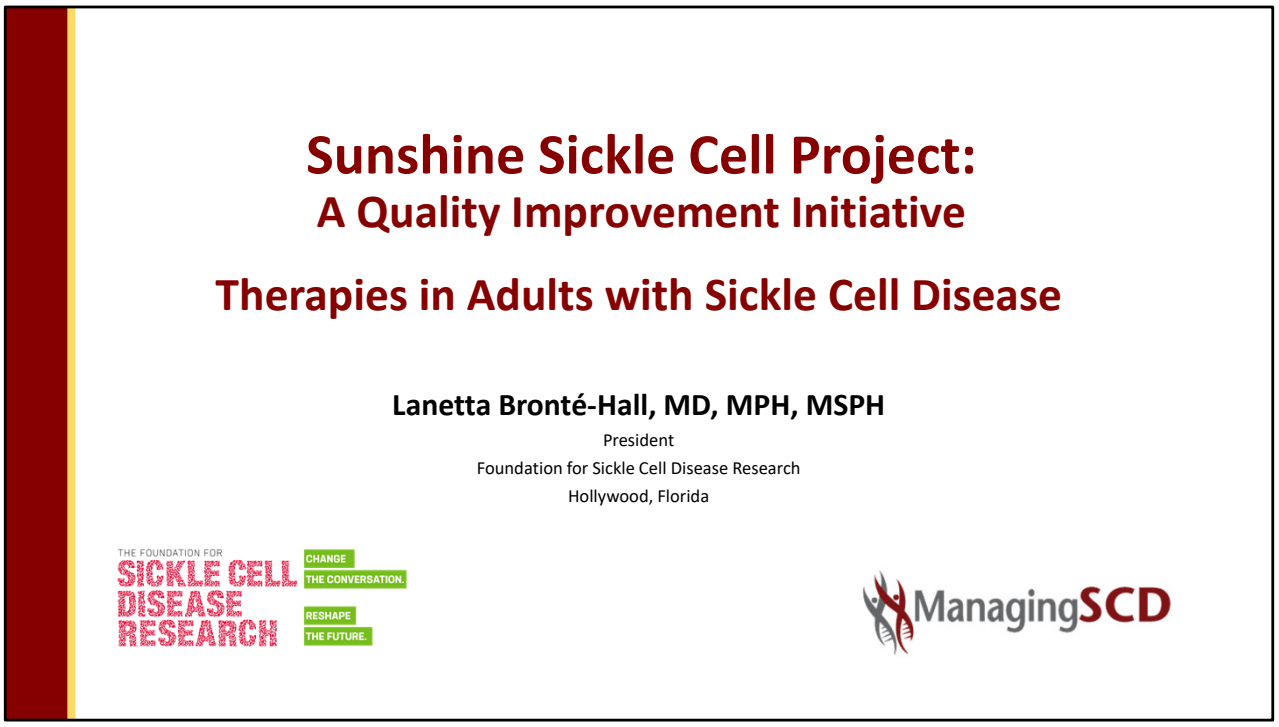
Sunshine Sickle Cell Project: A Quality Improvement Initiative

Therapies in Adults with Sickle Cell Disease



Good afternoon, everyone. I'm Dr. Lanetta Bronté-Hall, the President of the Foundation for Sickle Cell Disease Research. Welcome to The Sunshine Sickle Cell Project, a quality improvement initiative for therapies in adults with sickle cell disease. I have served in several national leadership positions for sickle cell disease, including the Chief Medical Officer of the Sickle Cell Disease Association of America, Senior Medical Advisor to the CDC, and also served on the National Heart, Lung, and Blood Institute Advisory Panel for the 2014 Expert Management Guidelines for Sickle Cell Disease. Thank you so much for attending, and we certainly look forward to, hopefully, your involvement in our quality improvement program.

Case Study: A 43 y/o Male with Sickle Cell Disease

- This is a 43-year-old male, weight 65 kg, Genotype HbS Bthal. Lab values: hemoglobin ranges 6 to 7 g/dL
- Patient has increased frequency of multiple organ failure and severe end-organ compromise
  - The first episode of multiple organ failure was 5/5/2015 with Hb decline to 4 g/dL along with neurocognitive decline and unresponsiveness 2-3 days during hospitalization
  - 11/23/2015 multiple organ failure with Hb decline to 4 g/dL
  - 1/4/2016 sickle cell crisis with Hb 4.9 g/dL. Patient has pulmonary artery hypertension, hypertension and chronic kidney disease
- Oxygen saturation:
  - Oxygen sat 85% on R.A. and
  - 92%-99% of 2L
  - Health status: chronically on oxygen supplementation
- Transfusion: multiple transfusions for acute decline associated with vaso-occlusive crisis, transfusional iron overload, relative intolerance to iron chelators due to chronic kidney disease

We'll start with a case study. This is a 43-year-old male with sickle cell disease, 65 kilograms. His genotype is hemoglobin S/beta-thalassemia. His lab values are hemoglobin in the range of six to seven. He has increased frequency of multiple organ failure and severe end-organ compromise. His first episode of multiple organ failure was in 2015, his hemoglobin dropped to four grams. He also had neurocognitive decline. He was unresponsiveness for two to three days. Ended up in the ICU and ventilated.

He also had another episode a few months later in 2015, multiple organ failure. This time his hemoglobin dropped to four grams. In 2016, he had another episode, hemoglobin dropped to 4.9, and also was diagnosed with pulmonary artery hypertension as well as chronic kidney disease. Oxygen saturation at 85% on room air, and then 92% to 99% on two liters. He was chronically on oxygen supplementation. His transfusion history for vaso-occlusive crisis was essentially non-existence because he was intolerant to the iron chelators due to chronic kidney disease.

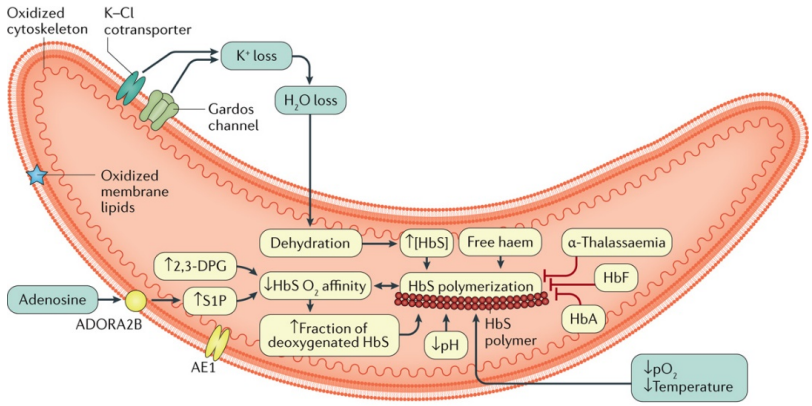
How Would You Treat This Patient?

- What would you do to optimize his sickle cell care?
- What would you choose as treatment options?

Let's discuss.

How would you treat this patient? What would you do to optimize his sickle cell care? What would you choose as his treatment options? We'll discuss that as we move through the presentation.

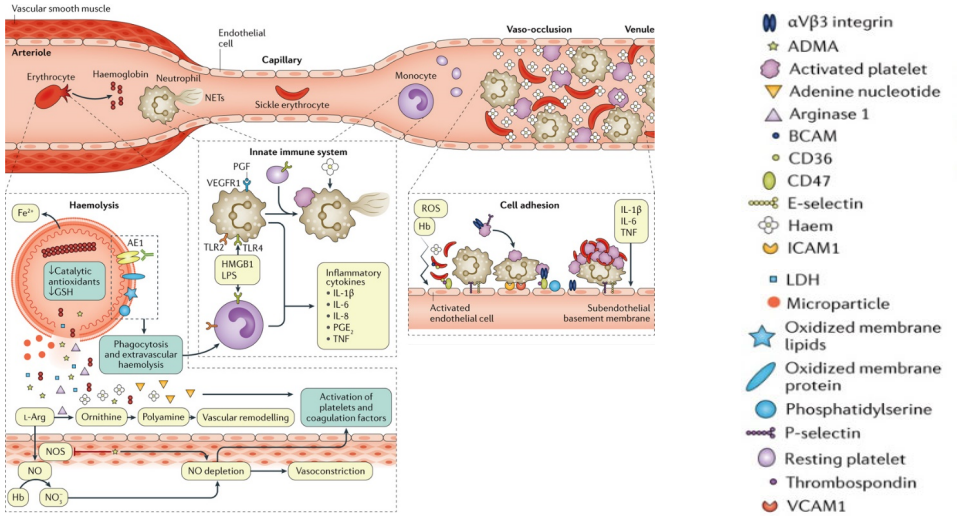
HbS Polymerization and Erythrocyte Deformation



Kato G, et al. *Nat Rev Dis Primers*. 2018;4:18010.

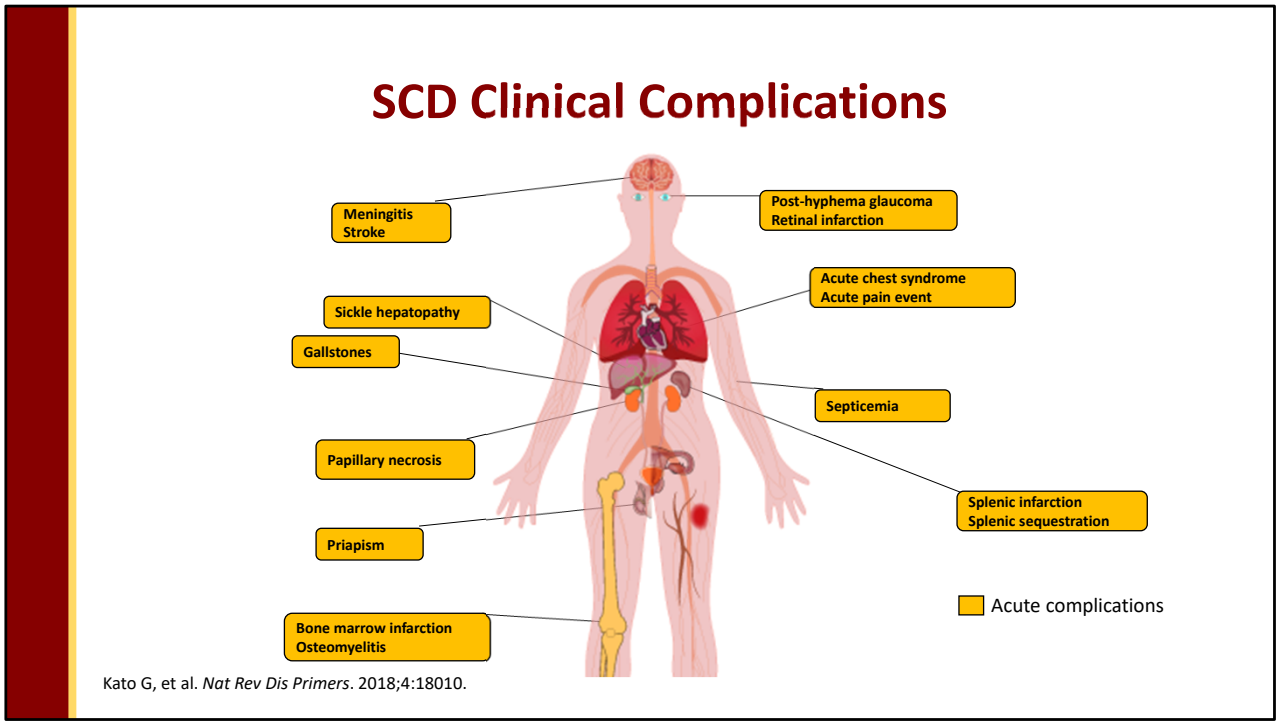
Hemoglobin S polymerization and erythrocyte deformation are the hallmarks of sickle cell disease. What we now know is there are a lot of transport mechanisms, co-transporters, various channels that we can now target to improve the red cell rheology, and therefore improve the oxygen delivery.

