

| Disorder / Deficiency | Marker Analyte | Rate of Occurrence (per live birth) | Method of analysis |
|------------------------------|-----------------------|--------------------------------------------|---------------------------|
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Congenital Hypothyroidism (CH)

Thyroxine

1 / 5000

Auto-DELFLIA
Immunofluorescence

CH is the result of the body's inability to produce adequate amounts of thyroid hormone. Left untreated, this congenital deficiency of thyroid hormone can result in mental retardation and stunted growth. Newborns may appear normal up to three months of age. If detected early (before three weeks) and maintained on appropriate levels of thyroid hormone medication, infants diagnosed with CH can have normal growth and development.

- Symptoms - Most affected infants have few or no symptoms, because they only have a mild decrease in thyroid hormone production. However, infants with severe hypothyroidism often have a distinctive appearance of a puffy-appearing face, dull look or a thick, protruding tongue.

Galactosemia (GALT)

Gal-1-P / Galactose

1 / 50,000

Buetler Method

GALT is caused by a deficiency in the enzyme (Galactose-1-Phosphate Uridyl Transferase) needed to metabolize galactose, a milk sugar. Newborns typically appear normal, however, within a few days to two weeks after initiating milk feedings, vomiting, diarrhea, lethargy, jaundice and liver damage develops. Untreated, the disorder may result in developmental retardation, hepatomegaly, growth failure, cataracts, and in severe cases death. With early detection and strict adherence to a galactose-free diet, infants diagnosed with GALT can be expected to achieve general health. However, since some galactose can be produced in the body and cause negative effects, close developmental monitoring and assessment is recommended.

- Symptoms - Galactosemia usually causes no symptoms at birth, but jaundice, diarrhea, and vomiting soon develop and the baby fails to gain weight. If not detected and treated immediately, GALT can result in liver disease, cataracts, mental retardation, and even death, possibly from an infection. Death can occur as early as one to two weeks of age.

Biotinidase Deficiency (BIOT)

Biotinidase

1 / 75,000

Colorimetric Assay

BIOT is caused by the lack of the biotinidase enzyme causing the inability to liberate biotin from a bound form, so it can be metabolized by the body. Without sufficient biotin, several other critical enzyme systems are unable to function properly. BIOT can lead to seizures, developmental delay, eczema, and hearing loss. Newborns with the disorder appear normal, but can develop critical symptoms after the first weeks or months of life. With early detection and treatment, infants diagnosed with BIOT can lead a healthy life.

- Symptoms – BIOT could cause hypotonia, ataxia, seizures, developmental delay, hair loss, seborrheic dermatitis, hearing loss and optic nerve atrophy. Metabolic acidosis can result in coma and death. BIOT is treated with daily biotin supplement, and with early diagnosis and treatment, all symptoms can be prevented.

Congenital Adrenal Hyperplasia (CAH)

17-hydroxy-progesterone

1 / 25,000

Auto-DELFLIA
Immunofluorescence

CAH is a group of disorders caused by the deficiency of an adrenal enzyme resulting in decreased cortisol and sometimes aldosterone production. Without sufficient cortisol and aldosterone, the affected newborn may appear normal but can quickly develop symptoms. In severe cases death may occur within a few weeks if left untreated. Infants with milder forms of the disorder are at risk for reproductive and growth difficulties. If detected early and maintained on appropriate medication, infants diagnosed with CAH can have normal growth and development.

- Symptoms – CAH could cause lethargy, vomiting, muscle weakness and dehydration. In female infants, CAH sometimes can result in masculinization of the genitals.

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| Cystic Fibrosis (CF)** | <u>Immunoreactive Trypsinogen (IRT)</u> | 1 / 4,000 | Auto-Delfia Immunofluorescence |
|-------------------------------|-----------------------------------------|-----------|-----------------------------------|

CF is an autosomal recessive disorder caused by a mutation on the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene. There have been over 1,600 found mutations of this gene, with the most common being ΔF508. CF affects the normal movement of chloride ions in and out of the many types of cells, including those lining the lungs, sweat glands, intestines and exocrine pancreas. Without the proper movement of these ions, the cells secrete sticky thick mucus. This mucus build-up in the lungs causes frequent infections, breathing problems, thus leading to lung damage and/or cancer. The mucus build-up in the digestive track may clog ducts leading from the pancreas to the small intestine, causing digestive problems and slow growth. CF eventually will lead to disrupt all major functions in multiple organs, including the exocrine pancreas, lungs, sweat glands, and intestines, eventually leading to death. While there is not a cure for CF early diagnosis in infants can increase life expectancy, reduce incidences of hospitalizations, decrease mortality rates, and improve nutrition and better overall development.

