

## 2017 Alabama Newborn Screening Conference



Marriott Hotel and Conference Center  
Prattville, Alabama  
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## Newborn Screening for Sickle Cell Disease

Felicia L. Wilson, M.D.  
Professor of Pediatrics  
Director, Division of Hematology / Oncology  
University of South Alabama

### Disclosures

- Medical Consultant and Speaker Bureau for Novartis Pharmaceuticals, Inc.
- Grant funding from the Children's Oncology Group
- Grant funding from the Alabama Department of Public Health

### Disclosures

- Clinical trial agreement with Selexys Pharmaceuticals Corporation with Quintiles providing clinical research organization services
- I will discuss off label use or investigational uses

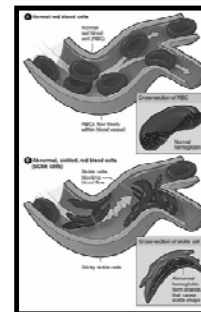
### Sickle Cell Disease

- Sickle cell disease is a genetic blood disorder that affects the hemoglobin protein within the red blood cells that carries oxygen to all parts of the body




### Sickle Cell Disease

- Normal red blood cells are flexible and flow freely within a blood vessel
- They last an average of 120 days in the bloodstream



### Sickle Cell Disease


- Sickle cells are rigid and tend to stick to the blood vessel which blocks blood flow to areas of the body
- They last an average of 19 days in the bloodstream



The diagram illustrates the difference between normal red blood cells and sickle cells. In the top panel, normal red blood cells are shown as smooth, flexible discs that can easily pass through a narrow blood vessel. In the bottom panel, sickle cells are shown as rigid, crescent-shaped cells that get stuck to the vessel walls, blocking the flow of blood.

### Sickle Cell Disease

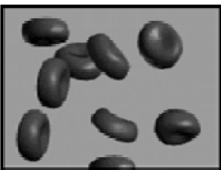
- This abnormality can result in chronic anemia, serious infections, severe painful episodes, strokes, damage to body organs, and early death



The diagram illustrates the difference between normal red blood cells and sickle cells. In the top panel, normal red blood cells are shown as smooth, flexible discs that can easily pass through a narrow blood vessel. In the bottom panel, sickle cells are shown as rigid, crescent-shaped cells that get stuck to the vessel walls, blocking the flow of blood.

### Sickle Cell Disease

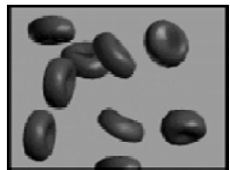
- In the 1970s, SCD was recognized as a major public health concern
- 20% children were dead by age 3



A microscopic image showing several sickle cells, which are characterized by their rigid, crescent-shaped appearance, contrasting with the smooth, round shape of normal red blood cells.

### Sickle Cell Disease

- 50% died before the age of 20 years
- The average lifespan was only 14 years



A microscopic image showing several sickle cells, which are characterized by their rigid, crescent-shaped appearance, contrasting with the smooth, round shape of normal red blood cells.

### Cooperative Study of Sickle Cell Disease

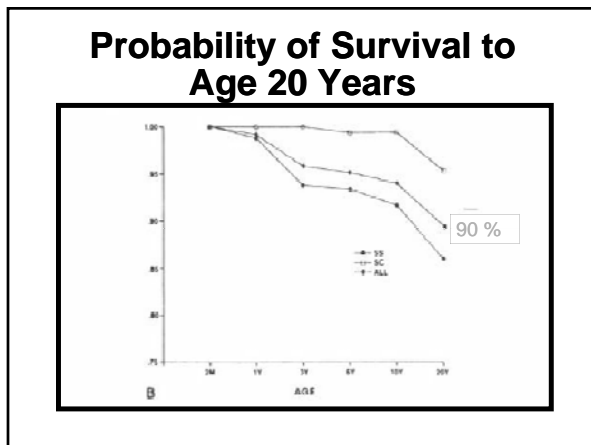
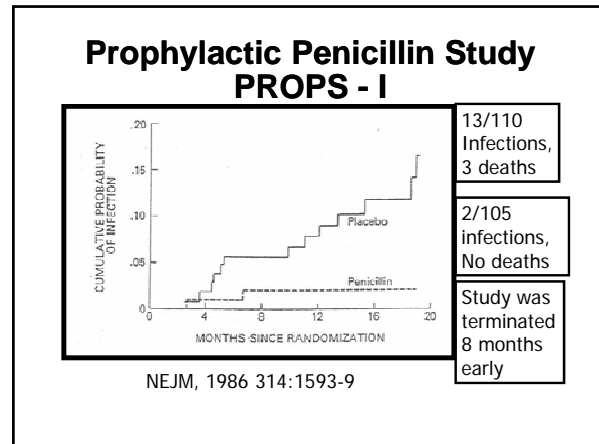
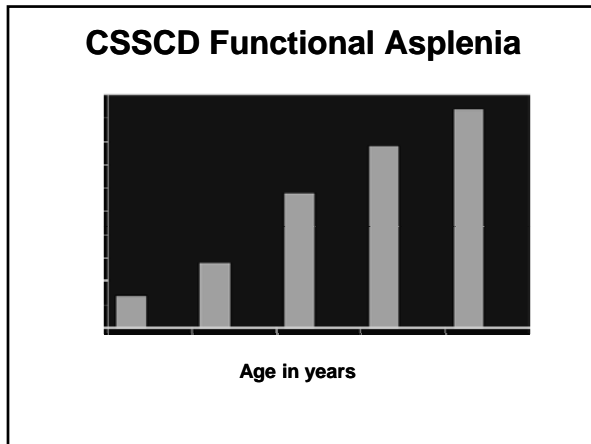
- Initiated in 1978 by the National Institutes of Health to gather data prospectively on the natural history of SCD
- Cohort of 2824 patients registered, followed, and managed (4007 registered)
- 23 clinical centers in the US