Mechanisms in Sickle Cell Disease

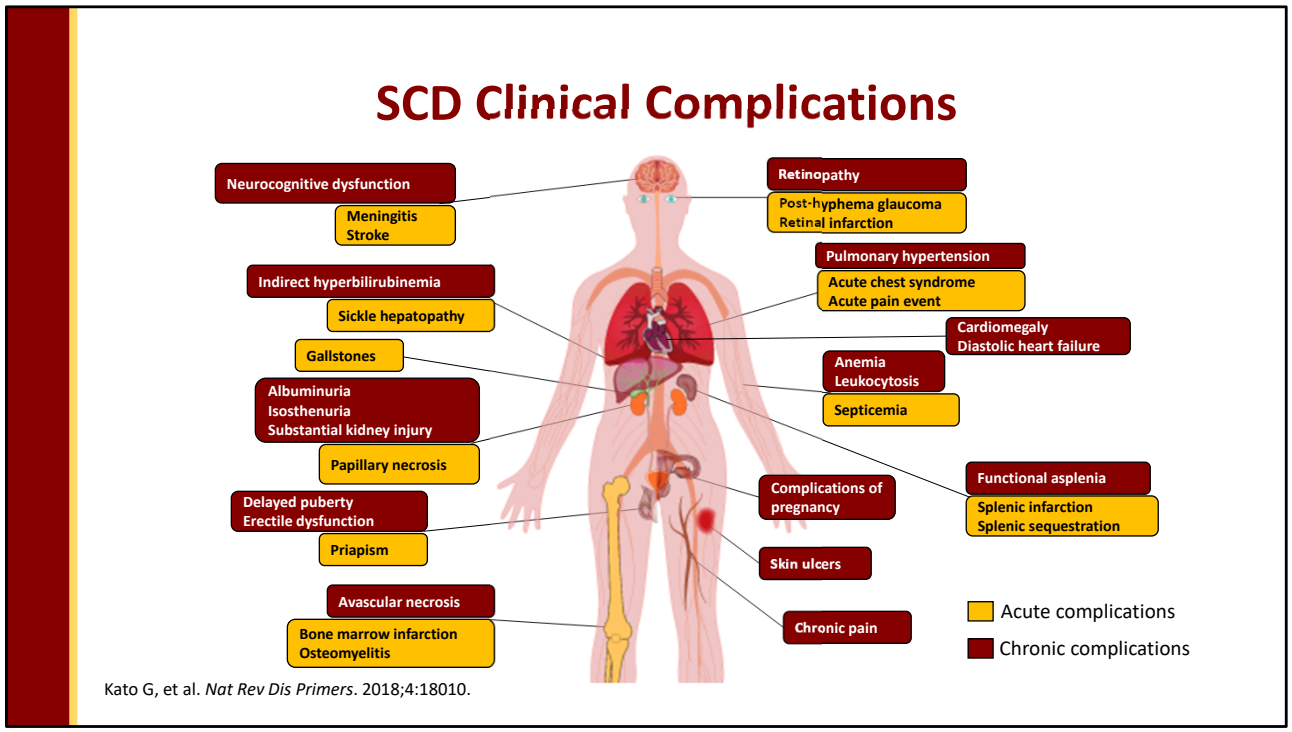


Kato G, et al. *Nat Rev Dis Primers*. 2018;4:18010.

The several mechanisms can interact with the endothelium in terms of looking at some of the biomarkers that we are now assessing for sickle cell disease, such as P-selectin, VCAM, and also looking at the red cell rheology in terms of how functional is the red blood cell. We have some data to share with you as well. What we're now able to do is actually target some of these biomarkers, create more of an anti-inflammatory environment, which leads to a reduction in pain crises for these patients.



And also can lead to a reduction in acute complications such as we see in this population: meningitis, sickle hepatopathy, gallstones, papillary necrosis, priapism, septicemia. We don't see as much septicemia as we did in the pediatric years. Now you see more of acute chest syndrome as it relates to pain crises. The septicemia, because of penicillin prophylaxis, we've done well with that.



Then there are also chronic complications: the neurocognitive dysfunction, hyperbilirubinemia. There are so many issues: retinopathy, pulmonary hypertension, pregnancy complications. The females need to be referred to high-risk OB oftentimes. They could be in the first trimester and are very slow to even go for care, or prenatal care can sometimes also be a challenge. Lots of complications, both acute and chronic.

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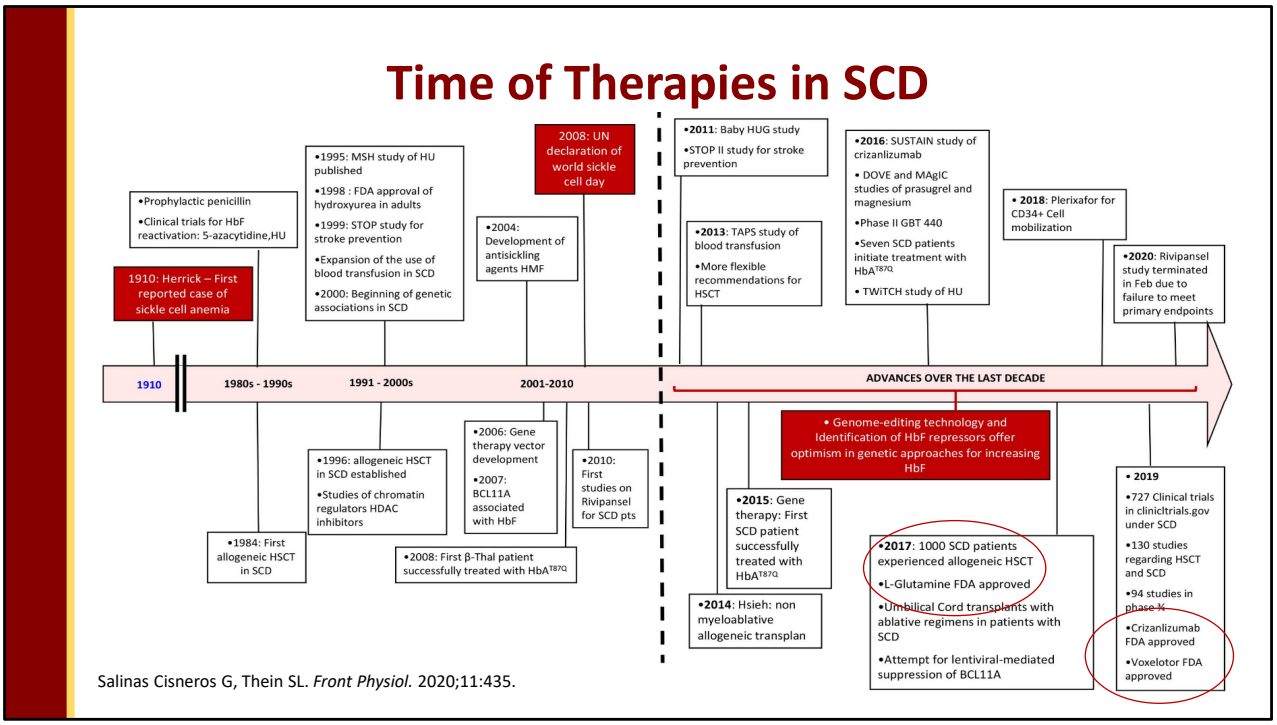
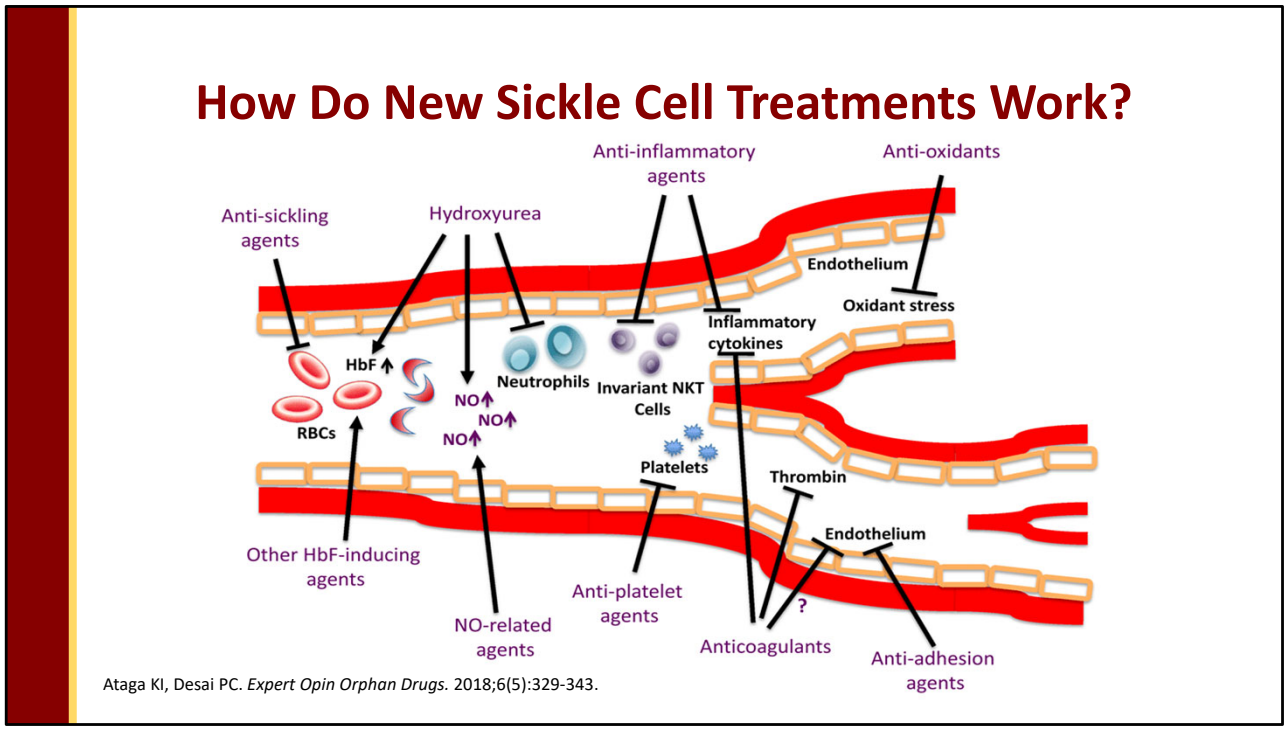


Salinas Cisneros G, Thein SL. *Front Physiol.* 2020;11:435.

