



*Saving lives with
a simple blood spot*

Health Care Provider Manual

Newborn Screening Program

The Complete Guide to Newborn
Screening in Washington State

Washington State Department of Health
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INTRODUCTION

Newborn screening is a population-based, preventive public health program that is carried out in every state in the United States and in many countries throughout the world. It enables early identification of selected disorders that, without detection and treatment, can lead to permanent mental and physical damage or death in affected children. The goal of newborn screening is to facilitate prevention of developmental impairments (such as mental disability and neurological deficits), delayed physical growth, severe illness, and death through early detection and intervention.

Across the United States, there are variations in the disorders for which each state screens. Click [here](#) to see the list of disorders tested for in Washington State. Although testing is possible for many other disorders, Washington adds tests to the newborn screening panel only after careful consideration of the following criteria set by the State Board of Health:

- Available Technology: Sensitive, specific and timely tests are available that can be adapted to mass screening.
- Diagnostic Testing and Treatment Available: Accurate diagnostic tests, medical expertise and effective treatment are available for evaluation and care of all infants identified with the condition.
- Prevention Potential and Medical Rationale: The newborn identification of the condition allows early diagnosis and intervention.
- Public Health Rationale: Nature of the condition justifies population-based screening rather than risk-based screening or other approaches.
- Cost-Benefit / Cost-Effectiveness: The outcomes outweigh the costs of screening.

See the [Washington State Board of Health Process to Evaluate Conditions for Inclusion in the Required Newborn Screening Panel](#) for more information.

Successful newborn screening requires collaboration between the State Newborn Screening Program, health care facilities (hospitals, clinics, laboratories, and birth centers), health care providers (pediatricians, family practice physicians, nurse practitioners, midwives), and families of newborns. The Washington State Newborn Screening Program is within the Department of Health and is located at the State Public Health Laboratories facility in Shoreline. It is a coordinated system of screening services comprised of laboratory, follow-up, and support staff. In October 2019, the Washington State Newborn Screening Program established a contract with the Hawaii Department of Health and began providing newborn screening services for babies born in Hawaii.

Responsibilities of the Washington State Newborn Screening Program are:

- Perform rapid, efficient screening of children born in the state for the disorders required by state regulation ([WAC 246-650](#))
- Verify each newborn has had access to screening and if not, take action to assure screening is available
- Provide appropriate follow-up and recommendations to health care providers for newborns with abnormal screening test results to facilitate prompt diagnostic and treatment services
- Consult with health care providers regarding test implications and recommend follow-up actions
- Perform long-term follow-up and tracking of affected children to evaluate outcomes of the program, improve effectiveness and promote continued access to appropriate specialty health care
- Collect, analyze, and disseminate data on newborn screening requirements, including cost effectiveness of the system and health outcomes
- Provide technical assistance and education regarding all components of newborn screening to hospitals, health care professionals, families of affected children, and the general public

Responsibilities of the health care facilities and providers are:

- Provide proper collection, labeling, and handling of newborn screening specimens
- Collect and send specimens to the State laboratory within the required timeframes ([RCW 70.83.020](#))
- Document the screening status of each infant
- Quickly respond to information and specimen requests from the Newborn Screening Program
- Ensure prompt follow-up on infants requiring further testing to rule out or confirm a diagnosis
- Provide parent education about newborn screening and refer for diagnostic and clinical care services as needed
- When appropriate report to the Newborn Screening Program the date the parent/guardian was notified of the need for further diagnostic testing

Responsibilities of the families are:

- Educate themselves about the newborn screening tests that will be performed on their infant
- Report to their health care provider the presence of a family history of any screened or unscreened disorder
- Respond quickly to requests from the health care provider or Department of Health for repeat screening
- Cooperate with health care providers and institutions when required for follow-up

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HEALTH CARE PROVIDERS AND INSTITUTIONS: SPECIMEN COLLECTION AND HANDLING

RESPONSIBILITY FOR OBTAINING A NEWBORN SCREENING SPECIMEN

Washington State law (RCW 70.83.020) requires newborn screening for all infants born in Washington State. Each hospital or health care provider attending a birth outside of a hospital is required to collect a newborn screening blood specimen (or signed parental refusal) within 48 hours of an infant's birth. This specimen (or signed parental refusal) must be received by the Newborn Screening Laboratory within 72 hours of collection. Healthcare providers are to inform parents or guardians about newborn screening prior to collection of the specimen, including the legal requirement for screening and the right to refuse based on valid reasons (see next section).

PARENTAL RIGHT TO REFUSE

According to state law (RCW 70.83.020), a newborn screening specimen should not be obtained for any infant whose parents or guardian object due to religious tenets and practices. In the instance that the parents/guardians refuse screening for religious reasons, it is the responsibility of the birth hospital or out of hospital birth attendant to document the refusal appropriately. To document, complete the demographic information on the screening card **and** obtain the signature of the infant's parent/guardian on the reverse side of the card in the space provided. As with a blood specimen, the refusal signature must be obtained within 48 hours of birth, and the card must be received by the Newborn Screening Laboratory within 72 hours of collection. A record of the refusal should be included in the infant's medical records.

It is important to note that *religious reasons are the only valid basis for refusal per State law*. Newborn screening statistics indicate that the majority of infants whose parents sign a refusal in the hospital are later tested, suggesting that the refusal was not truly based on religious principles. *This dangerous practice could result in a delayed diagnosis for an affected infant and place them at significant risk of permanent damage or possibly death.* The provider should make certain that the parent/guardian understands the risks to their child for refusing screening prior to signing the refusal. Copies of the text on the reverse side of the card regarding [parental right to refuse](#) are available for reference on the website in several languages.

TIMING OF SCREENING

In addition to the required first newborn screening specimen for each infant, it is strongly recommended that every newborn have a second screening specimen collected. This recommendation has been carefully considered relative to the specific disorders included on the Washington State Newborn Screening Panel. The first screen is essential for ensuring an early diagnosis to prevent life threatening events such as a salt-wasting crisis in a child with CAH, a fatal bacterial infection in a baby with Galactosemia, or a fatal metabolic crisis in a baby with inborn errors of metabolism. The second specimen optimizes detection of the disorders and is especially important for detection of cystic fibrosis, homocystinuria, congenital hypothyroidism, and milder forms of the other disorders. All specimens are tested for all disorders on the State Newborn Screening Panel.

The timeframes for collection of each specimen are as follows:

1st Newborn Screen: Collect for every newborn between 18 to 48 hours of age.

State law requires that a specimen be collected for each newborn prior to 48 hours of age. It is the recommendation of the Department of Health that the first newborn screening specimen be collected after 18 hours of age whenever possible, as specimens collected earlier than 18 hours yield higher rates of false positive results. Under certain circumstances, a specimen may be collected prior to 18 hours of age - please see [Special Considerations](#) for infants who are premature, sick, or will receive interfering

substances. If an infant will not be with a medical provider during the recommended timeframe of 18-48 hours of age, it is also acceptable to collect a specimen earlier.

2nd Newborn Screen: Collect for every newborn between 7 and 14 days of age.

The standard of care in Washington State is to collect a second newborn screen within this time frame regardless of the results on the first newborn screen. The 2nd specimen may be collected earlier than 7 days if it fulfills any of the following criteria:

- Newborn screening program staff have specifically requested an early second specimen
- Uncertainty that the child will be seen by a medical provider during the 7-14 day period

When collecting an early 2nd screen, please allow for at least 72 hours between the collection of the 1st and 2nd screens.

3rd Newborn Screen: A third specimen collected at one month of age is recommended for all sick (requiring three or more weeks of hospitalization) and premature infants. Infants who have received interfering substances prior to collection of the 1st or 2nd newborn screen, may require a 3rd specimen. Please review the [Special Considerations](#) guidelines for the appropriate timeframe to collect a 3rd screen depending on the infant's circumstances.

If there are immediate clinic concerns for an infant, we recommend pursuing diagnostic testing in addition to collecting a routine 2nd or 3rd newborn screen.

If the screening status of an infant is unknown, such as for infants moving to Washington from out of the country, closed adoptions, or foster care cases, a specimen may be collected up to 6 months of age.

NOTE: It is no longer necessary for an infant to feed prior to specimen collection.

BIRTH ROSTERS

The Newborn Screening Program requests all birth facilities and birth attendants at home births to report live births directly to the Newborn Screening Program by completing a weekly roster. This requested information is used to ensure timely newborn screening participation by actively comparing live births that occur in Washington State with newborn screening specimens at the Newborn Screening Laboratory. The Live Birth Roster is submitted by fax or secure e-mail weekly for births that occurred the previous week (Sunday – Saturday). If it appears an infant may not have participated in newborn screening as mandated by State Law, the Newborn Screening Program will work with health care providers to facilitate screening for the infant.

[Live Birth Roster for Hospitals and Birth Centers \(PDF\)](#)

[Live Home-Birth Roster \(PDF\)](#)

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COMPLETING THE SPECIMEN COLLECTION CARD

Washington State screening cards may be ordered online at www.doh.wa.gov/nbs. Click “Order Collection Cards” on the left-hand menu and complete the order form. Screening cards are provided free of charge. A copy of the current screening card with instructions on completing is shown below:

Demographic Information Filter Paper

DO NOT USE THIS AREA

WASHINGTON STATE NEWBORN SCREENING
 PO BOX 55729 SHORELINE WA 98155-0729
www.doh.wa.gov/nbs
 DOH 304-001 (rev. 9/19)

MOTHER'S INFORMATION | **CHILD'S INFORMATION**

1 → LAST NAME | Birth: Mo Day Yr Hr : Min am pm

2 → FIRST NAME | Collection: Mo Day Yr Hr : Min am pm

2 → Maternal Steroids (within 7 days) Date last ___/___/___ | Name: First Last

3 → MISCELLANEOUS INFORMATION | Med Rec #: _____

3 → Sex: M F Gestational Age ___ weeks

4 → BIRTH FACILITY | Birth Order: single if multiple A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

4 → Facility ID (born at): _____ | Birthweight: _____ grams

4 → Name of Facility: _____ | (ONLY use grams, not pounds/ounces)

4 → Race/Ethnicity: (Fill in all that apply)

4 → White Black Asian Hawaiian / Pacific Islander Native American Other Unknown Hispanic

5 → SUBMITTER ID | FOLLOW-UP CARE | CHILD'S SPECIAL CONSIDERATIONS

5 → Collected at (facility): _____ | Follow-up Clinic ID: _____ | NICU HA/TPN Steroids Antibiotics

5 → Same as Birth Facility | Same as Submitter | (within 24 hours) | (within 7 days) | (within 24 hours)

6 → REFUSED: Check box if refused and sign form on reverse (required) | Transfused (RBC) Date last ___/___/___

Barcode number: 5398601X

Expires 2024-07-31

SATURATE EACH CIRCLE COMPLETELY BEFORE MOVING TO THE NEXT

The information requested on the screening card is critical to interpreting the laboratory test results and facilitating rapid communication with the baby’s medical provider. Complete all information on the card using a ballpoint pen. Please fill in bubbles completely. Avoid touching the filter paper while completing the form as this could contaminate the specimen. Instructions for completing each field on the card are as follows. See [How to Fill Out Newborn Screening Collection Cards](#) for a quick guide:

- Mother’s Information:** Write the mother’s legal first and last name. Do not use middle names. Be mindful of two-word names and which row is appropriate for which part of the name. The mother’s first and last name is used to link the infant’s first and second newborn screening specimens in the Newborn Screening Program computer system. This linking may not occur if this information is different on the two specimen cards. Without this linkage, the Newborn Screening Program may contact the health care provider to collect an unnecessary specimen because it appeared a specimen was not collected.
- Maternal Steroids:** Indicate if the mother received steroids in the last 7 days by filling in the “Maternal Steroids” bubble. Write the date when steroids were last administered to the mother. Maternal steroids can produce a false negative screening result for congenital adrenal hyperplasia (CAH). Steroids, in any form (oral, nasal, topical), can be transferred to the unborn baby through the mother if

received within seven days prior to delivery. Also, if the mother is nursing, steroids can be passed through the breast milk to the baby if the mother received steroids after delivery.

3. **Miscellaneous Information:** Indicate anything relevant, such as: adoption, foster care, surrogacy, child protective services, family history of a newborn screening disorder, or moving/transferring out of state. If none of these apply, this area may be used for your internal purposes (such as who collected the specimen, tracking numbers, etc.)
4. **Birth Facility:** Write the ID# for the hospital or birth center where the infant was born. The ID#s for birthing facilities are listed on the inside of the manila-colored portion of the screening card. If a home birth, write the individual midwife ID#. Individual midwife ID#s are available online, see [Midwife ID#s](#). If the infant is born in another state or country, please use the code “X-9999, Out of State” in this field and further identify the location of birth in the Miscellaneous Information section. For a complete list of ID#s, please visit our online [ID# Directories](#). The birth facility field assists in identifying the child when transferred as well as linking first and second specimens for all infants.
5. **Submitter ID:** Write the ID# of the facility that collected the infant’s specimen. If the collection facility is the same as the birth facility, you may fill in the “same as birth facility” bubble instead. If collected at the infant’s home, write the individual midwife ID#. The ID#s for birthing facilities are listed on the back of the screening card. For a complete list of ID#s, please visit our online [ID# Directories](#). The screening results will be sent to the submitter listed on the specimen card.
6. **Follow-Up Care:** Write the ID# of the facility where the child will receive outpatient care. If the child will remain in-house at the hospital, write the hospital’s ID#. If the child will be seen by a midwife, write the individual midwife ID#. If the same facility/midwife that collected the specimen will remain the infant’s outpatient care, fill in the “same as submitter” bubble. The facility or midwife listed on the card will be contacted when abnormal results require follow-up. Following-up on abnormal results promptly requires identifying the health care provider caring for the child. Every effort should be made to ensure the follow-up care ID# is provided. For a complete list of ID#s, please visit our online [ID# Directories](#).
7. **Blank Space:** This space is intentionally left blank to allow submitters an area to place bar code stickers or other internal use information. Do not allow stickers to cover any demographic information on the card or the shaded “Do Not Use This Area” box to the left. If you have a sticker that is too large to fit in this space, place it on the reverse side of the card. Information provided on stickers must be for your internal use only – any information provided by the sticker (such as baby name, sex, date of birth, mother’s name, etc.) will not be data-entered into the Newborn Screening computer system, all requested information must be written in the provided fields on the card.
8. **Date & Time of Infant’s Birth:** Write the date and time the child was born. Use of 24-hour based time or 12-hour time (with appropriate AM/PM bubble indicated) is acceptable. The date/time of birth and date/time of collection are used to calculate the exact age of the infant at the time the specimen was collected. The infant’s age when the specimen was collected is crucial to correctly interpret the screening results. Small age differences may determine whether a result will be classified as normal or abnormal.
9. **Date & Time of Specimen Collection:** Write the date and time when the specimen was collected. Use of 24-hour based time or 12-hour time (with appropriate AM/PM bubble indicated) is acceptable. The date/time of birth and date/time of collection are used to calculate the exact age of the infant at the time the specimen was collected. The infant’s age at the time when the specimen was collected is crucial to correctly interpret the screening results. Small age differences may determine whether a result will be classified as normal or abnormal.
10. **Child’s Name & Medical Record Number:** Write the child’s legal name if known and their medical record number. This allows for faster communication with healthcare providers.

11. **Sex:** Fill in the bubble corresponding with the biological sex of the infant. This information is used for determining follow-up advice for certain conditions detected.
12. **Gestational Age:** Write the obstetrical estimate of the newborn's gestation in completed weeks. Do not use punctuation.
13. **Birth Order:** Indicate the infant's birth order. Indicate "single" if there is only one birth or indicate the appropriate bubble for a multiple birth in that pregnancy. This information ensures the correct child is being identified.
14. **Birth Weight:** Write the weight of the child at birth. Do not write the weight of the child at the time of specimen collection; always write the infant's birth weight. This must be provided in grams. Do not provide pounds/ounces and do not use any punctuation (decimals or commas). The infant's birth weight is crucial to correctly interpret the screening results. Weight differences may determine whether a result will be classified as normal or abnormal.
15. **Race/Ethnicity:** Fill all the bubbles that apply for the infant. Include Aleut and Eskimo under Native American. Include all of the following under Asian: Asian Indian, Cambodian, Filipino, Japanese, Korean, Laotian, and Vietnamese. Include all the following under Hawaiian/Pacific Islander: Native Hawaiian, Guamanian, Samoan, Tongan, Fijian, Marshallese, and Tahitian. In addition to race, please indicate whether or not the child is of Hispanic ethnicity.
16. **Child's Special Considerations:** Indicate when the child is in the NICU or Special Care Nursery by filling in the "NICU" bubble. If the infant has received interfering substances such as HA/TPN, Steroids, Antibiotics, or a Red Blood Cell Transfusion prior to specimen collection, fill the appropriate bubble *if the substance was received within the timeframe below*:
 - **NICU:** When an infant is or will be in the NICU or Special Care Nursery
 - **HA/TPN:** If the child received HA/TPN within *24 hours prior* to specimen collection
 - **Steroids:** If the child received steroids within *7 days prior* to specimen collection
 - **Antibiotics:** If the child received antibiotics within *24 hours prior* to specimen collection
 - **RBC Blood Transfusions:** If received within 4 weeks. Indicate the date of last transfusion
 - **Dopamine:** Write this substance in the "Miscellaneous Information" section

These substances can interfere with screening tests by causing falsely elevated or lowered results. It is important to indicate when these substances have been received so the Laboratory can appropriately interpret the screening test results. See [Special Considerations](#) for more information.

17. **Refusals:** If a parent or guardian refuses the newborn screening test for religious reasons, fill the Refused bubble at the bottom of the card and have the parent or guardian sign the back of the card in the space provided. Still complete all demographic information on the card. See [Parental Right to Refuse](#) for more information.

SPECIMEN COLLECTION

The blood collection instructions described below are based on the approved standard published by the Clinical and Laboratory Standards Institute (CLSI). A video produced by this organization is available for loan. Posters on specimen collection and unsatisfactory specimen quality examples are also available. If you would like to borrow the video or order posters, please contact us. These are provided at no cost.

- [Specimen Collection Instructions](#)
- [Unsatisfactory Specimen Quality Examples](#)

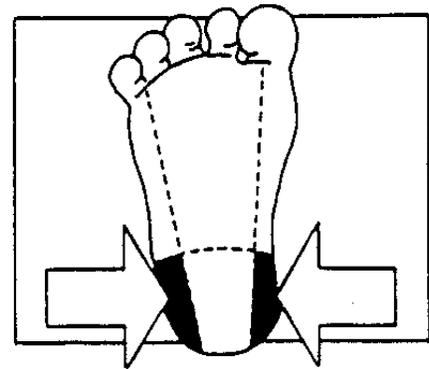
The following equipment will be needed for specimen collection: a sterile disposable lancet with a depth less than 2.0 mm, a sterile 70% isopropyl alcohol pad, sterile gauze, a moist towel or heel-warmer, the blood collection form, and gloves.

Gloves should be worn for personal safety. To prevent specimen contamination, do not touch the filter paper section of the specimen card with gloved or ungloved hands, or contaminate with alcohol, formula, water, powder, antiseptic solution, lotion, or other substances.

After confirming the identity of the infant and ensuring the expiration date of the card has not passed, place the infant's feet lower than the level of their heart in order to increase blood flow to the foot. To increase the blood flow at the puncture site, warm the heel for three to five minutes using a heel-warmer or a moist towel at a temperature no greater than 42°C (temperatures greater than this can burn the infant's skin.)

Select the puncture site. This should be the lateral or medial plantar surface of the heel, illustrated in the diagram below. Do not use a previous puncture site or the area at the heel curvature. The puncture must not be performed on the central area of the foot as this could result in damage to the nerves, tendons, and cartilage of the foot.

Cleanse the puncture site with the sterile alcohol pad and allow the heel to air dry. Using the sterile lancet, perform a swift clean puncture. Wipe away the first drop of blood with a sterile gauze pad. Allow another large drop of blood to form. To enhance blood flow, apply very gentle intermittent pressure with the fingers and thumb to the area surrounding the puncture. Avoid excess squeezing or "milking" as it contaminates the blood specimen with tissue fluid.



Appropriate puncture site for infant newborn screening specimen draw.

Lightly touch the blood drop to the filter paper circle and allow a sufficient quantity of blood to soak all the way through the paper to completely fill the circle. Do not press the paper against the puncture site. Apply blood to one side of the filter paper only and allow full saturation before continuing to the next circle. Repeat this until all circles are filled. It is permissible to "piggyback" successive drops of blood to the same circle only if you apply the additional drop of blood immediately after the previous incomplete drop was collected on the card (if you wait more than a few seconds, the blood will begin drying/clotting and will cause layering of the specimen). If a circle cannot be filled due to diminished blood flow, repeat the procedure on a new circle. It is important that complete saturation occur for each circle due to the quantitative measurements used by the testing equipment for screening. Results are based on a specific blood quantity within a particular sized sample. When blood does not soak completely through, the results are not comparable to lab standards and will be returned to the submitter as unsuitable.

After blood collection, elevate the foot above the body and gently press the puncture site with a sterile gauze pad or cotton swab until the bleeding stops.

Although the heel stick procedure is preferable, use of sterile capillary tubes for blood collection is acceptable (however, EDTA or citrate are unacceptable and will invalidate some test results). Follow the above procedures and apply approximately 75-100 μ L to each circle, using a new tube for each circle. Touch the tube to the formed blood drop and make a single application immediately to the paper. Do not touch the capillary tube to the filter paper when applying the blood: this can scratch or abrade the specimen, invalidating it for screening.

Blood collection from the dorsal hand vein is also an acceptable blood collection technique. However, do not use a vein into which IV fluids or blood is being or has been infused, as this will contaminate the specimen. After venipuncture, follow the steps outlined above for the heel puncture. For complete guidelines on specimen

collection please read the Clinical and Laboratory Standards Institute (CLSI) approved standard for [Blood Collection on Filter Paper for Newborn Screening Programs NBS01-A6](#).

DRYING & SHIPPING SPECIMENS

Drying Specimens: Allow the blood to air-dry horizontally on a drying rack or a clean, non-absorbent surface at ambient temperature (18 °C to 25 °C) for three hours. When drying multiple specimens, arrange so the blood from one specimen does not touch another specimen. Do not expose specimens to direct heat, sunlight, or high humidity. Do not store specimens in plastic bags as condensation will degrade the blood and cause the specimen to become unsuitable for testing. Once dry, fold the biohazard flap over the blood circles (do not tape or staple). Double check that all demographic information on the card has been completed prior to shipping.

Shipping Specimens: Place each specimen into the provided envelope. If sending more than one specimen, still use one envelope per specimen; otherwise, alternate so that the blood specimens do not come into contact with one another and place into a larger envelope (such as a FedEx package).

As required by law, specimens must be received at the Newborn Screening Laboratory within 72 hours after collection. This timeframe is critical as some newborn screening disorders can be deadly within days of birth. For high priority specimens (i.e., infants suspected to have one of the conditions screened), arrange for expedited specimen delivery and call our office to facilitate STAT testing (206) 418-5410, 1-866-660-9050 (toll free).

Please visit our website for the current laboratory [Specimen Receiving Hours](#).

SCREENING RESULTS

Screening results will be mailed to the facility that submitted the specimen. These results are to be used as a record for the child's medical chart. Carefully read the results for each child to verify that the specimen was suitable for testing and that no further actions are recommended. When possible, forward the results to the child's health care provider, especially when results are abnormal or unsuitable. The Newborn Screening Disorder Follow-up team will also follow-up on abnormal results. See the [Abnormal Results](#) section for more information.

REQUESTING SCREENING RESULTS

If the results are not received via mail within two weeks for a specimen that you submitted, please contact the Newborn Screening Program to obtain a copy of the results. Before calling, however, please verify that the results have not been misfiled, for example, under the mother's name. If you need NBS results urgently for clinical care of a child, please call the Newborn Screening Program at (206) 418-5410 and have the necessary demographic information available. When requesting multiple results, please fax your request to (206) 363-1610 using the Result Request form.

If you are requesting results for a specimen that you did not submit, i.e., to verify that a first or second test has been done, please contact the health care facility or provider that submitted the specimen, prior to contacting the Newborn Screening Program.

When requesting screening results please provide the following key demographic information: Mother's First, Mother's Last Name, Infant's Full Name, Infant's Date of Birth, and Date of Specimen Collection. If you do not know the date of collection, please specify if it is a first or second screen. If your facility did not collect the screen, please provide the submitter name/ID number.

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NEWBORN SCREENING PROGRAM: SCREENING TESTS, REPORTING RESULTS AND FOLLOW-UP**REPORTING RESULTS**

Results are sent to the facility that submitted the specimen. Over 90% of results are finalized and mailed within five days of specimen receipt; over 99% are mailed within seven days. If you receive a result report or letter that does not belong to a patient within your facility, please fax the results back to the Newborn Screening Program indicating such (fax: 206-363-1610). Newborn screening results fall within three broad categories: normal, abnormal, and unsatisfactory. Abnormal and unsatisfactory result reports contain an additional page of information including our interpretation of the results and recommendations for follow-up testing, when necessary. An additional page may also be included to note modifications made to demographic information on the screening card that was missing, invalid, or incorrect.

The NBS Follow-Up program responds to abnormal and unsuitable results, a separate document for each disorder detailing the [screening tests, result classifications and corresponding follow-up actions](#) is available and linked for each disorder within this document.

NORMAL RESULTS

Normal results will be sent to the submitter and are to be placed in the child's medical record. Collect the routine second screen for each infant at 7-14 days of age even when the results of the first screen are normal. The first screen is essential for making an early diagnosis to prevent immediately life-threatening complications from some of the disorders. See [Timing of Screening](#) section for additional details. **IMPORTANT: Further testing may benefit a child presenting with pertinent signs and symptoms regardless of normal newborn screening results. Normal NBS results should not prevent a diagnostic work-up in cases where a particular disorder is highly suspected.**

ABNORMAL RESULTS

Abnormal screening results are generally divided into two groups depending on their urgency ("predictive value"): borderline and presumptive positive. Each abnormal result is reviewed by Disorder Follow-up to determine the appropriate follow-up actions which are influenced by a variety of factors including the age at collection, birthweight, severity of the disorder, previous results, the value of the abnormal analyte and the infant's clinical status. The majority of abnormal results are resolved by normal results on the routine second screen.

In general, for borderline results or hemoglobin traits, the results are mailed to the submitter with a request to collect a follow-up screen. If a second specimen is not received within two to four weeks to verify results, the child's primary health care provider will be contacted. See the [Requests for Repeat Screening](#) section.

In the event of significant abnormal results, such as presumptive positive levels or a clinically significant hemoglobin disorder, the child's primary health care provider (as indicated by the screening card) is immediately contacted with appropriate recommendations for further testing. The recommendations may involve submitting another newborn screening specimen or following up with diagnostic testing and referral to a medical specialist. All abnormal results are also reported by mail to the submitter with a note indicating the recommended follow-up actions.

Special requirement only for babies needing diagnostic testing based on abnormal newborn screening results: State law requires that health care providers notify the Newborn Screening Program of the date they communicated the need for diagnostic testing to the parent(s) or guardian(s). You will be sent a form requesting the date whenever it is required.

REQUESTS FOR REPEAT SCREENING

When necessary, the Newborn Screening Program will contact the primary health care provider to advise of the need for a repeat specimen. This will occur, for example, if a previous specimen was unsuitable for screening or if there was a previous abnormal test result. This request does not mean that the child has one of the disorders screened, but that another specimen is needed to evaluate the child's status. If you receive a request for another specimen, please contact the parent or guardian as soon as possible to help facilitate.

UNSUITABLE SPECIMENS

Some specimens are considered unsatisfactory due to improper collection, transport, or drying. Nevertheless these specimens can still provide valuable information for an affected child. The Newborn Screening Laboratory will test all unsuitable specimens for extreme values, however, the accuracy of the results is compromised and another specimen must be submitted for the child as soon as possible. This postpones proper screening and risks delaying treatment for a baby affected with one of the disorders. When a specimen is considered unsatisfactory by our laboratory, the results will include an additional page with a disclaimer stating the results are invalid, the reason why, and request the collection of another specimen for the infant. Please see the [Specimen Quality Examples](#) and the [Unsatisfactory Specimen Descriptions](#) for the various causes of unsuitable specimens.

REPORT FORMAT

The Newborn Screening Result Reports are mailed to the submitter of the specimen upon completion of testing. Reports include:

- Many results reports will contain an address cover sheet. It may contain an important message from the screening program about a recent change in reporting or follow-up recommendation.
- The first page contains the results for an individual child. The State lab number and medical record number for that child are listed on the top and followed by the demographic information as completed on the newborn screening card by the submitting facility. The next section contains the screening results for all disorders tested, including the result and the classification.
- The second page provides normal ranges for the tests. If normal ranges are blank for some tests, relevant demographic information was missing from the collection card, i.e. date and time of birth, date and time of collection or birth weight. We use this demographic information to determine normal ranges for several tests.
- A third page is included for specimens with abnormal or unsuitable results. It contains more detailed information: interpretation of the results, recommendations for follow-up, and actions taken by the Newborn Screening staff. It is important that this page be stored with the results on the previous page.

PROGRAM REQUESTS FOR INFORMATION

The Newborn Screening Program sometimes needs more information to correctly identify the infant, to interpret the results for the infant, or to contact the infant's follow-up care provider. To obtain this information, the hospital or other known health care provider is contacted. As a public health program, the Newborn Screening Program is exempt from the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) and is allowed to collect and receive protected health information to provide our services. The information that is provided is kept confidential, as is the information on the screening card. Prompt responses to requests for information are appreciated.

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SPECIAL CONSIDERATIONS

TRANSFUSIONS

Specimens collected following red blood cell transfusions will yield invalid results for galactosemia and hemoglobinopathy screening. Thus, the first newborn screening specimen should be obtained prior to transfusion whenever possible. In the event that the first screening specimen is collected after a transfusion, please write the date of the last transfusion on the screening card. To obtain a valid screen for babies in these circumstances, the following schedule should be followed.

Collection Schedule: Collect the two routine specimens within the recommended timeframes (because screening results for the remaining disorders are not affected by transfusions) and a subsequent specimen at least four weeks after the last transfusion.

PREMATURE INFANTS AND SICK INFANTS

The Washington State Newborn Screening Program recommends that all infants weighing less than 1500 grams at birth and sick infants requiring a hospital stay of three weeks or more should have a third specimen collected and submitted. Recent studies and our own experience in Washington State indicate that premature and sick infants with congenital hypothyroidism can have a late onset of thyroid stimulating hormone (TSH) elevation that is not detected on the earlier specimens. This delay may be caused by the immaturity of the hypothalamic pituitary-thyroid axis or side effects of some medications such as dopamine, topical povidone iodine and steroids.

Collection Schedule: Collect the first NBS between 18 and 48 hours of age (or prior to interfering substances), the second at 7 to 14 days and the third between 4 to 6 weeks of age, or prior to discharge (whichever comes sooner).

There is no extra charge for the additional specimen; our one-time fee covers all testing that may be needed. Please see a one page synopsis of [Special Considerations](#) for NICU and Special Care Nurseries for more information.

TRANSFERRED INFANTS

The facility of birth or birth attendant (if the child is born out of the hospital) is legally responsible to collect a newborn screening specimen or signed parental refusal. Therefore, they should inform the new facility of the screening status and ensure that a specimen is collected within the recommended timeframe. Screening status should be documented in the infant's records at transfer. If possible, a specimen should be collected prior to transfer to another facility; even if the infant is less than 18 hours old. If the new facility finds no record of screening status, a specimen should be obtained within the recommended timing for screening (18-48 hours of life), or as soon as possible. This rule also applies to infants who are transferred to or from a hospital outside of Washington State.

BIRTH OR RESIDENCE OUTSIDE OF WASHINGTON STATE

Newborn screening is a state-run public health program. Therefore, it is preferred that infants are tested in the state of their birth (or arrangements made for the specimen to be collected on the state-specific newborn screening card and sent to the appropriate laboratory). However, the Washington State Laboratory will test all specimens it receives regardless of place of birth --please note that Washington State bills the submitter of the first specimen for each infant tested. When it is unclear if an infant has received screening in a different state or

country, we encourage the collection of a newborn screening specimen to be tested here in Washington. See [Timing of Screening](#) and [Screening Older Children](#) sections for recommended specimen collection timeframes.

If an infant is born outside of Washington State but is having a newborn screening specimen collected from a Washington health care facility, it is important that this be noted on the newborn screening card. In the Birth Facility field use the code “X-9999, Out of State” (also means “out of country”) and add any further details identifying the previous facility and state of birth to the Miscellaneous Information section.

If an infant will not reside in Washington State after birth or discharge from a Washington health care facility, it is important that this be noted on the newborn screening card. In the Follow-Up Facility section use the code “X-9999, Out of State” and add any further details identifying the anticipated health care provider, facility, and state of residence to the Miscellaneous Information section. Alternatively, a limited number of facilities outside of Washington State have ID numbers that can be found on our website, see [Out of State ID#s](#).

CHILDREN WHO ARE ADOPTED, IN FOSTER CARE OR IN PROTECTIVE CUSTODY

We recommend the collection of a newborn screening specimen for an infant whose screening status is unknown because they have been adopted or are in foster care or protective custody.

Complete the demographic information on the card as best as possible and add any additional information known about the child in the Miscellaneous Information section of the screening card.

- For babies who will be adopted or foster care or protective custody: please provide the infant’s adoptive name, adoptive parent or legal guardian’s name (if known), and the name and contact info of the social worker or adoption agency involved to facilitate follow-up as necessary.
- For babies who have already been adopted or are in foster care or protective custody: please indicate any previous names or medical record numbers of the infant, date and time of birth, and facility (if known) or geographic location where baby was born to facilitate linking to previous results.

These additional details will expedite follow-up when the first test has the biological mother’s name and the second has the adoptive mother’s name. Without this information, the two tests may not be linked and would be treated as two different infants. Information on adoptions will be kept confidential as with all information provided to the Newborn Screening Program. Please contact us for additional guidance.

INFANTS WITH CLINICAL SIGNS OF THE DISORDERS SCREENED

As with all laboratory testing, newborn screening may yield false negative results. **Regardless of the results of the newborn screen, the child’s health care provider should proceed with diagnostic testing on any infant exhibiting clinical signs and symptoms.** In this situation please alert the Newborn Screening Program by calling (206) 418-5410.

INFANTS WITH FAMILY HISTORY OF THE DISORDERS SCREENED

For any infant with a first-degree relative affected by one of the newborn screening disorders, please alert the Newborn Screening Program by calling (206) 418-5410 to expedite testing. In addition, please contact an appropriate medical specialist, ideally prenatally, to determine if any diagnostic testing or genetic counseling is indicated.

SCREENING OLDER CHILDREN

Some children are not tested at birth, including those who immigrate into the United States. In addition, there may be children for whom screening status is not known, including children who have been adopted or are in

foster care or protective custody. We recommend that a specimen be obtained for these children at the first well-child visit. Screening older children is valid for most of the disorders up to 6 months of age. It is very important that the date of birth be written on the card so that the results may be correctly interpreted. The newborn screening tests are validated for newborns and results diminish in value as a child ages. Please indicate the immigration or adoption status in the Miscellaneous Information section.

SCREENING FOR DISORDERS NOT DETECTED IN WASHINGTON'S PANEL

There are other disorders that may be screened for at birth that are not included in the Washington State Newborn Screening Panel. If the family is interested in obtaining expanded newborn screening beyond what we offer, there are laboratories that will perform supplemental screening for over 20 additional metabolic disorders for a fee. [Mayo Medical Laboratories](#) offers expanded screening through hospitals, physicians and other health care providers only. [PerkinElmer Genetics Inc.](#) (formerly Pediatrix Screening) has a screening kit that can be ordered online by providers or parents. Please contact these laboratories directly, ideally prenatally, for further information.

STORAGE OF NEWBORN SCREENING CARD

The Newborn Screening Program retains all specimen cards for 21 years after the birth of the child. These forms are retained as a part of the child's medical records consistent with requirements for hospital records for minors. As health care information, the specimens and associated information are protected by law (Chapter 70.02 Revised Code of Washington, Medical Records - Health Care Information Access and Disclosure) and cannot be used for purposes other than newborn screening except as allowed by the law. Such uses have included testing the specimen for a disease diagnosed in the child later in life. For more information, please see the Newborn Screening [Privacy Policies](#).

NEWBORN SCREENING FEE

The Newborn Screening Program is a self-supporting fee-based program. A fee for each infant tested is charged to the facility that collected the infant's initial specimen (typically the hospital of birth). This one-time fee is charged per infant screened, not per specimen. The fee funds all activities of this comprehensive screening program. Diagnostic testing and medical treatment, when necessary, will involve additional costs. Please see [Screening Cost](#) for more information.

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Amino Acid Disorders

(1 in 10,000 Washington births)

The Washington State Newborn Screening Program screens for the following six Amino Acid Disorders. The disorders highlighted in red can be life-threatening if not detected and treated within days following birth:

Argininosuccinic acidemia (ASA)

Citrullinemia (CIT)

Homocystinuria (HCY)

Maple syrup urine disease (MSUD)

Phenylketonuria (PKU)

Tyrosinemia type I (TYR-I)

Definition	Inability to break down amino acids, found in all foods containing protein
Screening Test	Measure amino acid levels by tandem mass spectrometry
Impact without Early Treatment	Intellectual and developmental disability, seizures, coma & death
Treatment	Dietary restriction of offending amino acid(s) & needs special metabolic formula
Benefits of Early Treatment	Prevent death, intellectual and developmental disability and other neurological damage

ARGININOSUCCINIC ACIDEMIA (ASA) & CITRULLINEMIA (CIT)

Argininosuccinic acidemia (ASA) and Citrullinemia (CIT) are amino acid disorders affecting the urea cycle and caused by a deficiency of argininosuccinate lyase and argininosuccinic acid synthetase, respectively. A deficiency in either enzyme causes a build-up of citrulline and ammonia in the bloodstream. High ammonia levels in the blood are severely toxic to the brain and can lead to seizures, coma and death. Early detection and treatment can reduce the mortality and morbidity associated with these disorders. However, even with treatment, the clinical presentation of these conditions varies.

CLINICAL FEATURES

ASA/CIT has two forms:

1. A severe, early form that presents within 2 days to 5 months of age (frequently misdiagnosed as sepsis)
2. A sub-acute, late form presents in adolescence and adulthood (the less severe course can make diagnosis difficult).

Both forms may present with lethargy, feeding difficulties and vomiting. Seizures progressing to coma and death are typical in untreated patients. Even with early treatment, some patients may have progressive mental disability depending on ammonia surges associated with metabolic imbalances, dietary protein load and incurrent infections. The prognosis is generally better for the late-onset form than the early-onset form.

ETIOLOGY

Argininosuccinic acidemia is caused by a deficiency of argininosuccinate lyase enzyme and results in elevated plasma argininosuccinic acid, citrulline and ammonia levels. Citrullinemia is caused by a deficiency of argininosuccinic acid synthetase enzyme and results in elevated plasma citrulline and ammonia levels. Both disorders are inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for these disorders is performed by tandem mass spectrometry (MS/MS). The primary marker for both ASA and CIT is citrulline (cit). If citrulline is elevated, secondary markers are analyzed. Screening result classifications are available following the links below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

The best developmental outcomes are achieved by keeping ammonia concentrations less than 480 $\mu\text{mol/L}$. This is accomplished with a high-caloric, protein-restrictive diet, supplemented with arginine. Sodium phenyl butyrate is the drug of choice used to clear ammonia from the body. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Liver transplant is a radical alternative therapy to the classical dietary and medical regimen. Ammonia concentrations in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms without impairing growth and intellectual development. Treatment must continue throughout life and people with ASA and CIT should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. **Parents should always travel with a letter from the child's physician with treatment guidelines in any case that may necessitate hospital admission during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of ASA and CIT includes a plasma amino acid profile, urine amino acid and urine organic acid analyses, which are performed at Seattle Children's Biochemical Genetics laboratory.
- Citrulline levels increase moderately during the first few weeks of life in many babies so the normal ranges are based on the age of the baby at the time of blood collection. Some babies with mild CIT or mild ASA may have normal NBS results.
- General anesthesia should be avoided as this may cause elevated ammonia levels.
- Hyperammonemia is not specific to ASA and CIT. It may be seen transiently in newborns within the first 24 hours of life or may be associated with congenital herpes simplex virus (HSV) infection, or seen in other organic acid disorders.
- Late-onset cases of ASA/CIT are likely to be missed if blood is collected when the baby is less than 72 hours old.
- Washington State began screening for ASA and CIT in July 2008.

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HOMOCYSTINURIA (HCY)

Homocystinuria is characterized by a defect in the metabolism of the amino acid methionine, usually due to a deficiency of the enzyme cystathionine β -synthase. If untreated, approximately 50% of those with homocystinuria die before the age of 25 years, typically from thromboembolic events. Developmental delay, mental disability, psychiatric disturbances, seizures, displacement of the lens of the eye, nearsightedness, scoliosis and osteoporosis are also commonly present. Initial treatment of homocystinuria consists of providing the baby with a formula that does not contain methionine. A methionine-restricted cysteine-supplemented diet may be required throughout life and administration of vitamin B6 (pyridoxine) is also often prescribed. The birth prevalence homocystinuria in the United States is approximately 1 in 200,000.

CLINICAL FEATURES

Infants with homocystinuria appear normal at birth and early symptoms of the disorder are indistinct. Delayed development is usually noticed before 3 years of age. Nearsightedness is the first sign of lens dislocation. Signs of homocystinuria are similar to that of Marfan syndrome. Besides ocular abnormalities, affected individuals also have tall, thin statures with long limbs, spidery fingers and pectus deformity of the chest. Mental disability, psychiatric disturbances, and thinning and weakness of the bones are also common. Individuals frequently develop blood clots, which can cause life threatening thromboembolic episodes.

ETIOLOGY

Homocystinuria is commonly caused by a deficiency in one of the enzymes needed to properly metabolize the amino acid methionine. At least nine genetic defects have been shown to disrupt the major pathway in which methionine is metabolized. Cystathionine β -synthase deficiency is the most common and results in high levels of serum methionine. Homocystinuria is inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for homocystinuria is performed by tandem mass spectrometry (MS/MS). The primary marker for homocystinuria is methionine (met). If methionine is elevated, then secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment for homocystinuria varies, but usually consists of a methionine-restricted, cysteine-supplemented diet, folic acid supplements and, if effective, high doses of vitamin B6. Slightly less than 50% respond to vitamin B6 therapy, and those that do should continue throughout their life. Treatment appears to reduce the risk of thromboembolic episodes, seizures, and mental disability and delays lens dislocation. Treatment must continue throughout life and people with homocystinuria should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.

MISCELLANEOUS INFORMATION

- Diagnostic work-up of Homocystinuria includes a plasma amino acid profile and plasma total homocysteine analyses, which are performed at Seattle Children's Biochemical Genetics laboratory.

- Some babies with homocystinuria may have normal results on the first NBS since methionine levels sometimes take several days to build up to abnormal levels.
- The homocystinuria screening test may yield equivocal results for babies who have received hyperalimentation or other therapeutic infusions. The result will be reported as “invalid” and a follow-up screen will be recommended when treatment is concluded.
- Washington State began screening for homocystinuria in June 2004.

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MAPLE SYRUP URINE DISEASE (MSUD)

Maple syrup urine disease (MSUD) is characterized by an inability to metabolize the branched-chain amino acids leucine, isoleucine and valine due to an enzyme deficiency in the branched-chain alpha-keto acid dehydrogenase complex. If untreated, the most severe form of MSUD can result in death within the first weeks of life. Less severe forms of MSUD will result in mental disability and metabolic decompensation during times of stress. Treatment consists of a special diet low in leucine, isoleucine and valine. The birth prevalence MSUD in the United States is approximately 1 in 200,000.

CLINICAL FEATURES

There are four general classifications used to describe the variants of MSUD: classic, intermediate, intermittent and thiamine-responsive. In the most common type, classic MSUD, infants appear normal at birth but develop symptoms within four to seven days. Symptoms include poor feeding and failure to thrive, vomiting, lethargy, hypotonia or hypertonia and the characteristic maple syrup smell of their urine. Babies with classic MSUD will die within the first year of life if untreated.

ETIOLOGY

MSUD is caused by a deficiency of one of the enzymes involved in the branched-chain alpha-keto acid dehydrogenase complex, which is needed to metabolize the essential amino acids leucine, isoleucine and valine. It is inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for MSUD is performed by tandem mass spectrometry (MS/MS). The primary marker for MSUD is leucine (leu). If leucine is elevated, then secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of MSUD involves dietary restriction of branched-chain amino acids and requires frequent dietary monitoring that must continue throughout life. Levels of plasma branched-chain amino acids are measured to calculate the appropriate dietary restriction required for an individual to avoid symptoms of MSUD without impairing growth and intellectual development. Glucose and insulin infusions are commonly given during episodes of acute metabolic decompensation. Treatment must continue throughout life and people with MSUD should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. **Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of MSUD includes a plasma amino acid analysis, which is performed at Seattle Children's Biochemical Genetics laboratory.
- Some babies with non-classic MSUD may have normal results on the first NBS.
- The MSUD screening test may yield equivocal results for babies who have received hyperalimentation or other therapeutic infusions. The result will be reported as "invalid" and a follow-up screen will be recommended when treatment is concluded.

- Washington State began screening for MSUD in June 2004.

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PHENYLKETONURIA (PKU)

Phenylketonuria (PKU) was the first disorder targeted by universal newborn screening. PKU is characterized by the inability to metabolize the essential amino acid phenylalanine due to the lack of the enzyme phenylalanine hydroxylase. If untreated, PKU results in severe neurological and developmental damage. Treatment consists of a special diet low in phenylalanine. Affected infants develop normally with early identification and proper dietary management. The birth prevalence of PKU in the United States is approximately 1 in 10,000-25,000. On average, seven infants with PKU are detected each year in Washington State.

CLINICAL FEATURES

Infants with PKU appear normal at birth. The symptoms of untreated PKU develop gradually, so they may not be noticed until irreversible mental disability has occurred. The most common symptoms of untreated PKU are the following: a “musty” odor to the skin and urine, increased muscle tone and tendon reflexes, an eczema-like rash, and progressive neurological damage. With early treatment virtually all symptoms of the disorder are eliminated.

ETIOLOGY

PKU is caused by a deficiency in the enzyme phenylalanine hydroxylase, which metabolizes the common amino acid phenylalanine. It is inherited in an autosomal recessive fashion. Although the exact pathogenesis of the damage to the central nervous system is still not clear, it seems likely that an increased concentration of phenylalanine in the blood is associated in some way with the neurodegenerative effects.

SCREENING TEST

PKU screening is no longer performed by the bacterial inhibition assay developed by Dr. Robert Guthrie, commonly known as the “Guthrie test.” Screening is now performed by tandem mass spectrometry (MS/MS). The primary marker is phenylalanine (phe). If phe is elevated, then the phenylalanine-tyrosine (tyr) ratio is analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Early and proper initiation of a low-phenylalanine diet will prevent the mental disability that occurs in untreated PKU. Strict dietary restriction of natural protein is required to reduce high blood phenylalanine levels. This is accomplished by the intake of a special metabolic formula (i.e. Phenyl-Free®) supplemented by low-protein foods and avoidance of aspartame (NutraSweet®). Treatment should be started as soon as the diagnosis is confirmed and should be continued indefinitely to optimize normal physical and mental development. Ongoing medical management with regular monitoring of phenylalanine levels is provided by a multidisciplinary team at the University of Washington (UW) PKU Clinic. The staff consists of a pediatric biochemical geneticist, nutritionists, a social worker, and genetic counselor. The special metabolic formula is distributed by the Newborn Screening Program in collaboration with the PKU Clinic.

MATERNAL PKU

As stated above, treatment for PKU should be continued throughout one’s life. It is especially critical that women of childbearing age maintain very strict dietary control. Women with high levels of phenylalanine during pregnancy are at increased risk of fetal loss, fetal brain damage, and other birth defects. If blood phenylalanine

levels can be kept very low prior to conception and throughout the entire pregnancy, damage to the fetus can be minimized or avoided.

Offspring of women who have PKU may have a transient elevation of phenylalanine on their newborn screening test. This level will fall to normal within a few days, unless the child has PKU (a 1 in 200 chance).

MISCELLANEOUS INFORMATION

- Diagnostic work-up of PKU includes a plasma amino acid profile and urine and blood samples for bipterin testing. Diagnostic testing is performed at Seattle Children’s Biochemical Genetics laboratory and coordinated through the Newborn Screening Program in collaboration with the UW PKU Clinic.
- The false negative rate for PKU depends on the age at which the infant is screened. A small percentage will be missed if the screening is done very early (prior to 12 hours of age). In Washington State, approximately 96% of infants with PKU are detected on the first newborn screen. Occasionally, milder forms of PKU may not be detected until the second screen.
- The PKU screening test may yield equivocal results for babies who have received hyperalimentation or other therapeutic infusions. The result will be reported as “invalid” and a follow-up screen will be recommended when the infusion treatment is concluded.
- Prior feeding is not necessary to detect PKU, contrary to the previously common belief that infants must have at least 24 hours of feeding before the PKU test is accurate.
- Washington State began voluntary screening for PKU in 1963 and it was mandated by law starting in 1976.

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TYROSINEMIA TYPE I (TYR-I)

Tyrosinemia type I (TYR-I) is an amino acid disorder caused by a deficiency of fumaryl acetoacetate hydrolase. Deficiency of this enzyme causes a build-up of tyrosine and succinylacetone in the bloodstream. This is severely toxic to the liver, kidneys, heart and the nervous system, which can lead to multi-organ failure, seizures, coma and death. Early detection and treatment can reduce the mortality and morbidity associated with this disorder. However, even with treatment, the clinical presentation of this condition varies. The birth prevalence of TYR-I in the United States is approximately 1:100,000.

CLINICAL FEATURES

TYR-I has two forms: 1) An early-onset form (which is more common) that presents within the first 3 months of age and 2) A late-onset form that presents in older children and adulthood. Without early treatment, both forms may present with diarrhea, vomiting, poor weight gain, jaundice, enlarged liver, edema (swelling of the abdomen or feet), painful abdominal crises, irritability and a characteristic “cabbage-like” odor in the skin and urine. Current treatment is highly effective in avoiding these clinical complications.

ETIOLOGY

TYR-I is caused by a deficiency of fumaryl acetoacete hydrolase enzyme and results in elevated tyrosine and succinyl acetone levels. It is inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for these disorders is performed by tandem mass spectrometry (MS/MS). The most sensitive and specific primary marker for TYR-I is succinylacetone (SUAC). If this is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of TYR-I involves dietary restriction of protein, particularly the amino acids tyrosine and phenylalanine, through use of a special dietary formula. **2-nitro-4-trifluoro-methylbenzoyl-1, 3-cyclohexanedione** (NTBC), also known as Nitisinone (generic name) and Orfadin (brand name), is the drug of choice. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Clinical monitoring of affected individuals is done by measuring plasma amino acids, albumin, succinylacetone and NTBC levels. Treatment must continue throughout life and people with TYR-I deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. **Parents should always travel with a letter from the child’s physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of TYR-I includes a plasma amino acid profile, urine organic acid and urine succinylacetone analyses, which are performed by Seattle Children’s Biochemical Genetics laboratory.
- TYR-II, TYR-III and the late onset form of TYR-I will most likely not be detected by our newborn screening methods.
- False negative results can occur when specimens are obtained following a blood transfusion.

- TYR-I is common among people of French-Canadian descent. The birth prevalence in this population is 1:2,000.
- Washington State began screening for TYR-I in September 2008.

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Fatty Acid Oxidation Disorders

(1 in 13,000 Washington births)

The Washington State Newborn Screening Program screens for the following five Fatty Acid Oxidation Disorders. The disorders highlighted in red can be life-threatening if not detected and treated within days following birth:

Carnitine uptake deficiency (CUD)

Long-chain L-3-hydroxy acyl-CoA deficiency (LCHAD)

Trifunctional protein (TFP) deficiency

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency

Definition	Inability to process or break down fats in the body
Screening Test	Measure acylcarnitine levels by tandem mass spectrometry
Impact without Early Treatment	Serious damage to brain, liver, heart, eyes, muscles & death
Treatment	High carbohydrate, low-fat diet & avoidance of fasting
Benefits of Early Treatment	Prevent death, intellectual and developmental disability and other neurological damage

CARNITINE UPTAKE DEFICIENCY (CUD)

Carnitine Uptake Deficiency (CUD) is a fatty acid oxidation disorder characterized by a defect in the transport of carnitine. This condition can cause heart disease, mental disability, developmental delay in both motor and cognitive functions, and possibly death. Early identification and treatment reduces the mortality and morbidity associated with CUD. Even with treatment, the clinical presentation of CUD varies.

CLINICAL FEATURES

The onset may occur during the first two years of life, the most vulnerable period for metabolic crises. An illness or period of fasting can precipitate a metabolic crisis. Acute episodes are associated with refusal to feed, vomiting, listlessness, and lethargy, progressing to coma and death if not managed aggressively. Cardiomyopathy, liver complications, mental disability, developmental delay and muscle weakness may present later in life. With early detection and treatment, children with CUD often live healthy lives with normal growth and development.

ETIOLOGY

CUD is caused by a defect in the sodium-dependent organic cation transporter-1 enzyme. This defect affects the transport of carnitine into the skeletal muscles, heart and kidneys, leading to an impairment of fatty acid oxidation. Normal carnitine transport is also essential in renal reabsorption of carnitine to maintain normal plasma carnitine levels. CUD is inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for CUD is performed by tandem mass spectrometry (MS/MS). The primary marker is free carnitine (CO). If CO is low, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of CUD consists of avoiding fasting, supplementing the diet with carnitine, and consuming high-carbohydrate, low-fat meals. Treatment must begin immediately upon diagnosis before irreversible organ damage occurs. Treatment must continue throughout life, and people with CUD should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of CUD includes plasma acylcarnitine profile and blood free carnitine analyses, which are performed by Seattle Children's Biochemical Genetics laboratory.
- Some babies have abnormal CUD screening results because their mothers have low free carnitine (either from undiagnosed maternal CUD or from nutritional carnitine deficiency). Therefore, when diagnostic work-up occurs for the infant, maternal samples for plasma acylcarnitine profile and blood free carnitine analyses should be collected concurrently.

- In some cases bacterial metabolism in the intestine results in carnitine degradation and production of trimethylamine (a non-toxic chemical with a very unpleasant odor). This responds well to oral therapy with metronidazole (an antibiotic effective against anaerobic bacteria).
- Administration of certain drugs such as valproic acid and other compounds like benzoic acid and pivalic acid can cause false positive test results.
- Other differential diagnoses for reduced plasma carnitine concentrations include: 1) patients with renal Fanconi's syndrome and 2) carnitine-free feedings in neonates on intravenous alimentation
- Other names for CUD include Primary Carnitine Deficiency and Carnitine Transporter Deficiency.
- Washington State began screening for CUD in July 2008.

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LONG-CHAIN L-3-HYDROXYL ACYL-CoA DEFICIENCY (LCHAD) & TRIFUNCTIONAL PROTEIN (TFP) DEFICIENCY

Long-chain hydroxy-acyl CoA dehydrogenase (LCHAD) deficiency and trifunctional protein (TFP) deficiency are inborn errors of fatty acid oxidation characterized by deficiencies in a multi-enzyme complex deficiency that results in failure to break down long-chain fatty acids for energy metabolism. These conditions can damage the heart, brain, kidneys and vision and can rapidly progress to death. Early identification and treatment reduces the mortality and morbidity associated with LCHAD and TFP deficiencies. Even with treatment, the clinical presentations of these disorders vary. Their combined birth prevalence is approximately 1 in 105,000.

CLINICAL FEATURES

The clinical presentation of these disorders is classified into three groups:

1. A severe, neonatal cardiac form characterized by early onset of heart disease (cardiomyopathy) and sudden infant death. Even with early detection and treatment, due to multi-system involvement and recurrent metabolic crises only a few patients have survived.
2. An early onset form affecting the liver presents in the first month of life. It is characterized by failure to thrive, vomiting, episodes of low blood sugar levels, seizures, and lethargy. With early detection and treatment, survival rate is improved.
3. A later onset form is noted after childhood and generally presents with muscle pain and weakness induced by exercise and strenuous physical activities. In most patients, nerve sensations such as tingling precedes breakdown of muscle tissues. With early detection and treatment, symptoms may be preventable.

ETIOLOGY

LCHAD deficiency is caused by an isolated deficiency of the long-chain hydroxyl-acyl CoA dehydrogenase enzyme. TFP deficiency is caused by markedly reduced activity of a multi enzyme complex (including long-chain hydroxy-acyl Co-A dehydrogenase and two other enzymes: long-chain enoyl Co-A hydratase and long-chain keto-acyl Co-A thiolase). These three enzymes play important roles in the fatty acid oxidation pathway that produces energy during periods of metabolic stress and glycogen depletion after prolonged fasting. They are both inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for these disorders is performed by tandem mass spectrometry (MS/MS). The primary marker for LCHAD and TFP deficiencies is 3 hydroxy-hexadecanoylcarnitine (C16OH). If C16OH is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of LCHAD and TFP deficiencies consists of avoidance of fasting with frequent high-carbohydrate, low-fat meals, and medium chain triglyceride (MCT) oil to replace long chain fatty acids. Treatment must begin immediately upon diagnosis before irreversible organ damage occurs. Oral carnitine supplementation and docosahexanoic (DHA) diet may also be prescribed. People with LCHAD or TFP deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should**

always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.

MISCELLANEOUS INFORMATION

- Diagnostic work-up of LCHAD and TFP deficiencies includes a blood acylcarnitine profile and urine organic acid analysis. If these are abnormal, they are followed by enzyme studies in fibroblasts and DNA analysis. Diagnostic testing is performed at Seattle Children's Biochemical Genetics laboratory.
- LCHAD deficiency in a fetus predisposes the mother to the gestational complications of HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and AFLP (acute fatty liver of pregnancy). Prenatal molecular diagnosis is possible and valid in guiding the management of pregnancies in families with confirmed TFP and LCHAD deficiency.
- Washington State began screening for LCHAD and TFP deficiencies in July 2008.

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MEDIUM-CHAIN ACYL-COA DEHYDROGENASE (MCAD) DEFICIENCY

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is characterized by the inability to produce adequate amounts of an enzyme involved in the metabolism of medium chain fatty acids. Proper production of the MCAD enzyme is critical in the process of providing fuel for the body during periods of extended fasting and higher energy demands. If untreated, MCAD deficiency can lead to metabolic failure, seizures, coma and death. Treatment consists of avoiding fasting by eating frequent meals, reducing dietary fat, and carnitine supplementation. The birth prevalence of MCAD deficiency in the United States is approximately 1 in 20,000.

CLINICAL FEATURES

Infants with MCAD deficiency appear normal at birth but often develop symptoms between three and 24 months of age in response to either prolonged fasting or common illness. However, without these environmental triggers survival can continue through adulthood. Clinical signs are variable and may be confused with other fatty acid oxidation disorders. Infants may present with hypoglycemia, vomiting, and lethargy, which may progress to seizures, coma, and sudden death. Hepatomegaly and acute liver disease are often present. Approximately 20% of those affected die during the first crisis.

ETIOLOGY

MCAD deficiency is caused by a deficiency in the medium-chain acyl-CoA dehydrogenase enzyme, which results in a defect of fatty acid beta-oxidation, a major source of energy when the body's hepatic glycogen stores are depleted. MCAD deficiency is inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for MCAD deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker for MCAD deficiency is octanoyl carnitine (C8). If C8 is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment for MCAD deficiency is simple and appears to be very effective. Those affected need to avoid fasting by having frequent meals and limiting their intake of medium- and long-chain fatty acids. In circumstances where food cannot be tolerated, such as during an illness, intravenous glucose support may be required. Carnitine supplementation is sometimes prescribed to correct for secondary carnitine deficiency and to help eliminate toxic metabolites. People with MCAD deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of MCAD deficiency includes a blood acylcarnitine profile, urine organic acid and acylglycine analyses and MCAD DNA sequencing, which are performed at Seattle Children's Biochemical Genetics laboratory.

- False Negative/Positive: The predictive value of a referral for MCAD deficiency is about 50%. We are not aware of any false negative cases of MCAD deficiency. The prevalence in Washington State for MCAD deficiency is about 1:19,000 births.
- Some babies with MCAD deficiency who are feeding regularly will have normal results on a subsequent NBS. For this reason, it is important for babies with abnormal NBS results on the first NBS for MCAD deficiency to have diagnostic testing to confirm or rule out the disorder. DNA testing is helpful making a final diagnosis for some babies.
- The MCAD deficiency screening test may yield equivocal results for babies who have received hyperalimentation or other therapeutic infusions. The result will be reported as “invalid” and a follow-up newborn screen will be recommended when treatment is concluded.
- Washington State began screening for MCAD in June 2004.

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VERY LONG-CHAIN ACYL-COA DEHYDROGENASE (VLCAD) DEFICIENCY

Very long-chain acyl CoA dehydrogenase (VLCAD) deficiency is an inborn error of fatty acid metabolism. It is caused by a deficiency in the very long-chain acyl CoA dehydrogenase enzyme which results in the failure to break down very long-chain fatty acids (12-18 carbon molecules) for energy metabolism. This condition can damage the heart, muscles and kidneys, and can cause seizures or death. Early identification and treatment reduces the mortality and morbidity associated with VLCAD deficiency. Even with treatment, the clinical presentation of VLCAD deficiency varies. The birth prevalence for VLCAD deficiency in the United States is approximately 1 in 121,000 babies.

CLINICAL FEATURES

VLCAD deficiency presents in the following forms:

1. An infantile form characterized by non-specific signs and symptoms such as irritability, decreased muscular activity and lethargy. The associated heart disease (cardiomyopathy) can eventually lead to death. With early detection and treatment, cardiomyopathy can be resolved and death can be prevented.
2. A later onset form manifested by muscle pains and weakness, which is induced by strenuous physical activities or prolonged episodes of fasting. If detected early and treatment is started, metabolic imbalances and complications to the kidneys can be prevented. This form may not always be detected by newborn screening.

ETIOLOGY

Normal production and function of the VLCAD enzyme in the mitochondrial membrane is critical to the process of providing fuel for the body during periods of extended fasting and higher energy demands. VLCAD deficiency is inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for VLCAD deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker for VLCAD deficiency is tetradecenoylcarnitine (C14:1). If C14:1 is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of VLCAD deficiency consists of avoidance of fasting, with frequent high-carbohydrate, low-fat meals, and medium chain triglyceride (MCT) oil to replace long chain fatty acids. Treatment must begin immediately upon diagnosis before irreversible organ damage occurs. Oral carnitine supplementation may be necessary. People with VLCAD deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of VLCAD deficiency includes a blood acylcarnitine profile and DNA sequencing. When inconclusive, they are followed by enzyme studies in fibroblasts to establish a diagnosis. Diagnostic testing is performed at Seattle Children's Biochemical Genetics laboratory.
- The C14:1 marker may also be elevated in carnitine palmitoyl transferase (CPT) deficiency, multiple acyl CoA dehydrogenase (MAD) deficiency and long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency.
- Administration of certain drugs such as valproic acid, antibiotics containing pivalic acid, and other compounds like benzoic acid and can cause false positive results.
- Screening for VLCAD deficiency is optimal in the first seven days of life because acylcarnitine levels rapidly decrease with time. VLCAD deficiency may be missed if the child is first screened at over 7 days of age. Therefore, a mutation analysis should be done if an older baby is clinically symptomatic or the medical provider is considering VLCAD deficiency as one of differential diagnoses (based on a positive family history) to help confirm or rule out the diagnosis.
- Washington State began screening for VLCAD deficiency in July 2008.

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Organic Acid Disorders

(1 in 25,000 Washington births)

The Washington State Newborn Screening Program screens for the following eight Organic Acid Disorders. The disorders highlighted in red can be life-threatening if not detected and treated within days following birth:

3-hydroxy-3-methylglutaric aciduria (HMG)

Beta-ketothiolase (BKT) deficiency

Glutaric acidemia type I (GA-I)

Isovaleric acidemia (IVA)

Methylmalonic acidemia- *cbl A,B* (MMA-*cbl A,B*)

Methylmalonic acidemia- *mutase* (MMA-*mut*)

Propionic acidemia (PROP)

Multiple carboxylase deficiency (MCD)

Definition	Inability to process or break down organic acids, byproducts of protein and fatty acid metabolism
Screening Test	Measure acylcarnitine levels by tandem mass spectrometry
Impact without Early Treatment	Severe nerve and physical damage & death
Treatment	Dietary restriction of offending amino acid(s) & needs special metabolic formula
Benefits of Early Treatment	Prevent death, intellectual and developmental disability and other neurological damage

3-HYDROXY-3-METHYLGLUTARIC ACIDURIA (HMG)

3-hydroxy-3-methyl glutaryl CoA lyase (HMG) deficiency is an organic acid disorder characterized by the inability to process the amino acid leucine due to lack of the 3-hydroxy-3-methyl glutaryl CoA lyase enzyme. This condition can cause damage to the brain that may lead to death. Early identification and treatment reduces the mortality and morbidity associated with HMG deficiency. Even with treatment, the clinical presentation of HMG deficiency varies. The birth prevalence of HMG deficiency is unknown.

CLINICAL FEATURES

Acute episodes are associated with vomiting, decreased muscle tone or activity, and lethargy. An illness or period of fasting can precipitate a metabolic crisis manifested by hypoglycemia and can lead to death. With early detection and treatment, the child has a better chance of normal neurodevelopmental outcomes.

ETIOLOGY

HMG deficiency is a very rare condition caused by a deficiency of the 3-hydroxy 3-methyl glutaryl CoA lyase enzyme, which disrupts the normal metabolism of leucine. It is inherited in an autosomal recessive fashion. The birth prevalence of HMG deficiency is unknown.

SCREENING TEST

Screening for HMG deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker for HMG deficiency is 3-hydroxy-isovaleryl carnitine (C5-OH). If C5OH is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of HMG deficiency involves avoiding fasting, with a high carbohydrate, low protein diet with restriction of leucine, through use of a special dietary formula. Leucine concentrations in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms of HMG deficiency without impairing growth and intellectual development. Oral carnitine may be supplemented. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with HMG deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of HMG deficiency includes a blood acylcarnitine profile and urine organic acid analysis, which is performed at Seattle Children's Biochemical Genetics laboratory.
- A large number of babies with persistently abnormal C5OH screening results have a biochemical abnormality called 3-methylcrotonyl carboxylase deficiency (3MCC), which is almost always a benign condition. Some babies have abnormal C5OH screening results because their moms have undiagnosed 3MCC deficiency. If the baby has abnormal diagnostic lab results, maternal samples may be requested as well.

- Washington State began screening for HMG deficiency in July 2008.

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BETA-KETOTHIOLASE (BKT) DEFICIENCY

Beta-ketothiolase (BKT) deficiency is an organic acid disorder characterized by the inability to process the amino acid isoleucine and fats due to lack of BKT enzyme. This condition can cause brain damage that may lead to death. Early identification and treatment reduces the mortality associated with BKT deficiency. Even with treatment, the clinical presentation varies.

CLINICAL FEATURES

The onset may occur during the first two years of life. Acute episodes are associated with vomiting, diarrhea, failure to thrive, and seizures. Intercurrent infections or increased protein intake can precipitate a metabolic crisis leading to coma and death if left untreated. The frequency of decompensation falls with age and is not common after the age of ten. With early detection and treatment, the child has a better chance of normal neurodevelopmental outcomes.

ETIOLOGY

BKT deficiency is a very rare condition caused by a lack of the BKT enzyme, which disrupts the normal metabolism of isoleucine and fats. It is inherited in an autosomal recessive fashion. The birth prevalence of BKT deficiency is unknown.

SCREENING TEST

Screening for BKT deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker for BKT deficiency is 3-methylcrotonyl carnitine (C5:1), also known as tiglyl carnitine. If C5:1 is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of BKT deficiency involves avoiding fasting, with high carbohydrate, low protein diet and restriction of isoleucine, through use of a special dietary formula. Isoleucine concentrations in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms of BKT deficiency without impairing growth and intellectual development. Oral carnitine may be supplemented. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Families must be taught how to monitor urinary ketones to be alert for impending metabolic crisis. Treatment must continue throughout life and people with BKT deficiency should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of BKT deficiency includes a blood acylcarnitine profile and urine organic acid analysis, which is performed at Seattle Children's Biochemical Genetics laboratory.
- Washington State began screening for BKT deficiency in July 2008.

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GLUTARIC ACIDEMIA TYPE I (GA-I)

Glutaric acidemia type I (GA-I) is an organic acid disorder characterized by the inability to process the amino acids lysine, hydroxylysine and tryptophan due to lack of the glutaryl co-A dehydrogenase enzyme. This condition can cause damage to the brain that may lead to death. Early identification and treatment reduces the mortality and morbidity associated with GA-I. Even with treatment, the clinical presentation of GA-I varies. The birth prevalence of GA-I is approximately 1 in 137,000.

CLINICAL FEATURES

The most suggestive and earliest sign before a neuro-metabolic crisis occurs is progressive macrocephaly (head circumference more than 95th percentile at birth). Typically between 2-18 months of age, a nonspecific illness such as a respiratory or gastro-intestinal infection, or even an adverse reaction to immunization may lead to an acute metabolic crisis progressing to neurologic complications. Early signs of an encephalopathic crisis include irritability, lethargy, and hypotonia (e.g. sudden head lag) which may progress to stupor and coma within hours. Hence, a metabolic decompensation must be treated aggressively to avoid permanent brain damage. With early detection and treatment, neurodevelopmental complications can be prevented but for patients who are already neurologically impaired, treatment can minimize further brain damage.

ETIOLOGY

GA-I is caused by a deficiency in the glutaryl Co-A dehydrogenase enzyme. This enzyme is active in the liver, kidneys, fibroblasts and leukocytes and helps break down lysine, hydroxylysine and tryptophan. GA-I is inherited in an autosomal recessive fashion. The birth prevalence of GA-I is approximately 1 in 137,000.

SCREENING TEST

Screening for GA-I is performed by tandem mass spectrometry to measure the levels of glutarylcarnitine (C5DC) in the blood. If C5DC is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment for GA-I involves dietary restriction of lysine, hydroxylysine and tryptophan, through use of a special dietary formula. Concentrations of these amino acids in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms of GA-I without impairing growth and intellectual development. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with GA-I should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose and pharmacological doses of carnitine may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of GA-I includes a blood acylcarnitine profile, urine organic acid analysis and urine acylglycine analysis, which are performed at Seattle Children's Biochemical Genetics laboratory.

- C5DC is a secondary analyte for glutaric academia type II (also known as multiple acyl co-A dehydrogenase (MAD) deficiency) and may be elevated as well in medium-chain acyl-CoA dehydrogenase (MCAD) deficiency.
- Washington State began screening for GA-I in July 2008.

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ISOVALERIC ACIDEMIA (IVA)

Isovaleric acidemia (IVA) is an organic acid disorder characterized by a deficiency of the isovaleryl Co-A dehydrogenase enzyme. This condition can cause brain damage and rapidly progresses to coma and death from cerebral edema or hemorrhage. Early identification and treatment reduces the mortality and morbidity associated with IVA. However, even with treatment, the clinical presentation of IVA varies. The birth prevalence of IVA is approximately 1 in 96,000 births.

CLINICAL FEATURES

The acute form of IVA usually presents within the first 14 days of life. Acute episodes are associated with nonspecific signs and symptoms such as vomiting, irritability, seizures, and lethargy progressing to coma and death. A characteristic “sweaty feet odor” may also be noted. With early detection and treatment, infants can survive the neonatal period without serious complications or neurologic damage.

A later-onset form occurs in the first year of life and is often triggered by respiratory infections or excessive consumption of protein. It presents with failure to thrive and recurrent episodes of vomiting, lack of appetite and lethargy. With early detection and treatment, mental disability, speech and other developmental delays can be avoided.

ETIOLOGY

IVA is caused by a deficiency of the isovaleryl Co-A dehydrogenase enzyme, which disrupts the normal metabolism of the amino acid leucine and results in the buildup of isovaleric acid. It is inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for IVA is performed by using tandem mass spectrometry (MS/MS). The primary marker for IVA is isovalerylcarnitine (C5). If C5 is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of IVA involves dietary restriction of leucine, through use of a special dietary formula. Leucine concentrations in the blood are regularly measured to calculate the appropriate level of dietary restriction required for an individual to avoid symptoms of IVA without impairing growth and intellectual development. Oral glycine and carnitine may be supplemented. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with IVA should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child’s physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of IVA includes a blood acylcarnitine profile, urine organic acid analysis and urine acylglycine analysis, which are performed at Seattle Children’s Biochemical Genetics laboratory.
- Aspirin and benzoic acid will block the beneficial effects of glycine, and should be avoided.

- Administration of antibiotics prior to specimen collection can produce elevated C5 values. The result will be reported as “invalid” and a follow-up screen will be recommended when treatment is concluded.
- Washington State began screening for IVA in July 2008.

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METHYLMALONIC ACIDEMIAS (MMA) & PROPIONIC ACIDEMIA (PROP)

Methylmalonic acidemias (MMA) and propionic acidemia (PROP) are organic acid disorders caused by mutations in the genes encoding methylmalonyl Co-A mutase and propionyl Co-A carboxylase, respectively. Metabolic imbalances can cause brain damage and rapidly progress to coma and death. Early detection and treatment reduces the mortality and morbidity associated with these disorders. However, even with treatment, the clinical presentation of these conditions varies. The combined birth prevalence of MMAs and PROP is approximately 1:48,000.

CLINICAL FEATURES

The clinical presentation of these disorders is classified in two main groups:

1. The early onset, severe form is characterized by poor feeding, vomiting, dehydration, respiratory distress, lethargy, seizures, posturing or poor muscle tone. Acute episodes are usually precipitated by fever, vaccinations or intercurrent infections and can lead to death. It appears that early identification and treatment improves the survival rate. Many patients identified clinically showed poor nutritional status with growth disability and neurologic impairment.
2. A late onset, milder form is often manifested by refusal to feed, vomiting, dehydration, respiratory distress, seizures, lethargy and can lead to death. It can be precipitated by excessive protein intake, fever or intercurrent infection. Despite adequate treatment, many MMA patients develop a progressive renal disease by adolescence or early adulthood and neurologic complications may be manifested. The milder forms have a better prognosis than the early-onset forms and patients will benefit from early detection and treatment through newborn screening.

ETIOLOGY

Methylmalonic acidemia is caused by a deficiency in either the methylmalonyl Co-A mutase enzyme or defects in the production of adenosyl cobalamin. Propionic acidemia is caused by a deficiency in the propionyl Co-A carboxylase enzyme. Both disorders are inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for these disorders is performed by tandem mass spectrometry (MS/MS). The primary marker for methylmalonic acidemia and propionic acidemia is propionylcarnitine (C3). If C3 is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

The aim of treatment is to prevent damage to the brain and other vital organs (kidneys, heart, liver, pancreas) while maintaining normal development and nutritional status. This is accomplished by frequent feeding of high-energy, low-protein diet. Oral biotin, Vitamin B12, and L-carnitine may be supplemented. Avoidance of fasting is recommended. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with MMAs or PROP should receive specialized treatment through a metabolic clinic that has experience in treating these disorders. In circumstances where food cannot be tolerated, such as during an illness, IV glucose or total parenteral nutrition (TPN) support may be required.

Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.

MISCELLANEOUS INFORMATION

- The newborn screening profiles for MMA and PROP can be very similar, so diagnostic testing is necessary to differentiate between the conditions. It includes a blood acylcarnitine profile, urine organic acid analysis, plasma amino acid and plasma total homocysteine measurements, which are performed at Seattle Children's Biochemical Genetics laboratory.
- Not all forms of MMA will be detected by newborn screening.
- Elevated C3 levels in newborns can also be caused by maternal Vitamin B12 deficiency
- Washington State began screening for MMA and PROP in July 2008.

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MULTIPLE CARBOXYLASE DEFICIENCY (MCD)

Multiple carboxylase deficiency (MCD) is a very rare organic acid disorder caused by an inborn error of biotin metabolism. It is also known as holocarboxylase synthetase deficiency (HCSH). This condition can cause respiratory, skin, and neurodevelopmental problems. Even with treatment, the clinical presentation of MCD varies.

CLINICAL FEATURES

The onset may occur from birth to 15 months of age (in contrast to biotinidase deficiency which may occur later in infancy). An illness or period of fasting can precipitate a metabolic crisis. Acute episodes are associated with skin rashes, hair loss, vomiting, breathing problems, and seizures. If left untreated this may lead to poor growth, learning disabilities, and mental disability. With early detection and treatment, the child has a good chance of normal neurodevelopmental outcomes.

ETIOLOGY

MCD is caused by a lack of the holocarboxylase synthetase enzyme, which disrupts the normal binding of biotin and, consequently, the metabolism of proteins, carbohydrates and fats. Biotin is a B-complex vitamin (also known as vitamin B₇ or vitamin H) that is essential in the metabolism of carbohydrates, proteins, and fats for energy production. Holocarboxylase synthetase catalyzes the transfer of biotin to four biotin-dependent enzymes, namely: 1) beta-methylcrotonyl Co-A carboxylase, 2) propionyl Co-A carboxylase, 3) pyruvate carboxylase, and 4) acetyl Co-A carboxylase. It is inherited in an autosomal recessive fashion.

SCREENING TEST

Screening for MCD deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker is 3-hydroxy-isovaleryl carnitine (C5OH). If C5OH is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of MCD involves avoiding fasting and prompt administration of biotin upon diagnosis to ensure normal growth and development. Treatment must begin immediately upon diagnosis before irreversible damage occurs. Treatment must continue throughout life and people with MCD should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- Diagnostic work-up of MCD includes a blood acylcarnitine profile and urine organic acid analysis, which is performed at Seattle Children's Biochemical Genetics laboratory.
- A large number of babies with persistently abnormal C5OH screening results have a biochemical abnormality called 3-methylcrotonyl carboxylase deficiency (3MCC), which is almost always a benign condition. Some babies have abnormal C5OH screening results because their moms have undiagnosed

3MCC deficiency. If the baby has abnormal diagnostic lab results, the specialists may want to test the mother as well.

- Washington State began screening for MCD in July 2008.

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Endocrine Disorders

The Washington State Newborn Screening Program screens for the following two endocrine disorders. The disorders highlighted in red can be life-threatening if not detected and treated within days following birth:

Congenital adrenal hyperplasia (CAH)
(1 in 14,000 Washington births)

Congenital hypothyroidism (CH)
(1 in 950 Washington births)

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Congenital adrenal hyperplasia (CAH) is characterized by the excessive production of androgenic hormones due to lack of an enzyme involved in converting cholesterol to cortisol. If untreated, CAH can lead to electrolyte imbalance, particularly sodium and potassium, which in turn can rapidly lead to shock and death. CAH also causes excessive masculinization and extremely premature sexual maturation. Treatment consists of cortisol, which normalizes hormone production. Proper treatment prevents death and stops the masculinization process. Affected females may require surgical correction of masculinized genitalia. The prevalence in the United States is approximately 1 in 16,000. In Washington State, there are, on average, four infants with CAH detected each year.

CLINICAL FEATURES

Male infants with CAH usually appear normal at birth but develop symptoms within the first week of life. Female infants may show the effects of the virilizing hormones at birth. This usually presents itself as an enlarged clitoris and fusion of the labia majora over the vaginal opening. Occasionally the female infant may be so virilized at birth as to result in erroneous gender assignment. Such newborns should not have a palpable gonad in the labial/scrotal sac. Please alert the newborn screening program immediately if virilizing symptoms are present in an infant so that testing for CAH can be expedited.

Since infants with CAH may experience a life-threatening salt-wasting crisis within the first week of life, it is critical that the first newborn screening specimen be collected and mailed according to the requirements (prior to discharge and no later than 48 hours of age).

ETIOLOGY

CAH is caused by a genetic defect in one of several enzymes involved in converting cholesterol to cortisol. All forms are inherited in an autosomal recessive fashion. The newborn screening test is designed to detect 21-hydroxylase enzyme deficiency, which is responsible for over 90% of all forms of CAH. Therefore, providers should remember that a normal newborn screening result does not rule out other forms of CAH due to other enzyme deficiencies. As with all disorders, providers should proceed with diagnostic testing if clinical symptoms are present despite the results of the newborn screening test.

SCREENING TESTS

The newborn screening test for CAH measures the infant's hormone levels of 17-hydroxyprogesterone (17-OHP) using a fluoroimmunoassay technique. Due to the variability of the disorder and the age of the infant, the level of 17-OHP may not correlate with the clinical severity of the disease. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment for CAH includes hormone replacement therapy. Glucocorticoids such as hydrocortisone are given by mouth or injection. Mineralocorticoids are also given if the infant is unable to maintain normal levels of sodium and potassium. -Over treating can cause hypertension in some children; therefore, blood pressure should be regularly monitored. Medications need to be adjusted in the event of vomiting, serious illness, injury, or surgery, and as the infant matures. The [Other Disorders](#) page of our website page contains a list of pediatric endocrinologists in Washington and Oregon who should be consulted to help guide diagnosis and treatment.

Females who have virilized genitalia may need surgical correction. The first surgery is usually done before two years of age and is done in stages.

MISCELLANEOUS INFORMATION

In the first day of life, 17-OHP levels may be transiently elevated. In normal cases this level will resolve after the first 24 hours. In addition, premature or ill infants may exhibit an elevation in 17-OHP due to physiological stress. It is important that the infant receive follow-up to ensure that the adrenal levels return to the normal range as the infant matures.

Steroid medications given to a baby prior to collection of a newborn screen or administered to the mother during pregnancy (or while breastfeeding) can cause false-negative results by suppressing the amount of 17-OHP produced by the baby. The screening test is designed to detect the most common cause of CAH, which is 21 hydroxylase deficiency; it is not effective in detecting other forms of CAH.

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CONGENITAL HYPOTHYROIDISM (CH)

Congenital hypothyroidism (CH) is characterized by the inability to produce adequate amounts of the thyroid hormone, thyroxine (commonly known as T4). Proper production of T4 levels is critical for normal physical growth and mental development. If untreated, CH can result in severe neurological damage and developmental delay. Diagnosis and initiation of appropriate synthetic thyroid hormone replacement (levothyroxine), within the first few weeks of life, followed by regular clinic visits with a pediatric endocrinologist, can prevent growth failure and intellectual disability. The prevalence of CH in the United States is approximately 1 in 2,300. In Washington State, there are about 100 infants with CH detected each year (about half have a mild form of CH that will be treated, possibly for only the first few years of life during critical brain development).

CLINICAL FEATURES

Infants with CH usually appear normal until about three months of age, but it is likely that some brain damage will have already occurred. Clinical symptoms or signs, if present, include prolonged jaundice, constipation, somnolence, poor muscle tone, feeding problems, a large tongue, mottled and dry skin, distended abdomen, and umbilical hernias. Although these are classic manifestations, they are not reliable indicators of CH, as they are non-specific for CH.

ETIOLOGY

The insufficient production of the thyroid hormone T4, which characterizes CH, is most commonly caused by the sporadic malformation or malfunction of the thyroid gland. This includes the total or partial failure of the thyroid gland to develop normally (athyreosis or hypoplasia), improper location of the gland (ectopic - lingual thyroid gland), or an enzyme deficiency or other chemical disruption in the pathway of thyroid hormone production (dys hormonogenesis). About 15 to 20 percent of cases of congenital hypothyroidism are inherited in an autosomal recessive fashion.

SCREENING TESTS

The newborn screening test for CH measures the infant's TSH (thyroid stimulating hormone) level using a fluoroimmunoassay technique. TSH levels are stratified based on the baby's age when the blood specimen was collected to make final determinations of normal, borderline and presumptive positive categories. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment of CH is relatively simple and very effective. Thyroid hormone Levothyroxine, in a synthetic pill form (i.e., Synthroid®), is administered orally once daily. This medication should NOT be given with soy milk or iron tablets. The dosage of medication must be adjusted and monitored as the child grows. The goal is to keep total T4 or Free T4 in the upper half of reference range and TSH below 6 mIU/L. The [Other Disorders](#) page of our website contains a list of pediatric endocrinologists in Washington and Oregon who can be consulted for confirmation of diagnosis and treatment.

MISCELLANEOUS INFORMATION

False positives may occur due to early specimen collection. In the first day of life, TSH levels may be transiently elevated. In normal cases this level will resolve after the first 24 hours. It is important that these infants receive

follow-up to ensure that the thyroid levels return to the normal range as the infant matures. Other factors that can affect the newborn thyroid hormone levels and may result in an abnormal screening results are prematurity, maternal medications with ant thyroid drugs such as Methimazole and Propylthiouracil, or topical application of antiseptic povidone iodine treatment.

About 30% of babies with CH have normal first newborn screens. Another 20% of babies with CH have borderline TSH results, meaning that about half of infants with confirmed CH are detected only after their second newborn screen. For maximum detection of CH, the recommended second newborn screen must be carried out to achieve prompt diagnosis and treatment of affected infants.

MISCELLANEOUS INFORMATION

Premature (birth weight less than 1500 grams) and sick infants are at risk to develop a late onset form of CH. It is therefore recommended that a third newborn screening specimen be collected for these infants between four and six weeks of age. Please see the [Special Considerations section](#) of this document for more information on the recommended third newborn screen for premature or sick infants.

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Lysosomal Storage Disorders

The Washington State Newborn Screening Program screens for the following two lysosomal storage disorders. The disorders highlighted in red can be life-threatening if not detected and treated within days following birth:

Glycogen Storage Disorder Type II (Pompe disease)
(1 in 28,000 Washington births)

Mucopolysaccharidosis Type-I (MPS-I)
(1 in 36,000 Washington births)

GLYCOGEN STORAGE DISORDER TYPE II (POMPE DISEASE)

Glycogen Storage Disorder Type II (Pompe disease) belongs to a family of over 50 lysosomal storage disorders, and is characterized by a deficiency of the lysosomal enzyme acid alpha glucosidase (GAA). Sufficient GAA activity is critical for the normal breakdown of glycogen within the cell's lysosomes. If untreated, Pompe disease can result in progressive muscle weakness, respiratory and cardiac failure, or death. Diagnosis and prompt initiation of enzyme replacement therapy (ERT) with recombinant human GAA, a lifelong treatment, can improve heart and muscle function, development, and increase survival. The prevalence of Pompe disease is approximately one in every 28,000 births. In Washington State, we expect to detect one case of infantile Pompe disease each year, with additional cases of later-onset Pompe disease.

CLINICAL FEATURES

Infantile Pompe disease usually presents around two to three months of age with general muscle weakness or “floppy baby syndrome.” Cardiomegaly or cardiomyopathy may be present. Infants may also exhibit respiratory distress, feeding difficulties, or failure to thrive. Later-onset forms of Pompe disease may not present until adolescence or adulthood. Symptoms in those individuals are more likely to present as progressive loss of respiratory function and limb muscle weakness.

ETIOLOGY

The reduced GAA activity that leads to the accumulation of glycogen is caused by mutations within the acid alpha glucosidase gene. Pompe disease is inherited as an autosomal recessive trait. The disorder has been observed to occur across most ethnic groups.

SCREENING TESTS

The newborn screening test for Pompe disease measures the infant's GAA enzyme activity using a digital microfluidics technique. A newborn with low GAA enzyme activity on the newborn screen may have Pompe disease. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Pompe disease is treated via intravenous infusion with recombinant human GAA (Myozyme), which received FDA approval in 2006. The infusion typically lasts four hours and is administered every two weeks, for life. Because of this, most Pompe patients have a central line placed. ERT has been shown to significantly increase survival, decrease the need for assisted ventilation, and improve cardiac and skeletal muscle function. ERT has also been shown to improve respiratory function in later-onset cases of Pompe disease. Not all patients respond well to ERT for Pompe disease. About 25% of individuals with severe, early-onset Pompe disease have zero residual GAA activity, known as “CRIM negative” and may develop antibodies against the ERT.

MISCELLANEOUS INFORMATION

- Historically, Pompe disease cases were categorized into three phenotypes: classical infantile, non-classical infantile, and late-onset. However, today Pompe disease is recognized as a disease continuum with varying rates of disease progression and ages of onset.

- Some infants screened for Pompe disease will be found to have a pseudodeficiency- meaning that they have a measurably low diagnostic GAA enzyme activity, but do not develop symptoms of Pompe disease. Genetic testing can provide clarity by identifying known pseudodeficiency alleles.

MUCOPOLYSACCHARIDOSIS TYPE-I (MPS-I)

Mucopolysaccharidosis type-I (MPS-I) belongs to a family of over 50 lysosomal storage disorders, and is characterized by a deficiency of the lysosomal enzyme, alpha-L-iduronidase (IDUA). Sufficient IDUA activity is critical for the normal breakdown of mucopolysaccharides within the cell's lysosomes. If untreated, MPS-I disease can result in progressive skeletal and joint disease, progressive cognitive decline, and even death from heart and lung failure. Diagnosis and prompt treatment can increase survival, preserve cognition, and reduce other morbidity associated with the condition. The prevalence of MPS-I is approximately one in every 36,000 births. In Washington State, we expect to detect one to two severe cases of MPS-I every year, with fewer cases of less-severe MPS-I also detected.

CLINICAL FEATURES

Severe MPS-I usually presents by 6-14 months of age with skeletal malformations such as a "humpback," cognitive delay, and deafness or vision loss. Infants may also exhibit respiratory insufficiency and cardiac involvement. Less severe forms of MPS-I typically present between one and five years of age. Symptoms in those individuals include joint disease leading to loss of range of motion, slightly impaired cognition, chronic headaches, or gastrointestinal symptoms.

ETIOLOGY

The reduced IDUA activity that leads to the accumulation of mucopolysaccharides is caused by mutations within the alpha-L-iduronidase gene. MPS-I is inherited as an autosomal recessive trait.

SCREENING TESTS

The newborn screening test for MPS-I measures the infant's IDUA enzyme activity using a digital microfluidics technique. A newborn with low IDUA enzyme activity on the newborn screen may have MPS-I. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

MPS-I is treated based on the severity of the disease. For severe cases, a hematopoietic stem cell transplant (HSCT) is recommended before two years of age. A prompt HSCT is most effective to prolong survival and preserve brain function. Some severe forms of MPS-I are also treated with enzyme replacement therapy (ERT) using laronidase (recombinant human α -L-iduronidase) prior to and/or after HSCT. ERT is administered weekly via an intravenous infusion. For those with less-severe forms of MPS-I, ERT is the only recommended treatment and is administered weekly for life.

MISCELLANEOUS INFORMATION

- Historically, MPS-I cases were categorized into three disorders based on clinical presentation: Hurler syndrome (severe form) Hurler-Scheie syndrome (intermediate severity), and Scheie syndrome (mild severity). However, today MPS-I is recognized as a disease continuum with varying rates of disease progression and ages of onset.
- Some infants screened for MPS-I will be found to have a pseudodeficiency- meaning that they have a measurably low diagnostic IDUA enzyme activity, but do not develop symptoms of MPS-I. Genetic testing can provide clarity by identifying known pseudodeficiency alleles.

Other Disorders

The Washington State Newborn Screening Program screens for the following seven other disorders. The disorders highlighted in red can be life-threatening if not detected and treated within days following birth:

Biotinidase (BIOT) deficiency
(1 in 60,000 Washington births)

Cystic fibrosis (CF)
(1 in 5,000 Washington births)

Galactosemia (GALT)
(1 in 40,000 Washington births)

Sickle cell disease & other Hemoglobinopathies (Hb)
(1 in 10,000 Washington births)

Severe combined immunodeficiency (SCID)
(1 in 45,000 Washington births)

X-linked adrenoleukodystrophy (X-ALD)
(1 in 34,000 Washington births)

Spinal Muscular Atrophy (SMA)
(1 in 15,000 Washington births)

BIOTINIDASE (BIOT) DEFICIENCY

Biotinidase deficiency is characterized by an inability to recycle the vitamin biotin due to lack of the biotinidase enzyme. If untreated, profound biotinidase deficiency can lead to irreversible neurological damage, metabolic crisis and even death. Partial deficiency of the enzyme has far less effect. Treatment consists of oral doses of the unbound form of the vitamin biotin; typically 10 mg per day. Early diagnosis and proper treatment will avoid all damage from either form. The birth prevalence of profound biotinidase deficiency in the United States is approximately 1 in 60,000.

CLINICAL FEATURES

Infants with profound biotinidase deficiency appear normal at birth but signs of the disorder begin to emerge anywhere from a few weeks to several years. Affected children initially show combinations of neurologic and cutaneous symptoms, including seizures, ataxia, hypotonia, developmental delay, hearing loss, decreased vision, rash, conjunctivitis, hair loss and fungal infections. Death may even occur due to severe metabolic decompensation.

ETIOLOGY

Biotinidase deficiency is caused by a genetic deficiency in the biotinidase enzyme, which recycles the common vitamin biotin by cleaving it from lysine residues in certain proteins. The inability to recycle biotin interrupts the biotin cycle, leading to harmful byproducts collecting in the body and more free biotin required than supplied by a normal diet. Biotinidase deficiency is inherited in an autosomal recessive fashion.

SCREENING TESTS

Biotinidase deficiency screening is done by a colorimetric assay. Activity of the enzyme biotinidase, which is reduced in infants with this disorder, is measured. Diminished enzyme activity in the processed blood specimen indicates that the infant may have biotinidase deficiency.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Treatment for biotinidase deficiency is typically a daily 10 mg oral dose of unbound biotin. Early diagnosis and treatment before the onset of symptoms can avoid all negative consequences of the disorder. Treatment after onset will resolve some symptoms but will not reverse neurological damage. The biotin found in over the counter vitamin supplements is not effective because it is a bound form of the vitamin and the biotinidase enzyme is needed to process it.