### CSSCD Mortality Data

CAUSE	AGE AT TIME OF DEATH		
	< 5 YEARS	5-10 YEARS	10-20 YEARS
INFECTION	61.7	31.7	23.3
CVA	3.6	1.7	23.3
OTHER	10.7	26.7	33.3
UNKNOWN	26.5	40.5	20.3

% OF DEATHS IN AGE GROUP

Infection - major cause of morbidity and mortality  
 S. pneumoniae - most common during early childhood. Enteric organisms emerge as important pathogens in older patients  
 Leinken et al. Pediatrics. 1989;84:500.



- ### Newborn Screening
- This study provided the greatest impetus for widespread implementation of newborn screening for SCD to
    - Provide early dx and referral
    - Ensure prompt delivery of care starting with penicillin prophylaxis
    - Permit education and counseling

### Complications in Sickle Cell Disease

Organ	Complication (%)
Bones	Pain/Infarcts (> 70) AVN (50 – 60)
Spleen	Infarction (90) Sequestration (11) Infection (15)
Lungs	Acute chest syndrome (50) Pulmonary HTN (30)
Liver	Gallstones (42) Sequestration
CNS/Eyes	Strokes (10) Silent CVA (22) Retinopathy (12 – 50)
Renal	Hypostenuria (50) priapism Renal failure (5)

Vaso-occlusive Episodes

- ### Newborn Screening
- Learning about risk can help with
    - Early diagnosis
    - Better treatment
    - Understanding the chances of passing a disease on to future generation
  - Allows opportunity to discuss the availability of therapeutic and potentially curative interventions

### Sickle Cell Trait and Disease

- 3.5 million Americans are genetic carriers of SCD and have SCT



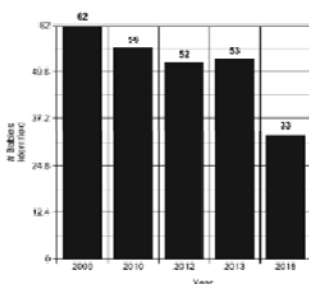
### Sickle Cell Trait and Disease

#### • Incidence of SCD

- 1 in 375 African Americans
- 1 in 1,200 Hispanics
- 1 in 3000 Native Americans
- 1 in 60,000 Whites



### Alabama NBS Statistics for SCD

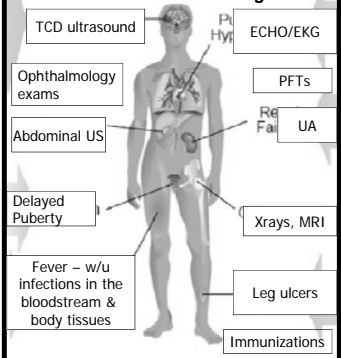


Screening for SCD in Alabama began in 1988

### 2016 Confirmed NBS Primary Disorders

Newborn Screening Primary Disorder	2016 Confirmed
Classical Galactosemia	3
Congenital Adrenal Hyperplasia (CAH)	4
Congenital hypothyroidism	26
Critical Congenital Heart Defect (CCHD)	3
Cystic Fibrosis	16
Hearing Loss	52
Hgb S/Beta Thalassemia	2
High SC Disease	14
High SS Disease	30
Hyperphenylalaninemia (secondary condition)	3
MCAD	2
PKU	2
VLCAAD	3
<b>TOTAL</b>	<b>160</b>

