To obtain clinical genetic services in Hawai‘i, please select from the appropriate genetic services below. Genetic services in Hawai‘i are provided by board certified clinical geneticists, genetic counselors, and allied health providers.

Hawai‘i Community Genetics
Provides pediatric and adult clinical genetic services
Special multidisciplinary clinics include Hemoglobinopathy and Metabolic Clinics.
1441 Kapi‘olani Boulevard, Suite 1800
Honolulu, HI 96814
(808) 973-3403

Fetal Diagnostic Institute of the Pacifi
Provides prenatal ultrasound, genetic screening and testing
1600 Kapi‘olani Boulevard, Suite 1025
Honolulu, HI 96814
(808) 945-2229

Kapi‘olani Medical Center for Women and Children Fetal Diagnostic Center
Provides pre-conceptional and prenatal genetic counseling, screening, and testing
1319 Punahou Street, Suite 540
Honolulu, HI 96826
(808) 983-8559

Queen’s Comprehensive Genetics Center and Queen’s Genetics Laboratory
Provides adult clinical genetic services including prenatal, cancer, and general genetics
1380 Lusitana Street, 3rd Floor
Honolulu, HI 96813
(808) 537-7633

January 2008
Questions or Comments?
For more information, please contact the Hawai‘i State Genetics Program at 808-733-9055, or you can visit our website at www.hawaiigenetics.org

Acknowledgements
We thank Laurie Seaver, M.D.; Ted Hsia, M.D.; and Kelley Woodruff, M.D. for their guidance and suggestions in developing this protocol.

Mahalo Nui Loa!

Nondiscrimination in Service:
The Hawai‘i Department of Health provides access to its activities without regard to race, color, national origin (including language), age, sex, religion, or disability. If you believe you have been discriminated against, write the State Department of Health Affirmative Action Officer at P.O. Box 3378, Honolulu, HI 96801.

Hawai‘i Genetics Program
741 Sunset Avenue
Honolulu, HI 96816
Phone: (808) 733-9055
Fax: (808) 733-9068
www.hawaiigenetics.org
**Sickle Cell Disease and Trait: Clinical and Counseling Protocol (Children 0-6 Years) in Hawai‘i is available on this website**.

Gene Reviews
http://www.genetests.org

National Library of Medicine Genetics Home Reference

NCBI Genes and Disease

Northern Comprehensive Thalassemia Center Children’s Hospital Oakland
Department of Hematology/Oncology
747 52nd Street
Oakland, CA 94609
Phone: (510) 428-3885, x4398
www.thalassemia.com
**Printable copy of Clinical Practice Guidelines for the Management of Thalassemia Patients California Consensus is available on this website**

Thalassaemia International Federation
P.O. Box 28807
2083 Nicosia
Cyprus
Phone: (357) 22-319129
Fax: (357) 22-314552
Email: thalassaemia@cytanet.com.cy
www.thalassaemia.org.cy
REFERENCES


RESOURCES

For more information about thalassemia and other hemoglobinopathies, please visit the following websites:

Cooley’s Anemia Foundation
330 Seventh Avenue, Suite 900
New York, NY 10001
Phone: (800) 522-7222
Fax: (212) 279-5999
Email: info@cooleyaneemia.org
www.cooleyaneemia.org
**Thalassemias and Other Hemoglobinopathies**

### Introduction

Hemoglobinopathies are a group of inherited disorders characterized by abnormal hemoglobin structure or production caused by gene mutations.

<table>
<thead>
<tr>
<th>Hemoglobin production defects</th>
<th>Hemoglobin structural abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha Thalassemia</td>
<td>Sickle cell anemia</td>
</tr>
<tr>
<td>Beta Thalassemia</td>
<td>Hemoglobin variants such as hemoglobin C, E, D, G, etc.</td>
</tr>
</tbody>
</table>

Examples

While iron deficiency is the most common cause of acquired anemia, thalassemia is the most common form of inherited anemia. Yet, many individuals who are familiar with anemia caused by iron deficiency may not be aware of thalassemia leading to anemia. For this reason, patients with thalassemia often go unrecognized or are misdiagnosed worldwide.

The diagnosis of the hemoglobinopathies can be a challenge because methods of diagnosis can differ among the different types. For example:

- Sickle cell anemia can be identified by hemoglobin electrophoresis alone, while both alpha and beta thalassemia need to be confirmed through molecular methods.
- Most cases of hemoglobin variants and alpha thalassemia are detected on the newborn screen, whereas beta thalassemia is not clinically apparent until about 4-6 months of life.

Therefore, it is important to understand the strengths and limitations of the different testing methods available for the hemoglobinopathies.

The detection and follow up for hemoglobinopathies is a significant issue for Hawai‘i. One in 46 individuals in Hawai‘i is a carrier for alpha thalassemia. One should also be aware that individuals can potentially inherit more than one type of hemoglobinopathy, leading to more severe symptoms and health outcomes. For all of these reasons, knowledge of the hemoglobinopathies is essential for health care providers in Hawai‘i.

### General Therapeutic Considerations: Guideline for Management and Evaluation

**Milder forms of thalassemia do not usually require specialized treatment.**

- Supplemental iron administration should be avoided unless iron deficiency is proven. In cases with documented iron deficiency, iron therapy should be monitored to avoid excessive treatment.
- Changes in hemoglobin from the patient’s usual baseline level should be evaluated. Decreased hemoglobin levels associated with pregnancy may occasionally worsen symptomatic anemia.

**Moderately severe forms of thalassemia (Hb H disease, β-thalassemia intermedia, and some Hb E/β thalassemias) require ongoing medical care.**

- Important considerations include administering supplemental folic acid, avoiding oxidant drugs and unnecessary iron, and monitoring for normal growth and development, hypersplenism, and progressive iron overload.
- Acute exacerbations of anemia require evaluation and support, including transfusions, and may occur with infection, splenic sequestration, aplastic crisis, pregnancy, and folate deficiency. The patient may also develop symptomatic gallstones and/or leg ulcers.
- Periodic consultation with a hematologist knowledgeable in management of thalassemia is strongly recommended.

**For severe forms of thalassemia, therapeutic considerations include regular transfusion therapy, iron chelation, and bone marrow transplantation.**

- All patients with these severe forms should be cared for by physicians with expertise in the management of thalassemia and iron overload. Ideally, centers that provide multidisciplinary management for patients with hemoglobin disorders should deliver comprehensive care because proper management dramatically improves longevity and quality of life.
INSTRUCTIONAL AND EDUCATIONAL TECHNIQUES

- Use lay language and common words for scientific terms whenever possible.
- Use visual aids to illustrate key points.
- Establish a dialogue/discussion rather than a lecture or information-giving format.
- Implement a pre- and post-assessment of the session.
- Use the post-assessment as an opportunity to clarify misinterpretation or uncertainties about the information discussed during the session.
- Provide literature written in lay language covering the essential facts.
- Make available resources of more detailed information for those who are interested.
- Communicate the availability of the provider for any follow-up questions.
- Provide a full description of the material covered, including a copy of all graphics, plus a summary of the highlights or key points in the form of a fact sheet.
- Genetic counseling for decision-making assistance should be nondirective and objective. Counselors should not introduce personal biases or offer specific recommendations.
- Follow a standard protocol to ensure that the essential topics are covered.

This protocol will provide general medical guidance suggesting current and best approaches to identifying, diagnosing, educating, and treating thalassemia and hemoglobin variants for Hawai‘i’s infants, children, and adults. The material is broadly organized into three main sections:

1. Identification and Diagnosis
2. Education and Genetic Counseling
3. Guidelines for Management and Evaluation

We hope to provide primary care physicians, nurses and allied health providers basic information they can use in their daily practice in caring for patients affected by these conditions. A set of references and local and national resources are listed at the end of the protocol for those wanting further information.
This section describes the three main ways to identify a child with thalassemia or a hemoglobin variant:

A. Evaluation of Red Blood Cell Indices
B. Newborn Screening Identification and Follow-up
C. Prenatal Screening and Family Planning

Once a hemoglobinopathy is suspected, the diagnosis is confirmed with DNA testing for some of the hemoglobinopathies. DNA testing is usually not done for structural variants. There are numerous laboratories nationwide that offer genetic testing for the hemoglobinopathies, including the Queen's Genetics Laboratory located in Honolulu. Not all laboratories offer DNA testing for every type of hemoglobinopathy. Providing instructions for how to order these tests is beyond the scope of this protocol as genetic technology is rapidly advancing and local and national laboratory procedures and guidelines change over time. We recommend you contact the appropriate clinical genetics health providers listed in the resources section for more information once an individual with a hemoglobinopathy has been identified in your practice.