MISCELLANEOUS INFORMATION

- The enzyme is prone to damage if the specimen is delayed in the mail or exposed to high temperatures. This may cause a false positive result.
- Washington State began screening for biotinidase deficiency in January 2004.

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CYSTIC FIBROSIS (CF)

Cystic fibrosis (CF) is a treatable disorder that affects salt transport across cells lining the lungs, intestines, liver and reproductive tract; this causes thick, sticky mucus to build up in various organs of the body. The disorder is characterized by chronic pulmonary disease and gastrointestinal abnormalities.

CLINICAL FEATURES

Approximately 15-20% of affected children have meconium ileus, an intestinal obstruction present at birth that usually requires surgery to correct. Other early indicators of CF include loose stools, failure to thrive, wheezing, chronic abdominal pain, recurrent cough, and repeated or prolonged bouts of pneumonia.

ETIOLOGY

CF is an autosomal recessive genetic disorder. Affected individuals have mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). About 90% of all cases have at least one copy of a single common mutation, $\Delta F508$. The CFTR functions as a chloride channel and controls the regulation of other transport pathways. Its malfunction affects the lungs and upper respiratory tract, gastrointestinal tract, pancreas, liver, sweat glands, and genitourinary tract.

SCREENING TESTS

Washington State began screening for CF in March of 2006. The screening test is performed using a fluoroimmunoassay to measure the level of immunoreactive trypsinogen (IRT), which is elevated in most infants with CF. Absent clinical suspicion of CF, no recommendations for diagnostic testing will be made on the basis of a single specimen; elevation on two consecutive newborn screening specimens will reflex to a DNA test for a panel of 41 CFTR variants. If a baby has two variants identified, DOH will refer the baby to a CF center. If one variant is identified, DOH will refer the baby for a diagnostic sweat chloride test. No further testing is indicated for a baby with zero CFTR variants UNLESS the baby is exhibiting symptoms of CF or has a positive family history of CF. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

DIAGNOSTIC TESTING

A positive CF screen should be followed by a diagnostic sweat test. The only acceptable method is the pilocarpine iontophoresis sweat collection followed by quantitative chloride measurement. The sweat test should be performed at a laboratory affiliated with a Cystic Fibrosis Foundation-accredited care center. There are three such centers in Washington State – Seattle Children’s Hospital in Seattle (satellite collection facility in Yakima), Sacred Heart Medical Center in Spokane, and Mary Bridge Children’s Health Center in Tacoma (also maintains a laboratory facility in Olympia) – and one center in Portland, Oregon (at Oregon Health & Science University).

TREATMENT

Treatment for CF depends on both the severity of the disease and the organs involved. Chest physiotherapy should be done daily to help clear thick mucus from the lungs. Patients with CF exhibiting pancreatic insufficiency should take daily vitamin and pancreatic enzyme supplements with meals to help absorb enough calories and nutrients to sustain normal growth. Other types of treatment include antibiotics to fight lung infections and drugs to thin the mucus and improve lung function.

MISCELLANEOUS INFORMATION

Approximately one out of three babies referred for diagnostic testing because of positive screening results will be diagnosed with CF. The screening protocol is designed to catch as many newborns with CF as possible; however, because the sensitivity of the screen is not 100 percent, a small number of cases will not be detected (we anticipate about one false negative case every two years of screening). The false negative rate for CF in Washington State by this screening method is approximately 4%.

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GALACTOSEMIA (GALT)

Galactosemia is characterized by the inability to metabolize the sugar galactose due to decreased activity of the enzyme galactose-1-phosphate uridylyltransferase (GALT). Galactose is a major constituent of milk sugar, lactose. If untreated, galactosemia results in severe neurological and developmental damage and often neonatal death due to *E. coli* sepsis. Treatment consists of immediately eliminating dietary intake of lactose by replacing breast or normal formula milk with a lactose-free, soy-based formula. Antibiotics are also prescribed to prevent sepsis. The prevalence of galactosemia in the United States is approximately 1 in 50,000 births.

CLINICAL FEATURES

Infants with galactosemia due to profound deficiency of the GALT enzyme usually appear normal at birth, but soon develop signs of the disorder after they begin feeding on milk. Symptoms may include a failure to thrive and vomiting or diarrhea after ingesting milk. Hepatomegaly and jaundice are common by the end of the first week of life. Infants who survive untreated may develop liver disease, kidney damage, cataracts, growth failure, mental disability, and ovarian failure in girls. Many of the problems associated with galactosemia can be prevented if the baby is diagnosed and treated early by switching to a soy-based formula and eliminating galactose and lactose intake for life. Infants with partial deficiency of the GALT enzyme typically experience few, if any, symptoms, even with continued exposure.

ETIOLOGY

Galactosemia is caused by a deficiency in the enzyme galactose-1-phosphate uridylyltransferase (GALT), which helps metabolize the sugar galactose. This deficiency decreases or eliminates activity of the GALT enzyme. It is inherited in an autosomal recessive fashion.

SCREENING TESTS

Galactosemia screening is done by a fluorometric assay that measures activity of the GALT enzyme. Diminished fluorescence in the processed blood specimen indicates that the infant may have galactosemia. A second-tier test will be performed on screen positive specimens to further clarify the significance of the initial test results. Screening result classifications are available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

The main treatment for galactosemia is elimination of galactose and lactose from the diet. Dietary management needs to begin as soon as possible and continue throughout life. Once diagnosed, the infant should be changed to a soy-based formula that does not contain galactose. Antibiotics are normally prescribed to prevent sepsis, even after a child has been switched to a soy-based formula, as sepsis can still arise if the child has previously ingested galactose. People with galactosemia should receive specialized treatment through a metabolic clinic that has experience in treating this disorder. In circumstances where food cannot be tolerated, such as during an illness, IV glucose support may be required. **Parents should always travel with a letter from the child's physician with treatment guidelines in case the child needs to be admitted to a hospital during an acute illness.**

MISCELLANEOUS INFORMATION

- The enzyme evaluated in screening is prone to damage if the specimen is delayed in the mail or exposed to high temperatures or direct sunlight. This may cause a false positive result.
- The NBS test for galactosemia detects the most common form of galactosemia cause by GALT enzyme deficiency. It will not identify babies with galactosemia caused by epimerase or galactokinase deficiencies.
- The first newborn screening specimen should be obtained prior to transfusion whenever possible. Specimens collected following red blood cell transfusions will yield invalid results for galactosemia and hemoglobinopathy screening. In the event that the first screening specimen is collected after a transfusion, please note this on the screening card. The galactosemia status and hemoglobin phenotype can be determined after the transfused cells have cleared. A specimen collected four to six weeks after the last transfusion will resolve galactosemia disease status and hemoglobin phenotype in most circumstances. The first and second specimens should still be collected within the recommended times because the detection of the remaining disorders is not affected by transfusions.
- Washington State began screening for galactosemia in January 2004.

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SICKLE CELL DISEASE & OTHER HEMOGLOBINOPATHIES (Hb)

Hemoglobinopathies are inherited abnormalities in the structure or amount of hemoglobin. Infants with normal hemoglobin will have a screening result of FA, indicating that both fetal and adult hemoglobin is present. In sickle cell disease, the predominant hemoglobin is hemoglobin S (HbS). When oxygenated, HbS functions normally; however, when under reduced oxygen, it forms crystal-like rods, distorting the red blood cells into a sickle shape. These red blood cells are easily destroyed and tend to stick together, blocking blood vessels. This causes many of the painful symptoms and organ damage associated with sickle cell disease.

The frequency of hemoglobinopathies varies among ethnic groups. Sickle hemoglobin is found most commonly among people with African, Mediterranean, Middle Eastern, and Indian ancestry. In the United States, sickle cell disease is found in virtually all ethnic groups with a prevalence of approximately 1 in 10,000 in the general population. However, it is present in approximately 1 in 400 persons of African ancestry. In Washington State, an average of seven infants with sickle cell disease is detected each year. In addition, screening detects another ten infants with other clinically significant hemoglobinopathies, such as transfusion-dependent thalassemias.

CLINICAL FEATURES

With the exception of alpha thalassemia major (Fetal Hydrops Syndrome), infants affected with hemoglobinopathies appear normal at birth. With sickle cell disease, anemia develops in the first few months of life when the amount of fetal hemoglobin decreases and HbS increases. Splenic sequestration of sickled red blood cells that are trapped may lead to an enlarged spleen. If acute, this can rapidly cause severe anemia and transfusions may be necessary. Splenic sequestration can result in death.

Infants and children with sickle cell disease are particularly susceptible to bacterial infections. This may manifest as pneumonia, meningitis, osteomyelitis, or acute septicemia. Prompt antibiotic treatment can be lifesaving. Studies have also shown that prophylactic oral penicillin and folic acid started early and maintained through age six decreases the number of episodes of infections and death.

Health problems due to sickle cell disease are highly variable. Pain is the most common symptom of sickle cell disease. Pain episodes can occur at any time and in any part of the body. However, they occur most often in the arms, legs, chest and abdomen. These episodes vary in frequency, severity, and length; some individuals rarely have painful episodes while others have them frequently. When they occur, they can last from a few hours to several days and can be severe enough to require hospitalization and the use of very strong pain medication.

Anemia (a low number of red blood cells) is another common medical problem of sickle cell disease. This occurs because sickled red blood cells don't live as long as normal red blood cells and a person with sickle cell disease cannot make red blood cells fast enough to keep up with the rapid breakdown.

In adolescents and adults with sickle cell disease, other complications can occur due to problems with impaired circulation, premature breakdown of the red blood cells, and damage to the spleen and other body organs. These complications include jaundice, slower growth and onset of puberty, fatigue, gallstones, shortness of breath, blood in the urine, and stroke. With appropriate medical care and management, the complications of sickle cell disease can be minimized.

The other significant hemoglobinopathies reported by the Newborn Screening Program include hemoglobin C, D, E, beta thalassemia major¹ and alpha thalassemias which have variable clinical manifestations ranging from mild to severe anemia. All have reproductive implications for families.

¹ The screening test cannot reliably detect beta thalassemia minor or beta thalassemia trait

ETIOLOGY

Sickle cell disease is a recessively inherited defect of the beta globin chains. A single nucleotide change in the beta globin gene results in the production of S hemoglobin. Sickle cell disease results if both beta globin genes carry the S mutation or if one gene has the S mutation and the other produces abnormal hemoglobin such as C, D or beta thalassemia.

The etiology of other clinically significant hemoglobinopathies stems from a structural change in the alpha or beta globin chain or a change in their rate of production. Thalassemias are caused by decreased synthesis of normal globin chains and therefore decreased production of hemoglobin A.

CARRIER DETECTION (HEMOGLOBIN TRAITS)

The identification of infants who are carriers of hemoglobin traits (i.e. those who have genes that produce both normal and abnormal hemoglobin) is a by-product of screening for sickle cell disease and other hemoglobinopathies. The Newborn Screening Program reports all traits detected, including hemoglobin S, C, D, E, Bart's and unidentified variants. Most hemoglobin traits are not associated with clinical symptoms or the need for treatment. However, because they have reproductive implications for the parents and the child, the health care provider is notified by mail of trait status and provided with information to share with the family. We recommend offering genetic counseling and testing of the parents of a child with a hemoglobin trait to determine if future children are at risk for disease.

SCREENING TESTS

Initial hemoglobin screening is performed by isoelectric focusing (IEF), in which hemoglobin bands are identified by their migration distance in an electric field. Abnormal findings on IEF are confirmed by High Performance Liquid Chromatography (HPLC). A second-tier test will be performed on screen positive specimens if needed to further clarify the significance of the initial test results.

Hemoglobins are by far the most complex of the conditions detected by Newborn Screening. More than a dozen genes are involved in hemoglobin production and over 800 abnormalities have been described by researchers and clinicians. Also, a variety of combinations are possible for any individual. A table listing some of the more commonly seen newborn hemoglobin screening findings is available following the link below.

[Screening Result Classifications and Corresponding Follow-up Actions](#)

TREATMENT

Infants with sickle cell disease should take prophylactic penicillin until the age of six. Parents need education on how to take and respond to their child's temperature, care for acute illness, and how to assess spleen size. It is also important that affected children receive all recommended vaccinations including the pneumococcal vaccine. Consultation with a pediatric hematologist is strongly advised. In addition, continued family education, support groups, and genetic counseling are an important part of treatment for the child and family.

MISCELLANEOUS INFORMATION

False positive hemoglobin results can happen when beta thalassemia occurs in combination with a structural change in the beta globin chain. For example, a child with hemoglobin S trait may appear to have sickle beta thalassemia due to the biological variation in the switch from fetal to adult hemoglobin. The Newborn Screening Program will provide appropriate recommendations for the follow-up of such infants. False negative results can result from degradation due to specimen age or unusual storage conditions; unstable hemoglobins such as Bart's are most susceptible.

Specimens collected following red blood cell transfusions will yield invalid results for hemoglobinopathy screening. Thus, the first newborn screening specimen should be obtained prior to transfusion whenever possible. In the event that the first screening specimen is collected after a transfusion, please note this on the screening card. To obtain a valid screen for babies in these circumstances, the following schedule should be followed: collect the two routine specimens within the recommended timeframes (because screening results for the remaining disorders are not affected by transfusions) and a subsequent specimen at least four weeks after the last transfusion.

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SEVERE COMBINED IMMUNODEFICIENCY (SCID)

Severe Combined Immunodeficiency (SCID) is a rare life-threatening condition caused by genetic defects in T-lymphocyte development. SCID is the most severe form of the Primary Immunodeficiency Disorders (PID) and results in profound deficiencies in immune system function leading to severe bacterial, viral, fungal or protozoan infections among affected patients. Typical signs and symptoms include failure to thrive, recurrent respiratory, gastro-intestinal (manifested by chronic diarrhea), skin and CNS infections. Without treatment SCID is typically fatal within the first year of life.

ETIOLOGY/CLASSIFICATION OF SCID

The majority of SCID cases are inherited in either an X-linked or autosomal recessive fashion. A few cases are autosomal dominant and about 10 percent of SCID patients have unknown etiology. SCID is classified into three categories:

- Classic/Typical SCID
- Leaky SCID – cases with limited T-cell maturation, such as Omenn syndrome
- Variant SCID – cases with no known gene defect, but have impaired immune function

The birth prevalence of classic/typical SCID ranges from 1:30,000 to 1:100,000 depending on the heterogeneity of the population. Based on Washington State's average annual birth rate, 1 to 2 cases of classic SCID may be detected per year through newborn screening. In addition, we expect to detect 6 to 7 other forms of congenital immune deficiency.

SCID can result from defects in at least 15 different genes involved in immune system development. Mutations at the molecular level interfere with the development and function of lymphocytes, thereby blocking proliferation and differentiation of T-cells, and in some cases, B-cells and NK-cells are also affected. The phenotype (presence or absence of T-cells, B-cells and NK-cells) is used when classifying SCID. For example, the most common form, X-linked gamma chain SCID, is classified as T (-) B (+) NK (-). These immune cell deficiencies contribute to severe impairment of antibody production rendering the patient susceptible to severe infections.

SCREENING TEST

Newborn screening for SCID uses quantitative polymerase chain reaction (qPCR) to measure the number of T-cell receptor excision circles (TRECs). TRECs are small pieces of DNA that are excised from lymphocytes during the formation of T-cells. The absence or low number of TRECs indicates that T-cells are not being produced in normal numbers and defines a positive screening test for SCID. Low TREC levels on a newborn screen indicate that an infant may have SCID or another form of primary immune deficiency (PID). Each newborn screening program determines the appropriate reference ranges or cutoffs based on the methodology of their TREC assay. Newborn screening programs that are currently screening for SCID report a limited number of false positive screening results. However, some programs have reported higher rates of false positive screening results in the NICU and LBW populations.

