CDC PUBLIC HEALTH GRAND ROUNDS

Improving the Lives of People with Sickle Cell Disease

November 15, 2016

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Using Data to Understand Gaps in Care and Outcomes

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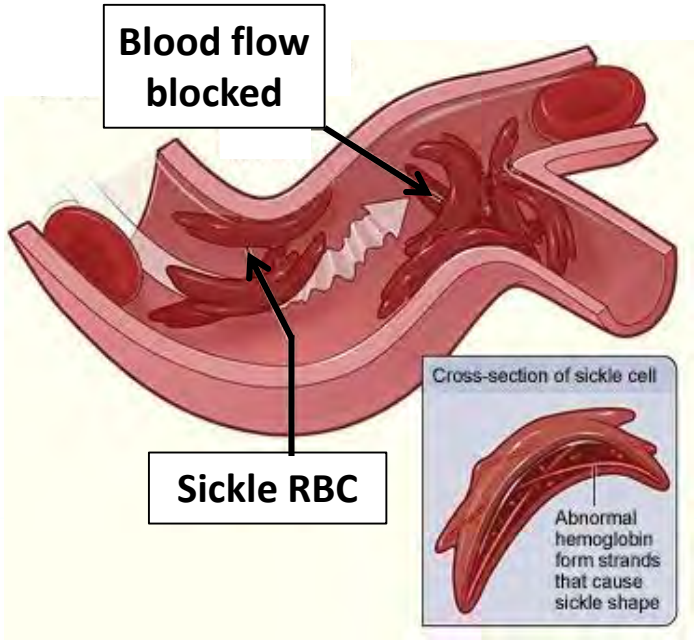
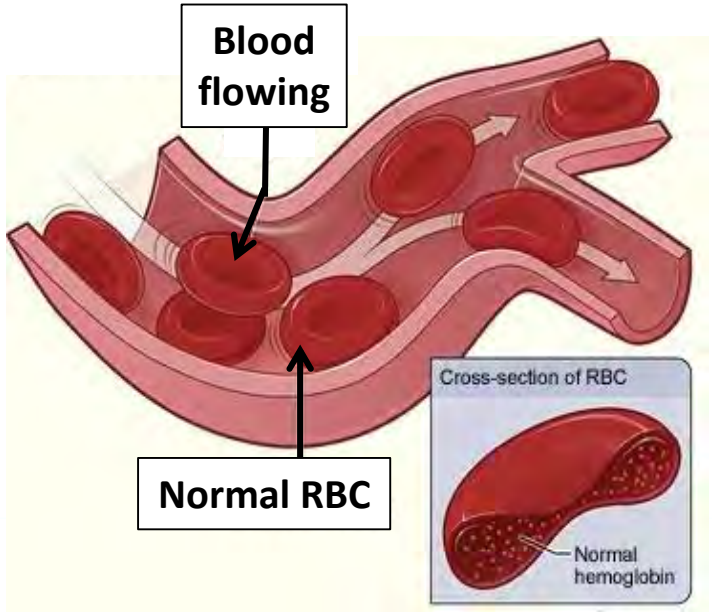
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Different Types of Hemoglobin Cause Sickle Cell Disease

- **Different types of hemoglobin (i.e., hemoglobin variants) affect how red blood cells (RBC) function**
  - The type of hemoglobin inherited through our genes determines whether a person has sickle cell disease and the type of sickle cell disease



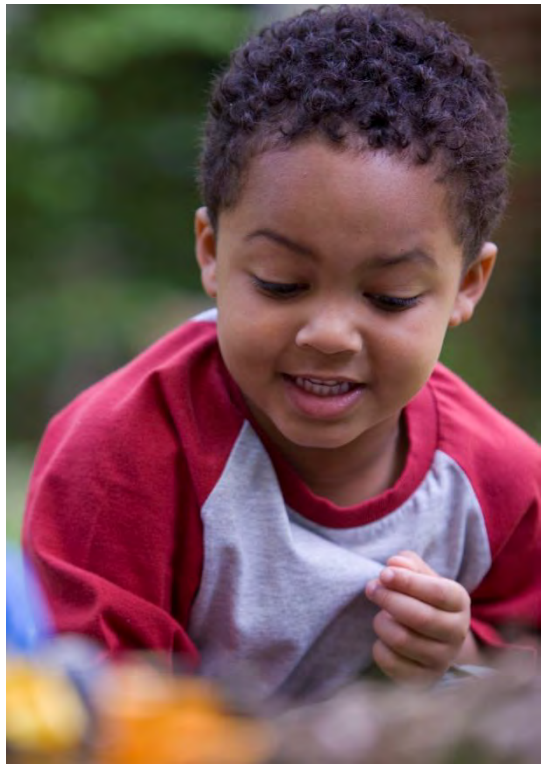
Sickle hemoglobin (HbS) causes the red blood cells to stick inside narrow blood vessels, thus blocking blood flow and oxygen supply



Normal hemoglobin (HbA) allows the red blood cells to flex and flow through narrow blood vessels without getting stuck

www.nhlbi.nih.gov/health/health-topics/topics/sca

Types of Hemoglobin and Sickle Cell Disease, Sickle Cell Anemia and Sickle Cell Trait



- **"Sickle cell disease" has different combinations of hemoglobin variants**
  - Hemoglobin S/S or "sickle cell anemia"
  - Hemoglobin S/β^0 thalassemia
  - Hemoglobin S/C
  - Hemoglobin S/β^+ thalassemia
- **"Sickle cell trait" is when one sickle gene is present**
  - Individuals with trait typically do not have any symptoms
  - Two parents with trait may have a child with sickle cell disease
  - Genetic counseling, including awareness of trait status, is important

Sickle Cell Disease (SCD) Throughout The World

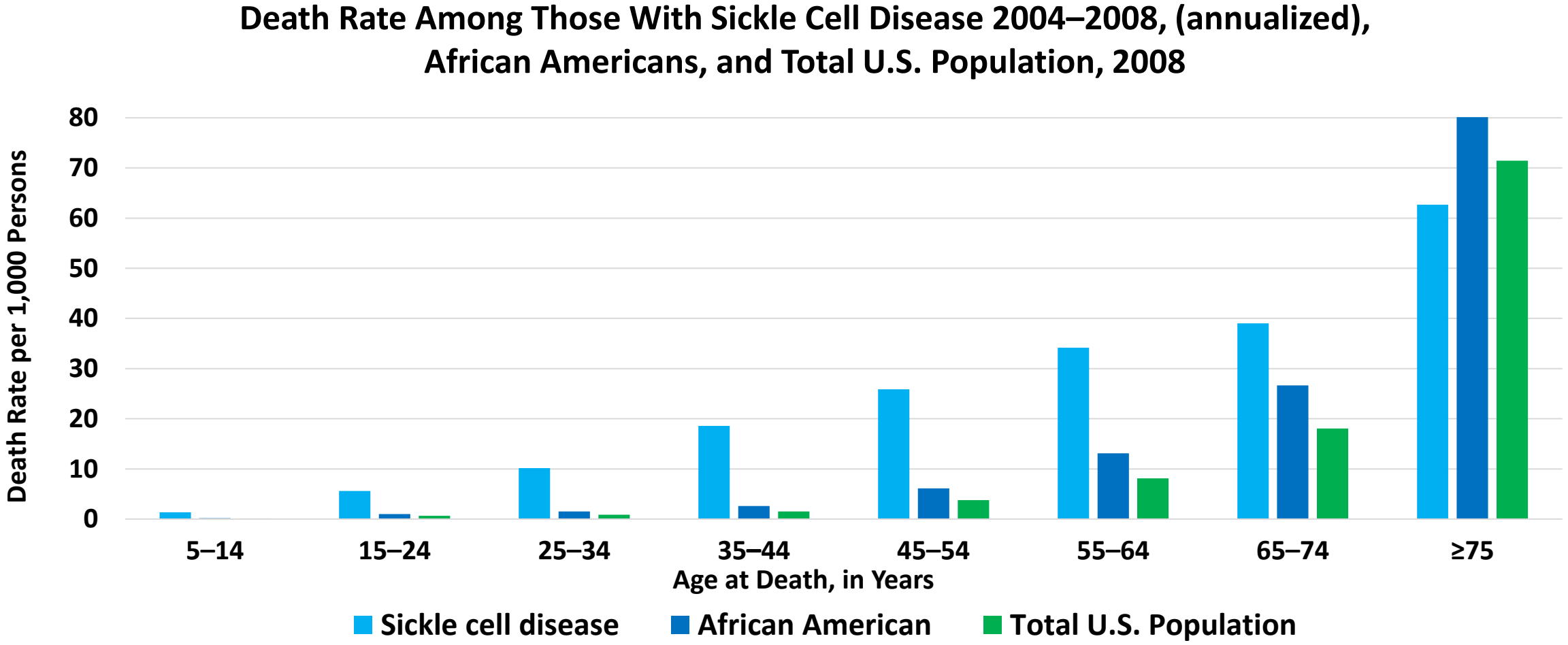
- **Worldwide about 300,000 annual births**
  - 79% infants born with sickle cell occur in sub-Saharan Africa
- **Mortality is associated with access to prevention and health care**
  - In the U.S., over 95% of children with SCD live past the age of 18
  - In low-income and middle-income countries, about 90% of children die before the age of 5
- **Access to public health infrastructure, universal screening programs, and specific medical interventions could lower global mortality**

Piel FB, Hay SI, Gupta S, et al. *PLoS Med*. 2013;10(7)

What Are Symptoms and Outcomes of Sickle Cell Disease?

