AMERICAN SOCIETY of GENE & CELL THERAPY

AMERICAN SOCIETY OF HEMATOLOGY

ASTCT
American Society for Transplantation and Cellular Therapy

PEDIATRIC HOSPITAL SICKLE CELL COLLABORATIVE

SICKLE CELL DISEASE ASSOCIATION OF AMERICA, INC. est. 1972

welcome you to a briefing on

Sickle Cell Disease: Progress in Treatment Options and Policies

in conjunction with

Representatives Barbara Lee, Michael C. Burgess, MD, and Danny K. Davis

November 19, 2019

Advancing knowledge, awareness, and education of gene and cell therapy

AMERICAN SOCIETY of GENE & CELL THERAPY

Gene Therapy Developments and Approaches

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Advancing knowledge, awareness, and education of gene and cell therapy

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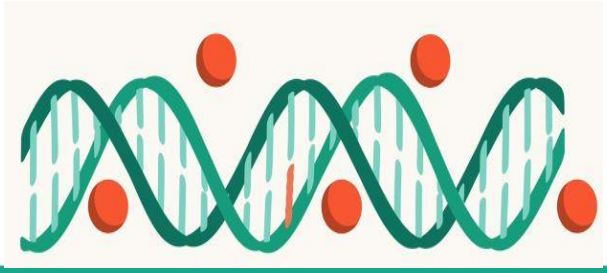
The Cause of Sickle Cell Disease

- **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 faulty hemoglobin termed sickle hemoglobin
- **Sickle hemoglobin** results in rigid, sickle-shaped red blood cells, which clog blood vessels and are destroyed rapidly
- **Causes symptoms** such as severe pain episodes/pain crises, strokes, weakness/fatigue, severe pneumonias and many others
- **Lucky Patients** maintain higher HgbF levels (fetal hemoglobin) and have less severe disease (and one drug (hydroxyurea) acts by increasing HgbF)



There are many different ways to prevent your pants from falling down (including not even wearing pants):

A diverse set of approaches to cure sickle cell disease are being developed

Allogeneic Hematopoietic Stem Cell Transplantation

Lentiviral Gene Therapy
-Add a non-sickling copy back (gene addition)
-Derepress fetal hemoglobin (HgbF)

Genome Editing: Derepress fetal hemoglobin (HgbF)

Genome Editing: Gene Correction

Allogeneic Bone Marrow Transplantation (aka Hematopoietic Stem Cell Transplant (HSCT)

- **HSC transplantation:** Take blood stem cells from one person who doesn't have sickle cell disease and give them to patient after patient receives very high doses of chemotherapy
  - Fully immune matched sibling donor (MSD)
  - Unrelated donor (URD)
  - Half-matched family donor (haplo)

Active and Recruiting Gene Therapy and Gene Editing Clinical Trials in the US (more on the way!)

Title	Phase	Modalities	Interventions	Location
Gene Transfer for Patients With Sickle Cell Disease	1/2	Gene Therapy, Viral Vector	lentivirus vector containing fetal...	USA - OH - Cincinnati
A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Ce...	1/2	Gene Therapy, Stem Cell Therapy	autologous CRISPR-Cas9 Modified CD34...	View Locations
Stem Cell Gene Therapy for Sickle Cell Disease	1/2	Gene Therapy, Stem Cell Therapy, Viral...	CD34+ cells transduced with...	USA - CA - Los Angeles
A Study to Assess the Safety, Tolerability, and Efficacy of BIVV003 for Autologous...	1/2	Gene Therapy, Immunosuppressiv...	CD34+ progenitor cells transfected wit...	View Locations
Gene Transfer for Sickle Cell Disease	1	Gene Therapy, Stem Cell Therapy, Viral...	CD34+ stem cells transduced with...	USA - MA - Boston

asgct.org/clinicaltrials

Gene Therapy: Adding Working Genes

- Before birth, humans produce **fetal hemoglobin**, which reduces 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***

