UCSF Benioff Children's Hospitals
Fetal Treatment Center

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Prenatal Screening for Hemoglobinopathies

Thalassemias are inherited anemias caused by variants in either the alpha- or beta-globin genes that result in decreased hemoglobin (Hb) synthesis. If both parents carry variants in the same globin gene, each of their children has a 25 percent chance of inheriting a severe form of that thalassemia. Both alpha and beta thalassemia major require treatment with serial blood transfusions. Alpha thalassemia major is unique in that treatment, if pursued, should be initiated prenatally.

Sickle cell disease (SCD) is another inherited anemia caused by having two S (sickle) variants in the beta-globin gene. Inherited anemias are also caused when one sickle variant and one beta thalassemia or other beta-globin variant occur together. Patients may experience recurrent pain episodes and are at risk for infection and pulmonary, neurological and other complications.

Globally, 5 percent of people carry a thalassemia trait. People whose ancestry traces to Asia, the Pacific Islands, the Mediterranean, the Middle East, Latin America or Africa are at greater risk for being carriers.

Types of Hemoglobinopathies

	BETA THALASSEMIA AND SICKLE CELL ANEMIA	ALPHA THALASSEMIA
ASYMPTOMATIC	**β Thalassemia Trait (β/-)** *1 of 2 functioning beta-globin genes* • Can lead to slight microcytic anemia • Parents who are both positive for this trait are at risk for having a child with beta thalassemia major • Other beta-globin-related genotypes include Hb E and sickle cell anemia (HB S and Hb C)	**Silent Alpha Thalassemia Carrier (α-/αα or αTα/αα)** *3 of 4 functioning alpha-globin genes, asymptomatic* • Common associated genotypes include alpha 3.7 deletion and alpha 4.2 deletion **α Thalassemia Trait: Either αα/-- (deletion of 2 α genes in cis, alpha-0 trait) or α-/α- (1 α gene deleted on each chromosome, homozygous alpha+ trait)** • Slight microcytic anemia • Couples who are both carriers for α-0 trait are at risk for a pregnancy with alpha thalassemia major • Common alpha-0 deletions are Southeast Asian (--^{SEA}), Filipino (--^{FIL}), Thai (--^{THAI}) and Mediterranean (--^{MED})
SYMPTOMATIC: NON-TRANSFUSION DEPENDENT	**β Thalassemia Intermedia and E Beta Thalassemia** • Can include the following genetic variant combinations: » Homozygosity for mild β+ thalassemia » Dominant forms of β thalassemia » Compound heterozygosity for β+/β° » Compound heterozygosity for β thalassemia Hb E » Sickle cell anemia including Hb SS, Hb SC and sickle/beta disease • Co-inheritance of β thalassemia with hereditary persistence of fetal hemoglobin • Co-inheritance of β thalassemia trait and triplicated or quadruplicated alpha genes (e.g., αα/ααα or αα/αααα)	**HbH Disease (-α/--, deletional HbH disease)** *1 of 4 functioning alpha-globin genes (3-gene deletion)* • Moderate, stable anemia • Increased anemia during viral infections **Non-Deletion Hemoglobin H (--/αTα)** *1 of 4 functioning alpha-globin genes* • One parent has alpha-0 thalassemia trait and the other has an alpha-globin gene variant • More severe anemia • Can present with hydrops, require in utero transfusion • May require transfusion support after birth • Common alpha-globin gene variants include Constant Spring, Quong Sze and Poly A mutation
SYMPTOMATIC: TRANSFUSION DEPENDENT	**β Thalassemia Major. Also Called Cooley's Anemia** *0 of 2 functioning beta-globin genes* • Individuals born with beta thalassemia major develop severe anemia during infancy and require regular blood transfusions to survive • Some patients are eligible for curative treatment with bone marrow transplant • Many individuals with HbE β thalassemia also require regular transfusions	**Alpha Thalassemia Major (ATM) or Hb Bart's Hydrops Fetalis (--/--)** *0 of 4 functioning alpha-globin genes* • Both parents have alpha-0 thalassemia trait • Leads to severe anemia in fetuses and is fatal unless treated with in utero blood transfusions • Individuals born with alpha thalassemia major continue to require regular blood transfusions and may be eligible for bone marrow transplant

T denotes non-deletion variant.

