

AMINO ACID DISORDERS

AMINO ACID DISORDERS

Amino acid disorders are a group of inherited metabolic conditions, each associated with a specific enzyme deficiency involved with protein metabolism that causes the accumulation of amino acids or metabolites in blood and urine. The accumulated compounds and metabolites are toxic, resulting in the clinical features of these disorders.

Amino Acid Disorders Screened in Kansas

The newborn screening program in the State of Kansas is designed to screen for six different amino acid disorders. These disorders include:

- Phenylketonuria (PKU)
- Maple Syrup Urine Disease (MSUD)
- Homocystinuria (HCY)
- Tyrosinemia, type I (TYR I)
- Argininosuccinic Acidemia (ASA)
- Citrullinemia (CIT)

Clinical Features in Children with Untreated Amino Acid Disorders

The age for onset and the types of symptoms that an infant may have can vary. Many babies with these conditions will appear normal at birth. Some of the disorders will cause developmental delay or mental retardation if not treated promptly. Other newborns may develop symptoms such as poor appetite, sleepiness, vomiting, or irritability. If the condition is not treated promptly, babies can develop more serious problems including breathing problems, seizures, swelling of the brain, and coma or death.

Laboratory Screening Tests

Amino acid disorders are screened using a tandem mass spectrophotometer (MS/MS). MS/MS technology tests for specific analytes which are present in the baby's blood sample. If a particular analyte is abnormal, the MS/MS instrument will flag that sample to indicate the abnormal result. The instrument will interpret positive samples as either low risk (LR), moderate risk (MR) or high risk (HR). Often, secondary markers are taken into consideration when determining the risk level. These secondary markers may be actual analyte levels or the ratio of two analytes. All results are reviewed by a trained technician prior to being reported.

The cutoffs values for MS/MS analytes are reviewed periodically, as more data is collected. Cutoffs are adjusted as needed, which can reduce false positive and false negative results.

Confirmatory Testing

Infants with low or moderate risk results on the initial newborn screening need to have the screening promptly repeated. If the initial results are high risk, consultation with a metabolic specialist and diagnostic testing should be promptly scheduled.

Treatment

With proper early treatment, symptoms of amino acid disorders can be avoided. The outcome in children identified and treated within the first two weeks is excellent compared to children treated later. However, studies have shown some increase in relatively mild learning problems even in some children treated optimally. Treatment should be started as soon after birth as possible in any infant and should be continued indefinitely. Frequent monitoring is required, especially in the first weeks.

If treatment is not started until several weeks of age, the outcome is poorer and the ultimate IQ will likely be lower. Affected children who are not treated until after six months may show some improvement in development with treatment, although they are likely to remain substantially delayed. Older untreated patients usually show little change in functional level with treatment, but diet may help to control behavior problems. Discontinuation of treatment is associated with variable loss of intellectual functioning, hyperactivity and onset of seizures and other neurological signs. Treatment is individualized and should be managed by a metabolic consultant. A child's needs depend on the severity of the enzyme deficiency and the child's age, growth rate, and current state of health.

Screening Practice Considerations

At least 24 hours of normal feeding on the breast or with formula is preferred in order to detect all infants with amino acid disorders. If an infant is tested "early" (before 24 hours of milk feedings) a repeat test should be done within 7-10 days since delayed treatment is associated with a poorer outcome.

Infants on Total Parenteral Nutrition (TPN) may have one or more elevated amino acid analytes on the newborn screening. Infant should be off TPN for 48 hours prior to retest. Contamination of the filter paper with food or liquids containing Nutra Sweet (Aspartame) may cause false positive results.

If the baby was transfused, repeat the screening on day 4 after transfusion.

Medical Consultant

A medical consultant is available to provide consultation for the follow-up, evaluation, and long-term management of children with amino acid disorders. Please contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
Office 913-588-6326

It is strongly recommended that prior to repeating the newborn screen practitioners should confer with the consultant. The consultant may recommend repeating the state newborn screen, or may suggest labs to draw and analyze in a practitioner's local lab. The consultant may wish to see the newborn in the office and do the lab work and assessment there. Whatever the case, we want to prevent unnecessary lab draws or inappropriate testing on these infants. In summary, please contact the consultant prior to drawing the repeat blood work.