### Health Maintenance Screenings for SCD



### RBC Transfusions Play a Major Role in the Management of SCD Complications


#### Regular, Long-Term (Chronic) Transfusions

- Stroke prevention
- Recurrent acute chest syndrome that is not helped by hydroxyurea\*
- Frequent acute pain\*
- Recurrent splenic sequestration\*
- Leg ulcers\*
- Progressive organ failure (hepatic, renal, cardiac, and pulmonary)\*
- Other indications (eg, priapism, complicated pregnancy)\*

#### Episodic Transfusions\*

- Acute stroke
- Symptomatic anemia
- Acute chest syndrome
- Multiorgan failure
- Preoperative management

A PUBLICATION OF SICKLE CELL DISEASE ASSOCIATION OF AMERICA INCORPORATED




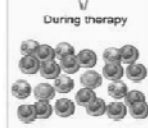




# VIEWPOINTS


HYDROXYUREA: THE FIRST EFFECTIVE TREATMENT FOR SICKLE CELL ANEMIA

Did you read or hear that the National Heart, Lung and Blood Institute (NHLBI) has notified all doctors about a study of a drug treatment for severe cases of sickle cell anemia? This edition of VIEWPOINTS answers some questions you may have about this very important development.

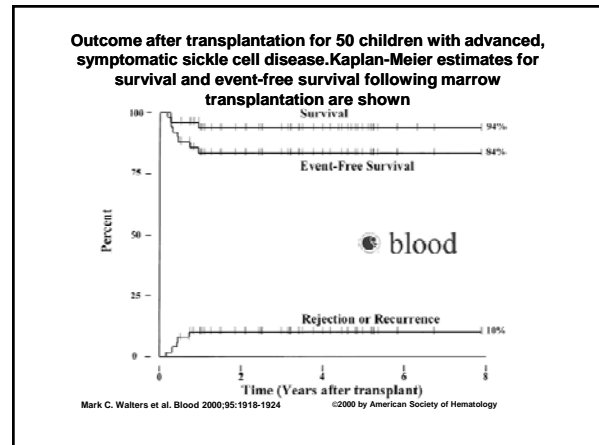
**Multicenter National Trial – 1991**  
**FDA approved 1995 for age 18 years and older**  
**50% reduction in pain crises, ACS and need for transfusion**  
**40% reduction in deaths**

Bone Marrow Before therapy	Blood Before therapy	Vasculature Before therapy
		
↓	↓	↓
<b>During therapy</b>	<b>During therapy</b>	<b>During therapy</b>
		
Reduced cellularity increased proportion of nucleated red cells producing hemoglobin F	Increased hemoglobin F Macrocytosis Increased hydration Fewer sickled cells Fewer reticulocytes Fewer granulocytes	Reduced atherosclerosis Improved endothelial function

## The Cure



**To date, > 1000 Bone Marrow Transplants have been performed around the world for Sickle Cell Disease**



THE NEW ENGLAND JOURNAL OF MEDICINE

BRIEF REPORT

### Gene Therapy in a Patient with Sickle Cell Disease

Jean-Antoine Ribeil, M.D., Ph.D., Salima Hachez-Ray-Abins, Pharm.D., Ph.D., Emmanuel Payer, Ph.D., Alessandra Magrari, M.D., Ph.D., Michaela Semeraro, M.D., Ph.D., Elisa Magrin, Ph.D., Laure Caccavelli, Ph.D., Benedicte Neven, M.D., Ph.D., Philippe Bourget, Pharm.D., Ph.D., Wassim El Nemer, Ph.D., Pablo Bartolucci, M.D., Ph.D., Leslie Weber, M.Sc., Hervé Puy, M.D., Ph.D., Jean-François Menitel, Ph.D., David Grevent, M.D., Yves Beuzard, M.D., Stany Chrétien, Ph.D., Thibaud Lefebvre, M.D., Robert W. Ross, M.D., Olivier Negre, Ph.D., Gabor Veres, Ph.D., Laura Sandler, M.P.H., Sandeep Soni, M.D., Marianne de Montlembert, M.D., Ph.D., Stéphane Blandin, M.D., Philippe Leboulch, M.D., and Marina Cavazzana, M.D., Ph.D.

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**SUMMARY**

**OBJECTIVE:** To assess the safety and efficacy of gene therapy for sickle cell disease in a patient with advanced, symptomatic sickle cell disease.