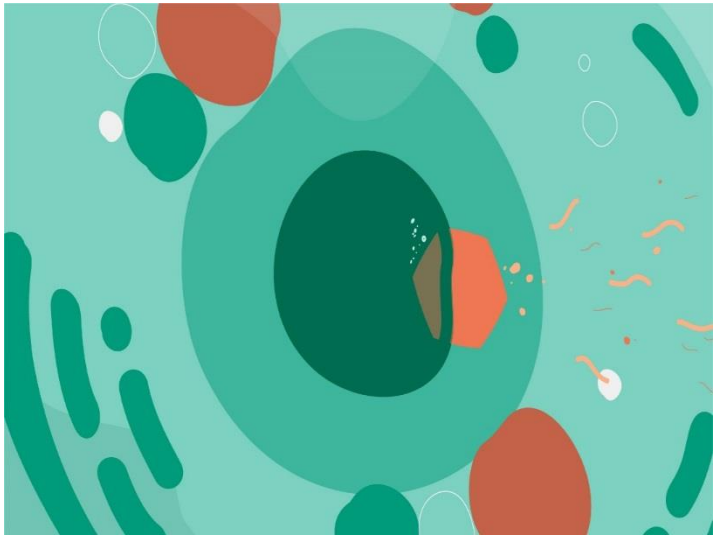
Genetically-Modified Cell Therapy

Or *ex-vivo* gene therapy (outside the body)

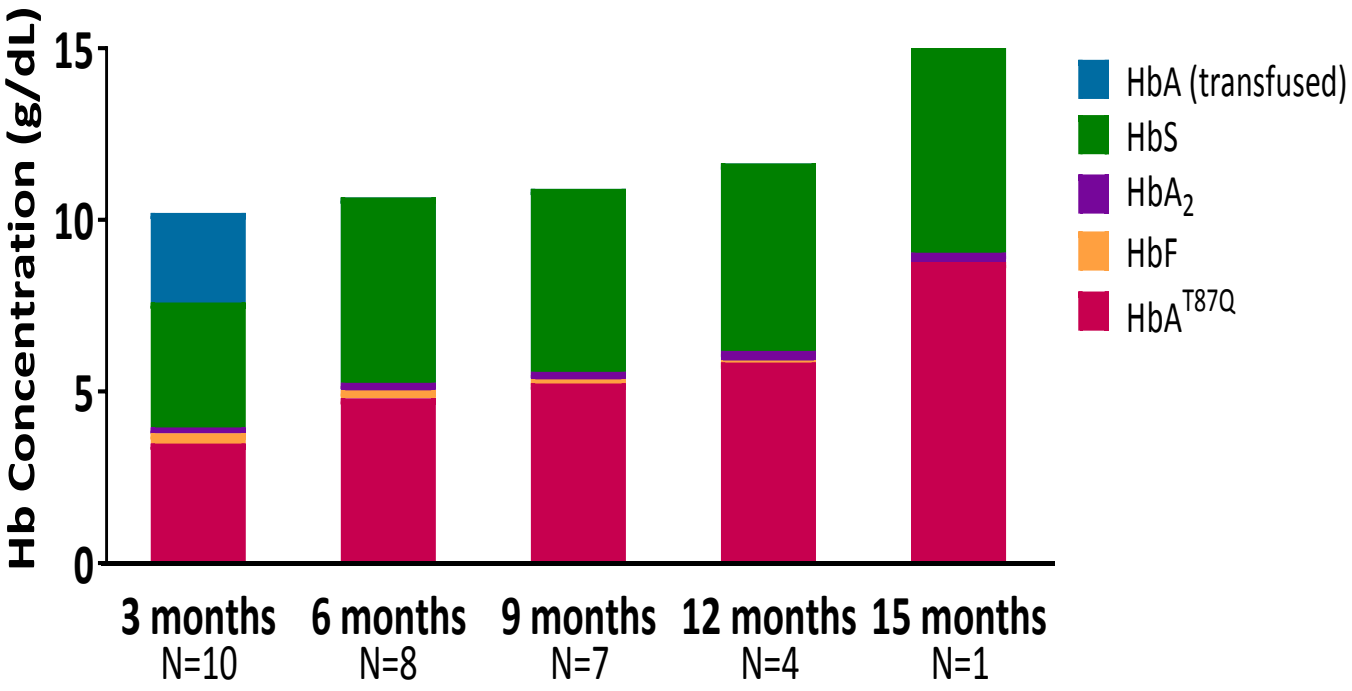
- Hematopoietic stem cells (HSCs) are removed from the patient via blood draw (cells that can develop into all types of blood cells)
- A functioning gene is inserted into the stem cells
- Meanwhile, typically high dose chemotherapy is given to the patient to completely destroy faulty blood stem cells and make space for corrected blood stem cells
- Then the gene-corrected cell product is given back via an intravenous infusion (IV)