- Symptoms - CF could cause coughing or wheezing, repeated lung infections such as pneumonia and bronchitis, shortness of breath, poor growth in spite of a big appetite, intestinal blockage called, meconium ileus, in a newborn (caused by thickening of the greenish stool newborns usually pass in the first days of life), greasy, bulky stools.

****KHEL incorporates a two tier method with CF. All specimens are run using the AutoDELFLIA method first. Only specimens that are found to have values >60ng/mL are retested using PCR/DNA method.**

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Gene
(Performed when IRT is ≥ 60 ng/mL on AutoDELFLIA)

InPlex™
PCR/DNA

CFTR InPlex™ assay 40-mutation panel
(ACMG recommended mutations in **bold**)

| | | | | |
|--------------------|---------------------|------------------------|-----------|------------|
| ▲F508 | R1162X | 2184delA | 394delTT | D1152H |
| G542X | 3120+1G>A | 3659delC | E60X | 1078delT |
| W1282X | R117H | A455E | Q493X | S549R T>G |
| G551D | 1717-1G>A | R560T | 3905insT | Y1092X C>G |
| 621+1G>T | 2789+5G>A | G85E | V520F | Y1092X C>A |
| N1303K | R347P | 1898+1G>A | S549R A>C | 2183AA>G |
| R553X | 711+1G>T | 3849+10kbC>T | Y122X | S549N |
| ▲I507 | R334W | 3876delA | R347H | 3849+4A>G |

Hemoglobinopathies (HGB)

Hemoglobin

>1 / 5,000 and Isoelectric Focusing
1 / 400 for African-Americans

The hemoglobin molecule is composed of four separate polypeptide chains of amino acids, two alpha chains and two beta chains, as well as four iron-bearing heme groups that bind oxygen. In general, HGB are divided into those in which the gene abnormality results in a change in the overall function of the hemoglobin molecule (qualitative) and those in which the change is the amount of viable hemoglobin (quantitative). Sickle cell anemia (sickle cell disease) is the prime example of the qualitative, and the group of disorders known as the thalassemias constitute the quantitative. Scientists estimate 300,000 people worldwide are seriously affected by one of these genetic disorders.

Sickle Cell Anemia

The sickle cell mutation (SSA) results in the substitution of the amino acid valine for glutamic acid in the sixth position of the beta polypeptide. In turn, this alters the shape of the hemoglobin molecule and causes the red blood cells to assume a characteristic sickle shape under certain conditions. These sickle-shaped cells, no longer able to pass smoothly through small capillaries, can block the flow of blood. This obstruction results in symptoms including growth retardation, severe pain crises, tissue and organ damage, splenomegaly, and strokes. Individuals with SSA are anemic and prone to infections, particularly pneumonia, a significant cause of death.

- Treatment: Vigilant medical care and treatment with penicillin, beginning in infancy, can dramatically reduce the risk of these adverse effects and the deaths that can result from them. Affected babies should receive all regular childhood vaccinations (including, but not limited to, hemophilus influenza B and pneumococcal vaccines) to help prevent serious bacterial infections. Additional treatments may vary according to severity of symptoms, but may include intermittent pain medications and regular blood transfusions.

Thalassemia

> 1 in 50,000

The thalassemias are a diverse group of disorders characterized by the causative mutations that result in a decrease in the amount of normal hemoglobin. Thalassemias are common in Mediterranean populations as well as in Africa, India, the Mideast, and Southeast Asia. The two main types of thalassemias are alpha-thalassemia due to mutations in the alpha polypeptide and beta-thalassemia resulting from beta chain mutations.