Overview of Follow-up Procedure Abnormal Newborn Screening for Amino Acid Disorders

- 1) Newborn screening follow-up team reviews the laboratory reports that are faxed overnight from the lab or the information provided per email from the laboratory.
- 2) If the result is considered **normal**:
 - a) Follow-up team does not receive results.
 - b) Lab will fax or mail results to doctor listed on NBS card.
- 3) If the result is **Low Risk (LR)** or **Moderate Risk (MR)**:
 - a) Lab will contact follow-up team via email with baby's information and lab results. Follow-up team will print lab results on color printer. Each infant's results will be on a separate page.
 - b) Follow-up team will print out baby's information from DHEL database on a yellow sheet of paper, attach the lab results and write the appropriate abnormal test and result on front of yellow sheet.
 - c) Follow-up team will enter infant's demographic data and reported test results into Access database.
 - d) Follow-up team will call healthcare provider listed on report and:
 - i) Verify that they are seeing the baby.
 - ii) Inform them of results.
 - iii) Ask them to get a repeat NBS card submitted to the KS lab.
 - iv) Confirm doctor's fax number.
 - v) Inform them that a letter will be faxed to their office with the results and instructions.
 - e) Follow-up team will print appropriate amino acid low risk or moderate risk letter and fax (or mail, if no fax) to healthcare provider.
 - f) Follow-up team will print amino acid parent letter and mail to baby's parents to inform them that their child has an abnormal result. NOTE: If infant is in the NICU, no parent letter is sent.
 - g) Follow-up team will enter data into Excel spreadsheet "Presumptive Totals" located on the "H" drive.
 - h) Lab will fax or mail results to doctor listed on NBS card. Lab will fax results to follow-up team. Report is attached to yellow sheet.
 - i) Follow-up team will enter lab information into WebBFH and set a follow-up reminder for 1 month from date of letter. NOTE: Name changes are documented on the copy of the lab report. Surname changes are also documented in WebBFH as an alias.
 - j) When complete, paperwork is filed by infant's date of birth.
- 4) If the results are considered **High Risk (HR)**:
 - a) Lab will contact follow-up team via email with baby's information and lab results. Follow-up team will print lab results on color printer. Each infant's results will be on a separate page.
 - b) Follow-up team will print out baby's information from DHEL database on a green sheet of paper, attach the lab results and write the appropriate abnormal test and result on front of green sheet.
 - c) Follow-up team will enter infant's demographic data and reported test results into Access database.
 - d) Follow-up team will call healthcare provider listed on report and:
 - i) Verify that they are seeing the baby.
 - ii) Inform them of results.
 - iii) Ask them to notify parents and arrange appointment with specialist.
 - iv) Confirm doctor's fax number.
 - v) Inform them that a letter will be faxed to their office with the results and instructions.
 - e) Follow-up team will print appropriate amino acid high risk letter and physician report

- form and fax (or mail, if no fax) to healthcare provider.
- f) Follow-up team will print amino acid parent letter and mail to baby's parents to inform them that their child has an abnormal result. NOTE: If infant is in the NICU, no parent letter is sent.
 - g) Follow-up team will enter data into Excel spreadsheet "Presumptive Totals" located on the "H" drive.
 - h) Lab will fax or mail results to doctor listed on NBS card.
 - i) Lab will fax results to follow-up team. Report is attached to green sheet.
 - j) Follow-up team will enter lab information into WebBFH and set a follow-up reminder for 1 month from date of letter. NOTE: Name changes are documented on the copy of the lab report. Surname changes are also documented in WebBFH as an alias.
 - k) When complete, paperwork is filed by infant's date of birth.
- 5) If the results show **multiple Low Risk (LR)** or **Moderate Risk (MR)** amino acid disorders:
- a) Lab will contact follow-up team via email with baby's information and test results. Follow-up team will print lab results on color printer. Each infant's results will be on a separate page..
 - b) Follow-up team will print out baby's information from DHEL database on a yellow sheet of paper, attach the lab results and write the appropriate abnormal test and the result on front of yellow sheet.
 - c) Follow-up team will enter infant's demographic data and reported test results into Access database. For analytes not elevated enter a "NR" for the result.
 - d) Follow-up team will call healthcare provider listed on report and:
 - i) Verify that they are seeing the baby.
 - ii) Inform them of results.
 - iii) Ask them to get a repeat NBS card submitted to the KS lab. If infant is on TPN, repeat should be done 48 hours after TPN has been discontinued.
 - iv) Confirm doctor's fax number.
 - v) Inform them that a letter will be faxed to their office with the results and instructions.



NEWBORN SCREENING ACT SHEET

SCREEN FOR: INCREASED CITRULLINE

CONDITION: AMINO ACIDURIA/UREA CYCLE DISORDER (CIT/ASA)

DIFFERENTIAL DIAGNOSIS: Citrullinemia I, argininosuccinic acidemia; citrullinemia II (citrin deficiency).

METABOLIC DESCRIPTION: The urea cycle is the enzyme cycle whereby ammonia is converted to urea. In citrullinemia and in argininosuccinic acidemia, defects in ASA synthetase and lyase, respectively, in the urea cycle result in hyperammonemia and elevated citrulline.