### Hemoglobin Structural Defects

**SICKLE CELL DISEASE OR HEMOGLOBIN SS**
- Detailed description in publication by Hawai‘i Genetics Program called [Sickle Cell Disease and Trait: Clinical and Counseling Protocol (Children 0-6 Years) in Hawai‘i](www.hawaiigenetics.org)

**HEMOGLOBIN CC, EE, DD, HEMOGLOBIN S-HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN**
- Usually clinically benign
- Abnormal red blood cell indices show anemia
- Potential health problems
- Regular, yearly appointments with the hematologist
- Genetic counseling strongly recommended for individuals considering pregnancy
- Iron supplementation should be avoided. Iron supplementation will not improve those with inherited anemia.

**HEMOGLOBIN Trait**

**Sickle cell trait and sickle cell trait/alpha thalassemia**
- Detailed description in publication by Hawai‘i Genetics Program called [Sickle Cell Disease and Trait: Clinical and Counseling Protocol (Children 0-6 Years) in Hawai‘i](www.hawaiigenetics.org)

**Hemoglobin C, D, E, O-Arab**
- Clinically benign, may show no or mild anemia
- Traits are not an illness, so no restrictions need to be placed on activities.
- Genetic counseling strongly recommended for individuals considering pregnancy
- Medical management as per needed basis
- Iron supplementation should be avoided. Iron supplementation will not improve those with inherited anemia.
BETA THALASSEMIA

The difference between beta thalassemia minor/trait, beta thalassemia major, and beta thalassemia major variations like beta thalassemia intermedia.

Beta thalassemia minor/trait is not a disease. No restriction needs to be placed on physical activities.

Both parents must have beta thalassemia trait or another hemoglobin trait for their child to have beta thalassemia major.

There is a 25 percent chance with every pregnancy that a child will be affected with beta thalassemia major.

Natural history of beta thalassemia major (including potential health problems, variability of severity, resources necessary to care for a child with beta thalassemia major, life span, etc.)

Treatement options available to persons affected with beta thalassemia major

Iron supplementation should be avoided. Iron supplementation will not improve those with inherited anemia.

Options for medical management:

Beta Thalassemia Minor
- As-needed basis
- Genetic counseling strongly recommended for individuals considering pregnancy

Beta Thalassemia Major
- Regular consultation with hematologist strongly recommended

Family planning options available to persons affected with beta thalassemia.

A. Evaluation of Red Blood Cell Indices

A low mean corpuscular volume (MCV) or mean corpuscular hemoglobin (MCH) is often the first or only clue to the presence of a hemoglobinopathy.

<table>
<thead>
<tr>
<th>Complete Blood Count (CBC)</th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>8.6</td>
<td></td>
<td>(6.8 - 16.0)</td>
</tr>
<tr>
<td>RBC</td>
<td>5.28</td>
<td></td>
<td>(3.5 - 5.5)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.0</td>
<td>L</td>
<td>(11.2 - 14.2)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>31.5</td>
<td>L</td>
<td>(33.0 - 39.0)</td>
</tr>
<tr>
<td>MCV</td>
<td>59.6</td>
<td>L</td>
<td>(71 - 91)</td>
</tr>
<tr>
<td>MCH</td>
<td>19.0</td>
<td>L</td>
<td>(22 - 32)</td>
</tr>
<tr>
<td>MCHC</td>
<td>31.8</td>
<td></td>
<td>(31 - 37)</td>
</tr>
<tr>
<td>RDW</td>
<td>18.3</td>
<td>H</td>
<td>(11 - 15)</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>350.0</td>
<td></td>
<td>(204 - 405)</td>
</tr>
</tbody>
</table>

When clinicians encounter a low MCV or MCH when interpreting a complete blood count (CBC) obtained for any purpose after one year of age, the primary care providers should consider Figure 1 (please note that the approach used to evaluate a low MCV during a pregnancy is different and will be addressed in the prenatal screening and family section).
INTENDED LEARNING OUTCOMES FOR CONSELEE

Hemoglobin Production Defects

ALPHA THALASSEMA

- The differences among the four types of alpha thalassemia (hydrops fetalis, hemoglobin H disease, alpha thalassemia trait, and silent carrier)
- Silent carrier and trait forms are not illnesses and lifespan is not shortened.
- Life style and life span for hemoglobin H are usually not greatly affected although they have a greater chance for medical complications compared to silent carrier and trait forms.
- Both parents must have either cis-type trait or hemoglobin H in order to have a child with hydrops fetalis. In such cases, there is a 25 percent chance that each pregnancy can result in a child with hydrops fetalis.
- Treatment options are available to parents who want to continue pregnancies identified early to be affected with hydrops fetalis.
- Natural history of the different types of alpha thalassemia (including potential health problems, variability of severity, and available resources)
- Iron supplementation should be avoided if the individual does not have iron deficiency. Iron supplementation will not improve those with inherited anemia.
- Options for medical management:
  
  **Silent Carrier and Trait**
  
  a. As-needed basis
  b. Genetic counseling strongly recommended for individuals considering pregnancy

**Hemoglobin H**

a. Regular, yearly appointments with hematologist
b. Avoid certain foods and drugs that induce hemolysis.

- Family planning options available to persons affected with alpha thalassemia.

---

* Iron deficiency may exist with ferritin values up to 150ng/ml. Ferritin is an acute phase reactant and values may be decreased for reasons other than iron deficiency including fevers, lupus, liver disease, etc., leading to possible false negative results of iron deficiency. It is best to order ferritin at a time when no acute illness is present.

* Iron deficiency may exist with ferritin values up to 150ng/ml. Ferritin is an acute phase reactant and values may be elevated in iron deficiency with chronic/tissue disease or inflammation.

* Alkaptonuria cases of beta thalassemia and alpha thalassemia silent carriers are not ruled out in this case.
2. Sickle Cell Trait/Alpha Thalassemia
- Clinically benign
- Less hemoglobin S than sickle cell trait
- MCV is decreased

3. Hemoglobin C Trait
- Clinically benign, no anemia

4. Hemoglobin D Trait
- Clinically benign

5. Hemoglobin E Trait
- High frequency in Southeast Asians (35% Cambodians; 15% Thai)
- Clinically benign, mild anemia
- Moderate microcytosis

6. Hemoglobin O-Arab
- Also known as hemoglobin O-Egypt; occurs in North Africa, Bulgaria, Yugoslavia, Arabia, Jamaica and in Americans with ancestry from those areas
- Clinically benign, no anemia

B. Newborn Screening Identification and Follow-up

Over 99% of infants born in Hawai‘i receive newborn screening (NBS) each year. The following flow chart summarizes the recommended follow-up plan for newborns with a positive screen for any hemoglobinopathy.
When interpreting a newborn screening result for a hemoglobinopathy, there are several different possible NBS outcomes. Those that require a follow-up evaluation for thalassemia are shown below.

Figure 2. Newborn Screening results requiring follow-up evaluation for thalassemia

**Possible NBS Results:**

1. Hb F + Hb A
2. Hb F + Hb A + Hb Bart’s

**Possible Implications of NBS Results:**

Normal

Alpha thalassemia syndrome

Structural Hemoglobin Diseases (Hemoglobin E, Sickle Cell Diseases, Sickle Beta, etc.)

