Other Genetic Disorders

Hemoglobinopathies

Hemoglobinopathies (hemoglobin disorders) are a group of disorders that affect the red blood cells and originate from genetically determined changes in the molecular structure of hemoglobin.

In the clinical laboratory, the hemoglobin Isoelectric Focusing (IEF), and High-Performance Liquid Chromatography (HPLC) tests will reveal multiple hemoglobin disorders with varying degrees of severity.

The effects range from mild anemia in Hemoglobin C disease (Hb CC) and C, Beta (β) Thalassemia, to severe pain episodes, growth delays, increased susceptibility to infections, and persistent anemia in Sickle Cell Disease (Hemoglobin SS) and S, β Thalassemia.

Hemoglobinopathies are inherited in an autosomal recessive pattern. Carriers of a single abnormal gene for one of these disorders are considered to have a trait. Persons with a trait will have red blood cells that contain a mixture of normal and abnormal hemoglobin.

Most hemoglobin traits cause no disease or anemia under normal physiologic conditions*. (See FAB, FAS, and *Special Considerations* below).

Inheritance:	Autosomal recessive
Estimated Incidence:	1:400 African Americans (sickling diseases) 1:2500 All Races & Ethnicities (sickling diseases)
Neonatal Presentation:	None
Method of Notification:	All abnormal results are called and faxed to the provider of record.
Next Steps if Abnormal:	**Sickling diseases - Refer to a pediatric hematologist** if the hemoglobin pattern is FS, FSA, FSB, FSC, FSD, FSE, FSG, FSO or FSV. **Report all subsequent findings to the SC Newborn Screening Program.** **Non-sickling disorders and/or thalassemia - Refer to a pediatric hematologist. Report all subsequent findings to the SC Newborn Screening Program.** If all other newborn screening results are normal, **a repeat newborn screening specimen is not required**. The initial sample will be sent to a reference lab for hemoglobin confirmation. All hemoglobinopathies and traits - Refer family to a sickle cell foundation for family testing, education, and genetic counseling.

Screening Results:

The following table outlines the most common results of the newborn hemoglobin screen. It is important to remember that PREMATURITY AND TRANSFUSIONS AFFECT TEST RESULTS. Each type of hemoglobin in the infant's blood is identified by a letter on the test result (e.g., F=Fetal, A=Adult or normal, S=Sickle, V=other unknown variant).

The position of the letter represents the amount of hemoglobin type present with the hemoglobin of greatest concentration listed first. (Example: "FSA" usually indicates a sickling disorder and "FAS" indicates a trait).

When hemoglobin disorder is suspected, specific instructions will be sent from the program. A portion of the abnormal bloodspot will also be sent to the Children's Hospital of Oakland Research Institute (CHORI) for confirmatory testing. **If all other newborn screening results are normal, a repeat specimen is not required.**

Newborn's Hemoglobin Result	**Potentially indicative of:**	**Sent to CHORI?**
FA	Normal Newborn Hemoglobin	NA
AF	Normal or transfused hemoglobin	NA
FS	Sickle cell disease, Sickle β0-thalassemia, or Sickle with Hereditary Persistence of Fetal Hemoglobin (S-HPFH)	Yes
FSA	Sickle β+-thalassemia or Sickle cell trait	Yes
FSB (FS + Fast Band) aka Hb Bart's	α Thalassemia with Sickle Hemoglobin	Yes
FSC	Sickle C disease, SC Harlem	Yes
FSD	Sickle D Disease	Yes
FSE	Hemoglobin SE Disease	Yes
FSG	Sickle cell Anemia, Sickle cell β Thalassemia, Sickle G Philadelphia	Yes
FSO	Sickle O Arab Disease	Yes
FSV	Sickle cell with Variant Hemoglobin pattern	Yes
FC	Homozygous Hemoglobin C disease or Hemoglobin C β0 thalassemia	Yes
FCA	Hemoglobin C β+ thalassemia or Hemoglobin C trait	Yes
FCE	Hemoglobin CE Disease	Yes
FCV	Hemoglobin C Variant	Yes
FDD	Homozygous Hemoglobin D, Hemoglobin D Thalassemia	No
FDA	Hemoglobin D/β Thalassemia or Hemoglobin D trait	No
FDV	Hemoglobin D Disease, Hemoglobin D Thalassemia, or Hemoglobin D trait	No

FE	Homozygous Hemoglobin E Disease, Hemoglobin E β+ thalassemia, or Hemoglobin E β0 thalassemia	Yes
FEA	Hemoglobin E β+ thalassemia or Hemoglobin E trait	Yes
FEV	Hemoglobin E Disease, Hemoglobin E β+ thalassemia, Hemoglobin E β0 thalassemia, or Hemoglobin E trait	Yes
FV	Unknown hemoglobin variant	Yes
FO	Homozygous Hemoglobin O-Arab	Yes
FVA	Unknown hemoglobin variant	No
FOA	Hemoglobin O-Arab/β+ Thalassemia or Hemoglobin O-Arab/β0 Thalassemia	No
FF	Premature Infant, Hereditary Persistence of Fetal Hemoglobin (HPFH) or Homozygous β thalassemia major	Yes
*FAB >= 15% (FA+ Fast Band) aka Hemoglobin Bart's	Hemoglobin Bart's - Alpha thalassemia of unknown severity to Hemoglobin H disease	Yes
*FAB < 15% (FA + Fast Band) aka Hemoglobin Bart's	Silent carrier, Alpha Thalassemia trait, or Hemoglobin Constant Spring Trait	No
FAC, FAD, FAE, FAG, FAO, FAS*, or FAV	Various Hemoglobin carriers/traits	No

Please contact a pediatric hematologist for further recommendations.

