

## HEMOGLOBINOPATHY SCREENING

### I. DEFINITIONS:

- A. Hemoglobinopathy screening is a detection method to identify individuals with sickle cell disease or other hemoglobin variants. The Public Health Laboratory provides testing for adults and newborns (see Newborn Blood Screening).
- B. In August 1991, the Oklahoma State Department of Health adopted rules requiring that all newborn infants be screened for Sickle Cell Disease.
- C. Hemoglobinopathies refer to all abnormal hemoglobin conditions including trait and disease (sickle cell disease and hemoglobin disease) conditions.
- D. Sickle Cell Disease is the term used to identify disorders in which the red blood cells sickle under stress. Sickle Cell Anemia (Hemoglobin SS Disease) is the most common form of Sickle Cell Disease, but other forms do exist.
- E. Sickle cell diseases are a group of genetic disorders that are autosomal recessive. For disease to occur in an autosomal recessive disorder, the individual must receive a non-working hemoglobin gene from each parent. For example, if an individual inherited one S hemoglobin gene from mom and an S hemoglobin gene from dad then the child will have Sickle Cell Anemia (Hemoglobin SS Disease).
- F. A "Trait" or "Carrier" condition indicates that the individual has inherited one working hemoglobin gene (A) and one non-working hemoglobin gene. For example, if an individual inherited one non-working (S) hemoglobin gene and one working (A) hemoglobin gene he/she is said to have sickle cell trait or AS hemoglobin. Individuals with a trait condition can pass the non-working gene to their offspring. Normally an individual with a trait condition does not experience adverse effects related to their hemoglobin type. However under extreme conditions such as high altitude (flying, mountain climbing), increased pressure (scuba diving), low oxygen (mountain climbing, exercising extremely hard), or dehydration an individual may experience complications of sickle cell disease. This would include splenic sequestration, pain crisis, and rarely, sudden death.
- G. Laboratories often identify the different kinds of hemoglobin by using a letter in the alphabet. There are over 600 different types of hemoglobin. Some of the more common hemoglobins include:
  - F Fetal Hemoglobin (present at birth to 6 months)
  - A Adult Hemoglobin (normal hemoglobin)
  - S Sickle Hemoglobin
  - C Hemoglobin C
  - D Hemoglobin D
  - E Hemoglobin E
- H. Hemoglobin isoelectric focusing is the laboratory screening method used to detect trait or disease conditions. This methodology is effective for detecting common hemoglobins such as F, A, S, C, D, G, O and E, but cannot detect thalassemia conditions in newborns.

1. The following are examples of hemoglobin isoelectric focusing screening results:

FA	Normal Newborn Hemoglobin
AA	Normal Adult Hemoglobin
FAS	Newborn with Sickle Cell Trait
FAC	Newborn with Hemoglobin C Trait
AC	Hemoglobin C Trait
AS	Sickle Cell Trait
SS	Sickle Cell Anemia (Hemoglobin SS Disease)
SC	Sickle Hemoglobin C Disease (Hemoglobin SC Disease)
SA	Sickle Beta <sup>+</sup> Thalassemia Disease
CC	Hemoglobin C Disease

## II. ETIOLOGY AND EPIDEMIOLOGY:

### A. Etiology

1. Malaria Hypothesis – Populations who have a high prevalence of sickle hemoglobin inhabit areas where malaria is or once was endemic. One theory is that individuals with hemoglobin AS may have been better able to survive malarial infection than persons without hemoglobin S, leading to the high carrier status in some populations. This protection from malaria is only true for trait conditions; individuals with disease are more prone to malarial infections.
2. Pathophysiology of Sickle Cell Disease - Deoxygenation of Hemoglobin S causes the internal structure of the red blood cell to polymerize and form long aligned fiber which distort the membrane, changing the cell shape from biconcave to a sickle shape. These sickled red blood cells break down more rapidly and result in anemia. The rigidity of the sickled cells cause blockage (vaso-occlusion) in small blood vessels. This vaso-occlusion can cause pain, tissue hypoxia, splenic sequestration, stroke, and organ damage. Lastly, there is an increased risk for infection. In young children with sickle cell disease, infection is the leading cause of death.

