Biotinidase Deficiency

Biotinidase deficiency is an autosomal recessive disorder that interferes with the body's ability to synthesize biotin, a B vitamin. Biotinidase is an enzyme responsible for recycling biotin in the degradation of carboxylases, as well as freeing the protein bound form in digestion. Biotin is an essential co-factor in several metabolic pathways, the deficiency of which ultimately results in neurologic damage.

Estimated Incidence (MI):	1: 27,325 (includes profound and partial deficiencies)
Laboratory Screening Test:	Biotinidase enzyme activity detected by colorimetric assay.
Timing of Test:	Valid at birth
Feeding Effect:	None
Transfusion Effect:	Transfusion of whole blood may interfere with the accuracy of testing, causing a false negative result. **Obtain newborn screen before transfusion.**
Confirmation:	All strong and persistent borderline positive tests are referred to the Children's Hospital of Michigan Metabolic Clinic (CHMMC) at 313-745-4513 for follow-up and diagnosis.
Treatment:	Daily oral biotin supplement is successful in preventing sequelae in those who are asymptomatic prior to initiation of treatment. Neurological complications occur in those with metabolic compromise and recurrent symptoms, thus frequent monitoring in the Metabolic Clinic is essential for ensuring proper treatment of the affected child.

For further information, contact the Newborn Screening Program
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Phenylketonuria (PKU)

Phenylketonuria is an inherited autosomal recessive disorder, which prevents the body from using the amino acid phenylalanine (Phe) properly. It is primarily a deficiency of the liver enzyme phenylalanine hydroxylase. Variant forms are caused by impaired synthesis or recycling of the biopterin (BH4) cofactor. Early detection and treatment is imperative to prevent mental retardation

Estimated Incidence (MI):	1:8,801 (includes Classic PKU, Mild PKU and non-PKU hyperphenylalaninemia)
Laboratory Screening Test:	Phenylalanine and Phenylalanine/Tyrosine ratio using Tandem Mass Spectrometry
Timing of Test:	≥ 24 hours of age: Results are valid
Feeding Effect:	Minimal, Tandem Mass Spectrometry can detect elevations in phenylalanine earlier than previously used qualitative methods.
Transfusion effect:	None
Confirmation:	All strong and persistent borderline positive tests are referred to the Children's Hospital of Michigan Metabolic Clinic (CHMMC) at 313-745-4513 for follow-up and diagnosis. **Do not send diagnostic labs before contacting CHMMC.**
Treatment:	Phenylalanine free infant formula that should be initiated as soon after birth as possible **once the diagnosis has been confirmed.** Long-term treatment consists of maintaining a low phenylalanine diet for life through the use of special formula and low protein food products. Females considering pregnancy must maintain controlled Phenylalanine (Phe) levels to normalize their risk for birth defects in their offspring.

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Maple Syrup Urine Disease (MSUD)

Maple Syrup Urine Disease (MSUD) is a very rare inherited autosomal recessive disorder. Newborns with MSUD have a deficiency of the enzyme branched-chain ketoacid dehydrogenase responsible for metabolizing the branched chain amino acids leucine, isoleucine, and valine found in protein. The purpose of newborn screening for MSUD is to identify affected infants rapidly, and initiate treatment to prevent neurological sequelae and death.

Estimated Incidence (MI):	1: 234,992
Laboratory Screening Test:	Leucine using Tandem Mass Spectrometry
Timing of Test:	≥ 24 hours of age: Results are valid
Feeding Effect:	Minimal. Tandem Mass Spectrometry can detect elevations in leucine earlier than previously used qualitative methods.
Transfusion Effect:	None
Confirmation:	All infants with strong and persistent borderline positive tests are referred to the Children's Hospital of Michigan Metabolic Clinic (CHMMC) at 313-745-4513 for follow-up and diagnosis.
Treatment:	Immediate treatment with branched-chain free MSUD formula is necessary. Specially prepared branched-chain free parenteral nutrition is available for acutely ill infants. Long-term treatment consists of a strict diet limiting the intake of branched chain amino acids while maintaining normal growth and development.

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Galactosemia

Galactosemia is an inherited autosomal recessive disorder of carbohydrate metabolism. Classic Galactosemia is due to a deficiency of the enzyme galactose-1-phosphate uridyl transferase, which leads to an accumulation of total galactose. In nature, galactose is combined with glucose to form lactose, the primary sugar in human milk and commercial (non-soy) infant formulas. Affected infants are not able to metabolize this causing the build up of galactose in the body, which can lead to cellular damage and even death. There are several benign genetic variants characterized by a less severe reduction in enzyme activity (e.g. Duarte variant). These children often present with a persistent positive newborn screen but are asymptomatic. They do not require treatment and remain clinically well on breast-milk and standard infant formulas.