Delivery mechanism – Lentiviral vector

- 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



Preliminary results: Lentiglobin gene therapy: Median HbS ≤ 50% at ≥ 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

Future Goal is to Reduce Amount of Chemotherapy needed to get enough of the gene therapy/genome editing cells to take

1. Reduce dose of chemotherapy
   - 2 patients were treated with the fetal hemoglobin gene cell product (ARU-1801) with lower chemotherapy
   - Both have had a significant reduction in disease symptoms (allowing discontinuation of daily opioid pain medicine)
   - Anti-sickling hemoglobin levels were 22% and 30% (> 20% provides benefit to patients).
   - Both recovered from acute side effects of transplant within 7-12 days (instead of one 1-2 months).

2. Replace chemotherapy with an antibody or a cell (clinical trials in other diseases have started or about to start)

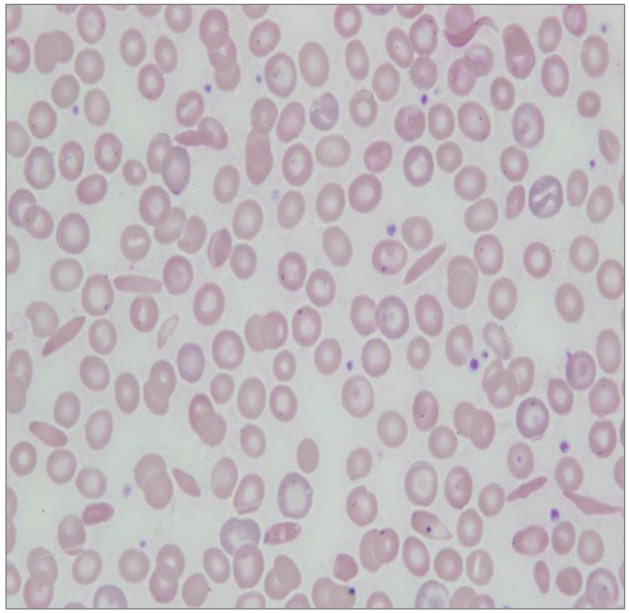
Another Gene Therapy Approach: Turning down the BCLA11A gene in order to turn on HgbF

- 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
- A lentiviral vector delivers instruction to the cell to silence or “knock down” the BCL11A gene product
- 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

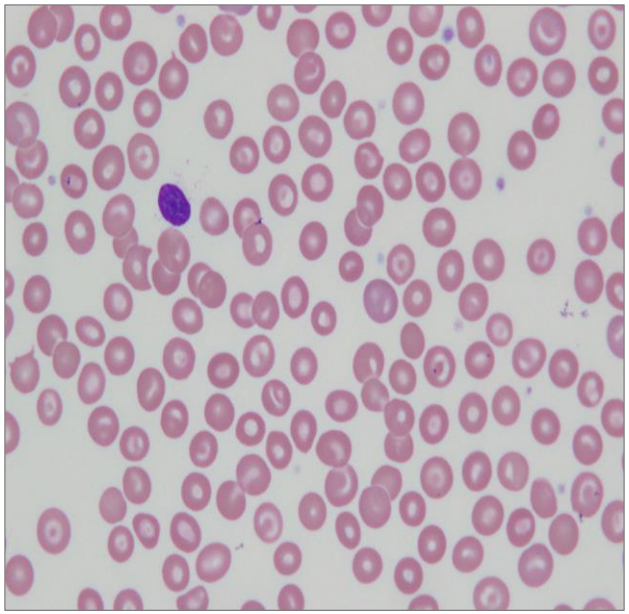
BCL-002: Reversal of Sickle Cell Phenotype