**Recommended Follow-Up:**

Further Medical Evaluation and Genetic Counseling by HCG Hemoglobinopathy clinic or Hematologist

**Types of hemoglobin:**

- HbF: Fetal Hemoglobin
- HbA: Adult Hemoglobin
- Hb Bart: Bart Hemoglobin (suggestive of alpha thalassemia)
- HbE: Hemoglobin E (structural variant)
- HbC: Hemoglobin C (structural variant)
- HbSS: Sickle Cell Anemia or Hemoglobin SS disease

**Hemoglobin EE**

- Clinically benign
- Mild anemia (Hb 10-12g/dL)

**Hemoglobin DD**

- Mild hemolytic anemia but usually with normal hemoglobin levels
- Enlarged spleen

**HEMOGLOBIN TRAITS**

1. Sickle Cell Trait
   - Not a disease
   - Occurs in about 10% of African Americans
   - Sickle cell trait is not associated with anemia.
   - Adults with sickle cell trait have mostly HbA and less than ~30% hemoglobin S. The amount of HbA is sufficient to prevent sickling under most physiological conditions; and hence, sickling does not occur.
   - Occasional microscopic hematuria and hyposthenuria (a condition characterized by failure to concentrate urine normally)
   - Splenic infarction reported to occur in altitudes greater than 8,000 feet. Flight travel is not discouraged as flight carrier cabins are reportedly pressurized to 4,000-5,000 feet.

Modified from Dumars et al., 1996
Common types of events that can affect illness include dehydration, alcohol consumption, high altitudes, extreme temperatures, stress, and depression.

Constitutional complications include delayed growth and development, increased risk for infections, allo-immunization, and skin ulcers.

Anemic complications include chronic hemolysis, hyper-hemolytic episodes, aplastic episodes, and splenic sequestration episodes.

Vaso-occlusive complications include microinfarction (pain), macroinfarction (stroke, proliferative retinopathy, cardiomyopathy, acute chest syndrome, RUQ syndrome, bone and joint complications, etc.)

2. Hemoglobin CC
   - Usually a benign condition
   - Should be followed by a hematologist
   - Can be associated with the following symptoms:
     - Mild hemolytic anemia (Hb 10-12g/dL)
     - Greater than 90% target cells on blood smear
     - Increased risk for gallstones
     - Infections can trigger aplastic episodes.
     - Usually no vaso-occlusive complication because decreased MCV facilitates passage through microcirculation

3. Hemoglobin S-Hereditary Persistence of Fetal Hemoglobin
   - Very rare condition occurring in about 1/25,000 individuals
   - No significant anemia or spontaneous sickling because the high intracellular concentration of HbF prevents sickling
   - If HbF is greater than 18%, there are few or no vaso-occlusive episodes and a decrease in episodes of acute chest syndrome.

C. Prenatal Screening and Family Planning

Thalassemias and structural hemoglobin variants are more difficult to diagnose or exclude during pregnancy because common nutritional deficiencies alter the MCV. Microcytosis, due to iron deficiency, is common during pregnancy. Coexistent folic acid deficiency may increase the MCV. Because exclusion of iron deficiency is important in the evaluation of thalassemia and iron studies may not reliably exclude iron deficiency during pregnancy, the diagnosis of thalassemia is best made before pregnancy. When a pregnant patient with low MCV presents in your clinic and thalassemia has not been ruled out, the algorithm shown in Figure 3 should be considered.

Figure 3. Algorithm using MCV for the detection of thalassemia syndromes during pregnancy.

---

(1) Given the need to diagnose expeditiously during pregnancy, fetsits is performed simultaneously with tests to rule out iron deficiency.
(2) Structural hemoglobin variants, eg., Hb E, G, C, or Constant Spring, will often not have a low MCV. In certain ethnic groups, Hb electrophoresis should be considered to detect structural variants.
(3) Silent carrier alpha thalassemia can have normal red blood cell indices.
(4) Hb F may be slightly elevated in normal women during pregnancy.
(5) References - Godal JG, Romins I, and Thevan HSG

modified from Dumars et al., 1996
Prenatal screening and family planning are extremely important in evaluating individuals at risk for hemoglobinopathies. This is because carriers may be at risk for having severely affected children despite the fact that they have no symptoms of their own and may be unaware of their carrier status. This is illustrated by the diagram below, where the parents are typically asymptomatic carriers of sickle cell anemia but could potentially have a child with sickle cell disease. This is an example of recessive inheritance.

**Hemoglobin Structural Defects**

**HEMOGLOBIN VARIANTS**

1. **Sickle Cell Disease or Hemoglobin SS**
   This protocol will provide a brief overview of sickle cell disease. A more thorough description of the diagnosis, management, and follow-up of Sickle Cell Anemia is found in another publication by the Hawai‘i Genetics Program, titled Sickle Cell Disease and Trait: Clinical and Counseling Protocol (Children 0-6 Years) in Hawai‘i. Please go to www.hawaiigenetics.org to obtain a copy.

Sickle cell disease is the term used to refer to disorders in which the red blood cell becomes deformed or sickle shaped under stress. Sickle cell anemia is the most common form of sickle cell disease, but other forms of sickle cell disease exist. The information below refers to all sickle cell disorders unless otherwise noted.

- Sickle cell anemias are inherited in an autosomal recessive fashion such that both genes need to be altered in order for the disease to be present.
- Sickle cell disease is most common in people from Africa, the Middle East, Southern India, Mediterranean (Greece and Turkey). This is believed to be due to past endemic malaria occurring in these areas such that individuals with some abnormal hemoglobins are more resistant to malaria and more likely to survive.
- Severity varies among the different forms of sickle cell disease and also among individuals. Some individuals with sickle cell disease are never seen for sickle cell related complications, while others spend their lives in and out of hospitals. Presently, there is no way to predict how severely someone will be affected.
4. Common Questions Regarding Beta Thalassemia

How is beta thalassemia different from structurally abnormal hemoglobins such as hemoglobin S and hemoglobin C?

- Hemoglobin S and C are detected on the newborn screen. Beta thalassemia is not detected on the newborn screen.

How is beta thalassemia different from alpha thalassemia?

- Alpha thalassemia is detected on the newborn screen. Beta thalassemia is not detected on the newborn screen.
- Decreased production of the beta chain rather than the alpha chain of hemoglobin
- Individuals have two copies of the beta globin gene while individuals have four copies of the alpha globin gene.
- The genes for the production of beta chains are on chromosome number 11; the genes for alpha chain production are on chromosome 16.

Will the anemia worsen over time?

- The baseline level of anemia will remain stable throughout the lifespan. It will neither improve nor worsen.

Will my child with beta thalassemia trait become more sick?

- Individuals with beta thalassemia trait will not experience more fatigue or lethargy.
- Beta thalassemia trait does not lead to an increased susceptibility to colds, flu, etc.
- Beta thalassemia trait does not cause decreased stamina or decrease life expectancy.

Will iron supplementation help this anemia?

- Iron supplementation will not improve this anemia unless iron deficiency co-exists.

Alpha thalassemia has a more complex inheritance pattern. Instead of two gene copies, each person has four copies of the alpha globin gene. Alpha thalassemia occurs when one or more of the alpha globin genes are not working. The form of alpha thalassemia diagnosed is dependent upon the number of working copies of the alpha thalassemia gene. Prenatal genetic counseling should be offered to couples who have red blood cell indices suggestive of thalassemia to explain the risk of having affected children given its complex inheritance pattern.

<table>
<thead>
<tr>
<th>Parents with alpha thal trait</th>
<th>Possible outcomes in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha thal trait</td>
<td>Alpha thal trait</td>
</tr>
<tr>
<td>Alpha thal trait</td>
<td>25% chance of having an unaffected child</td>
</tr>
<tr>
<td>Alpha thal trait</td>
<td>50% chance of having a child with alpha thal trait</td>
</tr>
<tr>
<td>Alpha thal trait</td>
<td>25% chance of having a child with alpha thal major</td>
</tr>
</tbody>
</table>

Genetic test results and their implications are not limited to the immediate family members who are affected. There may be relatives who have the condition as well. It is recommended that other family members be made aware of their risk for inherited anemia and that their family seek genetics services to discuss these concerns further.
In this section, we cover basic content that should be covered for genetic counseling and education. Frequently asked questions for each condition are also described. This section closes with intended learning outcomes for the counselee and a review of instructional and educational techniques for the provider. The information is not intended to replace the expertise of a medical specialist in this area. We highly encourage health providers to develop their own style and approach to conducting these educational sessions or when in doubt to refer to the appropriate specialists.