What do we now have in terms of addressing these complications? We do have some new therapies that are now in the market. Didn't have a lot, obviously, between 1910 and 2010. What we did have during this time period, particularly around in 1995, was hydroxyurea. We encourage the use of hydroxyurea. It is considered standard of care. We know that only about 40% of individuals with sickle cell disease are on hydroxyurea. We then advance to 2011 and beyond, and we are just so excited that we now have three new medications in our toolkit for sickle cell disease. You can see the timeline of the advancements.



How do the new sickle cell treatments work? There are anti-sickling agents, there's hydroxyurea, which we are familiar with. There are anti-inflammatory agents, antioxidants, anticoagulants, anti-adhesives. Again, we are now developing biomarkers to actually see pre- and post-medication, to see how the biomarkers respond and ultimately how the patient responds in terms of voicing their pain.

Sickle Cell FDA-approved Drugs (4)

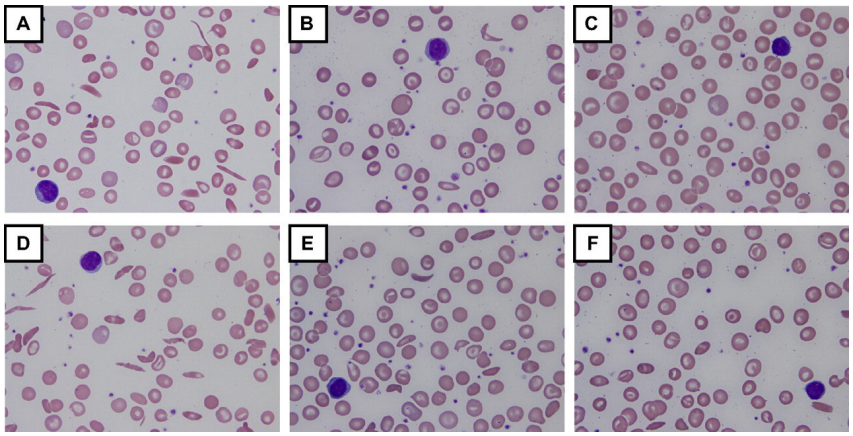
Agent	Mode of Action	FDA Approved	Indicated Pediatric Age
Hydroxyurea[1]	Increases fetal hemoglobin Anti-inflammatory Anti-adhesion	Adults: 1998 Children: 12/2017	18 y/o and older 2 years and older
L-glutamine[2]	Anti-oxidant	2017	5 years and older
Crizanlizumab[3]	Anti-adhesion	Children and adults: 11/2019	16 years and older
Voxelotor[4]	Increases hemoglobin Red blood cell allosteric modifier (increases O_2 to sickle cells)	Children and adults: 11/2019	12 years and older

1. US Food and Drug Administration. FDA approves hydroxyurea for treatment of pediatric patients with sickle cell anemia [press release]. December 21, 2017.; 2. US Food and Drug Administration. FDA approved L-glutamine powder for the treatment of sickle cell disease [press release]. July 2, 2017.; 3. US Food and Drug Administration. FDA approves crizanlizumab-tcma for sickle cell disease. [press release]. November 19, 2019.; 4. US Food and Drug Administration. FDA approves novel treatment to target abnormality in sickle cell disease [press release]. November 25, 2019.

The sickle cell FDA-approved drugs: hydroxyurea, L-glutamine, which is an antioxidant, crizanlizumab, which is an anti-adhesion, and then voxelotor, which increases the hemoglobin red blood cell allosteric modifier. You can see the indicated ages. Hydroxyurea, 18 and older. We also now have a formulation for children 2 years and older. L-glutamine, 5 years and older. Crizanlizumab, 16 years and older. Voxelotor, 12 years and older. We can tap into that young child market as well as the adolescents to get them early on these medications. Hopefully, we can delay or prevent the end-organ damage.

Hydroxyurea

- Acute and chronic transfusions
- Modulates endothelial activation and reduces neutrophil counts, contributing to the reduction of chronic inflammation
- Hydroxyurea[1]
  - ↓ frequency of painful episodes, acute chest syndrome, blood transfusions and hospitalization
  - May ↑ survival in patients with severe disease[2-4]



Hydroxyurea increases HbF which reduces hemoglobin S polymerization and clinical complications

HbF= fetal hemoglobin

1. Ware R, et al. *Blood*. 2012;119(17):3925-3932.; 2. Charache S, et al. *N Engl J Med.* 1995;332(20):1317-1322.; 3. Steinberg M, et al. *JAMA*. 2003;289(13):1645-1651.; 4. Steinberg M, et al. *Am J Hematol.* 2010;85(6):403-408.; 5. Voskaridou E, et al. *Blood*. 2010;115(12):2354-2363.

Hydroxyurea, in slide A, you see sickle cells in the peripheral blood smear, and as you move to slide C, you can see that those cells have been transformed to more normal-looking red blood cells. Hydroxyurea decreases the frequency of painful episodes, acute chest syndrome, blood transfusions and hospitalizations, and we do believe that it may increase survival in patients with severe disease.

Case Study: 39 y/o Male with Pulmonary Artery Hypertension and Renal Decline

- This is a 39-year-old male with Genotype: Hb SS.
  - His baseline hemoglobin is 6.5 g/dL
- Oxygen saturation:
  - Averaging 83%-86% at RA resulting in oxygen dependence
  - Patient's health status is also significant for oxygen supplementation dependence since March 7, 2017 at 4L via nasal cannula
- Patient has had deteriorating health since October 2016 marked by 18 vaso-occlusive crises in a year requiring intravenous opioids
- Hospitalizations are noted for significant acute drops in hemoglobin values to 5 g/dL requiring blood transfusions
- Prior to the acute deterioration in health, he worked full-time and served as senior pastor of his church. His quality of life (QOL) is poor, and he needed to apply for disability (SSI)

Another case study, this is a 39-year-old male with pulmonary artery hypertension and renal decline. His genotype is hemoglobin SS with a baseline hemoglobin of 6.5 grams. Oxygen saturation averages between 83% and 86% at room air. He's also oxygen-dependent. His health status is significant for oxygen supplementation since March 2017, and he's maintained at four liters. He's had deteriorating health since 2016, marked by 18 vaso-occlusive crises in a year requiring intravenous opioids.

Hospitalizations are noted for significant acute drops in hemoglobin. Almost a similar picture as before. Prior to the acute deterioration in his health, he worked full-time as a senior pastor at his church. Quality of life was very poor, and he also needed to apply for disability.

How Would You Treat This Patient?

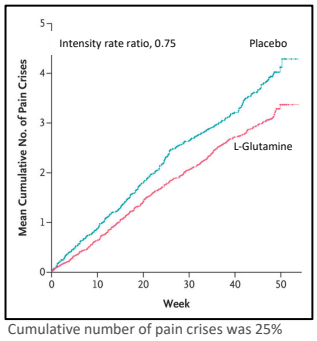
- What would you do to optimize his sickle cell care?
- What are his treatment options?
  - Crizanlizumab → Decrease pain crises?
  - L-glutamine → Decrease pain crises?
  - Voxelotor → Increase his Hgb?

Let's discuss.

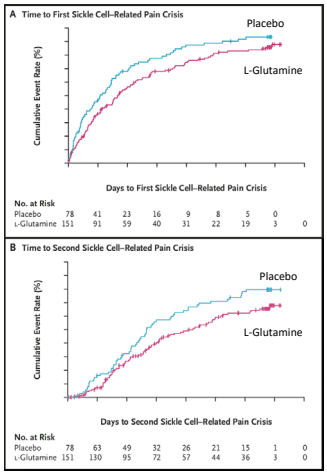
How would you treat this patient? What would you do to optimize his sickle cell care? What are his treatment options? Crizanlizumab maybe to decrease the pain crisis, L-glutamine, which also will decrease the pain crisis, or voxelotor to increase his hemoglobin.

L-glutamine – Phase 3 Clinical Trial Report

- Patients who were treated with L-glutamine experienced:
  - Fewer hospital visits for pain on average, compared to patients who received a placebo (median 3 vs median 4)
  - Fewer hospitalizations for sickle cell pain (median 2 vs median 3)
  - Fewer days in the hospital (median 6.5 days vs median 11 days)



Cumulative number of pain crises was 25% lower in the L-glutamine group than in the placebo group over the entire 48-week treatment period



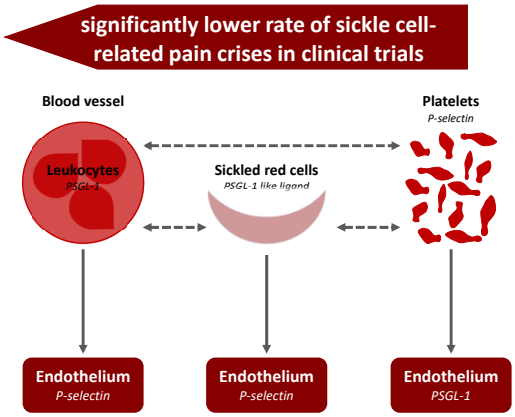
The median cumulative number of days in the hospital were 6.5 (range, 0 to 94) in the L-glutamine group and 11 (range, 0 to 187) in the placebo group (*P*=0.02).

https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm566097.htm.; Niihara Y, et al. *N Engl J Med.* 2018;379:226-235.

L-glutamine. In the phase 3 clinical trial report, patients who were treated with L-glutamine experienced fewer hospital visits for pain on average compared to patients who received a placebo. Also, there were reported fewer hospitalizations for sickle cell pain, as well as fewer days in the hospital when a patient was admitted.

Crizanlizumab P-Selectin

- Sickle cell-related pain crises (SCPCs) are a substantial cause of morbidity in patients with sickle cell disease (SCD)[1]
- P-selectin plays a role in the pathogenesis of vaso-occlusion in SCD, which leads to SCPCs[2,3]
- Crizanlizumab is a humanized IgG2 antibody that inhibits P-selectin[4]



Ig = immunoglobulin; PSGL-1 = P-selectin glycoprotein ligand

Kutlar A, Embury, SH. *Hematol Oncol Cl North Am* 2014; 28(2): 323-339.
1. Ballas SK, Lusardi M. *Am J Hematol.* 2005;79:17-25.; 2. Wagner DD, Frenette PS. *Blood.* 2008;111:5271-5281.; 3. Matsui NM, et al. *Blood.* 2001;98:1955-1962.; 4. Ataga KI, et al. *N Engl J Med.* 2017;376:429-439.

