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Wisconsin Newborn Screening Program

According to Wisconsin statute 253.13, "The attending physician or nurse certified under 441.15 shall cause every infant born in each hospital or maternity home, prior to its discharge therefrom, to be subjected to blood tests for congenital or metabolic disorders..."

This guide will help you comply with the statute and to better understand Wisconsin's Newborn Screening Program by providing information about:

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Visit the following Websites for more information

WSLH Newborn Screening Laboratory Website at:

<http://www.slh.wisc.edu/newborn>

Department of Health and Family Services Website at:

[www.dhfs.wisconsin.gov/dph_bfch/newborn screen](http://www.dhfs.wisconsin.gov/dph_bfch/newborn_screen)

The Test Panel

The newborn screening panel includes tests for the following disorders:

Argininosuccinic Acidemia (ASA)	Hemoglobin Variants
Biotinidase Deficiency	Homocystinuria
Citrullinemia (Types I & II)	Hypermethioninemia
Congenital Adrenal Hyperplasia	Hyperphenylalaninemia
Congenital Hypothyroidism	Maple Syrup Urine Disease
Cystic Fibrosis	Organic Acidemia Disorders (15)
Fatty Acid Oxidation Disorders (12)	Phenylketonuria (includes Biopterin Cofactor defects of regeneration and biosynthesis)
Galactosemia	Sickle Cell Disease
Hemoglobin S-Beta Thalassemia	Tyrosinemia (Types I, II, III)
Hemoglobin S/C Disease	

Newborn Screening Timeline

1965	Phenylketonuria
1978	Hypothyroidism, Galactosemia and Maple Syrup Urine Disease Testing centralized at WSLH
1983	Homocystinuria (Pilot Only)
1985	Cystic Fibrosis (Research Only)
1988	Hemoglobinopathies
1989	Blinded CDC HIV sero-prevalence study
1991	Biotinidase Deficiency
1992	Statute change allows DHSS to specify test panel by rule; Maple Syrup Urine Disease and Homocystinuria testing discontinued
1993	Congenital Adrenal Hyperplasia
1994	Cystic Fibrosis
1995	Blinded CDC HIV sero-prevalence study discontinued
2000	Fatty Acid Oxidation and Organic Acidemia
2002	Hearing Screening
2003	Aminoacidopathy Addition (Maple Syrup Urine Disease, Homocystinuria, Tyrosinemia, Argininosuccinic Acidemia, Citrullinemia)

When to Collect a Blood Specimen

Full-Term Infants

Collect a specimen before discharge from hospital of birth, as mandated by statute. If the initial specimen was collected before 24 hours of age, obtain a repeat specimen in about 14 days, as recommended by the American Academy of Pediatrics. (Pediatrics, Vol. 89 No. 2, Feb. 1992)

Home/Out-of-Hospital Births

The Newborn Screening Statute applies to all births in Wisconsin. The birth attendant (physician, midwife, or nurse certified under 441.15) is responsible for collecting a specimen before one week of life for out-of-hospital births.

Extended Hospital Stays (Low Birth Weight/Sick Infants)

Collect a specimen by the seventh day of life unless a transfusion is imminent (see below). For birth weight below 2,200g, collect second specimen around 2 weeks of age, a third around 30 days and monthly thereafter until discharge. If any of the collections occur post-transfusion, follow re-testing guidelines on the laboratory report. For babies weighing more than 2,200g and hospital stays greater than 14 days re-test at one month of age.

NOTE: Always collect a newborn screening specimen (filter paper) at discharge unless the previous specimen was collected within 6 days of discharge.

Transfused Infants

- Collect initial specimen before transfusion, if possible.
- If specimen is collected before transfusion and less than 24 hours of age, repeat testing at 30 and 60 days of life.
- If initial specimen was collected post-transfusion, testing should be done at 6, 30, and 60 days of life. Always list date of most recent transfusion on specimen collection card.

Transferred Infants

If transfer to another hospital is imminent, collect a specimen before transfer if at all possible. Be sure to inform the receiving hospital of collection status, including whether or not the specimen was collected, age at time of collection, transfusion status, etc.

Parent Refusal of Newborn Screening Testing

Parents may refuse newborn screening testing of their baby ONLY "*on the grounds that it conflicts with their religious tenets and practices.*" Parents refusing under this condition should sign a statement that is placed in the infant's medical record.

How to Collect a Blood Specimen

Instructions for Specimen Collection:

Note: Closely follow the collection instructions on the back of the blood collection card. (Reference: Blood Collection on Filter Paper for Neonatal Screening Program - Fourth Addition; NCCLS Document LA4-A4)

- To prevent specimen contamination, do not touch any of the filter paper circles before or after collection.
- Select puncture site and cleanse with 70% isopropanol.
- Use a sterile, disposable lancet with 2.0 mm or less, point to perform a swift, clean puncture.
- Keep heel in horizontal position (Heel Down) at or below heart level.
- Wipe away first blood drop.
- Allow a second LARGE blood drop to form and apply to surface of filter paper circle. If not completely filled, add a second LARGE drop immediately. FILL all required circles. FILL from only one side of the filter paper. Circles must be completely filled when observed from both sides of the filter paper. See below. NOTE: Heparinized capillaries can be used to apply blood to the filter paper.
- Dry specimen at room temperature 3-4 hours in HORIZONTAL position.
- Forward specimen to State Lab within 24 hours.
- IMPROPERLY COLLECTED SPECIMENS WILL BE REJECTED.
- If problems occur during collection, repeat collection using another form. The original form can be returned for replacement.