The conditions are described in the order listed below:

### Hemoglobin Production Defects

<table>
<thead>
<tr>
<th>Types of Alpha Thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HbBart’s Esoteria</td>
</tr>
<tr>
<td>2. Hemoglobin H Disease</td>
</tr>
<tr>
<td>3. Hemoglobin H-Constant Spring Disease</td>
</tr>
<tr>
<td>4. Alpha Thalassemia Trait</td>
</tr>
<tr>
<td>5. Alpha Thalassemia Silent Carrier</td>
</tr>
<tr>
<td>6. Alpha Thalassemia + Another Hemoglobinopathy</td>
</tr>
<tr>
<td>7. Common Questions about Alpha Thalassemia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Types of Beta Thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Beta Thalassemia Major</td>
</tr>
<tr>
<td>2. Beta Thalassemia Major Variations</td>
</tr>
<tr>
<td>a. Beta0 Thalassemia</td>
</tr>
<tr>
<td>b. Beta+ Thalassemia</td>
</tr>
<tr>
<td>c. Sickle Beta+ Thalassemia</td>
</tr>
<tr>
<td>d. Sickle Beta0 Thalassemia</td>
</tr>
<tr>
<td>e. Thalassemia Intermedia</td>
</tr>
<tr>
<td>f. Hemoglobin E/Beta Thalassemia</td>
</tr>
<tr>
<td>3. Beta Thalassemia Trait</td>
</tr>
<tr>
<td>4. Common questions about Beta Thalassemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>e. Hemoglobin E/Beta Thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Electrophoresis is usually HbEF (HbFE in newborns).</td>
</tr>
<tr>
<td>• Marked microcytosis (MCV in 50s), severe anemia (Hb&lt;8 and often transfusion dependent)</td>
</tr>
<tr>
<td>• Splenomegaly</td>
</tr>
<tr>
<td>• Blood smear shows marked hypochromia, microcytosis, teardrops, and target cells.</td>
</tr>
<tr>
<td>• Hepatosplenomegaly, bony changes, decreased exercise tolerance, and growth failure may occur.</td>
</tr>
<tr>
<td>• Most individuals become transfusion dependent by 5 years of age and do better with regular transfusions.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Beta Thalassemia Trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Also known as Beta Thalassemia Minor</td>
</tr>
<tr>
<td>• Persons with beta thalassemia trait have one gene for production of the usual amount of beta chains and one gene for a decreased amount of the beta chains.</td>
</tr>
<tr>
<td>• Is not a disease</td>
</tr>
<tr>
<td>• Can be confused with iron deficiency because of microcytosis</td>
</tr>
<tr>
<td>• Indicators:</td>
</tr>
<tr>
<td>o HbA2 elevated (&gt;3.5); HbF normal or elevated (&gt;2.5)</td>
</tr>
<tr>
<td>o Mild anemia (Hb 1-2g below normal)</td>
</tr>
<tr>
<td>o Microcytosis (MCV &lt;80 in adults)</td>
</tr>
<tr>
<td>o Hypochromia (MCH &lt;26)</td>
</tr>
<tr>
<td>o Cannot be detected at birth by standard methods</td>
</tr>
<tr>
<td>o Blood smear may show target cells</td>
</tr>
<tr>
<td>o Iron studies are normal.</td>
</tr>
<tr>
<td>o Also known as Beta Thalassemia Minor</td>
</tr>
</tbody>
</table>
2. Beta Thalassemia Major Variations
a. Beta0 Thalassemia
   - No beta chains produced
   - Severe anemia
   - Transfusion dependent
   - Usually seen in Southeast Asians or Mediterraneans

b. Beta+ Thalassemia
   - Small amounts of beta chains produced
   - Generally more mild than Beta0 Thalassemia
   - Commonly found in African Americans

c. Sickle Beta+ Thalassemia
   - Such persons have one gene for the production of hemoglobin S and one gene for decreased production of beta chains.
   - The red blood cells contain both HbS and HbA, but unlike sickle cell trait, there is more HbS than HbA.

d. Sickle Beta0 Thalassemia
   - Such persons have one gene for the production of hemoglobin S and one gene for decreased production of beta chains.
   - The red blood cells contain both HbS and HbA, but unlike sickle cell trait, there is more HbS than HbA.
   - Clinically more severe than Sickle Beta+ Thalassemia

Hemoglobin Structural Defects

Types of Hemoglobin Variants
1. Sickle Cell Disease or Hemoglobin SS
2. Hemoglobin CC
3. S-Hereditary Persistence of Fetal Hemoglobin
4. Hemoglobin EE
5. Hemoglobin DD

Types of Hemoglobin Traits
1. Sickle Cell Trait
2. Sickle Cell Trait/Alpha Thalassemia
3. Hemoglobin C Trait
4. Hemoglobin D Trait
5. Hemoglobin E Trait
6. Hemoglobin O-Arab
Hemoglobin Production Defects

**ALPHA THALASSEMIA**

Alpha thalassemia is commonly found in people of Asian origins (e.g., Filipino, Chinese, and Indonesian). However, it has also been seen in people of African, Middle Eastern, and Native American ancestry. Because many people in Hawai‘i are of mixed ethnic backgrounds, it is important to assess individuals for alpha thalassemia using laboratory tests in addition to ethnic markers.

There are four main clinical types of alpha thalassemia. These are classified by the number of genes that are working versus non-working. DNA analysis is necessary to differentiate one type of alpha thalassemia from another. The diagram below illustrates the four common forms of alpha thalassemia.

1. **Hydrops Fetalis**
   - due to alpha thal major

2. **Hemoglobin H Disease**

3. **Traits**
   - cis-type: Two altered genes occurring on the same chromosome
   - trans-type: Two altered genes occurring on different chromosomes

4. **Silent Carrier**

**BETA THALASSEMIA**

Beta thalassemia, historically known as Cooley’s Anemia, is caused by mutations in the beta globin chain gene. Everyone has two copies of the beta globin gene. Beta thalassemia major results when both copies do not work. Over 70 different beta chain mutations are known. The severity of the homozygous condition varies with the different mutations.

1. **Beta Thalassemia Major**
   - Inherited defect in beta chain synthesis resulting in a decreased production of normal hemoglobin A and an increase in available alpha chains
   - Early signs include paleness, weakness, and failure to thrive. Without treatment, death often results by age four years.
   - Anemia is generally severe and the patient is dependent on chronic transfusion and chelation therapy.
   - Other features include increased risk for infection, growth retardation, skeletal abnormalities, and shortened life span.
   - Beta thalassemia major is usually less severe in the African population than the Mediterranean or Asian population because of the specific gene mutations found in each group.
   - Blood smear shows extreme hypochromia, microcytosis, and target cells.
   - Decreased fertility
   - The life span of individuals with beta thalassemia has been drastically increased due to chelation therapy, which rids the body of excess iron produced by chronic transfusions. Presently, persons with beta thalassemia major have lived into the fifth decade of life.
5. Silent Carrier State of Alpha Thalassemia

- The individual inherits three working genes for alpha globin chain synthesis.
- No clinical signs of silent carrier status are evident.

6. Alpha Thalassemia + Another Hemoglobinopathy

Alpha Thalassemia Trait + Beta Thalassemia Major
- Please consult the hematologist or genetic specialist for more details and inheritance of this combination.

Alpha Thalassemia Trait + Beta Thalassemia Trait
- Please consult the hematologist or genetic specialist for more details and inheritance of this combination.

7. Common Questions regarding Alpha Thalassemia

Will the anemia worsen over time?
- The baseline level of anemia will remain stable throughout the lifespan. It will neither improve nor worsen.