Crizanlizumab, which is a P-selectin, this is that anti-adhesion, anti-stickiness, this resulted in a substantial decrease in pain-related crises. We know that P-selectin plays a role in the pathogenesis of vaso-occlusion in sickle cell disease, which leads to the sickle cell pain-related crises. Crizanlizumab is a humanized IgG2 antibody that inhibits the P-selectin. I'll share some data with you on how we monitor the P-selectin values in our patient population.

SUSTAIN Trial

- The primary endpoint
  - Annual pain rate calculated over the 12 months of participation
  - End point was met with crizanlizumab 5.0 mg/kg
- The annual rate of SCPC in the crizanlizumab 5.0 mg/kg group was reduced by 45% vs placebo (median 1.6 vs 3.0; *P*=0.01)
  - The annual rate of SCPC with crizanlizumab 2.5 mg/kg was reduced by 33% vs placebo (median 2.0 vs 3.0; *P*=0.18), indicating dose-dependent efficacy

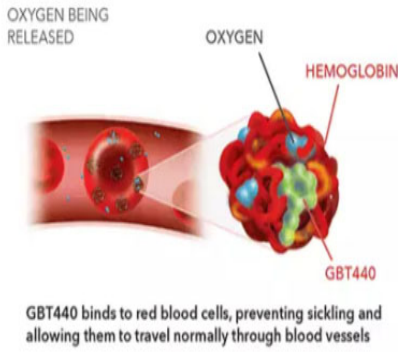
Event	Crizanlizumab 5.0 mg/kg (n=67)	Placebo (n=65)	Change	*P* value
Median annual rate of pain crises	1.6	3.0	–45%	0.01
Median time to first pain crisis (months)	4.1	1.4	-	0.001
Median time to second pain crisis (months)	10.3	5.1	-	0.02
Median annual rate of uncomplicated pain crises	1.1	2.9	–63%	0.02
Median annual rate of ACS	0.0	0.0	-	0.78
Median annual rate of days hospitalized	4.0	6.9	–42%	0.45

Ataga KI, et al. ASH 2016. Abstract 92707.; Ataga KI, et al. *N Engl J Med.* 2017;376:429-439.

The SUSTAIN trial, the primary endpoint was calculating the annual pain rate over 12 months of the subject's participation. The endpoint was met with crizanlizumab at 5.0 mg/kg. The annual rate of the sickle cell acute pain crises was reduced by 45% versus placebo. Extremely significant, the *P*-value was 0.01. The annual rate of the sickle cell painful crises with crizanlizumab, even at 2.5 mg/kg, it was reduced by 33% versus placebo, indicating that there is a dose-dependent efficacy.

Voxelotor

Mechanism of Action and Potential for Disease Modification



- Voxelotor binds to the a-globin chain of Hb resulting in an allosteric modification of Hb which increases Hb-O_2 affinity; leftward shift in Oxy-Hb dissociation curve
- Decreases polymerization tendency of deoxy-HbS
- Improves sickle red cell survival increases in Hb and decrease reticulocyte count

Blyden G, et al. *Am J Hematol.* 2018 May 12. doi: 10.1002/ajh.25139.; Howard J, et al. *Blood.* 2019; 133(17): 1865-1875.; Hutchaleelaha A, et al. *Br J Clin Pharmacol.* 2019; 85(6): 1290-1302

Voxelotor really hits the root cause of sickle cell disease, which is the polymerization. It binds to the alpha-globin chain of hemoglobin, resulting in an allosteric modification of hemoglobin, which increases the oxygen affinity. There's a leftward shift in the dissociation curve. It decreases polymerization and the tendency of the oxyhemoglobin S. Then improves the sickle cell red cell survival, thereby indirectly increasing hemoglobin and decreasing the reticulocyte counts. You really see this onset of action in about two weeks. It's pretty amazing. Patients also report marked increase in energy because their hemoglobin actually bumps up to at least a gram or two grams in about two weeks of starting voxelotor.

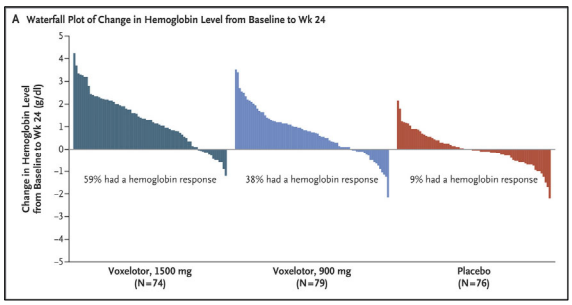
HOPE Study – Phase 3 Trial of Voxelotor in SCD

- 274 participants were randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of 1500 mg, 900 mg of voxelotor, or placebo
- 90% had severe genotype homozygous hemoglobin S or hemoglobin SB0 – thalassemia
- Approximately two-thirds (65%) were receiving hydroxyurea at baseline
- Voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis

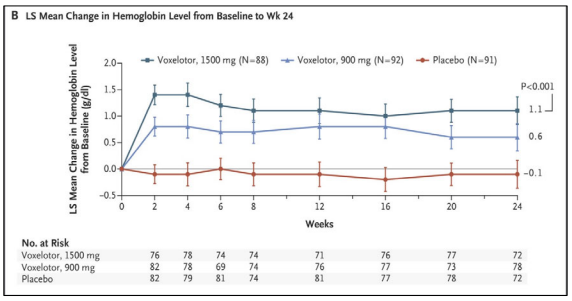
Vichinsky E, et al. *N Engl J Med*. 2019; 381(6):509-519.

The HOPE Study, which is the phase 3 trial of voxelotor, enrolled 274 participants. They were randomly assigned in a 1:1:1 ratio to receive a once-daily dose of 1,500 mg, or 900 mg, or placebo. 90% has a severe genotype, which is homozygous hemoglobin S, or hemoglobin beta-thalassemia zero. Approximately two-thirds, or 65%, were receiving hydroxyurea at baseline. Voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis in the patients on the medication.

Voxelotor Improves Hemoglobin in Majority of Patients – HOPE Study Results From Baseline to Week 24



59% of those on 1500 mg demonstrated a hemoglobin response compared to only 9% in placebo group[1]



1500 mg dose group had mean change of 1.1 in hemoglobin from baseline compared to 0.1 in placebo group[1]

72- week data from phase 3 HOPE Study showed significant and sustained improvement in hemoglobin levels, reduction in hemolysis and improved hemolysis in SCD, potentially mitigating life-threatening complications of the condition[2]

1. Vichinsky E, et al. *N Engl J Med*. 2019;381:509-519. 2. Ware RE, et al. Sickle cell disease. *Lancet*. 2017; 390: 311-323

This occurred from baseline to week 24, which is the timeframe of following the patients. We saw that 59% of those on 1,500 mg demonstrate the hemoglobin response, compared to only 9% in the placebo group. Then the 1,500-mg dose group had a mean change of 1.1 in hemoglobin from baseline, compared to 0.1 in the placebo group.

The 72-week data from the phase 3 HOPE Study shows significant and sustained improvement. That's a very important point, that we're actually seeing sustained improvement in hemoglobin levels, reduction in hemolysis, and improved hemolysis in sickle cell disease. We think that this will potentially mitigate life-threatening complications of the decision. Still early on, the drug was just approved a couple of years ago, but we are starting to venture into post-marketing studies and long-term studies of all of these medications. We are actually participating in one of those post-marketing studies.

Voxelotor

- Hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older[1]
- Given once-daily (1500 mg) as 500 mg tablets[1]
- Voxelotor is designed to work by ***helping hemoglobin,*** the molecules inside red blood cells, ***hold onto more oxygen as the red blood cells*** travel through the body[2]
- This keeps red blood cells in their normal shape and helps stop sickling[2]

REMINDER

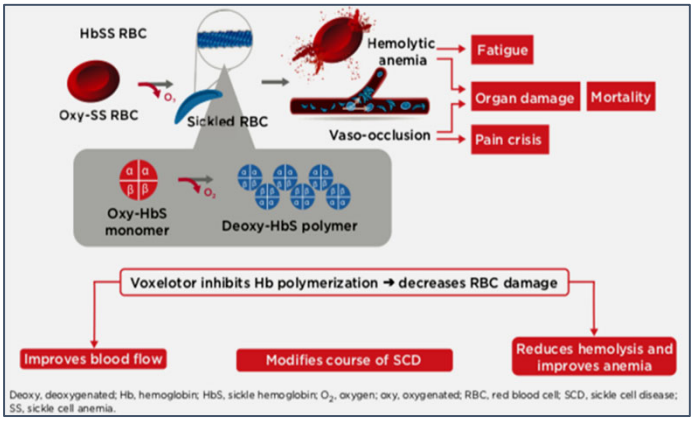
Reduce dose to 1000 mg daily in severe liver disease or if the patient is taking strong CYP3A4 inhibitors; increase dose to 2500 mg QD with CYP3A4 inducers

QD=daily
1. Oxbryta® (voxelotor) [package insert]. Global Blood Therapeutics, Inc: South San Francisco, CA. 2019. 2. Vichinsky E, et al. *N Engl J Med.* 2019;381(6):509-519.

Voxelotor, just to reiterate, is a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients, 12 years and older. It's given once daily, 1,500 mg, it's 500-mg tablets. Now you may need to reduce the dose to 1,000 mg in severe liver disease or if the patient is taking strong CYP3A4 inhibitors. We always reach out to our clinical pharmacists to give us some guidelines there. In those situations, you can increase the dose to 2,500 mg QD if they do have CYP3A4 inducers. Voxelotor is designed to work by helping hemoglobin, the molecules inside the red blood cells hold on to more oxygen as the red cells travel through the body. This keeps red blood cells in their normal shape and helps stop sickling, and also tremendously improves oxygen delivery.

Voxelotor Ongoing Trials

Phase III HOPE Study; Phase IIa HOPE Kids 1 Study



https://clinicaltrials.gov/ct2/show/NCT03036813.; https://clinicaltrials.gov/ct2/show/NCT02850406.; https://www.gbt.com/pipeline/sickle-cell-disease

The voxelotor ongoing trials, there's the phase 3 HOPE Study and the phase 2a HOPE-KIDS 1 Study.

What Will Define a Cure

- Biologic definition
  - Requires sufficient "new" hemoglobin to prevent sickling
  - Resolution of hemolysis
  - Requires equivalent (or better) rheology with sickle cell trait
  - Including endothelial adherence
  - Including inflammatory stimulus
- Functional definition
  - Pain episodes
  - Fatigue
  - Other patient-reported outcomes
- Organ-based definition
  - Minimally-we would hope this would mean stabilization of organ dysfunction
  - What amount of worsening organ function is acceptable?