- **When blood flow is blocked, sudden and severe pain arises**
  - Episodes are called “sickle cell crises” or “pain crises”
- **Sickle cell crises can be life threatening**
  - In the brain, can cause strokes
  - In the lungs, can cause acute chest syndrome
- **Sickle cell disease can cause chronic organ damage**
  - In the spleen, impairs immune function
  - In the bones, can result in avascular necrosis
  - In the kidneys, can result in chronic renal failure
- **Severity and lifelong impact of sickle cell disease is difficult to predict**

Increased Premature Mortality Related to Sickle Cell Disease

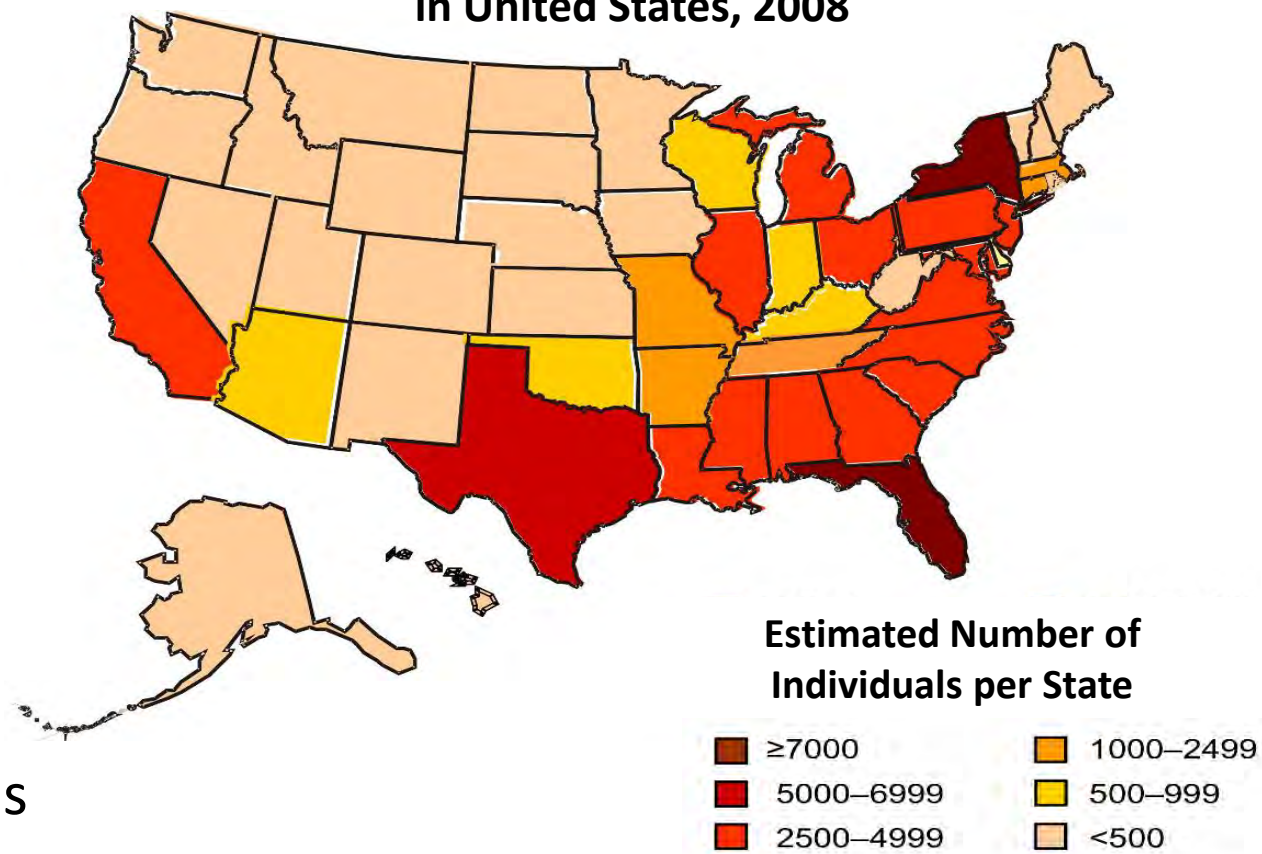


Paulukonis ST, Eckman JR, Snyder AB, et al. *Public Health Rep*. 2016 Mar-Apr;131(2):367-75

Understanding Who Has Sickle Cell Disease (SCD) Is Important To Improving Outcomes

- **Sickle cell disease can be life-threatening even at young ages**
- **Newborn screening for SCD in all 50 states**
  - 1,500–2,000 babies are identified each year
- **Approximately 100,000 Americans are affected**
  - No national registries to understand how to improve outcomes

Distribution of Individuals with SCD in United States, 2008



Hassell, KL. *Am J Prev Med*. 2010 Apr;38(4 Suppl):S512-21

Understanding Sickle Cell Disease Through Surveillance

Registry and Surveillance System for Hemoglobinopathies (RuSH), 2010–2012

Research, Epidemiology and Surveillance Continued through PHRESH

- **Public Health Research, Epidemiology, and Surveillance for Hemoglobinopathies (PHRESH) project was launched as next step**
  - Designed to evaluate and validate RuSH methods
  - Conducted from 2012–2014
- **Disseminate findings from RuSH**
  - Families, healthcare providers, policymakers
- **Sites included California, Georgia and Mississippi**

PHRESH
PUBLIC HEALTH RESEARCH • EPIDEMIOLOGY • SURVEILLANCE
FOR HEMOGLOBINOPATHIES

RuSH: Registry and Surveillance System for Hemoglobinopathies

Moving Forward: Sickle Cell Data Collection (SCDC) Program

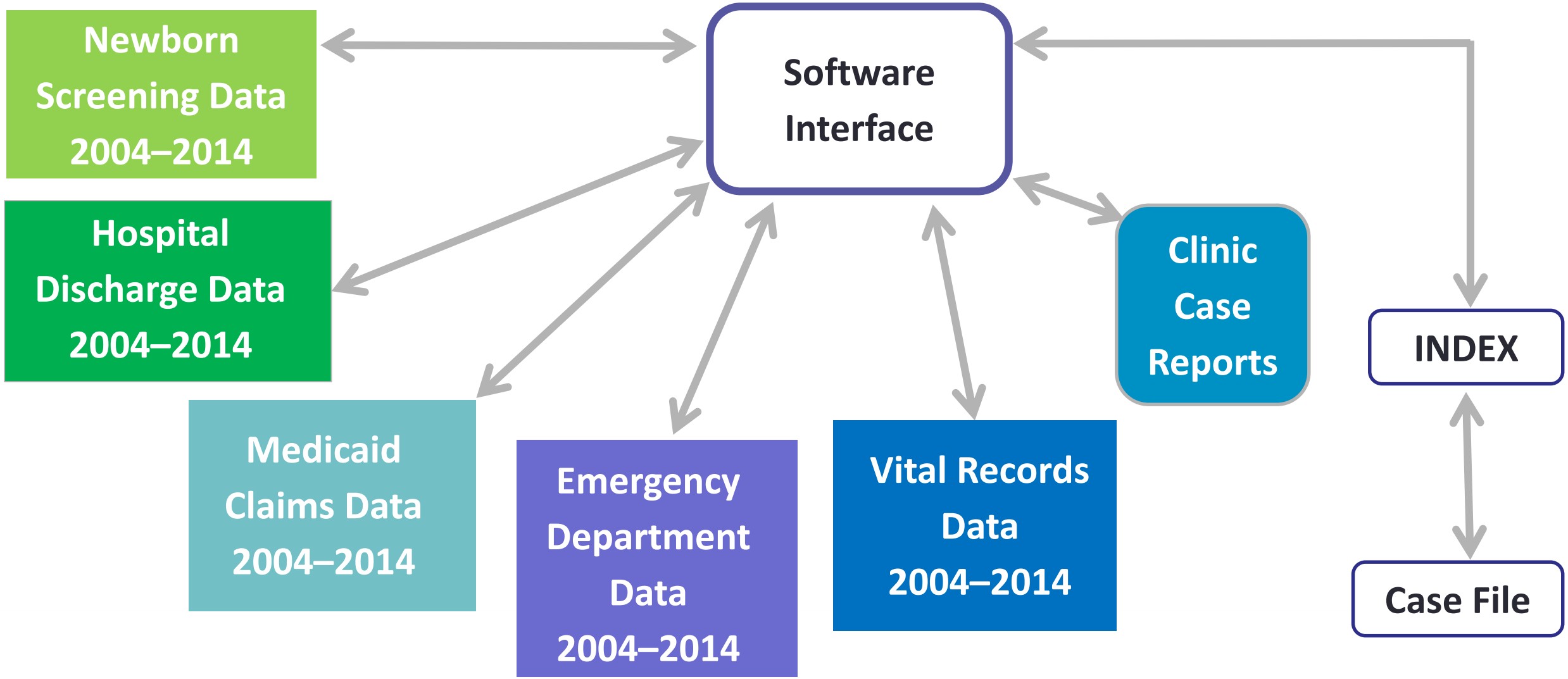
- **Collect, synthesize and disseminate multi-source, population-based, longitudinal data for people with sickle cell disease (SCD)**
  1. Establish a health profile of the SCD population
  2. Track changes in SCD outcomes over time
  3. Ensure credible, scientifically sound information to inform standards of care
  4. Inform policy and health care practices
- **Improve quality of life, life expectancy, and health among those living with SCD**

SCDC

Sickle Cell Data Collection

www.cdc.gov/ncbddd/hemoglobinopathies/scdc.html

SCDC Data Will Include Up to 10% of the U.S. SCD Population



SCDC Next Steps

- **Disseminate findings**
  - Peer-reviewed publications, scientific presentations, social media, policy briefs
- **Include additional states**
  - Establish training institute to help other states develop population-based surveillance system for sickle cell disease
- **Secure additional sustained support and funding**

Thank You to SCDC Partners, Families, and Participants

CALIFORNIA RARE DISEASE SURVEILLANCE PROGRAM

Georgia Health Policy Center

Biogen

gbt

CDC FOUNDATION
Helping CDC Do More, Faster

Pfizer

The Sickle Cell Community and Pediatric Care for SCD

Kim Smith-Whitley, MD

Chief Medical Officer (Immediate Past)

Sickle Cell Disease Association of America, Inc.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