Tips for Specimen Collection:

- Complete each item on the newborn screening collection form.
NOTE: If hearing screening results are not available before the blood screening is completed, pull the “blue” sheet from the blood collection card. When the hearing results are available, complete the “blue” sheet and mail to WSLH.
- Warm heel with a warm towel and hold heel at or below the heart.
- Sampling after a feeding promotes better blood flow.
- Fill one circle at a time.
- If capillaries are used to transfer blood from heel to paper:
 - a. Capillaries must be heparinized (Do not use EDTA).
 - b. Mix capillaries well before applying blood to filter paper.
 - c. Apply blood to filter paper immediately after filling.
 - d. Do not touch capillary to filter paper.
- When appropriate umbilical lines (arterial or venus) can be used as a blood collection site. Be sure there is appropriate draw back (~ 0.5 mL) before blood collection. It is recommended that the last specimen (at discharge) be taken from the baby’s heel.

COLLECTION CARD ORDERING AND PRICING

The Wisconsin State Laboratory of Hygiene (WSLH) conducts all newborn screening testing in the state. Specimens must be collected directly on a special filter paper request card available from the WSLH.

Ordering Collection Cards

To order newborn screening blood collection cards, mail your request for a specified quantity of Kit #213 (newborn screening kits) with your payment to:

Wisconsin State Laboratory of Hygiene
Customer Service
465 Henry Mall
Madison, WI 53706

A WSLH order form can be obtained by contacting the clinical orders department at 608-265-2966.

Current Pricing

As of January 1, 2006: \$69.50 per card

Specimen Handling and Mailing

Specimen Handling

After blood has been applied to the filter paper, proceed as follows:

- Allow blood-soaked collection card to dry in a horizontal (flat) position.
- Suspend blood-soaked area of collection card such that air can dry both sides of the card equally.

NOTE: Be sure the attached coverslip doesn't come into contact with the blood until completely dry. Do not allow the blood-soaked portion of the collection card to come into contact with another surface (desktop, absorbent paper, etc.)

- Allow blood to air dry at room temperature for a minimum of three (3) hours. **NOTE:** Do not use artificial heat (lamps, incubators, etc.) to dry the specimens.
- Evaluate specimen for acceptability.
- Replace the coverslip over the blood when completely dry.

Mailing of Specimens

- Mail specimens as soon after drying as possible.

DO NOT BATCH SPECIMENS from multiple days except on Sunday and holidays.

NOTE: Specimens older than seven (7) days from collection date are unsatisfactory for testing and a repeat collection will be requested.

- Place specimen(s) to be mailed in the United Parcel Service (UPS) mailer.
- For those hospitals using internet shipping, print and enclose (in the outside pocket) the shipping document (i.e shipping label).
- Shipping costs will be paid by the WSLH.
- Most institutions have a daily UPS pick-up. Make sure the UPS mailer gets to the appropriate department in time for the pick-up. If your institution does not have a daily pick-up, call (800) 742-5877 and ask for an "on demand" pick-up.

Laboratory Testing and Reporting

Specimen Analysis

Specimen analysis begins on the day specimens are received in the newborn screening laboratory. The availability of results is disorder dependent.

- Specimens with all normal results are generally reported within 48 hours.
- Abnormal results for galactosemia and CAH are available on the day of specimen receipt.
- Abnormal results for aminoacidopathies, thyroid, fatty acid oxidation and organic acidemia disorders are generally available in 24 hours.
- Hemoglobinopathies and abnormal biotinidase results are generally available in 48 hours.
- Abnormal cystic fibrosis results are generally available in three to five days.

Reporting Results

NORMAL RESULTS (White paper):

- Written report to specimen collection institution.
- Repeat of initial abnormal results: Written report to physician and collection institution.

DEFINITE ABNORMAL (Gold colored paper):

- Telephone call to baby's physician.
- Written report to baby's physician and collection institution.

POSSIBLE ABNORMAL (Blue colored paper):

- Written report to baby's physician and collection institution.

Note: Some possible abnormal thyroid results are also reported by telephone to the baby's physician.

Unsatisfactory Specimens

All specimens are judged for acceptability. Those not acceptable are reported as "Unsatisfactory."

When a specimen is judged "unsatisfactory":

- The specimen collection site is called
- A written report is issued
- Repeat collection is expected within two weeks

Treatment Centers

Infants with genetic disorders require specialized care. Infants identified by newborn screening as potentially having a genetic disorder should be seen at an appropriate treatment center listed below.

Metabolic Clinics

(Aminoacidopathies, Galactosemia, Biotinidase Deficiency,
Fatty Acid Oxidation and Organic Acidemia)

Waisman Center	Madison	608-263-5787
Marshfield Children's	Marshfield	715-387-5185
Children's Hospital of WI	Milwaukee	414-266-3347

Endocrine Clinics

(Hypothyroidism, Congenital Adrenal Hyperplasia (CAH))

Marshfield Children's	Marshfield	715-387-5185
Children's Hospital of WI	Milwaukee	414-266-2860
UW Children's Hospital	Madison	608-263-8565

Hemoglobinopathy Clinics

(Sickle Cell Disorders)

Children's Hospital of WI	Milwaukee	414-257-1232
UW Children's Hospital	Madison	608-263-6202
Marshfield Children's	Marshfield	715-387-5185

Cystic Fibrosis Clinics

Children's Hospital of WI	Milwaukee	414-266-6730
UW Children's Hospital	Madison	608-263-8555
St. Vincent Hospital	Green Bay	920-496-4700
Marshfield Children's	Marshfield	715-387-5251

For More Information

For more information about specimen collection, laboratory results or other technical questions, contact the WSLH Newborn Screening Laboratory at (608) 262-6547.