Slide Credit: Dr. Julie Kanter. UAB

There's always a discussion about the cure. When there's a report, or a news story about a transplant and a cure, then we start to get a lot of telephone calls from patients and families. How do we actually define a cure? What will define a cure? We have these three categories that have a framework for a cure for sickle cell disease. There's a biologic definition, a functional definition, and an organ-based definition.

The biologic definition requires sufficient new hemoglobin to prevent sickling. There has to be a resolution of hemolysis. It requires equivalent or better rheology with sickle cell trait, including endothelial adherence, including inflammatory stimulus. Then there's the functional definition. The functional definition is where we live now when we think about sickle cell disease, the pain episodes, the fatigue, and other patient-reported outcomes.

Then there is the organ-based definition. Minimally, we would hope that this would mean stabilization of organ dysfunction. What amount of worsening organ function is acceptable? These are questions that we're now starting to address for sickle cell.

Bone Marrow Transplant

Types of transplants

- Matched related donor (sibling)
- Matched unrelated donor (MUD)
- Haploidentical transplant

Benefits → **Cure!**

Complications and challenges of bone marrow transplant (BMT)

- High potential for short- term risks
- Infection
- Infertility
- Graft vs host disease
- Posterior reversible encephalopathy syndrome (PRES)
- Graft failure
- Veno-occlusive disease
- Social/emotional

Bone marrow transplant certainly has risk involved with it, so we're always weighing those benefits to risk ratios. We consider the type of transplants when we think about benefit to risks of match related donor, match unrelated donor, haploidentical. Then what are those risks, complications of bone marrow transplant? They will vary depending on the type of transplants you receive. There is high potential for short-term risks, infection, infertility, graft-versus-host disease. These are topics that we are starting to engage and educate our families so that they're aware of what a bone marrow transplant could entail.

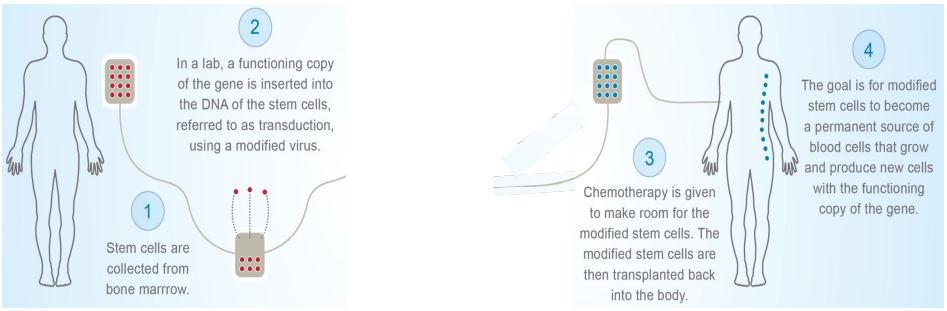
Gene Therapy Future Potential

- SCD is caused by a mutation in a single gene
  - If we can deliver a functional gene into the patient's cells, this could also reduce the symptoms of the disease
- Gene therapy of autologous cells
  - Circumvents the need for finding matched donors
  - Should have less immune mediated side-effects than allogenic HSCT

Hoban MD, et al. *Blood.* 2016;127:839-848.

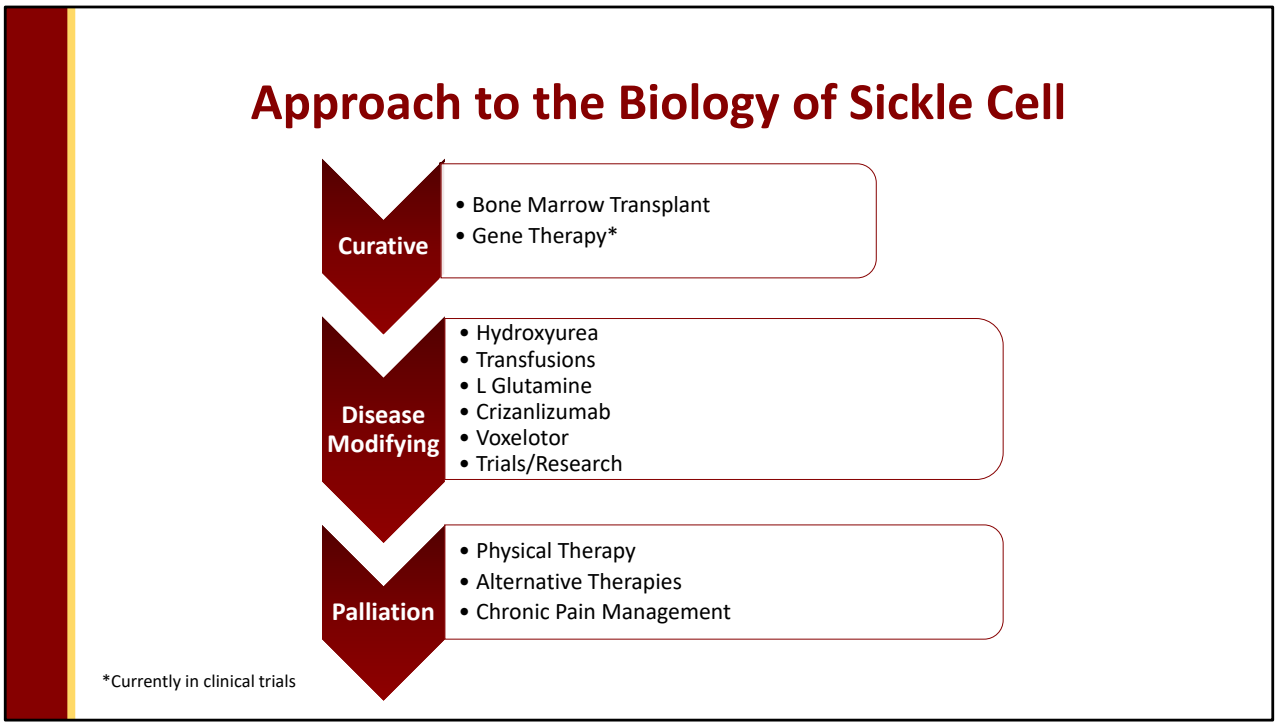
Gene therapy. Certainly, there's a lot of excitement about the future potential for gene therapy. Sickle cell disease is caused by a single-point mutation. You would think, what could be more simple than that? Can we just replace that somehow? If we can deliver a functional gene into the patient's cell, this could also reduce the symptoms of the disease. Gene therapy with autologous cells circumvents the need for finding matched donors and should have less immune-mediated side effects than allergenic stem cell transplant.

A Brief Overview of Gene Therapy for SCD

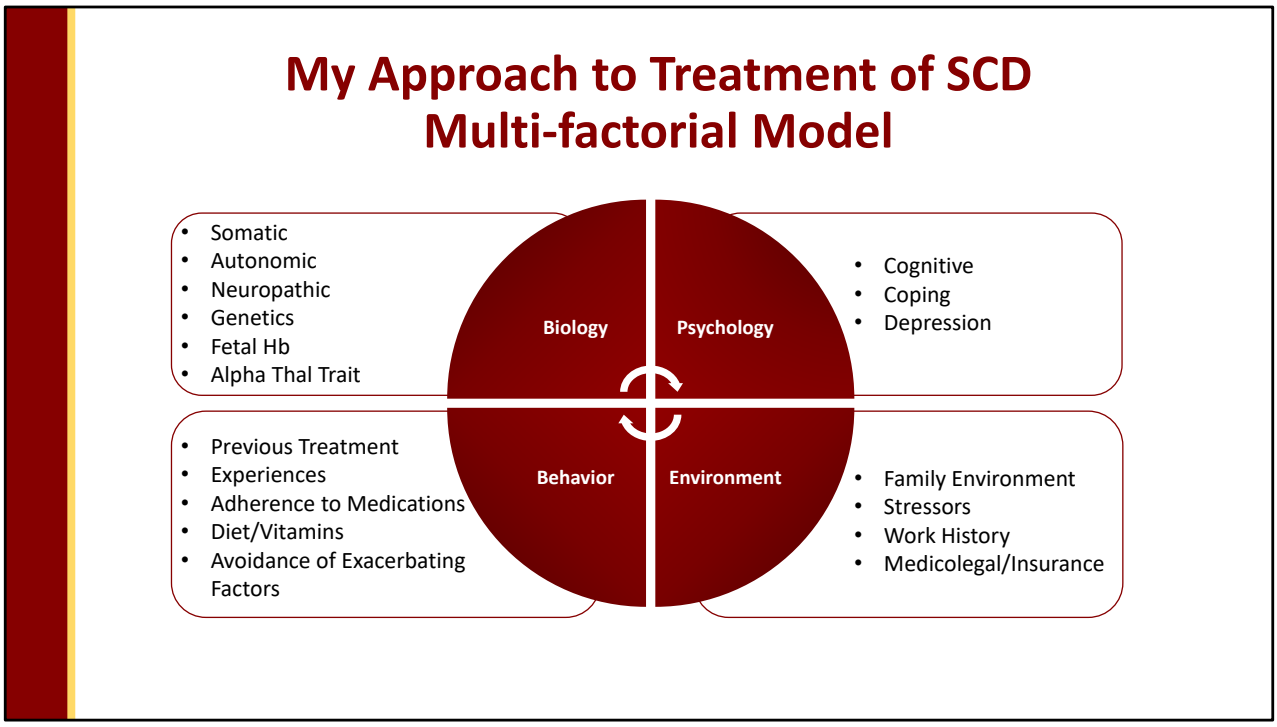


https://www.bluebirdbio.com/our-science/gene-therapy-techniques

A brief overview of gene therapy for sickle cell disease. The stem cells are collected from the bone marrow in a lab. A functioning copy of the gene is inserted into the DNA of stem cells, referred to as transduction, using a modified virus. There was some concern about the use of the HIV virus, but we explained that you're not going to get HIV, that part has been removed, but we certainly use it to help transduce.
Then chemotherapy is given to make room for the modified stem cells. The modified stem cells are then transplanted back into the body. The goal is for the modified stem cells to become a permanent source of blood cells that grow and produce new cells with the functioning copy of the gene.



The approach to the biology of sickle cell disease, either curative, disease-modifying, or palliation. Curative, bone marrow or gene therapy. Again, we have to look at the benefit-risk ratio. Disease-modifying, we have hydroxyurea, transfusions. Those two have been the mainstay for many years. Now we have L-glutamine, crizanlizumab, voxelotor, and clinical trials and research which are also very important and need to be a part of a patient's overall comprehensive care process. Then there's palliation, physical therapy, alternative therapies, and chronic pain management.