Treatment:

Sickling diseases – The National Institutes of Health (NIH) clinical guidelines suggest Penicillin/antibiotic prophylaxis beginning at 2 months of age and continuing through early. childhood. Prompt evaluation and management of acute illness to lessen development of sickling crises, particularly if fever is present.

An alternative antibiotic is available for children who are allergic to penicillin therapy. Health care monitoring and maintenance with appropriate immunizations are imperative to the health of the baby, and pneumococcal conjugate vaccine immunizations also are recommended, beginning at 2 months of age.

Appropriate pain management strategies (such as use of extra fluids, oral analgesics, and comfort measures) including rapid triage, if home management strategies are not sufficient. Transfusion may be necessary in certain instances. Medications to increase the production of fetal hemoglobin and lower leukocyte counts such as hydroxyurea may be used in certain children.

A blood or marrow transplant is the only known cure for Sickle Cell Disease (SCD). However, transplant has serious risks and is only used in patients with severe SCD who have symptoms including stroke, acute chest syndrome, and frequent pain episodes. The transplant replaces diseased blood-forming cells with healthy ones.

The type of transplant used to treat SCD is an allogeneic transplant. This type of transplant uses healthy blood-forming cells from a family member, unrelated donor, or umbilical cord blood unit. For an allogeneic transplant, a patient gets chemotherapy (with or without radiation) prior to transplant to prepare his or her body for the treatment.

Then, the replacement cells are infused into the patient's blood stream. From there, the cells find their way into the bone marrow, where they start making healthy white blood cells, red blood cells and platelets. The entire process, from the start of chemotherapy or radiation until hospital discharge, can last weeks to months followed by many months of recovery at home.

Special Considerations

Transfusion - Transfusion of red blood cells prior to drawing the newborn screening specimen will affect the hemoglobin result. Repeat screening for hemoglobinopathies should be done 120 days after the last transfusion. If the date of the last transfusion is unknown, put the date of hospital discharge on the collection form next to "**Transfused**".

Specimen Analysis at the Reference Laboratory - The initial newborn screening bloodspots for infants with hemoglobin results indicative of disease are sent to the Children's Hospital of Oakland Research Institute (CHORI) for more specific hemoglobin analysis and genetic testing. The result of the CHORI analysis is sent to the provider of record upon receipt by the Public Health Laboratory.

Follow-up Assistance and Coordination of Care - DHEC Children and Youth with Special Healthcare Needs (CYSHCN) Sickle Cell Program assists primary care providers to ensure infants identified with a sickling disorder are seen by a pediatric hematologist within the first six weeks of age. They can help coordinate activities with pediatric hematologists, Sickle Cell Foundations, local health departments and hospitals, so that families are directed to the services closest to them.

In coordination with the CYSHCN Sickle Cell Program and the Sickle Cell Foundations of South Carolina, counseling, education, and other resources are offered to families of infants diagnosed with a hemoglobin disorder or trait identified through newborn screening.

The goals of education and counseling are to increase the understanding of genetic diseases, discuss disease management options, and explain the risks and benefits of family testing. Counseling sessions focus on giving vital, unbiased information and non-directive assistance in the family's decision-making processes.

Participation in Sports or Extreme Physical Activity - Some persons with sickle cell trait (FAS or AS) may exhibit a sickling crisis associated with extreme physical activity. Precautions must be taken to lessen the chance for exertional rhabdomyolysis.

Hemoglobinopathies
(Core Condition Descriptions)

Hemoglobin FS

Diagnosis: Hemoglobin S/S or Hemoglobin S/Beta Zero Thalassemia (Hb S/S or Hb S/β 0 Thalassemia)

Differential Diagnosis: Homozygous Hemoglobin S; Hemoglobin S/Beta Zero (β 0) Thalassemia); Hemoglobin S/Beta Plus (β +) Thalassemia; or Hemoglobin S/Hereditary Persistence of Fetal Hemoglobin (HPFH).

Condition Description: Hemoglobin S/S and Hemoglobin S/β 0 Thalassemia are inherited red blood cell disorders characterized by abnormal hemoglobin production. They are due to genetic changes in the beta hemoglobin gene. Although asymptomatic at birth, symptoms begin as Hb F decreases and Hb S predominates. The clinical course is highly variable, ranging from asymptomatic to life-threatening infections, strokes, acute chest syndrome, end organ damage, and pain crises. Hb S/HPFH is clinically benign.

Clinical Considerations: Newborns with Hemoglobin S/S are generally asymptomatic. Hemolytic anemia and vaso-occlusive complications can develop during infancy or in early childhood. Without appropriate treatment, complications may include life-threatening infection, splenic sequestration, pneumonia, acute chest syndrome, pain episodes, aplastic crises, dactylitis, priapism, osteonecrosis, and stroke.