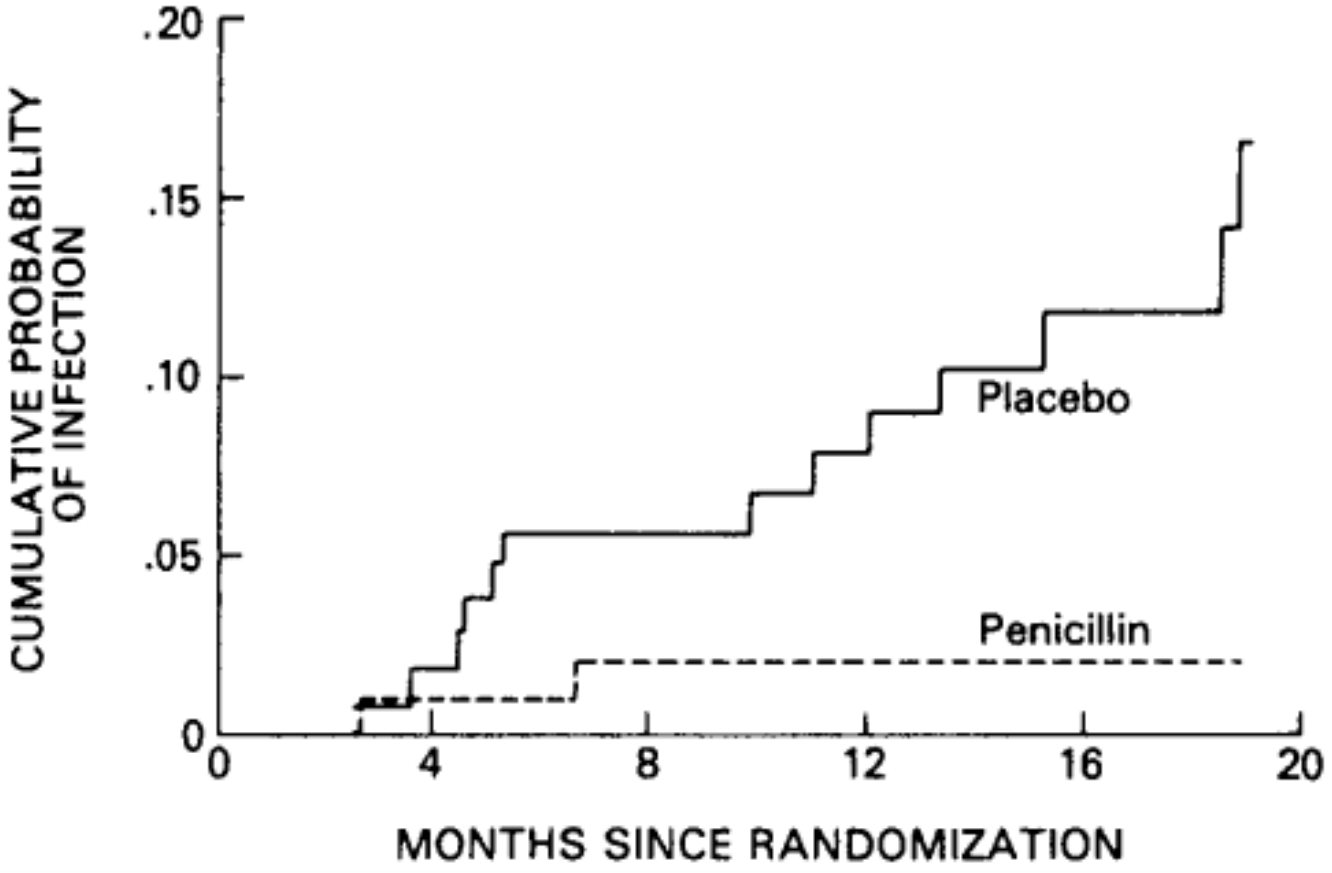
Historical Perspective

- Sickle cell disease is an inherited hemoglobinopathy
- Characterized by hemolysis, vascular occlusion
- Unpredictable clinical complications such as acute pain, life-threatening infection, stroke and acute chest syndrome (i.e., pneumonia-like illness)
- In 1971, Sickle Cell Disease Association of America formed
- In 1972, the National Sickle Cell Anemia Control Act passed

Helped found the Sickle Cell Disease Association of America

Dramatic Improvement for Children Given Oral Penicillin Prophylaxis to Prevent Pneumococcal Infection

Cumulative Infection Rates for All Patients in the Prophylactic Penicillin Study



Study recommended penicillin prophylaxis start at age 4 months

Gaston MH, Verter JI, Woods G, et al. *N Engl J Med*. 1986 Jun 19;314(25):1593-9

Penicillin Prophylaxis Breakthrough Lent Urgency to Newborn Screening

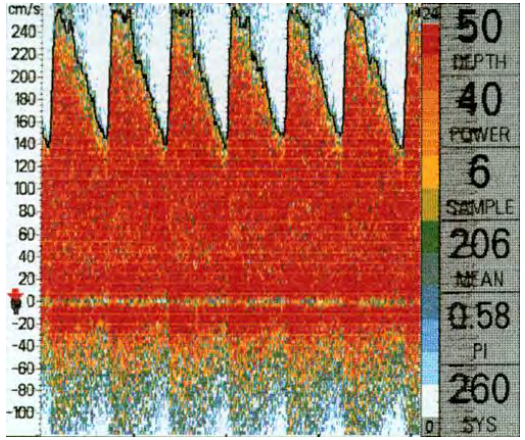
- **Infection prophylaxis meant infants with SCD needed to be identified early**
- **Newborn screening**
  - Universal screening recommended by NIH in 1987
  - State-by-state adoption of screening
  - By 2006, all states screening at birth
- **Specialized vaccine programs**
  - Pneumococcal vaccines developed

Benson JM, Therrell BL Jr. *Semin Perinatol*. 2010 Apr;34(2):134-44
Consensus Development Conference Statement, Sep 29-Oct 1 1986

Who Is At Risk for Stroke?

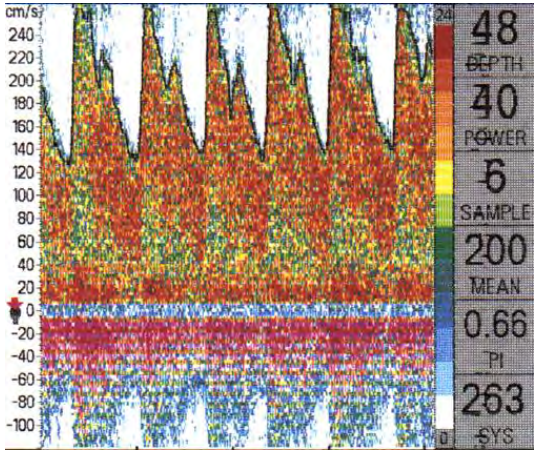
Transcranial Doppler Ultrasonography (TCD) in 3 Siblings with SCD-SS

RMCA



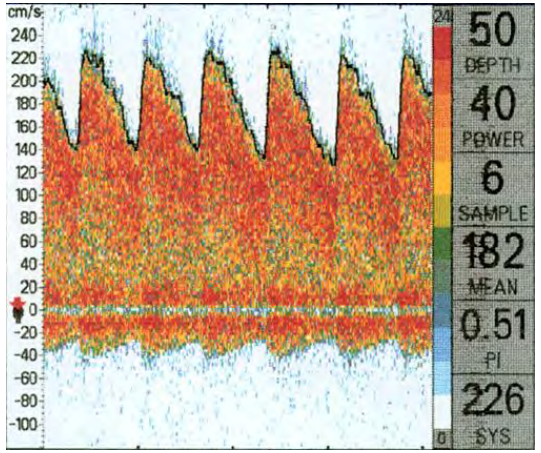
8 year-old Female

LMCA



9 year-old Male

RMCA



6 year-old Male

RMCA: Right middle cerebral artery

LMCA: Left middle cerebral artery

Adams R, McKie V, Nichols F, et al. *N Engl J Med*. 1992 Feb 7;326(9):605-10

Transfusion Therapy for Primary Stroke Prevention in SCD STOP Trial

- **Background**
  - Chronic red blood cell transfusions reduce recurrent stroke rate in children with SCD
  - Transcranial Doppler ultrasonography (TCD) detects children at risk for stroke
- **Hypothesis: Could children who have increased risk of stroke be helped by transfusions before a stroke occurs?**

Adams RJ, McKie VC, Hsu L, et al. *N Engl J Med*. 1998 Jul 2;339(1):5-11

Transfusion Therapy Reduces Risk of Primary and Secondary Stroke in Sickle Cell Disease

- 92% reduction in stroke risk, ($P < 0.001$)
- Chronic transfusion therapy greatly reduces the risk of first stroke in children with SCD-SS who have repeatedly abnormal transcranial Doppler ultrasonography results

Adams RJ, McKie VC, Hsu L, et al. *N Engl J Med*. 1998 Jul 2;339(1):5-11

Hydroxyurea Therapy Proven

Painful crises occurred later in patients receiving hydroxyurea than in those receiving placebo, and the effect was evident in less than six months

The New England
Journal of Medicine

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Volume 332 MAY 18, 1995 Number 20

EFFECT OF HYDROXYUREA ON THE FREQUENCY OF PAINFUL CRISES IN SICKLE CELL ANEMIA

SAMUEL CHARACHE, M.D., MICHAEL L. TERRIN, M.D., RICHARD D. MOORE, M.D., GEORGE J. DOVER, M.D., FRANCA B. BARTON, M.S., SUSAN V. ECKERT, ROBERT P. MCMAHON, PH.D., DUANE R. BONDS, M.D., AND THE INVESTIGATORS OF THE MULTICENTER STUDY OF HYDROXYUREA IN SICKLE CELL ANEMIA*

Hydroxyurea Works for SCD-SS

Adverse Event	Hydroxyurea		Placebo	
	Events Pt. Years=100	Subjects N=52	Events Pt. Years=96	Subjects N=49
Pain Alone	31	17	46	24
Dactylitis	6	4	35	14
Acute Chest	3	3	10	7
Hospitalization	80	31	149	43
Transfusion	11	6	27	14
Splenic Sequestration	3	2	10	7
Sepsis	0	0	3	3

Thornburg CD, Files BA, Luo Z, et al. *Blood*. 2012 Nov 22;120(22):4304-10
Hydroxyurea is not FDA approved for use in children

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Thornburg CD, Files BA, Luo Z, et al. *Blood*. 2012 Nov 22;120(22):4304-10
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Bone Marrow Transplantation Cures Sickle Cell Disease

The New England
Journal of Medicine

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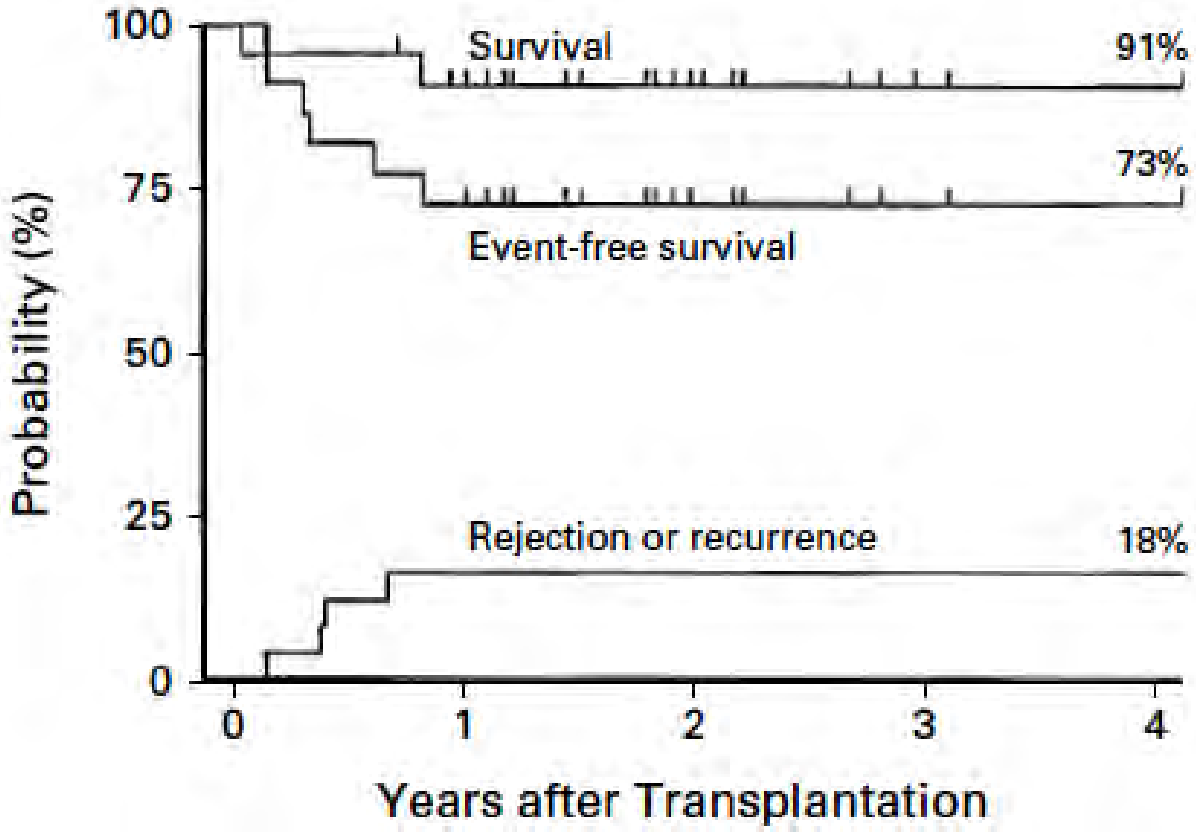
VOLUME 335 AUGUST 8, 1996 NUMBER 6

BONE MARROW TRANSPLANTATION FOR SICKLE CELL DISEASE

MARK C. WALTERS, M.D., MELINDA PATIENCE, R.N., M.S.N., WENDY LEISENRING, PH.D., JAMES R. ECKMAN, M.D., J. PAUL SCOTT, M.D., WILLIAM C. MENTZER, M.D., SALLY C. DAVIES, M.D., KWAKU OHENE-FREMPONG, M.D., FRANÇOISE BERNAUDIN, M.D., DANA C. MATTHEWS, M.D., RAINER STORB, M.D., AND KEITH M. SULLIVAN, M.D.