For parent brochures or administrative questions, contact the Wisconsin Division of Public Health at (608) 266-8904.

Newborn Screening Disorders

Argininosuccinic Acidemia (ASA)

NOTE: Newborn Screening can not differentiate ASA from Citrullinemia

Autosomal recessive urea cycle disorder caused primarily by a deficiency in argininosuccinic acid (ASA) lyase enzyme activity causing the build up of argininosuccinic acid, citrulline, and ammonia in the blood. Clinical symptoms include lack of appetite, vomiting, listlessness, seizures, and coma.

Prevalence (WI):	1:250,000
Analyte Measured:	Citrulline
Abnormal Levels:	≥ 85 μmol/L
Feeding Effect:	None
Timing Effect:	< 24 hours of age: Repeat at two weeks ≥ 24 hours of age: Results are valid
Confirmation:	Immediate consult with a metabolic specialist at a metabolic treatment center.
Treatment:	The treatment for ASA includes a high-calorie, protein restricted diet; arginine supplementation, and administration of sodium benzoate and sodium phenylacetate. Dialysis may be necessary in some affected individuals.

Newborn Screening Disorders

Biotinidase Deficiency

Autosomal recessive disorder of biotin recycling that leads to multiple carboxylase deficiencies. Individuals with biotinidase deficiency cannot recycle endogenous biotin and cannot release dietary protein-bound biotin.

Prevalence (WI):	1:110,000
Analyte Measured:	Biotinidase enzyme activity
Abnormal Levels:	No enzyme activity
Feeding Effect:	None
Timing Effect:	No effect
Confirmation:	Repeat newborn screen. If abnormal, quantitative serum assay is recommended. Contact a metabolic clinic.
Treatment:	Daily biotin supplement

Newborn Screening Disorders

Citrullinemia (type I and II)

NOTE: Newborn Screening can not differentiate Citrullinemia from ASA.

Autosomal recessive urea cycle disorder caused primarily by a deficiency in the argininosuccinic acid synthetase enzyme activity causing the build up of the amino acid citrulline and ammonia in the blood. Clinical symptoms include lack of appetite, vomiting, listlessness, seizures, and coma.

Prevalence (WI):	1:200,000
Analyte Measured:	Citrulline
Abnormal Levels:	≥ 85 μmol/L
Feeding Effect:	None
Timing Effect:	< 24 hours of age: Repeat at two weeks ≥ 24 hours of age: Results are valid
Confirmation:	Immediate consult with a metabolic specialist at a metabolic treatment center.
Treatment:	The treatment for citrullinemia includes a high-calorie, protein restricted diet; arginine supplementation, and administration of sodium benzoate and sodium phenylacetate. Dialysis may be necessary in some affected individuals.

Newborn Screening Disorders

Congenital Adrenal Hyperplasia

A family of diseases whose common feature is an enzymatic defect in the steroidogenic pathway leading to the biosynthesis of cortisol. The 21-hydroxylase deficiency accounts for 90 to 95 percent of CAH cases, resulting in ambiguous genitalia in females and salt-losing crisis in either males or females. Early detection and treatment is essential to prevent death in infants with salt-losing CAH.

Prevalence (WI): 1:13,500

Analyte Measured: 17-Hydroxyprogesterone (17-OHP)

Reporting Ranges: Reporting ranges are birth weight dependent.

<u>Birth Weight (g)</u>	<u>17-OHP (ng/mL)</u>	<u>Report (color)</u>
< 1,699	≥ 190	Possible (blue)
1,700 – 2,199	105 – 135 ≥ 136	Possible (blue) Definite (gold)
≥ 2,200	86 - 124 ≥ 125	Possible (blue) Definite (gold)

Feeding Effect: None

Timing Effect: False positive 17-OHP results may occur if specimen is collected before 24 hours of age.

Confirmation: Repeat newborn screen through the WSLH. Federal Express second specimen if result reported is received by phone.

Treatment: Salt-losing diagnosis: Cortisol or analogs and 9 α flurocortisol (florinef)

Non-salt-losing diagnosis: Cortisol or analogs

Ambiguous genitalia: Surgery

COMMENT: Repeat of non-normal 17-OHP newborn screening tests by a “reference” laboratory is not recommended due to the potential confusion in reporting units.

Newborn Screening Disorders

Congenital Hypothyroidism

Disorders of the thyroid-hypothalamus-pituitary axis resulting in inadequate production of thyroid hormones. Hypothyroidism is a family of disorders, including endemic cretinism, thyroid agenesis or ectopia, genetic disorders of thyroid hormonogenesis, or hypopituitarism.

Prevalence (WI): 1:3,350

Analyte Measured: Thyroid Stimulating Hormone (TSH)

Reporting Ranges: Reporting ranges are specimen collection age specific.