You Should Take the Following Actions:

- Inform the family of the newborn screening result.
- Ascertain clinical status (newborns are expected to be asymptomatic).
- Evaluate the newborn (assess for splenomegaly and check CBC).
- Administer prophylactic penicillin.
- Immediately consult with a sickle cell specialist and coordinate in person follow up no later than 12 weeks of age.
- Coordinate confirmatory diagnostic testing and management as recommended by specialist.
- Provide family with basic information about Hemoglobin S/S or Hemoglobin S/Beta Zero (β 0) Thalassemia including the need for urgent evaluation if fever of ≥ 38.5ºC (101ºF), or signs of stroke or splenic sequestration.
- Refer for genetic counseling.
- Report final diagnostic outcome to newborn screening program.

Comprehensive care, including family education, a modified immunization schedule, prophylactic penicillin, therapeutic interventions such as hydroxyurea, prompt treatment of acute vaso-occlusive events, and screening for early signs of organ damage reduces morbidity and mortality.

Most newborns with Hb S/β 0 Thalassemia have a clinical course like Hb S/S. Hb S/HPFH is typically benign. Solubility testing (*SICKLEDEX*) should **not** be used to confirm the diagnosis. Iron supplements should be avoided unless iron deficiency is documented.

Hemoglobin FSC

Diagnosis: Hemoglobin S/C; Differential Diagnosis: None.

Condition Description: Hemoglobin S/C is an inherited type of red blood cell disorder characterized by abnormal hemoglobin production. It is due to genetic changes in the beta hemoglobin chain.

Although asymptomatic at birth, symptoms begin as Hb F decreases and Hb S and Hb C predominate. The clinical course is highly variable, ranging from asymptomatic to infections, splenic sequestration, pain crises, acute chest syndrome, bone damage, retinopathy, and organ damage as the individual ages.

You Should Take the Following Actions:

- Inform the family of the newborn screening result.
- Ascertain clinical status (newborns are expected to be asymptomatic).
- Evaluate the newborn (assess for splenomegaly and check CBC).
- Administer prophylactic penicillin.
- Immediately consult with a sickle cell specialist and coordinate in person follow up no later than 12 weeks of age.
- Coordinate confirmatory diagnostic testing and management as recommended by specialist.
- Provide family with basic information about Hb S/C including the need for urgent evaluation for fever ≥38.5 C (101 F), pallor, unexplained irritability, risks of sepsis, or other signs of illness.
- Refer for genetic counseling.
- Report final diagnostic outcome to newborn screening program.

Clinical Considerations: Newborns with Hemoglobin S/C are generally asymptomatic. Hemolytic anemia and vaso-occlusive complications can develop during infancy or in early childhood. Although patients initially have a milder clinical course and have an increased life expectancy than those with sickle cell anemia (Hb S/S), symptoms can become more severe with age.

Without appropriate treatment, complications may include life-threatening infection, splenic sequestration, pneumonia, acute chest syndrome, pain crises, aplastic crises, dactylitis, priapism and osteonecrosis.

Comprehensive care including family education, a modified immunization schedule, prompt treatment of infection and of acute vaso-occlusive events, screening for early signs of organ damage, consideration of prophylactic penicillin and disease-modifying therapies reduces morbidity and mortality.

Management should be done under the direction of a sickle cell specialist. Solubility testing (*SICKLEDEX*) should **not** be used to confirm the diagnosis. Iron supplements should be avoided unless iron deficiency is documented.

Hemoglobin FSA

Diagnosis: Hemoglobin S/Beta Plus Thalassemia (Hb S/β + Thalassemia)
Differential Diagnosis: Sickle Cell Trait.

Condition Description: Hemoglobin S/Beta Plus (β +) Thalassemia is an inherited type of red blood cell disorder characterized by abnormal hemoglobin production. It is due to genetic changes in the beta hemoglobin chain. Although asymptomatic at birth, symptoms begin as Hb F decreases and Hb S predominates.

The clinical course is highly variable, ranging from asymptomatic to life-threatening infections, acute chest syndrome, splenic sequestration, organ damage, and pain crises; the phenotype is determined by the amount of Hb A present.

You Should Take the Following Actions:

- Inform the family of the newborn screening result.
- Ascertain clinical status (newborns are expected to be asymptomatic).
- Administer prophylactic penicillin.
- Evaluate the newborn (assess for splenomegaly and check CBC).
- Immediately consult with a sickle cell specialist and coordinate in person follow up no later than 12 weeks of age.
- Coordinate confirmatory diagnostic testing and management as recommended by specialist.
- Provide family with basic information about Hemoglobin S/Beta Plus (β +) Thalassemia including the need for urgent evaluation if fever of ≥ 38.5ºC (101ºF) or splenic sequestration.
- Refer for genetic counseling.
- Report final diagnostic outcome to newborn screening program.

Clinical Considerations: Newborns with Hemoglobin S/β + Thalassemia are generally asymptomatic. Hemolytic anemia and vaso-occlusive complications can develop during infancy or in early childhood. Without appropriate treatment, complications include life-threatening infection, splenic sequestration, pneumonia, acute chest syndrome, pain episodes, aplastic crises, dactylitis, priapism, and osteonecrosis.

