VANDERBILT UNIVERSITY MEDICAL CENTER

The importance of phenotype in genotype-phenotype studies in sickle cell disease

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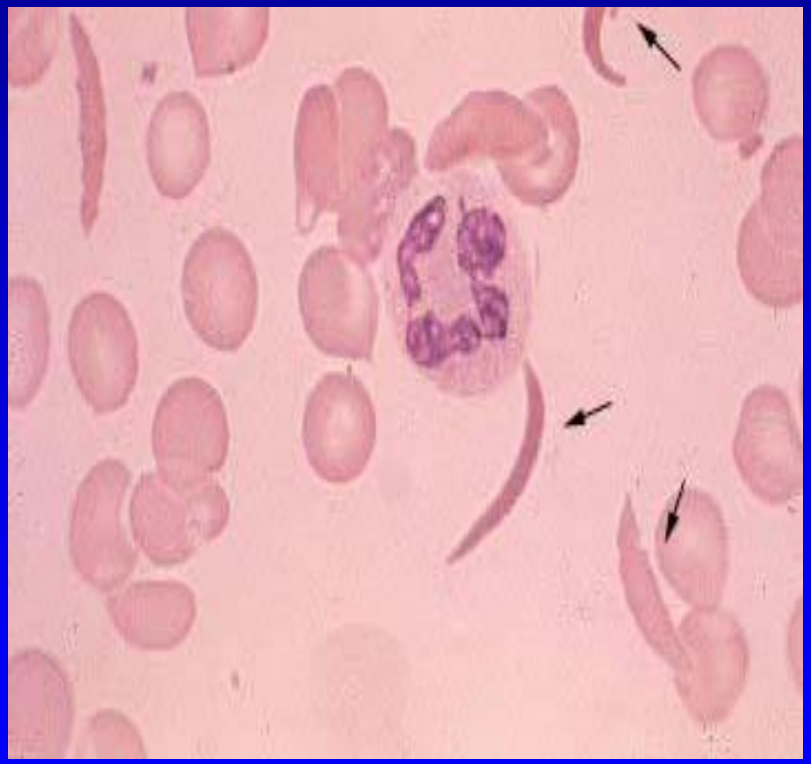
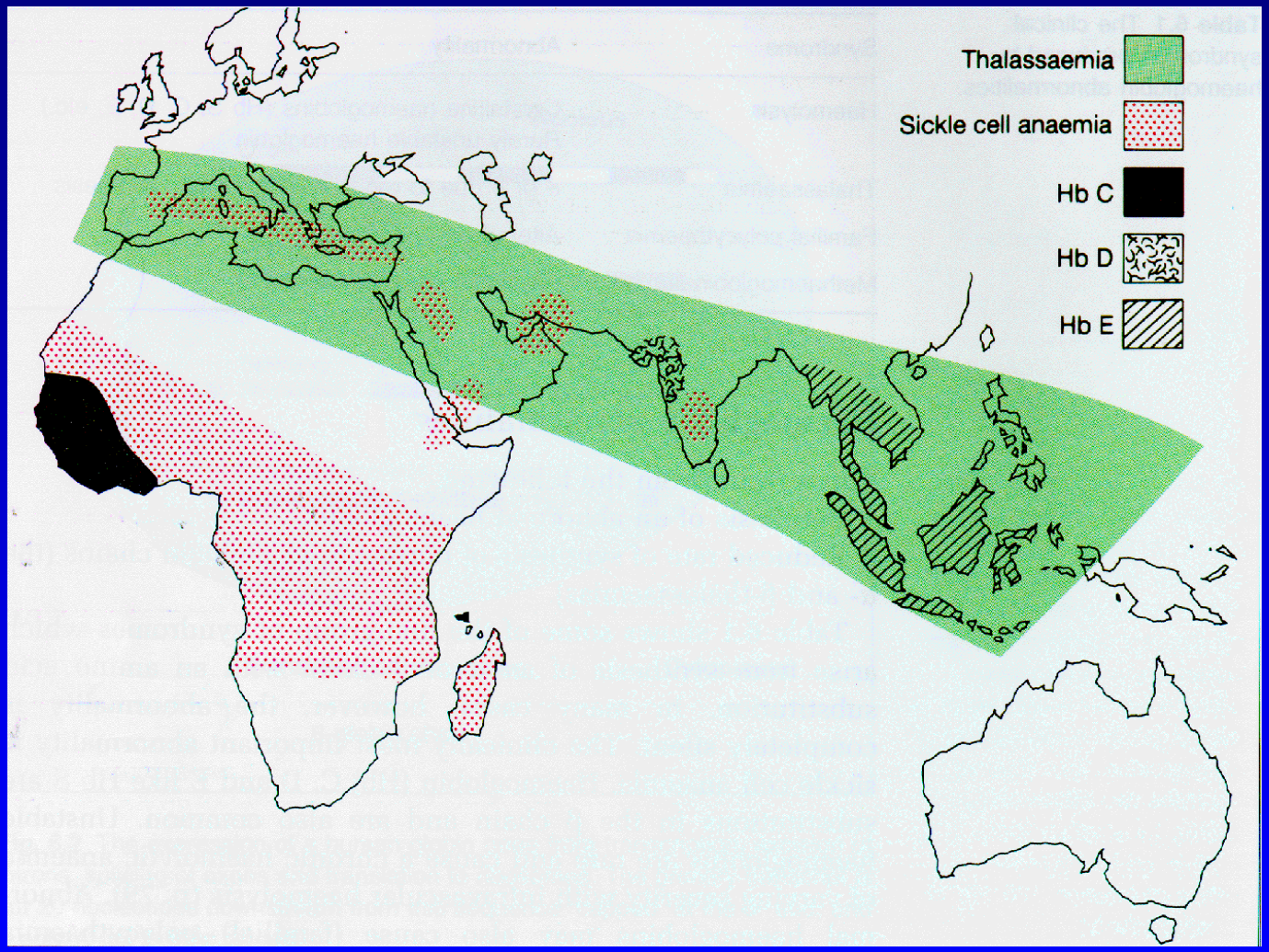
Objectives

