Senators Tim Scott and Cory Booker host a briefing on Progress in Sickle Cell Disease Treatment and Policy Implications

Hosted in partnership with the Pediatric Hospital Sickle Cell Disease Collaborative and











American Society of Hematology Helping hematologists conquer blood diseases worldwide

Importance of Sickle Cell Disease (SCD) Surveillance to Improve Access to New Therapies

Julie Kanter, MD University of Alabama at Birmingham

Sickle cell disease (SCD) epidemiology in the United States



Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med. 2010 Apr;38(4 Suppl):S512-21.

Barriers to Successful Development of Novel Therapeutics in SCD



Clinical Trials Recruitment Challenges. Jacobs Publishers. https://jacobspublishers.com/clinical-trials-recruitment-challenges/. Published December 14, 2018. Accessed May 23, 2019.
Ataga KI, Desai PC. Expert Opin Orphan Drugs. 2018;6(5):329-343. 3. Badawy SM, Barrera L, et al. EMRI, 2018;2018;1-8, 4. Dampier CD, Smith WR, et al. Clin Trials. 2013;10(2):319-331.

SCD and Mortality in the United States

- Childhood survival is 96% to 98% for all genotypes
- In 2014, most deaths (66%) occurred at ages 25 to 54 years
- More recent surveillance data from Georgia and California showed mean age at death was 43 years for women, 41 years for men



Quinn CT, et al. *Blood*. 2010;115:3447. Paulukonis ST, et al. *Public Health Reports*. 2016;131:367-375. Hassell KL, et al. *Am J Prev Med*. 2010;38:S512-S521.



What is Sickle Cell Disease Surveillance?



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Sickle Cell Data Collection (SCDC)









www.cdc.gov/ncbddd/hemoglobinopathies/scdc-state-data/georgia-2005.html

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Additional gaps in knowledge about SCD

- Where do individuals with SCD receive care?
- Who takes care of individuals with SCD outside of specialty centers?
- Does continuous care at a specialty center result in better health outcomes?
- Are individuals with SCD receiving recommended therapies?
- Are individuals with SCD receiving age-appropriate preventive care?
- Are the SCD-related complications for patients who live past the age of 50 different than for those who die at an earlier age?



How can population-based data help answer these questions?



| | Live or Receive Care in Alameda County | Received Care at SCD Center in Alameda County |
|--------------------------|---|--|
| Pediatric (<21 years) | 355 | 238 (67%) |
| Adult (≥ 21 years) | 488 | 264 (54%) |
| TOTAL | 843 | 502 (60%) |

Only 60% of people with SCD in Alameda County go to the local SCD Center for their health care.

www.cdc.gov/ncbddd/hemoglobinopathies/scdc-state-data/california-2005.html; communication with S. Paulukonis

Bone Marrow Stem Cell Transplant Strategies for SCD



CRISPR/CAS9, clustered regularly interspaced short palindromic repeats/Cas9 protein; HSC, hematopoietic stem cell.

1. Sürün D, Melchner HV, et al. *Drug Discov Today: Technol.* 2018;28:33-39. 2. *Bone Marrow (Stem Cell) Transplant for Sickle Cell Disease*. Memphis, TN; 2012:1-10. 3. Morgan RA, Gray D, et al. *Cell Stem Cell*, 2017:21(5):574-590.

Lentiglobin HGB 206 gene therapy study





Lentiglobin gene therapy: Median HbS \leq 50% at \geq 6 months after treatment



Total Hb and HbA^{T87Q} ranged from 10.2 – 15.0 g/dL and 4.5 – 8.8 g/dL, respectively, at last visit in patients with ≥ 6 months of follow-up

How do we put this surveillance data into practice?



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Policy Considerations to Advance Gene Therapies for Sickle Cell Disease

Francesca Cook, MPH

ASGCT Government Relations Committee Member Senior Director, Pricing & Market Access, REGENXBIO

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ASGCT is committed to advancing gene & cell therapies through science and policy

Policy and Advocacy Goals That Relate to Sickle Cell Disease

- Stimulate the discovery of transformative gene & cell therapies, especially for disorders with unmet need
- Promote sustainable patient access to the value of approved therapies
- Seek patient access solutions that prevent undue strain to key stakeholders in the healthcare system (e.g., patients, providers, payers)





Gene and cell therapies are starting to transform lives with approved treatments and trials