What has been my approach to the treatment of sickle cell disease? Well, it has always been a multifactorial approach. Looking at a model like this, incorporating the biology, the psychology, the behavior, the environment, may look nice in this schematic here, but when implemented can be a bit daunting if you don't have the resources. We are happy that we do have the resources to incorporate all of these aspects into comprehensively caring for this population, but to also assist you in your efforts to care for your patients. We'll be able to discuss that a little more as well.

The Future

"Transformation can only take place immediately; the revolution is now, not tomorrow."

Jiddu Krishnamurti

What is the future for sickle cell disease when we talk about transformation? Transformation can only take place immediately. The revolution is now, not tomorrow. Since the revolution is now, we want to transform the sickle cell care in the state of Florida.

Sunshine Sickle Cell Project: A Quality Improvement Initiative

Therapies in Adults with Sickle Cell Disease

The Sunshine Sickle Cell Project Quality Improvement Initiative

- **Goal**: Improve the quality of care for adult and pediatric patients with SCD in Florida
- **Participants**: Clinicians across Florida who participated in the educational interventions and provide care for patients with SCD
- **Lead investigator**: Dr. Lanetta Bronté-Hall

We want to do so through The Sunshine Sickle Cell Project Quality Improvement Initiative, where I will serve as your lead investigator. The goal is to improve the quality of care for adult and pediatric patients with sickle cell disease in Florida. We are inviting clinicians across Florida who participated in the educational interventions and provide care for patients with sickle cell disease to participate.

Why Should I Participate in a SCD QI Project?

- Disparities in care exist for patients with SCD and their families, which contributes to suboptimal outcomes
- Reimbursement for care has shifted from fee-for-service to value-based models in which payments are tied to the quality of services delivered, as opposed to the volume
- Quality improvement projects allow clinicians, working within a team, to identify an issue and implement interventions that can result in improvements in healthcare quality that result in improved outcomes for patients with SCD

What gaps in care have you identified in your practice setting?

Why should I participate in the SCD QI project? Well, we know that disparities in cure exist for patients with sickle cell disease and their families, which contributes to sub-optimal outcomes. Reimbursement for care has shifted from fee-for-service to value-based models, in which payments are tied to quality of services delivered as opposed to volume. Quality improvement projects allow clinicians working with a team to identify an issue and implement interventions that can result in improvements in healthcare quality, that result in improved outcomes for patients with sickle cell disease. What gaps in care have you identified in your practice setting?

Examples of Successful QI Projects in SCD

- Balsamo L, Shabanova V, Carbonella J, et al. Improving Care for Sickle Cell Pain Crisis Using a Multidisciplinary Approach. *Pediatrics.* 2019;143(5):e20182218; DOI: https://doi.org/10.1542/peds.2018-2218
- Adams-Graves P, Ostric E, Martin M, et al. Sickle cell hospital unit: a disease-specific model. *J Healthc Manag.* 2008;53(5):305-315; discussion 316-317.
- Kanter J, Jordan LB. Improving the healthcare model for management of adults with sickle cell disease in the PPACA era. *J Hematol Transfus.* 2015;3(1):1037.
- Third Annual Sickle Cell Disease Research and Educational Symposium and Grant Writing Institute and Annual National Sickle Cell Disease Scientific Meeting. Jordan L, Bruce B. Joint Commission Sickle Cell Disease Specific Care-Accountability that Works. 2009. Abstract# 403.
- **Hospital-A Solution That Works, Memorial Sickle Cell Day Hospital at Memorial Regional. 2011.**
- LaVista JM, Treise DM, Dunbar LN, et al. Development and evaluation of a patient empowerment video to promote hydroxyurea adoption in sickle cell disease. *J Natl Med Assoc.* 2009;101(3):251-257. doi: 10.1016/s0027-9684(15)30853-1.
- Florida Health Care Transition Services Task Force for Youth and Young Adults with Disabilities. Report and Recommendations Implementation of Senate Bill 988. Ensuring successful transition from pediatric to adult health care. http://www.floir.com/siteDocuments/2009_fl_hct_task_force_report-cms.pdf

Some examples of successful QI projects in sickle cell disease. I'll just jump down to the one that's highlighted in red. That's the Memorial Sickle Cell Day Hospital. I wrote an article and published it. They had a journal back then. They don't have that journal anymore. The title was *A Solution That Works*, and this was in 2011. The solution actually worked to the point that we were Joint Commission certified for sickle cell disease, the first and only in the nation. We developed indicators that lead to a reduction in the thousand unique patients that we had in the healthcare system, who were being admitted 90% of the time. We flipped that to 80%/20%. Only 80% of the patients were being admitted. They were now going to an outpatient setting for their acute pain treatment. In addition, their follow-up appointments and their adherence to medication and the physician recommendations also increased tremendously.

The Foundation For Sickle Cell Disease Research: What We Look at and How We Measure

Qualitative measures
- Routine health care maintenance
- Care planning for SCD patients
- Acute care
- Assessment, treatment, and management of acute pain crises
- Patient satisfaction with care
- Patient-reported outcomes measurement; PROMS

Quantitative measures
- Health care use
- ED visits
- Hospital readmission rates
- ICU admission rates

The Foundation for Sickle Cell Disease Research, this is what we look for and what we measure. When the Foundation comes out to work with you, we can make some on-site visits, we can also work virtually, we'll discuss qualitative measures and quantitative measures. The qualitative measures, you see about seven here. You don't have to select all of these. You can select maybe one or two from qualitative, one or two from quantitative. The goal is to, let's say, if you select five, there are only going to be about three that we can really focus on. We'll sit down with you. I think a survey will be sent to you as well so we can get an idea about what you think, where you've identified a gap, and what needs to be improved for your organization as it relates to caring for the sickle cell patients.

Sunshine Sickle Cell Project: A Quality Improvement Initiative

Therapies in Adults with Sickle Cell Disease

Quality Improvement Indicators

- ↑ Increase in care planning and management
- ↑ Increase in the appropriate assessment, treatment and management of sickle cell disease
- ↑ Increase in patient/family education and shared decision making
- ↓ Reduction in the number of ED visits for acute vaso-occlusive crisis

The quality improvement indicators will serve to increase in care planning and management, increase in the appropriate assessment, treatment, and management of sickle cell disease, increase in patient family education and shared decision-making. We work very closely with the case managers. The patients often have an assigned case manager from their health plan. They typically are with complex case management. I know with one of the plans that we work with, their unit is called the C3 unit. The C3 case managers send us their patients and we make sure they come into our system of care. We follow all the standard treatment recommendations. It really leads to a reduction in the number of ED visits for vaso-occlusive crisis, and again, really increases that engagement between patient and provider.

Quality Improvement Action Planning℠

6 Steps	4 Plans
1. What is the problem?	1. Plan A: Immediate actions to minimize harm
2. What is causing the problem?	2. Plan to get data
3. What is the goal?	3. Plan to act
4. What steps will we take to reach the goal?	4. Plan to validate
5. How will we know the staff are following the plan?	
6. How will we know the plan is working?	

There's action planning involved with quality improvement. The six steps will be to define what the problem is, what's causing the problem, what is the goal, what it will take to reach the goal, how we will know the staff are following the plan, and how we will know the plan is working. The four plans would be immediate actions to minimize harm, plan to get data, plan to act, and plan to validate. That's like a circle. That just goes around and around.

Personal Plans of Action

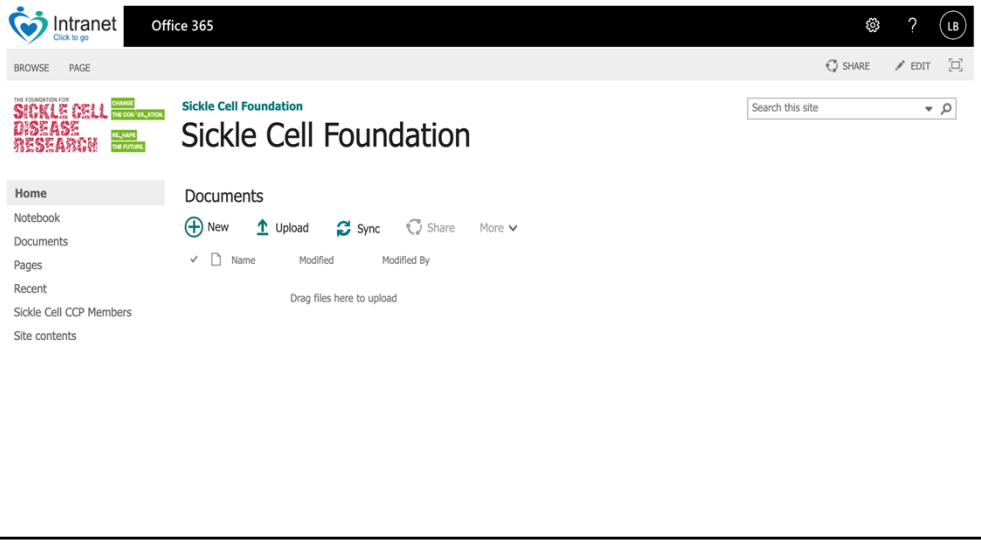
- **Write down *five things* you can do to improve healthcare quality for your patients with SCD**
- Example: I will:
  1. Study the barriers to best practices for my SCD patient population in the pediatric ED setting
  2. Implement a quality improvement project, utilizing measures selected from the Sunshine Sickle Cell Project quality improvement indicators, specifically focusing on pain management in the ED for pediatric patients with SCD in Florida
  3. Evaluate the impact of the quality improvement initiative by analyzing patient data and contributing to the larger body of research in Florida through the Sunshine Sickle Cell Project

What makes you unique?
What are your issues?
What would you like to study?

There are personal plans of actions, where, again, we'll write down the five things that you think that you can do to improve healthcare quality for your patients with sickle cell disease. Here's an example. I will study the barriers to best practices for my SCD patient population in the pediatric ED setting. I will implement a quality improvement project utilizing measures selected from The Sunshine Sickle Cell Project quality improvement indicators, specifically focusing on pain management in the ED for patients with sickle cell disease in Florida, or I will evaluate the impact of a quality improvement initiative by analyzing patient data and contributing to the larger body of research in Florida through the Sunshine Sickle Cell Project.