- Definitions
  - Hemoglobin SS, SC, other
- Beta globin Haplotype
- Phenotype
  - Pain
- Recommendations



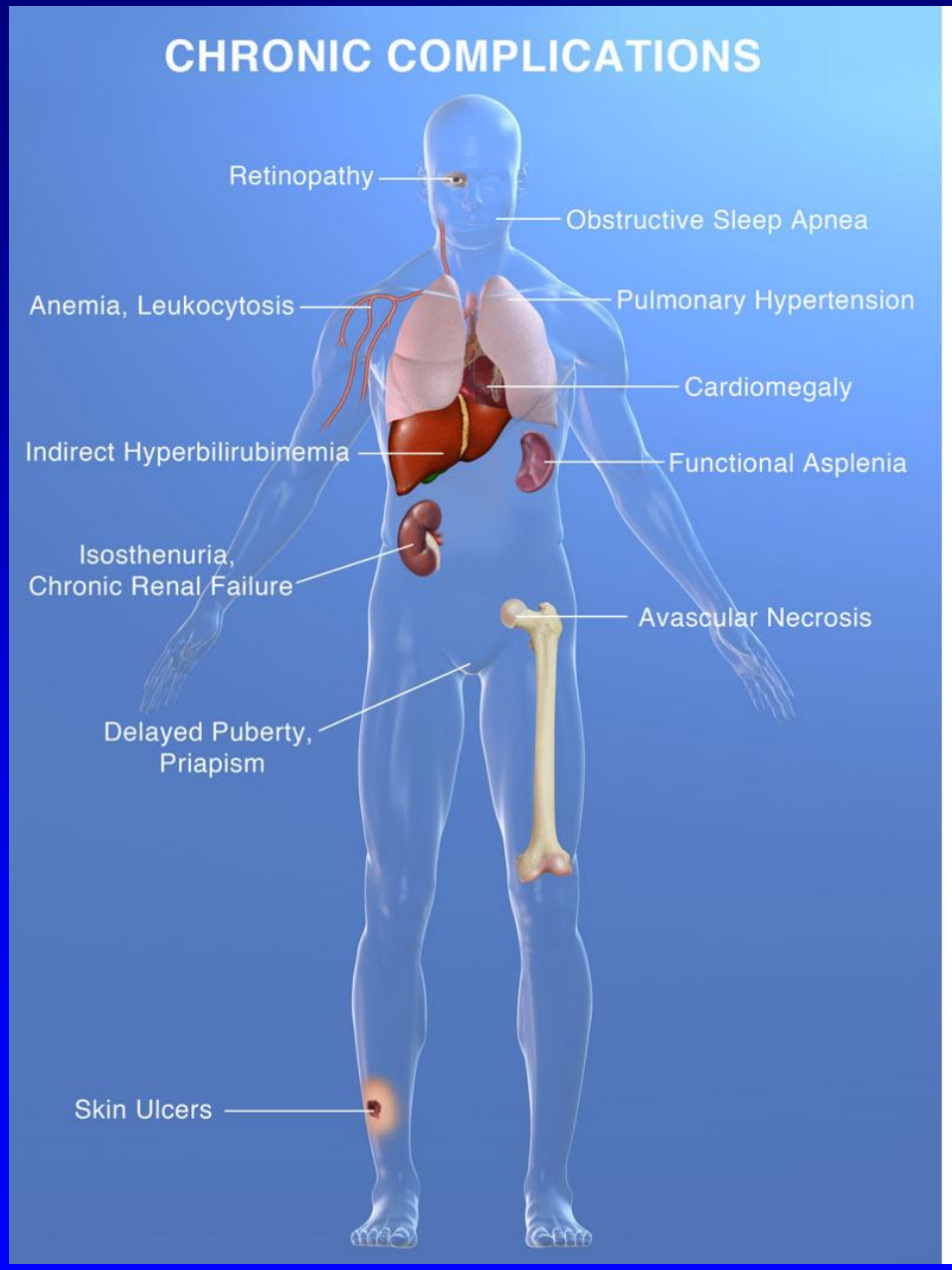
Sickle Cell Disese Genotypyes

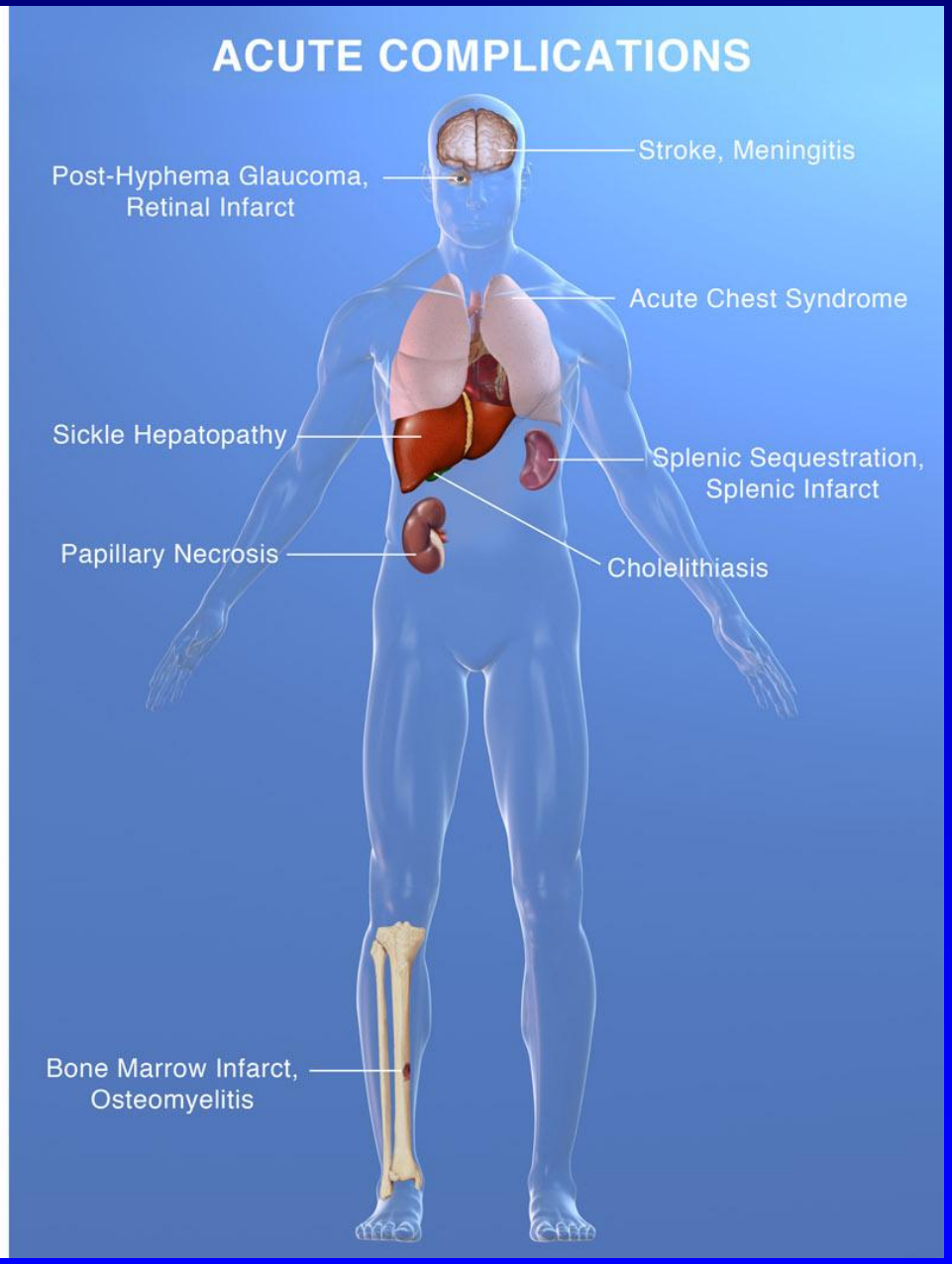