Comprehensive care including family education, a modified immunization schedule, prompt treatment of infections and of vaso-occlusive events, screening for early signs of organ damage, and consideration of prophylactic penicillin and other disease-modifying interventions, reduces morbidity and mortality.

Patients with Hb S/β + Thalassemia often have a clinical course that is similar to but less severe than those with sickle cell anemia (Hb S/S) and have a longer life expectancy. Their phenotype is determined by the thalassemia variant. Monitoring depends on the specific diagnosis and should be done under the direction of a sickle cell specialist. Solubility testing (*SICKLEDEX*) should **not** be used to confirm the diagnosis. Iron supplements should be avoided unless iron deficiency is documented.

Hemoglobin FE

Diagnosis: Hemoglobin E/E or Hemoglobin E/Beta Zero Thalassemia (Hb E/E or Hb E/β 0 Thalassemia)

Differential Diagnosis: Homozygous Hemoglobin E; Hemoglobin E/Beta Zero (β 0) Thalassemia; or Hemoglobin E/Beta Plus (β +) Thalassemia.

Condition Description: Hemoglobin E/E or Hemoglobin E/β 0 Thalassemia are inherited types of red blood cell disorders characterized by abnormal hemoglobin production. They are due to genetic changes in the beta hemoglobin chain.

Although Hb E/E is generally benign, Hb E/β 0 Thalassemia has a variable clinical course ranging from moderate anemia to transfusion dependency.

You Should Take the Following Actions:

- Inform family of the newborn screening result.
- Ascertain clinical status (newborns are expected to be asymptomatic).
- Evaluate the newborn (newborns are expected to be asymptomatic and have a normal clinical exam. If significant signs or symptoms are identified, it is likely related to a different underlying disorder).
- Consult a pediatric hematologist with expertise in hemoglobin disorders within the first week of life with follow up typically recommended between 2-4 months age
  (It is unusual to have symptoms before 2-4 months of life).
- Coordinate confirmatory diagnostic testing and management as recommended by specialist.
- Provide family with basic information about Hb E/E or Hb E/Beta Zero (β 0) Thalassemia.
- Refer for genetic counseling.
- Report final diagnostic outcome to newborn screening program.

Clinical Considerations: While hemoglobin E/E is clinically benign, Hb E/β 0 Thalassemia has a variable presentation. Most individuals with Hb E/β 0 Thalassemia have moderately severe anemia, hepatosplenomegaly, intermittent jaundice, growth restriction, and overexpansion of the bone marrow.

Severely affected individuals require life-long transfusion, possible splenectomy, and treatment for iron overload. Monitoring will vary depending on the specific diagnosis and should be done under the direction of a pediatric hematologist. Iron supplements should be avoided unless iron deficiency is documented.

Hemoglobin FC

Diagnosis**:** Hemoglobin C/C or Hemoglobin C/Beta Zero Thalassemia (Hb C/C or Hb C/β 0 Thalassemia)

Differential Diagnosis: Homozygous Hemoglobin C; Hemoglobin C/Beta Zero (β 0) Thalassemia, or Hemoglobin C/Beta Plus (β +) Thalassemia.

Condition Description: Hemoglobin C/C or Hemoglobin C/β 0 Thalassemia are inherited types of red blood cell disorders characterized by abnormal hemoglobin production. They are due to genetic changes in the beta hemoglobin chain. Although asymptomatic at birth, both lead to microcytic anemia within the first year of life.

Hb C/β 0 Thalassemia has a variable clinical course ranging from mild hemolytic anemia and splenomegaly to a moderate hemolytic anemia with jaundice, splenomegaly, and scleral icterus that may require intermittent transfusions. Hb C/C is typically asymptomatic.

You Should Take the Following Actions:

• Inform the family of the newborn screening result.
• Ascertain clinical status (newborns are expected to be asymptomatic).
• Evaluate the newborn (newborns are expected to be asymptomatic and have a normal clinical exam. If significant signs or symptoms are identified, it is likely related to a different underlying disorder).
• Consult a pediatric hematologist with expertise in hemoglobin disorders within the first week of life with follow up typically recommended between 2-4 months of age
(It is unusual to have symptoms before 2-4 months of life).
• Coordinate confirmatory diagnostic testing and management as recommended by specialist.
• Provide the family with basic information about Hb C/C or Hb C/Beta Zero (β 0) Thalassemia.
• Refer for genetic counseling.
• Report final diagnostic outcome to newborn screening program.

Clinical Considerations: Infants are usually asymptomatic. Hemoglobin C/C is associated with a mild microcytic hemolytic anemia and splenomegaly. Individuals with Hb C/β 0 Thalassemia have a moderately severe anemia and splenomegaly, and in some cases may require intermittent transfusions and develop iron overload. Iron supplements should be avoided unless iron deficiency is documented.

Hemoglobin FCA

Diagnosis: Hemoglobin C/Beta Plus Thalassemia (Hb C/β+ Thalassemia)
Differential Diagnosis: Hb C trait.

Condition Description: Hemoglobin C/Beta Plus (β+) Thalassemia is an inherited type of red blood cell disorder characterized by abnormal hemoglobin production. It is due to genetic changes in the beta hemoglobin chain.

Although asymptomatic at birth, microcytic anemia develops within the first year of life. Clinical manifestations vary from a mild microcytic anemia to a moderate hemolytic anemia with splenomegaly.

