Identifying Severe Sickle Cell Early in Life

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INDIANA HEMOPHILIA & THROMBOSIS CENTER, INC.

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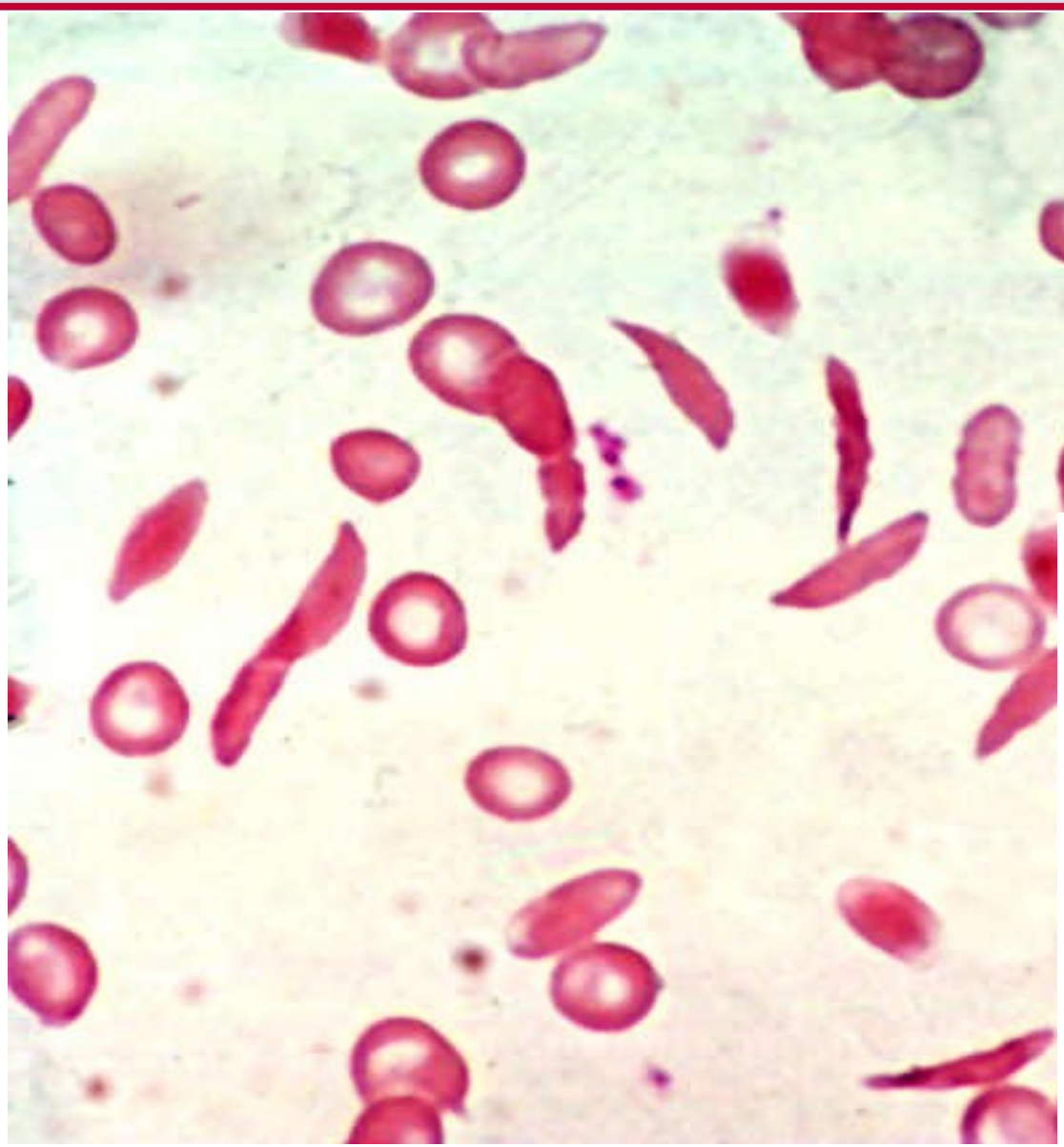
Disclosures

- Consultancy: CVS Caremark

Goals & Objectives

- Review complications of sickle cell anemia
- Discuss definitions of sickle cell severity
- Examine prediction models for sickle cell anemia severity
- Review three most commonly studied predictors of sickle cell anemia severity and how they might be used to make treatment decisions

Sickle Cell Disease



- Autosomal recessive
- Group of diseases with predominance of sickle hemoglobin (Hb): HbSS, HbSC, HbSβ+thalassemia, HbSβ0thalassemia
- Severity varies among and within the genotypes

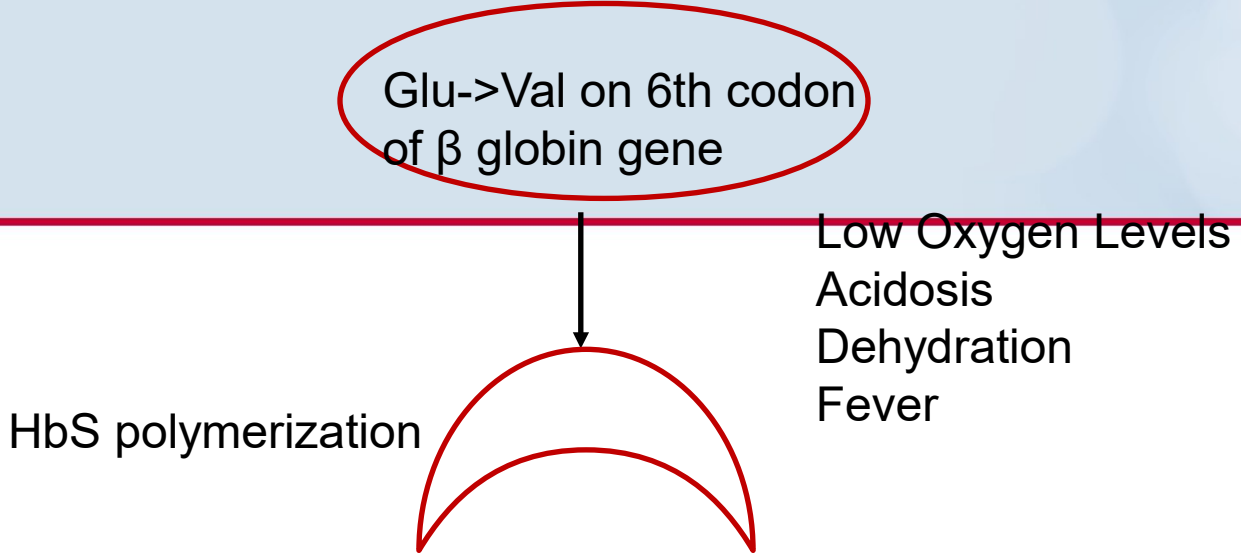
Glu->Val on 6th codon of β globin gene

Meier ER & Rampersad A
Pediatr Res 2017;81:249-258

Glu->Val on 6th codon of β globin gene

Low Oxygen Levels
Acidosis
Dehydration
Fever

Meier ER & Rampersad A
Pediatr Res 2017;81:249-258



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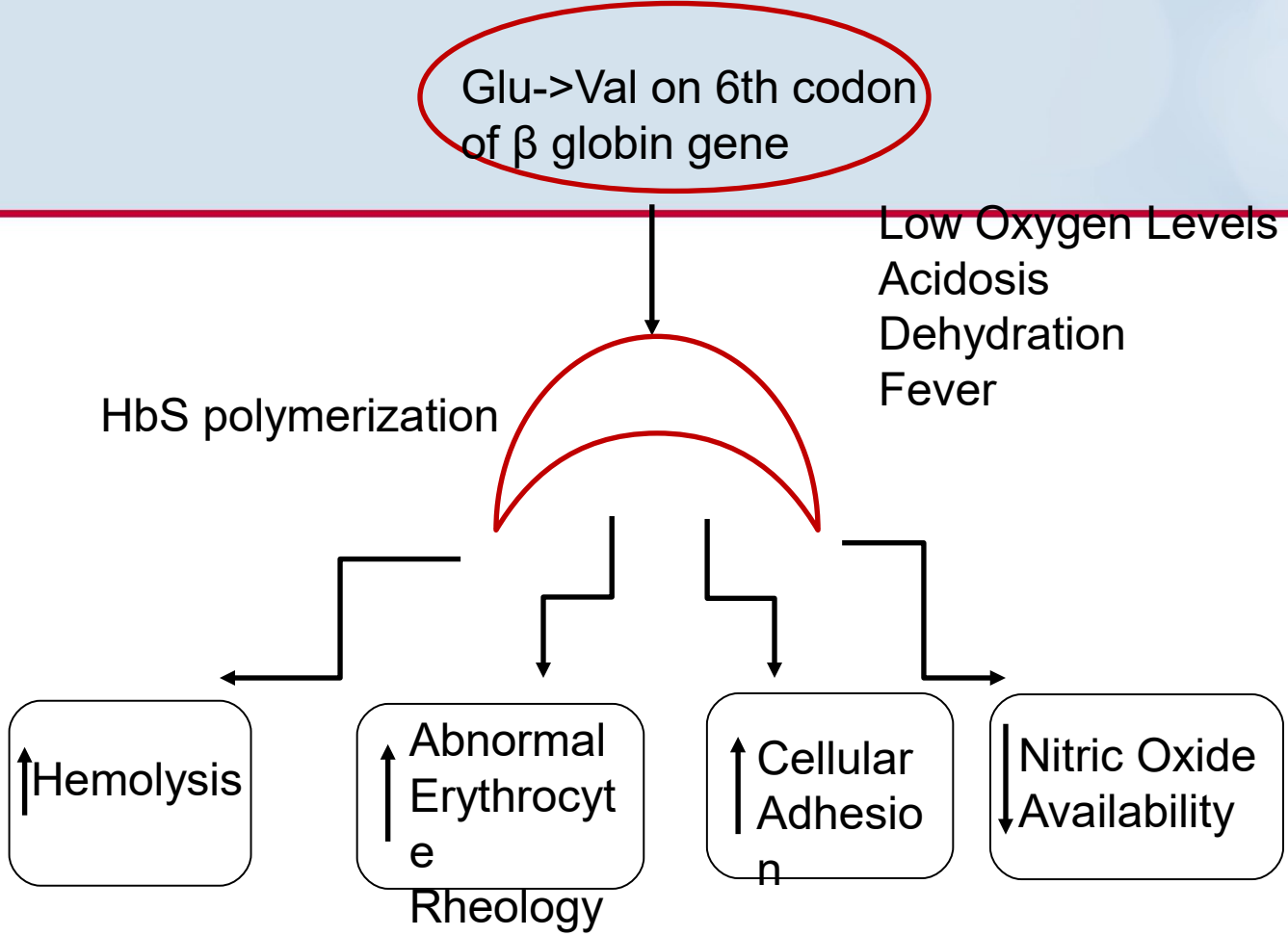