Estimated Incidence:	1:41,227
Laboratory Screening Test:	Quantitative GALT enzyme done on all infants . Quantitative fluorometric assay to detect Galactose + Gal-1- P (total galactose) done on all positive tests and transfused infants.
Timing of Test:	Valid at birth
Feeding Effect:	None. Enzyme activity not affected by feeding
Transfusion Effect:	Transfusion of red blood cells may interfere with the accuracy of testing causing a false negative result. **Obtain newborn screen before transfusion.**
Confirmation:	All strong and persistent borderline positive tests are referred to the Children's Hospital of Michigan Metabolic Clinic (CHMMC) at 313-745-4513 for follow-up and diagnosis. **Do not send diagnostic labs before contacting the CHMMC.**
Treatment:	Immediate change to soy/lactose free formula is needed with subsequent lifelong exclusion of galactose from the diet.

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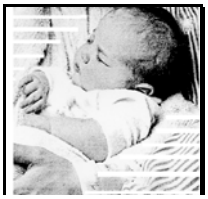

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)

Medium Chain Acyl-CoA Dehydrogenase Deficiency is an autosomal recessive fatty acid oxidation disorder (FOD) in which an enzyme defect in the fatty acid metabolic pathway inhibits the body's ability to utilize stored fat. Clinical symptoms include vomiting and lethargy following a period of fasting, often at times of intercurrent viral infection (gastrointestinal or upper respiratory). Hypoglycemia with low urinary ketone production (hypoketotic), hyperammomemia and elevated liver function tests may occur and can lead to encephalopathy, hepatic failure, coma or death.

Incidence (MI):	~1:26,205** **Screening for MCAD began April 1, 2003 so this figure is not based on a complete year of screening.
Laboratory Screening Test:	Acylcarnitine profiling by Tandem Mass Spectrometry
Timing of Test:	≥ 24 hours of age: results are valid.
Feeding Effect:	None
Transfusion Effect:	None
Confirmation:	All presumptive positive tests are referred to the Children's Hospital of Michigan Metabolic Clinic (CHMMC) at 313-745-4513 for follow-up and diagnosis. **Do not send diagnostic labs before contacting the CHMMC.**
Treatment:	Strict avoidance of fasting (frequent feedings) is essential. A low-fat/high-carbohydrate diet and supplemental carnitine are often used. Acute episodes (during illness) require aggressive medical management, especially if the infant/child is vomiting or is not receiving adequate nutritional intake. During these episodes, the administration of intravenous glucose and blood sugar monitoring is essential.

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Congenital Hypothyroidism (CH)

Congenital Hypothyroidism (CH) occurs in babies who do not have the ability to produce adequate amounts of thyroid hormone. Most cases are sporadic, but it occasionally occurs in siblings and may be inherited as an autosomal recessive disorder. The most common causes of primary Hypothyroidism include: thyroid gland aplasia or hypoplasia; ectopic thyroid gland; or enzyme deficiencies in thyroxine (T4) synthesis. Less commonly, Hypothyroidism is induced by medications (antithyroid drugs or excess iodine) in the mother. Newborn screening also detects secondary Hypothyroidism resulting from failure of the pituitary gland to release thyrotropin (TSH), and tertiary Hypothyroidism resulting from failure of the hypothalamus to secrete thyrotropin-releasing hormone (TRH).

Estimated Incidence (MI):	1:1,942
Laboratory Screening Test:	Fluorometric assay screens for TSH (thyrotropin)
Timing of Test:	≥24 hours of age: Results are valid **False positive results can occur on specimens obtained before 24 hours of age due to the normal physiologic TSH surge that occurs after birth.**
Feeding Effect:	None
Transfusion Effect:	None
Confirmation:	All strong and persistent borderline positive tests are referred to the Endocrine Follow-up Program (EFUP) at the University of Michigan (734) 647-8938. The EFUP coordinates follow-up for infants with suspected CH. Diagnosis and treatment is provided through a network of pediatric endocrinologists throughout the state.
Treatment:	Oral thyroid hormone (replacement) administered daily. This should begin as soon as possible after confirmation of the diagnosis.

Comment

Most, but not all cases of severe, early on-set Hypothyroidism are detected by newborn screening. The screening program is not designed to detect late-onset, clinically moderate or sub-clinical forms of Hypothyroidism. The newborn screen should not be relied on to rule out all abnormalities of thyroid function.

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Congenital Adrenal Hyperplasia (CAH)

Congenital Adrenal Hyperplasia is a family of inherited autosomal recessive disorders of adrenal steroidogenesis. It results from a defect in any of the five enzymes needed to synthesize cortisol from cholesterol in the adrenal gland, but about 80% of all cases are due to deficiency of the enzyme 21-hydroxylase (21-OH). About 15% of cases are due to 11β-hydroxylase deficiencies. The goal of newborn screening for CAH is to rapidly identify affected infants in order to prevent death from adrenal crisis, shock or its sequelae, and incorrect sex assignment in female newborns.