You Should Take the Following Actions:

- Inform the family of the newborn screening result.
- Ascertain clinical status (newborns are expected to be asymptomatic).
- Evaluate the newborn (newborns are expected to be asymptomatic and have a normal clinical exam. If significant signs or symptoms are identified, it is likely related to a different underlying disorder).
- Consult a pediatric hematologist with expertise in hemoglobin disorders within the first week of life with follow up typically recommended by 4 months of age
  (It is unusual to have symptoms before 3-6 months of life).
- Coordinate confirmatory diagnostic testing and management as recommended by specialist.
- Provide family with basic information about Hemoglobin C and Beta Plus (β+) Thalassemia.
- Refer for genetic counseling.
- Report final diagnostic outcome to newborn screening program.

Clinical Considerations: The specific β+ thalassemia variant determines the prognosis. Although asymptomatic at birth, individuals with Hb C/β+ Thalassemia develop a variable degree of anemia and splenomegaly, depending on the specific β+ thalassemia variant.

The typical clinical course includes mild microcytic anemia and possible splenomegaly, but treatment is seldom required. Iron supplements should be avoided unless iron deficiency is documented.

Hemoglobin FEA

Diagnosis: Hemoglobin E/Beta Plus Thalassemia (Hb E/β + Thalassemia)
Differential Diagnosis: Hb E trait.

Condition Description: Hemoglobin E/Beta Plus (β +) Thalassemia is an inherited type of red blood cell disorder characterized by abnormal hemoglobin production. It is due to genetic changes in the beta hemoglobin chain.

Although generally asymptomatic at birth, the clinical presentation is highly variable depending upon the severity of the beta thalassemia variant. Patients can remain asymptomatic or can develop any or all the following over the first year of life: growth or developmental delays, pallor, splenomegaly, decreased activity, and scleral icterus. If symptomatic, it is unusual to develop symptoms prior to 2-4 months of life.

You Should Take the Following Actions:

- Inform the family of the newborn screening result.
- Ascertain clinical status (newborns are expected to be asymptomatic).
- Evaluate the newborn (newborns are expected to be asymptomatic and have a normal clinical exam. If significant signs or symptoms are identified. It is likely related to a different underlying disorder).
- Consult a pediatric hematologist with expertise in hemoglobin disorders within the first week of life with follow up typically recommended between 2-4 months of age
  (It is unusual to have symptoms before 2-4 months of life).
- Coordinate confirmatory diagnostic testing and management as recommended by the specialist.
- Provide family with basic information about Hemoglobin E and Beta Plus (β +) Thalassemia.
- Refer for genetic counseling.
- Report the final diagnostic outcome to newborn screening program.

Clinical Considerations: The specific β + Thalassemia variant determines the prognosis. The typical clinical course includes moderate microcytic anemia, jaundice, and splenomegaly but treatment is seldom needed. In rare instances, affected individuals may require intermittent transfusions and treatment for iron overload. Iron supplements should be avoided unless iron deficiency is documented.

Hemoglobin Bart's & Alpha Thalassemia*

Hemoglobin Bart's is a tetramer of gamma (fetal) globin chains seen during the newborn period. Its presence indicates that 1 or more of the 4 genes that produce alpha globin chains are dysfunctional, causing **alpha thalassemia**. The more alpha genes affected, the more significant the thalassemia and clinical symptoms.

Alpha thalassemia occurs in individuals of all ethnic backgrounds. It is **one of the most common genetic diseases worldwide**. In brief, alpha thalassemia is a blood disorder that reduces the production of hemoglobin. Hemoglobin is the protein in red blood cells that carries oxygen to cells throughout the body.

In people with the characteristic features of alpha thalassemia, a reduction in the amount of hemoglobin prevents enough oxygen from reaching the body's tissues. Affected individuals also have a shortage of red blood cells (anemia), which can cause pale skin, weakness, fatigue, and more serious complications. Furthermore, the clinically significant forms (**Hemoglobin H disease**, **Hemoglobin H Constant Spring**, and **Alpha Thalassemia Major**) occur predominantly among Southeast Asians.

Summarized below are the manifestations associated with the different levels of Hemoglobin Bart's detected on the newborn screen, and recommendations for follow-up.

Note, the number of dysfunctional genes is estimated by the percentage of Bart's seen on the newborn screen. The presence of less than 25% Hb Bart's generally indicates the loss of 1 (silent carrier) or 2 (alpha thalassemia trait) genes:

Silent Carrier - Low % Bart's

If only 1 alpha gene is affected, the other 3 genes can compensate nearly completely and only a low level of Bart's is detected. Levels of Bart's below a certain percentage are not generally reported by the Newborn Screening Program as these individuals are likely to be clinically normal. However, a small number of babies reported as having possible alpha thalassemia trait will be **silent carriers**.

Alpha Thalassemia trait or Hemoglobin Constant Spring Trait- Moderate % Bart's

Alpha thalassemia trait produces a moderate level of Bart's. It typically results from the dysfunction of 2 alpha genes. Either due to gene deletions, or a specific change in the alpha gene that produces elongated alpha globin and has a thalassemia-like effect: hemoglobin Constant Spring. These conditions are usually benign although mild microcytic anemia is common.

However, two copies of the **Constant Spring** mutation may cause mild hemolytic anemia. Follow-up is for the benefit of avoiding **misdiagnosis of iron deficiency**, or diagnostic dilemmas of nonresponsive anemia. It is also for the benefit of determining reproductive risks for the family. This will differ depending on whether the individual has dysfunctional genes on the same chromosome or different chromosomes.

Hemoglobin H Disease- High % Bart's

A high level of Bart's in the newborn (above 25%) is most often the result of 3 dysfunctional alpha genes due to deletions and generally manifests in a moderate hemolytic anemia. This condition usually occurs when one parent is a silent carrier (1 dysfunctional alpha gene), and the other has alpha thalassemia trait (2 dysfunctional alpha genes on the same chromosome).

The clinical manifestations of this disorder are variable, but most patients are anemic and develop some degree of splenomegaly. **Hemoglobin H** is unstable and patients with hemoglobin H disease have chronic hemolysis in addition to alpha thalassemia. They are susceptible to accelerated hemolysis when exposed to the same drugs that cause hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Hemoglobin H Constant Spring Disease- High % Bart's

Hemoglobin H Constant Spring disease is often a more severe phenotype than the more common form of Hemoglobin H Disease. This occurs when there is a high level of Bart's in combination with at least one Constant Spring mutation. This typically results in only 1 functional alpha gene. Clinical manifestations of a compound heterozygote include moderate anemia, splenomegaly, and possible transfusion dependence.

Alpha Thalassemia Major (Fetal Hydrops Syndrome)

If **none of the alpha genes are functional**, a very severe hemolytic anemia begins in utero. The anemia is so severe that the disorder is lethal with fetal demise usually occurring in the third trimester. Also, pregnant women carrying an infant with fetal hydrops syndrome have a high rate of severe toxemia of pregnancy.

This usually occurs when both parents have alpha thalassemia trait (2 dysfunctional alpha genes on the same chromosome). Prospective parental screening and prenatal diagnosis is suggested if the potential for fetal hydrops syndrome is suspected.

Sickle Cell Foundation Contacts in South Carolina

Community Based Organizations (CBO's) for Support:

COBRA Human Services Agency Sickle Cell Program
3962 Rivers Ave
PO Box 71473
Charleston, SC 29415
Toll Free (800) 354-4704
(843) 225-4866, Service Line
(843) 225-4869, Fax
cobraagency@bellsouth.net

Orangeburg Area Sickle Cell Foundation
825 Summers Ave
PO Box 892
Orangeburg, SC 29116
(803) 534-1716, Phone
(803) 531-2422, Fax
orangeburgsickle@aol.com

James R. Clark Memorial Sickle Cell Foundation
1420 Gregg St
Columbia, SC 29201
Toll Free (800) 506-1273
(803) 765-9916, Phone
(803) 799-6471, Fax
www.jamesrclarksicklecell.org
office@jamesrclarksicklecell.org

Louvenia Barksdale Sickle Cell Anemia Foundation
645 S Church St
PO Box 191
Spartanburg, SC 29304
(864) 582-9420, Phone
(864) 582-9421, Fax
www.barksdalesicklecell.org
ldbarksdale@charter.net

Centers for Disease Control and Prevention
Sickle Cell Disease (SCD) National Resource Directory
https://www.cdc.gov/ncbddd/sicklecell/index.html

Other Genetic Disorders, continued

Cystic Fibrosis (CF)

Cystic fibrosis (CF) is a disorder characterized by pulmonary obstruction often accompanied by exocrine pancreatic dysfunction. A defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene leads to obstruction of exocrine pancreatic ducts. This causes an increase in the pancreatic enzyme immunoreactive trypsinogen (IRT) in blood. Elevated IRT can also occur in premature/stressed infants.

CF usually affects the lungs, pancreas, intestines, liver and sweat glands, causing failure to thrive, steatorrhea, intestinal obstruction, salt loss, and progressive obstructive lung disease.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:3,500 (varies by ethnic group)
1st tier screening result:	Elevated IRT
Abnormal 2nd tier result:	**1 or more CF mutations (variants) found.**
Method of Notification:	All elevated 1st tier screening results are sent to the provider of record and reflexed to CF 2nd tier confirmatory testing. Abnormal CF confirmatory lab reports may also be faxed to a regional pediatric pulmonologist, upon written request from the PCP.
Next Steps if Abnormal:	A portion of the initial sample will be tested by 2nd tier molecular method. If initial IRT is elevated and no mutations are found on CF 2nd tier test, see infant to ascertain health status. If CF 2nd tier test results are within normal limits, no further bloodspots are needed. **If 1 or more variants are found on CF 2nd tier test, send patient for sweat chloride testing.**

All infants with an elevated IRT >170 ng/ml should still be sent for sweat chloride testing, even if no mutations were detected on 2nd tier testing.

Neonatal Presentation:	Usually none. **Meconium ileus** or volvulus may occur in 5-10% of affected infants. Prolonged jaundice without other causes is more common than very early lung disease.

All infants with meconium ileus should be thoroughly evaluated for CF, regardless of the IRT screen. A normal IRT value does not rule out CF in these infants.