- No pain
- No respiratory or neurologic events
- No anemia and good HgbF levels (20-30%)
- No transfusions since engraftment

Pre-GT



6 months post-GT

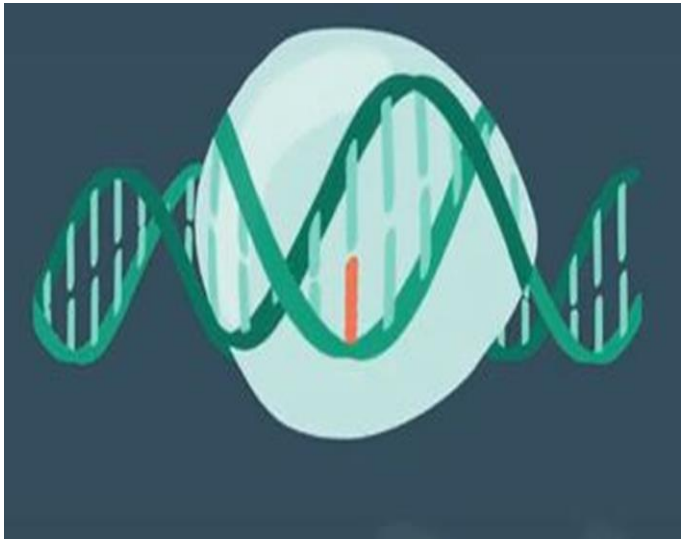


Gene editing

- 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

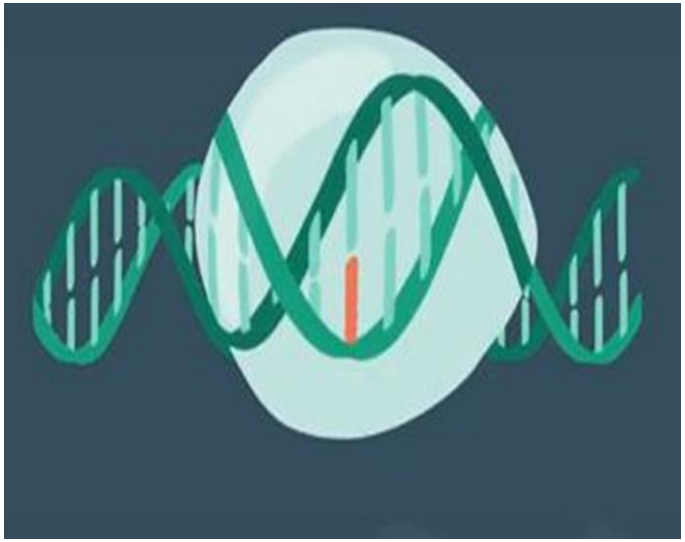
Two Basic Genome Editing Strategies for Sickle Cell Disease

- Re-activate protective fetal hemoglobin (HgbF)
  - 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.



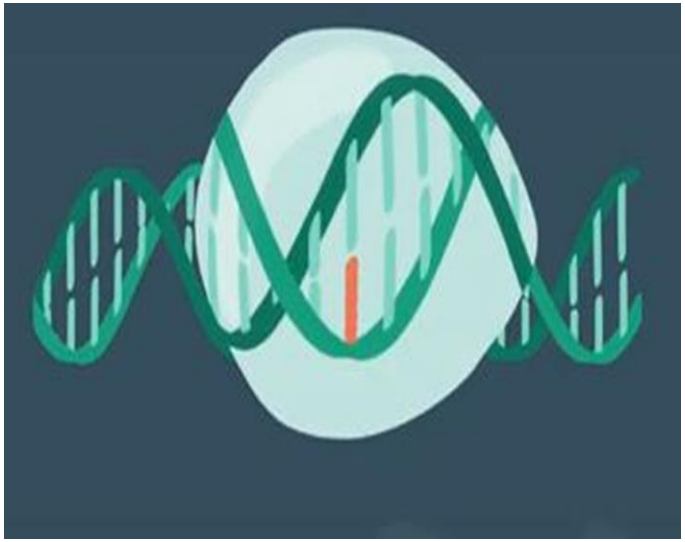
Example of Approach 1: Increasing Protective Fetal Hemoglobin