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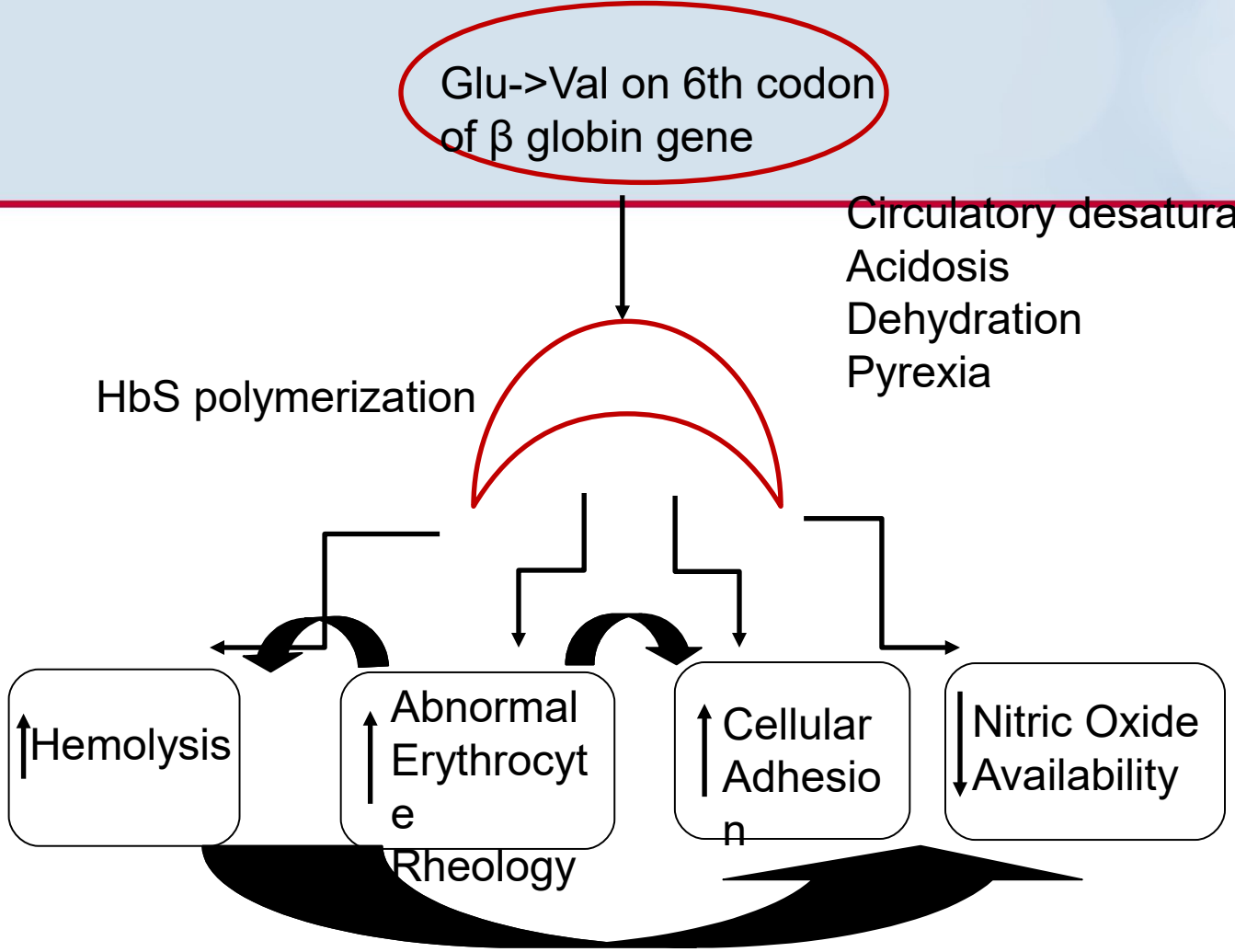

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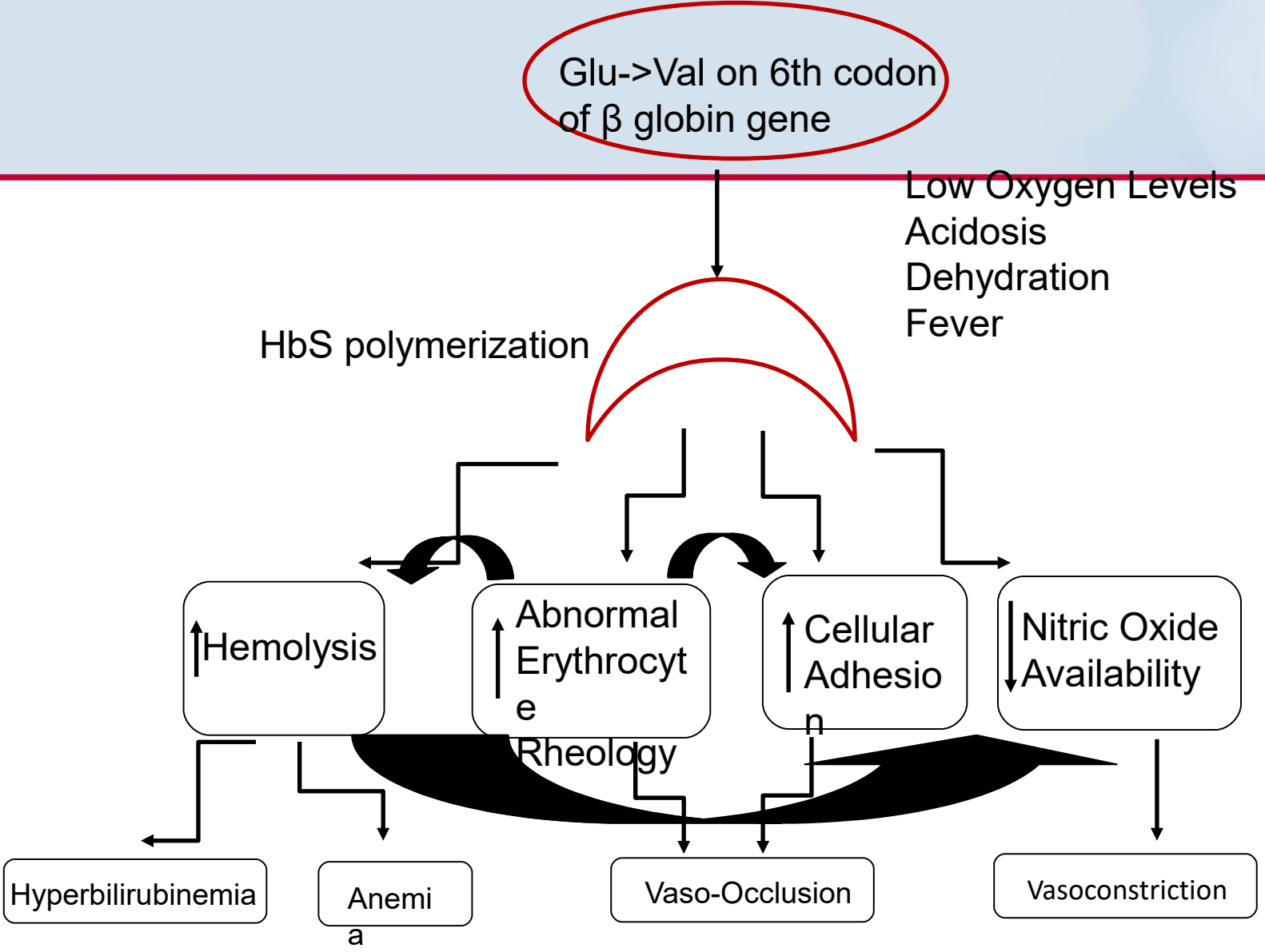

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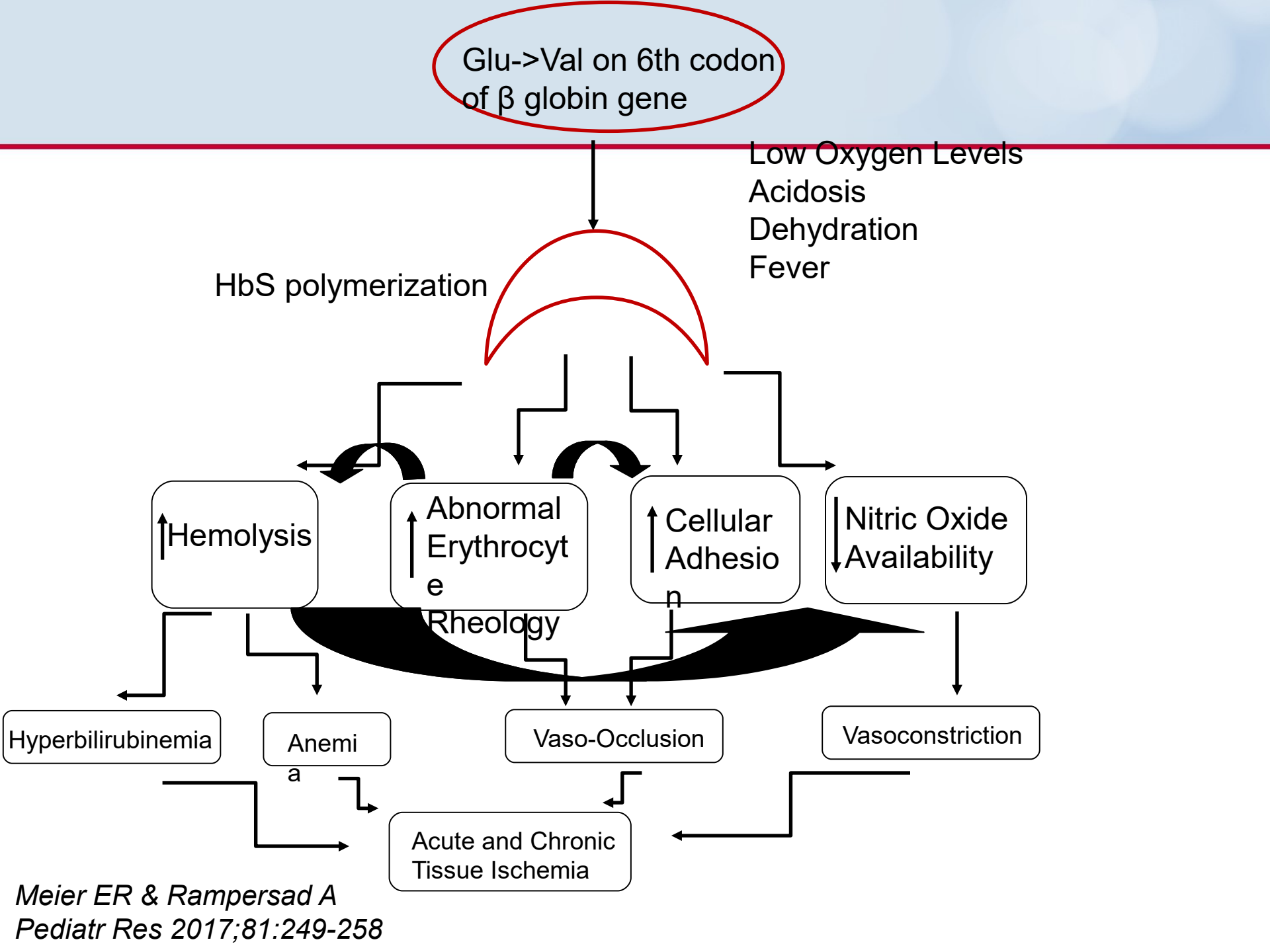

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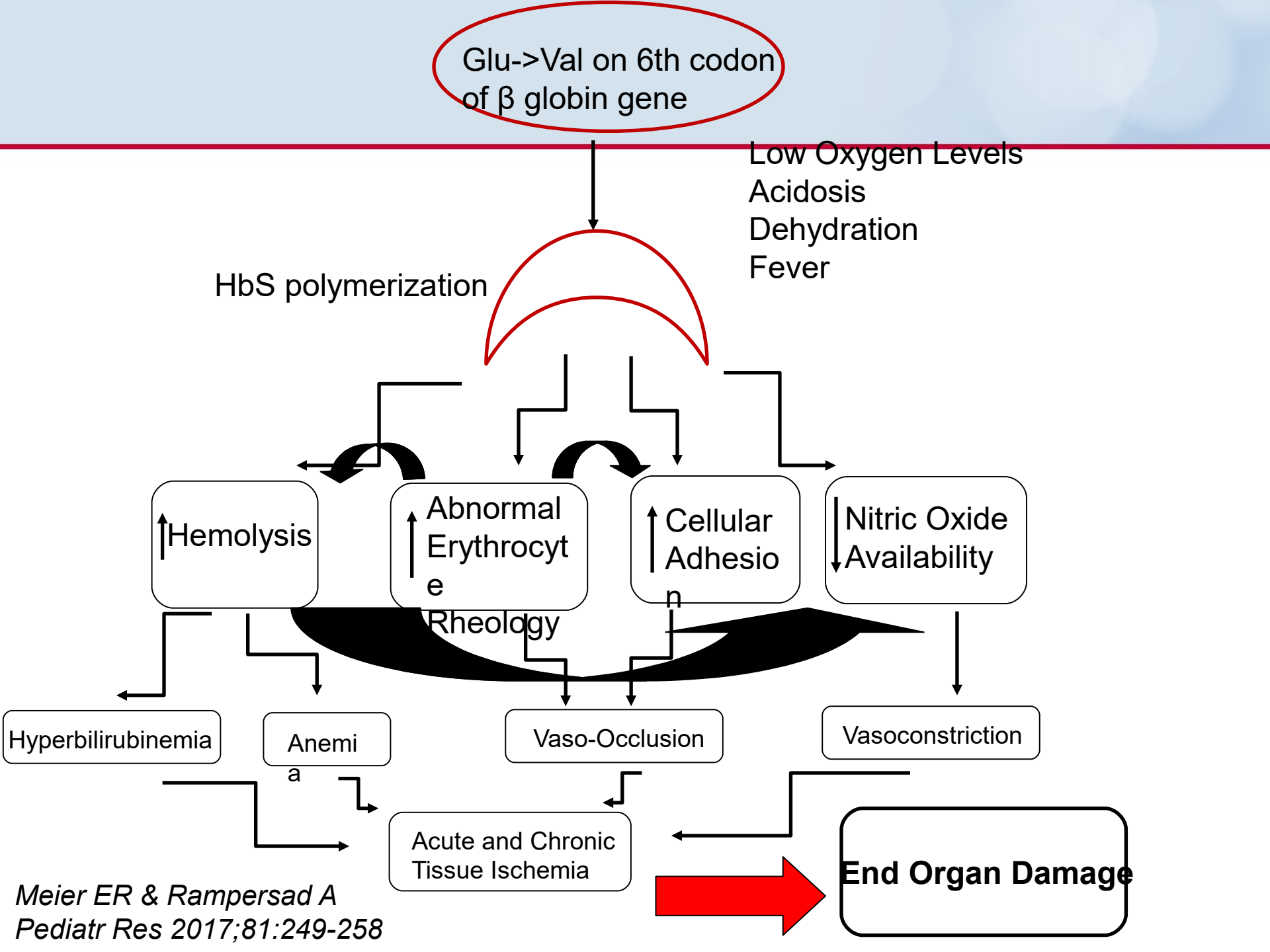

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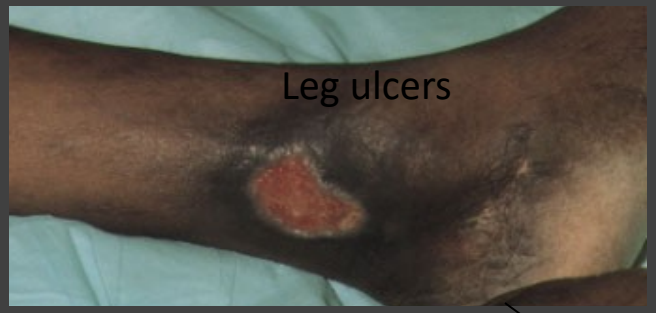
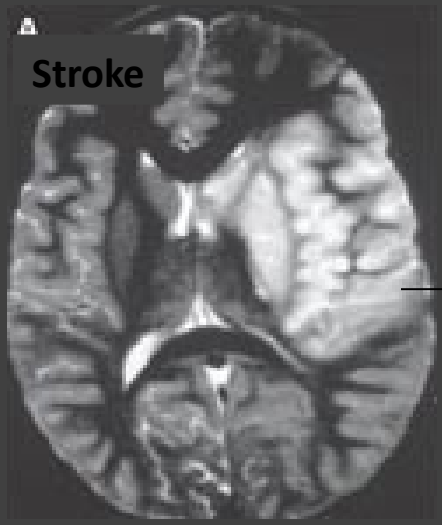
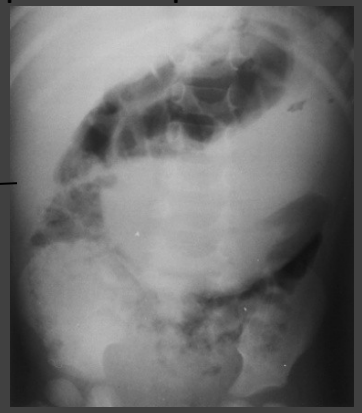
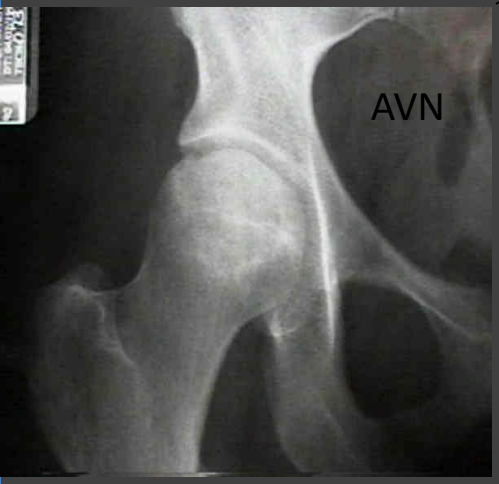
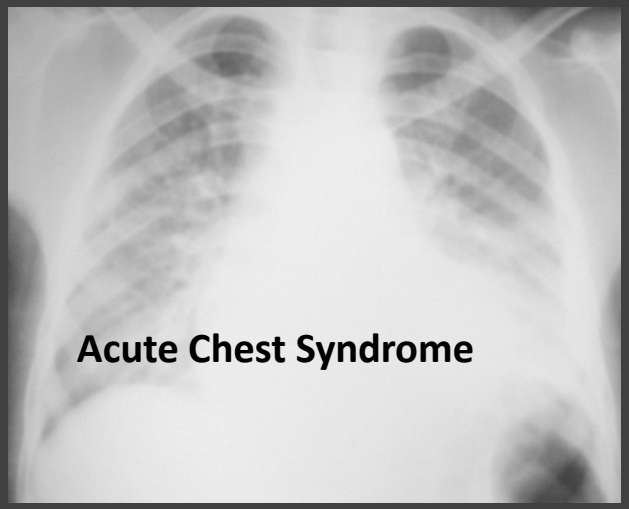




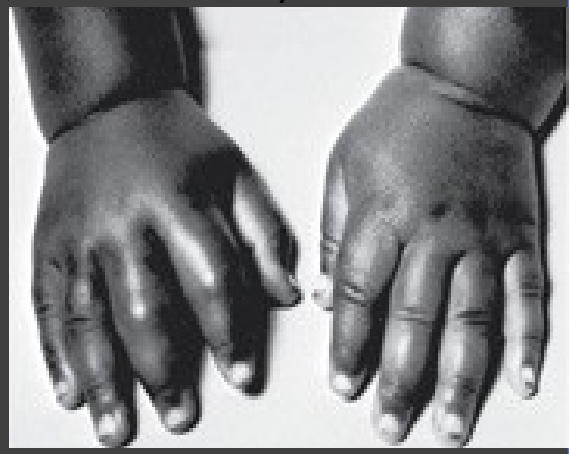
Splenic Sequestration







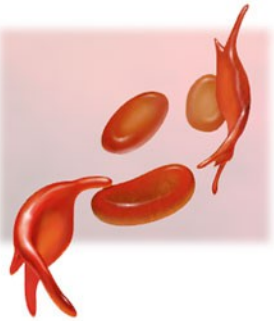
Pain-Dactylitis



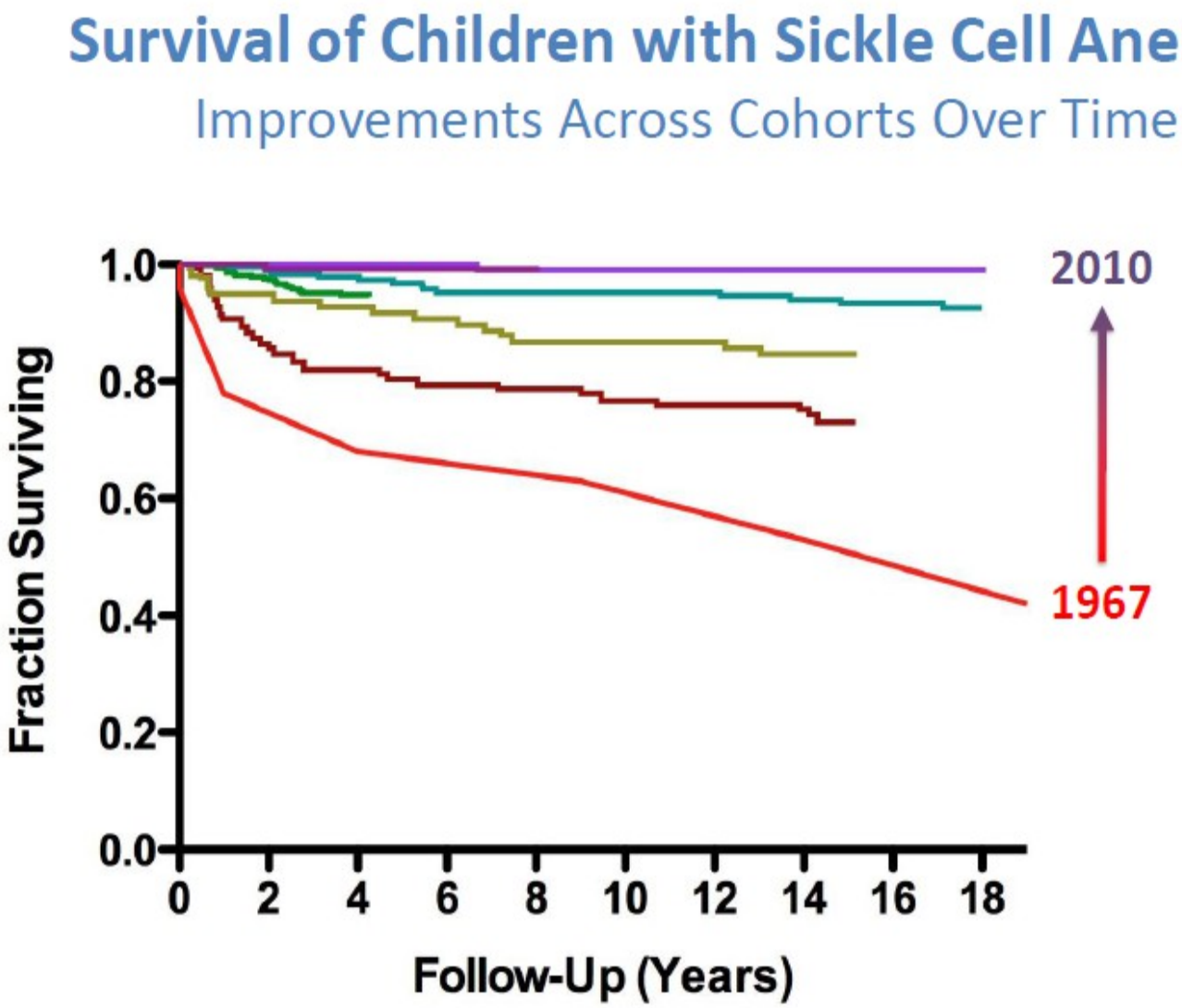
SCA Genotype vs. SCA Phenotype

- **<u>Genotype</u>: straightforward autosomal recessive inheritance**
  - Mutation known, well-defined

- **<u>Phenotype:</u> highly variable**
  - Currently difficult to predict in infancy which children will have significant complications



Where Are We? Improving Survival ….



Childhood Mortality

1.Infection (often with Acute Chest Syndrome)
2.Splenic sequestration
3. Stroke

Quinn CT, et al. Blood 2010;115:3447-3452

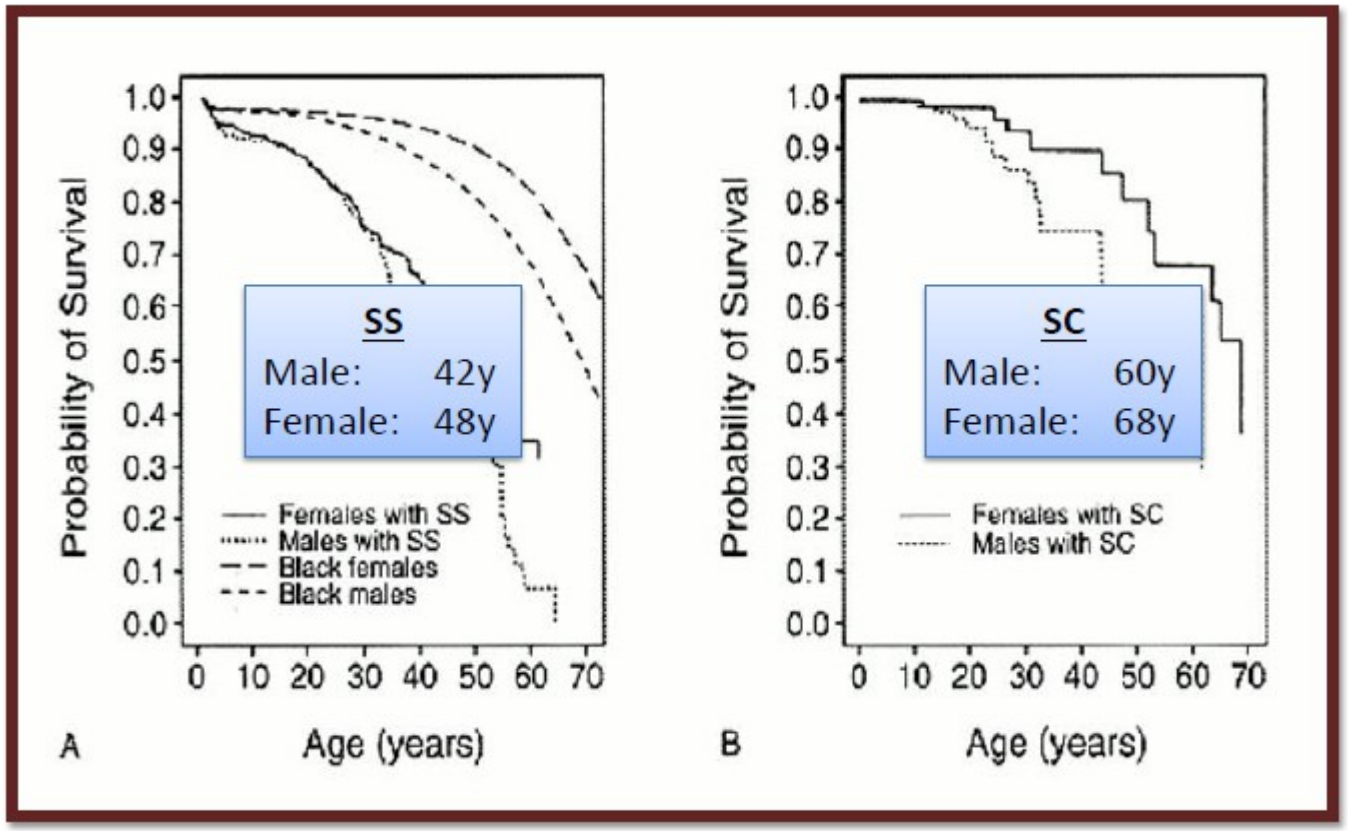
Research Has Improved the Survival of Children, but…

- Family education RE: spleen palpation to reduce mortality of splenic sequestration - 1977
- Penicillin Prophylaxis – 1986
- Universal Newborn Screening
- STOP trial (TCD screening to assess stroke risk) – 1998

Emond AM, et al. J Pediatr 1985;107:201-206.
Gaston MH, et al. N Eng J Med 1986;314:1593-1599
Adams RJ, et al. N Engl J Med 1998;339:5-11

…Overall Survival is Less than the Average American

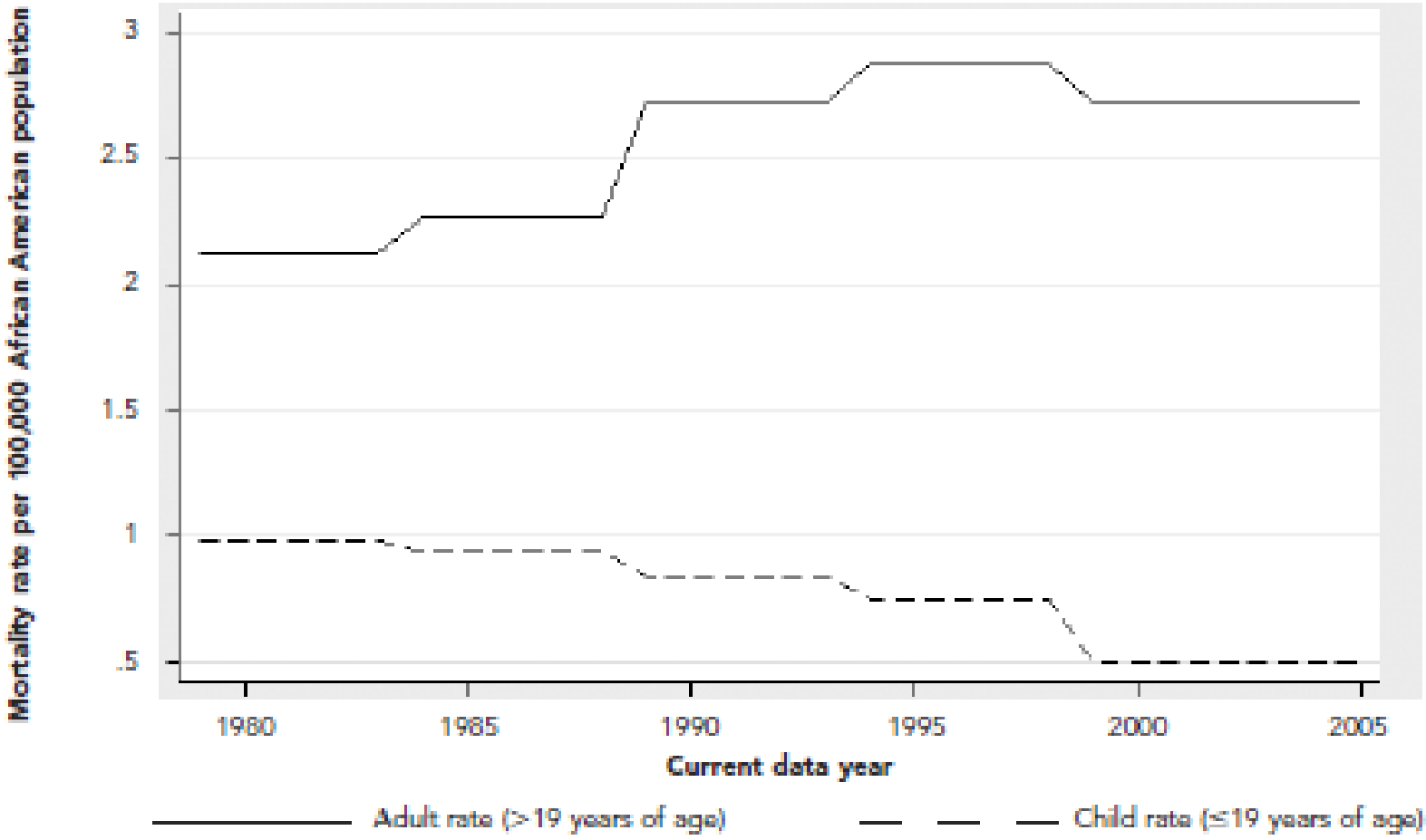
Cooperative Study of Sickle Cell Disease



Platt O, et al. N Engl J Med 1994;330:1639-1644

Mortality Rates in Adults Unchanged since CSSCD

Figure. Mortality rates for adults and children with sickle cell disease: U.S., 1979–2005



Lanzkron S et al. Public Health Reports 2013;128:110-116

Increasing Number of Therapeutic Options for Sickle Cell Disease

- Hydroxyurea
- L-glutamine
- Blood transfusion
- Selectin inhibitors
- Voxelotor (GBT440)
- Anti-platelet medications
- Hematopoietic stem cell transplant
- Gene therapy

- Need to balance risks and benefits of different

What Can We Learn from Pediatric Oncologists?

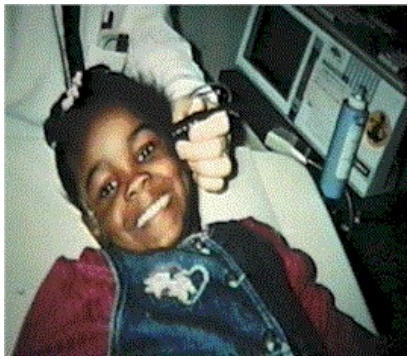
- Acute Lymphoblastic Leukemia (ALL) was universally fatal 50 years ago
- Initially all patients received the same treatment regimen
- Current treatment protocols stratify patients by various risk factors
  - Age
  - Initial White Blood Cell count
  - Cancer genetics
- Patients with low risk ALL receive less intense chemotherapy regimens to minimize toxicities while still preserving cure
- Patients with high risk ALL receive intensified regimens to increase chances of cure

Tasian SK, et al. Cancer. 2015;121:3577-3590.

"Ideal" Sickle Cell Severity Predictor

- Globally applicable
- Inexpensive
- Amenable for use in infants and children

- **Transcranial Doppler (TCD) is the only currently available, validated predictor of a severe SCA**



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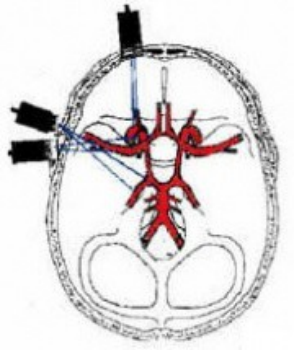
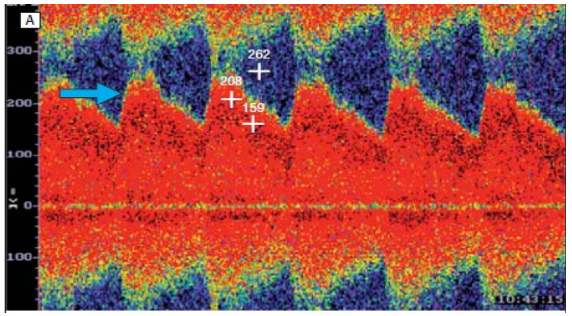




What is the Definition of Severe Sickle Cell Disease?

- **Criteria for Bone Marrow Transplant:**
  - Clinically significant neurologic event (stroke) ***OR***
  - History of two or more episodes of acute chest syndrome (ACS) ***OR***
  - Three or more pain crises per year in the 2-year period ***OR***
  - Administration of regular red blood cell (RBC) transfusion therapy, defined as receiving 8 or more transfusions per year for >1 ***OR***
  - Abnormal TCD (TAMMV $\geq$ 200cm/sec in MCA or dICA)

Hulbert ML and Shenoy S. Pediatr Blood Cancer 2018;65:e27263

Cooperative Study of Sickle Cell Disease (CSSCD)

- Multi-center, NHLBI funded, natural history study of SCD

- More than 3,000 SCD patients were enrolled

- CSSCD newborn cohort
  - Infants enrolled <6 months of age

Gaston M, et al. 1982

Assessing Severity in the CSSCD Newborn Cohort

- **380 newborns with HbSS enrolled in CSSCD at < 6 months of age**
  - Followed for at least 1 year
  - Mean follow up 10 ± 4.8 years
- **Events used as proxies for severe disease:**
  - Death
  - Stroke
  - 2 Vaso-Occlusive Crises/year for 3 years
  - 1 Acute Chest Syndrome/year for 3 years

Miller ST, et al. N Engl J Med 2000;342:83-89

Assessing Severity in the CSSCD Newborn Cohort

- Early predictors:

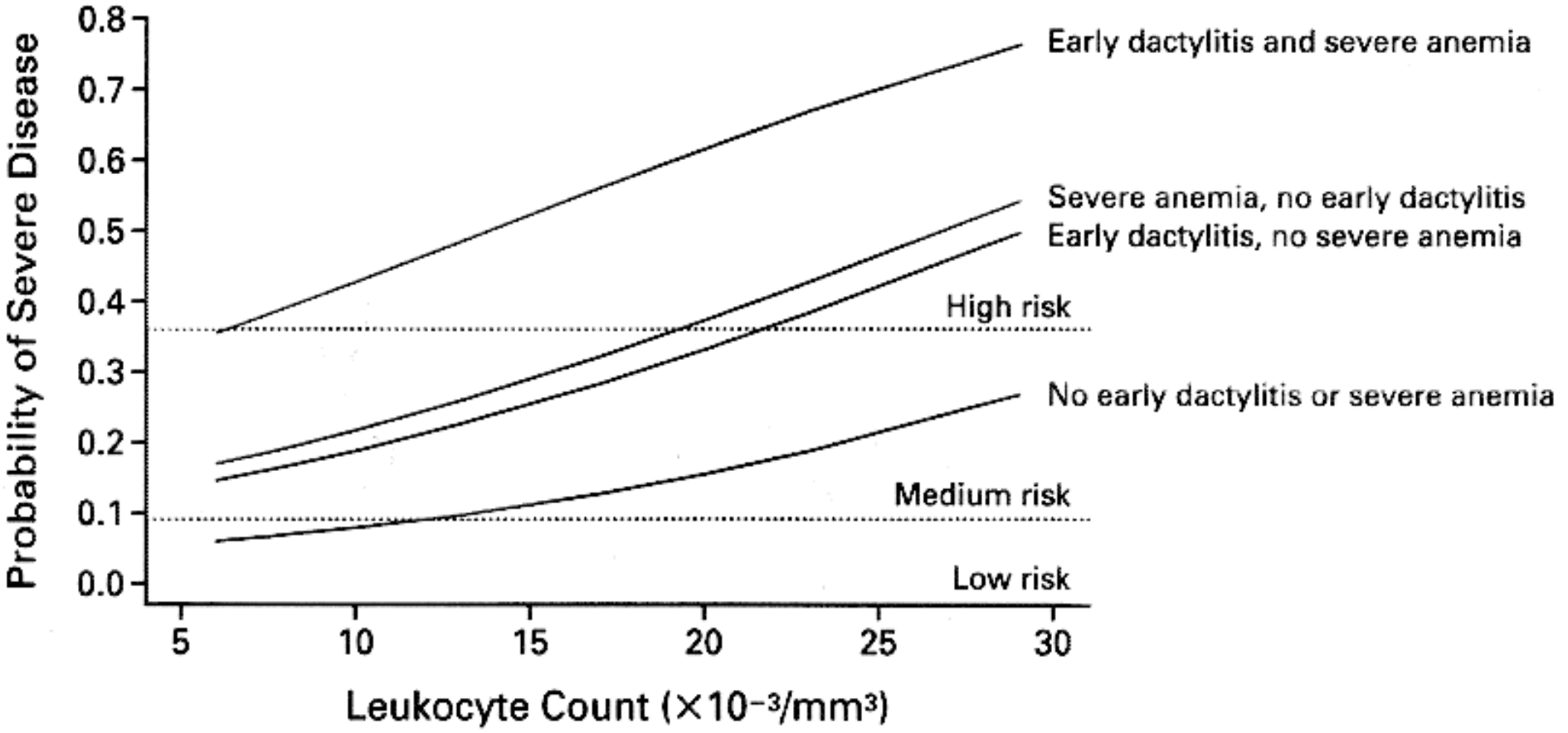
  Dactylitis before age 1 year

  Steady state hemoglobin <7 g/dL in 2nd year of life

  Steady state leukocytosis in 2nd year of life

Miller ST, et al. N Engl J Med 2000;342:83-89

Predicting Disease Severity



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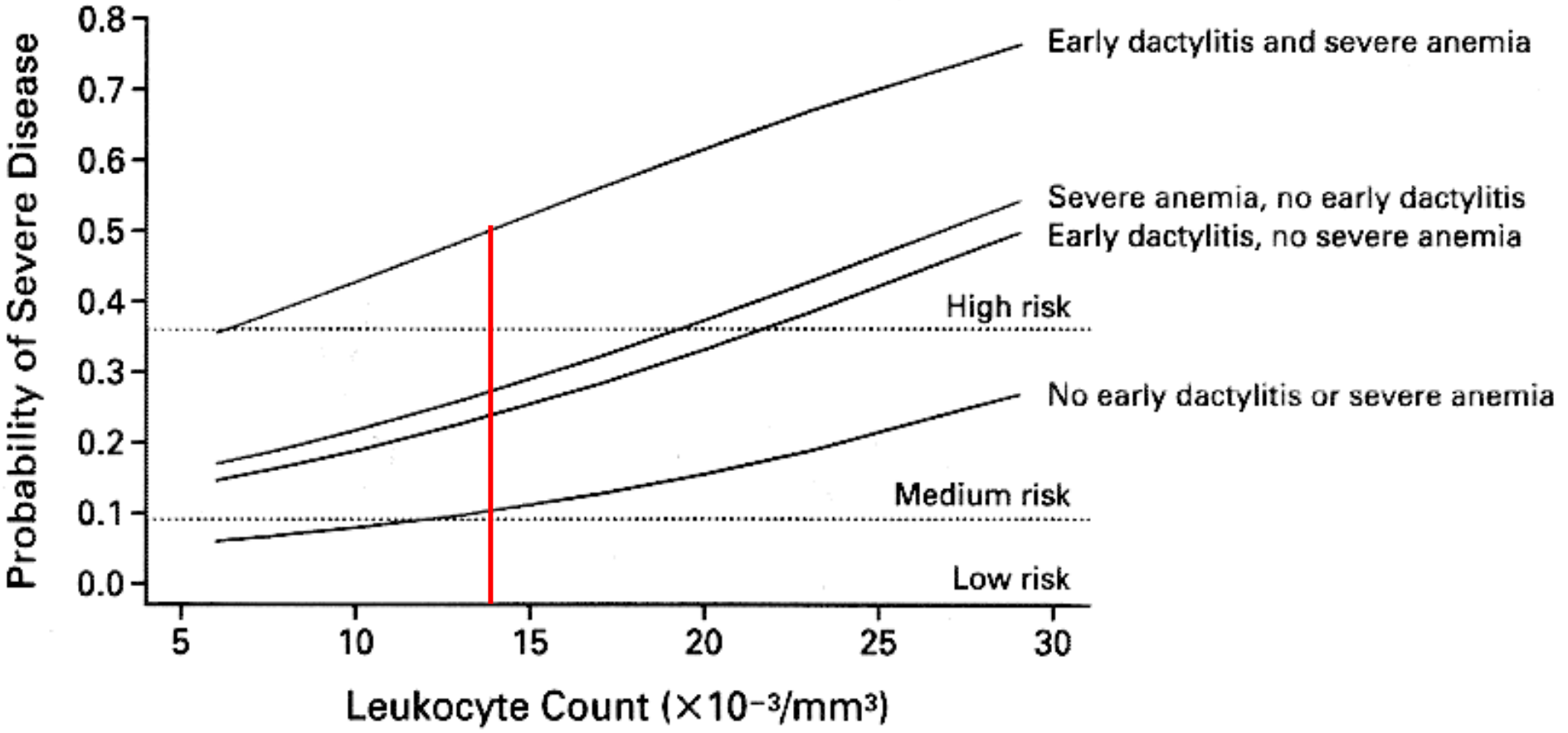
Predicting Disease Severity



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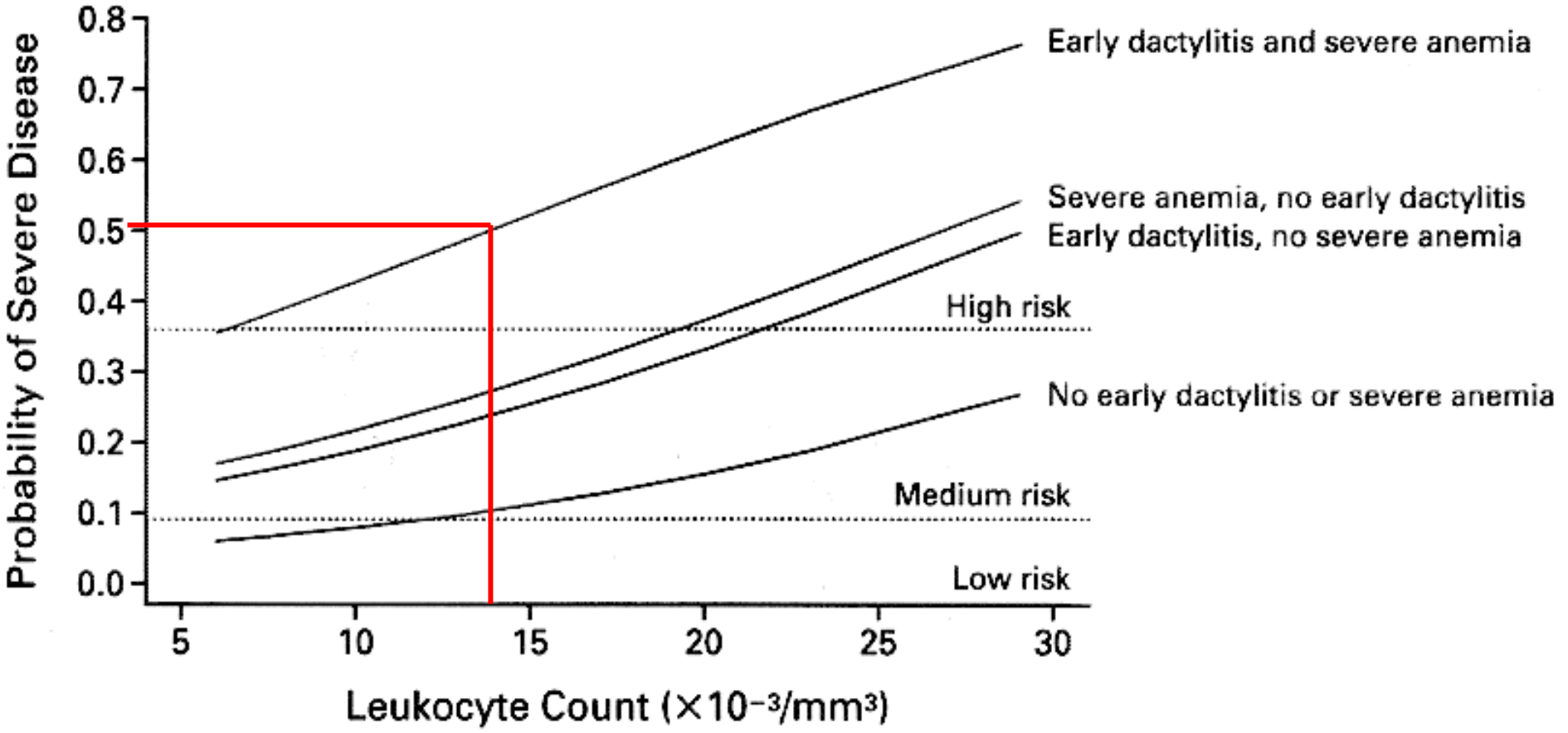
Predicting Disease Severity



Miller ST, et al. N Engl J Med 2000;342:83-89

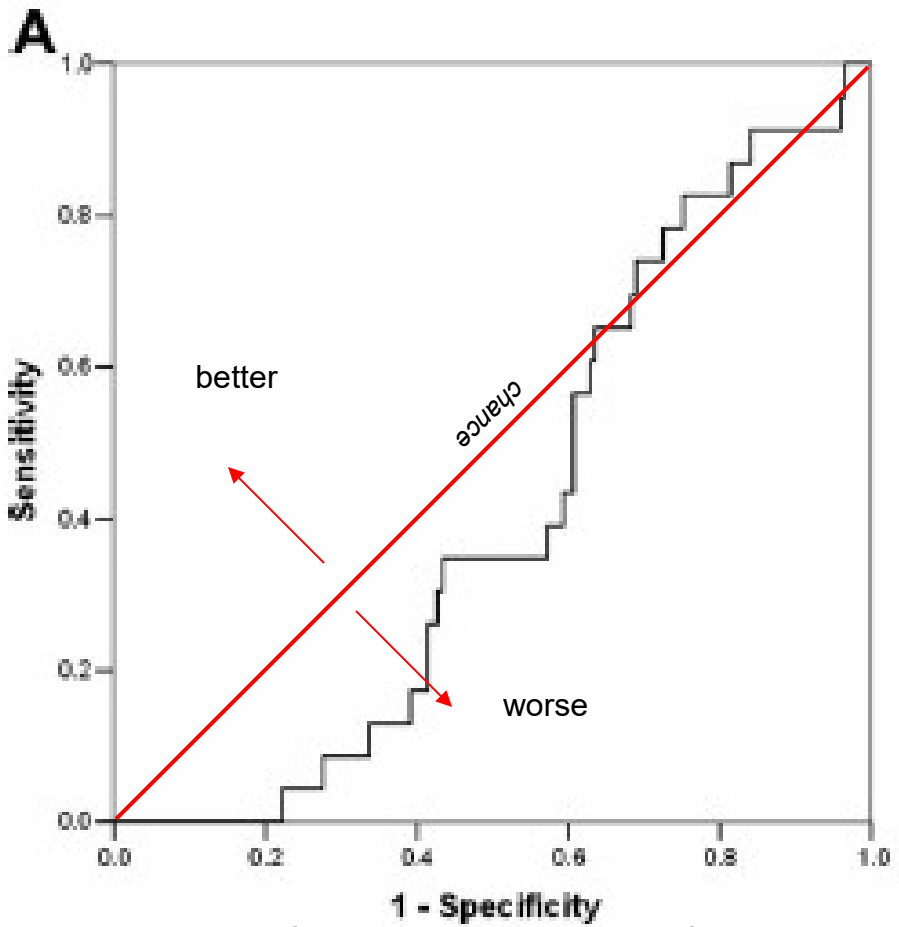
Dallas Newborn Cohort

- Newborn inception cohort
  - Patients enrolled 1983-2005
  - 168 newborns with HbSS analyzed
- Early predictors:
  - Dactylitis
  - Steady state hemoglobin in 2nd year of life,
  - Steady state leukocyte count in 2nd year of life

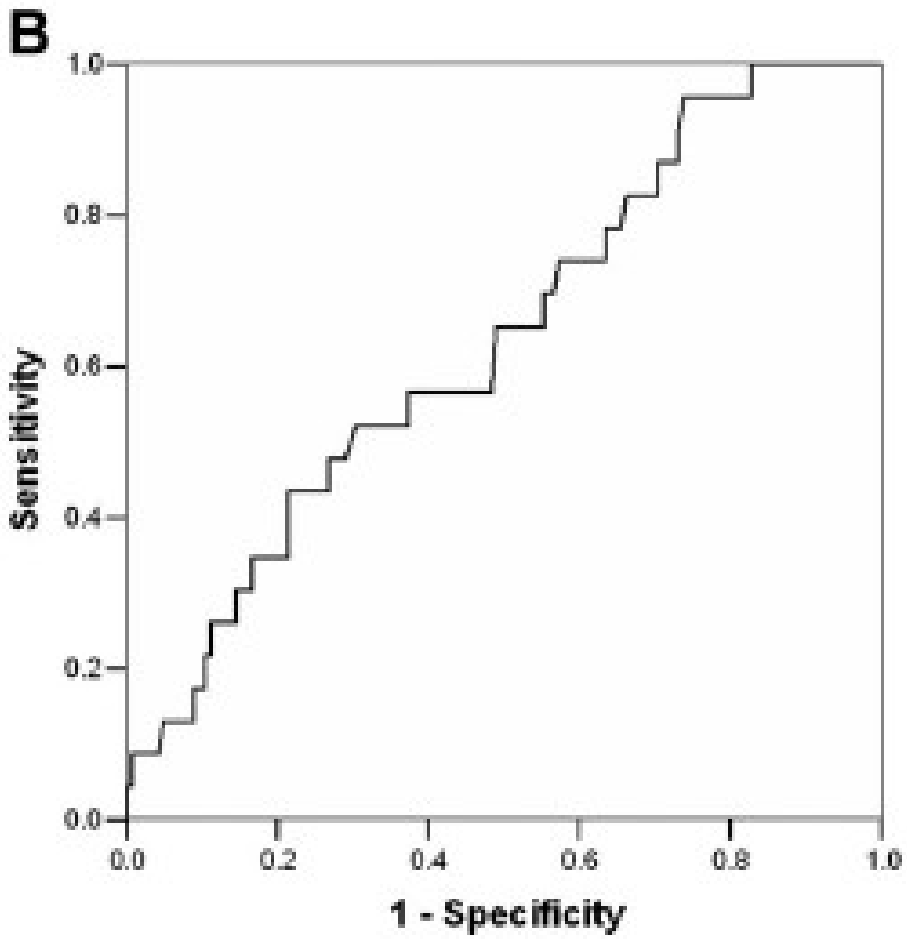
Quinn CT, et al. Blood 2008;111:544-548

Predicting Disease Severity in the Era of Penicillin and TCD

Dactylitis, Baseline Hb, WBC



Leukocyte count alone



Quinn CT, et al. Blood 2008;111:544-548

Useful Severity Prediction Model in Children?

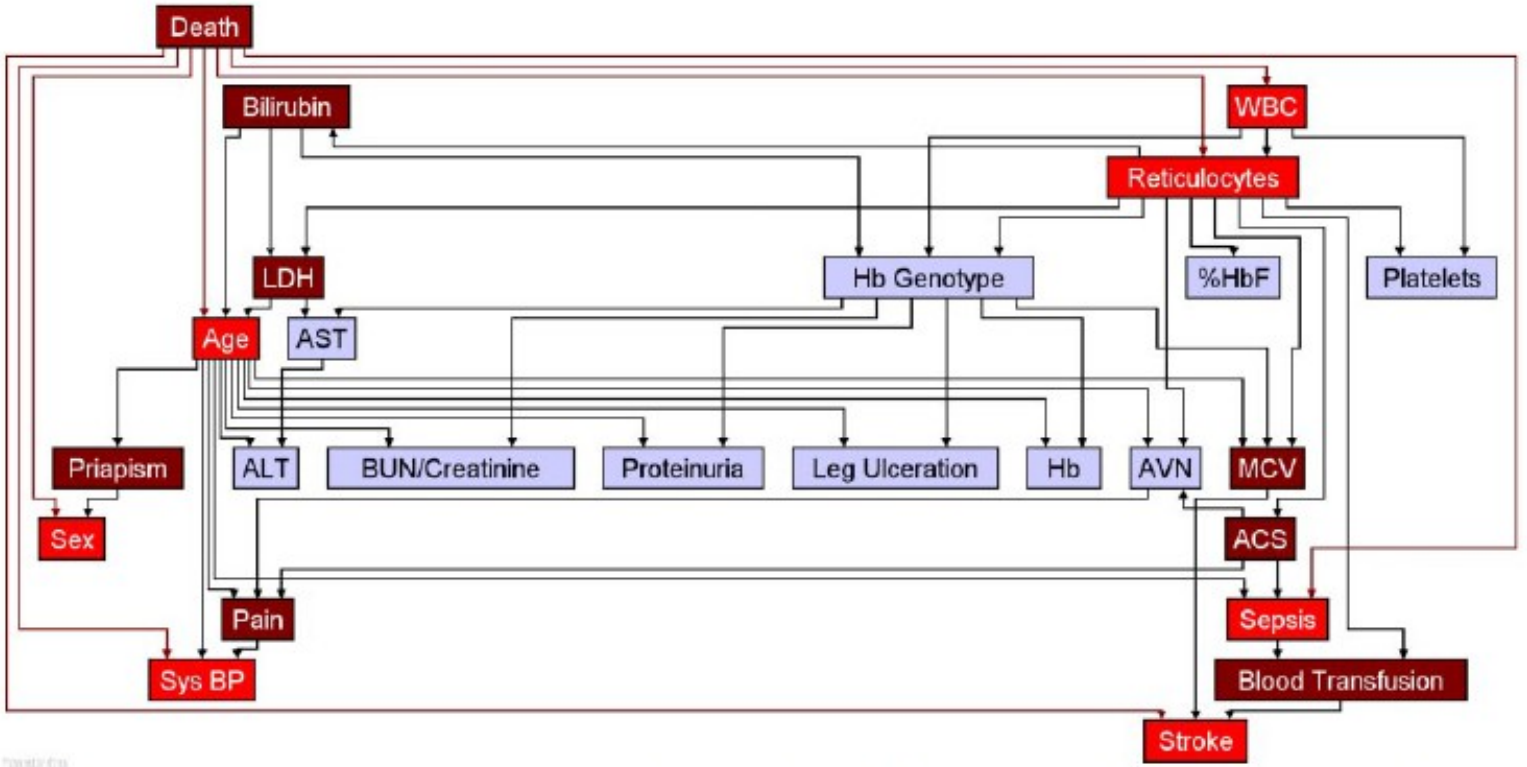


Figure 1. The network of associations between death, clinical complications, and laboratory findings in sickle cell disease. The arc (arrow) direction specifies the conditional probability tables that are sufficient to compute the overall distribution. Colored in red are the nodes that alone are sufficient to predict the risk for death (severity score). Nodes in blue are associated with predictive nodes in red. For example, the Hb genotype is associated with several laboratory variables including WBC and LDH and thus modulates disease severity indirectly through these nodes. See Tables 3,4. ACS indicates acute chest syndrome; AVN, avascular necrosis; BUN/creatinine, ratio of BUN to creatinine; Sys BP, systolic blood pressure; Hb, total hemoglobin concentration; %HbF, percentage of fetal hemoglobin; WBC, leukocyte count; Hb genotype, sickle cell anemia, sickle cell anemia-α thalassemia, HbSC disease.

Sebastiani P, et al. Blood 2007;110:2727-2735

Systematic Review of Severity Predictors

Meier ER, et al. Blood Cell Mol Dis 2017;65:86-94

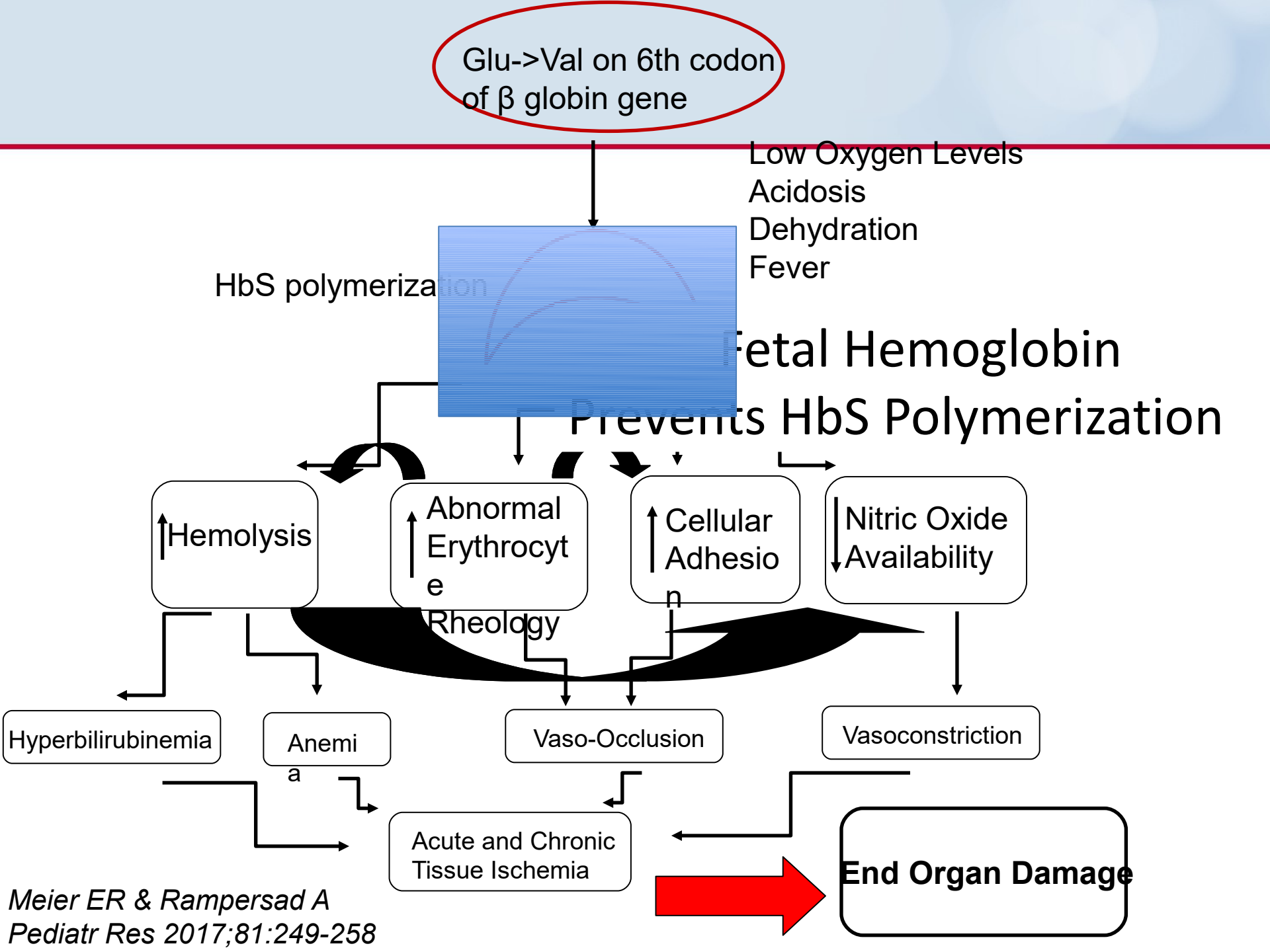
Most Studied Predictive Laboratory Tests

- Fetal Hemoglobin
- Alpha globin gene number
- Reticulocyte Count

- Additional predictors:
  - Asthma
  - White blood cell count
  - Hemoglobin
  - Beta globin gene haplotype
  - Multiple other genetic predictors