**DESIGN:** A single-center, open-label, phase 1 trial.

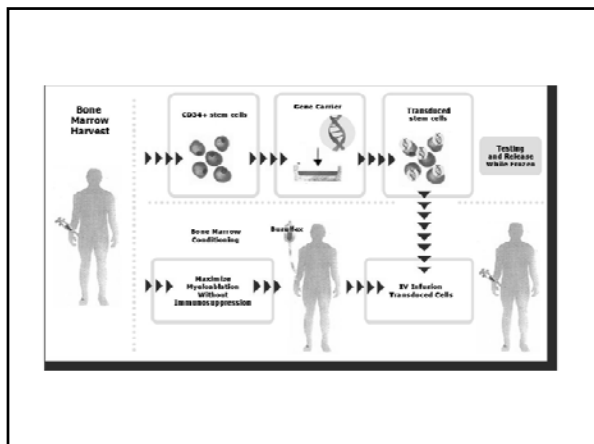
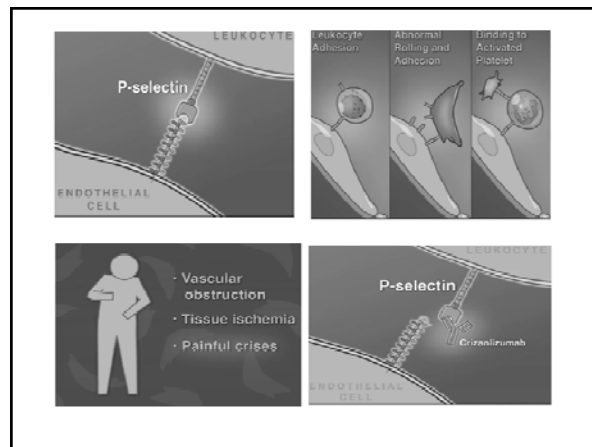
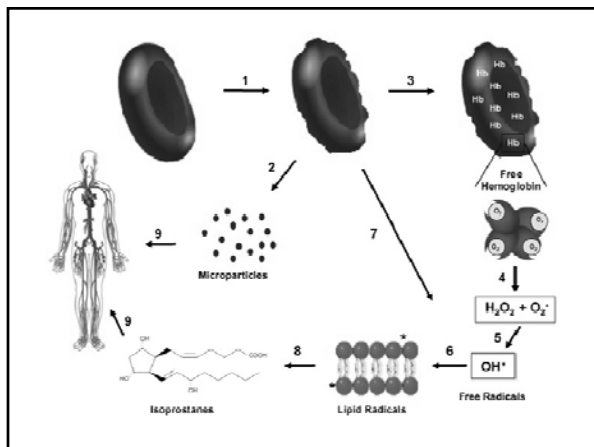
**SETTING:** A tertiary care center.

**PATIENTS:** One patient with advanced, symptomatic sickle cell disease.

**INTERVENTIONS:** Gene therapy using a lentiviral vector to introduce a functional copy of the beta-globin gene.

**MEASUREMENTS AND MAIN RESULTS:** The patient tolerated the procedure well. At 12 months, hemoglobin levels were stable, and there was no evidence of rejection or recurrence.

**CONCLUSIONS:** Gene therapy is a promising approach for the treatment of sickle cell disease.

### The SUSTAIN Study Overview

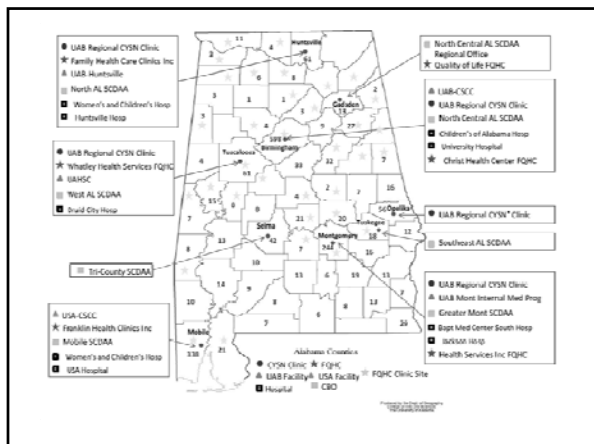
- In this yearlong trial involving patients with sickle cell disease, crizanlizumab, an antibody to P-selectin, was associated with a 45% lower rate of pain crises than placebo and a longer time to their onset

Ataga KI et al. N Engl J Med 2017;376:429-439

### The SUSTAIN Study Overview

- Adverse events included arthralgia, diarrhea, and pruritus

Ataga KI et al. N Engl J Med 2017;376:429-439



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**Alabama Department of Public Health**  
**(334) 206-5618**  
**alphtn@adph.state.al.us**  
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