Beta thalassemias can range from mild and clinically insignificant (beta thalassemia minor) to severe and life-threatening (beta thalassemia major, also known as Cooley's anemia), depending on the exact nature of the gene mutation and whether one or both copies of the beta gene are affected. While the milder forms may only cause slight anemia, the more severe types result in growth retardation, skeletal changes, splenomegaly, vulnerability to infections, and death as early as the first decade of life.

- Treatment: Since the clinically important thalassemias are characterized by severe anemia, the traditional treatment has been blood transfusion, but the multiple transfusions needed to sustain life lead to an iron overload throughout the tissues of the body and eventual destruction of the heart and other organs. For this reason, transfusion therapy must also include infusions of medications such as deferoxamine (desferroxamine) to rid the body of excess iron. Phlebotomy is another technique that has been used with some success to lower the concentration of iron in the patient's blood.

Below is a list of the normal and abnormal types of hemoglobin. There are many different variations of Hemoglobin. The types described below occur more often and are the types our Laboratory screens.

Normal Hemoglobins

- Hemoglobin A. This is the designation for the normal hemoglobin that exists after birth. Hemoglobin A has four parts with two alpha chains and two beta chains ($\alpha_2\beta_2$).
- Hemoglobin F. Hemoglobin F is the predominant hemoglobin during fetal development. The molecule is different from the adult because it has two alpha chains and two gamma chains ($\alpha_2\gamma_2$). Hemoglobin F production falls dramatically after birth, although some people continue to produce small amounts of hemoglobin F for their entire lives.

Clinically Significant Variant Hemoglobins analyzed by the Kansas Newborn Screening Laboratory

- Hemoglobin S. This is the predominant hemoglobin in people with sickle cell disease. The alpha chain is normal. The disease-producing mutation exists in the beta chain, giving the molecule the structure, $\alpha_2\beta^S_2$. People who have one sickle mutant gene and one normal beta gene has the sickle cell trait which carries the gene but does not produce any clinical symptoms.
- Hemoglobin C. Hemoglobin C results from a mutation in the beta globin gene and is the predominant hemoglobin found in people with hemoglobin C disease ($\alpha_2\beta^C_2$). Hemoglobin C disease is relatively benign, producing a mild hemolytic (bursting cells) anemia and splenomegaly. Hemoglobin C trait is benign.
- Hemoglobin E. This variant results from a mutation in the hemoglobin beta chain. People with hemoglobin E disease have a mild hemolytic anemia and mild splenomegaly. Hemoglobin E trait is benign. Hemoglobin E is extremely common in S.E. Asia and in some areas equals hemoglobin A in frequency.
- Hemoglobin G: is an α -chain variant which is often associated with deletion a thalassemia of the cis (linked) α gene. This hemoglobin variant has no clinical consequences. Individuals should be reassured that there are no clinical problems.
- Hemoglobin D: When only hemoglobin D is present, the red blood cells are broken down in the body a little faster than usual. This can cause mild anemia. Most people with homozygous hemoglobin D usually have no health problems.
- Hemoglobin A2. This is a minor component of the hemoglobin found in red cells after birth and consists of two alpha chains and two delta chains ($\alpha_2\delta_2$). Hemoglobin A2 generally comprises less than 3% of the total red cell hemoglobin.
- Hemoglobin Barts. Hemoglobin Barts develops in fetuses with four-gene deletion alpha thalassemia. With four-gene deletion alpha thalassemia no alpha chain is produced. The gamma chains produced during fetal development combine to form gamma chain tetramers. These molecules transport oxygen poorly.

For more information on Hemoglobinopathies please refer to:

- March of Dimes Website; http://www.marchofdimes.com/professionals/14332_15455.asp.
- Harvard website: <http://sickle.bwh.harvard.edu/hemoglobinopathy.html>
- Health A to Z <http://www.healthatoz.com/healthatoz/Atoz/common/standard/transform.jsp?requestURI=/healthatoz/Atoz/ency/hemoglobinopathies.jsp>
- Sickle Cell Information Center by James Eckman MD <http://www.scinfo.org/hemoglb.htm#By>.