Will my child with alpha thalassemia trait become more sick?
- Individuals with alpha thalassemia trait will not experience more fatigue or lethargy.
- Alpha thalassemia trait does not lead to an increased susceptibility to colds, flus, etc.
- Alpha thalassemia trait does not cause decreased stamina or decrease life expectancy.

Will iron supplementation help this anemia?
- Iron supplementation will not improve this anemia unless iron deficiency co-exists.

1. Hydrops Fetalis

- This condition occurs when the individual has inherited no working genes for alpha globin chain synthesis.
- Hemoglobin electrophoresis shows mostly Bart’s Hemoglobin (an abnormal hemoglobin that is not effective in oxygen transport) with small amounts of HbH and HbPortland.
- This produces a condition that is generally incompatible with life.
- The fetus cannot produce the usual type of hemoglobin. Without transfusion, the fetus is stillborn or dies within the first few minutes or hours of birth because the Bart’s Hemoglobin cannot release oxygen.
- The fetus is edematous with an enormous liver and spleen. The placenta is also edematous.
- Maternal complications include toxemia, placental abruption, and postpartum bleeding.
- Treatment has been attempted with in utero intravascular transfusion, transfusion after birth, and bone marrow transplantation.
2. Hemoglobin H Disease

- This is a condition in which an individual has only one working gene for alpha globin chain synthesis.
- This leads to decreased production of alpha globin chains, which results in an excess of beta globin chains.
- The excess of beta globin chains leads to the formation of tiny precipitates (or inclusions) in the red blood cell.
- The presence of these inclusion bodies leads to a more rapid destruction of the red blood cells as they circulate in the blood stream.
- The condition has a variable clinical presentation.
- This results in life-long anemia of mild to moderate degree. Hemoglobin is usually between 8-9 g/dL.
- The anemia can worsen and lead to medical complications such as enlarged spleen, gallstones, increased risk for infections, jaundice, increased hemolysis, and leg ulcers.
- Pregnancy may worsen the anemia and increase complications.
- Chronic transfusions may be indicated.
- It is important for individuals to maintain good nutrition and health, especially immunizations.

3. Hemoglobin H-Constant Spring Disease

- This is a condition in which an individual also has one working gene for alpha globin chain synthesis. Of the three non-working gene copies, one has a structural mutation called “constant spring”.
- This is a more severe condition than Hemoglobin H Disease.
- This condition is associated with an increased risk of an enlarged spleen, and individuals range from asymptomatic to blood transfusion dependent.

4. Alpha Thalassemia Trait

- This is a condition in which an individual inherits two working genes for alpha globin chain synthesis.
- Individuals with this condition will have a mild microcytic hypochromic anemia.
- This decrease in alpha globin chain production does not lead to health problems.
- Asians with alpha thalassemia usually, but not always, have the two non-working genes on the same chromosome (cis-type) making it possible to have a child with hydrops fetalis.
- African Americans with alpha thalassemia trait usually, but not always, have the two non-working genes on different chromosomes (trans-type) and therefore can only transmit one non-working gene to their offspring.
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- The baseline level of anemia will remain stable throughout the lifespan. It will neither improve nor worsen.

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- Individuals with alpha thalassemia trait will not experience more fatigue or lethargy.
- Alpha thalassemia trait does not lead to an increased susceptibility to colds, flu, etc.
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**Will iron supplementation help this anemia?**
- Iron supplementation will not improve this anemia unless iron deficiency co-exists.

17

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Hemoglobin Production Defects

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![Diagram of alpha thalassemia forms](image)

1. **Hydrops Fetalis**
   - due to alpha thal major

2. **Hemoglobin H Disease**

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   - cis-type: Two altered genes occurring on the same chromosome
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   - Beta thalassemia major is usually less severe in the African population than the Mediterranean or Asian population because of the specific gene mutations found in each group.
   - Blood smear shows extreme hypochromia, microcytosis, and target cells.
   - Decreased fertility
   - The life span of individuals with beta thalassemia has been drastically increased due to chelation therapy, which rids the body of excess iron produced by chronic transfusions. Presently, persons with beta thalassemia major have lived into the fifth decade of life.
2. Beta Thalassemia Major Variations

a. Beta0 Thalassemia
- No beta chains produced
- Severe anemia
- Transfusion dependent
- Usually seen in Southeast Asians or Mediterraneans

b. Beta+ Thalassemia
- Small amounts of beta chains produced
- Generally more mild than Beta0 Thalassemia
- Commonly found in African Americans

c. Sickle Beta+ Thalassemia
- Such persons have one gene for the production of hemoglobin S and one gene for decreased production of beta chains.
- The red blood cells contain both HbS and HbA, but unlike sickle cell trait, there is more HbS than HbA.

d. Sickle Beta0 Thalassemia
- Such persons have one gene for the production of hemoglobin S and one gene for decreased production of beta chains.
- The red blood cells contain both HbS and HbA, but unlike sickle cell trait, there is more HbS than HbA.
- Clinically more severe than Sickle Beta+ Thalassemia
In this section, we cover basic content that should be covered for genetic counseling and education. Frequently asked questions for each condition are also described. This section closes with intended learning outcomes for the counselee and a review of instructional and educational techniques for the provider. The information is not intended to replace the expertise of a medical specialist in this area. We highly encourage health providers to develop their own style and approach to conducting these educational sessions or when in doubt to refer to the appropriate specialists.

The conditions are described in the order listed below:

**Hemoglobin Production Defects**

### Types of Alpha Thalassemia
1. Hydrops Fetalis
2. Hemoglobin H Disease
3. Hemoglobin H-Constant Spring Disease
4. Alpha Thalassemia Trait
5. Alpha Thalassemia Silent Carrier
6. Alpha Thalassemia + Another Hemoglobinopathy
7. Common Questions about Alpha Thalassemia

### Types of Beta Thalassemia
1. Beta Thalassemia Major
2. Beta Thalassemia Major Variations
   a. Beta0 Thalassemia
   b. Beta+ Thalassemia
   c. Sickie Beta+ Thalassemia
   d. Sickie Beta0 Thalassemia
   e. Thalassemia Intermedia
   f. Hemoglobin E/Beta Thalassemia
3. Beta Thalassemia Trait
4. Common questions about Beta Thalassemia

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**e. Hemoglobin E/Beta Thalassemia**
- Electrophoresis is usually HbEF (HbFE in newborns).
- Marked microcytosis (MCV in 50s), severe anemia (Hb<8 and often transfusion dependent)
- Splenomegaly
- Blood smear shows marked hypochromia, microcytosis, teardrops, and target cells.
- Hepatosplenomegaly, bony changes, decreased exercise tolerance, and growth failure may occur.
- Most individuals become transfusion dependent by 5 years of age and do better with regular transfusions.

**3. Beta Thalassemia Trait**
- Also known as Beta Thalassemia Minor
- Persons with beta thalassemia trait have one gene for production of the usual amount of beta chains and one gene for a decreased amount of the beta chains.
- Is not a disease
- Can be confused with iron deficiency because of microcytosis
- Indicators:
  - HbA2 elevated (>3.5); HbF normal or elevated (>2.5)
  - Mild anemia (Hb 1-2g below normal)
  - Microcytosis (MCV <80 in adults)
  - Hypochromia (MCH <26)
  - Cannot be detected at birth by standard methods
  - Blood smear may show target cells
  - Iron studies are normal.
  - Also known as Beta Thalassemia Minor
4. Common Questions Regarding Beta Thalassemia

How is beta thalassemia different from structurally abnormal hemoglobins such as hemoglobin S and hemoglobin C?

- Hemoglobin S and C are detected on the newborn screen. Beta thalassemia is not detected on the newborn screen.

**How is beta thalassemia different from alpha thalassemia?**

- Alpha thalassemia is detected on the newborn screen. Beta thalassemia is not detected on the newborn screen.
- Decreased production of the beta chain rather than the alpha chain of hemoglobin
- Individuals have two copies of the beta globin gene while individuals have four copies of the alpha globin gene.
- The genes for the production of beta chains are on chromosome number 11; the genes for alpha chain production are on chromosome 16.