### B. Epidemiology

1. A common misconception about sickle cell disease and trait conditions is that they are limited to the African race and their descendants. Sickle Cell Diseases and other hemoglobin variants can be found in any race. This is the reason for universal newborn screening. However, there is an increased prevalence in some populations. For example:
  - a. Hemoglobin S is commonly found in Africans, Arabs, Egyptians, Turks, Greeks, Italians (chiefly Sicilians), Iranians and Asiatic Indians.
  - b. Hemoglobin C is common among Africans in West and Northern Africa.
  - c. Hemoglobin D is seen in Punjabis of India, and other Asiatic Indians, Pakistanis, Afghanistans and Iranians.
  - d. Hemoglobin E is common in people of the Asiatic Indians, Malaysians, Thias, Cambodians, Laotians, Indonesians, Vietnamese and Filipinos.

- e. Beta Thalassemia is seen among a diverse group of people including Africans, people of Southern Europe, the Middle East, Asia, Southeast Asia and the Pacific.

### III. CLINICAL FEATURES:

- A. Signs and Symptoms for Trait: None

Complications: The genetic risk of producing a child with a trait condition or disease.

- B. Signs and Symptoms for Sickle Cell Disease:

- 1. Not evident at birth. First clinical manifestation is typically infection. Other common complications include anemia, pain, and organ dysfunction.

**NOTE:** Penicillin prophylaxis should begin by two months of age for infants with suspected or confirmed sickle cell disease.

- 2. **FEVER ALERT:** A child with sickle cell disease who has a temperature of 101° or more requires prompt intervention. **Immediate referral to an emergency room or pediatric hematologist is required.** Medical management will include a blood culture and an initial dose of intravenous antibiotics. To prevent mortality, a febrile child with sickle cell disease should never be sent home without proper treatment. To obtain a copy of the fever treatment guidelines, contact Joyce Clytus, Sickle Cell Disease Nurse Coordinator, at (405) 271-5311 or Newborn Screening Program at (405) 271-6617.

- 3. Sickle cell disease can cause a variety of medical problems. Severity varies among the different forms of sickle cell disease and also among individuals. Some individuals with sickle cell disease rarely have sickle cell related complications, while others require frequent hospitalizations. Presently, there is no way to predict how severely someone will be affected. Conditions or situations that may trigger illness are dehydration, alcohol consumption, high altitudes, extreme temperatures, stress and depression.

### IV. MANAGEMENT PLAN:

- A. Hemoglobinopathy Screening:

- 1. Laboratory Studies: Hemoglobinopathies by hemoglobin isoelectric focusing.

- 2. Screening:

- a. Currently, all newborns are screened for hemoglobinopathies
- b. Children who were not screened as newborns, adults of childbearing age (females < 46 years of age, maternity or family planning patients of any age, males of any age) should be screened if they do not know their carrier status.
- c. The following surrounding states (Arkansas, Kansas, Missouri, and Texas) perform hemoglobinopathy screening on babies born at hospitals within their state.

- d. Upon confirmation of a disease or trait condition, family counseling should be provided. Resources for counseling statewide:

**Oklahoma City**

OUHSC Genetics Program  
940 N.E. 13<sup>th</sup> Street Room 2B2418  
Oklahoma City, OK  
(405) 271-8685