Transplantation Can Cure Sickle Cell Disease

Kaplan–Meier Estimates of Survival and Event-free Survival after Bone Marrow Transplantation in 22 Patients with Sickle Cell Disease



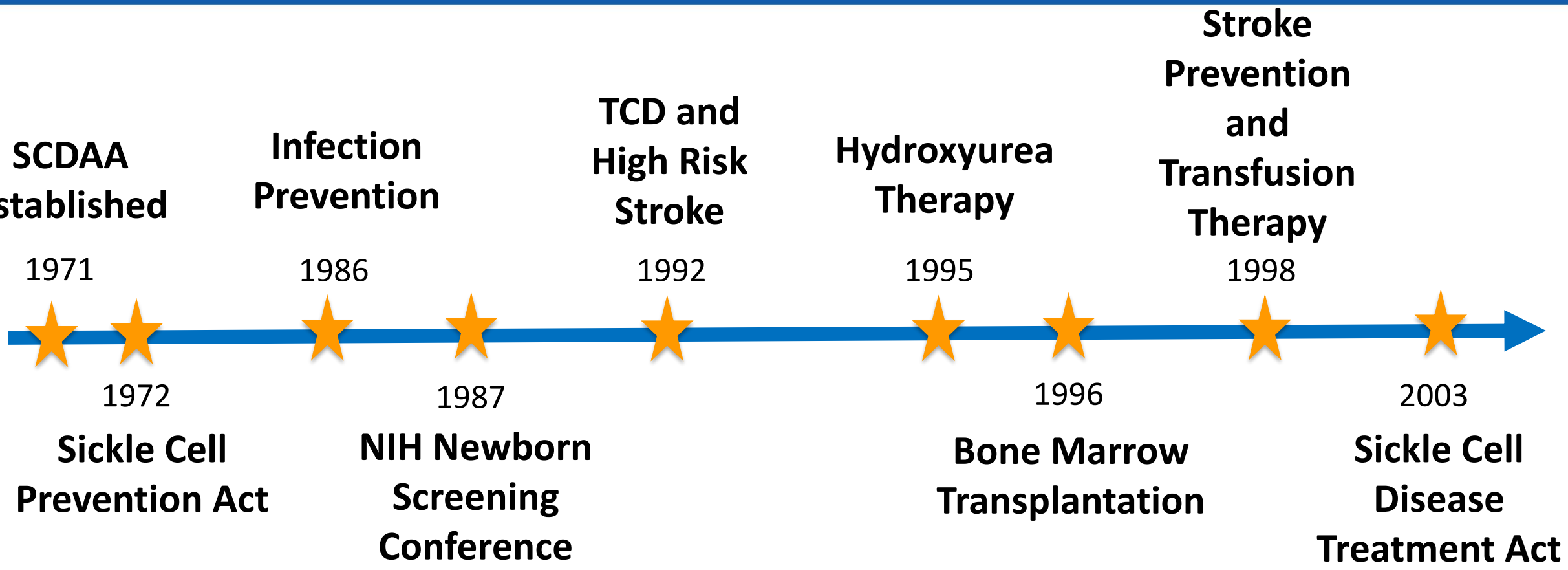
As of 2016, over 1,000 individuals have received transplants

Walters MC, Patience M, Leisenring W, et al. *N Engl J Med*. 1996 Aug 8;335(6):369-76

Approach to Pediatric Treatment

- **Prevent complications before they occur**
  - Penicillin prophylaxis
  - Transcranial Doppler
- **Prevent recurrence of complication**
  - Hydroxyurea therapy
  - Chronic transfusion therapy
  - Bone marrow transplantation

Sickle Cell Disease: Milestones



Sickle Cell Disease Association of America: Common Agenda and Goals

- **Increased access to high-quality health care across the lifespan**
- **Drug development, therapies and programs**
  - Improve quality of life
  - Decrease disease-related complications
- **Research towards a cure accessible for all people with sickle cell disease**

SCDAA's Get Connected
Sickle Cell Disease Registry Initiative

- **Establish a network to distribute information related to clinical care, research, health services, health policy, and advocacy**
  - Children, adults, and families living with sickle cell disease and sickle cell trait
  - SCDAA member organizations, and other community-based organizations
  - Health care providers and other stakeholders
- **Establish a mechanism to support care coordination**
- **Develop online communities for information sharing and psychosocial support**

Get Connected: Activities and Early Results

- **Identify, educate, and train community health workers**
  - 35 community health workers trained
- **Connect children and adults to services if not connected**
- **Enroll children and adults with sickle cell disease in Get Connected**
  - 3,152 children and adults enrolled in 15 states

Funding Opportunity Announcement: HRSA-11-031
www.scdfc.org/what-is-get-connected.html

Sickle Cell Disease: Challenges and Opportunities

- **Advances in pediatrics, but few across the lifespan**
  - Lack of data decreases ability to identify health care and policies to best support those with sickle cell disease
- **Get Connected and Sickle Cell Data Collection project will identify, inform, and fill gaps**
- **Limited access to healthcare professionals with expertise in sickle cell disease**
  - Not just for children but for transition and adult care
  - High mortality rate in young adult group

Working towards healthier lives for children and adults with sickle cell

SCDAA SCDNBS Program CBOs

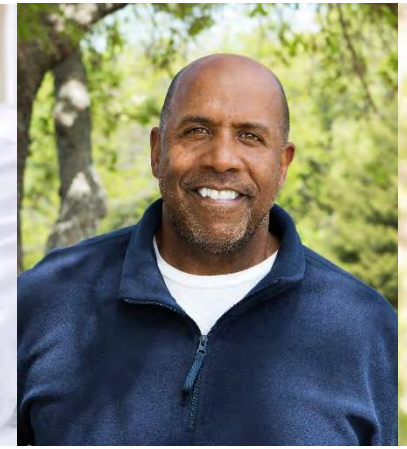
National Institute for Healthcare Quality
Dr. Suzette Oyeku
Dr. Scott Berns

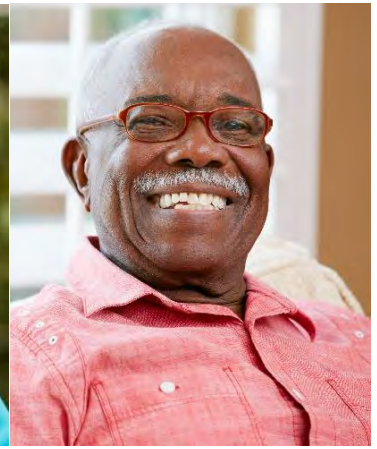
HRSA
Dr. Donnell Ivy
Andrea Williams

American College of Medical Genetics
Dr. Amy Brower

National SCDAA HRSA Project
Sonja L Banks
Sonya Ross
Meghan Ringgold
Leroy Hughes, Jr.

Improving Outcomes for Adults with Sickle Cell Disease





Kathryn Hassell, MD

Professor of Medicine, Division of Hematology

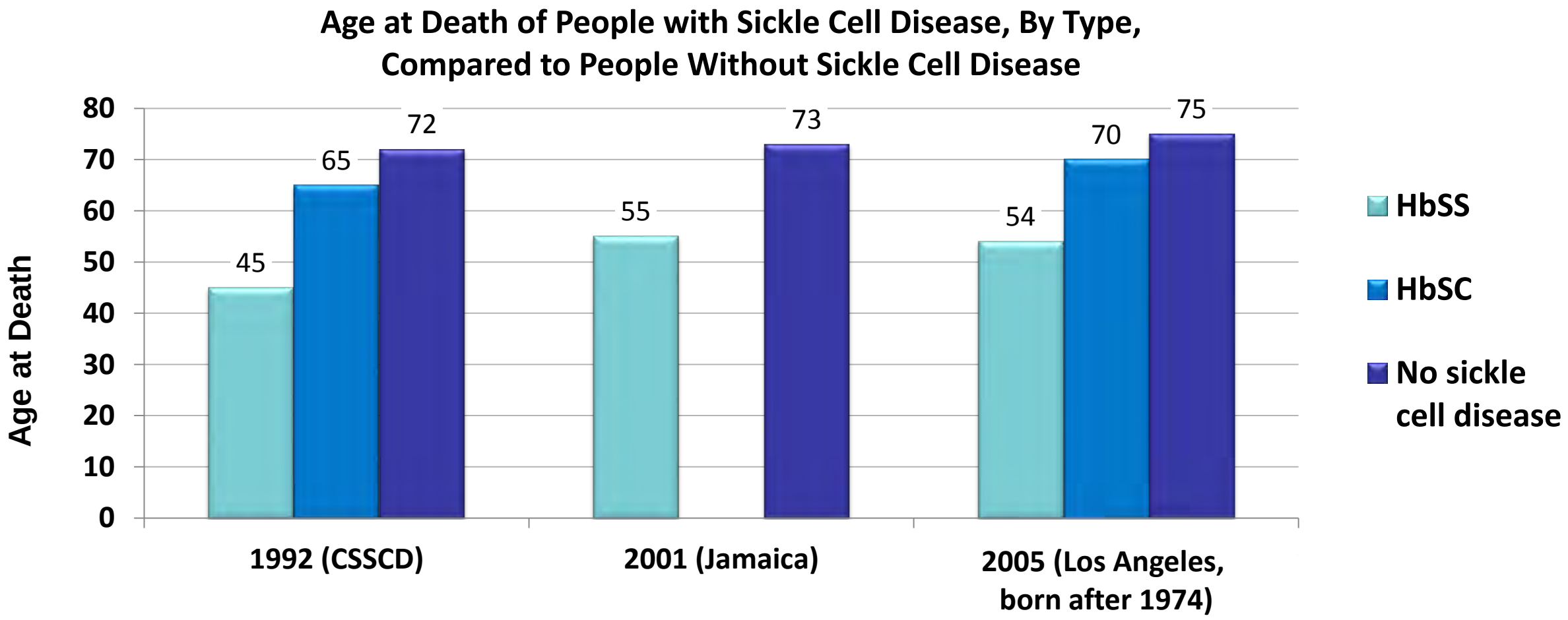
University of Colorado Denver

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Important Aspects of Adult Sickle Cell Disease