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asgct.org/clinicaltrials

| Title | Ąż | Phase 1 | Modalities | Interventions | Location |
|---|----|---------|---|---|------------------------|
| Stem Cell Gene Therapy for Sickle Cell Disease | Î | 1/2 | Gene Therapy, Stem Cell Therapy, Viral Vector | CD34+ cells transduced with lentiviral vector to express ßAS3-FB | USA - CA - Los Angeles |
| A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease | ÎÎ | 1/2 | Gene Therapy, Stem Cell Therapy | autologous CRISPR- Cas9 Modified CD34+ hHSPCs | View Locations 🗸 |
| A Study to Assess the Safety, Tolerability, and Efficacy of BIVV003 for Autologous Hematopoietic Stem Cell Transplantation in Patients With Severe Sickle Cell Disease | Ê | 1/2 | Gene Therapy, Immunosuppressive Agents, Non-Viral Vector, Stem Cell Therapy | CD34+ progenitor cells transfected with ZFN mRNA, plerixafor, busulfan | View Locations 🗸 |
| Gene Transfer for Patients With Sickle Cell Disease | ÎÌ | 1/2 | Gene Therapy, Viral Vector | lentivirus vector containing fetal hemoglobin gene | USA - OH - Cincinnati |
| A Study Evaluating the Safety and Efficacy of the LentiGlobin BB305 Drug Product in Severe Sickle Cell Disease | ÎÎ | 1/2 | Gene Therapy, Immunomodulatory Agent, Stem Cell Therapy, Viral Vector | cells with lentiviral vector encoding human betaA-T87Q- globin, plerixafor | View Locations 🗸 |
| Gene Transfer for Sickle Cell Disease | | 1 | Gene Therapy, Stem Cell Therapy, Viral Vector | CD34+ stem cells transduced with leniviral vector taraeting BCL11a | USA - MA - Boston |

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Support Robust NIH Research Funding

- Funds basic research that underpins gene therapies and clinical trials
- NHLBI is currently funding the Cure Sickle Cell Initiative, which aims to accelerate the development of genetic therapies to cure SCD within the next 5 – 10 years
- ASGCT has requested the Senate -
 - Appropriate at least a \$2 billion increase in NIH funding for FY2020, as proposed by the House
 - Appropriate the \$8 million authorized by 21st Century Cures for FY2020 for the Regenerative Medicine Innovation Project





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Reauthorize Newborn Screening



- The Newborn Screening Saves Lives Act is set to expire in September 2019
- Authorizes funding for states' screening programs and educational efforts
- All 50 states screen for sickle cell disease
- H.R. 2507 was introduced in the House by Reps. Roybal-Allard and Simpson
- Support reauthorization efforts led by the Energy and Commerce and HELP Committees



Thinking Ahead: Approvals of Gene Therapy for Sickle Cell Disease

To maximize patient access to approved gene and genetically-modified cell therapies ASGCT:

- Supports coverage and maximal reimbursement levels for approved therapies
- Does not endorse any specific gene therapy pricing decisions





Why Access is Crucial: Unique Value of Gene Therapy for SCD

- High efficacy, single administration
- Reduces or eliminates need for other costly treatments

The total lifetime costs of treating sickle cell disease through current standards of care is extremely high

"If this gene therapy works, I won't have to take off work every month for blood transfusions or deal with the daily pain. It would improve my life in ways that are hard to even imagine right now."

-Woman enrolled in a gene therapy trial for SCD



Coverage & Reimbursement Issues for Approved Gene Therapies



- Upfront costs for single administration will be challenging for payers, especially Medicaid programs and smaller commercial payers
- Recent Medicare actions for approved cell therapies raise concerns about system readiness (insufficient Inpatient Prospective Payment System reimbursement levels to providers)
- State Medicaid reimbursement practices vary, with some states reimbursing providers primarily for services, in a bundled payment, which is often insufficient to cover both services and the therapeutic product



Coverage & Reimbursement Solutions to Prepare for the Approval of SCD Therapies

- Enable novel payment models (outcomes-based payment and payment over time) by exempting such arrangements for gene and cell therapies from barriers—Medicaid best price requirements, Stark Law, and Anti-Kickback Statute
- For Medicare in the inpatient setting: Reform NTAP levels and formulas, and collect accurate cost and payment data from providers of cell and gene therapies.



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Gene Therapy with an Anti-Sickling Gene for Correction of Sickle Cell Disease: A Novel Approach

Punam Malik, MD Director, Cincinnati Children's Comprehensive Sickle Cell Center

Marjorie Johnson Chair of Cell and Gene Therapy, Cincinnati Children's Hospital

Professor of Pediatrics, University of Cincinnati

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The Cause of Sickle Cell Disease

- *Cause of Sickle Cell Disease*: a mutation in the HBB gene (that produces the adult hemoglobin protein in red blood cells) causes production of a mutant hemoglobin termed sickle hemoglobin.
- *Sickle Hemoglobin Results in* rigid, sickle-shaped red blood cells, which clog blood vessels and are destroyed rapidly.
- *The disease causes* severe pain episodes/pain crisis and weakness/fatigue from anemia.





Gene Therapy: Adding Working Genes

- Before birth, humans produce *Fetal Hemoglobin*, which prevents red blood cell sickling.
- Normally the Fetal Hemoglobin gene switches off shortly after birth
- Adding a modified Fetal Hemoglobin gene that cannot switch off and preferentially makes Fetal Hemoglobin over the faulty Sickle Hemoglobin can prevent red blood cells from sickling





How is Gene Therapy Typically Done?

1. Ex-vivo (outside the body) gene transfer

- Blood stem cells (blood-making cells) are removed from the body.
- A lentiviral vector delivers the anti-sickling gene into the blood stem cells
- The vector is a virus because it can get inside the cell – but the viral genes are fully removed and replaced with the anti-sickling gene



• Once the gene gets inside the cell, the functioning Fetal Hemoglobin gene will prevent sickling of red blood cells despite the presence of the faulty globin

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How is Gene Therapy Typically Done?