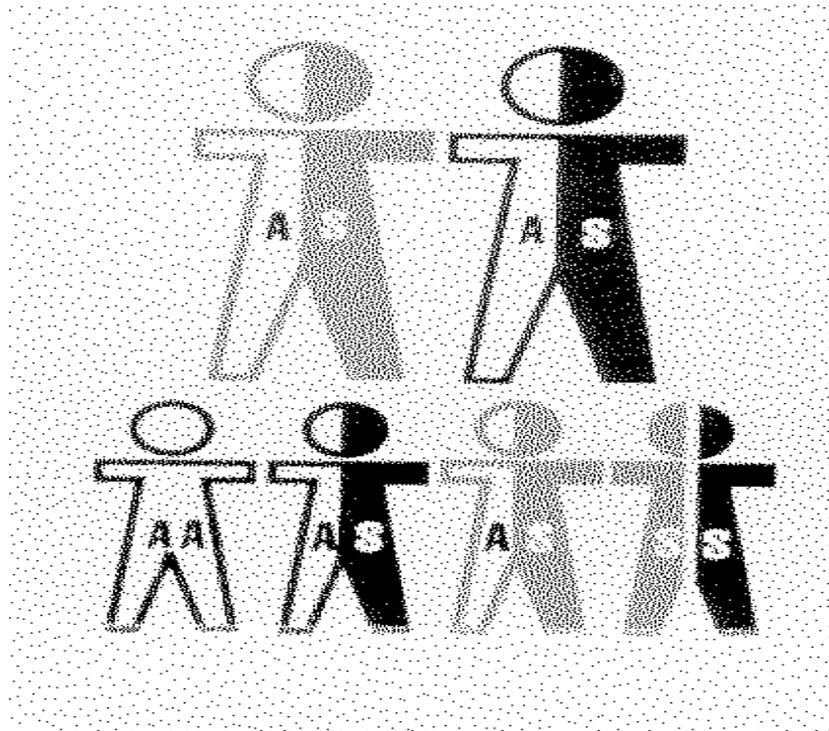
**Tulsa**

The Children's Hospital at Saint Francis  
6161 S. Yale Ave.  
Tulsa, OK  
(918) 502-8365

B. Genetic Trait Counseling:

Individuals found to have trait should be provided information on trait condition and counseling on the risk of disease transmission (fig. 1). Screening for other immediate family members should be offered. Please call Newborn Screening Division for assistance in scheduling genetic counseling at (405) 271-6617.

**Genetic Transmission**



**Figure 1: Genetic Transmission of Sickle Cell Anemia (Hemoglobin SS Disease)**  
Both parents have sickle cell trait (hemoglobin AS). They each possess one gene for normal hemoglobin (A) and one gene for sickle hemoglobin (S). With each pregnancy there is a 25% chance that their child will have normal hemoglobin (AA, FA), 50% chance of having sickle cell trait (AS, FAS) and 25% risk of having sickle cell anemia (SS, FS).

This risk applies to each pregnancy. There is a 1 in 4 (25%) chance of having a child with Sickle Cell Anemia (Hemoglobin SS Disease).

C. Consultation and Referral:

1. **Children with Sickle Cell Disease should be referred to a pediatric hematologist for follow-up:**

Oklahoma City:	Arpan Sinha, M.D., (405) 271-5311 Ashley Baker, M.D. (405) 271- 5311
Tulsa:	Ashraf Mohammad, M.D., (918) 502-6720
State Sickle Cell Disease Nurse Coordinator:	Joyce Clytus, R.N. (405) 271-5311

**Individuals identified with Sickle Cell Disease, Sickle Cell Trait (AS), Hemoglobin C Trait (AC), Hemoglobin D/G Trait (AD/G), and Hemoglobin E/O Trait (AE/O) should be referred for counseling:**

<u>Oklahoma City</u> OUHSC Genetics Program 940 N.E. 13 <sup>th</sup> Street Room 2B2418 Oklahoma City, OK (405) 271-8685	<u>Tulsa</u> The Children's Hospital at Saint Francis 6161 S. Yale Ave. Tulsa, OK (918) 502-8365
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2. **Community Education and Resource Coordination for Individuals with Sickle Cell Disease.**

Sickle Cell Disease Association of America, Inc.  
231 East Baltimore, Street, Suite 800  
Baltimore, Maryland 21202 (410) 528-1555  
Web Site: [www.sicklecelldisease.org](http://www.sicklecelldisease.org)

3. Consultation regarding the care of children with hemoglobinopathies can be obtained by contacting the Newborn Screening Follow-up nurse at (405) 271-6617 or 1-800-766-2223, or Sickle Cell Disease Nurse Coordinator at (405) 271-5311.
4. The following hemoglobinopathy information pamphlets are available for patient/family counseling guides:

**Hemoglobin C Trait:** Catalog Number P-545

**Sickle Cell Trait:** Catalog Number P-547

**About Sickle Cell Disease and Sickle Cell Trait:** Catalog Number P-562

**To order pamphlets send a request in writing (order form ODH 15):**  
OSDH, Shipping and Receiving, 1000 N.E. Tenth, Oklahoma City,  
Oklahoma, 73117-1299.

For more information regarding other educational materials please call the Newborn Screening Quality Assurance Nurse Coordinator at (405) 271-6617 or 1-800-766-2223.

REFERENCES:

- Miller, D.R., Baehner, R.L., McMillan, C.W., Blood Diseases of Infancy and Childhood, 7<sup>th</sup> ed., C.V. Mosby, 1995.
- Sickle Cell Disease: Screening, Diagnosis, Management, and Counseling in Newborns and Infants, U.S. Department of Health and Human Services Publication No. 93-0562, April 1993.
- OSDH - *Newborn Screening Program Regulations*, 2004.

**HEMOGLOBINOPATHY FOLLOW-UP PROCEDURES – updated September 22, 2010**

<b>Filter Paper Result</b>	<b>Screen Interpretation and Follow-up Recommendations</b>
<b>FA</b>	<b>Normal hemoglobin for an infant (F indicates fetal hemoglobin).</b> No follow-up indicated.
<b>AA</b>	<b>Normal hemoglobin for persons over 12 months of age (A indicates adult hemoglobin).</b> No follow-up indicated.
<b>AF</b>	<b>Normal newborn hemoglobin unless transfused.</b> If transfused prior to collection of the initial screen, then the infant has not been adequately screened for sickle cell disease and a follow-up hemoglobin electrophoresis should be done at four months of age or 3 months post transfusion.
<b>FAS (sickle cell trait)</b> <b>FAC (hemoglobin C trait)</b> <b>FA Other</b>	<b>Probable trait conditions in newborns.</b> A follow-up hemoglobin electrophoresis should be done at 3-4 months of age. These benign trait conditions should not cause any clinical symptoms.
<b>AS (sickle cell trait),</b> <b>AC (hemoglobin C trait)</b> <b>A and Other</b>	<b>Probable trait conditions for persons over 12 months of age.</b> Autosomal recessive inheritance counseling should be provided. Parents and siblings may require screening.
<b>FA Barts</b> <b>FAS Barts</b> <b>FAC Barts</b> <b>FA “Other Variant” and Barts</b>	<b>Hemoglobin “FA” or “A” with S, C, or Other indicates probable trait.</b> A follow-up hemoglobin electrophoresis should be done at 3-4 months of age.  <b>The finding of Hemoglobin Barts</b> can indicate a possible alpha thalassemia trait condition. Alpha thalassemia trait is a mild, familial, microcytic anemia. Often children with alpha thalassemia trait are treated mistakenly for iron deficiency. Long term treatment of infants with alpha thalassemia with supplemental iron will not correct the anemia and may be harmful. Therefore, iron deficiency in children with hemoglobin barts should be documented by iron studies prior to treatment. To confirm alpha thalassemia trait, a clinical evaluation and CBC with indices is indicated at 12 months of age or if of Asian descent (may be at risk for hemoglobin disease) at 3 months of age. Autosomal recessive inheritance counseling should be provided.
<b>F Other</b>	<b>May indicate immaturity, a trait condition or hemoglobin disease.</b> A follow-up hemoglobin electrophoresis should be done at 3-4 months of age.
<b>F Only</b>	<b>May indicate immaturity, a trait condition or hemoglobin disease.</b> A follow-up hemoglobin electrophoresis should be done at 2 months of age.

**NOTE:** The Public Health Laboratory no longer provides whole blood confirmatory testing. For confirmatory testing (whole blood hemoglobin electrophoresis or DNA), only a laboratory experienced in testing newborns should be utilized. For transfusion and possible trait conditions, a second filter paper (FP) screen submitted to the Public Health Laboratory will be recommended. A repeat FP will facilitate determination of trait or disease condition. If confirmatory testing is desired, a referral to a pediatric hematologist or geneticist will be needed.

**HEMOGLOBINOPATHY FOLLOW-UP PROCEDURES (CONT.)**

<b>Filter Paper Result</b>	<b>Screen Interpretation and Follow-up Recommendations</b>
<b>FC</b>	Probable Hemoglobin C Disease. A whole blood hemoglobin electrophoresis or DNA testing is indicated. Prompt referral to a pediatric hematologist is indicated for confirmatory testing, clinical evaluation, and autosomal recessive inheritance counseling.
<b>F with “other variant” in E/O region</b> <b>F with “other variant” in D/G region</b>	Possible Hemoglobin E, O, D or G Disease. A whole blood hemoglobin electrophoresis or DNA testing is indicated. Prompt referral to a pediatric hematologist is indicated for confirmatory testing, clinical evaluation, and autosomal recessive inheritance counseling. If confirmed, coordinated medical care between the primary care provider and pediatric hematologist is required.
<b>FS</b>	Probable Sickle Cell Anemia (Hemoglobin SS Disease). A whole blood hemoglobin electrophoresis or DNA testing is indicated. Prompt referral to a pediatric hematologist is indicated for confirmatory testing, clinical evaluation, and autosomal recessive inheritance counseling. If confirmed, treatment with prophylactic penicillin and coordinated medical care between the primary care provider and pediatric hematologist is required.
<b>FSC</b>	Probable Hemoglobin SC Disease. A whole blood hemoglobin electrophoresis or DNA testing is indicated. Prompt referral to a pediatric hematologist is indicated for confirmatory testing, clinical evaluation, and autosomal recessive inheritance counseling. If confirmed, treatment with prophylactic penicillin and coordinated medical care between the primary care provider and pediatric hematologist is required.
<b>FSA</b>	Probable Sickle Beta <sup>+</sup> Thalassemia. A whole blood hemoglobin electrophoresis or DNA testing is indicated. Prompt referral to a pediatric hematologist is indicated for confirmatory testing, clinical evaluation, and autosomal recessive inheritance counseling. If confirmed, treatment with prophylactic penicillin and coordinated medical care between the primary care provider and pediatric hematologist is required.

LABORATORY PROCEDURE: Hemoglobin Isoelectric Focusing is performed on filter paper

Normal Result (results may be invalid if the individual has had a blood transfused prior to specimen collection):  
FA, AA, AF

The Public Health Laboratory only provides **screening** for hemoglobinopathies. Screening can identify hemoglobin F (fetal), A (adult), S and C. The screening test cannot distinguish between abnormal hemoglobins “D or G” or between “E or O.” The screen can also identify “Other” possible abnormal hemoglobins. The term “Other” indicates a probable abnormal hemoglobin. There are over 600 types of hemoglobins. To confirm a hemoglobinopathy trait or disease condition, a whole blood hemoglobin electrophoresis or DNA testing is needed. If the parents desire to identify the specific type of hemoglobin, refer to a pediatric hematologist or geneticist for further testing. The Public Health Laboratory is unable to perform testing on whole blood specimens.

For **Pediatric Hematologist** referral, please contact Joyce Clytus, R.N., Sickle Cell Disease Nurse Coordinator at (405) 271-5311.

**Questions** regarding follow-up or confirmatory testing, please contact the Newborn Screening Short-term Follow-up Program at (405) 271-6617 or 1-800-766-2223, Fax: (405) 271-4892.

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