Abnormal Newborn Screening
Referral Guidelines
Texas Children's Cancer and Hematology Center

The purpose of a newborn hemoglobinopathy screening is to detect sickle cell disease. **Hemoglobins are generally reported in decreasing order of concentration.** In the newborn period, hemoglobin F will be listed first, followed by the hemoglobin(s) that will become dominant as the hemoglobin F declines.

Newborn hemoglobinopathy screenings may also identify:

- Sickle cell trait
- Hemoglobin C trait, hemoglobin C disease
- Hemoglobin E trait, hemoglobin E disease, and hemoglobin E thalassemia
- Hemoglobin Bart's (alpha thalassemia trait)
- Hemoglobin H disease (an alpha thalassemia disorder)
- Beta thalassemia major
- Presence of other hemoglobin variants

NOTE: *Newborn hemoglobinopathy screening will not identify beta thalassemia trait.*

Most Commonly Reported Newborn Screen Hemoglobinopathy Results

Newborn Screen Result: FA

Interpretation: Normal result. No referral to Pediatric Hematology is needed.

Newborn Screen Result: FAS

Interpretation: Sickle Cell Trait

General Information: Sickle cell trait is an inherited blood condition. It is not a disease. It occurs when a person has one gene for normal hemoglobin (hemoglobin A) and one for sickle hemoglobin (hemoglobin S). This gene can be passed along to his or her children.

Confirmatory testing: No confirmatory testing required.

Clinical Significance:

- **Most** individuals with sickle cell trait lead completely normal lives and usually show no outward signs of it. People with the trait will not get sickle cell disease.
- **Some** individuals with sickle cell trait may have sickle cell-related problems, such as pain or splenic infarctions, particularly when in extreme physiologic conditions.
- **Very rarely** individuals with sickle cell trait can have additional problems, such as a very rare form of kidney cancer found only in individuals with sickle cell trait.

Referral Guidelines:

- **No referral to Pediatric Hematology is needed**.
- **Genetic counseling *is* required,** and our Pediatric Hematology Center can offer genetic counseling via telemedicine to patients with sickle cell trait. Please specify this request in your referral.
- https://www.dshs.texas.gov/newborn-screening-program/sickle-cell-disease/sickle-cell-trait

Newborn Screen Result: FS

Interpretation: Hemoglobin SS Disease or Hemoglobin $S\beta^0$

General Information: Hemoglobin SS (HgbSS) and sickle beta thalassemia zero disease are moderate-severe form of sickle cell disease. The red blood cells are abnormally shaped, similar to a "sickle" shape. These cells affect how blood flows through blood vessels and block flood flow, which can cause pain, infections, and organ damage. Many babies with sickle cell disease are born healthy and do not show symptoms until they get closer to their 1st birthday.

Clinical Significance:

- **All** individuals with HgbSS or $HgbS\beta^0$ experience increased risk of infections, increased risk of stroke, anemia, and organ damage.
- **Most** individuals will experience one or more of the following complications: vaso-occlusive pain, neuropathic pain, jaundice or icterus, gallstones, bacteremia/sepsis, acute chest syndrome, acute splenic sequestration (sudden enlargement of the spleen and rapid drop in the hemoglobin), retinopathy, dactylitis (swelling of hands and feet), deep vein thrombosis, and leg ulcers.

Referral Guidelines:

- **Referral to Pediatric Hematology is needed.**
- Advise patients and caregivers to come to the emergency room for fever of 101 degrees Fahrenheit and the importance of NOT treating fever with fever reducing medication such as acetaminophen or ibuprofen until a medical assessment has been performed.
- Prophylactic penicillin use is highly recommended as early as possible in these patients at least until age of 5 years.
- Non-routine vaccinations related to infectious complications associated with sickle cell disease are necessary (use vaccination guidelines for asplenia at CDC site).
- Annual transcranial Doppler ultrasound is performed to assess for stroke risk, starting at 2 years of age.
- Annual screenings for retinopathy and renal disease starting at 10 years of age.
- There are multiple therapies available to patients with sickle cell disease. These therapies require special expertise and monitoring and are available through providers trained in sickle cell disease.
- The National Heart, Lung and Blood Institute (NHLBI) recommends all children with sickle cell disease are seen by a pediatric hematologist by 8 weeks of age.