MEDICAL EMERGENCY - ACTION TO BE TAKEN IMMEDIATELY:

- ✦ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, and tachypnea).
- ✦ Immediate consult with pediatric metabolic specialist.
- ✦ Evaluate the newborn (poor feeding, vomiting, lethargy, hypotonia, tachypnea, seizures and signs of liver disease). Measure blood ammonia. If any sign is present or infant is ill initiate emergency treatment for hyperammonemia in consultation with metabolic specialist.
- ✦ Transport to hospital for further treatment in consultation with metabolic specialist.
- ✦ Initiate timely confirmatory/diagnostic testing and management, as recommended by specialist.
- ✦ Provide family with basic information about hyperammonemia.
- ✦ Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Plasma **ammonia** to determine presence of hyperammonemia. In citrullinemia, plasma amino acid analysis will show increased **citrulline** whereas in argininosuccinic acidemia, **argininosuccinic acid** will also be present. **Orotic acid** may be increased in both disorders which can be determined by urine organic acid analysis. In citrin deficiency, liver enzymes, lactic acid and bilirubin may be elevated.

CLINICAL EXPECTATIONS: Citrullinemia and argininosuccinic acidemia can present acutely in the newborn period with hyperammonemia, seizures, failure to thrive, lethargy, and coma. Later signs include mental retardation. Citrin deficiency may present with cholestatic liver disease in the newborn period. Treatment for ASA and citrullinemia is to promote normal growth and development and to prevent hyperammonemia.

REPORTING: Report diagnostic result to family and Kansas NBS program.

SPECIALIST:

Dr. Majed Dasouki
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NEWBORN SCREENING ACT SHEET

SCREEN FOR: INCREASED METHIONINE

CONDITION: HOMOCYSTINURIA (CBS DEFICIENCY)

DIFFERENTIAL DIAGNOSIS: Classical homocystinuria (cystathionine β -synthase (CBS) deficiency); liver disease; hyperalimantation.

METABOLIC DESCRIPTION: Methionine from ingested protein is normally converted to homocysteine. In classical homocystinuria due to CBS deficiency, homocysteine cannot be converted to cystathionine. As a result, the concentration of homocysteine and its precursor, methionine, will become elevated.

ACTION TO BE TAKEN IMMEDIATELY:

- Contact family to inform them of the newborn screening result and ascertain clinical status.
- Consult with pediatric metabolic specialist.
- Evaluate the newborn with attention to liver disease and refer as appropriate.
- Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.
- Educate family about homocystinuria and its management, as appropriate.
- Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Quantitative plasma amino acids will show increased **homocystine** and **methionine** in classical homocystinuria but only increased methionine in other disorders. Plasma homocysteine analysis will show markedly increased homocysteine in classical Homocystinuria and normal or only slightly increased homocysteine in the other disorders. Urine homocysteine is markedly increased in classical homocystinuria.

CLINICAL EXPECTATIONS: Homocystinuria is usually asymptomatic in the neonate. If untreated, these children eventually develop mental retardation, ectopia lentis, a marfanoid appearance including arachnodactyly, osteoporosis, other skeletal deformities and thromboembolism.

REPORTING: Report diagnostic result to family and Kansas NBS program.

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NEWBORN SCREENING ACT SHEET

SCREEN FOR: INCREASED LEUCINE

CONDITION: MAPLE SYRUP URINE DISEASE (MSUD)

DIFFERENTIAL DIAGNOSIS: Maple syrup urine disease (MSUD); hydroxyprolinemia.

METABOLIC DESCRIPTION: In MSUD, leucine, isoleucine, and valine (branched chain amino acids) cannot be metabolized further than their α -ketoacid derivatives. The amino acids and organic acids accumulate and produce severe toxicity.

MEDICAL EMERGENCY - ACTION TO BE TAKEN IMMEDIATELY:

- ◆ Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea).
- ◆ Consult with pediatric metabolic specialist.
- ◆ Evaluate the newborn (poor feeding, lethargy, tachypnea, alternating hypertonia/hypotonia, seizures). If any sign is present or infant is ill, transport to hospital for further treatment in consultation with metabolic specialist.
- ◆ Initiate timely confirmatory/diagnostic testing and management, as recommended by specialist.
- ◆ Provide the family with basic information about MSUD and dietary management.
- ◆ Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: In MSUD, plasma amino acid analysis reveals elevations of **leucine, isoleucine, alloisoleucine, and valine** (the branched chain amino acids) and urine organic acid analysis reveals abnormal branched-chain **hydroxyl-** and **ketoacids**. In expanded screening, leucine/isoleucine and hydroxyproline cannot be differentiated, so if the baby has hydroxyprolinemia confirmatory amino acid analysis will show only increased **hydroxyproline**.

CLINICAL EXPECTATIONS: MSUD presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy and maple syrup odor to urine and cerumen. If untreated, it will progress to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Hydroxyprolinemia is probably benign.

REPORTING: Report diagnostic result to family and Kansas NBS program.

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NEWBORN SCREENING ACT SHEET

SCREEN FOR: INCREASED PHENYLALANINE

CONDITION: PHENYLKETONURIA (PKU)

DIFFERENTIAL DIAGNOSIS: Phenylketonuria (Classical PKU); non-PKU mild hyperphenylalaninemia; pterin defects; transient hyperphenylalaninemia.