- Hematopoietic and progenitor cells are removed from the body
- CRISPR/Cas9 technology is used to edit a portion of the BCL11A gene
- Or use genome editing to re-create natural “hereditary persistence of fetal hemoglobin” variants
- The edited cells are then infused back into the patient as part of an autologous stem cell transplant
- The edited cells should produce protective 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 non-sickling 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 (data to be reported next month but still too early to make any firm conclusions)

- 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 in 2020 and 2021

Which is going to be best? How will I choose?

More data and research will help us answer those questions

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Sickle Cell Disease from the Perspective of a Patient and Gene Therapy Recipient

Jennelle Stephenson

Policy Considerations to Advance Gene Therapies for Sickle Cell Disease

Remy L. Brim, PhD

Vice President Regulatory Policy and Strategy

BGR Group

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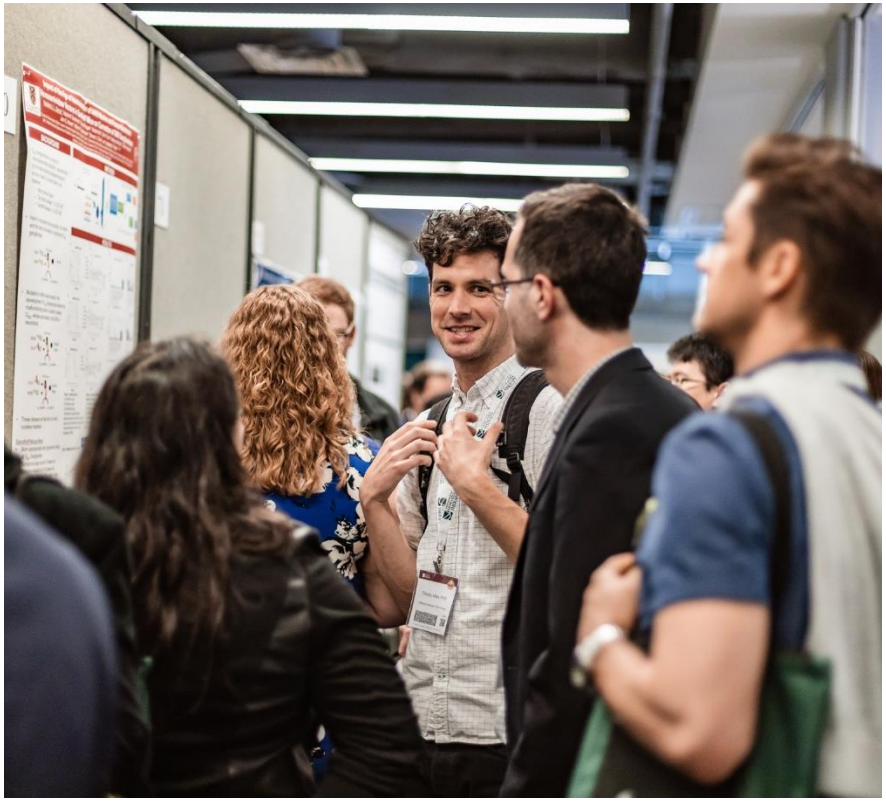
AMERICAN SOCIETY of GENE & CELL THERAPY

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

- Stimulates the discovery of transformative gene & cell therapies, especially for disorders with unmet need
  - NIH funding
- Promotes surveillance, diagnosis, and sustainable patient access to treatments
  - Newborn screening
  - House Resolution 606
  - CDCs SCDC Program
  - Outcomes-based and payment over time proposals
- Does not endorse any specific gene therapy pricing decisions