Newborn Screen Result: FSA

Interpretation: Sickle Beta Thalassemia Plus Disease

General Information: Sickle Beta-thalassemia plus ($HgbS\beta^+$) is a form of sickle cell disease characterized by the presence of small amount of normal hemoglobin A. The newborn screen result for $HgbS\beta^+$ is typically FSA, but if there is a very small amount of hemoglobin A at birth, may present as FS.

Clinical Significance:

- **Some** individuals with $HgbS\beta^+$ have overlapping findings to those with $HgbSS/HgbS\beta^0$ including anemia, increased risk of infections, organ damage, vaso-occlusive pain, neuropathic pain, jaundice or icterus, gallstones, bacteremia/sepsis, acute chest syndrome, acute splenic sequestration (sudden enlargement of the spleen and rapid drop in the hemoglobin), retinopathy, dactylitis (swelling of hands and feet), deep vein thrombosis, and leg ulcers.
- Individuals with $HgbS\beta^+$ are **not at increased risk of developing stroke**.

Referral Guidelines:

- **Referral to Pediatric Hematology is needed.**
- Advise parents to bring patient to ER for fever of 101 degrees Fahrenheit and the importance of NOT treating fever with fever reducing medication such as Tylenol of Ibuprofen.
- Prophylactic penicillin use in these patients is controversial, however provider may start penicillin at parental request.
- Non-routine vaccinations related to infectious complications associated with sickle cell disease are recommended (use vaccination guidelines for asplenia at CDC site).
- Screen annually for retinopathy and renal disease starting at 10 years of age.
- Medical therapies for $HgbS\beta^+$ are different than that of $HgbSS/HgbS\beta^0$ and should be offered and managed by providers trained in sickle cell disease.

Additional Resources:

- https://sicklecellspeaks.com/understanding-sickle-cell/types-of-sickle-cell/

Newborn Screen Result: FSC

Interpretation: Hemoglobin Sickle C Disease

General information: Hemoglobin Sickle C Disease (HgbSC) is a different form of sickle cell disease. The red blood cells of a child with HgbSC disease have two kinds of abnormal hemoglobin. Hgb SC occurs when a person inherits a HgbS (S trait) from one parent and a HgbC (C trait) from the other parent.

Clinical Significance:

- **Some** individuals with HgbSC have overlapping findings to those with HgbSS/HgbSβ^0 including anemia, increased risk of infections, organ damage, vaso-occlusive pain, neuropathic pain, jaundice or icterus, gallstones, bacteremia/sepsis, acute chest syndrome, acute splenic sequestration (sudden enlargement of the spleen and rapid drop in the hemoglobin), dactylitis (swelling of hands and feet), deep vein thrombosis, and leg ulcers.
- Individuals with HgbSC are **not at increased risk of developing stroke**.
- Compared to HgbSS/HgbSβ^0, individuals with HgbSC **are at increased risk of developing retinopathy** (retinal damage in the back of the eye).

Referral Guidelines:

- **Referral to Pediatric Hematology is needed.**
- Advise parents to bring patient to ER for fever of 101 degrees Fahrenheit and the importance of NOT treating fever with fever reducing medication such as Tylenol of Ibuprofen.
- Prophylactic penicillin use in these patients is controversial, however provider may start penicillin at parental request.
- Non-routine vaccinations related to infectious complications associated with sickle cell disease are recommended (use vaccination guidelines for asplenia at CDC site).
- Screen annually for retinopathy and renal disease starting at 10 years of age.
- Medical therapies for HgbSC are different than that of HgbSS/HgbSβ^0 and should be offered and managed by providers trained in sickle cell disease.