Diagnosis:	Sweat chloride testing at a CF Foundation accredited care center is necessary for final diagnosis. If sweat chloride test is abnormal, initiate treatment as recommended by pulmonology specialist.

Please report all diagnostic information to the SC Newborn Screening Program.
Standard Treatment: Chest physiotherapy to aid in airway clearance. Antibiotics or other medications to treat lung infections as needed. Pancreatic enzymes if indicated; vitamins; NaCl supplements. Close monitoring of growth parameters and use of nutritional supplements as needed to enhance/maintain appropriate growth/development.

Special Considerations

Premature/Sick Infants - The stress of prematurity and/or illness can lead to falsely elevated IRT test results.

Meconium Ileus - All infants with meconium ileus should be thoroughly evaluated for CF regardless of the IRT result. A normal IRT result does not rule out CF in these infants.

Neonatal Screening and confirmatory testing - For general population CF carrier screening, the American College of Medical Genetics (ACMG) and American College of Obstetricians and Gynecologists (ACOG) recommend a core panel of 23 mutations that will identify 49–98% of carriers, depending on ethnic background.

The SC DHEC Public Health Laboratory will perform an extended confirmatory panel of 60+ mutations for screen positive infants. The extended panel includes the recommended core panel of 23 mutations, thereby ensuring comprehensive mutation coverage.

However, negative carrier status in the infant or parents does not definitively rule out the possibility of CF in an infant. Infants may have other rare mutations that are not included in a standard CF 2nd tier test.

False Negative Test Results - Some infants with CF may have false negative IRT results.

Physicians must remain alert to clinical signs of CF in older infants despite normal initial screening results.

Spinal Muscular Atrophy
(Due to homozygous deletion of exon 7 in SMN1)

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative motor neuron disease caused by pathogenic changes in the Survival Motor Neuron 1 (*SMN1*) gene. Newborn screening (NBS) aims to detect patients with potential homozygous deletions in *SMN1*, which represents ~95% of cases.

SMA is clinically variable, with age of onset ranging from birth to adulthood. **SMA type 1**, also known as **Werdnig-Hoffman disease**, accounts for more than half of cases. It presents at or shortly after birth with hypotonia, breathing, and feeding difficulties. Tongue fasciculations are present in many affected individuals. If left untreated, **death typically occurs by 2 years of age**.

Inheritance:	Autosomal recessive
Estimated Incidence:	Approximately 1 in 50 Americans is a carrier of SMA. 1 in every 6,000 to 10,000 children is born with a type of SMA.
Abnormal Screen Result:	**Low to absent Survival Motor Neuron 1 (SMN) protein**
Method of Notification:	All abnormal results are shared and called to the provider of record and may be sent to a pediatric geneticist or SMA specialist, upon verbal and written request.

Next steps if Abnormal: Potential medical emergency when SMN1 is very low to absent!

See the infant as soon as possible to ascertain health status. **Consult a pediatric SMA specialist (pediatric neurologist or geneticist)** and initiate diagnostic evaluation and treatment as recommended.

Common diagnostic studies include *SMN1* and *SMN2* copy numbers with rapid molecular confirmation of *SMN1* gene variations via gene sequencing, with physical and neurological assessment by an experienced SMA specialist.

Neonatal presentation:

Individuals with the infantile-onset form of SMA can present with rapidly progressive symptoms at or shortly after birth. Symptoms can include hypotonia, weakness, trouble feeding, or respiratory failure. The more severe forms of infantile SMA are associated with high mortality unless diagnosed and treated promptly in the first weeks of life.

Infants with three or more *SMN2* copies may not become evident until later childhood or even adulthood.

Treatment:

The FDA has 3 currently approved medications to treat SMA, and possibly other emerging therapies. Standard-of care recommendations include monitoring respiratory, developmental, and nutritional status.

Zolgensma® is a form of intravenous gene therapy that treats the genes involved in SMA. The *SMN1* and *SMN2* genes give the body instructions for making SMN protein that helps control muscle movement.

The first FDA-approved prescription medicine for SMA in pediatric and adult patients was nusinersen, also known as Spinraza® . This drug and Evrysdi® target the central nervous system (CNS) where motor neuron loss begins. After initial loading doses, Spinraza is given intrathecally quarterly. Evrysdi oral solution is usually taken daily.

Report all findings to the SC Newborn Screening Program via fax at 803-898-0337.

Special Considerations

Premature/Sick Infants - Premature infants may have abnormal screening results due to immaturity of the immune system. However, prompt attention is indicated as a precaution.

NOTE: Low to absent *SMN1* with questionable RPP30 (internal lab control) may indicate poor quality sample, DNA amplification failure, anticoagulant interference, or other condition, (aka) inconclusive results. Prompt repeat screening is necessary to rule out SMA in these infants.

Severe Combined Immunodeficiency (SCID)

Extremely low levels of T-cell Receptor Excision Circles (TRECs) are associated with Severe Combined Immunodeficiency (SCID). Other conditions associated with decreased TRECs include reticular dysgenesis, coronin-1A deficiency, and thymic aplasia/complete DiGeorge syndrome. T lymphocytes fail to develop, and the affected infant may also have impaired B lymphocyte function.