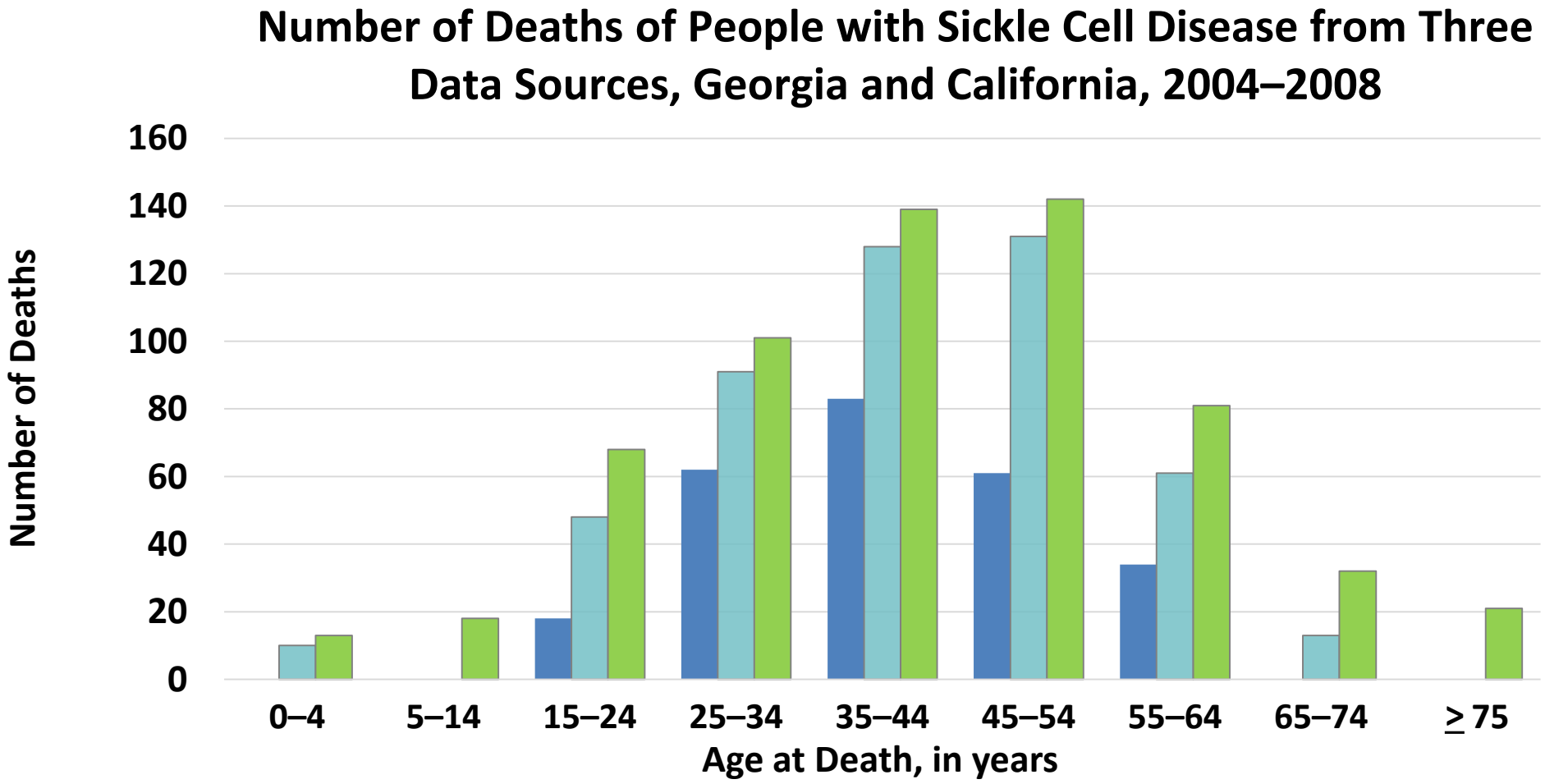
- Premature death and mortality
- Burden of chronic organ damage
- Health care access and utilization

Premature Death in Sickle Cell Disease



Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. *Blood*. 2010 Apr
Platt OS, Brambilla DJ, Rosse WF, et al. *N Engl J Med*. 1994 Jun
Charache S, Terrin ML, Moore RD, et al. *N Engl J Med*. 1995 May
Steinberg MH, Barton F, Castro O, et al. *JAMA*. 2003 Apr
Wierenga KJ, Hambleton IR, Lewis NA. *Lancet*. 2001 Mar

Surveillance Identifies Previously Missed Individuals



Mean age at death: 42.2 years

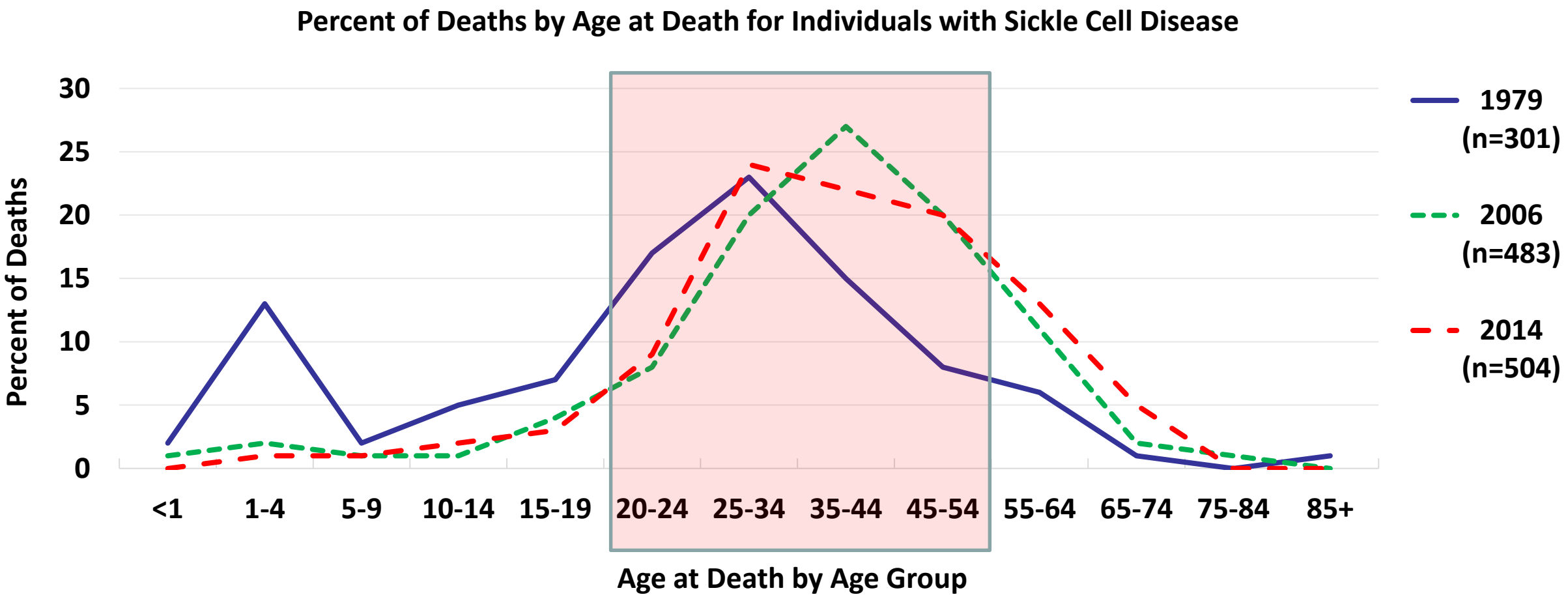
- NCHS Compressed Mortality Data
- MCOD Mortality Data
- Population Based Surveillance

NCHS: National Center for Health Statistics

MCOD: Multiple causes of death

Paulukonis ST, Eckman JR, Snyder AB, et al. *Public Health Rep*. 2016 Mar-Apr;131(2):367-75

Surveillance Can Assess Impact of Childhood Interventions



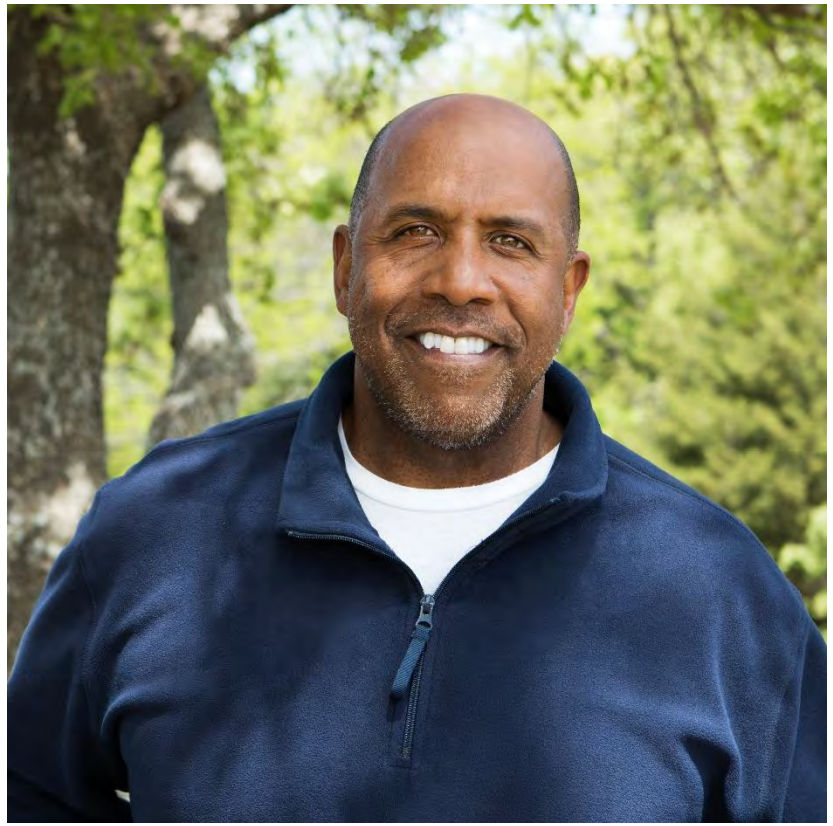
Update of Hassell, *Am J Prev Med*, 2010 on May 2016 http://wonder.cdc.gov

Limitations of the Sickle Cell Data Collection (SCDC) System

- **Whole population data can provide important information, but results must be interpreted with caution**
- **SCDC does not distinguish type of sickle cell disease for each person**
  - Type of hemoglobin can affect course of sickle cell disease
- **Significant differences in premature death related to type of sickle cell disease**
  - Overestimates lifespan in more severe types
  - Underestimates lifespan in milder types

Limitations of the Sickle Cell Data Collection (SCDC) System

- **Not all interventions are applied to all forms of sickle cell disease**
  - Hydroxyurea is of proven benefit in HbSS and HbSβ^{o}thalassemia
  - 40% of people have other types of sickle cell disease and thus would not be given this intervention
- **May miss important gains in care and outcomes made within a given subset**