<u>Collection Age</u>	<u>TSH (uIU/mL)</u>	<u>Report (color)</u>
0 – 25 hrs	≥ 37 ≥ 50	Possible (blue) Definite (gold)
26 – 96 hrs	≥ 30 ≥ 50	Possible (blue) Definite (gold)
4 – 14 days	≥ 20	Definite (gold)
> 14 days	≥ 15	Definite (gold)

Feeding Effect: None

Timing Effect: < 24 hours of age: Repeat at two weeks
 ≥ 24 hours of age: Results are valid

Confirmation: Definite Abnormal: Perform serum thyroxine(T4) and TSH assays.

Possible Abnormal: Repeat newborn screen through WSLH.

Treatment: Oral intake of thyroxine (synthyroid). Dose is weight-dependent, therefore consultation with a pediatric endocrinologist is recommended.

COMMENT: TSH increases dramatically shortly after birth and gradually returns to adult normal levels in about 72 hours. False positive results occur due to the specimen being collected at the height of the TSH spike, usually within the first hours of life. Although newborn screening can detect “primary” hypothyroidism with a high degree of accuracy, other forms of hypothyroidism may develop in the weeks after birth. **The physician must therefore remain alert to clinical symptoms in older infants despite normal newborn screening results. Perform serum total T4, free T4, and TSH if any doubt exists.**

Newborn Screening Disorders

Cystic Fibrosis

Autosomal recessive disorder characterized by pulmonary obstruction and/or exocrine pancreatic dysfunction. The major and most severe genetic mutation causing cystic fibrosis is a three-basepair deletion (F508) in the cystic fibrosis transmembrane regulator (CFTR) gene with a resulting increase in the pancreatic enzyme immunoreactive trypsinogen.

Prevalence (WI): 1:4,500

Analyte Measured: Immunoreactive Trypsinogen (IRT)

Mutation Analysis for 25 CF mutations:

ΔF508	2184delA	A455E	ΔI507	G542X
G551D	R553X	R560T	1717-1G>A	R1162X
3659delC	N1303K	W1282X	R334W	R347P
1078delT	R117H	I148T	621+1G>T	2789+5G>A
3849+10KbC>T	G85E	1098+1G>A	711+1G>T	3120+1G>A

NOTE: Mutation analysis is performed on the highest 4% of the daily IRT results.

Abnormal Levels: IRT > 170 ng/mL
One mutant allele
Two mutant alleles

Feeding Effect: None

Timing Effect: None

Confirmation: Sweat chloride testing by pilocarpine iontophoresis.

Treatment: Comprehensive approach to provide postural drainage with chest percussion, inpatient and outpatient antibiotics, pancreatic enzyme replacement, proper nutrition and psychosocial support.

COMMENT: Screening for cystic fibrosis using the two-tiered IRT / DNA approach cannot always distinguish babies who are CF carriers from babies who are affected. Sweat Chloride testing by the CFF-approved quantitative pilocarpine iontophoresis method is recommended for all reported positive screening results, i.e. babies with either one or two mutations detected. For babies with no detectable mutations but with an IRT > 170 ng/mL, the primary care provider should be alert for persistent diarrhea, poor weight gain, chronic cough or respiratory problems. If these signs appear, or if there is a family history of CF, contact should be made with a CF specialist. It is estimated that screening for 25 CF mutations will detect 99% of the CF affected babies.

Newborn Screening Disorders

Fatty Acid Oxidation Disorders

Fatty Acid Oxidation Disorders (FOD) are a class of inborn errors of metabolism in which there is an enzyme defect in the fatty acid metabolic pathway (use of dietary and stored fat). Clinical symptoms of FOD disorders include hypotonia, lethargy and vomiting; the hypoglycemia can lead to coma, encephalopathy, hepatic failure or death.

Analyte Measured: Acylcarnitine profiling by Tandem Mass Spectrometry

Disorders Reported, Reporting Ranges and Prevalence:

Disorder	Abbrev.	Abnormal Acylcarnitine (s) uM	Prevalence (estimated)
Medium Chain Acyl-CoA Dehydrogenase Deficiency	MCAD	C6 \geq 0.30 C8 \geq 0.50 C10:1 \geq 0.40 C8/C10 \geq 10.0	1:17,000
Long Chain 3-Hydroxyacyl CoA Dehydrogenase Deficiency Trifunctional Protein Deficiency	LCHAD	C16OH \geq 0.12 C16:1OH \geq 0.18 C18:1OH \geq 0.10 C18:2OH \geq 0.10	Unknown
Very Long Chain Acyl-CoA Dehydrogenase Deficiency	VLCAD	C14 \geq 0.80 C14:1 \geq 0.60 C14:2 \geq 0.25 C16:1 \geq 1.04 C14:1/C16 \geq 0.30	1:300,000
Short Chain Acyl-CoA Dehydrogenase Deficiency	SCAD	C4 \geq 1.20 C4/C2 \geq 0.08 C4/C3 \geq 0.91	1:14,000
Carnitine Palmitoyltransferase Deficiency Type II	CPT-II	C16 \geq 8.70 C18:1 \geq 2.80 C18:2 \geq 0.90	1:350,000
Glutaric Acidemia Type II	GA-II	C4 \geq 1.20 C5 \geq 0.44 C6 \geq 0.30 C8 \geq 0.50 C10 \geq 0.34 C5/C3 \geq 0.5	1:300,000
2,4 Dienoyl-CoA Reductase Deficiency	DRED	C10:2 \geq 0.10	Unknown
Carnitine/Acylcarnitine Translocase Deficiency	CAT	C16DC \geq 0.32 C18:1DC \geq 0.15	Unknown
Carnitine Uptake Defect	CUD	Free Carnitine \leq 3.80	Unknown
Medium/Short Chain Hydroxylacyl CoA Dehydrogenase	M/SCHAD	C4OH \geq 0.48 C6OH \geq 0.10	Unknown
Medium Chain 3-Ketoacyl CoA Thiolase Deficiency	MCKT	C3DC/C4OH \geq 0.48 C6DC \geq 0.20 C8DC \geq 0.10	Unknown