Inheritance: Autosomal recessive and X-linked

Estimated Incidence: 1:40,000 to 1:60,000

Abnormal Screen Result: Decreased TRECs (T-cell receptor excision circles)

Method of Notification: All abnormal results are shared with the provider of record and may be sent to an Immune Disorder Specialist, upon verbal and written request.

Next Steps if Abnormal: **Potential medical emergency when TRECs are very low to absent!**

See the infant as soon as possible to ascertain health status. **Consult a pediatric specialist (immunology or pediatric infectious disease)** and initiate diagnostic evaluation and treatment as recommended. Common diagnostic studies include specialized flow cytometry and molecular testing to determine specific mutations.

Report all findings to the SC Newborn Screening Program via fax at 803-898-0337.

In addition, repeat TREC on filter paper and send it to the DHEC Public Health Laboratory. Low TRECs with questionable RPP30 (internal lab control) may indicate poor quality sample, DNA amplification failure, anticoagulant interference, or other conditions, (aka) inconclusive results. Prompt repeat screening is necessary to rule out SCID in these infants.

Neonatal Presentation: Usually none. The median age for onset of symptoms is 8 weeks of age.

Emergency Treatment: Usually none.

Standard Treatment: Bone marrow transplantation by 3 months of age is associated with the best outcomes for SCID. Infants with other conditions may be treated with medications.

Special Considerations

Infectious Disease Precautions - Parents should be instructed to avoid exposure of the infant to anyone with viral/bacterial illnesses until immunodeficiency is definitively ruled out. No vaccines should be given until cleared to do so by the specialist.

The specialist may also advise mothers to suspend breastfeeding while their blood is checked for anti-CMV IgG antibodies and CMV DNA. These mothers should be encouraged to pump and freeze their breast milk during this time. Prompt resumption of breastfeeding is encouraged if the mother is seronegative.

Only leukoreduced, CMV negative, irradiated blood should be used if a transfusion is necessary.

Premature/Sick Infants—Premature infants may have low TRECs due to immaturity of the immune system. Prompt repeat screening is indicated. The pediatric specialist (immunology or pediatric infectious disease) may recommend flow cytometry if TRECs are low in a second blood spot specimen.

NOTE: Low TRECs may also be found in specimens obtained from infants who have undergone thymectomy/cardiac surgery if the specimen is collected after surgery.

X-Linked Adrenoleukodystrophy (X-ALD) - ***PENDING***

X-ALD is an X-linked disorder caused by pathogenic variants in the *ABCD1* gene resulting in a defect in the adrenoleukodystrophy protein (ALDP). This results in an abnormal accumulation of very long chain fatty acids (VLCFA) in the body affecting the nervous system white matter and the adrenal cortex. X-ALD has an estimated incidence of 1:17,000 live births.

There are 3 variants of X-ALD: a childhood cerebral form that occurs primarily in males, Addison-only disease in males, and adrenomyeloneuropathy (AMN) occurring in both males and females. Zellweger spectrum disorders are rare but may be identified through this testing.

1st tier screening result:	Elevated C24:0-LPC
2nd tier screening result:	Elevated C26:0-LPC
3rd tier molecular result:	**Abnormal *ABCD1* molecular sequencing**

Next steps if Abnormal:

All elevated 2nd tier screening results will be reflexed to 3rd tier molecular testing. If initial C26:0 is elevated and no variants (mutations) are found on 3rd tier test, see infant to ascertain health status.

If 1 or more variants are found on the 3rd tier test, contact a pediatric geneticist, and initiate diagnostic evaluation and treatment as recommended. Note: Female *ABCD1* heterozygotes may also be identified by this method.

Method of Notification:	All **abnormal** 3rd tier results are called and sent to the provider of record and may be sent to a pediatric geneticist or MD specialist, upon verbal and/or written request.

Diagnostic Evaluation:

Confirmatory VLCFA. Patients with elevated VLCFA indicative of X-ALD or another peroxisomal disorder should have follow-up testing.

If Zellweger spectrum disorder is suspected based on early clinical signs and symptoms, additional testing will be needed.

Presentation:

The childhood cerebral form of X-ALD manifests in approximately 1/3 of affected males most commonly at 4-10 years of age. Symptoms and signs may include attention deficit hyperactivity disorder, progressive cognitive and behavioral changes, adrenal impairment, and characteristic MRI abnormalities.

Treatment:

From the time of diagnosis, the specialty center will arrange for regular MRI imaging and adrenal testing to determine when (and if) to initiate therapy. Adrenal steroid replacement is essential for treating adrenal insufficiency. However, it does not prevent the development or the progression of neurological symptoms.

Hematopoietic stem cell transplantation (HSCT) is the only proven successful treatment for the cerebral form of X-ALD. However, it must be performed in the earliest stages of the childhood cerebral form to be effective.

Zellweger spectrum disorders have variable severity and clinical presentation; most lack specific therapy.

Note: Diagnosis of adrenoleukodystrophy in newborns should raise concern about unrecognized related diseases in other family members.

Hearing Loss (HL) and Critical Congenital Heart Defects (CCHD)*

*These point of care newborn screening tests (not blood tests) are administered at the hospital or other birthing facility.

For newborn hearing screening and hearing loss information, please contact the SC DHEC First Sound Hearing Screening Program. For CCHD information, contact the SC DHEC Birth Defects Program.

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