Adult SCD: Chronic Organ Damage

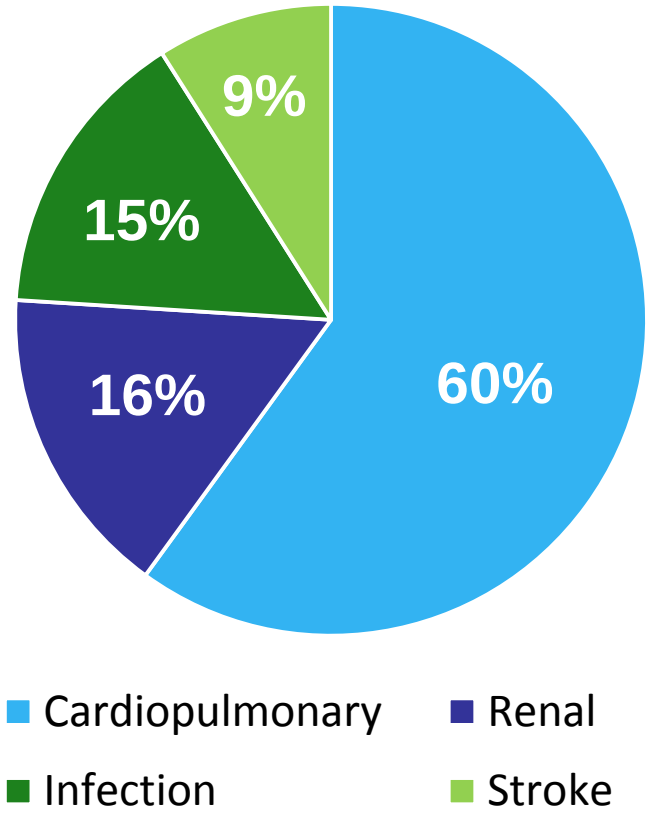
- **Autopsy Study (1929–1996)**
  - Evidence of chronic organ injury in 74% of 306 cases
  - Chronic organ damage second most common cause of death after infection, in >18 year-olds
- **Cohort Study, N=1,056 patients with 40-year follow-up**
  - 73% with chronic organ damage

Evidence of Injury at Autopsy		
Chronic Injury	**Chronic lung disease**	**56%**
	Chronic renal failure/atrophy	**38%**
	Stroke	**18%**
Secondary Organ Damage	**Liver failure/hepatitis**	**10%**
	Cardiomegaly	**58%**
	Congestive Heart Failure	**10%**

Manci EA, Culberson DE, Yang YM, et al. *Br J Haematol*. 2003 Oct;123(2):359-65
Powars DR, Chan LS, Hiti A, et al. *Medicine (Baltimore)*. 2005 Nov;84(6):363-76

Chronic Organ Damage Likely Now Leading Cause of Death

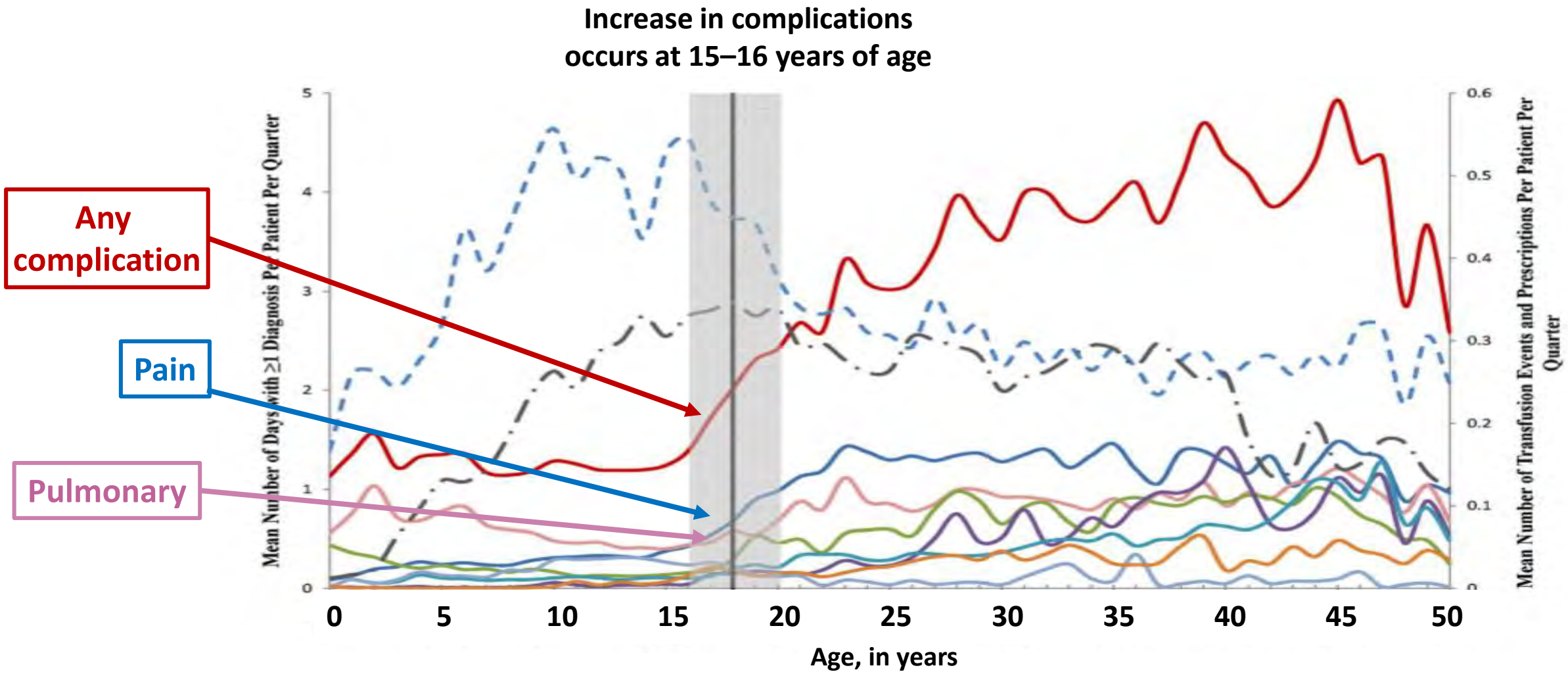
Most Common Causes of Death by System Among People with SCD, 1999–2009



- **CDC multiple causes death certificate data, 1999–2009**
- **Only 20% died during acute crisis**
- **Common premorbid conditions are often seen in sickle cell disease (SCD)**
  - Congestive heart failure
  - Hypertension
  - Pneumonia/Acute chest syndrome

Adapted from Hamideh D and Alvarez O. *Pediatr Blood Cancer.* 2013 Sep;60(9):1482-6

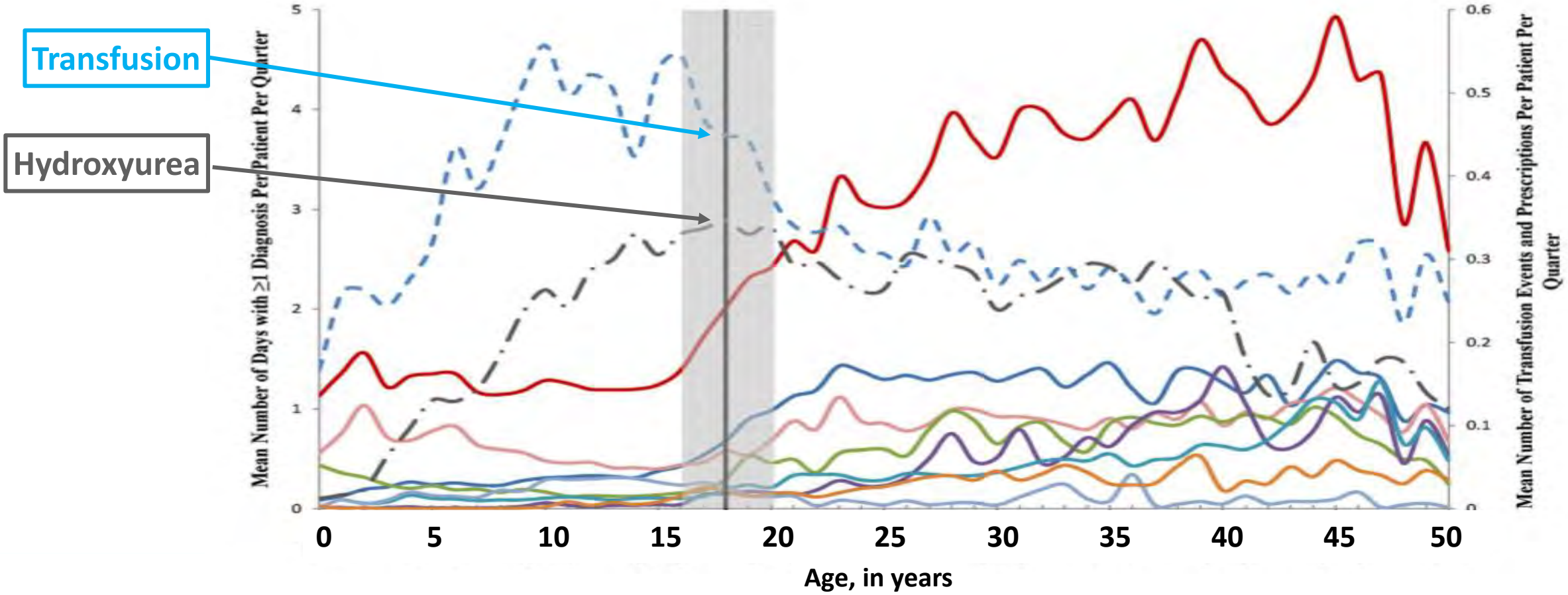
Population Surveillance Reveals Course of Disease



Blinder MA, Vekeman F, Sasane M, et al. *Pediatr Blood Cancer*. 2013 May;60(5):828-35