Summary of Sickle Cell Disease Types on Newborn Screen

DIAGNOSIS	CONFIRMATORY TEST in the neonate	Confirmatory result beyond infancy	CBC	INHERITANCE
Hemoglobin SS (HgbSS)	Hemoglobin FS	Majority hemoglobin S No hemoglobin A Normal A2 +/- mild increased F	Low Hgb Normal MCV Sickle cells on peripheral smear	Both parents AS
Sickle Beta Thalassemia Zero (HgbSβ^0)	Hemoglobin FS	Majority hemoglobin S No hemoglobin A Increased A2 +/- mild increased F	Low Hgb Low MCV Sickle cells on peripheral smear	One parent AS One parent Aβ^0 (Hemoglobin A with elevated A2)
Sickle Beta Thalassemia Plus (HgbSβ+)	Hemoglobin FSA	Majority hemoglobin S Some hemoglobin A Increased A2 +/- mild increased F	Normal or mildly low-Hgb Low MCV	One parent AS One parent Aβ+ (Hemoglobin A with elevated A2)
Hemoglobin SC (HgbSC)	Hemoglobin FSC	Majority hemoglobin S Presence of hemoglobin C No hemoglobin A Normal hemoglobin A2	Mildly low-Hgb Low MCV Target cells on peripheral smear	One parent AS One parent AC
Sickle Cell with Hereditary Persistent Fetal Hemoglobin (S HPFH)	Hemoglobin FS	Majority hemoglobin S No hemoglobin A Significantly increased hemoglobin F (>20%)	Normal Hgb Normal or high MCV Normal peripheral smear	One parent AS One parent AF

In Texas, newborn screen samples are analyzed for common genetic mutations that cause disease. However, most beta thalassemia mutations are deletions and **will not be identified** on this type of genetic analysis. Therefore, even a result reporting "2 copies of SS" may indicate that the only abnormality that was identified was the gene associated with hemoglobin S, but it **may have missed detecting** a missing beta globin gene that could represent sickle beta thalassemia zero.

Other Newborn Screen Possibilities

Newborn Screen Result	Interpretation(s)	ACTION REQUIRED
FA with Bart's*	Alpha thalassemia trait (2 gene deletion in the alpha globin gene)[#]	Genetic counseling for alpha thalassemia trait. https://www.stjude.org/disease/alpha-thalassemia.html
FA with Hemoglobin H	Hemoglobin H disease (3 gene deletion in the alpha globin gene)	Referral to pediatric hematologist. Variable severity.
F only	Beta thalassemia major	Referral to pediatric hematologist. Beta thalassemia major: lifetime dependence on red cell transfusions.
	Homozygous hereditary persistence of fetal hemoglobin (HPFH/HPFH)	Genetic counseling for HPFH.
FA, other	Fetal hemoglobin gene variant	Referral to pediatric hematologist for an appointment >6 months of age. OR Repeat testing with hemoglobin electrophoresis >6 months of age after hemoglobin F declines. If no abnormalities, no further workup or referral is needed.
	Beta globin gene variant not otherwise specified	Referral to pediatric hematologist for an appointment >6 months of age. OR Repeat testing with hemoglobin electrophoresis >6 months of age after hemoglobin F declines. A beta globin variant will persist as an abnormality on testing. Referral to pediatric hematologist is appropriate if continued.

*The presence of Bart's hemoglobin on newborn screen is consistent with alpha thalassemia trait. The absence of Bart's hemoglobin on newborn screen does NOT rule out alpha thalassemia trait.

[#]Alpha thalassemia trait (two alpha gene deletions) and beta thalassemia trait permit nearly normal hemoglobin production but there is typically a mild microcytic anemia. The disease in this form can be mistaken for iron deficiency anemia and treated inappropriately with iron. For patients with known thalassemia traits, an iron panel including a ferritin should be checked prior to initiating oral iron. For patients who have iron deficiency anemia that seems refractory to iron therapy, checking an iron panel with a ferritin along with review of the newborn screen (for Bart's hemoglobin indicating alpha thalassemia trait) and hemoglobin electrophoresis (for increased hemoglobin A2 indicating beta thalassemia trait) may help with appropriate diagnosis. Beyond the neonatal period, genetic testing of the alpha globin gene is usually the only way to confirm the diagnosis.