Estimated Incidence (MI):	1:17,716
Laboratory Screening Test:	Fluoroimmunoassay is used to detect elevated 17- hydroxyprogesterone (OHP)
Timing of Test:	Interpretation of values is based on birth weight and age at the time of specimen collection. **False positive may occur if sample is collected before 24 hours of age.**
Feeding Effect:	None
Transfusion Effect:	None
Steroid Effect:	Chronic use of dexamethasone in the mother during pregnancy can falsely depress 17-OHP levels, which can cause a false negative result in an affected newborn.
Confirmation:	All strong and borderline positive tests are referred to the Endocrine Follow-up Program (EFUP) (734) 647- 8938. The EFUP coordinates follow-up for infants with suspected CAH.
Treatment:	EFUP coordinates follow-up for infants with suspected CAH. Glucocorticoid is used to replace deficient cortisol while suppressing ACTH overproduction. Salt-retaining hormones may be used. Early intervention & surgical correction of ambiguous genitalia allow normal puberty, fertility and childbearing in females. Careful regulation of hormone treatment during illness and growth periods is required.

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Hemoglobinopathies (Sickle Cell)

There are over 600 hemoglobin variants, however only a few are clinically significant. The clinically significant Hemoglobinopathies are inherited autosomal recessive disorders of the adult β-hemoglobin chain. Children with two abnormal β-globin genes (homozygotes or double heterozygotes) have a hemoglobin disease whereas those with only one abnormal gene are said to have a hemoglobin trait, which is only of genetic significance. The purpose of newborn screening for Hemoglobinopathies is to prevent deaths from pneumococcal sepsis by instituting penicillin prophylaxis and to prevent deaths from splenic sequestration through parent education.

Estimated Incidence (MI):	Sickle Cell Anemia 1:1,956 1 in 600 African American newborns Also seen in individuals of Mediterranean, Indian and Middle Eastern heritage.
Laboratory Screening Test:	Abnormal hemoglobins S, C, D, andE are detected by High Performance Liquid Chromatography (HPLC). Secondary method is isoelectric focusing.
Timing of Test:	Valid at birth
Feeding Effect:	None
Transfusion Effect:	The test is invalid on transfused infants. Transfusion may cause false negative or false positive results. **Obtain newborn screen before transfusion.** A retest is required 3 months after the most recent transfusion.
Confirmation:	Infants with positive hemoglobin screening tests are referred to the Sickle Cell Disease Association of America (SCDAA), Michigan Chapter (313) 864-4406 for confirmatory diagnosis and follow up.
Treatment:	Penicillin prophylaxis should begin as soon as possible and continue until six years of age.

Comment

The purpose of the newborn Hemoglobinopathy-screening program is to identify infants with sickle cell related conditions. Therefore, initial test results that are sickle cell related are designated as positive, and all other results are considered negative. The responsibility for the follow-up of infants found to have non sickle cell related Hemoglobinopathies will be left to the discretion of the physician of record.

For further information, contact the Newborn Screening Program
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Email mdch-newbornscreening@michigan.gov

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Homocystinuria

Homocystinuria is a rare disorder caused by cystathionine β-synthase (CBS) deficiency. Deficiency of CBS, a pyridoxine (vitamin B6) dependent enzyme, will result in elevations of homocysteine and methionine. The purpose of newborn screening for Homocystinuria is to identify affected infants rapidly and to initiate treatment to prevent/minimize disease sequelae

Estimated Incidence (MI):	~1: 200,000** **Screening for Homocystinuria began October 1, 2004 so this figure is not based on a complete year of screening.
Laboratory Screening Test:	Methionine using Tandem Mass Spectrometry
Timing of Test:	≥ 24 hours of age: Results are valid
Feeding Effect:	None
Transfusion Effect:	None
Confirmation:	All strong and persistent borderline positives are referred to the Children's Hospital of Michigan Metabolic Clinic (CHMMC) 313-745-4513
Treatment:	Dietary restriction of methionine should be initiated. Supplemental cystine and betaine may be given. Pyridoxine supplements benefit many and folic acid as well as vitamin B12 supplements may be initiated.

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Citrullinemia and Argininosuccinic Aciduria (ASA)

Citrullinemia and Argininosuccinic Aciduria (ASA) are rare disorders of the urea cycle. Citrullinemia is caused by excess citrulline and ammonia in the blood resulting from a deficiency of argininosuccinic acid synthetase activity. ASA is the result of excess argininosuccinic acid, citrulline, and ammonia in the blood due to a deficiency of argininosuccinic acid lyase enzyme activity.

Estimated Incidence (MI):	1:250,000** ** Screening for Citrullinemia and Argininosuccinic Aciduria (ASA) began October 1, 2004 so this figure is not based on a complete year of screening.
Laboratory Screening Test:	Citrulline using Tandem Mass Spectrometry ** ** The newborn screening test detects elevated citrulline and can not differentiate Citrullinemia from Argininosuccinic Aciduria (ASA). Further diagnostic testing is needed.
Timing of Test:	≥ 24 hours of age: Results are valid
Feeding Effect:	None
Transfusion effect:	None
Confirmation:	Immediate contact with the Children's Hospital of Michigan Metabolic Clinic (CHMMC) at 313-745-4513 for follow-up and diagnosis.
Treatment:	The treatment for Citrullinemia and Argininosuccinic Aciduria (ASA) includes a high-calorie diet restricting protein. Arginine supplementation as well as administration of sodium benzoate and sodium phenylacetate is also initiated. Certain individuals may require dialysis.

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