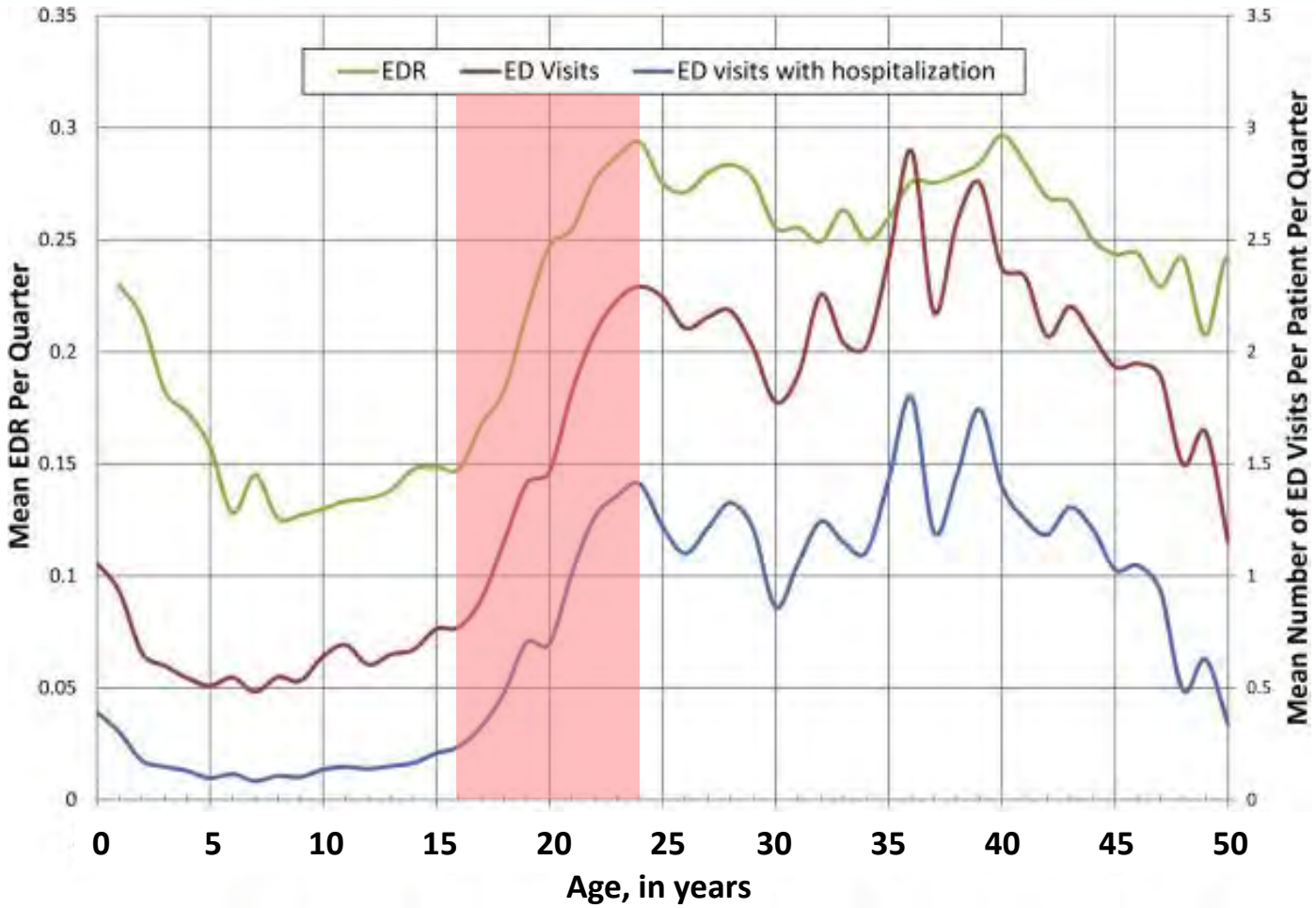
Population Surveillance Reveals Use of Interventions

Decrease in use of interventions occurs at 15–16 years of age



Blinder MA, Vekeman F, Sasane M, et al. *Pediatr Blood Cancer*. 2013 May;60(5):828-35

Increased Use of the Emergency Department Begins in Adolescence



EDR: Emergency department reliance = total emergency department visits/total ambulatory [outpatient + ED] visits

Blinder MA, Duh MS, Sasane M, et al. *J Emerg Med*. 2015 Oct;49(4):513-522

Sickle Cell Data Collection (SCDC): Clarifying the Course of Disease

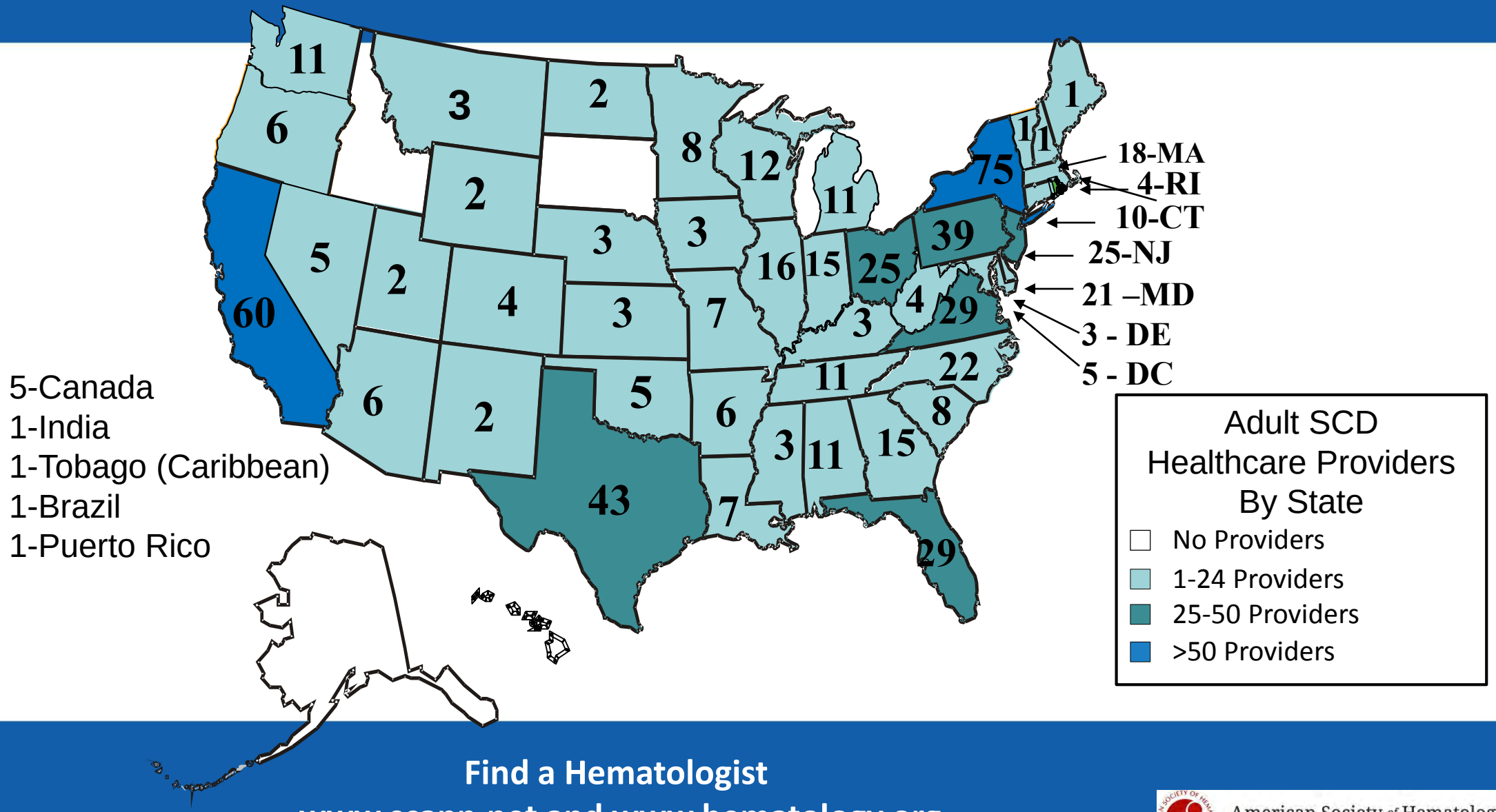
- **Longitudinal tracking**
  - Onset and progression of complications
  - Use and impact of complication-specific and overall disease-modifying therapy
- **Limitation: SCDC does not distinguish type of sickle cell disease**
  - Rate and severity of complications varies between types of sickle cell disease
  - Some disease-modifying therapies (e.g., hydroxyurea) are used only for some types of sickle cell disease (HbSS and HbSβ^{o}thalassemia)

Adult Healthcare Access and Utilization

- **Oft-stated assumption is that all children with sickle cell disease receive comprehensive sickle cell care from sickle cell providers**
  - Maryland Medicaid data: 38% of children had not seen a hematologist by age 2
- **Adult health care is often characterized as nonexistent, inaccessible, or rendered by providers without knowledge or interest**
  - Mostly based on anecdote, not data
  - Increase in complications, ED utilization, mortality in early adulthood said to be evidence for this, but data suggest change actually occurs in adolescence

Bundy DG, Muschelli J, Clemens GD, et al. *Pediatr Blood Cancer*. 2012 Nov;59(5):888-94

Quality Adult Sickle Cell Health Care Exists



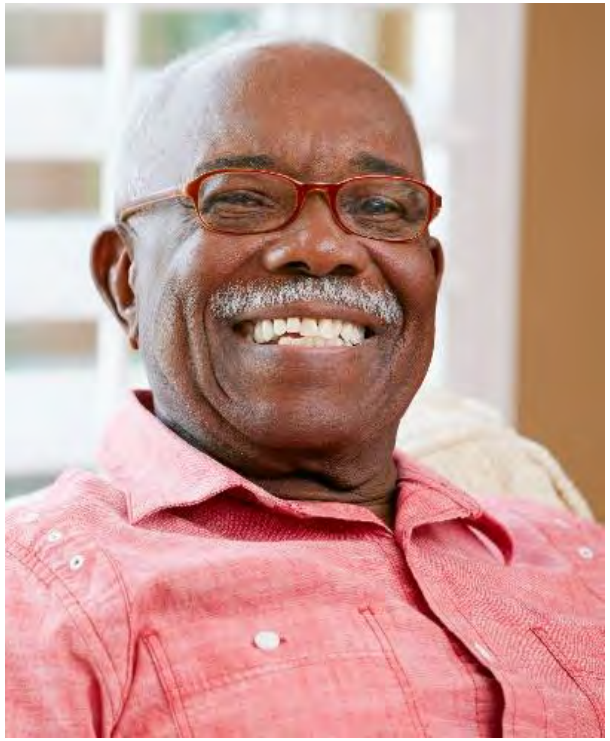
Find a Hematologist

www.scapn.net and www.hematology.org

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Insurance Is Not the Same as Access

- **Few adults with sickle cell disease are truly uninsured (<5%), but:**
  - May not cover necessary services
  - Limited or no access to expert providers
  - High-deductible plans may preclude use
- **Intermittent loss of coverage**
  - Loss of employment – lose employer-based plans
  - Gain of employment – no longer eligible for Medicaid, Medicare, or disability coverage



hcupnet.ahrq.gov/HCUPnet.jsp, National Inpatient Sample report, run 21 May 2016

Role of Self-Determination

- **Evaluation in adult sickle cell program, 1993–2009**
  - 22 patients with history of overt stroke on chronic transfusion
  - Mean age at transition (transfer): 22 years old
  - Mortality: 36% (8/22) within 5 years
    - All who died actively refused transfusion or stopped coming

TRANSFUSION PRACTICE

CME/SAM

High mortality among children with sickle cell anemia and overt stroke who discontinue blood transfusion after transition to an adult program

Joseph F. McLaughlin,[1,2] and Samir K. Ballas[1]