Support Robust NIH Funding

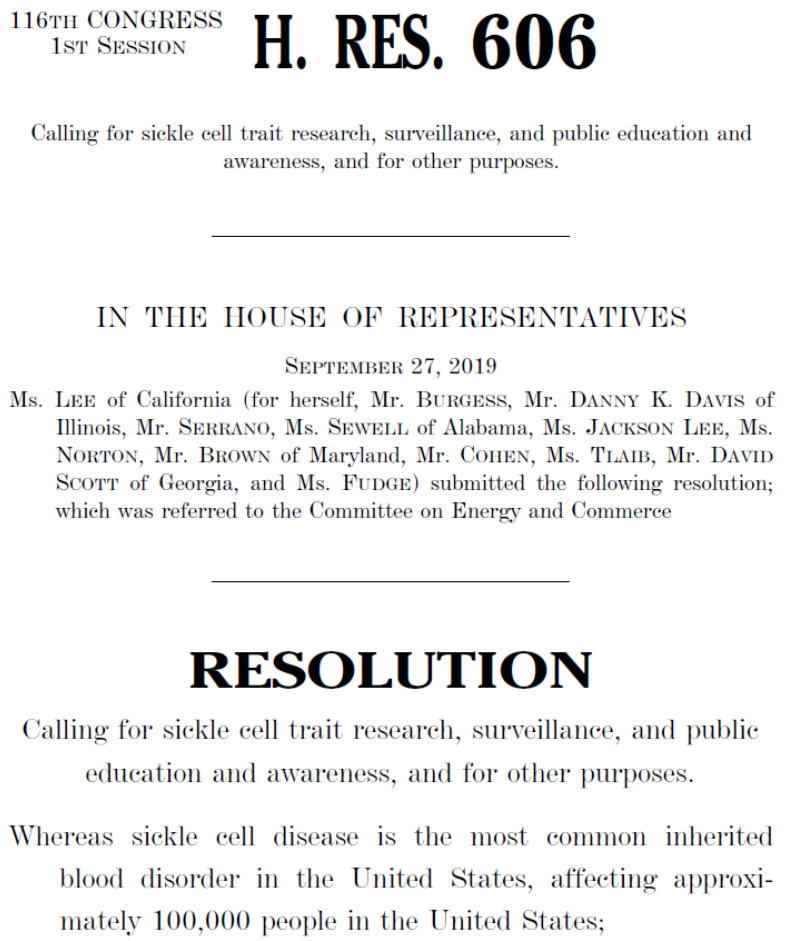
- Funds basic research that lays the scientific groundwork for new approaches to treatment
- Supports the Cure Sickle Cell Initiative
- Supports collaboration with Bill & Melinda Gates Foundation to find treatments for sickle cell and HIV that can be globally available in low-resource settings
- House Labor-H Appropriations bill provides a $2 billion increase over the 2019 budget of $39.1 billion

Reauthorize Newborn Screening

- Authorizes HRSA funding for states' screening programs and educational efforts
- Supports 50-state screening for sickle cell disease
- Supports the adoption of additional genetic disease screening tests
- H.R. 2507 (Reps. Roybal-Allard and Simpson) passed the House in July

Support House Resolution 606

- Awareness of trait status
- Screening, counseling, and informed decision making
- Improving health outcomes
- Development and equitable to new treatments



116TH CONGRESS
1ST SESSION

H. RES. 606

Calling for sickle cell trait research, surveillance, and public education and awareness, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

SEPTEMBER 27, 2019

Ms. LEE of California (for herself, Mr. BURGESS, Mr. DANNY K. DAVIS of Illinois, Mr. SERRANO, Ms. SEWELL of Alabama, Ms. JACKSON LEE, Ms. NORTON, Mr. BROWN of Maryland, Mr. COHEN, Ms. TLAIB, Mr. DAVID SCOTT of Georgia, and Ms. FUDGE) submitted the following resolution; which was referred to the Committee on Energy and Commerce