Feeding Effect: None

Timing Effect: Early specimen collections may enhance the detection of these disorders.

Confirmation: Referral to metabolic center for specific enzyme analysis, metabolite analysis and/or mutation analysis.

Treatment: Low fat diet, carnitine supplements, avoid fasting

Newborn Screening Disorders

Galactosemia

Autosomal recessive disorder of galactose metabolism. The genetic disturbance is expressed as a cellular deficiency of either, galactose-1-phosphate uridyl transferase (classic form), galactokinase, (variant) or uridine diphosphate galactose 4 epimerase (variant) - the enzymes catalyzing the reaction by which galactose is converted to glucose. The main dietary source of galactose is lactose, the principle carbohydrate in milk.

Prevalence (WI):	1:60,000
Analyte Measured:	Galactose-1-Phosphate Uridyl-1-Transferase (GALT)
Abnormal Levels:	Lack of GALT enzyme activity
Feeding Effect:	NONE (See COMMENT below)
Timing Effect:	< 24 hours of age: Repeat at two weeks ≥ 24 hours of age: Results are valid
Confirmation:	Quantitative plasma metabolites Quantitative enzyme activity Mutation analysis
Treatment:	Elimination of dietary lactose, including breast milk, cow's milk and/or lactose-based infant formula.

COMMENT:

Although detection of classical galactosemia using the GALT enzyme test is not depended upon the feeding status, galactosemic babies that have been transfused will appear to have normal enzyme activity. This is due to the GALT activity in the red cells. To help identify galactosemic babies that have been transfused, a 2nd tier metabolite (galactose and galactose-1-phosphate) assay will be performed on those specimens. If the metabolite levels are abnormal the baby will be reported as positive for galactosemia.

Screening for galactosemia using the GALT enzyme test will NOT detect the variant forms of galactosemia (galactosekinase or uridine diphosphate galactose 4 epimerase).

Newborn Screening Disorders

Hemoglobinopathies

Hemoglobin Diseases

A group of autosomal recessive disorders characterized by synthesis of abnormal hemoglobin molecules (e.g. S, E, C) or decreased synthesis of a beta globin chain. Those hemoglobinopathies characterized by synthesis of an abnormal molecule are detectable at birth. Affected individuals with sickle cell disease may have early overwhelming sepsis and require prompt evaluation at a comprehensive care facility.

Prevalence (WI): 1:400 (Sickle Cell Disease in African-Americans)
1:2,500 (General Population)

Analytes Measured: Hemoglobin Fractions

Fetal (F), Adult (A), Sickle (S),
C-Hemoglobin (C), E-Hemoglobin (E)

Patterns Reported: FA = Normal
FS = Hemoglobin SS disease
FC = Hemoglobin C disease
FSC = Sickle Hemoglobin-C disease
FSA = Sickle Beta Thalassemia
FE = Homozygous E disease

Feeding Effect: None

Timing Effect: None

NOTE: Specimen collection after a transfusion invalidates hemoglobin test results for a minimum of 60 days post transfusion. It is recommended that a specimen be collected prior to a transfusion, if at all possible. If a baby has been transfused or a transfusion is imminent, see *When to Collect a Specimen* (page 3).

Confirmation: Whole blood specimen at one month of age. The WSLH will provide a blood collection kit and no-cost testing.

Treatment: Prophylactic penicillin until age five.

Newborn Screening Disorders

Hemoglobinopathies

Common Hemoglobin Traits

Prevalence (WI): 1:10 (Sickle cell trait in African-Americans)

Analytes Measured: Hemoglobin Fractions
Fetal (F), Adult (A), Sickle (S)
C-Hemoglobin (C)
E-Hemoglobin (E)

Patterns Reported: FA = Normal
FAS = Sickle cell trait
FAC = Hemoglobin C trait
FAE = Hemoglobin E trait

Feeding Effect: None

Timing Effect: None (unless transfused)

NOTE: Specimen collection after a transfusion invalidates hemoglobin test results for a minimum of 60 days post transfusion. It is recommended that a specimen be collected prior to a transfusion, if at all possible. If a baby has been transfused or a transfusion is imminent, see *When to Collect a Specimen (page 3)*.

Confirmation: Quantitation of adult and sickle hemoglobin is recommended at one year of age to rule out S-Beta thalassemia.

Treatment: None

COMMENT: Persons with sickle cell trait are by definition carriers of an abnormal hemoglobin gene. While this fact has little clinical significance to the individual, genetic counseling is important because both parents may also be carriers creating a significant risk for a future baby to have a hemoglobin disease.

Newborn Screening Disorders

Hemoglobinopathies

Hemoglobin Variants

Prevalence (WI):	1:1,000 (Approximation)
Analytes Measured:	Hemoglobin Fractions Fetal (F), Adult (A)
	Hemoglobins D and Bart
Patterns Reported:	FAD FA + Bart
Feeding	Effect: None
Timing Effect:	None (unless transfused - see <i>When to Collect a Specimen</i>).
Confirmation:	See comment below.
Treatment:	None

COMMENT: These represent various types of hemoglobin traits and, as such, are asymptomatic and non-emergent. Most of these rare and variant hemoglobin's have little known clinical significance even in the homozygous state (i.e. lack of normal hemoglobin A). Genetic counseling is recommended primarily for general parental education and to assess the risk for significant hemoglobin disease in future children.

Any concern for the rare symptomatic variant can be monitored through clinical observations (anemia, jaundice, cyanosis) combined with a hemoglobin electrophoresis, CBC, and reticulocyte count. By one year of age, some children may show a mild microcytic anemia. The presence of Bart Hemoglobin is an exception, as it may be clinically significant, especially in Southeast Asians. Specific hematologic consultation is recommended for babies who show Bart hemoglobin at newborn screening. Recommended follow-up at one year of age is CBC, reticulocyte count, and hemoglobin quantitation.

Newborn Screening Disorders

Homocystinuria & Hypermethioninemia

Autosomal recessive amino acid disorder caused primarily by a deficiency in cystathionine beta synthase enzyme activity causing the build up of the amino acid methionine in the blood. Early detection and treatment can prevent associated mental retardation, seizures, motor development delays, weakening of bones, and venous and arterial blood clots.

Prevalence (WI):	1:200,000 (general population)
Analyte Measured:	Methionine
Abnormal levels::	$\geq 100 \mu\text{mol/L}$
Feeding Effect:	None
Timing Effect:	< 24 hours of age: Repeat at two weeks ≥ 24 hours of age: Results are valid
Confirmation:	Immediate consult with a metabolic specialist at a metabolic treatment center.
Treatment:	The treatment for homocystinuria is the dietary restriction of methionine as well as large doses of vitamin B6 and betaine.

Newborn Screening Disorders

Maple Syrup Urine Disease (MSUD)

Autosomal recessive amino acid disorder caused by deficiencies in the branched chain keto-acid dehydrogenase enzymes causing the build up of leucine, isoleucine, and valine in the blood. Early detection and treatment is essential to prevent associated mental retardation and/or neurological complications.

Prevalence (WI):	1:150,000 (general population) 1:1000 (Mennonites)
Analyte Measured:	Leucine, Valine (Isoleucine and Leucine are measured as one analyte)
Abnormal Levels:	305 - 399 $\mu\text{mol/L}$ Possible Abnormal (blue report) ≥ 400 $\mu\text{mol/L}$ Definite Abnormal (gold report) ≥ 250 $\mu\text{mol/L}$ Definite Abnormal (gold report) leu/phe ≥ 5.9 ≥ 305 $\mu\text{mol/L}$ Definite Abnormal (gold report) Valine ≥ 250 $\mu\text{mol/L}$
Feeding Effect:	Minimal
Timing Effect:	< 24 hours of age: Repeat at two weeks ≥ 24 hours of age: Results are valid
Confirmation:	Immediate consult with a metabolic specialist at a metabolic treatment center.
Treatment:	The treatment for MSUD is dietary restriction of the branched chain amino acids leucine, isoleucine, and valine. Treatment should begin as soon after birth as possible and continue through childhood and adolescence. Special infant formulas for treatment of MSUD are available free of charge through the metabolic clinics.

Newborn Screening Disorders

Organic Acidemia Disorders

Organic Acidemias (OA) are a class of inherited metabolic disorders that lead to accumulation of organic acids in biological fluids (blood and urine). This, in turn, produces disturbances in the acid-base balance and causes alterations in pathways of intermediary metabolism. Clinical symptoms of OA disorders may include vomiting, metabolic acidosis, ketosis, dehydration or coma, hyperammonemia, lactic acidosis, hypoglycemia, failure to thrive, hypotonia, global developmental delay, sepsis and hematological disorders.

Analyte Measured: Acylcarnitine profiling by Tandem Mass Spectrometry

Disorders Reported, Reporting Ranges and Prevalence:

Disorder	Abbrev.	Abnormal Acylcarnitine (s) uM	Prevalence (estimated)
Glutaryl CoA Dehydrogenase Deficiency Type I GA-I	C5DC	≥ 0.10	1:150,000
Propionyl CoA Carboxylase Deficiency	PA	C3 ≥ 6.92 C3/C2 ≥ 0.20	1:150,000
Methylmalonic Acidemia - mutase Clb A & B Clb C & D	MMA	C3 ≥ 6.92 C3/C2 ≥ 0.30	1:26,000*
Isovaleryl CoA Dehydrogenase Deficiency	IVA	C5 ≥ 0.44	1:150,000
2-Methylbutyryl CoA dehydrogenase Deficiency	2MBCD	C5/C3 ≥ 0.50 C5/C2 ≥ 0.05	1:20,000
3-Methylcrotonyl CoA Carboxylase Deficiency	3-MMC	C5OH ≥ 0.60	1:15,500
Mitochondrial Acetoacetyl CoA Thiolase Deficiency	β -KT	C5:1 ≥ 0.13	1:400,000
2-Methyl-3-Hydroxybutyryl CoA Dehydrogenase	MHBD	C5OH ≥ 0.60	unknown
3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency	HMG	C5OH ≥ 0.60 C6DC ≥ 0.20	Unknown
Multiple CoA Carboxylase Deficiency	MCD	C5OH ≥ 0.60 C3 ≥ 6.92	Unknown
Malonyl CoA Decarboxylase Deficiency	MA	C3DC ≥ 0.48	Unknown
Isobutyryl CoA Dehydrogenase Deficiency	IBD	C4 ≥ 1.20	Unknown
3 Methylglutaconyl CoA Hydratase Deficiency	3MGA	C6DC ≥ 0.20	Unknown