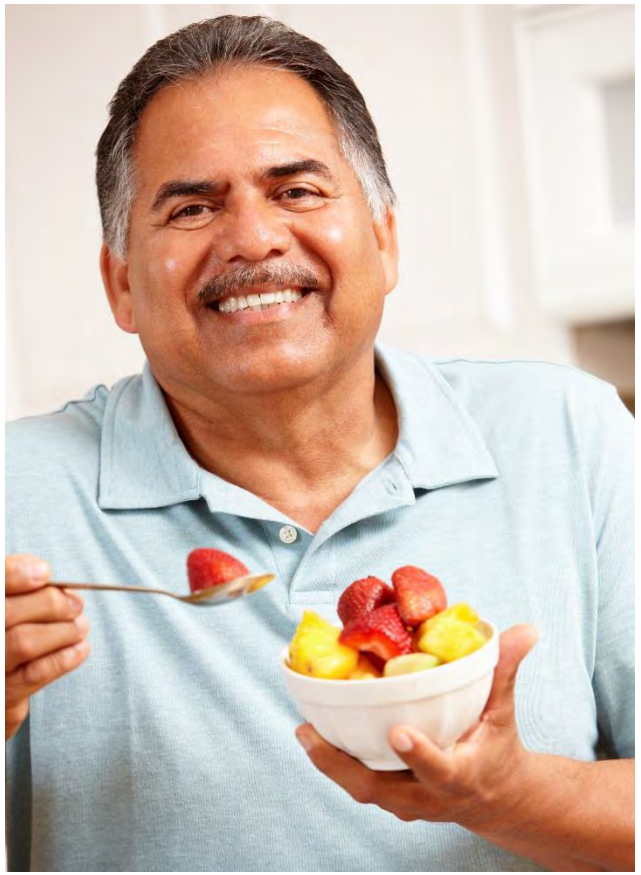
McLaughlin JF, Ballas SK. *Transfusion*. 2016 May;56(5):1014-21

Opportunities and Limitations of Sickle Cell Data Collection

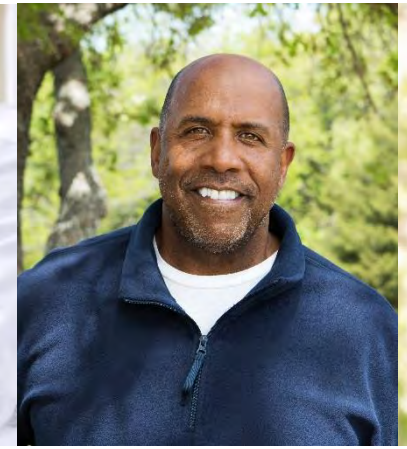
- **Identify sites of care and use during the critical period of adolescence and young adulthood**
  - Observe disease course while still in pediatric care, without change in provider
- **However, lack of use may not mean lack of access**
  - Data regarding referrals, arranged transfers and scheduled appointments that were not kept are not captured

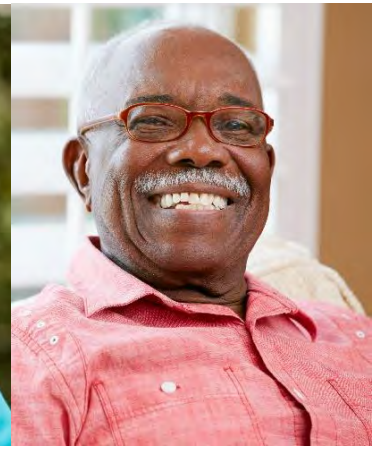
Important Aspects of the Sickle Cell Data Collection Program

- **Population-level data regarding**
  - Premature death
  - Disease course
  - Impact of interventions
  - Healthcare utilization
- **Identify providers and sites of care**
- **Data can be used to develop strategies to prevent and reduce the burden of sickle cell disease and its complications**



A Health Policy Approach to Sickle Cell Disease





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U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Objectives

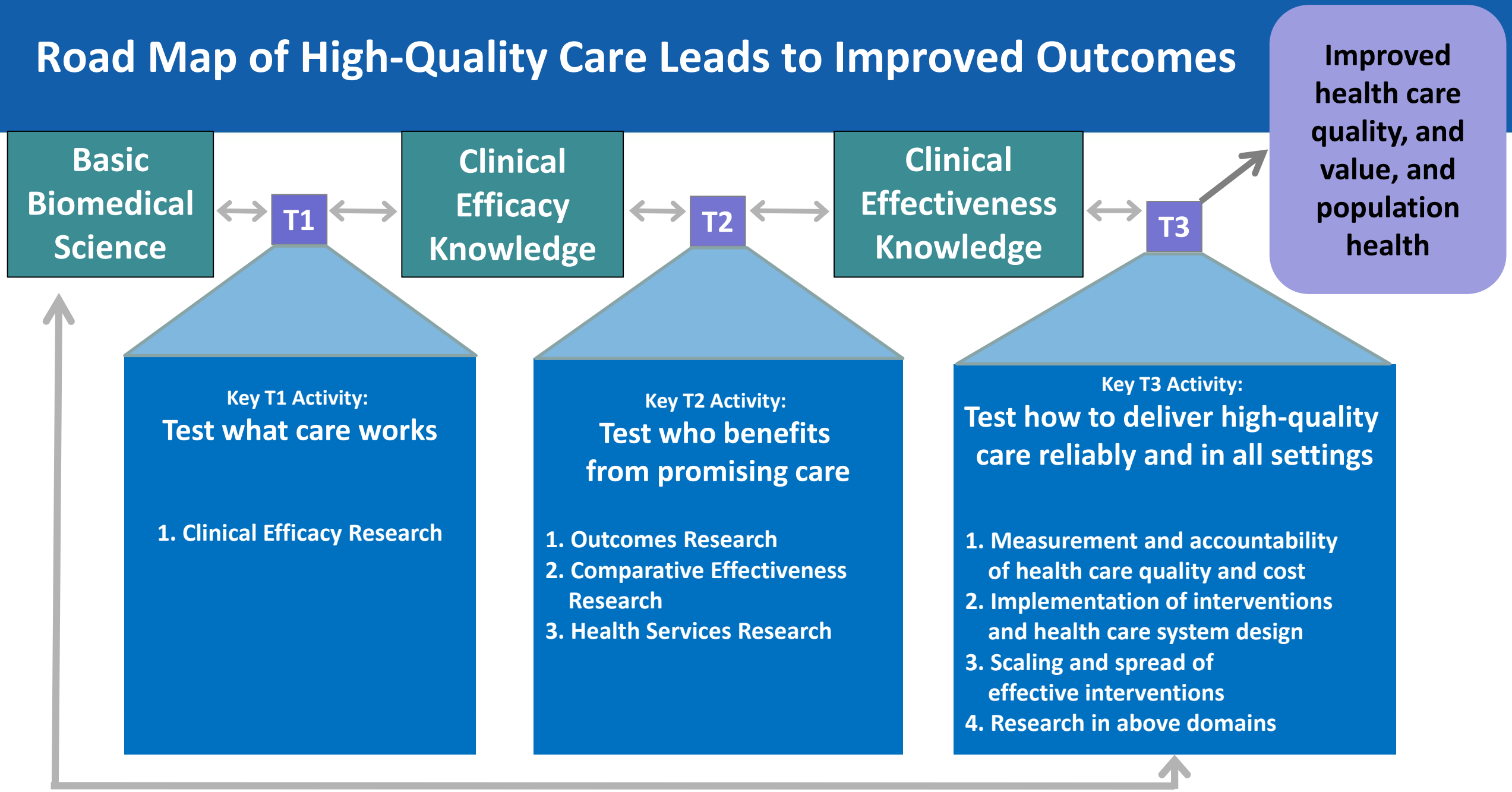
- Describe current guiding principles in health care policy
- Identify policy challenges in sickle cell disease
- Outline a policy agenda for sickle cell disease

Triple Aim for Population Health

1. **Reduce costs**
   - Eliminate overuse or misuse of diagnostic tests or therapies
2. **Improve population health**
   - Identify systematic variations in care or outcomes
   - Apply knowledge to develop policies for improvement
3. **Enhance patient experience**
   - Actively survey patient experience
   - Involve patients and families in system redesign

Berwick DM, Nolan TW, Whittington J. *Health Affairs*. 2008 May-June;27(3):759-769

Road Map of High-Quality Care Leads to Improved Outcomes



Dougherty D, Conway PH. *JAMA*. 2008. 299(19):2319-2321

Healthy People 2020

- **Hemoglobinopathies were *previously* well represented**
- **Focus on treatment**
  - Screening for complications, and disease-modifying therapies
- **Focus on access to medical home, community resources, and educational support**

These objectives were retired because existing data systems could not assess them!

www.healthypeople.gov/2020/topics-objectives/topic/blood-disorders-and-blood-safety/objectives

Advances in Care Are Opportunities to Improve Outcomes

- **Advances in care**
  - Hydroxyurea
  - TCD screening for stroke risk
  - Chronic transfusions
- **Extended life expectancy**
  - In 1973, life expectancy was 14 years
  - In 2008, life expectancy was 42 years

TCD: Transcranial Doppler ultrasonography

Challenges Remain to Improve Outcomes

- **Persistently high resource use**
  - Especially for acute care
- **High risk of mortality at early adulthood**
  - Transition to adult care
- **Poorly studied population**
- **Poor funding and organizing relative to other conditions**

Challenges for Further Research in SCD

- Lack of data sources with adequate numbers of people with SCD or sufficient clinical detail
- Limited evidence base for management guidelines
- Limited number of dedicated clinical providers

www.nhlbi.nih.gov/files/docs/guidelines/sc_mngt.pdf

Agenda for Sickle Cell Disease: Research and Policy

- **Population health and big data**
- **Comparative effectiveness research of treatments**
- **Technology-based interventions**
  - Outreach through technology that patients are already using (e.g., health apps)
- **Development of new funding strategies**

Agenda for Sickle Cell Disease: Healthcare Delivery

- **Building medical neighborhoods**
  - Primary care providers and specialists collaborate to manage patients
- **Supporting adult providers with expertise (e.g., ECHO Model)**
- **Modifying existing reimbursement models**
  - Reimbursement for care coordination
- **Addressing social determinants of health**

ECHO: Extension for Community Healthcare Outcomes, echo.unm.edu
Arora S, Geppert CM, Kalishman S, et al. *Acad Med*. 2007 Feb;82(2):154-60

What Do We Need Now?

- Health care policy strategies are needed to fully realize benefits of basic and clinical science advancements for sickle cell disease (SCD)
- Strategies must align with current priorities in reforming health care system
- Policy solutions in SCD should be patient-centered, provider-centered, and health system-oriented

Improving the Lives of People with Sickle Cell Disease

- **Continue progress in advancing care**
  - Translating research into treatment and practice
- **Use data to identify gaps in care**
  - Variability in disease course and management
  - Availability, use, and access to care
  - Transitions from pediatric to adult care, and for adult care
- **Need more support to meet healthcare needs**
  - Connect people to care
  - Understand better which care is best for each individual
  - Better systems to provide patient-centered care

CDC PUBLIC HEALTH GRAND ROUNDS

Improving the Lives of People with Sickle Cell Disease

November 15, 2016

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention