NORTH DAKOTA DEPARTMENT OF HEALTH

NEWBORN SCREENING PROGRAM

GUIDELINES FOR HEALTH-CARE PROVIDERS

NORTH DAKOTA
DEPARTMENT *of* HEALTH

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INTRODUCTION

The purpose of these Newborn Screening Program guidelines are to assist North Dakota health-care providers in understanding the components of a successful newborn screening program – screening, follow-up, diagnosis and medial management – and their importance in ensuring that infants affected with these conditions have the best possible outcomes and are able to achieve their highest potential.

The purpose of newborn screening is the early identification of infants at risk and in need of more definitive testing. The North Dakota Newborn Screening Program (NDNSP) dates back to the 1960s when screening activities were initiated in an effort to identify newborns with phenylketonuria (PKU). Screening is mandated by law. (See chapter 25-17 of the North Dakota Century Code at www.state.nd.us/lr/cencode/T25C17.pdf.) Administrative Rules for the program may be found at www.state.nd.us/lr/information/acdata/pdf/33-06-16.pdf. These also may be found in the appendices.

The Newborn Screening Program is designed to provide early testing of all newborns, follow-up on questionable test results, determine a diagnosis and initiate appropriate therapy if necessary. The time frame to accomplish this successfully is limited; in most cases, fewer than three weeks. However, the earlier treatment begins, the better! Needless delays often occur because of errors or omissions in completing the newborn screening form and in sample collection technique.

This manual delineates the various responsibilities of parties involved in newborn screening and provides guidelines for carrying out the responsibility, as well as mechanisms for implementing quality control measures for the process.

We request health care providers use the term "newborn screen" rather than "PKU test" when referring to the newborn screening test panel, because tests for many other conditions besides PKU are included in the newborn screening panel. The misuse of the term "PKU test" can lead to confusion and misunderstanding and could delay appropriate retesting of an infant with an abnormal screening test result for one of the other conditions on the newborn screen panel.

Each year, the NDNSP identifies newborns with one of the disorders screened for by the program. Without a screening program, disorders would remain undetected until it became too late for treatment to prevent, reduce or reverse its effects.

The North Dakota Newborn Screening Program has designated the University of Iowa Hygienic Laboratory (UHL) as the central screening laboratory for the program.

NORTH DAKOTA NEWBORN SCREENING PROGRAM HISTORY

1964
Screening for phenylketonuria (PKU) began.

1977
Screening for hypothyroidism began.

1991
Screening for galactosemia began.

1992
Due to the number of tests, North Dakota entered into an agreement with the Iowa Metabolic Screening Program for the lab testing.

1992
Screening for congenital adrenal hyperplasia (CAH) and maple syrup urine disease (MSUD) began.

November 2002
Participated in pilot project with the Iowa lab for testing of an expanded panel of disorders detectable by tandem mass spectrometry.

April 2003
Screening for medium-chain acyl-CoA dehydrogenase deficiency (MCADD), biotinidase, sickle cell and other hemoglobinopathies began.

August 2004
Screening for disorders detected by tandem mass spectrometry officially became part of newborn screening.

NEWBORN SCREENING RESPONSIBILITIES

NORTH DAKOTA DEPARTMENT OF HEALTH

1. The North Dakota Newborn Screening Program has designated the University of Iowa Hygienic Laboratory (UHL) as the central screening laboratory for the program.
2. The North Dakota Department of Health will be assisted by program medical consultants from the Iowa Newborn Screening Program, as well as North Dakota specialists. The Iowa Newborn Screening Program consultants assist attending North Dakota physicians in confirming a diagnosis, recommending treatment and advising follow-up care.
3. The department shall develop and implement a metabolic disease educational program for physicians, hospital staff, public health nurses and the citizens of the state. The educational program must include information about the nature of the diseases and about screening for the early detection of these diseases so that proper measures may be taken to reduce mortality, morbidity and associated disabilities.
4. The department will provide, on a statewide basis, a newborn screening system and short-term follow- up services for metabolic diseases.
5. The department will coordinate with or refer individuals to public and private health-care service providers for long-term follow-up services for metabolic diseases.
6. The department will follow-up with attending physician-cases with positive tests for metabolic diseases in order to determine the exact diagnosis.
7. The department will refer every diagnosed case of metabolic disease to a qualified health-care provider for necessary treatment of the metabolic disease.
8. The department will maintain a registry of cases of metabolic disease.

PHYSICIANS/HOME-BIRTH PROVIDERS

1. North Dakota law defines the legal responsibility of the physician attending a newborn child for testing and reporting.
2. A health-care provider who attends to a newborn is responsible for causing the test to be performed regardless of where the birth occurred. A physician attending to a child at home should ensure the test is performed regardless of the time lag between birth and physician care.
3. The physician's duty to cause a newborn to be subject to the test carries with it the responsibility to ensure that the test is proper. The responsibility to do the test correctly, however, is shared by the facility and personnel actually administering the test.
4. The physician shall conduct repeat screening tests when notified that a specimen was unable to be tested.
5. The physician shall conduct confirmatory testing of positive screening test results.
6. The physician shall report positively diagnosed cases to the Department of Health and shall initiate medical follow-up.

7. Newborn screening requires assurance of confidentiality and security of all patient records and program data.

MEDICAL CENTER/HOME-BIRTH PROVIDER

The medical center is responsible for collection of the blood specimen for all infants delivered in the medical center and submitting them to the University of Iowa Hygienic Laboratory.

1. The blood collection procedures shall be those recommended in this manual.
2. Refusal to have the test done must be obtained in writing from the parent. Parents or guardians may refuse the newborn screening test for religious reasons. After a thorough discussion of the risks and benefits of testing with the primary care provider, these parents are required to sign a waiver documenting their refusal. A signed copy of this refusal must be sent to the North Dakota Newborn Screening Program: Division of Family Health, North Dakota Department of Health, 600 E. Boulevard Ave., Bismarck, ND 58505-0200. (See Refusal Form)
3. The hospital shall screen all infants prior to hospital discharge.
4. The hospital shall submit the screening specimen as designated by the North Dakota Department of Health.
5. The patient's chart must include a record of blood collection and screening results.
6. The hospital shall assist in follow-up testing procedures as requested.
7. Assurance of confidentiality and security of all patient records must be maintained.

EXCEPTIONS AND OTHER ISSUES

1. **Transferred or Transported Infants**

   If the infant is transferred from the institution of birth to another institution before 24 hours of age, the receiving institution shall obtain the specimen. The transferring facility must inform the receiving facility that a test was not done. A collection must be done on or before 7 days of age.
2. **Premature – Sick Infants**

   Initial specimen of sick or premature infants shall be obtained on or before 7 days of age if the infant is still hospitalized or prior to discharge if earlier than 7 days of age.

   Specimens shall be obtained prior to blood transfusion regardless of the age of the infant.
3. **Out-of-Hospital Births**

   It shall be the duty of the person responsible for registering the birth to collect and submit the blood sample according to the North Dakota Department of Health's guidelines.
4. **Early Discharge**

   When hospital discharge occurs less than 48 hours after birth of the infant, a blood specimen **must** be collected.
5. **Contaminants**

   Contaminants on filter paper such as perspiration, antiseptics or alcohol may cause inhibition.

North Dakota Newborn Screening Program
Refusal of Newborn Screening Tests

Infant's Name: _____ Medical Record # _____

Date of Birth: _____

Attending Physician or Practitioner: _____

Place of Birth: _____

I have received and read the parent informational brochure entitled "Screening for a Healthy Baby" describing newborn screening in North Dakota. I understand that these disorders are easily detected by testing a blood sample from my baby's heel.

I have been informed and I understand that it is the Law of the State of North Dakota that all newborns shall be screened for these disorders, unless the parents/guardians refuse "on the grounds that testing for metabolic diseases conflicts with their religious tenets and practices."

I have been informed and I understand that, if untreated, these conditions may cause permanent damage to my child, including serious mental retardation, growth failure and even death.

I have discussed this screening with _____ and I understand the risks to my child if this screening is not completed.
(Physician or practitioner)

I do not want to have _____ screened for these disorders.
(Name of Infant)

My decision was made freely and I accept the legal responsibility for the consequences of this decision.

_____ _____
Parent or legal guardian printed name Date

_____ _____
Parent or legal guardian signature Date

_____ _____
Witness signature Date

Original: Infant's medical record
Copy: North Dakota Newborn Screening Office
Family Health Division, North Dakota Department of Health
600 E. Boulevard Ave., Dept 301
Bismarck, ND 58505-0200
Copy: Parent/Guardian

Rev. 5/2005

IMPORTANT SCREENING CONSIDERATIONS

Newborn screening tests are not diagnostic. Due to biologic variability, some affected infants may have normal screening results. The possibility of a false negative or a false positive result must always be considered, especially when screening newborns for metabolic disorders. A newborn screen may detect specific mutations only (e.g. Congenital Adrenal Hyperplasia [CAH] due to 21-hydroxylase or 11-betahydroxylase deficiency).

1. **Collection Form Information:** It is imperative to **provide complete information** on the collection form. The lab needs the information to correctly assign test result interpretations. Complete information also makes it possible to positively identify the baby in the event of similar names and to contact the hospital or attending physician if necessary.
2. **Collection Times:** Early collections compromise some of the test results. Recommended time for screening is between 24 hours and 7 days of age. If an infant is less than 24 hours old at the time of collections, another specimen should be collected and sent for testing as soon as possible.
3. **Specimen Collection:** Blood should be applied directly from the infant's heel onto the filter paper. Blood collections into containers with preservatives (e.g. EDTA) may cause false positive and/or false negative results, depending on the testing technology.
4. **Premature or Ill Infants:** Infants in the neonatal intensive care unit have so many critical needs that their newborn metabolic screening may be overlooked. All infants transferred to another medical facility must be screened by the receiving facility unless the infant has already been screened.
5. **Transferred Infants:** Hospitals transferring a newborn to another facility are responsible for notifying the receiving facility of the status of the newborn screen.
6. **Transfusions:** Red blood cell (RBC) transfusions interfere with the interpretation of some newborn screening results. Whenever possible, the newborn screen should be collected prior to a RBC transfusion, even if less than 24 hours of age. It is recommended to do the newborn screen before 24 hours of age if you expect to have to do a transfusion. If an infant was transfused before the first specimen collection, a follow-up filter paper specimen must be collected at least 8 weeks after the last transfusion.
7. **Treatment**: Under no circumstances should treatment be initiated without consultation from program medical consultants. Treatment prior to diagnostic confirmation may interfere with confirmatory testing. Moreover, it may cause irreversible harm to the baby.
8. **Total Parenteral Nutrition:** Infants on some types of total parenteral nutrition (TPN) may show elevated levels of amino acids (e.g. phenylalanine). Indications of TPN status on the collection form is necessary for clarifying some test results.

FILLING OUT THE SCREENING FORM

1. It is **extremely important** that **all** requested information on the laboratory slip portion of the screening form is filled out **completely and legibly**. The information requested is **vitally important** for the process of screening and follow-up.
2. **Accurate and complete patient and physician information is critical for rapid follow-up in the event of an abnormal result.**
3. Name, birth date and specimen date are particularly important. Include mother's first and last names and other critical identifiers (e.g., twin A, triplet C).
4. Rapid follow-up of an abnormal screen depends upon identifying the health-care provider who is caring for a child. The responsibility for follow-up of an abnormal result rests with the physician of record, as identified on the lab slip. For these reasons, every effort should be made to **ensure that this physician information is accurate and complete**.
5. The time of collection and the medical information on transfusions, medications, prematurity and other requested data are needed by the screening laboratory to interpret results and determine appropriate follow-up procedures.
6. If a specimen is a second screen being submitted to follow-up an abnormal result on the initial screen, this should be noted on the lab slip. This alerts the laboratory regarding which condition(s) to test for. Labs have different definitions of normal for initial and follow-up specimens.
7. On a second specimen submitted on a child for any reason, include information on a **name change** if one has occurred.
8. When filling out this information, **use a ballpoint pen**, as soft-tip pens will not copy through to the carbon copies; **do not use plastic imprint cards**, as they produce unreadable information; **do not use a typewriter** to fill out the form because it may contaminate the filter paper.
9. **The lab slip is a legal record**; the submitter is legally responsible for the accuracy and completeness of the information it contains.
10. Do not put labels or tape on the screening collection form or filter paper; it makes logging and tracking specimens in the lab very difficult. If the plies of the screening form becomes detached, reattach with a paper clip rather than adhesive tape.
11. Collection forms, envelopes and information pamphlets are available at no cost. To order collection forms, contact the Iowa laboratory at 515.725.1630 or by FAX at 515.725.1650.

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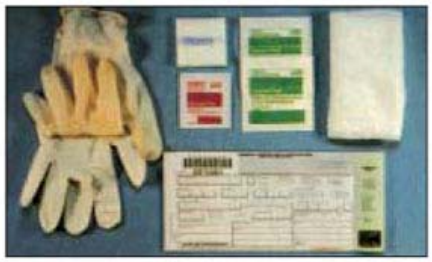
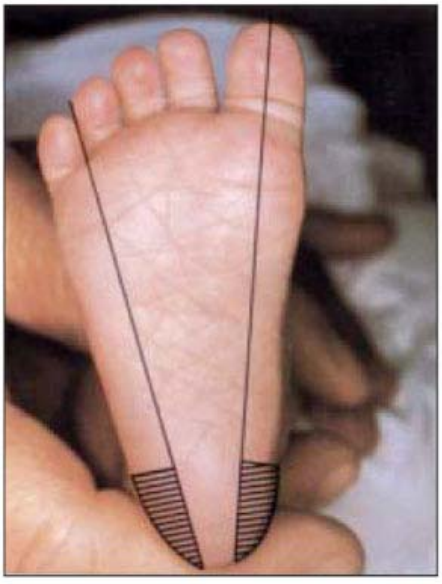
Neonatal Screening

Blood Specimen Collection and Handling Procedure

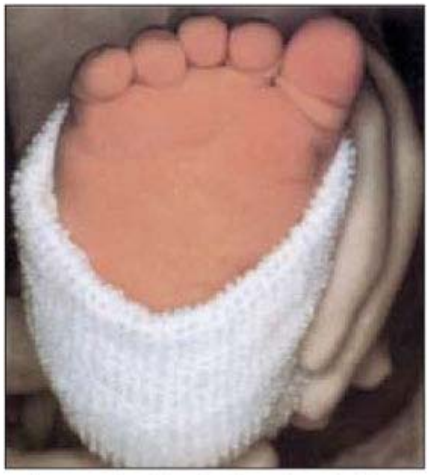


1 Equipment: sterile lancet with tip approximately 2.0 mm, sterile alcohol prep, sterile gauze pads, soft cloth, blood collection form, gloves.

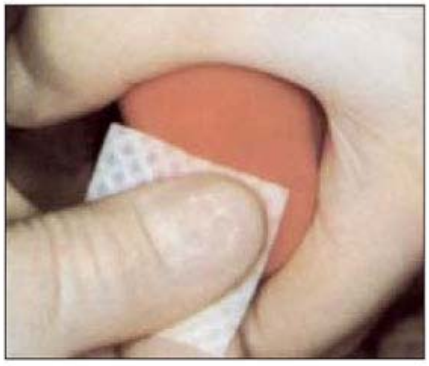
2 Complete ALL information. Do not contaminate filter paper circles by allowing the circles to come in contact with spillage or by touching before or after blood collection. Keep "SUBMITTER COPY" if applicable.



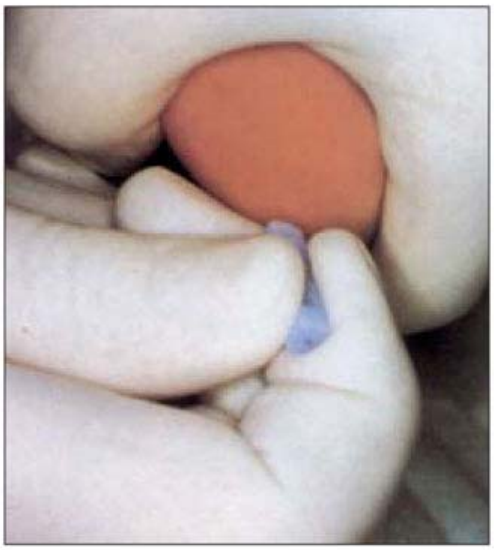
3 Hatched area (▨) indicates safe areas for puncture site.



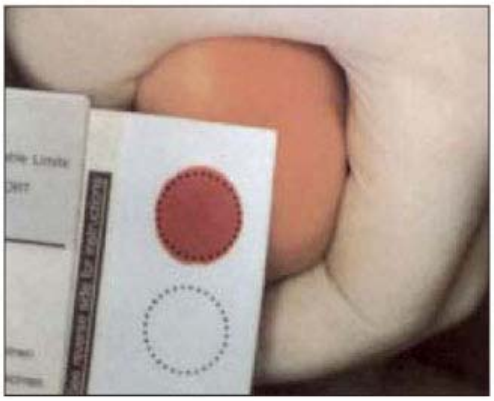
4 Warm site with soft cloth, moistened with warm water up to 41°C, for three to five minutes.



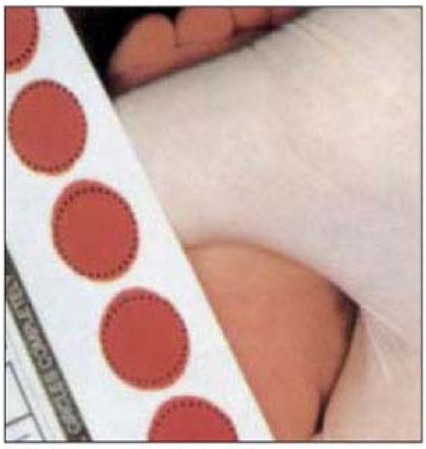
5 Cleanse site with alcohol prep. Wipe DRY with sterile gauze pad.



6 Puncture heel. Wipe away first blood drop with sterile gauze pad. Allow another LARGE blood drop to form.



7 Lightly touch filter paper to LARGE blood drop. Allow blood to soak through and completely fill circle with SINGLE application to LARGE blood drop. (To enhance blood flow, VERY GENTLE intermittent pressure may be applied to area surrounding puncture site). Apply blood to one side of filter paper only.



8 Fill remaining circles in the same manner as step 7, with successive blood drops. If blood flow is diminished, repeat steps 5 through 7. Care of skin puncture site should be consistent with your institution's procedures.

9 Dry blood spots on a dry, clean, flat non-absorbent surface for a minimum of four hours.

10 Mail completed form to testing laboratory within 24 hours of collection.

Information provided by The New York State Department of Health.

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HANDLING AND SHIPPING THE COLLECTED SPECIMEN

- Dry the blood spots thoroughly at room temperature **for at least four hours**.
- Keep specimens away from direct heat or sunlight.
- Dry in a horizontal position.
- Do not allow blood to come into contact with **any** other surface while drying.
- Do not refrigerate specimen.
- Do not place specimen in envelope until completely dry.
- Cover with end-flap only after specimen is completely dry.
- Double-check that patient information section has been **completely** filled out before mailing.
- If mailing more than one specimen in an envelope, alternate the forms so that the dried blood spots do not come into contact with each other.
- Double-check that a return address is present on the specimen envelope.
- Mail specimen as soon as possible after it is thoroughly dry.
- Do not transport in plastic bags. (They allow accumulation of condensation and can contribute to contamination and bleeding of the blood spots.)
- Ensure prompt delivery to the screening laboratory.
- Do not accumulate specimens, as they may become too old for testing.

Practitioners are encouraged to have systems in place to log and track specimens by name and form number to assist with **rapid follow-up in the event of an abnormal newborn screening test result**.

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Simple Spot Check

Valid Specimen

Allow a sufficient quantity of blood to soak through to completely fill the pre-printed circle on the filter paper. Fill all required circles with blood. Do not layer successive drops of blood or apply blood more than once in the same collection circle. Avoid touching or smearing spots.

Invalid Specimens:

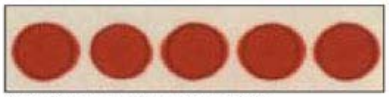
Possible Causes:

1. Specimen quantity insufficient for testing

- Removing filter paper before blood has completely filled circle or before blood has soaked through to second side.
- Applying blood to filter paper with a capillary tube.
- Touching filter paper before or after blood specimen collection with gloved or ungloved hands, hand lotion, etc.
- Allowing filter paper to come in contact with gloved or ungloved hands or substances such as hand lotion or powder, either before or after blood specimen collection.

2. Specimen appears scratched or abraded.

- Applying blood with a capillary tube or other device.



3. Specimen not dry before mailing.

- Mailing specimen before drying for a minimum of four hours.

4. Specimen appears supersaturated.

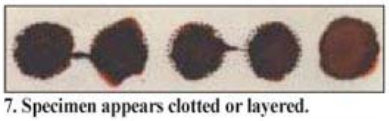
- Applying excess blood to filter paper, usually with a device.
- Applying blood to both sides of filter paper.

5. Specimen appears diluted, discolored or contaminated.

- Squeezing or "milking" of area surrounding the puncture site.
- Allowing filter paper to come in contact with gloved or ungloved hands or substances such as alcohol, formula, antiseptic solutions, water, hand lotion or powder, etc., either before or after blood specimen collection.
- Exposing blood spots to direct heat.

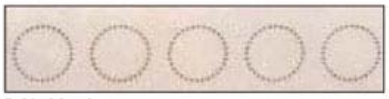
6. Specimen exhibits serum rings.

- Not wiping alcohol from puncture site before making skin puncture.
- Allowing filter paper to come in contact with alcohol, hand lotion, etc.
- Squeezing area surrounding puncture site excessively.
- Drying specimen improperly.
- Applying blood to filter paper with a capillary tube.



7. Specimen appears clotted or layered.

- Touching the same circle on filter paper to blood drop several times.
- Filling circle on both sides of filter paper.



8. No blood.

- Failure to obtain blood specimen.

Information provided by The New York State Department of Health.

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UNSATISFACTORY SPECIMENS

Newborn screening laboratories receive specimens that are unacceptable for testing. If the specimen is improperly collected, the accuracy of the screening test results is compromised, so the laboratory ***must*** reject them. This delays the screening of the newborn and **requires that the submitter locate the infant and repeat the collection procedure**.

The following table outlines the most common errors in specimen collection.

INVALID SPECIMEN	POSSIBLE CAUSES
Quantity of blood not sufficient for testing (QNS)	Filter paper circles incompletely filled out or not saturated/not all circles filled. Blood applied with needle or capillary tube. Contamination of surface of filter paper circle before or after specimen collection by gloved or ungloved hands, or by substances such as hand lotion, powder, etc.
Blood spots appear scratched or abraded	Blood applied improperly using capillary tube or other means (blotter has been damaged or torn by device).
Blood spots wet	Specimen not properly dried before mailing.
Blood spots appear supersaturated	Excess blood applied (usually with capillary tube or needle). Blood applied to both sides of filter paper.
Blood spots appear diluted, discolored or contaminated	Puncture site squeezed or "milked." Exposure of blood spots to direct heat. Contamination of filter paper before or after specimen collection by gloved or ungloved hands, or by substances such as alcohol, formula, water, powder, antiseptic solutions or hand lotion. Contamination during transit.
Blood spots exhibit "serum rings"	Alcohol not wiped off puncture site before skin puncture is made. Filter paper has come into contact with alcohol, water, hand lotion, etc. Puncture site squeezed excessively. Specimen dried improperly. Blood applied to the filter paper with a capillary tube.
Blood spots appear clotted or layered	Same filter paper circle touched to a blood drop several times. Circle filled from both sides of the filter paper.
Blood will not elute from the blotter paper	Blood specimen has been heat-fixed. Blood specimen is too old (more than two weeks between collection and receipt by the screening laboratory).

Consult the North Dakota Newborn Screening Program for additional information and assistance with specimen collection at 800.472.2286 or 701.328.4538.

FREQUENTLY ASKED QUESTIONS

What is the purpose of the North Dakota Newborn Screening Program?
The purpose of the North Dakota Newborn Screening Program is to screen all newborns in North Dakota for metabolic disorders that can lead to serious health consequences. By early identification of these disorders, a newborn can be treated before symptoms appear, preventing mental retardation, serious illness and death. The North Dakota Newborn Screening Program has designated the University of Iowa Hygienic Laboratory (UHL) as the central screening laboratory for the program.

What is the chance that a baby actually will have one of the disorders detectable by screening?
The chance that a baby will have one of these disorders is rare. In the rare cases when a disorder is found, early diagnosis and treatment can usually prevent the problems associated with these disorders. All abnormal screen results should be taken seriously, and recommended follow-up should be done as soon as possible.

Is there a charge for repeat screening?
Although there is a charge for the initial screen, the testing lab does not charge for repeat screens. However, the hospital or clinic that collects the repeat may have a specimen collection charge.

Why is it necessary to retest some babies?
Premature babies may have immature enzyme systems or thyroid functioning. It may be necessary to monitor their progress to be certain they reach normal levels. Unnecessary repeat testing can be avoided by collecting blood specimens 24 hours after birth, before a transfusion, and using correct specimen collection procedures.

Why do the collection forms require birth date and time and collection date and time information?
Recording the date and time for both infant birth and specimen collection is necessary to ensure that the specimen has been collected at least 24 hours after birth. Blood specimens should be collected from newborns between 24 and 48 hours. If the specimen collection time is not recorded on the form, the testing laboratory must assume for the benefit of the infant that the specimen was collected early and a recollection is required.

Why is it necessary to wait 24 hours before collecting a newborn screening specimen?
A screening specimen collected before 24 hours of age could give a false positive or false negative test result. Blood specimens should be collected from newborns between 24 and 48 hours.

****Exception to the 24-hour rule:*** A newborn screen should always be collected prior to transfusion or discharge. Facilities responsible for transferring an infant to another facility are encouraged to collect a newborn screen prior to transfer.

Why is the infant's weight at the time of specimen collection required?
Transient elevations of 17-OHP, the analyte for the congenital adrenal hyperplasia (CAH) screen may occur in pre-term and low birth weight babies. Because of this, four weight-related 17-OHP ranges are in place to minimize the number of false positive results. Without a weight indicated on the collection form, CAH results cannot be reported. If the weight is inadvertently omitted, you can fax the weight at the time of collection to the lab and they will reissue the report based on the new information. The fax number is 515.725.1650.

I am having trouble collecting blood. Should I try to get some blood inside each circle?
No, it is better to have 3 or 4 fully filled circles than many partially filled ones. Please review the section on specimen collection instructions.

Why was the screening specimen reported as poor quality when I know there was plenty of blood in the circles?
All tests performed by the testing laboratory are calibrated to an expected blood volume contained in an 1/8-inch punch of paper. There must be an even penetration of blood for the test to be accurate. This means soaking through the filter paper with ONE application and filling the entire circle.

Submitting a poor quality specimen results in the inconvenience of recollecting another specimen and delays the screening of the newborn. This places the newborn at risk for delayed diagnosis of a metabolic condition. It is important that another sample is collected from the newborn as soon as possible.

Why do some newborn screens have "false positive" results?
False positive results may be due to immature endocrine or enzyme function in the newborn, the stress of birth on an infant, or the specimen being collected prior to 24 hours after birth. The testing laboratory establishes screen cutoff values which keep the number of false positives at a minimum, yet minimizes the likelihood of an affected newborn being missed.

What do I do if the parents refuse the screen?
North Dakota century code 25-17-04 mandates: "the testing requirements of this section do not apply if the parents of a newborn child object to the testing on the grounds that testing for metabolic disease conflicts with their religious tenets and practices." The parents or legal guardians and the licensed health-care provider should sign a waiver for newborn screening refusal. The original should be placed in the child's medical record, a copy should be provided to the parents or guardians and a copy should be sent to the North Dakota Newborn Screening Program. The waiver serves as documentation that the parents were informed about the possible adverse outcomes of not performing newborn metabolic screening and that they accept legal responsibility for the consequences of their decision.

If newborn metabolic screening is not done for some reason in the first week of life, is it worthwhile to still screen the baby later?
Yes. While some disorders may begin to be expressed and some damage may have already been occurred, treatment begun at any time will always be beneficial to the infant. Additionally, the family should be made aware of the infant's metabolic disorder and its genetic implications and be given appropriate counseling. Ideally, all babies should be screened in the first week of life, but screening a baby later is better than never screening at all.

Is there an age limit for newborn metabolic screening?
Infants can be screened for all disorders up to one year of age. Congenital and congenital adrenal hyperplasia ranges apply to the newborn period, and interpretation of results from specimens collected after the newborn period should be performed in consultation with the appropriate specialist.

Will breastfeeding alter the results of the newborn screen?
Breastmilk is an adequate source of protein challenge and should not adversely affect results of the newborn screen.

What do I do if a baby has moved here from out of state?
Collect another specimen if you don't have documentation that the infant had a newborn metabolic screen prior to the move.

Whose responsibility is it to advise the parents about the screen?
The attending health-care provider (which includes midwives, nurse practitioners and physician assistants) has the ultimate responsibility for ensuring that an infant under his or her care has newborn metabolic screening. A parent or guardian should be informed of the type of specimen collected, how it is obtained, the nature of the disorders being screened and the consequences of treatment and nontreatment. The responsibility includes following up on any abnormal screening results.

Can newborn metabolic screening be done if a baby is born at home?
Yes. Parents should make arrangements with a health care practitioner, hospital, public health agency or midwife to have a newborn screening specimen collected. The specimens should be collected between 24 and 48 hours.

RECOMMENDATIONS – QUALITY ASSURANCE FOR HOSPITALS

Adherence to predetermined standards and criteria will minimize the possibility of errors occurring in the screening procedures. The following suggestions for developing hospital quality assurance procedures are offered to assist you in implementing requirements of the Newborn Screening Program.

SPECIMEN COLLECTION

1. Implement a process for ensuring that a test is done (written or standing order). The health-care provider has the ultimate responsibility.
2. Designate individuals responsible for:
    a. Actual collection of specimen.
    b. Recording collection in infant's chart.
    c. Sending sample to the lab.
    d. Ensuring test results are recorded in infant's chart.
3. Establish procedure for:
    a. Ensuring that specimen collection prior to discharge was actually done.
    b. Informing parent or guardian of need for retesting if discharge was prior to 24 hours of birth or 24 hours of protein intake.
    c. Testing under special circumstances (transfers, sick/preterm infants).
    d. Documentation should a parent or guardian refuse testing.
4. Implement a process for ensuring that employees are informed of their responsibilities in the screening process.

LABORATORY PROCEDURES – TECHNIQUES

Ensure appropriate procedures are followed for collection technique by implementing "Standards of the National Committee for Clinical Lab Standards" (NCCLS).

Appendix A – NORTH DAKOTA LAW

CHAPTER 25-17 – TESTING AND TREATMENT OF NEWBORNS

25-17-00.1. Definitions.

As used in this chapter, unless the context otherwise requires:

1. "Low-protein modified food product" means a food product that is specially formulated to have less than one gram of protein per serving and is intended to be used under the direction of a physician for the dietary treatment of a metabolic disease. The term does not include a natural food that is naturally low in protein.

2. "Medical food" means a food that is intended for the dietary treatment of a disease or condition for which nutritional requirements are established by medical evaluation and is formulated to be consumed or administered under the direction of a physician.

3. "Metabolic disease" means a disease as designated by rule of the state health council for which early identification and timely intervention will lead to a significant reduction in mortality, morbidity, and associated disabilities.

25-17-01. Newborn screening education programs and tests. The state department of health shall:

1. Develop and implement a metabolic disease educational program among physicians, hospital staff, public health nurses, and the citizens of this state. This educational program must include information about the nature of the diseases and about screening for the early detection of these diseases so that proper measures may be taken to reduce mortality, morbidity, and associated disabilities.

2. Provide, on a statewide basis, a newborn screening system and short-term follow-up services for metabolic diseases.

3. Coordinate with or refer individuals to public and private health care service providers for long-term follow-up services for metabolic diseases.

25-17-02. Rulemaking requirement. The state health council and the department of human services shall adopt rules necessary to implement this chapter.

25-17-03. Treatment for positive diagnosis - Registry of cases.

1. The state department of health shall:

a. Follow-up with attending physicians cases with positive tests for metabolic diseases in order to determine the exact diagnosis.

b. Refer every diagnosed case of a metabolic disease to a qualified health care provider for necessary treatment of the metabolic disease.

c Maintain a registry of cases of metabolic diseases.

2. The department of human services, as a program provided under chapter 50-10, shall:

a. Provide medical food at no cost to males under age twenty-two and females under age forty-five who are diagnosed with phenylketonuria or maple syrup urine disease, regardless of income. If treatment services under this subsection are provided to an individual by the department, the department may seek reimbursement from any government program that provides coverage to that individual for the treatment services provided by the department.

b. Offer for sale at cost medical food to females age forty-five and over and to males age twenty-two and over who are diagnosed with phenylketonuria or maple syrup urine disease, regardless of income. These individuals are responsible for payment to the department for the cost of medical food.

c. Provide low-protein modified food products, if medically necessary as determined by a qualified health care provider, to females under age forty-five and males under age twenty-two who are receiving medical assistance and are diagnosed with phenylketonuria or maple syrup urine disease.

25-17-04. Testing and reporting requirements. The physician attending a newborn child, or the birth attendant in the case of an out-of-hospital birth, shall cause that newborn child to be subjected to testing for metabolic diseases, in the manner prescribed by the state department of health. A physician attending a patient with a metabolic disease shall report the case to the state department of health. The testing requirements of this section do not apply if the parents of a newborn child object to the testing on the grounds that testing for metabolic diseases conflicts with their religious tenets and practices.

25-17-05. Testing charges. The state health council may adopt rules that establish reasonable fees and may impose those fees to cover the costs of administering tests under this chapter. All test fees collected by the state department of health must be deposited in the state department of health operating account.

Appendix B – NORTH DAKOTA ADMINISTRATIVE RULES

CHAPTER 33-06-16 – NEWBORN SCREENING PROGRAM

Section

33-06-16-01. Definitions. As used in this chapter:

1. "Diagnostic test" means a test that is used to establish a definitive diagnosis of some condition in an affected newborn.

2. "Newborn screening system" means the routine testing of newborn infants for congenital conditions by analysis of a dried blood specimen through laboratory procedures that identify infants with an increased risk for specified diseases and conditions, and that justify follow-up actions and diagnostic tests or procedures.

3. "Program" means the North Dakota Newborn Screening Program in the division of maternal and child health in the state department of health.

4. "Protected health information" has the meaning set forth in North Dakota Century Code section 23-01.3-01.

5. "Tandem mass spectrometry" is a laboratory technology that uses a machine consisting of two mass spectrometers joined by a fragmentation chamber. Tandem mass spectrometry technology allows the identification of an array of metabolic conditions, such as amino acid, fatty acid, and organic acid disorders, from a single dried blood spot.

History: Effective December 1, 1996; amended effective March 1, 2003.
General Authority: NDCC 23-01-03(3), 23-01-03.1, 23-01-04, 23-01-15, 25-17-01, 25-17-02
Law Implemented: NDCC 23-01-03.1, 25-17-01(3), 25-17-02, 25-17-03

33-06-16-02. Testing of newborns. Under the newborn screening system, except as authorized by section 33-06-16-04, each newborn infant born in this state shall be tested for the metabolic diseases phenylketonuria, hypothyroidism, galactosemia, congenital adrenal hyperplasia, biotinidase deficiency, sickle cell disease, and other hemoglobinopathies, and any other disease that can be identified through tandem mass spectrometry that is designated on the

department's test schedule with a designated laboratory engaged to perform this testing on behalf of the program.

History: Effective March 1, 2003.
General Authority: NDCC 23-01-03(3), 23-01-03.1, 23-01-04, 23-01-15, 25-17-01, 25-17-02
Law Implemented: NDCC 23-01-03.1, 25-17-01(3), 25-17-02, 25-17-03

33-06-16-03. Physician responsibility.

1. The physician or other birth attendant shall order that:

   a. A specimen of blood be collected from a newborn in accordance with directions supplied by the laboratory designated by the state department of health and the program; and

   b. The specimen be sent to that laboratory.

2. If a patient, who has a condition for which the program conducts a screening test, but which has been detected by another mechanism or by an out-of-state screening program, the patient's physician shall within thirty days of becoming aware of the patient's condition, notify the program of the patient's name, parent's name if the patient is under eighteen years of age, date of birth, address, and condition.

History: Effective March 1, 2003.
General Authority: NDCC 23-01-03(3), 23-01-03.1, 23-01-04, 23-01-15, 25-17-01, 25-17-02
Law Implemented: NDCC 23-01-03.1, 25-17-01(3), 25-17-02, 25-17-03

33-06-16-04. Refusal of testing.

1. If the parents or guardians refuse to have their infant receive newborn screening testing as authorized by North Dakota Century Code section 25-17-04, that refusal shall be documented by a written statement signed by the parents or guardians.

2. The original refusal statement shall become a part of the infant's medical record and a copy of the statement shall be submitted to the program.

History: Effective March 1, 2003.
General Authority: NDCC 23-01-03(3), 23-01-03.1, 23-01-04, 23-01-15, 25-17-01, 25-17-02
Law Implemented: NDCC 23-01-03.1, 25-17-01(3), 25-17-02, 25-17-03

33-06-16-05. Research and testing materials. Information and testing materials generated by the newborn screening program under North Dakota Century Code chapter 25-17 are strictly confidential information subject to North Dakota Century Code chapter 23-01.3 and section 23-01-15.

1. Access to information or testing materials may be obtained only as follows:

   a. Information may be disclosed for statistical purposes in a manner such that no individual person can be identified.

   b. Information may be disclosed to the individual tested, that person's parent or guardian, or that person's physician or dietitian, or to the children's special health services program of the department of human services for purposes of coordination of services and provision of medical and low-protein modified foods.

   c. Information and testing materials may be disclosed to a person engaged in a bona fide research project concerning medical, psychological, or sociological issues provided all of the following conditions are met:

      (1) The research project must be sponsored by a public or private college or university; a governmental entity; a nonprofit medical, sociological, or psychological association; or the pharmaceutical industry.

      (2) The research project must be reviewed and approved pursuant to policies and procedures pertaining to research utilizing human subjects by the institutional review board or equivalent panel of the institution or entity where the research is being done or which is sponsoring the research.

      (3) Protected health information may not appear in any report, summation, thesis, or other document arising out of the research project.

      (4) Protected health information may not be provided to a person engaged in a bona fide research project until that person has submitted a written proposal explaining and justifying the need to examine such information which is satisfactory to the state health officer. The state health officer may require the research to be approved by the university of North Dakota institutional review board.

      (5) All documents or testing materials received by the researcher and all documents containing protected health information made by or on behalf of the researcher, by whatever means, including hard

copies, typewritten or handwritten copies, photocopies, facsimiles, or electronic or electromagnetic recording or imaging, must be returned to the department on or before a date that the state health officer shall set.

(6) The researcher shall submit a written plan explaining how all protected health information in the researcher's possession will be kept secure to the satisfaction of the state health officer who shall obtain written assurance that the plan will be implemented.

(7) The researcher shall agree to provide the state health officer a copy of any report, summation, thesis, or other document arising out of the research project for departmental review of compliance with this section before providing it to the publisher.

(8) The researcher shall consent in writing to the use and reproduction of the document by the department.

(9) The researcher shall agree in writing to pay all costs of the state health officer or the department incurred in providing access to testing materials or other information, including copy or research services.

d. Disclosure may be made as otherwise provided by statute.

2. Retention and destruction of information and testing materials.

a. Information and testing materials provided to the university of North Dakota school of medicine and health sciences may be retained indefinitely or destroyed according to this subsection.

b. Information and testing materials may be destroyed by any available means that preserves individual confidentiality and, for the testing materials, complies with any applicable standards for destruction of human blood samples.

c. Information and testing materials may be destroyed based upon the following schedule:

(1) Information and testing materials created less than ten years before the present date may be destroyed only with the state health officer's prior written approval.

(2) After ten years, information and testing materials may be destroyed without prior approval.

History: Effective March 1, 2003.
General Authority: NDCC 23-01-03(3), 23-01-03.1, 23-01-04, 23-01-15, 25-17-01, 25-17-02
Law Implemented: NDCC 23-01-03.1, 25-17-01(3), 25-17-02, 25-17-03

SUMMARY OF DISORDERS SCREENED

Condition	Compound Tested for	Incidence	Symptoms if Not Treated	Treatment
Endocrine Disorders: Congenital Adrenal Hyperplasia (CAH)	17-OH Progesterone	1:12,000 1:300 Yupik Eskimos	Addisonian crisis in all infants; salt wasting in 2/3: dehydration, shock, hyperkalemia; virilization of females	Glucocorticoid and/or mineralocorticoid (Florinef)
Congenital Hypothyroidism	Thyroid hormones (T_4 with TSH confirmation)	1:3,000	Mental retardation, other brain damage; growth delay	Thyroid hormone (L-Thyroxine)
Hemoglobin Disorders: Hemoglobinopathies including sickle cell anemia	Hemoglobin patterns	1:15,000 (1:400 in African Americans)	In sickle cell disease: death by sepsis or splenic sequestration anemia; sickling crises	Penicillin and comprehensive care
Metabolic Disorders: Biotinidase Deficiency	Biotinidase	1:60,000	Mental retardation, seizures, skin rash, alopecia, hearing loss, death	Biotin
Galactosemia	Galactosemia enzyme (GALT)	1:60,000	Severe brain damage; liver disease; cataracts; death	Galactose-restricted diet
Urea Cycle Disorders: Aginase Deficiency	Arginine	1:60,000	Irritability; developmental delay; spastic tetraplegia	Low-protein diet, medication
Arginosuccinate Lyase Deficiency (ASA)	Arginine/Citrulline	1:60,000	Hyperammonemia; mental retardation; seizue; death	Low-protein diet, medication
Citrullinemia	Citrulline	1:60,000	Hyperammonemia; mental retardation; seizue; death	Low-protein diet, medication
Amino Acids: Homocystinuria	Methionine	1:100,000	Mental retardation; dislocation of lenses; marfanoid body habitus	Pyridoxine; methionine restricted, cysteine supplemented diet

Hyperphenylal-aninemia, including phenylketonuria	Phenylalanine	1:10,000	Profound mental retardation; seizures	Low-phenylalanine diet
Tyrosinemia	Tyrosine	1:100,000	Vomiting, lethargy; liver disease; coagulopathy renal tubular acidosis	Medication; low phenylalanine and/or low tyrosine diet
Organic Acidemias: • Beta-ketothiolase deficiency • Glutaric acidemia, Type 1 • Isobutyryl CoA dehydrogenase deficiency • Isovaleric acidemia • Malonic aciduria • Maple syrup urine disease (MSUD) • Methylmalonic acidemias (8 types) • Propionic acidemia • 3-Hydroxy-3-methylglutaryl (HMG) CoA lyase deficiency • 2-Methyl-3-hydroxybutyryl CoA dehyrogenase deficiency • 2-Methylbutyryl CoA dehydrogenase deficiency • 3-Methylcrotonyl CoA carboxylase deficiency • 3-Methylglutaconyl CoA hydratase deficiency • Multiple carboxylase deficiency	Acylcarnitines	1:53,000	Neonatal onset: irritability; lethargy; ketoacidosis; coma; death Late onset; failure to thrive; hypotonia; mental retardation Some will be asymptomatic	Dietary therapy and/or medications

Fatty Acid Oxidation Defects: • Carnitine translocase deficiency • Carnitine transport defect • Carnitine palmitoyl transferase 1 deficiency (CPT1) • Carnitine palmitoyl transferase 2 deficiency (CPT2) • Multiple acyl-CoA dehydrogenase (MADD) deficiency • Short chain acyl-CoA dehydrogenase (SCAD) deficiency • Medium chain acyl-CoA dehyrogenase (MCAD) deficiency • Long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency • Very long chain acyl-CoA dehyrogenase (VLCAD) deficiency	Acylcarnitines	1:9,300	"Reyes Like" episodes; hypoketotic hypoglycemia; lethargy; cardiomyopathy; hypotonia; mental retardation; coma; death Some will be asymptomatic Mother may have had AFLP/HELLP syndrome; acute fatty liver of pregnancy	Dietary therapy/ medications

Draft

NEWBORN SCREENING PROTOCOLS TABLE OF CONTENTS

Amino Acid Disorder
5-Oxoprolinuria
Pyroglutamicaciduria, Glutathione Synthetase Deficiency

DEFINITION	5-Oxoprolinuria is a biochemical finding that can arise from two underlying metabolic disorders. It is characterized by excretion of massive amounts of the chemical 5-oxoproline.
INCIDENCE	The faulty gene only emerges when 2 carriers have children together and pass it off to their offspring. Very rare – only 8 cases reported worldwide.
NBS ABNORMALITIES	
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Studies have concluded that early supplementation with Vitamins C & E may improve the long-term clinical outcome of these patients.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) All patients with 5-oxoprolinase deficiency have been identified because of 5-oxoprolinuria (4-10g/day), but they lack a consistent clinical picture. 2) They have normal acid-base balance. 3) Different clinical symptoms reported in individuals with 5oxoprolinase deficiency are renal stone formation, enterocolitis, mental retardation, neonatal hypoglycemia, microcytic anemia and microcephaly.
SERVICES	Consultation with a pediatric endocrinologist or geneticist is strongly encouraged for ongoing management.
REFERENCES	1) www.savebabies.org/diseasedescriptions/5oxoprolinuria.php 2) www.ncbi.nlm.nih.gov 3) www.orpha.net/data/patho/GB/uk-oxopro.pdf 4) www.icomm.ca/geneinfo/5ox.htm 5) www.clinchem.org/cgi/content/full/44/2/336

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Amino Acid Disorder

Argininemia, also known as Arginase Deficiency, ARG1 Deficiency, Hyperargininemia, Arginase (ARG)

DEFINITION	Babies born with these disorders cannot metabolize or process amino acids properly. Argininemia is caused by a deficiency of the enzyme arginase. Individuals with this disorder have hyperammonia as a result of their inability to break down arginine as part of the urea cycle. The accumulation of ammonia and arginine results in neurological manifestations.
INCIDENCE	Very rare condition.
NBS ABNORMALITIES	Abnormalities with elevated arginine levels (arg/orn cit)
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If on TPN and elevated Leu, Met, Phe or Tyr, likely secondary to TPN. 5) If isolated, likely need to get plasma amino acids and ammonia level immediately with a clinical evaluation. 6) Therapy with dietary restriction of protein and specific formula.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) Symptoms can be spastic paraplegia, epileptic seizures, and severe mental retardation, growth retardation, episodic nausea and vomiting.
SERVICES	Consultation with a pediatric endocrinologist or geneticist is strongly encouraged for ongoing management.
REFERENCES	1) www.ncbi.nlm.nih.gov 2) www.savebabies.org/diseasedescriptions/argininemia 3) www.healthatoz.com/healthatoz/Atoz/ency/amino_acid_disorders

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Amino Acid Disorder
Argininosuccinic Aciduria (ASA)
(also known as Argininosuccinic Academia, Argininosuccinic Deficiency and Argininosuccinate Lyase Deficiency [ALD])

DEFINITION	Babies born with this disorder cannot metabolize or process amino acids properly. ASA is a disorder of the urea cycle. Patients with urea cycle disorders cannot convert nitrogen from protein into urea and get a build-up off ammonia and glutamine. Ammonia is toxic and can cause brain damage. Nitrogen in ammonia comes from protein in the food we eat or the breakdown of protein from the muscle when we are sick. ASA is one of the urea cycle disorders and is caused by deficiency of an enzyme called argininosuccinic acid lyase in the body. This prevents the conversion of ASA into arginine. The build up in ASA if too high ultimately causes a build up of ammonia.
INCIDENCE	1 in 70,000 live births
NBS ABNORMALITIES	1) Citrulline is elevated, may show elevated argininosuccinic peak 2) If any ASA is detected, infant needs STAT plasma amino acids, ammonia.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Along with NBS Abnormalities #2, infant needs to be seen that day. 5) Treatment consists of a low-protein diet, arginine supplementation to help complete the urea cycle, ammonia scavenging drugs in some cases and supplement carnitine if the patients have a secondary deficiency. Liver transplant offers a partial correction of the enzyme deficiency and improved metabolic status. Patients must avoid fasting and during stressors, like illness, need to supplement with high carbohydrates, non-protein calories to avoid catabolism.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) Neonatal onset presents in the first 2 to 3 days of life with vomiting, lethargy, respiratory alkalosis and hypothermia progressing to hyperammonemic encephalopathy, cerebral edema, hepatomegaly and death. 2) Late onset patients may present with non-specific mental retardation, seizures, hepatomegaly and/or skin and hair abnormalities, between a few months to years of age.
SERVICES	Patients should be counseled as to the considerable burden of care these patients represent.

REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) Iowa Protocol's and Practitioner's Manual 3) www.savebabies.org 4) http://my.webmd.com 5) www.emedicine.com 6) www.icomm.ca/geneinfo/asl.htm
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Amino Acid Disorder
Citrullinemia Type 1 (CTLN1)

DEFINITION	Babies born with these disorders cannot metabolize or process amino acids properly. The result is an amino acid and protein imbalance and buildup in the body. Citrullinemia is a rare inherited disorder caused by deficiency or lack of the enzyme argininosuccinate synthetase (ASS). This is one of six enzymes that play a role in the breakdown and removal of nitrogen from the body, a process known as the urea cycle. The deficiencies cause an excess of ammonia in the blood and body tissue. CTLN1 presents as a clinical spectrum ranging from an acute neonatal form (the classic form) to a milder late-onset from to a form without symptoms and/or hyperammonemia to a form in which women have onset of severe symptoms at pregnancy and postpartum. Newborn screening cannot differentiate Citrullinemia from ASA.
INCIDENCE	1 in 57,000
NBS ABNORMALITIES	1) Elevated citrulline
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Confirmatory diagnostic testing may include: • Plasma ammonia concentration • Plasma quantitative amino acids • Urine organic acids 5) Treatment may include: • High-caloric, protein-restrictive diet • Arginine supplement • Administration of sodium benzoate and sodium phenylacetate • Dialysis may be necessary in some affected individuals.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) This defect produces hyperammonemia, encephalopathy and respiratory alkolosis. 2) Infants are generally well for the first 24 to 72 hours, but then demonstrate: lethargy, poor feeding, vomiting, grunting respirations, tachypnea, hypothermia, seizures, cerebral edema, coma, apnea, and/or death if not treated. 3) Milder variants, asymptomatic individuals and intra-family variability have been reported.
SERVICES	Regularly scheduled appointments with health care provider and/or nutritionist.

REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) www.orpha.net 3) www.icomm.ca/geneinfo 4) http://my.webmd.com 5) www.genetests.org
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Amino Acid Disorders

Citrullinemia Type 2 (CTLN2)

Citrullinemia Type 2 - Adult Onset; Citrullinemia Type 2 - Neonatal Onset; Cholestasis, Neonatal Intrahepatic; Caused by Citrin Deficiency

DEFINITION	Babies born with these disorders cannot metabolize or process amino acids properly. The result is an amino acid and protein imbalance and buildup in the body. The neonatal cholestasis develops between 1 – 5 months of age. The adult onset is 11 – 64 years of age. CTLN2 is caused by citrin deficiency which leads to mild hyperammonemia and citrullinemia. It is not known why CTLN2 is milder and later in onset than CTLN1; distinguishing between these two disorders depends on mutation and/or enzyme testing
INCIDENCE	Unknown- majority of patients have been identified in Japan
NBS ABNORMALITIES	Elevated citrulline
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Treatment of choice is liver transplant in the adult form, it is not known if the neonatal form patients will go on to develop adult form. Neonatal symptoms tend to resolve with protein restrictions.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) Neonatal intrahepatic cholestasis has been diagnosed in over 70 infants between 1 and 5 months of age. They may have jaundice and fatty liver at biopsy. 2) Liver disease generally resolves by 1 year of age. 3) Three patients developed liver failure necessitating transplants before 12 months of age. 4) Among patients with CTLN2 presentation may be in childhood or adulthood (11 – 64 years). 5) Symptoms may be acute or develop gradually and include enuresis, delayed menarche, insomnia, night sweats and terrors, recurrent vomiting, diarrhea, tremors, confusion, lethargy, convulsions, delusions, hallucinations, and episodes of coma. 6) Hypercitrullinemia and hyperammonia are present.
SERVICES	
REFERENCES	1) Oregon Practitioner's Manual and Oregon Protocols 2) www.genetests.org

Amino Acid Disorder
Hypermethioninemia

DEFINITION	Hypermethioninemia is the term used to describe an abnormal elevation of plasma methionine that persists after the neonatal period in the absence of homocystinuria, can be due to prematurity. It is a metabolic disorder associated with cirrhosis, islet cell hyperplasia and renal tubular degeneration.
INCIDENCE	Unknown.
NBS ABNORMALITIES	Elevated levels of methionine.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If the baby is severely affected, may consider liver biopsy for diagnostic purposes. 5) Administration of L-methionine orally.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) Neonatal hepatitis 2) Neonatal cirrhosis
SERVICES	Consultation with a pediatric endocrinologist or geneticist is strongly encouraged for ongoing management.
REFERENCES	1) www.ncbi.nlm.nih.gov 2) www.savebabies.org/diseasedescriptions/hypermethioninemia.php 3) www.boehringer-ingelheim.es/workshop-methionina/anglesa/cap1.htm 4) http://pediatrics.aappublications.org/cgi/content/abstract/36/2/236

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Amino Acid Disorder
Tyrosinemia (TYR) – Type 1, 2 & 3

DEFINITION	Babies born with one of these disorders cannot metabolize or process amino acids properly. The result is an amino acid and protein imbalance and buildup in the body. Tyrosinemia is an inborn error of metabolism. Early treatment helps prevent brain damage, mental retardation, coma, seizures and autistic-like disorders. Affected persons commonly develop cirrhosis of the liver and will eventually require liver transplantation to survive.
INCIDENCE	1 of every 100,000 live births. Both sexes affected equally.
NBS ABNORMALITIES	Abnormalities with TYR/Phe
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If on TPN – then repeat newborn specimen when off TPN 5) If not on TPN, but other levels elevated, likely from liver disease, can do plasma amino acids. 6) Treatment includes a diet low in phenylalanine, methionine, and tyrosine. 7) Therapy with NTBC blocks the formation of toxic metabolites. 8) Transient tyrosinemia, may in some cases be treated with protein restriction to 2g/kg/day and administration of ascorbic acid (50-200 mg/day orally for 1-2 weeks) to infants found to have elevated tyrosine. If infant is breastfeeding, ascorbic acid alone may be administered.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding.
CHARACTERISTICS	1) Clinical features involve only the skin, eyes and central nervous system. Clinical onset is variable. Skin and eye symptoms often present within the first year of life and include excessive tearing, photophobia, eye pain and redness, and skin lesions. Presentation at infancy includes vomiting, lethargy, diarrhea and failure to thrive. 2) The clinical presentation of this form is not well known. Transient tyrosinemia: elevated tyrosine levels in a healthy newborn with no liver, renal or skin abnormalities. Risk factors include prematurity, high protein intake and deficient intake of Vitamin C. 3) The severest form of the disease causes symptoms within the first months of life including poor weight gain, enlarged liver and spleen, swelling of the legs and increased tendency of bleeding.
SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis and ongoing management.

REFERENCES	1) www.fodsupport.org 2) www.jiulsite.com 3) www.umdf.org 4) www.clinchem.org 5) Iowa Neonatal Metabolic Screening Program 6) Oregon Neonatal Metabolic Screening Program
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Organic Acid Disorders

2-Methyl Butyryl-CoA Dehydrogenase Deficiency (2MBDH Deficiency)

(Short/Branched Chain Acyl-CoA Dehydrogenase Deficiency; 2-Methylbutyrylglycinuria)

DEFINITION	Organic aciduria and fatty acid metabolism defect.
INCIDENCE	1) Rare, less than 20 patients identified. 2) Increased in the Hmong population with frequency about 1 in 500 live births.
NBS ABNORMALITIES	C5 isovaleryl-carnitine elevated.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Treatment: • Protein restriction • Carnitine supplement • Avoid fasting
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	Symptoms onset is in infancy and childhood, but several asymptomatic individuals have been identified. 1) Symptoms noted in one enzyme confirmed patient included neonatal onset of hypotonia, lethargy and apnea, and hypoglycemia. 2) Another patient presented in the second year of life with motor delay, muscular atrophy and strabismus. 3) A sibling identified prenatally and 8 Hmong patients identified prospectively by newborn screening have remained asymptomatic on treatment.
SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child.
REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) www.ncbi.nlm.nih.gov

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Organic Acid Disorders
3-Methylcrotonyl-CoA Carboxylase Deficiency (3-MCC)
(3-MCC; 3-Methylcrotonylglycinuria)

DEFINITION	Babies born with an organic acid disorder have a chemical imbalance in their body that can be toxic. Organic acids play an important role in the breakdown of fats, sugars and protein for the body's use and storage. 3-MCC is a defect in the breakdown of Leucine. The symptoms are caused by a buildup of methylcitrate and methylsuccinate in the body fluids.
INCIDENCE	1:50,000
NBS ABNORMALITIES	3-OH – elevated
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Confirmatory testing • Urine organic acids • Plasma Acylcarnitine profile with free and total carnitine levels • Urine acylglycines 5) Treatment when confirmed • Supplement with biotin 5mg/day • Carnitine supplementation if carnitine levels are low
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	Symptoms onset is generally after 3 months of age, but can be variable. Many individuals with no symptoms into adulthood. 1) Some infants have presented with a Reye-like illness with hypoketotic hypoglycemia, metabolic acidosis and liver dysfunction often precipitated by an intercurrent illness, which has led to liver failure and death in some cases. 2) Others present with muscle hypotonia and failure-to-thrive in conjunction with recurrent episodes of vomiting and diarrhea. 3) In general, the earlier presentation the poorer the prognosis.
SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child. Aggressive management of vomiting illnesses, treat acidosis and dehydration with IV fluids.

REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) Iowa Protocol's and Practitioner's Manual 3) www.ncbi.nlm.nih.gov 4) www.oaanews.org

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Organic Acid Disorders

3-Methylglutaconyl-CoA Hydratase Deficiency (3MGH Deficiency)

(3-Methyglutaconic Aciduria Type 1; 3-MG-CoA-Hydratase Deficiency; MGA, Type 1)

DEFINITION	Organic aciduria.
INCIDENCE	Rare, less than 20 cases described.
NBS ABNORMALITIES	C5-OH methylcrotonyl carnitine – elevated.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 3) Consult with metabolic consultant. 4) Carnitine supplementation. 5) Modest leucine restriction may be beneficial for these children, especially if diagnosed pre-symptomatically.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	Symptoms range from minimal to severe. Two different phenotypes have been identified. Symptom onset is variable from minimal to severe. 1) Mildly affected individuals have had speech retardation, short attention span. 2) Severely affected individuals have presented with acidosis, hypotonia, hepatomegaly; microcephaly, macrocephaly, spastic quadriplegia, dystonia, atrophy of the basal ganglia, insomnia, irritability, self-mutilation, crying fits, dementia; enuresis, developmental delay, coma and gastroesphageal reflux disease. 3) Fasting has produced hypoglycemia and acidosis in some patients. 4) The neurological changes on MRI have been progressive in some patients even when clinically stable and on therapy.
SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child .
REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) www.ncbi.nlm.nih.gov

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Organic Acid Disorders

Beta-Ketothiolase Deficiency (Ketone Utilization Disorder)

(Mitochondrial Acetoacetyl-CoA Thiolase Deficiency, B-KT/3-Ketothiolase)

DEFINITION	Babies born with an organic acid disorder have a chemical imbalance in their body that can be toxic. Organic acids play an important role in the breakdown of fats, sugars and protein for the body's use and storage. An enzyme is a substance in the body that enables chemical reaction to occur. The enzyme missing in ketone utilization disorder would normally help the body break down proteins from foods, and proteins stored in the body. Since children with this disorder lack this enzyme, they are unable to break down proteins, causing toxic build-up in body tissues. Ketone utilization disorder is an inherited metabolic problem. Children born with this disorder must follow a strict food pattern (another term for diet) limiting protein in order to stay healthy. Mean age at presentation is 15 months (range is 3 days to 48 months). There are documented cases of asymptomatic patients with enzyme deficiency. Frequency of decompensation attacks falls with age and is uncommon after age of 10. Infancy is the period of highest risk for decompensation.
INCIDENCE	Rare. Incidence is unknown and no known specific ethnic predisposition.
NBS ABNORMALITIES	Elevated C5OH and C5:1
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) For confirmatory diagnosis, get urine organic acids and plasma acylcarnitine profile ASAP. 5) Treatment: • IV glucose and bicarbonate during crisis episodes. • The family should monitor urinary ketones to be alert for impending metabolic crisis. • There are 3 parts to successful treatment of ketone utilization defect: 1. A low protein food pattern. This is ***not*** a protein-free food pattern. The most effective treatment for ketone utilization disorder is a food pattern low in protein. The body needs small amounts of protein to function properly. The amount of protein which can be tolerated ranges from child to child. Frequent visits to the health provider and/or nutritionist are recommended to be sure the food pattern is appropriate for your child. Meals and snacks should not be delayed or skipped. 2. Supplementation forms of carnitine and/or bicitra. Carnitine is essential for muscle energy production and helps transport fat to cells in the body where it can be converted into energy. Bicitra is a compound which helps your child maintain what is called an acid-base balance in the blood. These compounds also help decrease harmful by-products of normal protein breakdown. Check with your health care provider to see if these medications are needed.

	3. Immediate contact with your child's health provider when illness occurs. Your child with ketone utilization disorder will need to take special precautions during times when your child gets a cold or flu. Typical childhood illnesses can the body to break down its own sources of protein, causing toxic protein build up. To prevent this, give you child fluids and foods with extra energy, but no protein. Extra energy foods, such as sugar, will decrease the amount of protein break down by the body. Feeding an ill child can sometimes be difficult, as sick children often have very little appetite. Encourage drinking of fluids as much as possible. Many children enjoy popsicles or drinks which are frozen, then chipped into ice chunks. **Always call your child's health provider when your child is vomiting, has diarrhea, has an infection, or has a fever of more than 101 degrees Fahrenheit.** 6) With early diagnosis and treatment, apparently normal development occurs.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) Symptoms if untreated: • Episodic metabolic ketoacidosis • Vomiting and diarrhea • Coma and death possible • Mental retardation, dystonia • Cardiomyopathy • Poor weight gain • Short stature • Renal failure
SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child.
REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) Ketone Utilization Disorder – a Guide for Parents. Sponsored by the Pacific Northwest Regional Genetics Group. 3) www.med.gazi.edu.tr/gmj/betaketo.html 4) http://pediatrics.aappublications.org/cgi/content/abstract/53/2/221 5) www.pdg.cnb.uam.es/UniPub/iHOP/gg/86173.html 6) www.ncbi.nlm.nih.gov 7) www.orpha.net/data/patho 8) http://wchs.health.wa.gov.au/health/b/beta_prof.htm
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Organic Acid Disorders
Glutaric Acidemia Type 1 (GA1)
Glutaryl-CoA Dehydrogenase Deficiency

DEFINITION	Babies born with an organic acid disorder have a chemical imbalance in their body that can be toxic. Organic acids play an important role in the breakdown of fats, sugars and protein for the body's use and storage. GA1 is an inborn error in the metabolism of lysine, hydroxylysine and tryptophan. The progressive neurological manifestations and acute metabolic episodes characteristic of this disorder are the result of the build up of glutaric acid in the brain and other tissues.
INCIDENCE	1 in 40,000 in caucasians and 1 in 30,000 in Sweden
NBS ABNORMALITIES	Elevated C5 DC
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Get STAT urine organic acids, plasma free and total carnitine levels and plasma acylcarnitine. 5) Dietary restriction of lysine (very low protein diet with lysine free metabolic formula). * The diet should provide only enough natural protein (including the offending amino acids) to support adequate growth; any more may lead to the accumulation of toxic intermediate compounds and can precipitate metabolic instability. 6) Riboflavin and carnitine supplement upon receipt of presumptive positive result until confirmed or ruled out 7) Hospital admission is mandatory for IV fluids with any vomiting illness. Treatment with IV fluids, glucose, and bicarbonate during illness are indicated.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) 70% of patients have macrocephaly at or shortly after birth. 2) There may be soft neurologic signs like jitteriness, irritability and truncal hypotonia in the newborn period. 3) After a period of normal development, the disorder may appear suddenly and present as hypotonia, seizures, fisting, dystonia, rigidity and loss of head control secondary to basal ganglia injury. 4) The clinical progression may result in a form of cerebral palsy. 5) Without early diagnosis and dietary restrictions, affected individuals may have central nervous system degenerations and episodes of metabolic acidosis, vomiting, coma, convulsions and hepatomegaly. No loss of intellectual function.
SERVICES	These babies should have regularly scheduled visits at the metabolic clinic.

REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) Iowa Protocol's and Practitioner's Manual 3) www.epeconline.com 4) www.meadjohnson.com 5) http://pediatrics.aappublications.org 6) www.glutaricacidemia.org 7) www.ncbi.nlm.nih.gov 8) www.oaanews.org
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Organic Acid Disorders

Glutaric Acidemia Type 2 (GA2)

Glutaric Aciduria Type 2; Ethylmalonic – Adipic Aciduria; Electron Transfer Flavoprotein Dehydrogenase Deficiency; ETF/ETF QO Deficiency

DEFINITION	Babies born with an organic acid disorder have a chemical imbalance in their body that can be toxic. Organic acids play an important role in the breakdown of fats, sugars and protein for the body's use and storage. Individuals with GA2 have an enzyme that does not work properly. Enzymes are substances in the body that enable chemical reactions to occur. GA2 is a disorder of fatty acid, amino acid and chlorine metabolism. Individuals with GA2 are unable to completely break foods or body stores into fats and proteins for energy use.
INCIDENCE	Not a rare disease, but incidence is unknown.
NBS ABNORMALITIES	1) Elevated C5 DC 2) C4, C5, C6, C8, C10 – multiple elevations 3) C6 hexanoyl carnitine – mild elevations 4) C8 octanoyl carnitine – elevated 5) C16;C18:1 – multiple elevations
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) This has been implicated as a cause for SIDS. 5) Mothers have been reported with HELLP syndrome. 6) Urine organic acids may only be abnormal during acute episodes. 7) Treatment of the severe neonatal presentations is not effective. 8) Treatment for GA2 often includes eating frequently and a diet high in CHO, low in protein, and low in fat. 9) In addition, supplements with riboflavin, glycine, and carnitine may be helpful. 10) There are three parts to a successful treatment of GA2: • A high-carbohydrate, low fat, low-protein, food pattern. Although children with glutaric academia type 2 can't turn fats and proteins into energy very well, their bodies can use carbohydrates for energy. This means your child should eat foods with very little fat or protein in them, since he or she lacks one of the enzymes needed to break these foods down. Instead, your child should eat plenty of carbohydrates in order to get enough calories for energy. It should be noted that this is ***not*** a fat-free or protein-free food pattern, but simply ***low*** in fats and proteins. Your child's body needs small amounts of fats and proteins to function properly, so these should never be completely eliminated from the diet. Your health provider and nutritionist can help you create a food pattern that will ensure your child will be well nourished.

	• Supplementation forms of carnitine and/or riboflavin. Carnitine is essential for muscle energy production, and helps transport fat to cells in the body where it can be converted into energy. Riboflavin is a very important vitamin that helps the body carry out many chemical reactions. Children with GA2 may be lacking these nutrients. The use of these supplements varies with the needs of each individual child. Contact your health provider to see if these treatments are appropriate for your child. • Immediate contact with your child's health provider when illness occurs. All children become ill at times, whether or not they have GA2. Sometimes they catch a cold, the flu, or something more severe. Your child with GA2 will need to take special precautions during these times. Typical childhood illnesses can cause harmful glutaric acid to build up in the body, because the body is breaking down its own sources of fat and protein source of energy. This can create toxic build-up in tissues. During these times, be sure to give your child extra fluids to help the body get rid of excess glutaric acid. Give you child fluids and foods with extra calories, but no protein. Extra energy foods, such as sugar, will decrease the body's need to break down more protein. Feeding an ill child can sometimes be difficult, as sick children often have very little appetite. Encourage drinking fluids as much as possible. Many children enjoy popsicles or drinks which are frozen, then chipped into ice chunks. **Always call your child's health provider when your child is vomiting, has diarrhea, has an infection, or has a fever of more than 101 degrees Fahrenheit.**
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	Three different phenotypes that stay consistent within families: 1) Neonatal onset with congenital anomalies: Infants often premature, present during the first 24 to 48 hours of life with hypotonia, hepatomegaly, hypoglycemia, metabolic acidosis, sweaty feet odor, kidneys are often palpably enlarged and cystic, facial dysmorphisms, rocker-bottom feet, muscular defects of the anterior abdominal wall and anomalies of the external genitalia (hypospadias and chordee). Virtually all die within the first week of life. 2) Neonatal onset without anomalies: Infants develop problems within the first few days of life with hypotonia, tachypnea, metabolic acidosis, hepatomegaly, hypoglycemia, and sweaty feet odor. The few who have survived beyond the first week of life have died within a few months usually with severe cardiomyopathy. A few others have been hypoglycemic as newborns and later developed typical episodes of Reye syndrome-like illness and have survived somewhat longer. 3) Mild or late onset: Mild or late onset is extremely variable in its course and age at presentation, but typically include episodes of hypoketotic hypoglycemia and hepatic dysfunction. There is progressive lipid storage myopathy and carnitine deficiency and few had progressive extrapyramidal movement disorders similar to GA1. There are reports of asymptomatic adults.
SERVICES	These babies should have regularly scheduled visits at the metabolic clinic.

REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) Iowa Protocol's and Practitioner's Manual 3) www.epeconline.com 4) www.meadjohnson.com 5) http://pediatrics.aappublications.org 6) www.glutaricacidemia.org 7) www.ncbi.nlm.nih.gov
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Organic Acid Disorders
Isobutyryl – CoA Dehydrogenase Deficiency (IBD)
(Acyl-CoA Dehydrogenase Family, Member 8)

DEFINITION	Isobutyryl – CoA Dehydrogenase Deficiency is an inborn error of valine metabolism. The disorder is caused by a deficiency in the enzyme isobutyryl – CoA dehydrogenase.
INCIDENCE	Rare, less than 5 cases.
NBS ABNORMALITIES	C4 butyryl carnitine – isolated elevation
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Treatment is carnitine therapy to reverse the cardiomyopathy. 5) Treat with moderate protein restriction to reduce valine intake and avoid fasting.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) There is variable detection of this disorder during the immediate newborn period.
CHARACTERISTICS	1) Onset of symptoms is at 12 months of age. 2) Initial patient presented with dilated cardiomyopathy, low carnitine and anemia. Was small for age at presentation, but normal growth resumed with treatment. 3) A three-year old, identified as a newborn through screening, has remained asymptomatic.
SERVICES	These babies should have regularly scheduled visits at the metabolic clinic.
REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) Iowa Protocol's and Practitioner's Manual 3) www.ncbi.nlm.nih.gov 4) www.ingentaconnect.com 5) www.oaanews.org

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Organic Acid Disorders
Isovaleric Acidemia/Aciduria (IVA)
Isovaleric Acid CoA Dehydrogenase Deficiency (IVD)

DEFINITION	Babies born with an organic acid disorder have a chemical imbalance in their body that can be toxic. Organic acids play an important role in the breakdown of fats, sugars and protein for the body's use and storage. Isovaleric Acidemia is a hereditary metabolic disorder. It is characterized by a deficiency of the enzyme isovaleryl CoA dehydrogenase. The disorder occurs in both an acute and a chronic intermittent form. Isovaleryl CoA is itself a breakdown product of leucine which is an essential amino acid found in protein containing foods.
INCIDENCE	Uncertain, 1 in 230,000
NBS ABNORMALITIES	Elevated C5 isovaleryl carnitine
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Treatment: • Low-protein diet with restricted leucine intake, in combination with glycine and carnitine supplements. 5) Glycine and carnitine allow for the nontoxic removal of excess isovaleric-CoA. 6) Patients will often self-select low protein diet.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) Onset of symptoms usually occur within the first 14 days of life in the acute form and later in the chronic form. 2) Infants with acute neonatal form present after a few days of normalcy with poor feeding, vomiting, severe metabolic keto-acidosis, progressing to coma and death. Dehydration, hyperammonia, hypocalcemia, hepatomegaly and hyper/hypoglycemia are often present. Depressed bone marrow function with neutropenia, thrombocytopenia and pancytopenia can lead to infection and/or cerebral hemorrhage. Most, but not all, will have the characteristic odor of "sweaty socks" which comes from the accumulation of isovaleryl acids. 3) The chronic intermittent form presents later in infancy or childhood with episodes of metabolic acidosis as described above, usually associated with an intercurrent illness or increased protein load. Pancreatitis has occurred in a number of patients. The different forms can occur in the same family, so are not related to genotype.
SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child .

REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) www.icomm.ca/geneinfo/isovacid 3) www.savebabies.org/diseasedescription/iva.php
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Organic Acid Disorders

Methylmalonic Acidemia, Vitamin B12 Non-Responsive (MMA)

(Methylmalonic Aciduria due to MethylmalonicCoA Mutase Deficiency; Methylmalonicaciduria due to MCM Deficiency; MMA due to MCM Deficiency; MCM Deficiency; Complementation Group mut; Methymalonyl CoA Mutase, Included; MUT, included)

DEFINITION	MMA is an inherited disorder of organic acid metabolism caused by a defect in the conversion of methylmalonyl-CoA to succinyl-CoA.
INCIDENCE	1 in 48,000 live births.
NBS ABNORMALITIES	1) C3 propionyl carnitine – elevated 2) C4 DC methylmalonyl carnitine – elevated
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Treatment regimens include: protein-restricted diet and OH-CbL injections as soon as diagnosis of MMA is suspected. 5) Supplement with carnitine. 6) Oral antibiotic therapy may be useful to decrease gut production of propionate. 7) Liver transplant or combined liver/kidney transplant are options for metabolic control. 8) Any type of transplant is limited because MMA enzyme is in all tissues and the transplants do not affect the levels made in the cerebral spinal fluid and brain.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) Most common signs and symptoms are: lethargy, failure to thrive, recurrent vomiting, dehydration which can lead to profound metabolic acidosis, respiratory distress, hypotonia and/or death if not recognized. 2) Complications of acute episodes can include: metabolic stroke, extrapyramidal signs, dystonia, bilateral lucencies of globus pallidus. 3) Survivors may have significant neurological damage. 4) Renal failure may appear during childhood. 5) Patients do not have to have a clinical crisis in order to have neurological or other organ system compromise.
SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child .

REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) www.ncbi.nlm.nih.gov

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Organic Acid Disorders

Methylmalonic Acidemia, Vitamin B12 Responsive (MMAA)

(Methylmalonicaciduria, Vitamin B12-Responsive, due to Defect in Synthesis of Adenosylcobalamin, cblA Complementation Type; Methylmalonicaciduria, cblA Type; MMAA; Methylmalonicaciduria, Vitamin B12-Responsive, due to Defect in Synthesis of Adenosylcobalamin, cblB Complementation Type)

DEFINITION	MMAA is a genetically heterogenous disorder of methylmalonic aciduria and cobalamin (Vitamin B12) metabolism.
INCIDENCE	1 in 75,000 births (Australia).
NBS ABNORMALITIES	1) C3 propionyl carnitine – elevated 2) C4 DC methylmalonyl carnitine – elevated
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Treatment includes: • Low-protein diet • Vitamin B12 for responsive forms • Carnitine supplement. • Oral antibiotic therapy may be useful to decrease gut production of propionate. 5) The body makes the majority of the odd chain fatty acids and cholesterol so they cannot be limited solely by manipulating the diet. However, using special formulas that are deficient in these amino acids can decrease the problematic metabolic precursors.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) Symptoms may include: stomatitis, glossitis, convulsions and/or developmental delay. 2) Symptoms if untreated: episodic metabolic ketoacidosis, hyperammonia, vomiting, feeding problems, coma and death possible, mental retardation and/or later onset and milder forms occur.
SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child .
REFERENCES	1) Oregon Practitioner's Manual and Protocols 2) www.ncbi.nlm.nih.gov

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Organic Acid Disorders
Multiple CoA Carboxylase Deficiency
Holocarboxylase Synthetase Deficiency; Multiple Carboxylase Deficiency, Neonatal Form

DEFINITION	This is a group of disorders where there is an absence or deficiency of an enzyme that is needed to breakdown proteins (amino acids). This prevents the body from being able to use them for growth and repair and leads to build up of chemicals, usually acids, in the body.
INCIDENCE	1 in 87,000 live births
NBS ABNORMALITIES	Elevated C3 propionyl carnitine, elevated 3-OH isovalerylcarnitine, elevated C5-OH methylcrotonyl carnitine
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Confirmatory testing may include: • Urine organic acids • Serum electrolytes • Blood ammonia 5) Children with holocarboxylase synthetase deficiency, treated with biotin have normal growth and development. However, some only respond to therapy and one has been reported to be unresponsive to biotin therapy. Biotin increases the functional activation of the carboxylase enzymes.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) The symptom onset can occur from birth to 15 months of age. 2) Infants generally present with food refusal, vomiting, breathing problems, hypotonia, seizures and lethargy. 3) Severe metabolic/lactic acidosis, organic aciduria, mild hyperammonia and variable hypoglycemia can lead to coma and death if not treated. 4) Survivors can have neurological damage. 5) Patients may have skin rash and alopecia at later stages.
SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child .
REFERENCES	1) Oregon Practitioner's Manual and Protocols

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Organic Acid Metabolism Disorders
Propionic Acidemia (PA)

DEFINITION	Babies born with an organic acid disorder have a chemical imbalance in their body that can be toxic. Organic acids play an important role in the breakdown of fats, sugars and protein for the body's use and storage. Propionic academia (PA) is an inherited genetic disorder in which the body is unable to process certain proteins and lipids (fats) properly. The condition, which usually appears in early infancy, is characterized by poor feeding, vomiting, weak muscle tone (hypotonia) and lethargy. The effects of propionic academia can be life threatening.
INCIDENCE	Occurs in about 1 in 100,000 live births in the United States. The condition appears to be more common in Saudi Arabia, with a frequency of 1 in 2,000 to 5,000 people.
NBS ABNORMALITIES	1) C3 elevated 2) Elevated C3/C2 ratio.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If C3 elevated with elevated C3/C2, then need baby evaluated in E.R. STAT. 5) Treatment for propionic acidemia includes dietary protein restriction and often calls for supplementation by medical foods. Fluids and electrolyte therapy may be needed by some individuals. In addition, acidosis can be resolved by sodium bicarbonate. In some individuals, secondary carnitine deficiency is likely to occur, requiring supplementation. 6) Most patients are so ill at presentation that they already have been admitted to a hospital, which should facilitate appropriate diagnosis and treatment. 7) Since the usual major metabolic precursors of PA are the essential amino acids, isoleucine, valine, threonine, and methionine, strop all protein ingestion and emphasize alternative sources of calories on a temporary basis. 8) Ketoacidosis is treated best with increased carbohydrate calories, bicarbonate replacement and increased fluids to enhance excretion. In very severely ill patients, metabolic reversal can be expedited by an insulin drip with extra glucose, but this should only be in an I.C.U. setting. 9) Reinstate protein feeding after the patient's condition has normalized at a level of protein no greater than 1.5 g/kg/d. From this point, the patient should be under the care of a biochemical geneticist who may prescribe a special diet prior to discharge. 10) Appropriate dietary management is the mainstay of treatment. Several commercially produced formulas are available that provide a protein supplement without any of the 4 amino acids that result in propionate production. However, since they all are essential in humans, closely monitored quantities of isoleucine, valine, threonine, and methionine must be added. For this reason, collaboration between the biochemical geneticist and nutritionist is imperative.

SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Unable to differentiate between methylmalonic aciduria and propionic aciduria on newborn screening
CHARACTERISTICS	1) Symptoms of PA can include protein intolerance, vomiting, failure to thrive, lethargy and profound metabolic acidosis. 2) If not treated early, brain damage, including coma and generalized seizures and death can occur. 3) Symptoms most commonly become apparent during the first weeks of life and may include abnormally diminished muscle tone, poor feeding, dehydration and seizures. 4) Often these infants will require a g-tube to get adequate calories.
SERVICES	Periodic consultations with a geneticist and nutritionist is strongly encouraged.
REFERENCES	1) www.emedicine.com 2) http://my.webmd.com 3) www.drgreene.com 4) www.pafoundation.com 5) www.savebabies.org 6) http://ghr.nlm.nih.gov/condition=proprionicacidemia 7) Oregon Practitioner's Manual 8) University of Iowa Practitioner's Manual
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Fatty Acid Oxidation Disorder
2,4 Dienoyl CoA Reductase Deficiency

DEFINITION	An enzyme defect related only to unsaturated fatty acid oxidation. The 2-trans 4-cis-decadienoylcarnitine is derived from incomplete oxidation of linoleic acid.
INCIDENCE	Very rare.
NBS ABNORMALITIES	1) Newborn screening 2) Urine and plasma organic acids.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Supplement with L-carnitine and changing the dietary fat to mainly medium-chain triglyceride.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) Hypotonic 2) Feeding difficulties 3) May be hypotonic 4) May have small ventricular septal defect 5) Short trunk, arms and fingers with small feet and a large face.
SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child.
REFERENCES	1) www.savebabies.org/diseasedescriptions/24dienoylcoareductase.php 2) www.jbc.org/cgi/content/full/273/1/349 3) www.ncbi.nlm.nih.gov 4) www.pubmedcentral.nih.gov/artclerender.fcgi?artid=296625

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Fatty Acid Oxidation Disorder

3-Hydroxy 3-Methylglutaryl-CoA Lyase Deficiency (HMG)

(Hydroxymethylglutaric Aciduria; HMG-CoA Lyase Deficiency; HL Deficiency; Hydroxymethylglutaric Aciduria)

DEFINITION	Babies born with one of these disorders cannot metabolize or process amino acids properly. The result is an amino acid and protein imbalance and build-up in the body. This deficiency is an inborn error of leucine and ketone body metabolism. Patients with this disorder are unable to properly break down leucine, an amino acid found in all proteins.
INCIDENCE	1) Unknown, rare. 2) Ethnic incidence – increased in Saudi Arabia
NBS ABNORMALITIES	1) Elevated C5-OH methyl-crotonyl carnitine 2) Elevated C5OH 3) C6OH/DC – elevated 4) C6-DC methyl-glutaryl – elevated
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If diagnosed early, treated patients may have normal development. 5) If this disorder is untreated, it is likely to result in death during childhood. 6) Treatment consists of: • Leucine restriction combined with general protein restriction. • Fat intake restriction. • Avoid fasting with a high CHO diet. • Carnitine supplementation has been used, but efficacy unknown.
SCREENING PRACTICE CONSIDERATIONS	2) Presumptive positive screens should be confirmed as soon as possible.
CHARACTERISTICS	1) About 1/3 present in neonatal period (2 to 5 days) and about 2/3 present between 3 and 11 months. There are reports of asymptomatic individuals detected because of an affected sibling. 2) Clinical features may include: metabolic acidosis, hypoglycemia, tachypnea, vomiting, hypoonia, lethargy, hepatomegaly, and/or hyperammonia 3) Episodes can be precipitated by fasting, infections, protein loading and the fetal neonatal transition. 4) Without early diagnosis and treatment, coma and death can occur. 5) Clinical presentation may be similar to Reye syndrome. 6) Typically appear normal between episodes.

SERVICES	Frequent visits to the health care provider and/or nutritionist are recommended to be sure the food pattern is appropriate for child.
REFERENCES	1) Iowa Practitioner's Manual and Protocols 2) Oregon Practitioner's Manual and Protocols 3) www.newbornscreening.info 4) www.ncbi.nlm.nihgov/
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Fatty Acid Oxidation Disorder
Carnitine Acylcarnitine Translocase Deficiency (CACT)

DEFINITION	Babies born with fatty acid oxidation disorders are unable to break down stored fats into energy. Energy from fat keeps the body running whenever it runs out of its main source: glucose. CACT is an inborn error of fatty acid oxidation caused by a deficiency in the carnitine acylcarnitine translocase enzyme. This enzyme is critical for mitochondrial acylcarnitine transport. The mitochondrial B-oxidation pathway plays a major role in energy production, especially during periods of fasting.
INCIDENCE	Unknown. Disorder is very rare.
NBS ABNORMALITIES	Abnormality with C16
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Confirmation, diagnosis and ongoing management with Pediatric Endocrinologist (Dr. Alan Kenien at 701.234.2431).
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding.
CHARACTERISTICS	1) Symptoms include cardiomyopathy, seizures, coma and apnea.
SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis and ongoing management.
REFERENCES	1) www.fodsupport.org 2) www.jiulsite.com 3) www.umdf.org 4) www.clinchem.org 5) Iowa Neonatal Metabolic Screening Program

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Fatty Acid Oxidation Disorder
Carnitine Palmitoyl Transferase Deficiency – Type 1 (CPT1)

DEFINITION	Babies born with fatty acid oxidation disorders are unable to break down stored fats into energy. Energy from fat keeps the body running whenever it runs out of its main source: glucose. CPT is an inborn error of fatty acid oxidation caused by a deficiency of the enzyme carnitine palmitoyl transferase. Deficiency of this liver enzyme results in a failure of acylcarnitine formation. The mitochondrial B-oxidation pathway plays a major role in energy production, especially during periods of fasting.
INCIDENCE	Unknown. Is a rare disorder, increased in the Hutterite community.
NBS ABNORMALITIES	Abnormalities occur with C0/C16, C0/C18
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Have attending physician order: - Free and total carnitine levels - Acylcarnitine profile 5) For confirmatory diagnosis, order skin biopsy for CPT 1 enzyme activity. 6) Avoid fasting, MCT oil supplement and anoid dietary long-chain fatty acids
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding.
CHARACTERISTICS	1) Usually presents between 8 – 18 months, but a few have presented in the first weeks of life. 2) Initial symptoms have occurred with or after episodes of fasting, infection or diarrhea. 3) Clinical presentation includes hypoketotic hypoglycemia, hepatomegaly, coma and seizures. This can lead to death if not recognized and treated aggressively. 4) Hepatic dysfunction with elevated ammonia and enzymes is common. 5) Renal tubular acidosis and transient hypertriglyceridemia has also been seen.
SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis and ongoing management.

REFERENCES	1) www.fodsupport.org 2) www.jiulsite.com 3) www.umdf.org 4) www.clinchem.org 5) Iowa Neonatal Metabolic Screening Program 6) Oregon Neonatal Metabolic Screening Program
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Fatty Acid Oxidation Disorder
Carnitine Palmitoyl Transferase Deficiency – Type 2 (CPT2)

DEFINITION	Babies born with fatty acid oxidation disorders are unable to break down stored fats into energy. Energy from fat keeps the body running whenever it runs out of its main source: glucose. CPT 2 is a disorder in which the body cannot oxidize fatty acids. This disorder is caused by a deficiency of the liver enzyme carnitine palmitoyl transferase. This deficiency results in a failure of acylcarnitine formation. The mitochondrial B-oxidation pathway plays a major role in energy production during periods of fasting.
INCIDENCE	Unknown
NBS ABNORMALITIES	Abnormalities occur with C16. Usually associated with low/normal C0 levels if real disease.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If elevated together with low C0 then need STAT: - Plasma acylcarnitine - Free and total carnitine levels 5) Make sure infant is eating every 2-4 hours. 6) If on formula, consider switching to Pregestamil. If breastfeeding, wait until have results.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding.
CHARACTERISTICS	1) Fasting may trigger symptoms. 2) The classic form presents with episodic muscle weakness, pain and myoglobinuria usually prompted by prolonged exercise, fasting, infection, and stress or cold exposure. 3) These infants usually have dysmorphic features including cystic renal dysplasia, cataracts and neuronal migration defects, specifically brain dysplasia and/or intracerebral calcifications. These patients usually die in the first month of life. 4) The major symptoms are myalgia, skeletal and/or cardiac muscle weakness, fatigue and reddish-brown urine.
SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis and ongoing management.

REFERENCES	1) www.fodsupport.org 2) www.jiulsite.com 3) www.umdf.org 4) www.clinchem.org 5) Iowa Neonatal Metabolic Screening Program 6) Oregon Neonatal Metabolic Screening Program
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Fatty Acid Oxidation Disorder
Long-Chain Acyl-CoA Dehydrogenase Deficiency (LCADD)

DEFINITION	LCAD is a rare genetic disorder of fatty acid metabolism. It is characterized by hypoglycemia, muscle weakness and hepato, and cardiomegaly.
INCIDENCE	Unknown
NBS ABNORMALITIES	Abnormalities with C18:1-0H, C14-0H, C16:1, C16, C16-0H/C16, C18, C18:1
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with a metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If all Carnitines or a couple are elevated we need to treat like a real disease and get STAT: * Plasma acylcarnitine profile with free and total carnitine levels. * Make sure infant is eating every 2-4 hours and consider if on formula, switching to Pregestamil. If breastfeeding, wait until have results. 5) Avoidance of fasting. 6) High carbohydrate intake. 7) Low long-chain fats.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding.
CHARACTERISTICS	1) Affected infants typically begin to experience sudden (acute) usually recurrent symptom episodes provoked by stress, such as with fasting and/or during infection. 2) Episodes may be characterized by low blood sugars, sudden cessation of breathing and/or the pumping action of the heart, listlessness (lethargy) and coma and/or other abnormalities. 3) Additional characteristic findings may include hypertrophy, cardiomyopathy, hepatomegaly, hypotonia. 4) May present with SIDS.
SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis and ongoing management. 2) Parents should be instructed to carry emergency protocol letter from physician.

REFERENCES	1) www.ncbi.nlm.gov 2) www.emedicine.com/ped/topic1284.htm 3) www.icomm.ca/geneinfo/lcad.htm 4) www.pedresearch.org/cgi/content/abstract/30/3/211 5) http://oxmedinfo.jr2.ox.ac.uk/Pathway/Disease/37646.htm

Fatty Acid Oxidation Disorder
Long-Chain Hydroxy Acyl-Co-A Dehydrogenase Deficiency/3-Hydroxyacyl CoA Dehydrogenase Deficiency (LCHADD)

DEFINITION	Babies born with fatty acid oxidation disorders are unable to break down stored fats into energy. Energy from fat keeps the body running whenever it runs out of its main source: glucose. Metabolic crisis can occur during periods of fasting and can cause episodes of hypoglycemia, vomiting, coma and even death.
INCIDENCE	Unknown
NBS ABNORMALITIES	Elevations in C18:1-0H, C14-0H, C16:1, C16, C16-0H/C16, C18, C18:1or pattern of elevations
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If all Carnitines or a couple are elevated we need to treat like a real disease and get STAT: * Plasma acylcarnitine profile with free and total carnitine levels. * Make sure infant is eating every 2-4 hours and consider if on formula, switching to Pregestamil. If breastfeeding, wait until have results. 5) Fasting should be avoided and a high-carbohydrate diet with frequent feedings followed. 6) Intake of long-chain fatty acids should be limited. 7) The diet should be supplemented with MCT oil - once confirmed. 8) Early identification and treatment can prevent life-threatening episodes.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding. 3) All siblings of infants confirmed to have LCHADD deficiency should also be tested.
CHARACTERISTICS	1) Symptoms may include hypoglycemia, lethargy, failure to thrive, hypotonia, and cardiomyapathy. 2) Severe, untreated cases may present as SIDS. 3) The mother of a child with LCHADD may have medical complications during their third trimester of pregnancy including maternal acute fatty acid liver of pregnancy and jaundice.
SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis and ongoing management. 2) Parents should be instructed to carry emergency protocol letter from physician.

REFERENCES	1) www.ncbi.nlm.gov 2) www.fodsupport.org 3) www.jiulsite.com 4) www.umdf.org 5) Oregon Pracitioners' manual 6) Iowa Protocol's and Practitioner's Manual
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Fatty Acid Oxidation Disorder
Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCADD)

DEFINITION	MCAD is a disorder of lipid metabolism characterized by a defect in the oxidation of medium chain fatty acids. Babies born with fatty acid oxidation disorders are unable to break down stored fats into energy. Energy from fat keeps the body running whenever it runs out of its main source: glucose. Urgent follow-up is required. Metabolic crisis can occur during periods of fasting and can cause episodes of hypoglycemia, vomiting and coma. It is an inherited autosomal recessive condition.
INCIDENCE	1 in 13,000 to 20,000 live births. Higher incidence in Northern Europeans and U.S. Caucasians.
NBS ABNORMALITIES	Elevations of C6, C8, C10 and C10:1.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. * Repeat the newborn screening specimen. * Urine organic acid profile, acylcarnitine profile, and/or another reference lab through Mayo Clinic. 4) Recommend consult with Dr. Alan Kenien at 701-234-2431. Instruct parents on the treatment. 5) Treatment: MCAD deficiency is a chronic disease with lifelong risk of episodes of hypoglycemia. The primary goals for MCADD patients include providing adequate caloric intake (low fat, high carbohydrate diet), supplemental carnitine, avoidance of fasting and aggressive glucose monitoring and support during infectious episodes. Avoid fasting for more than 3-4 hour as a neonate.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding. 3) All siblings of infants confirmed to have MCADD deficiency should also be tested.
CHARACTERISTICS	1) Although a few children are clinically diagnosed with MCADD, most will not develop problems until after the age of 3-12 months. 2) It is a chronic disease with a lifelong risk for episodes of hypoglycemia. 3) Patients present with vomiting, lethargy, hypoglycemia, mild hyperammonemia, hypocarnitinemia, and abnormal liver function tests. 4) These patients may require IV support (NO INTRALIPIDS) for fluid and calories during periods of infections and/or illness. 5) These children are at significant risk of death with either initial or later episodes. 6) Significant disability can also result from severe, prolonged hypoglycemic episodes.

SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis. 2) Parents will be instructed to carry letter from physician at all times in case of the need to present to the E.R. 3) A metabolic clinic is held quarterly at Meritcare in Fargo, ND.
REFERENCES	1) www.ncbi.nlm.gov 2) www.fodsupport.org 3) www.jiulsite.com 4) www.umdf.org 5) Oregon Pracitioners' manual 6) Iowa Protocol's and Practitioner's Manual
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Fatty Acid Oxidation Disorder
Short Chain Acyl-CoA Dehydrogenase Deficiency (SCADD)

DEFINITION	Babies born with fatty acid oxidation disorders are unable to break down stored fats into energy. Energy from fat keeps the body running whenever it runs out of its main source: glucose. SCADD is a condition in which the body cannot oxidize fatty acids because an enzyme is either missing or not functioning correctly. Metabolic crisis can occur during periods of fasting and can cause episodes of hypoglycemia, vomiting and coma.
INCIDENCE	1:40,000 – 1:100,000
NBS ABNORMALITIES	Elevations in C4, C4/C2 and C4/C3.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) Attending physician to order: - Urine organic acids - Plasma acylcarnitine - Urine acylglycines 5) Treatment of SCADD usually consists of avoidance of fasting (by frequent feedings) and use of glucose IV required when food cannot be tolerated (such as with a virus, cold, flu). Intake of short-chain fatty acids should be avoided. Supplemental carnitine is recommended for some affected children.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding. 3) However, after several years of expanded newborn screening and increased detection of infants without any problems, the general consensus is that the vast majority of patients will not have any symptoms at all 4) There is a common gene change in the general population that causes increased excretion of C4 alone, and is not associated with any known disease.
CHARACTERISTICS	1) Symptoms of the congenital form of SCADD appear with the first days to two weeks after birth and include poor feeding, vomiting, hypoglycemia, skeletal or cardiac muscle weakness, and hypotonia. 2) There is a common gene change in the general population that causes increased excretion of C4 alone, and is not associated with any known disease. 3) Over time without proper treatment, development may be delayed. 4) Symptoms are triggered in response to a period of fasting and/or an infection. 5) Clinical manifestations vary widely, majority will be asymptomatic.

SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis and ongoing management.
REFERENCES	1) www.fodsupport.org 2) www.jiulsite.com 3) www.umdf.org 4) www.clinchem.org 5) Iowa Neonatal Metabolic Screening Program 6) Oregon Neonatal Metabolic Screening Program
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Fatty Acid Oxidation Disorder
Trifunctional Protein Deficiency (TFP)

DEFINITION	TFP is a mitochondrial fatty acid oxidation disorder. Individuals with this disorder are unable to break down long-chain fatty acids into an energy source. Metabolic crisis can occur during periods of fasting and can cause episodes of hypoglycemia, vomiting, coma and even death.
INCIDENCE	Unknown Autosomal recessive disorder of mitochondrial fatty acid oxidation
NBS ABNORMALITIES	Elevated C16-0H and C18:1-0H
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If all Carnitines or a couple are elevated we need to treat like a real disease and get STAT: * Plasma acylcarnitine profile with free and total carnitine levels. * Make sure infant is eating every 2-4 hours and consider if on formula, switching to Pregestamil. If breastfeeding, wait until have results. 5) Avoidance of fasting. 6) High carbohydrate diet with frequent feedings. 7) Intake of long-chain fatty acids should be limited. 8) TFP tends to mimic LCHAD. 9) Aggressively treat infections and fever. 10) Carnitine supplementation may be indicated.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding.
CHARACTERISTICS	1) Symptoms include: hypoglycemia, lethargy, hypotonia, myopathy, failure to thrive, cardiomyopathy and/or neuropathy. 2) Severe untreated cases may present as SIDS. 3) The mother of a child with TFP may have medical complications during their third trimester of pregnancy, including maternal acute fatty liver of pregnancy.
SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis and ongoing management. 2) Parents should be instructed to carry emergency protocol letter from physician.

REFERENCES	1) www.savebabies.org/diseasedescriptions/trifunctionalproteindeficiency.php 2) www.savebabies.org/familystories/james&samuelTFP.php 3) www.ncbi.nlm.gov 4) www.jci.org/cgi/content/abstract/102/6/1193 5) www.orpha.net/static/GB/mitochondrial_trifunctional_protein_deficiency.html 6) www.fodsupport.org/caleb_tfp.htm
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Fatty Acid Oxidation Disorder
Very-Long-Chain Acyl-COA Dehydrogenase Deficiency (VLCADD)
(Ayl-CoA Dehydrogenase, Very Long-Chain, Included; ACADVL, Included VLCAD, Included)

DEFINITION	Babies born with fatty acid oxidation disorders are unable to break down stored fats into energy. Energy from fat keeps the body running whenever it runs out of its main source: glucose.. Prolonged fasting (i.e. going for long periods without eating, such as during illness) can lead to severe life-threatening symptoms such as hypoglycemia. It is estimated that 1 to 2/100 "SIDS" cases are the result of an undiagnosed fatty acid oxidation disorder.
INCIDENCE	Unknown
NBS ABNORMALITIES	Elevations in C14, C14:2 and/or C14:1/C12:1
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with a metabolic consultant. 3) North Dakota follow-up staff will notify ASAP the attending physician, via phone and fax, the following information: * The physician must contact the family ASAP. 4) If other levels are elevated, need STAT: * Plasma acylcarnitine profile with free and total carnitine levels. * Make sure infant is eating every 2-4 hours and consider if on formula, switching to Pregestamil, if breastfeeding, wait until have all of lab results.
SCREENING PRACTICE CONSIDERATIONS	1) Presumptive positive screens should be confirmed as soon as possible. 2) Upon receiving the presumptive positive report, the attending physician should check on the feeding and clinical status of the baby and advise the parent to avoid any significant time gap in feeding. 3) All siblings of infants confirmed to have VLCADD deficiency should also be tested.
CHARACTERISTICS	1) Initial manifestation of VLCADD include hypoketotic hypoglycemia, hypotonia, myopathy, cardiomyopathy, and liver dysfuntion. 2) Severe, untreated cases may present as SIDS. 3) In older undiagnosed children, rhabdomyolysis and muscle pain may be the presenting symptom. 4) There are 3 ways VLCADD can present: * In the newborn period with significant hypoglycemia and cardiomyopathy. * Later in infancy with hypoglycemia. * In adolescents or young adulthood with rhabdomyolysis. 5) All babies with confirmed VLCADD should be given a VLCAD deficiency emergency protocol letter.
SERVICES	1) Consultation with a pediatric endocrinologist or geneticist (Dr. Alan Kenien) is strongly encouraged for confirmation and diagnosis and ongoing management. 2) Parents should be instructed to carry emergency protocol letter from physician.

REFERENCES	1) www.fodsupport.org 2) www.jiulsite.com 3) www.umdf.org 4) www.clinchem.org 5) Iowa Neonatal Metabolic Screening Program 6) Oregon Neonatal Metabolic Screening Program
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Biotinidase Deficiency (BT)

DEFINITION	Biotinidase deficiency is an inherited inborn error of metabolism caused by the lack of the enzyme (biotinidase) which normally enables the body to recycle biotin. Biotin is a water-soluble vitamin belonging to the B complex, and is essential for normal metabolism in humans.
INCIDENCE	The incidence of biotinidase deficiency is 1 in every 60,000 births.
NBS ABNORMALITIES	The lab method used is a semi-quantitative colorimetric assay to determine the presence or absence of biotinidase activity..
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) North Dakota follow-up staff will notify, via phone and fax, the local attending physician who must notify the family ASAP. 4) Recommend to repeat the newborn screen ASAP. 5) If the repeat is abnormal, a quantitative serum assay is recommended. 6) Confirmatory studies are necessary to differentiate profound biotinidase deficiency from partial deficiency. 7) Consult with pediatric endocrinologist (Dr. Alan Kenien at 701-234-2431). 8) Treatment is oral Biotin replacement and needs to be a lifelong treatment.
SCREENING PRACTICE CONSIDERATIONS	1) Screening results are affected by blood transfusions, always collect a newborn specimen prior to transfusions. 2) Test is not dependent on timing and type of feeding. 3) The enzyme activity may be affected if the sample is delayed in the mail or exposed to high temperatures. 4) Family studies are indicated when an affected newborn is identified.
CHARACTERISTICS	1) The symptoms of biotinidase deficiency are variable with respect to age of onset, frequency and severity. 2) Signs and symptoms generally appear in infancy or early childhood. 3) The signs and symptoms may include seizures, skin rash, hair loss, hypothermia, ataxia, hearing loss, optic nerve atrophy, developmental delay and metabolic acidosis which can result in death.
SERVICES	1) Consult with the Pediatric Endocrinologist Specialist (Dr. Alan Kenien, 701-234-2431) for confirmation and diagnosis. 2) Confirmation of biotinidase deficiency is done by precise measurement of biotinidase enzyme activity of a reference lab.
REFERENCES	1) The North Dakota Practitioner's manual. 2) Newborn Screening Practitioner's manual (2001). 3) www.slh.wisc.edu/newborn/guide/biotinidazse 4) www.newbornscreening.com/main 5) www.doh.wa.gov

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Congenital Adrenal Hyperplasia (CAH)

DEFINITION

Congenital adrenal hyperplasia refers to a group of inherited disorders related to the adrenal glands, characterized by a deficiency in the hormones cortisol and aldosterone and an over production of androgen.

INCIDENCE

About 1 in 12,000 children are born with congenital adrenal hyperplasia.

NBS ABNORMALITIES

The laboratory method used is a time-resolved fluoroimmunoassay for 17-OHP.
Because of low birth weight and premature infants often have elevated 17-OHP levels, INMSP uses four weight dependent ranges adjusted for these variables. ≥

Ranges*

Weight in Grams	Normal	Borderline	Presumptive Positive
< 1250	<135	≥135 - <160	≥160
≥1250-<1750	<90	≥90-<135	≥135
≥1750-<2250	<65	≥65-<90	≥90
≥2250	<50	≥50-<90	≥90

*Results are in ng/mL. Unit conversion ng/mL = 100 ng/dL (example: 90 ng/mL – 9000 ng/dL)

PLAN OF ACTION

1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366.
2) Consult with metabolic consultant.
3) North Dakota follow-up staff will notify the local attending physician, via phone and fax, the following information:
   a) Notify the family and repeat the newborn screen as soon as possible – if the result is borderline.
   b) Abnormal results are confirmed by measurement of serum 17 – hydroxyprogesterone level. Consult with Dr. Alan Kenien (Pediatric Endocrinology Consultant) regarding confirmatory testing.
   c) Treatment requires Hydrocortisone and Florinef as the medications most often used. Female infants may require surgical correction of ambiguous genitalia. Children with CAH should be followed by a Pediatric Endocrinologist.
   d) Parents of children with this disorder need instructions on the side effects of steroid therapy. They should report signs of infection and stress to their health care provider because increase in medication may be required. In addition, steroid medications cannot be stopped suddenly.

SCREENING PRACTICE CONSIDERATIONS	1) CAH results are weight dependent. If a weight is not provided on the collection form, a result cannot be given. Please include weight on collection form. 2) Hormone (steroid) therapy administered to the mother during pregnancy, or to the infant immediately after birth, can interfere with CAH test results. Contact the Pediatric Endocrinology Consultant regarding management for these situations (Dr. Alan Kenien, 701-324-2431). 3) Premature or sick infants may have a false-positive screen. 4) Specimens collected prior to 24 hours of age may exhibit a false-positive or false-negative result. It is extremely important to perform a second screening on these infants as soon as possible to ensure that an infant, whose 17-OH progesterone level has not stabilized and is continuing to rise, is not missed. 5) Blood transfusions may give false negative results due to hemodilution in low birth weight babies. 6) Blood collection with preservatives (EDTA) can result in false-positive results. 7) CAH ranges apply to the newborn period. Interpretation of results from specimens collected after the newborn period should be performed in consultation with the Pediatric Endocrinology Consultant.
CHARACTERISTICS	1) Infants severely affected with the classical "salt-wasting" type of CAH may quickly develop vomiting, dehydration and vascular shock and present in the E.R. in a life-threatening adrenal crisis. 2) In girls: - ambiguous genitalia - early appearance of pubic and axillary hair - excessive hair growth - deep voice - abnormal menstrual periods - failure to menstruate 3) In boys: - early development of masculine characteristics - enlarged penis - small testes - early appearance of pubic and axillary hair 4) Both boys and girls will be tall as children, but significantly shorter than normal as adults.
SERVICES	Consultation with a pediatric endocrinologist (Dr. Alan Kenien) must be done for confirmation, diagnosis and ongoing management of the child.
REFERENCES	1) The North Dakota Newborn Screening Practitioner's manual. 2) Mountain States Genetics Network Practitioner's manual. 3) www.nih.gov/medlineplus 4) www.hopkinsmedicine.org/pediatricendocrinology/cah

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Congenital Hypothyroidism (CH)

DEFINITION	Most commonly caused by failure of thyroid gland to develop correctly. This may range from complete absence of thyroid tissue to partial formation of thyroid tissue. In the first hour after birth, there is a surge in TSH release, probably caused by a drop in the infant's temperature. This leads to a rise in both T3 and T4. These elevated levels may last 4-6 weeks.
INCIDENCE	1 in 3,000 live births
NBS ABNORMALITIES	**TSH RESULTS:** <25 = within normal limits 25 - <60 = borderline ≥60 = presumptive positive
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with metabolic consultant. 3) Follow-up staff will notify the local attending physician, via phone and fax, the following information: a) If the result is borderline, request a repeat specimen as soon as possible. b) If the result is presumptive positive and if TSH is >100 = i) Recommend ASAP a T4, TSH, free T4 at a regional reference lab. ii) Repeat newborn screen ASAP. iii) Recommend beginning thyroxin therapy. iv) Recommend a consult with Dr. Kenien at 701-234-2431. 4) Begin therapy by 14 days of life with thyroid medication.
SCREENING PRACTICE CONSIDERATIONS	1) Question if the mother has hypothyroidism. 2) Was the infant exposed in the perinatal period to iodine or drugs that interfere with thyroid function. 3) Do not screen initially <24 hours of birth. 4) Measure TSH and free T4: a) 2 and 4 weeks after starting treatment—then b) Every 1-2 months until 1 year of age—then c) Every 2-3 months until 3 years of age—then d) Every 3-12 months until growth is completed 5) Soy formula and drugs that interfere with 1-thyroline absorption should not be given within 1 hour of the 1-thyroline dose.

CHARACTERISTICS	Clinical symptoms may be: • facial puffiness • large tongue • delayed passage of stools • cold hands or feet • poor feeding • respiratory distress in infant weighing >2.5 kg • large anterior/posterior fontanel • poor weight gain • hypotonia • lethargy • hypothermia
SERVICES	Consultation with Dr. Kenien with any abnormal results is strongly encouraged.
REFERENCES	1) North Dakota Practitioner's Manual 2) Northwest Regional Newborn Screening Practitioner's Manual 3) www.drgreene.com 4) www.magicfoundation.org/congthyr.html

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Galactosemia (GALT)

DEFINITION	Galactosemia is an inherited disorder of carbohydrate metabolism, in which galactose cannot be converted to sugar because of a missing or deficient enzyme GALACTOSE-1-PHOSPHATE URIDYLYLTRANSFERASE (GALT). Galactosemia (elevation of blood galactose levels) results when an infant is fed regular infant formula or breast milk. The galactose builds up in the body, causes cellular damage to the liver, eyes and brain, and even death. Urgent follow-up is important!
INCIDENCE	Classic galactosemia (absence of the GALT enzyme) is rare, occurring in 1 in 70,000 live births. Variants of galactosemia with reduced GALT activity are more frequent and occur in 1 in 6,000 live births.
NBS ABNORMALITIES	**RESULTS** >3.7 GALT units/g Hb = within normal limits 3.2 - ≤3.7 GALT units/g Hb = borderline ≤3.1 GALT units/g Hb = presumptive positive
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with a metabolic consultant. 3) Follow-up staff will notify the local attending physician via telephone and fax with the following information: a) If the result is borderline and/or inconclusive, request a repeat newborn screen specimen ASAP. In the letter to the physician, note that if the repeat specimen result is abnormal, a recommended consult with Dr. Alan Kenien, Pediatric Endocrinologist of MeritCare in Fargo, North Dakota at 701-234-2431. If infant is breastfed and doing well can stay on breastmilk, if on formula, switch to soy. b) If the result is presumptive positive, recommend the infant must be on soy formula, have liver functions, PT/PTT and CBC, confirmatory testing and see primary physician or ER within 24 hours of notification and must see Dr. Kenien for genetic counseling as soon as possible. 4) A strict diet is essential for life. The treatment is to restrict galactose and lactose from the diet for life. 5) Examples of soy formulas are: a) Isomil (Ross) b) ProSobee (Mead Johnson) c) Good Start Supreme Soy (Carnation)
SCREENING PRACTICE CONSIDERATIONS	1) Prompt follow-up of an abnormal screen is important. 2) False negatives results can result following a blood transfusion. 3) Heat and humidity can influence results- giving false positive.

CHARACTERISTICS	1) The infant may appear normal at birth, but symptoms appear within a few days. 2) The early clinical features of classic galactosemia include: a) symptoms typically start about the third day of life. The skin is jaundiced, which doesn't go away with the usual procedures. Cataracts, enlarged liver, vomiting and failure to thrive are the most common and apparent symptoms. b) liver dysfunction, manifested by jaundice and hypoglycemia proceeds to liver failure if untreated c) neurological findings of irritability and seizures d) gastrointestinal findings of poor feeding, failure to thrive, vomiting and diarrhea e) death may result from gram negative sepsis within 1-2 weeks of birth. f) If the infant is untreated and survives the neonatal periods, cataracts, cirrhosis and mental retardation are usual consequences.
SERVICES	1) North Dakota Children's Special Health Services (CSHS) supports a metabolic clinic 4 times a year at the MeritCare Coordinated Treatment Center, 736 Broadway Avenue, 3rd floor, Fargo, N.D. (1-800-828-2901, #2 option). These clinics are supported through a grant from CSHS, Department of Human Services. a) A multidisciplinary team provides coordinated services. b) Family travel expenses may be reimbursed when needed.
REFERENCES	1) North Dakota Newborn Screening Practitioner's Manual 2) www.galactosemia.org 3) Oregon Practitioner's Manual 4) http://www.tdh.state.tx.us/newborn/handbook.htm 5) http://www.savebabies.org 6) Nutrition Support Protocols (4th Edition) 2001
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Hemoglobinopathies (HGB)

DEFINITION	1) Hemoglobin is a protein found in red blood cells that carries oxygen and gives blood its red color. Most people have the type of hemoglobin called Hemoglobin A (also called normal or adult hemoglobin). We inherit our hemoglobin type from our parents. Hemoglobinopathies are a group of disorders that cause changes in the amount of the hemoglobin that is produced. 2) Hemoglobin trait means that a person makes the usual hemoglobin A and another hemoglobin in the red blood cells. Trait is a common word for a condition where a person gets an abnormal gene from one parent and the normal type of the gene from the other parent. 3) Hemoglobin traits may be passed along form many generations and not cause disease in offspring.
INCIDENCE	1 in 12 black Americans in the United States carry the sickle cell trait, about 1 in 375 will have the disease.
NBS ABNORMALITIES	Results: Traits are indicated with the results of FAV, FAD, FAS, FAC, FAF, Beta thalassemia, FAE, FAJ, FAG, FAN.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) All traits: a) collect repeat newborn specimen and send to the Iowa lab b) at 2 months of age, arrange fro confirmatory testing by hemoglobin electrophoresis. This testing should be done through a reliable regional reference lab such as Mayo Clinic Lab. c) Family screening and genetic counseling is recommended with Dr. Martsolf. Appointments can be made for these clinics by calling 701-777-4243 and speaking with Mary Riske, the nurse geneticist. d) Family screening should consist of hemoglobin electrophoresis and CBC with red cell indices on each parent. Family screening should be done prior to genetic counseling, so that parents can be given specific information about their chances of having future children with major hemoglobinopathies. e) Confirmatory testing is a covered service from Children's Special Health Services. Application forms can be obtained from the local social service agency.

QUICK GLANCE

Traits	Genetic counseling recommended.		
Common Lab Results	**Likely Cause**	**Physician Actions**	**Refer**
FA	Normal pattern in newborn <3 weeks of age	None	No
AF	Normal pattern in newborn ≥3 weeks of age provided, no transfusion has taken place within the last 8 weeks and anemia is not suspected.	None, unless transfused. If transfused, submit another specimen collected at least 8 weeks after last transfusion.	No
FF	May only indicate delayed appearance of hemoglobin A (prematurity), but could indicate hereditary persistence of fetal hemoglobin, or beta thalassemia major.	Needs follow-up specimen to determine if caused by prematurity or the absence of the hemoglobin A (adult) gene or confirmatory testing at 2 months of age.	If repeat testing is abnormal refer to Hematologist
AS	Heterozygous sickle cell trait (rarely sickle β-thalassemia or sickle cell anemia after blood transfusion).	Confirmatory testing by 2-4 months of age.	Geneticist
AC	Heterozygous hemoglobin C trait	Confirmatory testing by 2-4 months of age.	Geneticist
AV	Heterozygous unknown trait that may not be clinically significant	Confirmatory testing by 2-4 months of age.	Geneticist
AE	Heterozygous hemoglobin E trait	Confirmatory testing by 2-4 months of age.	Geneticist
AD	Heterozygous hemoglobin D trait	Confirmatory testing by 2-4 months of age.	Geneticist
FA + Bart's	This pattern MAY indicate alpha-thalassemia	Confirmatory testing at 4 months of age.	Hematologist
AS + Bart's	Heterozygous sickle cell trait and possible alpha-thalassemia	Confirmatory testing at 4 months of age.	Hematologist
AE + Bart's	Hemoglobin E trait with possible alpha-thalassemia	Confirmatory testing at 4 months of age.	Hematologist
Note: Beta thalassemia trait cannot be detected on newborn screening.			