METABOLIC DESCRIPTION: In PKU the phenylalanine from ingested protein cannot be metabolized to tyrosine because of deficient liver phenylalanine hydroxylase (PAH). This causes elevated phenylalanine. Pterin defects result from deficiency of tetrahydrobiopterin (BH4), the cofactor for PAH and other hydroxylases. This produces not only increased phenylalanine but also neurotransmitter deficiencies.

ACTION TO BE TAKEN IMMEDIATELY:

- ◆ Contact the family immediately to inform them of the newborn screening result.
- ◆ Consult with a pediatric metabolic specialist.
- ◆ Evaluate the newborn and refer as appropriate.
- ◆ Initiate confirmatory/diagnostic tests in consultation with a metabolic specialist.
- ◆ Provide the family with basic information about PKU and dietary management.
- ◆ Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Plasma amino acid analysis which shows increased phenylalanine without increased tyrosine (increased phenylalanine/tyrosine ratio). Urine pterin analysis and red blood cell DHPR assay will identify pterin defects. Consider PAH mutation testing.

CLINICAL EXPECTATIONS: Asymptomatic in the neonate. If untreated, PKU will cause irreversible mental retardation, hyperactivity, autistic-like features, and seizures. Treatment will usually prevent these symptoms. Pterin defects cause early severe neurologic disease (developmental delay/seizures) and require specific therapy.

REPORTING: Report diagnostic results to the family and Kansas NBS program.

SPECIALISTS:

Dr. Leona Therou
KU Medical Center
Kansas City, KS
Office: 913-588-5908

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
Office: 913-588-6326

Dr. Brenda Issa
KU School of Medicine - Wichita
Wichita, KS
Office: 316-962-7386

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KANSAS DEPARTMENT OF HEALTH AND ENVIRONMENT

NEWBORN SCREENING ACT SHEET

SCREEN FOR: INCREASED TYROSINE

CONDITION: TYROSINEMIA (TYR I)

DIFFERENTIAL DIAGNOSIS: Tyrosinemia I (hepatorenal); tyrosinemia II (oculocutaneous); tyrosinemia III; transient hypertyrosinemia; liver disease.

METABOLIC DESCRIPTION: In the hepatorenal form, tyrosine from ingested protein and phenylalanine metabolism cannot be metabolized by fumarylacetoacetate hydrolase to fumaric acid and acetoacetic acid. The resulting fumarylacetoacetate accumulates and is converted to succinylacetone, the diagnostic metabolite which is hepatotoxic and leads to elevated tyrosine. Tyrosinemia II and III are due to other defects in the tyrosine degradation.

ACTION TO BE TAKEN IMMEDIATELY:

- ✦ Contact family to inform them of the newborn screening result.
- ✦ Consult with pediatric metabolic specialist.
- ✦ Evaluate the newborn and refer as appropriate.
- ✦ Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.
- ✦ Provide family with basic information about tyrosinemia.
- ✦ Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Plasma amino acid analysis will show increased **tyrosine** in all of the Tyrosinemias. Urine organic acid analysis will reveal increased **succinylacetone** in tyrosinemia I only.

CLINICAL EXPECTATIONS: Tyrosinemia I is usually asymptomatic in the neonate. If untreated, it will cause liver disease and cirrhosis early in infancy. Nitisinone (NTBC) treatment will usually prevent these features.

REPORTING: Report diagnostic result to family and Kansas NBS program.