**Will the anemia worsen over time?**

- The baseline level of anemia will remain stable throughout the lifespan. It will neither improve nor worsen.

**Will my child with beta thalassemia trait become more sick?**

- Individuals with beta thalassemia trait will not experience more fatigue or lethargy.
- Beta thalassemia trait does not lead to an increased susceptibility to colds, flu, etc.
- Beta thalassemia trait does not cause decreased stamina or decrease life expectancy.

**Will iron supplementation help this anemia?**

- Iron supplementation will not improve this anemia unless iron deficiency co-exists.

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Alpha thalassemia has a more complex inheritance pattern. Instead of two gene copies, each person has four copies of the alpha globin gene. Alpha thalassemia occurs when one or more of the alpha globin genes are not working. The form of alpha thalassemia diagnosed is dependent upon the number of working copies of the alpha thalassemia gene. Prenatal genetic counseling should be offered to couples who have red blood cell indices suggestive of thalassemia to explain the risk of having affected children given its complex inheritance pattern.

**Parents with alpha thal trait**

<table>
<thead>
<tr>
<th>Working Gene</th>
<th>Non-working Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha thal trait</td>
<td>Alpha thal trait</td>
</tr>
</tbody>
</table>

**Possible outcomes in children**

- 25% chance of having an unaffected child
- 50% chance of having a child with alpha thal trait
- 25% chance of having a child with alpha thal major

Genetic test results and their implications are not limited to the immediate family members who are affected. There may be relatives who have the condition as well. It is recommended that other family members be made aware of their risk for inherited anemia and that their family seek genetics services to discuss these concerns further.
Prenatal screening and family planning are extremely important in evaluating individuals at risk for hemoglobinopathies. This is because carriers may be at risk for having severely affected children despite the fact that they have no symptoms of their own and may be unaware of their carrier status. This is illustrated by the diagram below, where the parents are typically asymptomatic carriers of sickle cell anemia but could potentially have a child with sickle cell disease. This is an example of recessive inheritance.

### Hemoglobin Structural Defects

#### HEMOGLOBIN VARIANTS

1. **Sickle Cell Disease or Hemoglobin SS**
   - This protocol will provide a brief overview of sickle cell disease. A more thorough description of the diagnosis, management, and follow-up of Sickle Cell Anemia is found in another publication by the Hawai‘i Genetics Program, titled *Sickle Cell Disease and Trait: Clinical and Counseling Protocol (Children 0-6 Years)* in Hawai‘i.

   Please go to [www.hawaiigenetics.org](http://www.hawaiigenetics.org) to obtain a copy.

   Sickled cell disease is the term used to refer to disorders in which the red blood cell becomes deformed or sickle shaped under stress. Sickle cell anemia is the most common form of sickle cell disease, but other forms of sickle cell disease exist. The information below refers to all sickle cell disorders unless otherwise noted.

   **Sickle Cell Disorders**

<table>
<thead>
<tr>
<th>Hemoglobin Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbSS</td>
<td>Sickled Cell Anemia or Hemoglobin SS Disease</td>
</tr>
<tr>
<td>HbSC</td>
<td>Sickled Cell Hemoglobin C Disease</td>
</tr>
<tr>
<td>HbSD</td>
<td>Sickled Cell Hemoglobin D Disease</td>
</tr>
<tr>
<td>HbSE</td>
<td>Sickled Cell Hemoglobin E Disease</td>
</tr>
<tr>
<td>HbS or HbSA</td>
<td>Sickled Cell Beta Thalassemia</td>
</tr>
</tbody>
</table>

   - Sickled cell anemias are inherited in an autosomal recessive fashion such that both genes need to be altered in order for the disease to be present.
   - Sickled cell disease is most common in people from Africa, the Middle East, Southern India, Mediterranean (Greece and Turkey). This is believed to be due to past endemic malaria occurring in these areas such that individuals with some abnormal hemoglobins are more resistant to malaria and more likely to survive.
   - Severity varies among the different forms of sickle cell disease and also among individuals. Some individuals with sickle cell disease are never seen for sickle cell related complications, while others spend their lives in and out of hospitals. Presently, there is no way to predict how severely someone will be affected.
Common types of events that can affect illness include dehydration, alcohol consumption, high altitudes, extreme temperatures, stress, and depression.

Constitutional complications include delayed growth and development, increased risk for infections, allo-immunization, and skin ulcers.

Anemic complications include chronic hemolysis, hyper-hemolytic episodes, aplastic episodes, and splenic sequestration episodes.

Vaso-occlusive complications include microinfarction (pain), macroinfarction (stroke, proliferative retinopathy, cardiomyopathy, acute chest syndrome, RUQ syndrome, bone and joint complications, etc.).

2. Hemoglobin CC

- Usually a benign condition
- Should be followed by a hematologist
- Can be associated with the following symptoms:
  - Mild hemolytic anemia (Hb 10-12g/dL)
  - Greater than 90% target cells on blood smear
  - Increased risk for gallstones
  - Infections can trigger aplastic episodes.
  - Usually no vaso-occlusive complication because decreased MCV facilitates passage through microcirculation

3. Hemoglobin S-Hereditary Persistence of Fetal Hemoglobin

- Very rare condition occurring in about 1/25,000 individuals
- No significant anemia or spontaneous sickling because the high intracellular concentration of HbF prevents sickling
- If HbF is greater than 18%, there are few or no vaso-occlusive episodes and a decrease in episodes of acute chest syndrome.

C. Prenatal Screening and Family Planning

Thalassemias and structural hemoglobin variants are more difficult to diagnose or exclude during pregnancy because common nutritional deficiencies alter the MCV. Microcytosis, due to iron deficiency, is common during pregnancy. Coexistent folic acid deficiency may increase the MCV. Because exclusion of iron deficiency is important in the evaluation of thalassemia and iron studies may not reliably exclude iron deficiency during pregnancy, the diagnosis of thalassemia is best made before pregnancy. When a pregnant patient with low MCV presents in your clinic and thalassemia has not been ruled out, the algorithm shown in Figure 3 should be considered.

Figure 3. Algorithm using MCV for the detection of thalassemia syndromes during pregnancy.

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1. Given the need to diagnose expediently during pregnancy, ferritin is performed simultaneously with tests to rule out iron deficiency.
2. Structural hemoglobin variant, e.g., Hb S, C, D, or Constant Spring, will often not have a low MCV. In certain ethnic groups, Hb electrophoresis should be considered to detect structural variants.
3. Silent carrier alpha thalassemia can have normal or low blood cell index.
4. Hb F may be slightly elevated in normal neonates during pregnancy.
5. References - Golo J.K, Romans J., and Therman H.G.

(modified from Dumars et al., 1996)
When interpreting a newborn screening result for a hemoglobinopathy, there are several different possible NBS outcomes. Those that require a follow-up evaluation for thalassemia are shown below.

**Figure 2. Newborn Screening results requiring follow-up evaluation for thalassemia**

<table>
<thead>
<tr>
<th>Possible NBS Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hb F + Hb A</td>
</tr>
<tr>
<td>1. Hb F + Hb A + Hb Bart’s</td>
</tr>
<tr>
<td>1. Hb F only</td>
</tr>
<tr>
<td>2. Hb F + Structural Variant (eg., Hb B, C, E)</td>
</tr>
<tr>
<td>3. Hb F + Hb E</td>
</tr>
<tr>
<td>4. Hb SS</td>
</tr>
</tbody>
</table>

**Possible Implications of NBS Results:**

- Normal
- Alpha thalassemia syndrome
- Structural Hemoglobin Diseases (Hemoglobin E, Sickle Cell Diseases, Sickle Beta 0 Thalassemia, etc.)