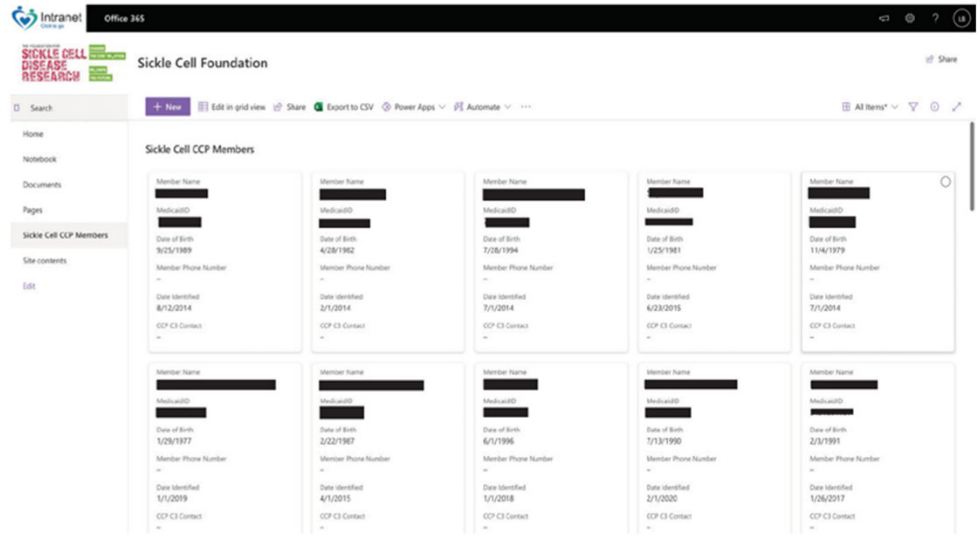
You may now ask what is this larger body of research in Florida? I do work very closely with the Florida Department of Health Closing the Gap grant. Actually, I had a conversation a couple of days ago with Dr. Quinones, who is with the Florida Department of Health, on ICD-10 codes because the state wants to implement in their chart system codes to monitor sickle cell hospitalizations. There is a larger body of research in Florida that is ongoing. We really are trying to reach as many clinicians as we can who treat these patients to really improve their quality of care and quality of life. We'll look at where are you currently and where do you want to be? What makes you unique? What are your issues? What would you like to study?

Example QI Monitoring Tool – Sharepoint Dashboard View



Here's an example. This is real, a monitoring tool. This is through Microsoft. This is the SharePoint dashboard. You may be familiar with SharePoint. This is typically an intranet tool. This is the intranet tool for Community Care Plan. They've added us to this tool to access the patients that they have populated for us to follow.

Example QI Monitoring Tool – Sharepoint
Easy Monitoring Tool Available to You During Project



This SharePoint tool here shows you the sickle cell CCP members. They're blinded, obviously. It highlights the date that they were enrolled with us, and also who their C3 or their case manager is. We also populate this particular database with the dates of their last outpatient appointment, the date of their last transcranial Doppler if they're between the ages of 2 and 16 years old, among other standards that we monitor that's recommended by the National Institutes of Health 2014 guidelines. We're able to provide this information to the plan. The plan has been able to take this data and report it as a part of their HEDIS, pull out those measures that are HEDIS-related. We are helping the Medicaid plans with their HEDIS data for sickle cell patients.

Biomarkers – Support of Subjective Pain Score

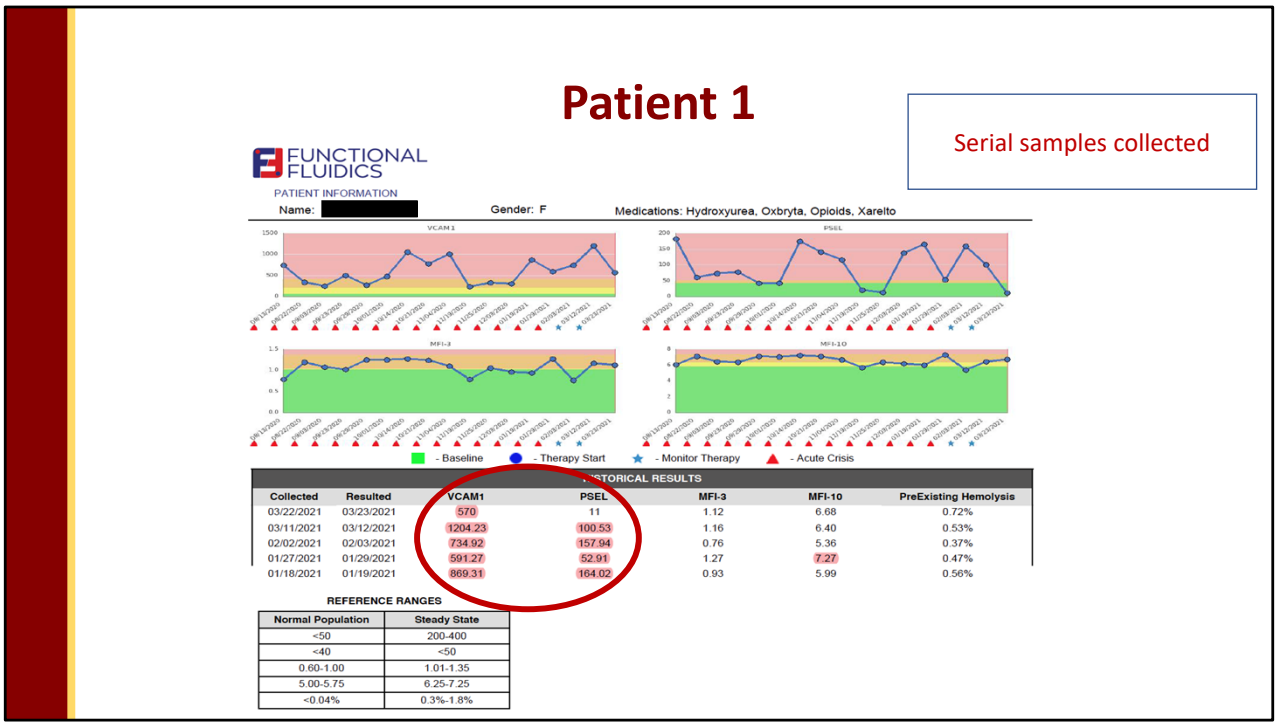
Biomarker critical value in one or more of the following areas:

Whole Blood Cell Adhesion on VCAM1 (>400)
Whole Blood Cell Adhesion on PSEL (>50)
Red Blood Cell Membrane Fragility Index at 3 min (>1.35) and 10 min (>7.25)

Many, many questions. I think there's a lot of angst oftentimes around these subjective pain score. Are the patients really in that much pain? Sometimes you really can't look at their face and tell that they're in pain because they've developed this level of stoicism. We are accustomed to seeing those in pain in a fetal position, and that's where we're like, "Okay, yes, they're really in pain." What about those who look stoic and don't grimace a whole lot, but calmly tell you that their pain is an 8 or a 9? We now are able to, through biomarker assessment, look at VCAM-1, P-selectin, as well as red blood cell membrane fragility index at 3 minutes and at 10 minutes. This lets us know how functional is that red blood cell? Is it going to hemolyze? Is it hemolyzing at 3 minutes, is it hemolyzing at 10 minutes?

Sunshine Sickle Cell Project: A Quality Improvement Initiative

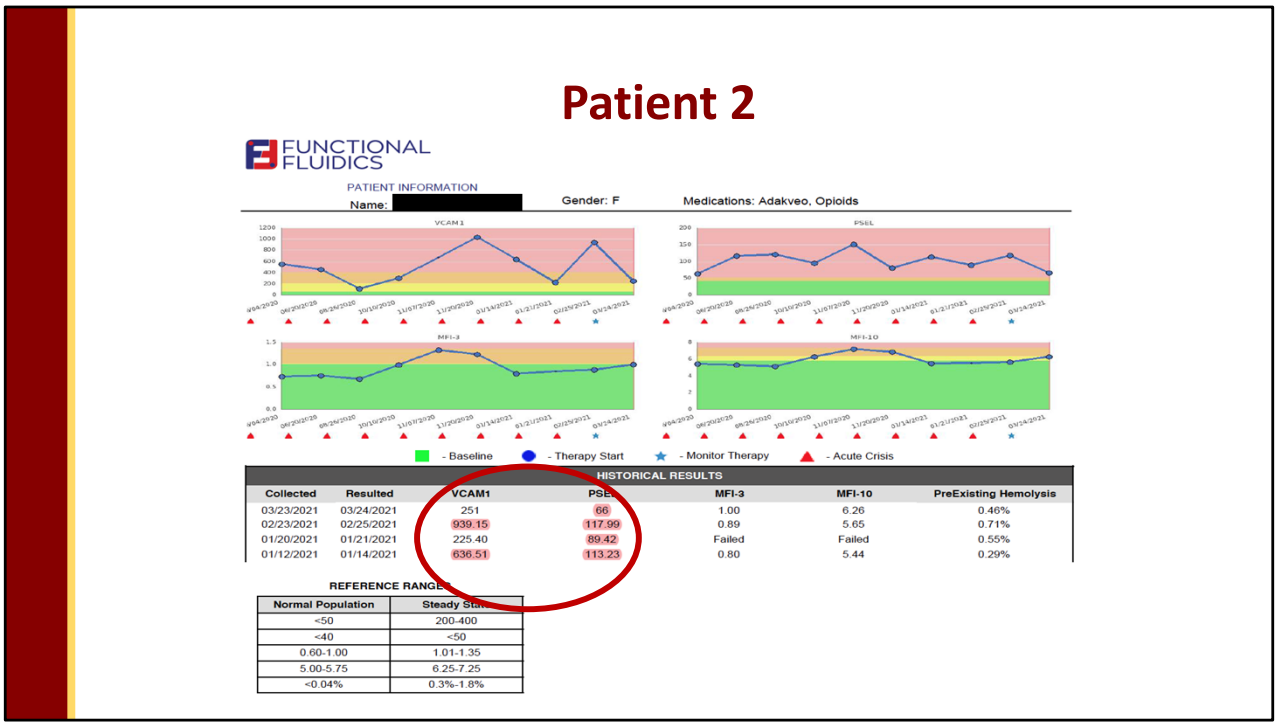
Therapies in Adults with Sickle Cell Disease



What are we finding out? It's almost a little heartbreaking, actually, because we certainly always are on the patient's side and believe the patient when they say that they're in pain, but I don't think we actually realize how much pain and how often they are in pain every day.

This graph shows several biomarkers, primarily the VCAM-1 and the P-selectin. These are the ones that really create this inflammatory environment within the endothelium and causes a lot of stickiness, and therefore, a lot of pain. The dots are several points that the patient came in to the foundation for treatment, and anything in the red zone means that their subjective pain score match their biomarkers. Rarely is the patient not in the red zone. I think that was a surprise to all of us, although there've been studies about pain, the tip of the iceberg with the PISCES study, but we're actually now able to quantify it with the biomarkers.