Meier ER, et al. Blood Cell Mol Dis 2017;65:86-94

Fetal Hemoglobin



Meier ER & Rampersad A
Pediatr Res 2017;81:249-258

High Fetal Hemoglobin Levels

Protective	No Benefit/Unknown
Painful Crisis	Silent Cerebral Infarct
Acute Chest Syndrome	Elevated TCD Velocities
Acute Splenic Sequestration	
Hospitalization	
pRBC Transfusion	

Limitations:

- Different definitions of “High HbF levels”
- No standard age at HbF measurement
- Different laboratory techniques to measure HbF distribution

Meier ER, et al. Blood Cell Mol Dis 2017;65:86-94

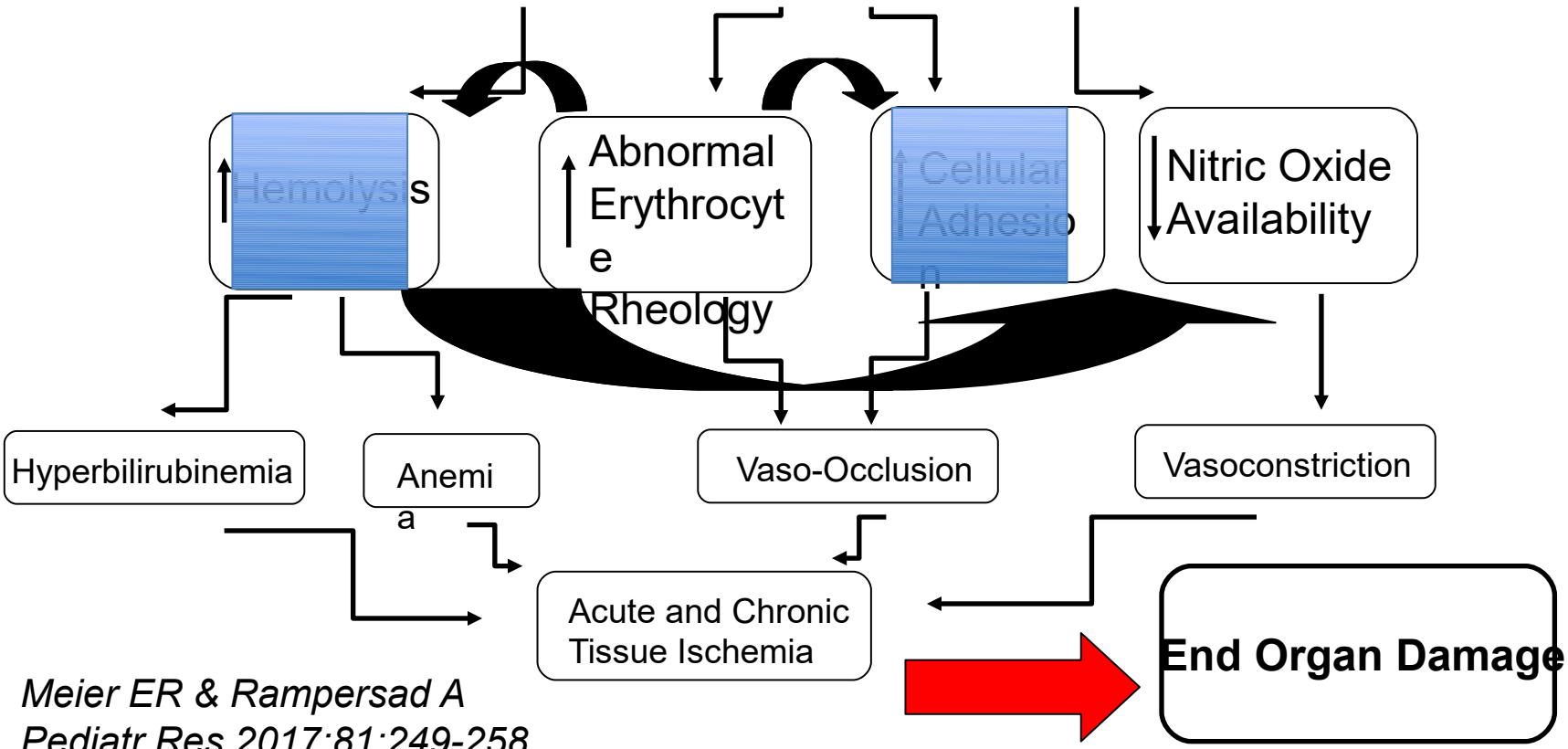
Alpha Globin Gene Number

Glu->Val on 6th codon of β globin gene

Low Oxygen Levels

Decreased Alpha globin production decreases RBC adhesion and increases RBC deformability

HbS



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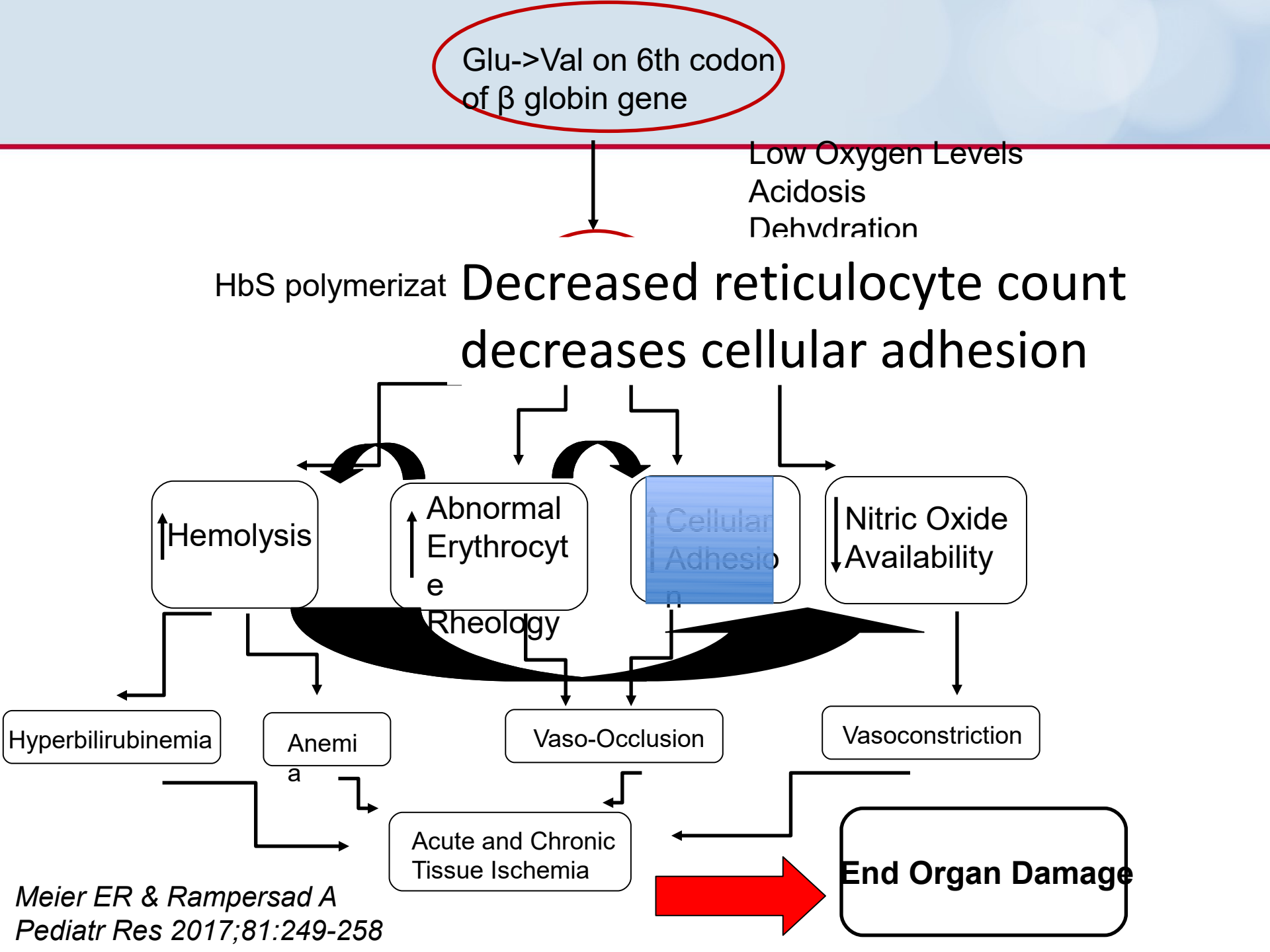
Alpha Thalassemia Trait and Sickle Complications

Protective	No Benefit/Unknown
Stroke	Painful Crisis
Abnormal TCD	Silent Cerebral Infarct

Meier ER, et al. Blood Cell Mol Dis 2017;65:86-94

Reticulocyte Count



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Pediatr Res 2017;81:249-258

High Reticulocyte Levels

Increased Risk	No Benefit/Unknown
Painful Crisis	Silent Cerebral Infarct
Acute Splenic Sequestration	
Elevated TCD Velocities	
Stroke	
Death	

- Reticulocytosis at a young age (between 2 and 6 months of age) is associated with increased risk of painful crisis, splenic sequestration, stroke,death and elevated TCD velocities.

Meier ER, et al. Blood Cell Mol Dis 2017;65:86-94

How Could These Predictors Be Combined?

- **Abnormal TCD**
- Number of children who need to start chronic transfusions once they have an abnormal TCD to prevent one stroke: 7
  - Could children be further risk stratified with additional risk markers to decrease the number needed to treat?

- **Asymptomatic Infants with an HLA-matched sibling**
  - Could the highest risk infants be identified before they experience any complications?

Future Direction and Challenges

- Lack of validated definition of “Severe Sickle Cell Disease”
  - Which complications are most severe?
  - What is the patient/family perspective of Severe Sickle Cell Disease?
- Changes in Hydroxyurea prescribing practices need to be taken into account
  - Risk stratification may need to include poor responders to hydroxyurea, factors that affect medication adherence
- Mechanistic studies to better understand phenotypic variability of the disease

Summary

- Clinical complications of sickle cell disease vary among patients
- Currently difficult to predict which children are at highest risk for complications
- Number of therapies for sickle cell disease is increasing and providers need a way to risk stratify patients so that the appropriate therapy can be utilized
- Fetal hemoglobin, alpha thalassemia and reticulocyte count are the three most frequently studied risk markers
- Fetal hemoglobin protects against most sickle-related complications
- Alpha thalassemia trait protects against stroke, but increases the risk of painful crisis
- Elevated reticulocyte count is associated with higher rates of painful crisis, splenic sequestration, abnormal TCD, stroke and death

Thank you!

Questions?