SCD Genotypes

- Hemoglobin SS
- Hemoglobin SC
- Hemoglobin S beta thalassemia
  - Zero
    - no production of hemoglobin A
  - Plus
    - production of hemoglobin (2,30%)
- Hemoglobin S Persistent Fetal Hemoglobin

Complications of Sickle Cell Disease





What do families living with sickle cell disease want health care providers to address?

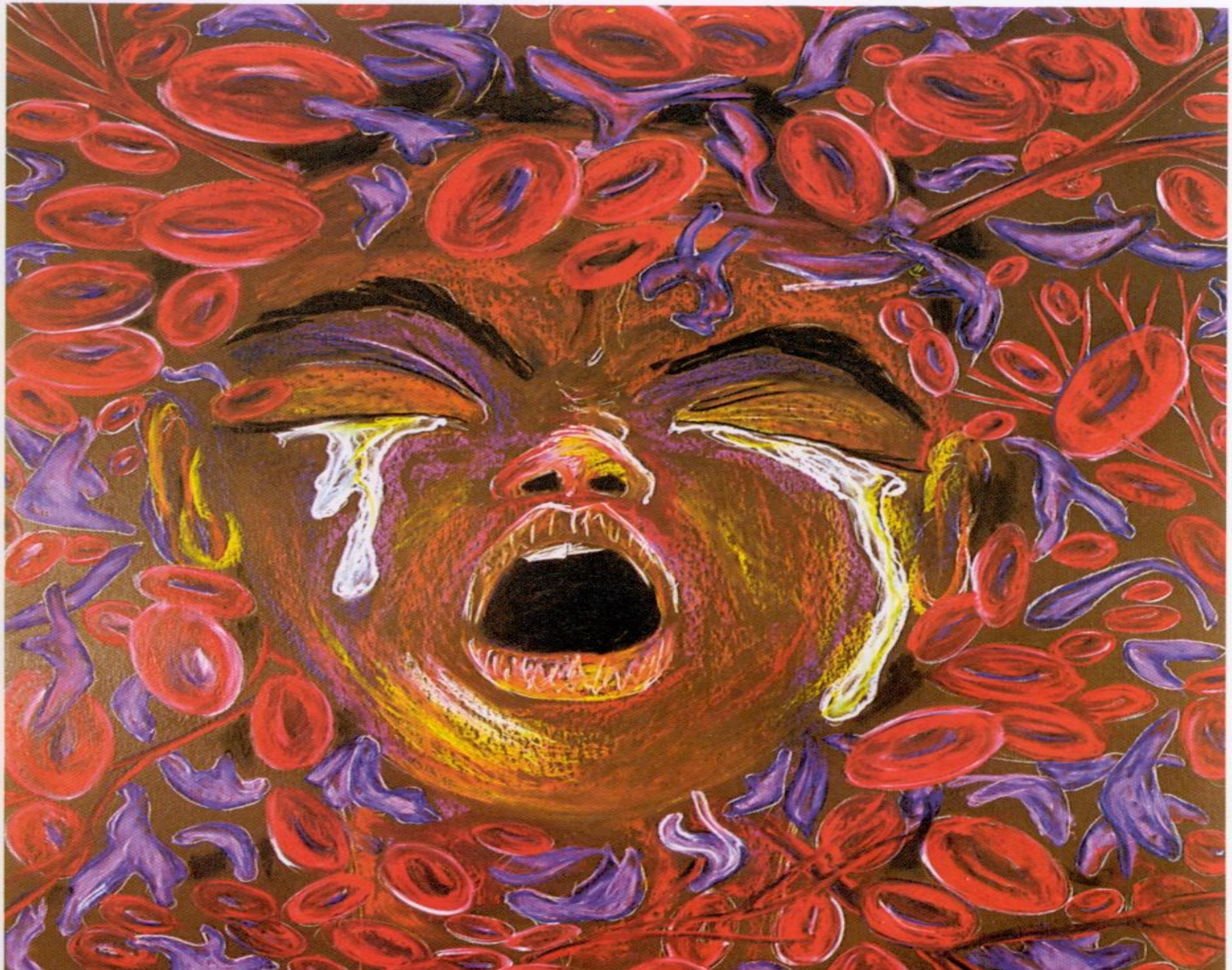
Topic Suggestions for Future Events (n= 62 families)