**Recommended Follow-Up:**

Further Medical Evaluation and Genetic Counseling by HCG Hemoglobinopathy clinic or Hematologist

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**Types of hemoglobin:**

- HbF: Fetal Hemoglobin
- HbA: Adult Hemoglobin
- Hb Bart: Bart Hemoglobin (suggestive of alpha thalassemia)
- HbE: Hemoglobin E (structural variant)
- HbC: Hemoglobin C (structural variant)
- HbSS: Sickle Cell Anemia or Hemoglobin SS disease

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**Hemoglobin Traits**

1. **Sickle Cell Trait**
   - Not a disease
   - Occurs in about 10% of African Americans
   - Sickle cell trait is not associated with anemia.
   - Adults with sickle cell trait have mostly HbA and less than ~30% hemoglobin S. The amount of HbA is sufficient to prevent sickling under most physiological conditions; and hence, sickling does not occur.
   - Occasional microscopic hematuria and hyposthenuria (a condition characterized by failure to concentrate urine normally)
   - Splenic infarction reported to occur in altitudes greater than 8,000 feet. Flight travel is not discouraged as flight carrier cabins are reportedly pressurized to 4,000-5,000 feet.

2. **Hemoglobin EE**
   - Clinically benign
   - Mild anemia (Hb 10-12g/dL)

3. **Hemoglobin DD**
   - Mild hemolytic anemia but usually with normal hemoglobin levels
   - Enlarged spleen

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*modified from Dumars et al., 1996*
2. Sickle Cell Trait/Alpha Thalassemia
   - Clinically benign
   - Less hemoglobin S than sickle cell trait
   - MCV is decreased

3. Hemoglobin C Trait
   - Clinically benign, no anemia

4. Hemoglobin D Trait
   - Clinically benign

5. Hemoglobin E Trait
   - High frequency in Southeast Asians (35% Cambodians; 15% Thai)
   - Clinically benign, mild anemia
   - Moderate microcytosis

6. Hemoglobin O-Arab
   - Also known as hemoglobin O-Egypt; occurs in North Africa, Bulgaria, Yugoslavia, Arabia, Jamaica and in Americans with ancestry from those areas
   - Clinically benign, no anemia

Over 99% of infants born in Hawai‘i receive newborn screening (NBS) each year. The following flow chart summarizes the recommended follow-up plan for newborns with a positive screen for any hemoglobinopathy.

B. Newborn Screening Identification and Follow-up

- Positive screen result for a hemoglobinopathy
- The OSPHL informs the infant’s primary care physician (PCP) of the newborn screening results.
- The OSPHL returns the results to the Hawai‘i Newborn Metabolic Screening Program (NBMP).
- As the Medical Home, the PCP manages the patient’s care and makes appropriate referrals.
- The NBMS provides the PCP with educational materials and referral information for the Hawai‘i Community Genetics (HCG) Hemoglobinopathy Clinic.
- Long-term tracking of individuals with the hemoglobinopathy
- Patient/family is seen by a hematologist and the genetics team for evaluation and genetic counseling.
- Recommendations for testing, medical management, etc. are made to the PCP.

- Hawai‘i infants’ newborn screening samples are collected and sent to Oregon State Public Health Laboratory (OSPHL).
- PCP Referral Options
  - Hematologist
  - Hawai‘i Children with Special Health Needs Program (808-733-9055) for eligible families
  - HCG Hemoglobinopathy Clinic
INTENDED LEARNING OUTCOMES FOR COUNSELEE

**Hemoglobin Production Defects**

**ALPHA THALASSEMIA**

- The differences among the four types of alpha thalassemia (hydrops fetalis, hemoglobin H disease, alpha thalassemia trait, and silent carrier)
- Silent carrier and trait forms are not illnesses and lifespan is not shortened.
- Life style and life span for hemoglobin H are usually not greatly affected although they have a greater chance for medical complications compared to silent carrier and trait forms.
- Both parents must have either cis-type trait or hemoglobin H in order to have a child with hydrops fetalis. In such cases, there is a 25 percent chance that each pregnancy can result in a child with hydrops fetalis.
- Treatment options are available to parents who want to continue pregnancies identified early to be affected with hydrops fetalis.
- Natural history of the different types of alpha thalassemia (including potential health problems, variability of severity, and available resources)
- Iron supplementation should be avoided if the individual does not have iron deficiency. Iron supplementation will not improve those with inherited anemia.
- Options for medical management:
  - **Silent Carrier and Trait**
    - a. As-needed basis
    - b. Genetic counseling strongly recommended for individuals considering pregnancy

**Hemoglobin H**

- a. Regular, yearly appointments with hematologist
- b. Avoid certain foods and drugs that induce hemolysis.
- Family planning options available to persons affected with alpha thalassemia.
BETA THALASSEMIA

- The difference between beta thalassemia minor/trait, beta thalassemia major, and beta thalassemia major variations like beta thalassemia intermedia
- Beta thalassemia minor/trait is not a disease. No restriction needs to be placed on physical activities.
- Both parents must have beta thalassemia trait or another hemoglobin trait for their child to have beta thalassemia major.
- There is a 25 percent chance with every pregnancy that a child will be affected with beta thalassemia major.
- Natural history of beta thalassemia major (including potential health problems, variability of severity, resources necessary to care for a child with beta thalassemia major, life span, etc.)
- Treatment options available to persons affected with beta thalassemia major
- Iron supplementation should be avoided. Iron supplementation will not improve those with inherited anemia.
- Options for medical management:
  - Beta Thalassemia Minor
    a. As-needed basis
    b. Genetic counseling strongly recommended for individuals considering pregnancy
  - Beta Thalassemia Major
    a. Regular consultation with hematologist strongly recommended
- Family planning options available to persons affected with beta thalassemia.

A. Evaluation of Red Blood Cell Indices

A low mean corpuscular volume (MCV) or mean corpuscular hemoglobin (MCH) is often the first or only clue to the presence of a hemoglobinopathy.

<table>
<thead>
<tr>
<th>Complete Blood Count (CBC)</th>
<th>WBC</th>
<th>8.6</th>
<th>(6.8 - 16.0)</th>
<th>10(9)/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>5.28</td>
<td>(3.5 - 5.5)</td>
<td>10(12)/L</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.0</td>
<td>L</td>
<td>(11.2 - 14.2)</td>
<td>g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>31.5</td>
<td>L</td>
<td>(33.0 - 39.0)</td>
<td>%</td>
</tr>
<tr>
<td>MCV</td>
<td>59.6</td>
<td>L</td>
<td>(71 - 91)</td>
<td>fl</td>
</tr>
<tr>
<td>MCH</td>
<td>19.0</td>
<td>L</td>
<td>(22 - 32)</td>
<td>pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>31.8</td>
<td></td>
<td>(31 - 37)</td>
<td>g/dL</td>
</tr>
<tr>
<td>RDW</td>
<td>18.3</td>
<td>H</td>
<td>(11 - 15)</td>
<td>%</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>350.0</td>
<td></td>
<td>(204 - 405)</td>
<td>10(9)/L</td>
</tr>
</tbody>
</table>

When clinicians encounter a low MCV or MCH when interpreting a complete blood count (CBC) obtained for any purpose after one year of age, the primary care providers should consider Figure 1 (please note that the approach used to evaluate a low MCV during a pregnancy is different and will be addressed in the prenatal screening and family section).
This section describes the three main ways to identify a child with thalassemia or a hemoglobin variant:

A. Evaluation of Red Blood Cell Indices
B. Newborn Screening Identification and Follow-up
C. Prenatal Screening and Family Planning

Once a hemoglobinopathy is suspected, the diagnosis is confirmed with DNA testing for some of the hemoglobinopathies. DNA testing is usually not done for structural variants. There are numerous laboratories nationwide that offer genetic testing for the hemoglobinopathies, including the Queen’s Genetics Laboratory located in Honolulu. Not all laboratories offer DNA testing for every type of hemoglobinopathy. Providing instructions for how to order these tests is beyond the scope of this protocol as genetic technology is rapidly advancing and local and national laboratory procedures and guidelines change over time. We recommend you contact the appropriate clinical genetics health providers listed in the resources section for more information once an individual with a hemoglobinopathy has been identified in your practice.

### Hemoglobin Structural Defects

**SICKLE CELL DISEASE OR HEMOGLOBIN SS**
- Detailed description in publication by Hawai‘i Genetics Program called *Sickle Cell Disease and Trait: Clinical and Counseling Protocol (Children 0-6 Years) in Hawai‘i*
  Please go to [www.hawaiigenetics.org](http://www.hawaiigenetics.org) to obtain a copy.