* Includes benign and mild cases

Feeding Effect: None

Timing Effect: Early specimen collections may enhance the detection of these disorders.

Confirmation: Referral to metabolic center for urine organic acids analysis, specific enzyme analysis and/or mutation analysis.

Treatment: Low protein diet, carnitine or vitamin supplements, avoid fasting

Newborn Screening Disorders

Phenylketonuria (PKU)

(Hyperphenylalaninemia and Biopterin Cofactor defects of regeneration and biosynthesis)

Autosomal recessive hyperphenylalaninemia caused primarily by a deficiency of phenylalanine hydroxylase activity or impaired synthesis or recycling of the biopterin (BN4) cofactor. Early detection and treatment is essential to prevent associated mental retardation.

Prevalence (WI):	1:16,200
Analytes Measured:	Phenylalanine (Quantitative)
Abnormal Levels:	≥ 150 $\mu\text{mol/L}$
Feeding Effect:	Minimal (See comment below.)
Timing Effect:	<24 hours of age: Repeat at two weeks. ≥ 24 hours of age: Results are valid.
Confirmation:	Repeat newborn screen. If repeat result is greater than first result, contact a metabolic clinic. NOTE: If initial result is greater than 1210 $\mu\text{mol/L}$, contact metabolic clinic immediately.
Treatment:	The mainstay of treatment for PKU is the low-phenylalanine diet. Treatment should begin as soon after birth as possible and be continued throughout life. Low phenylalanine infant formulas are available from the state's metabolic clinics.

COMMENT: The use of quantitative phenylalanine measurements increases the ability to detect PKU earlier in the baby's life than previously used qualitative assays. This, and the fact that phenylalanine levels are often (greater than 90% of the time) above normal at birth and continue to rise in the first hours of life, decrease the need for a protein feeding for the detection of PKU. The program has detected PKU in babies when specimens were collected before 8 hours of age and prior to a protein feeding.

Newborn Screening Disorders

Tyrosinemia (Types I, II, III)

Autosomal recessive amino acid disorder caused by a deficiency in fumarylacetoacetate hydrolase enzyme activity causing the build up of the amino acid tyrosine in the blood. Early detection and treatment is successful in preventing poor growth, liver damage, swelling of the legs, and inappropriate bleeding.

Prevalence (WI):	1:250,000
Analyte Measured:	Tyrosine
Abnormal Levels:	$\geq 360 \mu\text{mol/L}$
Feeding Effect:	Minimal
Timing Effect:	< 24 hours of age: Repeat at two weeks ≥ 24 hours of age: Results are valid
Confirmation:	Immediate consult with a metabolic specialist at a metabolic treatment center.
Treatment:	The treatment for tyrosinemia is the dietary restriction of phenylalanine, methionine, tyrosine and administration of the drug NTBC. Although this treatment regimen is successful in delaying the clinical symptoms of tyrosinemia, the only effective long-term treatment is liver transplantation.

Newborn Hearing Screening

Each year approximately 200 babies are born deaf or have significant hearing impairment in Wisconsin. Studies have shown that early detection and intervention dramatically improves language skills, cognitive abilities, and social development. Technology has recently improved such that screening for hearing loss can be done in the nursery before the baby is discharged. The Wisconsin Division of Public Health Sound Beginning Program is charged with monitoring the status of hearing testing in the state of Wisconsin. An electronic surveillance program called We-Trac has been developed to assure timely follow up testing for those babies that fail hearing testing. The We-Trac data base is populated by the collection of hearing results on the newborn screening blood collection card. The hearing results are entered into the newborn screening data base at the State Laboratory of Hygiene and then transferred to the We-Trac data base where DPH staff can access the data. Hospital staff can also access We-Trac to check on babies born in their institutions to assure that the testing has been completed or the status of follow up testing for those babies that initially failed the hearing screening.

Below are a number of key issues regarding hearing screening in Wisconsin.

- Hearing screening is done in the hospital before discharge.
- The hearing results are recorded on the newborn screening blood collection card (pink shaded area).
- The recording/reporting of hearing results **must not delay the blood collection** and/or **sending** of the blood specimen to the State Laboratory.
- For those babies that have hearing testing after the blood sample is taken, pull the blue sheet from the card.
 - When the hearing test is completed, fill in the appropriate fields on the blue sheet and send to the state laboratory.
- Tips for completing the hearing portion of the newborn screening blood collection form
 - Always record screening date when different from the date of specimen collection.
 - Be sure that the results, pass or refer, for each ear is recorded properly
 - Record the proper screening method (ABR or OAE). Both is a valid entry
 - If the baby is not screened, be sure to record the proper reason for not completing the screening.
- If the hearing screening will not take place shortly after the birth due to an extended NICU stay, record “NICU” as the Not Screened reason on the initial and subsequent blue slips. Hearing results can be entered directly into We-Trac when completed
- More information regarding the general benefits of hearing screening can be found on the following website: www.infanthearing.org.
- For more information related to the Wisconsin newborn hearing screening activities, contact the Sound Beginnings Program at (608) 267-9191.