Pain Management
School Intervention
Coping with SCD
Advocacy of Local Events
Financial Resources
Community Resources

What Does sickle cell anemia look like for a 22 year old?

I know that it has been long overdue since we've last talked ,but I'm hoping to break that silence today…..I wanted to ask you if you knew of any adult hematologists (that you personally approved of) who provides good care.

Since I have been here, despite doing everything that I have been told to do (taking hydroxyurea and folic acid "the right way" and even taking oxycontin and oxycodone around the clock, non-stop), I have still been in constant pain. My hemoglobin will not stay up past 3.7 (sometimes lower) for more than a week at a time despite receiving constant blood transfusions and a series of shots every 3 weeks. I feel as though the longer I stay here, the worse my health becomes……..



Vaso-occlusive pain episode

- Most generous (Smith et al. Ann Intern Med. 2008 Jan 15;148(2))
  - Pain that requires opioid treatment at home or with a physician contact
  - Limitations
    - Difficult to quantify because requires a diary
- Most conservative (SIT Trial)
  - Pain that requires hospitalization
  - Limitations
    - Most patients with severe pain manage their pain at home
    - Lower estimate of the burden of pain

Most Recent Definition of Pain

Am J Hematol. 2009 Sep; 85(1):6-13.)

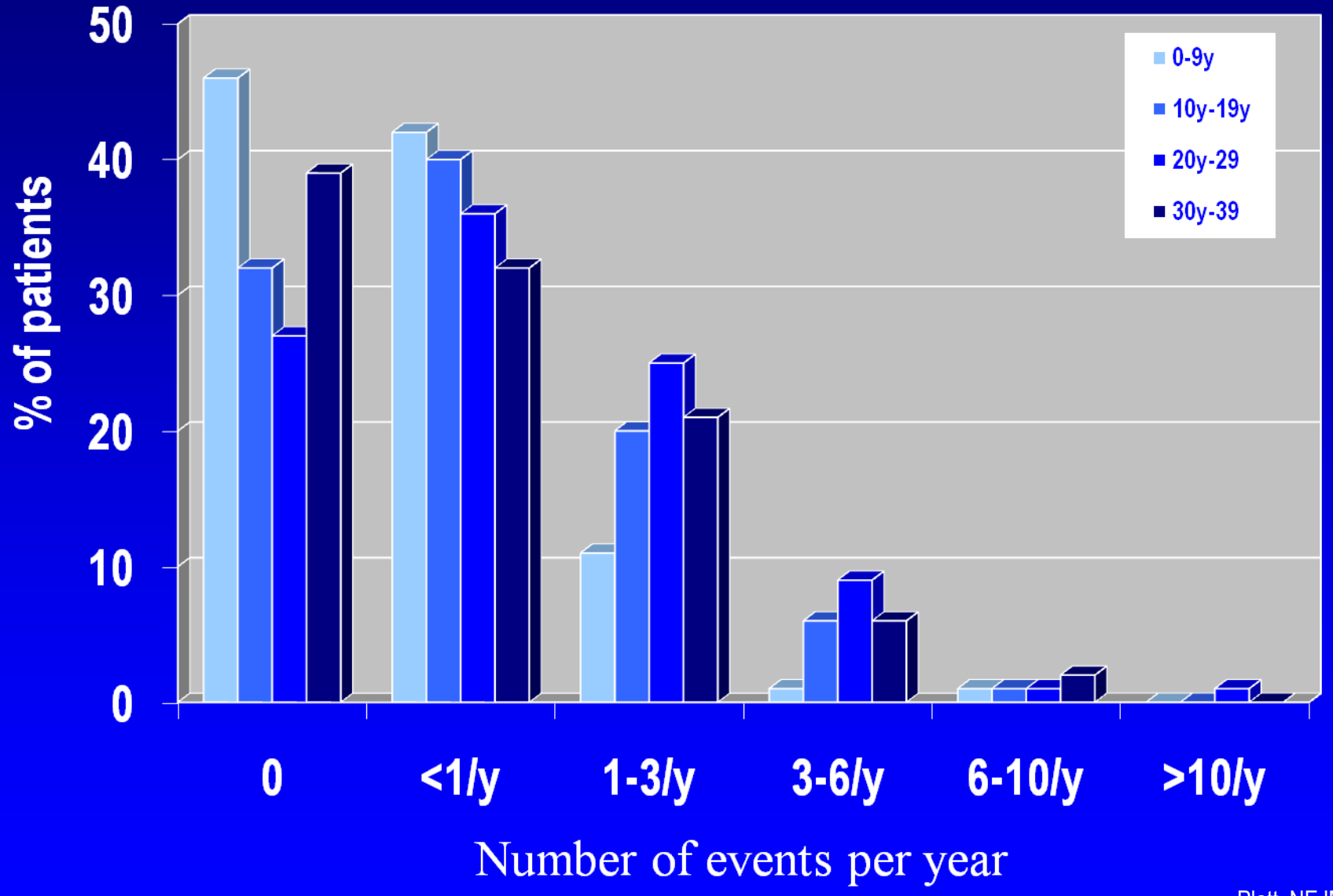
- Comprehensive Sickle Cell Centers
  - New onset of pain that lasts at least 4 hours for which there is no explanation other than vaso-occlusion, and which requires therapy with either opioids or ketorolac in a medical setting

Incidence of Pain by Genotype Defined as pain that last for two hours and requires physician contact-pre HU era

Complication	Beta Globin Genotype		