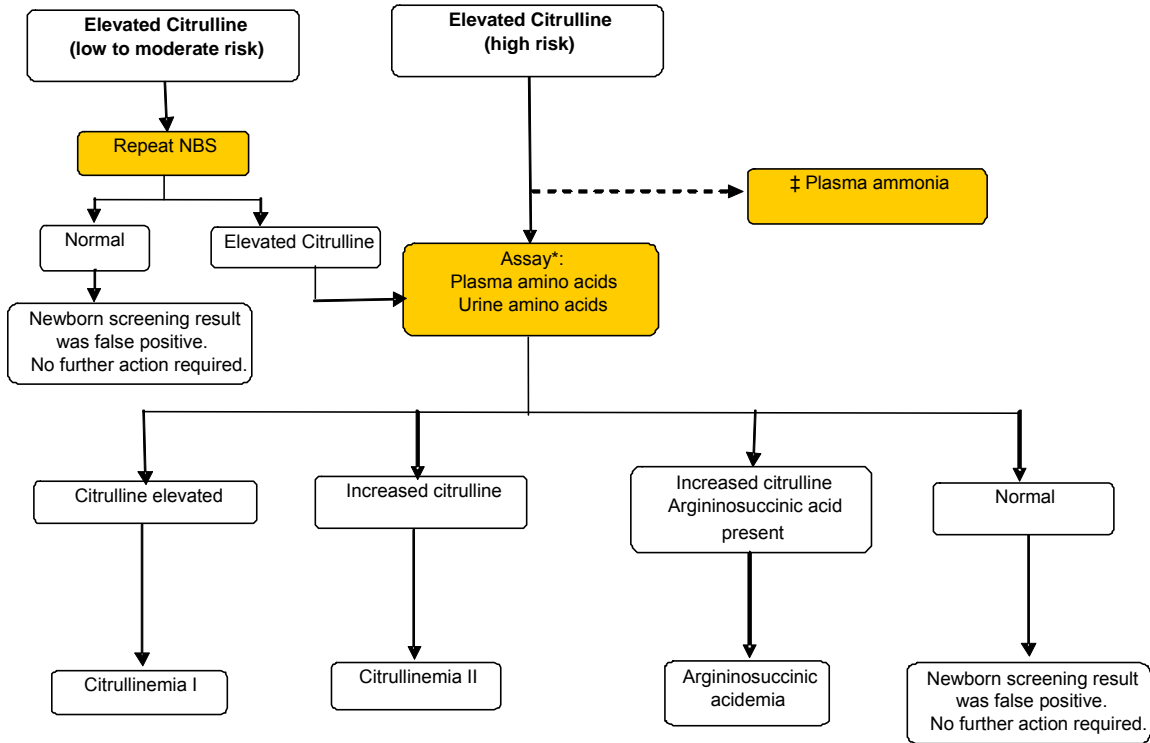
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ELEVATED CITRULLINE



Action steps are shown in gold (shaded) boxes; results are in plain boxes.
Dash lines indicate optional steps

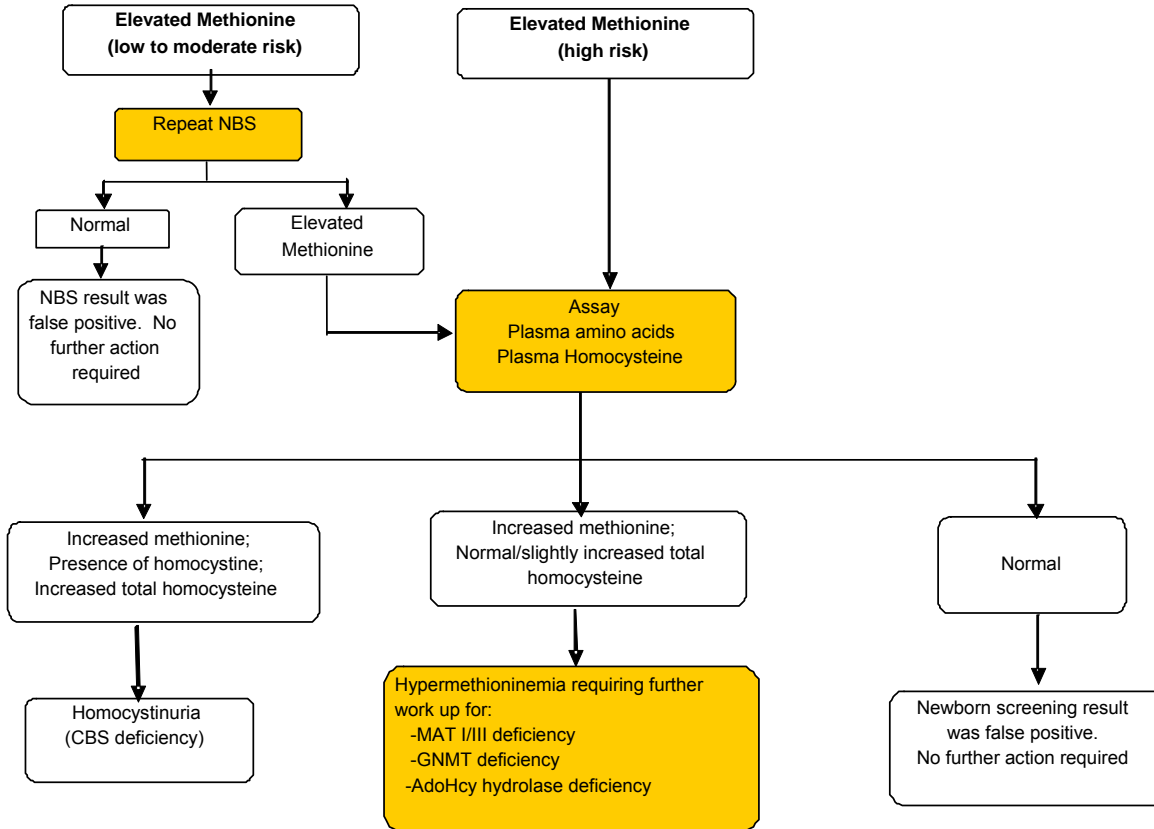
Abbreviations/Key

NBS = Newborn Screening

± = When the positive predictive values of screening are sufficiently high and the risk to the infant is high, some initiate diagnostic studies that are locally available at the same time as confirmation of the screening result is done.
* = Urine organic acids (orotic) may be informative.