SCREENING PRACTICE CONSIDERATIONS

1) Blood transfusions may result in false negative results. Always obtain a newborn screening specimen prior to a transfusion.
2) The newborn screen for hemoglobinopathies is not affected by age at collection.

CHARACTERISTICS

Traits may cause mild anemia or low blood count.

SERVICES

Consultation may be referred to:

- Baruti Serabe, MD – Pediatric Hematology – Oncology
  Q & R Clinic, Bismarck, ND 701-323-6530
- Nathan Kobrinsky, MD – Pediatric Hematology – Oncology
  Merticare Roger Maris Center, Fargo, ND 701-234-7544
- John Martsolf, MD – Medical Geneticist
  University of North Dakota – Department of Pediatrics – Grand Forks, ND 701-777-4277

REFERENCES	1) Northwest Oregon Practitioner's Manual 2) Iowa Practitioner's Manual 3) www.scinfo.org/faqNBS.htm 4) www.dhss.mo.gov/Lab/Newborn/Hemoglobinopathies.html 5) Genetics in Medicine – February, 2005
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Maple Syrup Urine Disease (MSUD)

DEFINITION	MSUD is an inherited rare metabolic disorder that, if untreated, causes mental retardation, physical disabilities, and death. MSUD derives its name from the sweet, burnt sugar, or maple syrup smell of the urine. The disorder affects the way the body processes certain components of protein. These components are the 3 branched-chain amino acids, leucine, isoleucine, and valine. The amino acids accumulate in the blood causing a toxic effect that interferes with brain functions.
INCIDENCE	The national incidence is 1 in 225,000 births, believed to be in all ethnic groups worldwide. *It was first described as a disease in 1954. * It is about 1 in 760 among mennonities.
NBS ABNORMALITIES	Generally, blood is analyzed for elevated levels of leucine and isoleucine and ratios as well.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) Consult with a metabolic consultant. 3) North Dakota follow-up staff will notify the local attending physician, via phone and fax, the following information: - the physician must contact the family ASAP. - any newborn in whom the leucine level is 4 mg/dL or greater should be considered to have MSUD until proven otherwise. - contact Dr. Alan Kenien (pediatric endocrinologist) at 701-234-2431 ASAP for diagnosis and management. 4) If the infant has symptoms of MSUD, the infant should be hospitalized for specialized emergency intervention. 5) Long-term treatment consists of a carefully controlled diet which strictly limits dietary protein in order to prevent the accumulation of BCAAs in the blood. 6) An MSUD infant formula has been developed which provides all the vitamins and minerals necessary for proper development without the BCAAs. This can be supplemented with very small amounts of regular baby formula.
SCREENING PRACTICE CONSIDERATIONS	1) BCAA levels begin to rise immediately after birth, however, significant increases in the levels usually requires protein ingestion or catabolism. 2) Early discharge of infants may result in inadequate increases in BCAA levels for detection by newborn screening. 3) Prompt confirmatory testing is required even if there is evidence to suggest that one of the situations associated with false positive screens is present (these include early specimen collection, prematurity, heart-damaged specimen, hyperalimentation, or antibiotic therapy). The presence of any of these does not exclude the possibility of disease.
CHARACTERISTICS	1) Symptoms of MSUD begin shortly after birth with the ingestion of dietary protein. 2) Signs and symptoms progress from poor feeding, irritability, and vomiting to lethargy and coma in the first weeks of life. 3) Hypoglycemia and a strongly positive test for urine ketones may be present. 4) High-pitched cry, seizures and the characteristic maple syrup smell of the urine – more noticeable in a diaper after it is dried.
SERVICES	1) Consult with Dr. Alan Kenien must be done for confirmation of diagnosis and ongoing management.

REFERENCES	1) Newborn Screening Practitioners Manual for Mountain States Genetics Network (2001) 2) www.msud-support.org 3) www.doh.wa.gov/ehsphl/PHL/newborn/msud.htm

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Phenylketonuria (PKU)

DEFINITION	PKU is a rare, inherited metabolic disorder that, if untreated, causes mental retardation. Detection of elevated phenylalanine levels requires urgent follow-up. This disorder is due to a recessively inherited enzyme defect in which the body cannot use the amino acid phenylalanine properly. All other metabolic processes are intact, but phenylalanine, which comes from all dietary protein, accumulates in the blood to toxic levels.
INCIDENCE	1 in 10,000 to 15,000 in all ethnic groups
NBS ABNORMALITIES	The screen is considered "presumptive positive" for PKU if the Phenylalanine concentration is 3.1mg/dL or greater.
PLAN OF ACTION	When the initial screen on a newborn is presumptive positive: 1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) The follow-up staff will notify the local physician via telephone and fax with the lab results and letter with recommendations: * the physician must contact the family ASAP * a repeat specimen must be done ASAP as well as a quantitative plasma amino acid (sent by overnight delivery) to a reference lab. 3) Upon confirmation of the diagnosis, the follow-up staff should notify: Dr. Alan Kenien, a Pediatric Endocrinologist at MeritCare Medical Center; Cathy Breedon, a nutritionist at MeritCare Medical Center; and Kora Dockter of Children's Special Health Services (CSHS) regarding need for formula. 4) Treatment for PKU consists of a special formula and foods that have little or no phenylalanine, which decreases the high levels the phenylalanine and prevents the occurrence of mental retardation and other symptoms.
ADDITIONAL FOLLOW-UP	1) Follow-up staff will contact the local physician via fax of the results of the repeat tests as well as the confirmatory testing.
SCREENING PRACTICE CONSIDERATIONS	1) The screening test is often abnormal within 24 hours and almost uniformly abnormal within 48 hours of birth. 2) Important that diagnosis and treatment begin with a minimum of delay, certainly by 14-21 days of age. 3) Antibiotics do not interfere with the screening method. 4) Screen is valid if baby is >24 hours of age. 5) Screen is valid even if baby is not feeding well. 6) TPN is the most common cause of a false positive test result. 7) Any baby with an abnormal PKU screen should be referred to a metabolic treatment center. 8) It is very important that no infant with an abnormal PKU screen be placed on any kind of protein restriction or special diet prior to referral and a medical workup by a pediatric metabolic specialist or geneticist.

CHARACTERISTICS	1) At birth the baby with classical PKU appears completely normal. 2) If untreated, the baby usually progresses as expected for the first few months of life, but then begins to show signs of developmental delay. 3) If treatment is not started for some weeks, the results are more variable and the I.Q. tends to be lower. 4) Patients whose treatment begins after 6 months are likely to remain mentally retarded. 5) Some signs (symptoms may be vomiting, feeding difficulties, eczema, autistic-like behaviors, poor growth, seizures and a musty-smelling body odor.
SERVICES	1) Free monitoring of blood Phenylalanine levels if provided through the Newborn Screening Program. Call 1-800-472-2286 (Press 1) to order PKU monitoring collection forms. Family will have to purchase lancets for doing the finger/heel punctures. 2) Children's Special Health Services shall provide medical food at no cost to males under age 21 and females under age 45 who are diagnosed with phenylketonuria or maple syrup urine disease, regardless of income. The Children's Special Health Services program is in the North Dakota Department of Human Services and the toll-free phone number is 1-800-755-2714. 3) A metabolic clinic is conducted four times a year at the MeritCare Coordinated Treatment Center, 736 Broadway Avenue, 3rd floor, Fargo, ND (1-800-828-2901 #2 Option). A multidisciplinary team (pediatric endocrinologist, pediatric nutrition specialist, education specialist, psychiatrist, social worker and nurse) provides coordinated services. Family travel expenses may be reimbursed when needed. Call to schedule appointment times and verify clinic dates. The metabolic clinics are supported through a grant from Children's Special Health Services (CSHS), Department of Human Services.
REFERENCES	1) www.pkunews.org 2) (N.I.H.) National Institutes of Health and National Institute of Child Health and Human Development (2001) Phenylketonuria (PKU): Screening and management. 3) The Northwest Regional Newborn Screening Program Practitioner's Manual (2002) 4) North Dakota Practitioner's Manual 5) Nutrition Support Protocols (4th Edition) (2001)

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Draft

Sickle Cell Disease

DEFINITION	Sickle cell disease is a disease of red blood cells. These are responsible for carrying oxygen. The red blood cells contain a red colored pigment called hemoglobin which picks up oxygen in the lungs and takes it around the body. This is usually hemoglobin A. In people with sickle cell disease, this red pigment is slightly different and is called hemoglobin S. Sickle cell disease is a lifelong condition that can cause severe anemia, stroke, lung and kidney damage and painful crisis. Children with sickle cell disease are at risk for serious infection and need to take antibiotics to prevent infection. It is very important that these antibiotics start as early in life as possible.
INCIDENCE	Sickle cell disease affects 1 in 375 African Americans and more than 1 in 50,000 Americans. It is estimated that 8% of the African American population carries the sickle cell trait. The disease can also affect those of Mediterranean, Caribbean, South and Central American, Arabian or East Indian ancestry.
NBS ABNORMALITIES	Sickle cell disease is indicated with the result of HSS, HSC, HSE, HCC, HEE, and Bart's hemoglobin.
PLAN OF ACTION	1) Iowa lab will notify ND follow-up staff of lab results at (p) 701.328.4538, (f) 701.328.1412 or (on-call) 701.220.0366. 2) At 2 months of age, recommended hemoglobin electrophoresis and CBC with red cell indices. This testing could be done through a regional reference lab such as Mayo Clinic Lab (there is a fee for this). **Children's Hospital Oakland Research Institute offers testing for Bart's and/or any potential thalassemias free of charge.** 3) When confirmatory results are available, make an appointment with Dr. Martsolf for genetic counseling. Appointments can be made for these clinics by calling 701-777-4243 and speaking with Mary Riske, the nurse geneticist. 4) This confirmatory testing is a covered service from Children's Special Health Services. Application forms can be obtained from the local social service agency.

QUICK GLANCE

Disease	Contact pediatric hemoglobinopathy specialist regarding follow-up testing and treatment.		
Common Lab Results	**Likely Cause**	**Physician Actions**	**Refer**
CC	Homozygous hemoglobin CC	Confirmatory testing by 2 months of age	Hematologist
EE	Homozygous hemoglobin EE	Confirmatory testing by 2 months of age	Hematologist
EE + Bart's	Homozygous hemoglobin EE, with possible alpha-thalassemia.	Confirmatory testing by 2 months of age	Hematologist
S-Beta-Thalassemia	Homozygous hemoglobin S and beta-thalassemia	Confirmatory testing by 2 months of age	Hematologist
SC	Homozygous hemoglobin S and C: Sickle-hemoglobin C disease	Confirmatory testing by 2 months of age	Hematologist
SS	Homozygous hemoglobin SS: Sickle cell anemia or sickle B-thalassemia	Confirmatory testing by 2 months of age	Hematologist
SS + Bart's	Bart's Homozygous hemoglobin SS, with possible alpha-thalassemia	Confirmatory testing by 2 months of age	Hematologist
VV	Homozygous hemoglobin unknown variant which may or may not be clinically significant.	Confirmatory testing by 2 months of age	Hematologist

SCREENING PRACTICE CONSIDERATIONS

1) Blood transfusions may result in false negative results. Always obtain a newborn screening specimen prior to a transfusion.
2) The newborn screen for hemoglobinopathies is not affected by age at collection.

CHARACTERISTICS	1) Sickle Cell Disease a. moderate to severe anemia b. increased severity of certain infections c. recurrent pain episodes d. tissue infarction with organ damage and failure. 2) Infants with sickle cell disease should receive standard well baby care, including pneumococcocal vaccination. 3) Infants with documented or suspected sickle cell anemia or HB Sar-thalassemia should be started on twice-daily oral prophylactic penicillin as soon as possible, but no later than two months of age.
SERVICES	Consultation may be referred to: • Baruti Serabe, MD – Pediatric Hematology – Oncology Q & R Clinic, Bismarck, ND 701-323-6530 • Nathan Kobrinsky, MD – Pediatric Hematology – Oncology Merticare Roger Maris Center, Fargo, ND 701-234-7544 • John Martsolf, MD – Medical Geneticist University of North Dakota – Department of Pediatrics – Grand Forks, ND 701-777-4277
REFERENCES	6) Sickle cell disease – Resource Disc (2004) American Academy of Pediatrics 7) www.scinfo.org 8) Health Supervision for Children With Sickle Cell Disease (March 2002) American Academy of Pediatrics 9) Sickle Cell Disease and Other Hemoglobinopathies (October 2000) The Journal of Pediatrics 5) www.marchofdimes.com 6) www.sicklecelldisease.org
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RESOURCES OF NEWBORN SCREENING INFORMATION

NATIONAL NEWBORN SCREENING AND GENETICS RESOURCE CENTER; 1912 W. Anderson Lane, #210; Austin, TX 78757; 512-454-6419; http://genes-r-us.uthscsa.edu.

PUBLICATIONS ON NEWBORN SCREENING FROM THE AMERICAN ACADEMY OF PEDIATRICS

The American Academy of Pediatrics (AAP) Committee on Genetics publishes *Newborn Screening Fact Sheets* (1996; RE9243; www.aap.org/policy/01565.html) for each of the conditions covered in this manual, and others. Also available is their policy paper *Issues in Newborn Screening* (1992; RE9243; www.aap.org/policy/04619.html). *Recommendations from the Newborn Screening Task Force: A Blueprint for the Future of Newborn Screening* was published as a supplement to *PEDIATRICS* in August, 2000. These documents may be viewed online (www.aap.org), or ordered from the AAP Publications Department, 141 Northwest Point Blvd., Elk Grove Village, IL 60007-1098; 847-228-5005; 847-228-5097 (FAX).

NEWBORN SCREENING VIDEO

The National Committee for Clinical Laboratory Standards (NCCLS) has produced a video on newborn screening specimen collection entitled *Making a Difference Through Newborn Screening: Blood Collection on Filter Paper*. (1999; $175 [non-member price]; order code LA4-A3-V). It can be ordered from NCCLS, 610-525-2435 (www.nccls.org).

BLOOD COLLECTION ON FILTER PAPER FOR NEONATAL SCREENING PROGRAMS; APPROVED STANDARDS – 3RD ED.

The National Committee for Clinical Laboratory Standards (NCCLS) produces and periodically updates this consensus document designed to produce a standard that will result in uniform techniques for collecting specimens for use in neonatal screening programs. This 25-page booklet goes into greater detail on specimen collection and handling than is practicable in this manual. (1997; $75 [non-member price]; order code LA4-A3). It can be ordered from NCCLS, 610-525-2435 (www.nccls.org).

VISUAL AIDS TO ASSIST IN SPECIMEN COLLECTION

Two full-color wall charts on specimen collection:

"Newborn Screening Blood Specimen Collection and Handling Procedure" and
"Simple Spot Check" (invalid specimens and their causes)

are available at no charge from: Schleicher & Schuell, Inc.; 10 Optical Avenue; Keene, NH 03431; 800-437-7003; 603-355-6524 (FAX).

MARCH OF DIMES BIRTH DEFECTS FOUNDATION (MOD); 1275 Mamaroneck Ave., White Plains, NY 10605; 888-MODIMES or 914-428-7100; www.modimes.org; email: *resourcecenter@modimes.org*.

MUMS NATIONAL-PARENT-TO-PARENT NETWORK; 150 Custer Court, Green Bay, WI 54301-1243; 920-336-5333; www.waisman.wisc.edu/rowley/mums/home.html; email: *mums@net-net.net*.

MAGIC FOUNDATION FOR CHILDREN'S GROWTH; 1327 North Harlem Avenue, Oak Park, IL 60302; 800-362-4423 or 708-383-0808; www.magicfoundation.org.

AMERICAN SOCIETY OF HUMAN GENETICS (ASHG); www.faseb.org/genetics

http://www.medhelp.org/agsg/agsg21.htm

www.nbsnews@savebabies.org