult side. So hydroxyurea is the standard of care. And if the patients participate in a trial or if they even start any other newer medications, we encourage them to maintain their hydroxyurea and we just do encourage the use of it. It reduces hospitalization rates. It improves or eliminates acute chest syndrome, reduces the pain visits that patients just don't like it a whole lot. It darkens their skin. So the females complain about that. They know it is chemotherapy drugs. So many challenges. But what does an effective medication program look like? I think one where there's real partnership with the patient. It just takes time. It takes building a trust relationship with that patient. And they do become more responsive, I found, to any of the new therapies that we're trying to introduce. But it's not always the easy, they're reluctant and we just have to keep knocking on the door until they open it, but they do open it. What are the ages of the people in these trials? Ages two up to age 25 for the gene therapy trials. They don't like to have aging population for the gene therapy. So it's relatively for a pediatric population, but there are some adults. Jonathan Tisdale [?] out of the NIH and Courtney

Fitzhue [?] have a great adult sickle cell trial- transplant trial. And they've had some great outcomes.

What are the main obstacles to progressing gene therapy for sickle cell disease treatment? Well, the pediatric side of the house and the transplant doctors have to kind of get a little more aligned, I think, on the same page. I know that there's like some barriers with the pediatricians really talking a whole lot about gene therapy with the sickle cell patients. I've heard, you know, the risk-benefit, you know, if I take care of my child, she's to grow up and she can live well, why would I risk a transplant now? So I think as we continue to have more improved outcomes, less stringent type of conditioning or no conditioning at all, then I think we'll be more open to transplant in sickle cell versus not. Disease versus trait, have you seen those with trait experienced pain? Yes, we actually have, and that always kind of creates the conundrum because the ideas that people with trait can never have pain, but we do look at that hemoglobin evaluation carefully and some patients do have a very high percentage of S and are still considered carrier. So I think just a good medical history and a good overall assessment, just to make sure that we ruled everything out, but we have seen patients with trait who experienced pain.

Are there any costs involved? Is gene therapy covered by insurance? Well, we're involved with the [inaudible] with Emory university. We have one patient, he's on the standard of care. Since we're not a transplant center, our patients couldn't go for a transplant unless the donor search came back positive, and then he could go up to the university of Florida. But transplant- what Dr. Chris [?] at Emory was able to do with campaign to CMS and Medicaid, and was able to get approval for reimbursement for transplant by Medicaid. So they're very, very exciting. Let's see. How best could people with sickle cell disease cope with the COVID-19 Delta variant? Well, the ones that want to be vaccinated have been, so that's how they're coping with it. And the ones that are resistant like the rest of the people in the US just because they have sickle cell doesn't mean that they're not going to be resistant or think like everybody else. So they're as just resistant as those who are resistant. So we have various educational campaigns

and public gift cards and all kinds of things that we're trying to do to encourage vaccination awareness and uptake. Let's see. What would you consider the modern standard therapy for adult sickle cell patients at this time? Well, absolutely looking at these new FDA approved therapies, what we do hear at our center, one is that we get the biomarker assessment on all of our patients. So we have VCAM p-selectin data. We can see- and also red blood cell rheology data. The red blood cell rheology allows us to assess at three minutes and then at 10 minutes, how functional the red blood cell is.

So in other words [inaudible] And so if we see a high life rate, then that patient may be a candidate for voxelotor. If we see a lot of critical values in VCAM and p-selectin, the inflammatory biomarkers in those patients will more likely respond to Adakveo or crizanlizumab. So for the adult, we are recommending these treatments, these new therapies in addition to hydroxyurea. So if they have been on hydroxyurea, we maintain them on hydroxyurea and then add on these other medications. Hydration, always and vitamin therapy. Many of the patients are deficient in vitamins. So we are now looking at some nutritional, what can we do in terms of enhancing the nutrition of these patients and Endari is actually one of those medications that can enhance their nutrition as well. What is the success rate with gene therapy? Yes, we're looking at 75% and 93% success rate. So disease-free rate or the individual looks like a sickle cell carrier status versus sickle cell disease. What is the perception and interest in gene therapy from the sickle cell community? Very high, very hopeful and confusing because when they start- when the patients and family start asking questions, they're sort of turned away because they don't have severe disease. We just need to start getting a lot of education out there, but the families are very interested. Even if they're hesitant at first, they want to know a lot about it. It's incumbent on us to really start to provide this information. Is it difficult to find donors? Yes, it is difficult to find donors, which is why some of the conditioning will be helpful if we don't have less stringent- don't have a stringent conditioning. Do carriers undergo any treatment at all since they are susceptible to pain as well? We have not treated anyone, who's a carrier with how we treat someone with hemoglobin SS or beta thal zero or any of the sickle cell variant. We

do a complete assessment, but we have not treated anyone with trait the way we treat anyone with sickle cell disease.

Sarah Chart:I'm just going to jump in here. I know you're getting a lot of questions. Great presentation. I think there's time for one final question.

Dr. Lanetta Bronté-Hall: Okay. Do you feel- this is a trait- are there any costs involved with participating in the clinical trials and other trials being conducted in most states? So there's no cost for patients to participate. Actually, there's a lot of support for the patients. So there may be a stipend for travel or so there's usually, you know, something there to assist the patients. And in terms of every state, probably not, because the investigator has to be interested. So you'll likely see these at major pediatric centers. But you know, as it becomes more open and widespread, then yes. Hopefully, we can look like the cancer centers where, you know, protocol comes out and not only are the academic physicians participating, but the community oncologists participate as well. So we hope the future for that for sickle cell disease [inaudible]. I was going to say that there are, what, 78 or so slides, so please feel free to meander through those. And if you have any questions afterwards, you can email me.