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ELEVATED METHIONINE



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Abbreviations/Key

AdoHcy hydrolase = adenosylhomocysteine hydrolase

CBS = Cystathionine β -synthase

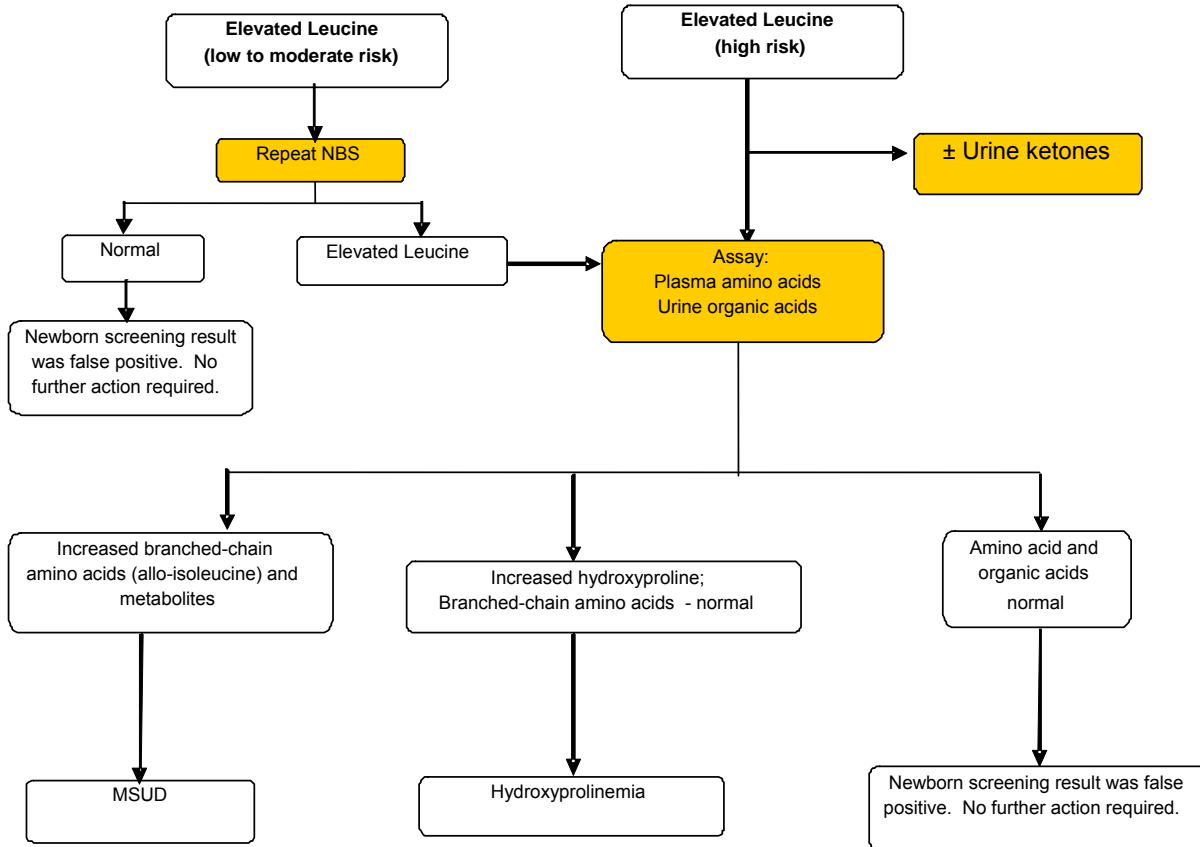
GNMT = Guanidinoacetate methyltransferase

Mat = Methyladenosyltransferase

NBS = Newborn Screening

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ELEVATED LEUCINE



Action steps are shown in gold (shaded) boxes; results are in plain boxes.