Newborn Screening Statute WS 253.13

Tests for Congenital Disorders:

(1) **BLOOD TESTS.** The attending physician or nurse certified under s. 441.15 shall cause every infant born in each hospital or maternity home, prior to its discharge therefrom, to be subjected to blood tests for congenital and metabolic disorders, as specified in rules promulgated by the department. If the infant is born elsewhere than in a hospital or maternity home, the attending physician, nurse certified under s. 441.14 or birth attendant who attended the birth shall cause the infant, within one week of birth, to be subjected to these blood tests.

(1m) **URINE TESTS.** The department may establish a urine test program to test infants for causes of congenital disorders. The State Laboratory of Hygiene board may establish the methods of obtaining urine specimens and testing such specimens, and may develop materials for use in tests. No person may be required to participate in programs developed under his subsection.

(2) **TEST; DIAGNOSTIC, DIETARY AND FOLLOW-UP COUSELING PROGRAM; FEES.** The department shall contract with the State Laboratory of Hygiene to perform the test specified under this section and to furnish material for use in the tests. The department shall provide necessary diagnostic services, special dietary treatment as prescribed by a physician for a patient with a congenital disorder as identified by tests under sub. (1) or (1m) and follow-up counseling for the patient and his or her family. The State Laboratory of Hygiene board on behalf of the department, shall impose a fee for tests performed under this section sufficient to pay for services provided under the contract and shall include as part of this fee and pay the department an amount the department determines is sufficient to fund the provision of diagnostic and counseling services, special dietary treatment and periodic evaluation of infant screening programs under this section.

(3) **EXCEPTIONS.** This section shall not apply if the parents or legal guardian of the child object thereto on the grounds that the test conflicts with their religious tenets and practices. No tests may be performed under sub (1) or (1m) unless the parents or legal guardian are fully informed of the purposes of the testing under this section and have been given reasonable opportunity to object as authorized in this subsection or in sub (1M) to such tests.

(4) **CONFIDENTIALITY OF TESTS AND RELATED INFORMATION.** The State Laboratory of Hygiene shall provide the test results to the physician, who shall advise the parents or legal guardian of the results. No information obtained under this section from the parents or guardian or from specimens from the infant may be disclosed except for use in statistical data compiled by the department without reference to the identity of any individual and except as provided in s. 146.82 (2). The State Laboratory of Hygiene board shall provide to the department the names and addresses of parents of infants who have positive test results.

(5) **RELATED SERVICES.** The department shall disseminate information to families whose children suffer from congenital disorders and to women of child-bearing age with a history of congenital disorders concerning the need for and availability of follow-up counseling and special dietary treatment and the necessity for testing infants. The department shall also refer families of children who suffer from congenital disorders to available health and social services programs. The department shall periodically consult appropriate experts in reviewing and evaluating the state's infant screening program.

Newborn Screening Funding

Newborn screening is funded with user generated fees. The fee is collected with the purchase of the blood collection card from the WSLH. The collection site (hospital, clinic, physician or nurse) is responsible for billing the patient. Often the patients insurance will cover the cost of screening.

For ordering and current pricing information, see *Collection Card Ordering*. The price includes a laboratory fee and a surcharge.

The laboratory fee supports all testing activities, including staff salaries, reagents, and equipment.

The surcharge fee supports confirmatory testing, treatment, and counseling for affected children and their families. For example, children with PKU require a special formula that is purchased with surcharge monies and made available to the parents. Also, children identified with a genetic disorder through newborn screening are referred to specialty clinics for treatment and genetic counseling.

Although the newborn screening program is a state-run program, no state tax dollars are provided to support it.

The Wisconsin Newborn Screening Advisory Group

Umbrella Committee

Division of Public Health Representative
State Laboratory of Hygiene Representative
American Academy of Pediatrics Wisconsin Chapter Representative
Wisconsin State Medical Society Representative
Ethics Representative
Local Public Health Representative
Consumer Representative
Metabolic Subcommittee Chair
Endocrine Subcommittee Chair
Hemoglobinopathy Subcommittee Chair
Molecular Cystic Fibrosis Subcommittee Chair

Technical Subcommittees

Endocrine
Hemoglobinopathy
Metabolic
Molecular Cystic Fibrosis

Designated members:

Division of Public Health Representative
State Laboratory of Hygiene Representative
Local Public Health Representative
Consumer/Parent Representative
Qualified expert members with expertise in the technical area relevant to the subcommittee.

- Medical Consultants
- Certified Dietitians
- Genetic Counselors
- Registered Nurses

Education Subcommittee

Designated members:

Division of Public Health Representative
State Laboratory of Hygiene Representative
Local Public Health Representative
Consumer/Parent Representative
Qualified expert members with an interest in promoting newborn screening to health care providers and the public.

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