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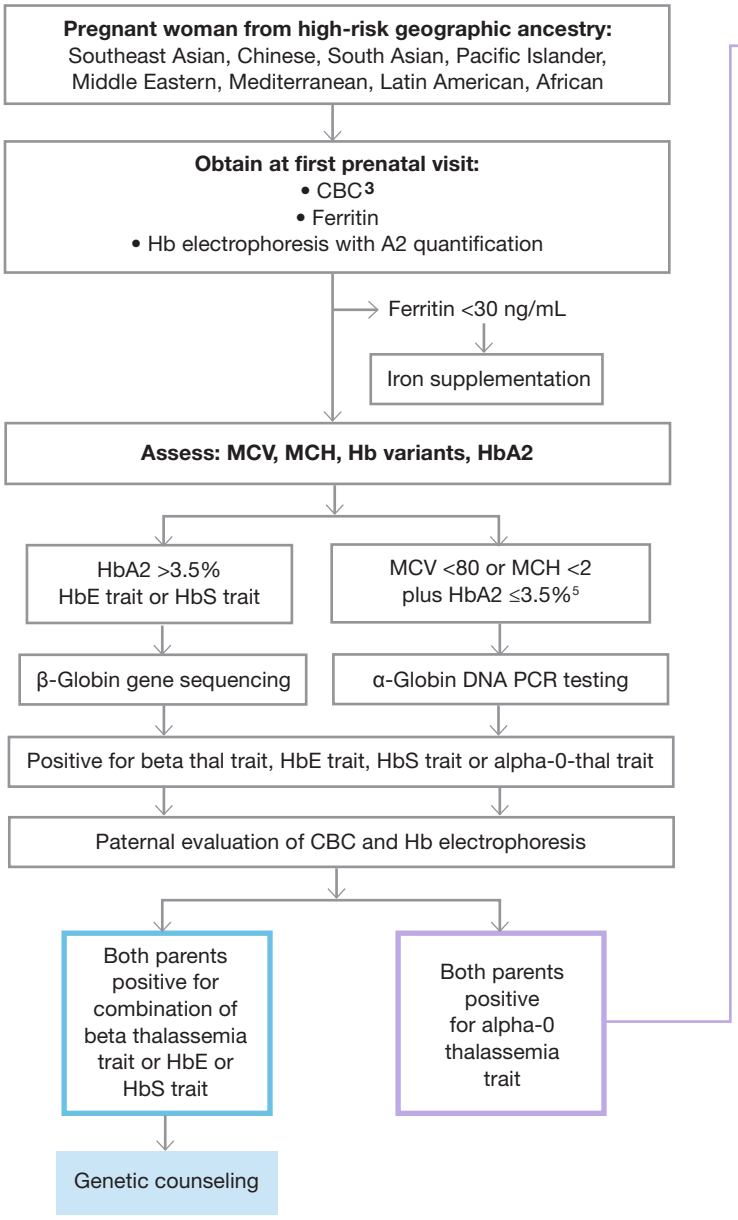
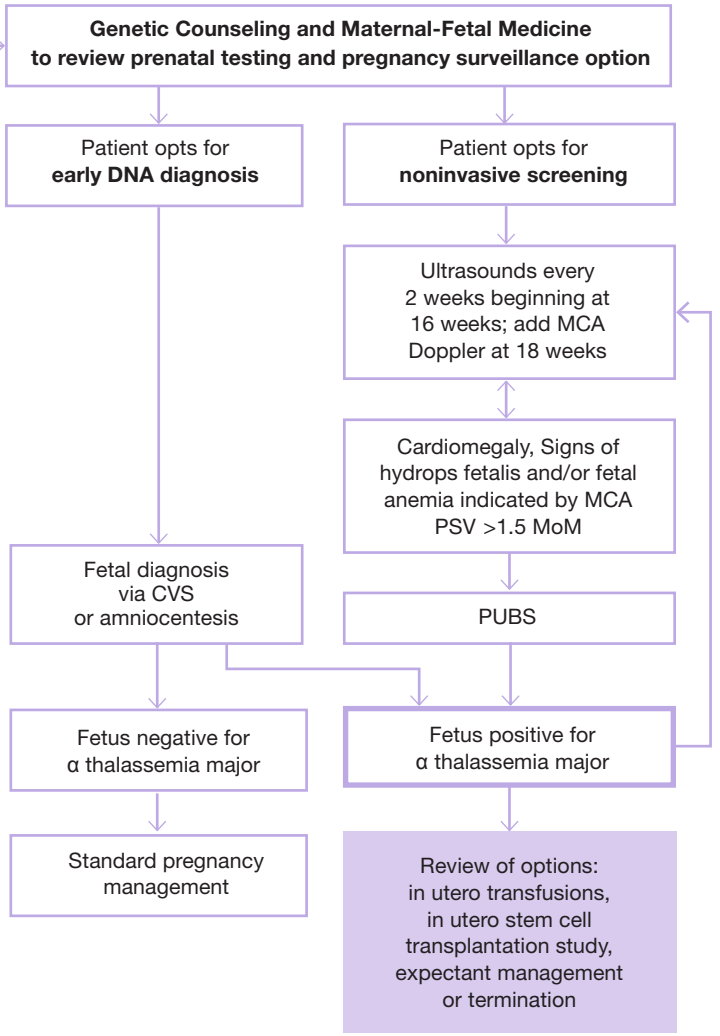
Hemoglobinopathy Carrier Screening[1,2,4]