Abbreviations/Key

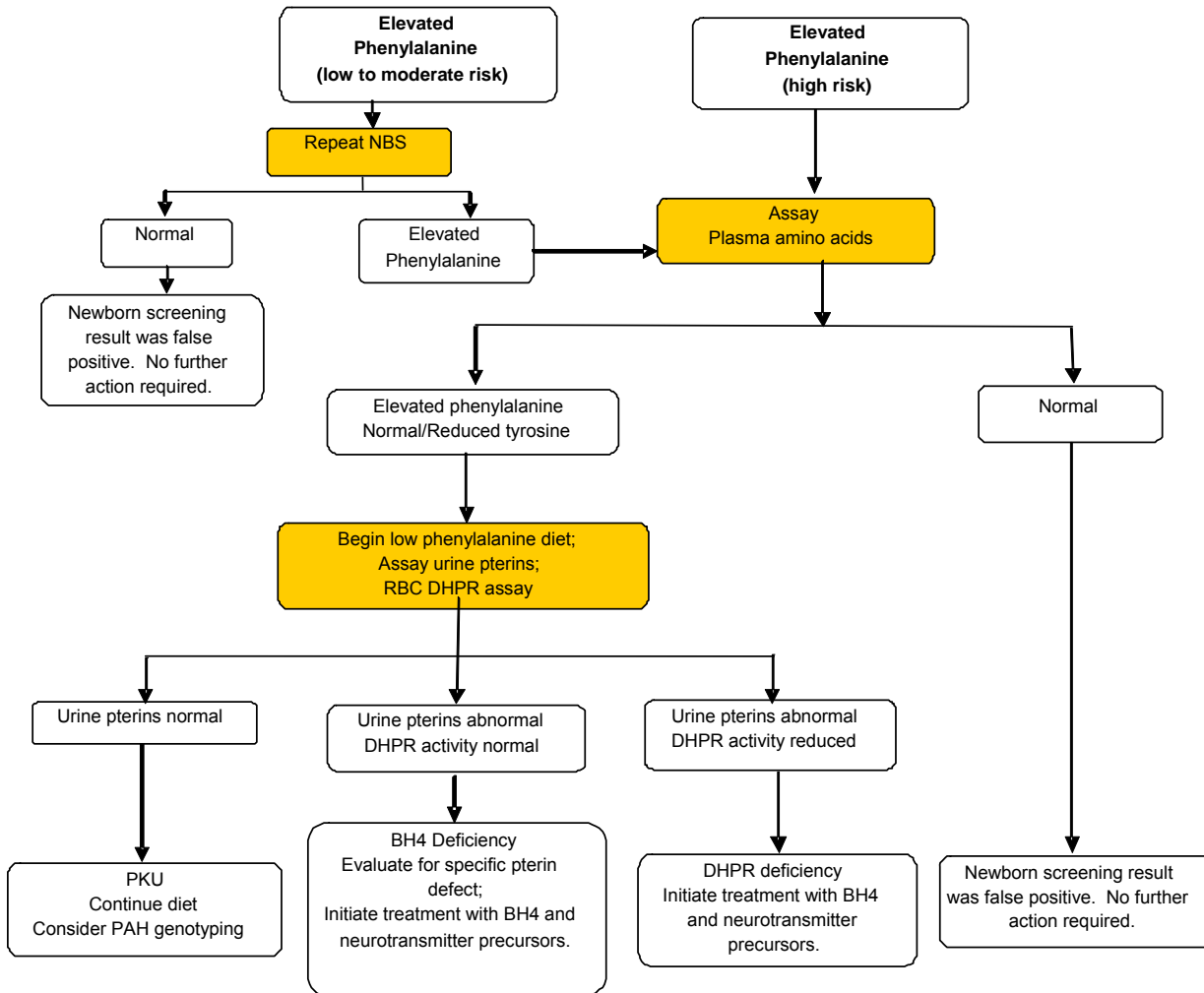
MSUD = Maple syrup urine disease

NBS = Newborn Screening

± = When the positive predictive values of screening are sufficiently high and the risk to the baby is high, some initiate diagnostic studies at the same time as confirmation of the screening result is done.