2. Typically, very high dose chemotherapy is given to completely destroy faulty blood stem cells and make space for corrected blood stem cells

- Then the gene-corrected cell product is given back via a vein
- A month or more later, the corrected stem cells start producing red blood cells that do not sickle
- We tested a new gene therapy approach with reduced-dose chemotherapy because red blood cells from corrected stem cells outcompete the faulty sickle red blood cells
 - This approach makes the transplant process less complicated
 - Causes fewer chemotherapy-related immediate and long-term side effects
 - Reduces hospitalization and costs



Preliminary results of Gene Therapy with a functional Fetal Hemoglobin Gene using a Reduced-dose chemotherapy

- 2 patients were treated 21 and 15 months back with the fetal Hemoglobin gene cell product (ARU-1801). The 3rd patient is enrolled and many interested.
- Both recovered from acute side effects of transplant within 7-12 days (typical recovery with full dose chemotherapy is 1-2 months).
- Both have had a >95% reduction in disease symptoms
 - 0 and 2 pain crises in 15 and 21 months, as compared to 20 crises and 48 crises in patients 2 and 1 in the 18 months prior
 - Both have relief from their chronic daily pain, allowing discontinuation of daily opioids.
- Anti-sickling hemoglobin levels were 22% and 30% (> 20% provides benefit to patients).

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A New Approach: Gene Silencing

David Williams, MD

Senior Vice President and CSO, Boston Children's Hospital President, Dana-Farber / Boston Children's Cancer and Blood Disorders Center

Leland Fikes Professor of Pediatrics, Harvard Medical School

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Silencing the BCLA11A gene

- The BCL11A gene acts as an "off" switch to fetal hemoglobin production shortly after birth for most people
- While most people then switch to making healthy adult hemoglobin, people with sickle cell disease transition to making a mutated, sickled hemoglobin
- Silencing the BCL11A gene simultaneously increases fetal hemoglobin, which does not sickle and has potent anti-sickling characteristics, and directly reduces the creation of adult, sickling hemoglobin







Ex vivo lentiviral vector approach

- Blood stem cells are removed from the body
- A lentiviral vector delivers instruction to the cell to silence or "knock down" the BCL11A gene product
- These genetically-modified cells are returned to the body



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BCL-002: Reversal of Sickle Cell Phenotype

- No pain
- No respiratory or neurologic events •

Pre-GT

- No anemia
- No transfusions since engraftment

6 months post-GT







Update

- Adult cohort complete
 - Kinetics of engraftment very similar in all patients
 - Kinetics of fetal hemoglobin production and reduced sickle hemoglobin production very similar in all patients
 - No adverse events attributed to gene therapy product
- DSMB interim review complete
- Age 12-18 cohort opened and enrollment already completed
- Age 2-12 now opening, many patients interested



Many interested families

- 51 families with children under age 12
- 23 adolescents
- 49 adults
- Worldwide interest:
 - U.S. (Rhode Island, Massachusetts, Minnesota, Texas, Indiana, Florida, Louisiana, New York, New Hampshire...)
 - International (UK, Canada, Nigeria, Kenya, Argentina...)





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Gene Editing

Matthew Porteus, MD, PhD Professor of Pediatrics (Stem Cell Transplantation) Stanford University

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Gene editing

- Removes, disrupts, or corrects faulty elements of DNA within a gene
- An enzyme cuts DNA at one location
- The specific DNA cut allows one to change the sequence with high precision





Two Basic Genome Editing Strategies for Sickle Cell Disease

- Re-activate protective fetal hemoglobin
 - Multiple academic labs around the world
 - Two open clinical trials run by different biotechnology companies
- Directly correct variant that causes the disease ("gene correction")
 - Several different programs moving towards clinical trials in next 6-18 months.





Example of Approach 1: Increasing Protective Fetal Hemoglobin

- Hematopoietic and progenitor cells are removed from the body
- CRISPR/Cas9 technology is used to edit a portion of the BCL11A gene
- The edited cells are then infused back into the patient as part of an autologous stem cell transplant
- The edited cells produce high levels of fetal hemoglobin (HbF) in red blood cells





Example of Approach 2: Direct Correction of the Sickle Cell Disease Gene

- Hematopoietic and progenitor cells are removed from the body
- CRISPR/Cas9 technology is used to correct the sickle cell disease gene
- The edited cells are then infused back into the patient as part of an autologous stem cell transplant
- The edited cells produce the nonsickling hemoglobin instead of the sickling hemoglobin





Preliminary Data

• Upregulation of Protective Fetal Hemoglobin

- In pre-clinical studies achieve 40-60% expression of fetal hemoglobin
 - Higher than 20% likely provide benefit to patients
- Patient enrolled in the United States (no data reported, too early to tell)

Gene Correction

- In pre-clinical studies, achieve 20-60% gene correction
 - Higher than 5-20% correction frequency that is predicted to change lives of patients
 - Moving towards clinical trials





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