	SS	SC	$S\beta^+$
Painful Episodes	80	40	40

Cooperative Stud of Sickle Cell Disease;
All rates expressed per 100 patient-years

Distribution of pain rates in SS



Platt, NEJM, 1991

Problem

- Multiple Modifiers of pain
  - Hydroxyurea, genotype, age, asthma, therapy
- Multiple definitions of pain
  - Any physician contact- CSSCD
  - Home diary- Smith et al.
  - Hospital records -SIT Trial
- Duration of evaluation
  - Lifetime- CSSCD- gold standard
  - Home diary-6 months
  - Hospitalization for pain- previous 3 years

Replication Strategies: The Key to Validating NCI and NHGRI Workshop

Nature 2007;447(7145):655-60.

Three key components

1. Sufficient sample size
2. Independent data set
3. Identical phenotype

Validation of CSSCD pain models in SITT dataset
Life time pain rate with MD contact versus
3 year retrospective hospitalization for pain
(Lettre *et al*., PNAS 2008 105 (33): 11869-11874)

Model	CSSCD†		SITT‡	
	Chisq (df)	P-value	Chisq (df)	P-value
HbF vs Basic	17.9 (1)	2.0×10^{-5}	16.4 (1)	5.12×10^{-5}
Genotype vs Basic	20.4 (5)	0.001	12.2 (3)	0.0067
† **Full vs HbF**	14.4 (5)	0.01	8.2 (3)	0.042

Basic model: Pain rate* = gender + age registration
HbF model: Pain rate* = basic model + HbF
Genotype model: Pain rate * = basic model + Hb F SNPs
Full model: Pain rate* = basic model + HbF + Hb F SNPs

Suggestions for Future Work

- Common phenotype definitions for all NIH funded sickle cell disease trials and observation studies
- Central biological repositories for NIH SCD studies linked to pre-defined common phenotypes
- Large consortia for addressing specific genotype phenotype studies or pathway-phenotype studies

Thank You!

James Casella, Emilly Casella, Pallav Bhatnagar, Dan Arking- Johns Hopkins; SIT Trial Investigators and Families