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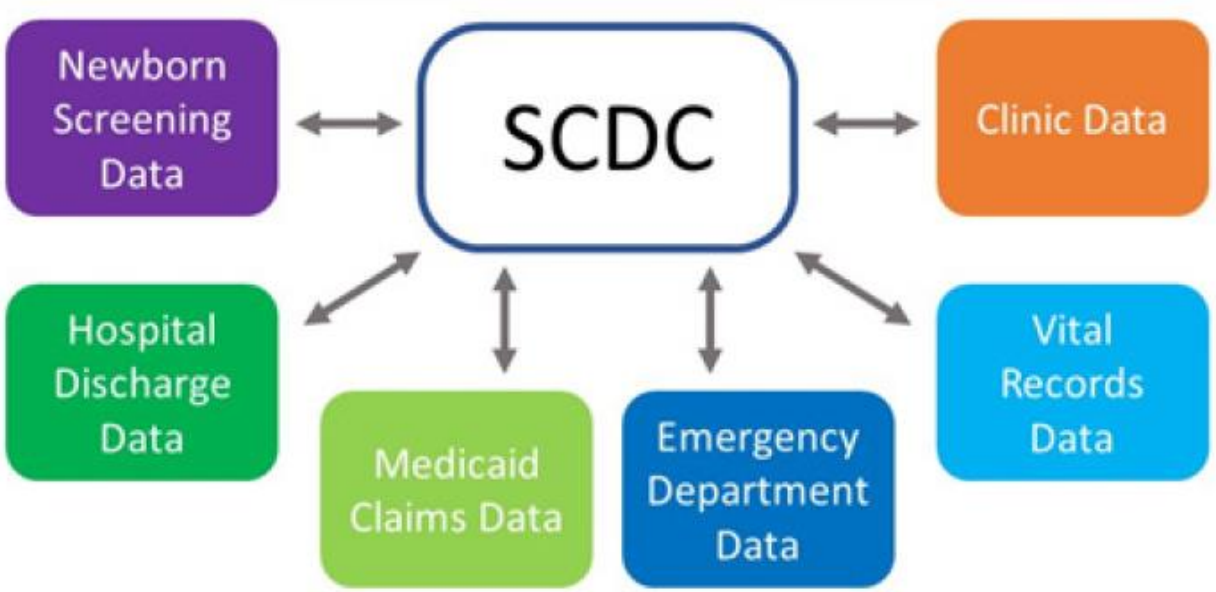
RESOLUTION

Calling for sickle cell trait research, surveillance, and public education and awareness, and for other purposes.

Whereas sickle cell disease is the most common inherited blood disorder in the United States, affecting approximately 100,000 people in the United States;

Support Appropriations for the CDC Sickle Cell Data Collection Program

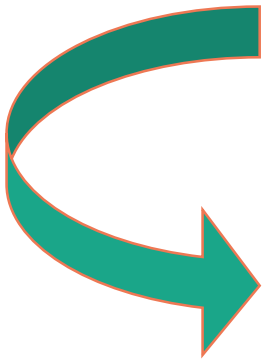
- Improves understanding of the health outcomes and health care system utilization patterns of people with SCD
- Increases evidence for public health programs and to establish cost-effective practices to improve and extend the lives of people with SCD



The Payment System is Not Ready for Gene Therapies

Current treatments -

- **Treat symptoms**
- **Are given repeatedly**
- **Spread accumulating high costs over a patient's lifetime**



Gene therapies may -

- **Treat the underlying disease**
- **Be offered in single or few doses**
- **Increase quality of life**
- **Offer long-term savings**

Advocate for payment models that facilitate access, protect payers, and reward innovation

- Pay for products over several years
- Pay based on value and/or outcomes

- Broad adoption of these structures require addressing current regulatory and legal barriers, including Medicaid best price requirements, Anti-Kickback Statute, and the Stark Law
- Support language like that contained in Section 208 of the Prescription Drug Pricing Reduction Act which demonstrates bipartisan action to enable these structures

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