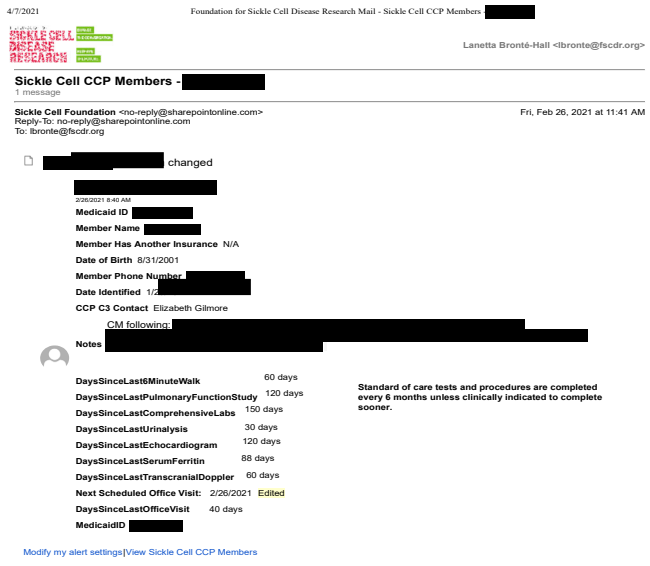
Sunshine Sickle Cell Project: A Quality Improvement Initiative
Therapies in Adults with Sickle Cell Disease



This is a different patient. Look at the VCAM-1 and the P-selectin. Now, crizulizumab (Adakveo) is the drug that goes and attacks this area, these biomarkers. We do have preimposed, where the patient was all in the red, started crizulizumab (Adakveo) and then went down to the green zone. That was pretty fascinating.

What Your Report Will Look Like

Example QI Monitoring Tool - Report



4/7/2021 Foundation for Sickle Cell Disease Research Mail - Sickle Cell CCP Members [redacted]

Lanetta Bronté-Hall <lbronte@fscdr.org>

Sickle Cell CCP Members - [redacted]
1 message

Sickle Cell Foundation <no-reply@sharepointonline.com> Fri, Feb 26, 2021 at 11:41 AM
Reply-To: no-reply@sharepointonline.com
To: lbronte@fscdr.org

[redacted] changed

[redacted]
2/26/2021 8:40 AM

Medicaid ID [redacted]
Member Name [redacted]
Member Has Another Insurance N/A
Date of Birth 8/31/2001
Member Phone Number [redacted]
Date Identified 1/2[redacted]
CCP C3 Contact Elizabeth Gilmore
CM following: [redacted]
Notes [redacted]

DaysSinceLast6MinuteWalk	60 days
DaysSinceLastPulmonaryFunctionStudy	120 days
DaysSinceLastComprehensiveLabs	150 days
DaysSinceLastUrinalysis	30 days
DaysSinceLastEchocardiogram	120 days
DaysSinceLastSerumFerritin	88 days
DaysSinceLastTranscranialDoppler	60 days
Next Scheduled Office Visit:	2/26/2021 Edited
DaysSinceLastOfficeVisit	40 days
MedicaidID	[redacted]

Standard of care tests and procedures are completed every 6 months unless clinically indicated to complete sooner.

Modify my alert settings|View Sickle Cell CCP Members

I did touch on what will the report look like. Again, we have the member's information there, as well as all of the indicators that we monitor: date since last pulmonary function study, comprehensive labs, urinalysis, echocardiogram because we're assessing for TR jet velocity. In addition to the case manager that we have at the foundation also working with the patient to make sure they're adherent to the recommendations, so is the C3 or the case manager with the health plan, and we're all working together. We double-team on the patient. They probably get tired of us, but I think at the end of the day, they really like the attention and the close monitoring.

What they're realizing and what they're experiencing is that they're just not in a hospital as much anymore. I have patients who are not on any of the new therapies and have not participated in clinical trials, but have been out of the hospital for two or three years. That has been really from close monitoring and just making sure they had good access to all the services that they need, including the wraparound services. You cannot dismiss those wraparound services because a lot of the stressors that they have can really be addressed by making sure they have the social support. Those stressors can lead to pain episodes for these patients.

Example Methodology of Tracking Indicators

- Create and implement a protocol for pain management in the ED for adult patients with SCD in Florida with the goals of improving
  - Mean time from triage to first analgesic dose
  - Percentage of patients that received their first analgesic dose within 30 minutes of triage, and
  - Percentage of patients who had pain assessment performed within 30 minutes of triage and who were re-assessed within 30 minutes after the first analgesic dose
  - Health plan per member per month health care utilization decrease and cost savings
  - Assess differential diagnosis for pain
  - Assess new therapeutic treatment options

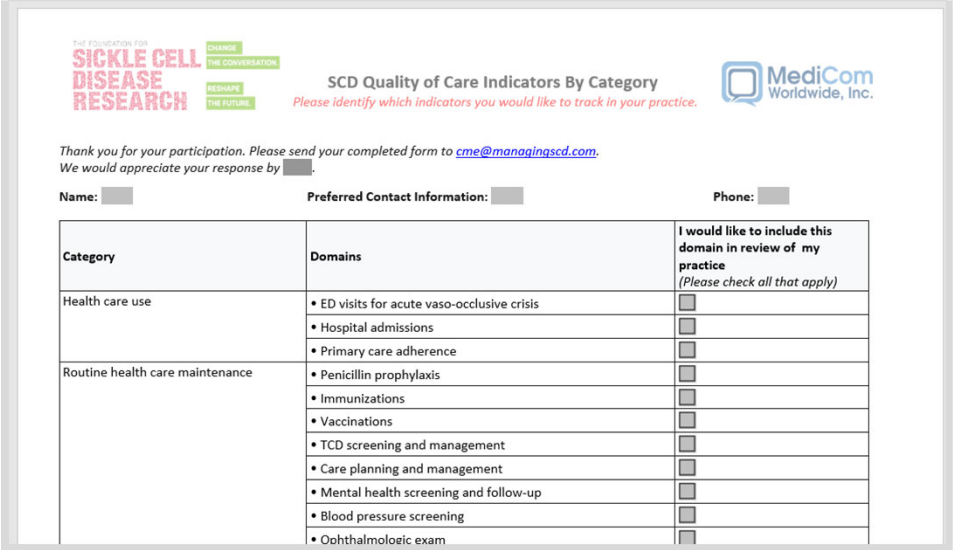
We'll create a methodology to track the indicators. We'll create and implement a protocol for pain management, whether that's in the ED or in your private practice. Now, when I created these indicators for the Joint Commission, what I tracked was mean time from triage to first analgesic dose. We didn't create this part in the ED, it was actually in the Day Hospital at Memorial, but you can implement this in the ED. Mean time from triage to first analgesic dose, the ED physicians are accustomed to meeting indicators like this. Percentage of patients that received their first analgesic dose within 30 minutes of triage, percentage of patients who had pain assessment performed within 30 minutes of triage, and who were reassessed within 30 minutes after the first analgesic dose. This is important because you may need to adjust, either tweak up or tweak down. Health plan per member per month, healthcare utilization decreases cost savings. We will assess that. Right now, with one of the health plans, we're saving them about $342 per member per month. We would assess the differential diagnosis for pain. For example, a patient who comes in complaining of back pain over and over and over and over again. What do we do for that? The patient may need to be referred to orthopedics or to another specialist who may order scans. That's exactly what we did. We found all kinds of facet deformity in patients who had this back pain. They went to a neurosurgeon and had some of that cleaned out, back pain essentially went away. Also, assessing new treatment options for pain. Do we have to use opioids all the time or can we use opioids in conjunction with something else? There's a lot of research on IV Tylenol, for example. Is that an alternative or an addition with the reduction in the opioids? Then, also, the new therapies with crizulizumab (Adakveo), voxelotor, and L-glutamine (Endari). We can track all of those for you. -

Next Steps – How Do You Participate?

- Approximately three months following conclusion of all educational interventions, interviews (60–90 minutes) will be conducted with multiple stakeholders at the patient-, provider-, and clinic-level using semi-structured interview guides
- In addition, quantitative data will be obtained from **chart reviews and ICD-10 codes provided by participating clinicians**
- Data will be collected and analyzed concurrently using the quantitative + qualitative approach
- Qualitative data will be secondary to the quantitative assessment
- The target participation in the QI initiative is 50-100 clinicians

What are our next steps? Approximately 3 months following conclusion of our educational interventions, there will be 60- to 90-minute interviews. Will be conducted with multiple stakeholders at the patient, provider, and clinic level using a semi-structured interview guide. In addition, quantitative data will be obtained from chart reviews and ICD-10 codes provided by participating clinicians. Data will collected and analyzed concurrently using the quantitative-qualitative approach. The qualitative data will be secondary to the quantitative assessment. Again, the target population in the QI initiative is 50 to 100 clinicians.

Identify The Quality Indicators That Are Right For Your Practice



THE FOUNDATION FOR SICKLE CELL DISEASE RESEARCH — CHANGE THE CONVERSATION. RESHAPE THE FUTURE.

SCD Quality of Care Indicators By Category

Please identify which indicators you would like to track in your practice.

MediCom Worldwide, Inc.

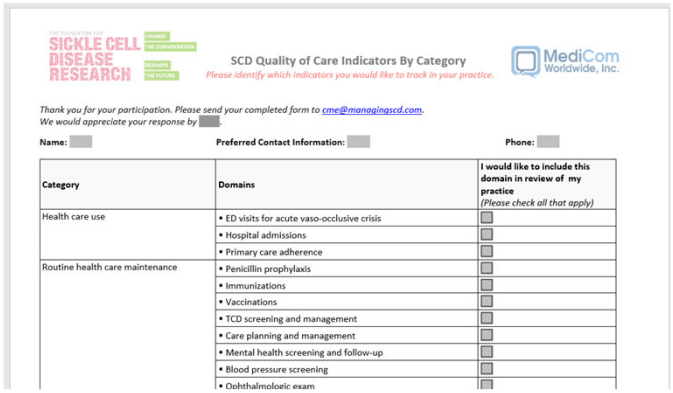
Thank you for your participation. Please send your completed form to cme@managingscd.com.
We would appreciate your response by [redacted].

Name: [redacted] **Preferred Contact Information:** [redacted] **Phone:** [redacted]

Category	Domains	I would like to include this domain in review of my practice *(Please check all that apply)*
Health care use	• ED visits for acute vaso-occlusive crisis	☐
	• Hospital admissions	☐
	• Primary care adherence	☐
Routine health care maintenance	• Penicillin prophylaxis	☐
	• Immunizations	☐
	• Vaccinations	☐
	• TCD screening and management	☐
	• Care planning and management	☐
	• Mental health screening and follow-up	☐
	• Blood pressure screening	☐
	• Ophthalmologic exam	☐

Interested in Participating?

- Click the "Complete Form" button below the video window and complete an interest form
- Once your form is submitted, you will receive an email from *ManagingSCD.com*



SICKLE CELL DISEASE RESEARCH — CHANGE THE CONVERSATION. RESHAPE THE FUTURE.

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	• Care planning and management	☐
	• Mental health screening and follow-up	☐
	• Blood pressure screening	☐
	• Ophthalmologic exam	☐

This is the quality indicators form that we will send out to you. You can select those that you think are right for you and your organization.