Most couples are unaware of their risk for conceiving a child with thalassemia or SCD. **Carrier screening ideally occurs preconception or with the initial prenatal labs by assessing the patient's CBC and hemoglobin electrophoresis.** When microcytic anemia is detected, testing for alpha-0 trait is performed because **normal hemoglobin electrophoresis/HPLC results do not exclude alpha-0 trait.** This additional testing is required for women of Southeast Asian and Chinese ancestry and recommended for the other groups.



Prenatal Monitoring for ATM (Hb Bart's Hydrops Fetalis)

If alpha-0 thalassemia trait is identified in both parents, education about options including prenatal diagnosis and pregnancy management is essential. Because fetuses affected with alpha thalassemia major develop severe anemia and hydrops fetalis, monitoring the pregnancy for these complications (below) is necessary to mitigate risk to the mother and adverse sequalae to the fetus.



1. This tool is not a replacement for referral to genetic counseling, which may happen at any time in this pathway. Genetic counseling provides guidance for genetic testing and management options for families with pregnancies at risk for severe forms of thalassemia.
2. The sensitivity and specificity are not definitive and not all carriers will be detected by this screening.
3. The American College of Obstetricians and Gynecologists recommends that all pregnant women have a CBC with assessment of MCV.
4. Rare mutations, such as delta-beta thalassemia, non-deletional alpha thalassemia and others, may not be captured in this algorithm. In high-risk cases, or where hemoglobin electrophoresis is abnormal, consultation with a genetic counselor and/or hematologist is recommended.
5. Presence of HbA2 >3.5 does not exclude co-existing alpha-0 thalassemia trait. In individuals of Southeast Asian, Filipino or Chinese descent who have microcytic hypochromic anemia, perform alpha-globin gene deletion and common variant studies irrespective of HbA2 level.

Abbreviations: ATM, alpha thalassemia major; CBC, complete blood count; CVS, chorionic villus sampling; Hb, hemoglobin; HPLC, high-performance liquid chromatography; MCA, middle cerebral artery; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; MoM, multiples of the median; PCR, polymerase chain reaction; PSV, peak systolic velocity; PUBS, percutaneous umbilical blood sampling; SCD, sickle cell disease.

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Diagnostic Codes and Parameters

Complete Blood Count	
85025	• Hemoglobin <11 g/dL indicates anemia • Mean corpuscular volume <80 fL indicates microcytic anemia • Mean corpuscular hemoglobin <27 pg indicates hypochromic anemia
Hemoglobin Analysis	
83021	• Hemoglobin electrophoresis/HPLC: HbA2 >3.5% indicates beta thalassemia trait, ≤3.5% rules out beta thalassemia but does not exclude alpha thalassemia
Imaging for ATM (Hb Bart's Hydrops Fetalis)	
76811	• Fetal ultrasound to assess for signs of hydrops or evidence of alpha thalassemia major
76821	• Middle cerebral artery doppler Ultrasound MCA PSV >1.5 MoM indicates fetal anemia
76816	• Follow-up fetal ultrasound for hydrops surveillance
Iron Studies	
82728	• Serum ferritin <30 ng/mL indicates iron deficiency anemia with or without thalassemia
Genetic Analysis	
81364	• Beta-globin complete gene sequencing
81257	• Alpha-globin common deletions/mutations analysis • If negative, consider alpha-globin gene sequencing
Thalassemia Diagnosis ICD-10 Codes	
D56.3	Diagnosis of parental alpha or beta thalassemia trait
D56.0	Diagnosis of alpha thalassemia major
D56.1	Diagnosis of beta thalassemia major
O35.8XX0	Maternal care for suspected fetal condition

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