**HEMOGLOBIN CC, EE, DD, HEMOGLOBIN S-HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN**
- Usually clinically benign
- Abnormal red blood cell indices show anemia
- Potential health problems
- Regular, yearly appointments with the hematologist
- Genetic counseling strongly recommended for individuals considering pregnancy
- Iron supplementation should be avoided. Iron supplementation will not improve those with inherited anemia.

**HEMOGLOBIN Trait**

**Sickle cell trait and sickle cell trait/alpha thalassemia**
- Detailed description in publication by Hawai‘i Genetics Program called *Sickle Cell Disease and Trait: Clinical and Counseling Protocol (Children 0-6 Years) in Hawai‘i*
  Please go to [www.hawaiigenetics.org](http://www.hawaiigenetics.org) to obtain a copy.

**Hemoglobin C, D, E, O-Arab**
- Clinically benign, may show no or mild anemia
- Traits are not an illness, so no restrictions need to be placed on activities.
- Genetic counseling strongly recommended for individuals considering pregnancy
- Medical management as per needed basis
- Iron supplementation should be avoided. Iron supplementation will not improve those with inherited anemia.
INSTRUCTIONAL AND EDUCATIONAL TECHNIQUES

- Use lay language and common words for scientific terms whenever possible.
- Use visual aids to illustrate key points.
- Establish a dialogue/discussion rather than a lecture or information-giving format.
- Implement a pre- and post-assessment of the session.
- Use the post-assessment as an opportunity to clarify misinterpretation or uncertainties about the information discussed during the session.
- Provide literature written in lay language covering the essential facts.
- Make available resources of more detailed information for those who are interested.
- Communicate the availability of the provider for any follow-up questions.
- Provide a full description of the material covered, including a copy of all graphics, plus a summary of the highlights or key points in the form of a fact sheet.
- Genetic counseling for decision-making assistance should be nondirective and objective. Counselors should not introduce personal biases or offer specific recommendations.
- Follow a standard protocol to ensure that the essential topics are covered.

This protocol will provide general medical guidance suggesting current and best approaches to identifying, diagnosing, educating, and treating thalassemia and hemoglobin variants for Hawai‘i’s infants, children, and adults. The material is broadly organized into three main sections:

1. Identification and Diagnosis
2. Education and Genetic Counseling
3. Guidelines for Management and Evaluation

We hope to provide primary care physicians, nurses and allied health providers basic information they can use in their daily practice in caring for patients affected by these conditions. A set of references and local and national resources are listed at the end of the protocol for those wanting further information.
Introduction

Hemoglobinopathies are a group of inherited disorders characterized by abnormal hemoglobin structure or production caused by gene mutations.

Examples

<table>
<thead>
<tr>
<th>Hemoglobin production defects</th>
<th>Hemoglobin structural abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alpha Thalassemia</td>
<td>• Sickle cell anemia</td>
</tr>
<tr>
<td>• Beta Thalassemia</td>
<td>• Hemoglobin variants such as hemoglobin C, E, D, G, etc.</td>
</tr>
</tbody>
</table>

While iron deficiency is the most common cause of acquired anemia, thalassemia is the most common form of inherited anemia. Yet, many individuals who are familiar with anemia caused by iron deficiency may not be aware of thalassemia leading to anemia. For this reason, patients with thalassemia often go unrecognized or are misdiagnosed worldwide.

The diagnosis of the hemoglobinopathies can be a challenge because methods of diagnosis can differ among the different types. For example:

- Sickle cell anemia can be identified by hemoglobin electrophoresis alone, while both alpha and beta thalassemia need to be confirmed through molecular methods.
- Most cases of hemoglobin variants and alpha thalassemia are detected on the newborn screen, whereas beta thalassemia is not clinically apparent until about 4-6 months of life.

Therefore, it is important to understand the strengths and limitations of the different testing methods available for the hemoglobinopathies.

The detection and follow up for hemoglobinopathies is a significant issue for Hawai‘i. One in 46 individuals in Hawai‘i is a carrier for alpha thalassemia. One should also be aware that individuals can potentially inherit more than one type of hemoglobinopathy, leading to more severe symptoms and health outcomes. For all of these reasons, knowledge of the hemoglobinopathies is essential for health care providers in Hawai‘i.

GENERAL THERAPEUTIC CONSIDERATIONS: GUILDELINE FOR MANAGEMENT AND EVALUATION

Milder forms of thalassemia do not usually require specialized treatment.
- Supplemental iron administration should be avoided unless iron deficiency is proven. In cases with documented iron deficiency, iron therapy should be monitored to avoid excessive treatment.
- Changes in hemoglobin from the patient’s usual baseline level should be evaluated. Decreased hemoglobin levels associated with pregnancy may occasionally worsen symptomatic anemia.

Moderately severe forms of thalassemia (Hb H disease, β-thalassemia intermedia, and some Hb E/β thalassemias) require ongoing medical care.
- Important considerations include administering supplemental folic acid, avoiding oxidant drugs and unnecessary iron, and monitoring for normal growth and development, hypersplenism, and progressive iron overload.
- Acute exacerbations of anemia require evaluation and support, including transfusions, and may occur with infection, splenic sequestration, aplastic crisis, pregnancy, and folate deficiency. The patient may also develop symptomatic gallstones and/or leg ulcers.
- Periodic consultation with a hematologist knowledgeable in management of thalassemia is strongly recommended.

For severe forms of thalassemia, therapeutic considerations include regular transfusion therapy, iron chelation, and bone marrow transplantation.
- All patients with these severe forms should be cared for by physicians with expertise in the management of thalassemia and iron overload. Ideally, centers that provide multidisciplinary management for patients with hemoglobin disorders should deliver comprehensive care because proper management dramatically improves longevity and quality of life.
REFERENCES


RESOURCES

For more information about thalassemia and other hemoglobinopathies, please visit the following websites:

Cooley's Anemia Foundation
330 Seventh Avenue, Suite 900
New York, NY 10001
Phone: (800) 522-7222
Fax: (212) 279-5999
Email: info@cooleyanaemia.org
www.cooleyanaemia.org

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Questions or Comments?
For more information, please contact the Hawai‘i State Genetics Program at 808-733-9055, or you can visit our website at www.hawaiigenetics.org

Acknowledgements
We thank Laurie Seaver, M.D.; Ted Hsia, M.D.; and Kelley Woodruff, M.D. for their guidance and suggestions in developing this protocol.
Mahalo Nui Loa!

Nondiscrimination in Service:
The Hawai‘i Department of Health provides access to its activities without regard to race, color, national origin (including language), age, sex, religion, or disability. If you believe you have been discriminated against, write to the State Department of Health Affirmative Action Officer at P.O. Box 3378, Honolulu, HI 96801.
To obtain clinical genetic services in Hawai‘i, please select from the appropriate genetic services below. Genetic services in Hawai‘i are provided by board certified clinical geneticists, genetic counselors, and allied health providers.

**Hawai‘i Community Genetics**
Provides pediatric and adult clinical genetic services
Special multidisciplinary clinics include Hemoglobinopathy and Metabolic Clinics.
1441 Kapi‘olani Boulevard, Suite 1800
Honolulu, HI 96814
(808) 973-3403

**Fetal Diagnostic Institute of the Pacific**
Provides prenatal ultrasound, genetic screening and testing
1600 Kapi‘olani Boulevard, Suite 1025
Honolulu, HI 96814
(808) 945-2229

**Kapi‘olani Medical Center for Women and Children Fetal Diagnostic Center**
Provides pre-conceptional and prenatal genetic counseling, screening, and testing
1319 Punahou Street, Suite 540
Honolulu, HI 96826
(808) 983-8559

**Queen’s Comprehensive Genetics Center and Queen’s Genetics Laboratory**
Provides adult clinical genetic services including prenatal, cancer, and general genetics
1380 Lusitana Street, 3rd Floor
Honolulu, HI 96813
(808) 537-7633