Screening Result Classification and Corresponding Follow-up Actions

DIAGNOSIS

Confirmatory diagnosis of SCID is performed by evaluation and characterization of lymphocytes including measurement of the absolute number of T-cells, B-cells and NK-cells. Diagnostic testing will be done by the expert team of pediatric immunologists at Seattle Children's Hospital. All babies with positive newborn screening results will have samples submitted to the Immunology Diagnostic Laboratory Center for Immunity

and Immunotherapies at Seattle Children's Research Institute for specialized cellular characterization and molecular studies. Babies diagnosed with SCID or other PIDs will receive the appropriate clinical care from the immunology team.

TREATMENT

Hematopoietic stem cell treatment (HSCT) or HLA-matched bone marrow transplantation (BMT) is the treatment of choice and, if done before three months of age, can cure most patients with SCID. If HSCT is not successful or available, other treatments such as enzyme replacement therapy (ERT) or gene therapy may be used. Additionally, prior to successful treatment, intravenous immunoglobulin infusions (IVIG) and prophylactic antibiotics are essential to protect against infections.

MISCELLANEOUS INFORMATION

Interfering substances - several factors and some substances may interfere with the TREC assay which can lead to false positive results, namely:

1. Prematurity - premature infants (<37 weeks AOG) may present a challenge in SCID newborn screening. T-cells tend to populate the peripheral lymphoid tissues during the third trimester, thus low T-cell count could be observed as a normal physiologic process in severe prematurity. We recommend that three routine NBS specimens be collected and submitted per [NICU standard protocols](#).
2. Corticosteroids - many premature infants receive corticosteroids for lung maturation which may decrease circulating T-cells. As for CAH screening, we recommend that the 1st newborn screen be collected prior to administering corticosteroids to the infant.

If the patient is suspected to have SCID or has been diagnosed with SCID, the following vaccines are contraindicated:²

- Rotavirus
- OPV (oral polio vaccine)
- BCG (Bacillus of Calmette & Guerin)
- MMR (measles, mumps, rubella)
- Varicella (chicken pox) & HZV (Herpes Zoster)
- Salmonella typhi
- LAIV (Live attenuated influenza vaccine)

If the diagnosis of SCID has not been confirmed or if SCID is considered a differential diagnosis, discontinue breastfeeding if unsure of mom's CMV status and isolation is highly recommended to protect the patient from infectious organisms that may be transmitted by aerosol droplets, medical equipment, hospital staff, other patients, family members and visitors. The immunology specialists at Seattle Children's Hospital are available for consultation.

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² For more information, see the following CDC publication about [vaccinations of persons with primary and secondary immune deficiencies](#).

X-LINKED ADRENOLEUKODYSTROPHY (X-ALD)

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder characterized by the accumulation of very long-chain fatty acids (VLCFA) that can affect the nervous system and adrenal glands. It is an X-linked recessive disorder that can manifest in early childhood, adolescence or adulthood. If untreated, the most severe form of X-ALD can progress from good health to poor performance in school, other behavioral problems, muscle weakness, hearing loss, blindness and death. For the most severe form of X-ALD, treatment with stem cell transplant can stop disease progression and prevent death and disability. It occurs in about 1 in every 14,000 boys; three to four boys with X-ALD in Washington State will be detected each year through newborn screening. Screening programs identify some girls as carriers of an X-ALD mutation who may develop mild symptoms as adults.

CLINICAL FEATURES

Infants with X-ALD appear normal at birth. The disease can manifest in early childhood, adolescence or adulthood. X-ALD mainly affects the nervous system and adrenal glands leading to deficits in the sensorimotor, behavioral and cognitive functions.

There are three main manifestations of X-ALD:

1. The earliest manifestation of X-ALD is adrenal insufficiency (“Addison-only” if X-ALD is diagnosed). About 80 percent of X-ALD patients develop adrenal insufficiency within the first two years of life, the earliest cases at 1-2 months of age. It can be life threatening if left untreated. Many Addison-only patients have a change in diagnosis when the disease progresses to involve the brain or spinal cord (see below).
2. Childhood cerebral ALD (CALD) is the most severe form and affects about 35% of males with X-ALD. Manifestation of signs and symptoms is noted between 2 and 10 years of age, and is usually associated with progressive decline in neurologic function. Typical signs and symptoms include a progression starting with poor performance in school, leading to other behavioral problems, muscle weakness, hearing loss, blindness, and death. Without treatment, X-ALD often leads to death or significant disability within 2-4 years after onset of symptoms. The rapid neurologic decline is caused by severe inflammatory and demyelination processes mainly in the cerebral hemispheres of the brain. Most CALD patients also have adrenal insufficiency which can result in death if not recognized early. Cerebral involvement rarely occurs in females.
3. Adrenomyeloneuropathy (AMN) is a less severe form of X-ALD and presents variably with sensory ataxia, progressive spastic paraparesis, and spinal and peripheral nerve involvement. Onset of signs and symptom can manifest between 13 to 30 years of age. Approximately 70% of patients with AMN also develop adrenal insufficiency, although this is rare in females. Heterozygous females may develop AMN, usually in the fourth to sixth decade of life. The most common symptom in females is fecal incontinence.

Because the ABCD1 mutation causing X-ALD is found on the X chromosome, typically only males are affected with the severe form of the disorder. However, many females with a pathogenic ABCD1 mutation will develop symptoms later in life. There is no genotype-phenotype correlation, meaning that the same ABCD1 mutation in a given family can have different manifestations in the individual family members.

ETIOLOGY

X-ALD is the most common peroxisomal disorder, caused by mutations in the gene encoding the peroxisomal ATP-binding cassette transporter, also known as the ABCD1 gene (formerly known as adrenoleukodystrophy

protein, ALDP). X-ALD is inherited in an X-linked recessive pattern. Saturated and unbranched very long chain fatty acids (VLCFA) are normally degraded in the peroxisomal matrix by the acyl-CoA oxidase enzymes or the beta-ketothiolase enzyme of the beta oxidation pathway. Disruption of this pathway can lead to accumulation of VLCFA in tissues and vital organs of the body, particularly the central and peripheral nervous system as well as the adrenal glands. These VLCFA are significantly elevated and used as the primary analyte in newborn screening for X-ALD.

SCREENING TEST

Screening for X-ALD is performed by tandem mass spectrometry (MS/MS). The primary marker for X-ALD is lysophosphatidylcholine (C26:0 LPC). The levels of C26:0 can be increased more than fivefold in the blood spots of individuals with X-ALD compared to unaffected newborns. If C26:0 LPC is elevated, secondary markers are analyzed. Screening result classifications are available following the link below.

[Screening Result Classification and Corresponding Follow-up Actions](#)

DIAGNOSIS AND LONG-TERM FOLLOW-UP

A positive X-ALD screen should be followed by a diagnostic evaluation, involving an initial blood specimen for a comprehensive VLCFA profile that consists of C26, C22, C24, C26/C22, phytanic and pristanic acid analysis. This specimen is analyzed at Seattle Children's Hospital. Depending on the results of this profile, additional tests for pipercolic acid, plasmalogen and DNA analysis may be ordered to confirm or rule out a diagnosis of X-ALD or other peroxisomal storage disease.

Once diagnosed, the baby's X-ALD medical care will be with the biochemical genetics group at Seattle Children's Hospital. They will ensure that babies receive baseline adrenal function tests and a brain MRI. On a prescribed schedule, the patient with X-ALD will undergo serial adrenal function tests and a brain MRI. About 80 percent of boys with X-ALD will develop adrenal insufficiency within the first years of life. If this happens, they will be started on hormone replacement. If changes in the white matter of the brain are found on the annual MRI, the patient will be linked into the services for a bone marrow transplant.

TREATMENT

Patients diagnosed with X-ALD will initially be evaluated by a biochemical geneticist at Seattle Children's Hospital. Not all patients with X-ALD will require treatment but the biochemical geneticists will periodically reevaluate them to determine the best time to begin treatment and connect them with other specialists and services (endocrinologists and neurologists).

Hormone replacement therapy is the treatment for patients with adrenal insufficiency. Hematopoietic stem cell transplant (HSCT) is currently the primary treatment for the CALD form, capable of halting the demyelinating process in X-ALD patients, preventing death and improving the long-term quality of life, provided the procedure is performed during the initial stage of the disease. HLA-matched bone marrow transplantation (BMT) usually achieves the best outcome. Doctors treat the symptoms for AMN as they arise.

MISCELLANEOUS INFORMATION

- Gene therapy is a promising treatment on the horizon.
- Babies with X-ALD or girls with one ABCD1 mutation detected through newborn screening often have family members with undiagnosed X-ALD. A genetic counselor at Seattle Children's Hospital can facilitate cascade testing of any older brothers and other family members as clinically indicated. This will allow affected family members to be diagnosed also, sometimes prior to symptoms.

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SPINAL MUSCULAR ATROPHY (SMA)

Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder caused by the lack of survival motor neuron (SMN) protein. This protein is essential to the normal development of motor neurons that are predominantly located in the spinal cord. Without sufficient SMN protein, the disorder is characterized by progressive muscular atrophy from degradation and loss of motor neuron cells in the spinal cord. Typical signs and symptoms of SMA in infants include poor muscle tone, difficulty breathing, and/or failure or delay in meeting motor milestones such as holding one's head up, sitting, or walking. Diagnosis and prompt treatment can prevent mortality and morbidity. The prevalence of SMA is approximately one in every 15,000 births. In Washington State, we expect to detect 5-6 cases of SMA each year.

ETIOLOGY

SMA is caused by mutations of the survival motor neuron 1 (SMN1) gene. Approximately 95% of SMA cases are homozygous for an exon 7 deletion of SMN1, while about 5% have a point mutation in combination with a deletion. SMA is inherited as an autosomal recessive trait, meaning that an individual needs to inherit two non-functional SMN1 genes to be affected, while those with one non-functional SMN1 gene are carriers, and clinically normal. The disorder has been observed to occur across most ethnic groups.

SMN2

SMN2 is the "back-up" gene for SMN1. The two genes are similar in structure, but SMN2 only makes about 10% functional SMN protein. The number of SMN2 gene copies an individual has is variable. In an individual with SMA, the more SMN2 copies they have, the less severe their disease tends to be. In other words, a high SMN2 copy number helps to compensate more for the absence of SMN1. Because of this, SMN2 copy number testing is an important part of the diagnostic work-up for suspected SMA cases. Based on the number of SMN2 copies, pediatric neurologists can estimate the severity of disease and whether treatment is indicated, and how urgently.

CLINICAL FEATURES

SMA is a spectrum disorder with a large amount of variability in the age of onset and severity of symptoms. Historically, cases of SMA have been categorized into five types, based on the age of symptom onset and the highest physical milestone achieved. Today, with the potential for earlier diagnosis and treatment, it may not be possible to categorize a case of SMA into a historical "type".

HISTORICAL CLASSIFICATIONS OF SMA

- **Type 0 (0 copies of SMN2):** SMA type 0 is rare with prenatal onset of symptoms that include decreased fetal movement and joint deformities. Babies typically present with difficulty swallowing and respiratory failure shortly after birth. Because of the severity and early onset of this form, the decision whether or not to initiate treatment will be made by the family and health care providers. If untreated, the life expectancy of this form of SMA is less than six months.
- **Type 1 (1-2 copies SMN2):** Accounting for approximately 60% of cases, SMA type 1 is the most common form and one of the most severe. If not diagnosed early, these babies typically present with poor muscle tone and respiratory insufficiency within the first few months of life. If untreated, babies with SMA type 1 will never sit independently and typically pass away before two years of age.
- **Type 2 (3 copies SMN2):** Approximately 30% of cases of SMA are Type 2. These cases typically present between 6 and 18 months with delay or failure to meet motor milestones. If untreated, these infants can sit, but never stand or walk. These individuals may have a normal life expectancy.

- **Type 3 (3-4 copies SMN2):** Approximately 10% of cases of SMA are Type 3. These cases typically present between 18 months and three years of age with increasingly limited mobility. If untreated, they may walk initially, but develop the need to use a wheelchair over time. These individuals have a normal life expectancy.
- **Type 4 (4-6 copies SMN2):** This type of SMA is also rare. Symptoms of mild motor impairment typically develop after the age of 35 and these individuals are usually ambulatory until 60 years of age.

SCREENING TEST

Newborn screening for SMA uses quantitative polymerase chain reaction (qPCR) to test for the presence of exon 7 of the SMN1 gene. The absence of this section of SMN1 defines an abnormal screening test for SMA. Approximately 5% of SMA cases have a point mutation rather than the homozygous deletion. These babies will screen “normal” even though they have SMA and are referred to as “false negative” screens. Therefore, clinical concern for SMA should always prompt a diagnostic workup, regardless of the newborn screening results. An abnormal newborn screen for SMA is not able to predict how severe their disease is likely to be. Low amplification of SMN1 or an “indeterminate” result on a newborn screen could indicate that an infant has SMA or that the blood specimen is of poor quality. False positive screening results for SMA that are not linked to a quality issue are rare.

Screening Result Classification and Corresponding Follow-up Actions

DIAGNOSIS

Confirmatory diagnosis of SMA and predictions of disease severity are made by diagnostic SMN1 DNA testing and SMN2 copy number testing. Following a presumptive abnormal newborn screen, these tests will be ordered by the pediatric neurologists at Seattle Children’s Hospital or Mary Bridge Children’s Hospital during a baby’s initial clinical evaluation. Babies diagnosed with SMA will receive the appropriate ongoing clinical care from these teams.

TREATMENT

Several treatment options are available for babies diagnosed with SMA and additional treatments are currently undergoing clinical trials. The type of treatment and timeframe for initiating any treatment will depend on the severity of SMA the baby is predicted to have and findings of their clinical evaluations.

- Spinraza/nusinersen is a FDA-approved, antisense oligonucleotide drug that targets the “back up” gene for SMA, called SMN2. The drug helps create a more complete SMN protein that can improve patient outcomes. Nusinersen is administered via intrathecal injection and taken every few months, for life.
- The other currently available FDA-approved treatment is Zolgensma. Zolgensma is a gene therapy treatment that replaces the missing/mutated SMN1 gene. This treatment is administered once via infusion and appropriate for individuals under two years of age. .

EARLY HEARING LOSS

Hearing loss affects approximately three newborns per one thousand but can often be detected at birth by a simple, inexpensive test performed before hospital discharge. This early detection allows for timely diagnosis and intervention.

Newborn hearing screening is not mandated in Washington State but is currently done in all birthing hospitals. In 20124, over 99% of hospital-born infants were screened for hearing loss in Washington.

The Department of Health established the Early Hearing-loss, Detection, Diagnosis, and Intervention (EHDDI) program to help coordinate a statewide effort to improve and support screening, diagnostic, and early-intervention services for infants born with hearing loss, or increased risk for late onset hearing loss in childhood.

The primary goals of the EHDDI program are to ensure that all infants born in the state of Washington:

- Are screened for hearing loss before hospital discharge or by **one** month of age
- Receive a diagnostic audiological evaluation by **three** months of age if the infant did not pass two newborn hearing screens
- Are enrolled in early intervention services by **six** months of age if a hearing loss was found

To achieve these goals, the EHDDI program developed a tracking and surveillance system, which follows infants from hearing screening to early intervention. Hearing screening results are reported to the EHDDI program by hospitals and clinics using a revised Newborn Screening collection card. These cards are processed in collaboration with the Newborn Screening Program at the State Public Health Laboratory.

If you would like more information about EHDDI, please contact the Washington State Department of Health EHDDI Program at (206) 418-5613 (toll free at (888) WAEHDDI) or ehddi2@doh.wa.gov. Or visit them on their website at www.doh.wa.gov/earlyhearingloss.

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