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ELEVATED PHENYLALANINE



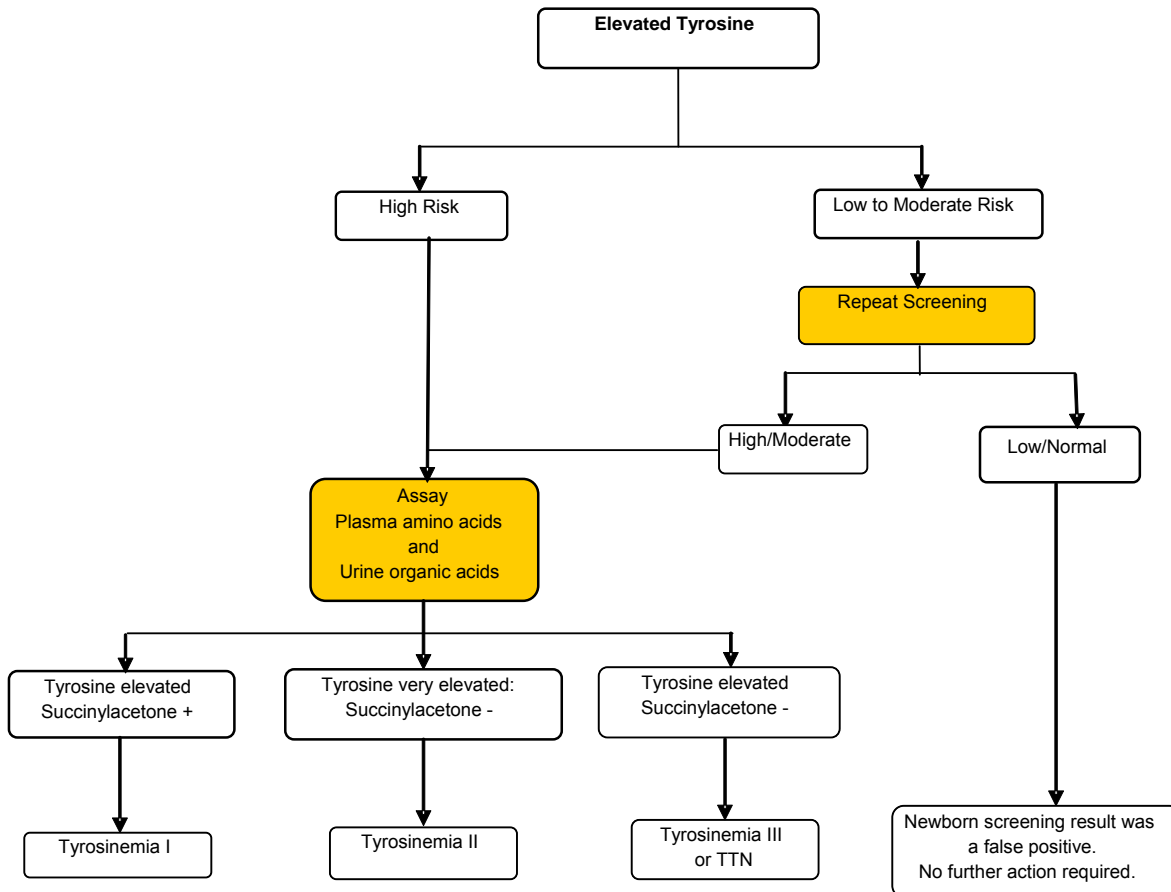
Abbreviations/Key

BH4 = Tetrahydrobiopterin
DHPR = Dihydropteridine reductase
NBS = Newborn Screening
PAH = Phenylalanine hydroxylase
PKU = Phenylketonuria
RBC = Red blood cell

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ELEVATED TYROSINE



Action steps are shown in gold (shaded) boxes; results are in plain boxes.

Abbreviations/Key

TTN = Transient tyrosinemia of the neonate

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EXAMPLE LOW RISK AMINO ACID FIRST LETTER

**Elevated Argininosuccinic Acid Lab Report
Kansas Newborn Screening Program**

January 6, 2011

Dr. John Smith
100 Main St.
Anywhere, KS 66666

RE: Baby Girl Doe
DOB: 01/01/11

MOTHER'S NAME: Jane Doe
PHONE NUMBER: 785-111-1111

Specimen date: 01/02/11

Argininosuccinic acid: Result $\mu\text{mol/L}$
Expected range: $< 0.48 \mu\text{mol/L}$

The newborn screening result above is consistent with a **low** risk for argininosuccinic acidemia. This argininosuccinic acid level is considered to be indeterminate because argininosuccinic acidemia cannot be ruled out. Increased amino acid levels may be seen if the specimen is collected from an infant less than 24 hours of age; a premature infant; an acutely ill infant or receiving TPN.

The final newborn screening lab report will be sent when all testing is completed.

RECOMMENDATION:

Repeat the newborn screening test within 1 to 3 days of receiving this notice, and send the specimen to the State lab for analysis. (If the baby was transfused, repeat the screening on day 4 after transfusion). If the repeat screen is positive or indeterminate, additional testing and consultation with a specialist will be required.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

For consultation, please contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City
Office 913-588-6326
Pager 913-917-3647

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF MODERATE RISK AMINO ACID FIRST LETTER

**Elevated Argininosuccinic Acid Lab Report
Kansas Newborn Screening Program**

January 6, 2011

Dr. John Smith
100 Main St.
Anywhere, KS 66666

RE: Baby Girl Doe
DOB: 01/01/11

MOTHER'S NAME: Jane Doe
PHONE NUMBER: 785-111-1111

Specimen date: 01/02/11

Argininosuccinic acid: Result $\mu\text{mol/L}$
Expected range: $< 0.48 \mu\text{mol/L}$

The newborn screening result above is consistent with a **moderate** risk for argininosuccinic acidemia. This argininosuccinic acid level is considered to be indeterminate because argininosuccinic acidemia cannot be ruled out. Increased amino acid levels may be seen if the specimen is collected from an infant less than 24 hours of age; a premature or an acutely ill infant.

The final newborn screening lab report will be sent when all testing is completed.

RECOMMENDATION:

Repeat the newborn screening test within 1 to 3 days of receiving this notice, and send the specimen to the State lab for analysis. (If the baby was transfused, repeat the screening on day 4 after transfusion). If the repeat screen is positive or indeterminate, additional testing and consultation with a specialist will be required.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

For consultation, please contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City
Office 913-588-6326
Pager 913-917-3647

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF HIGH RISK AMINO ACID FIRST LETTER

**Elevated Argininosuccinic Acid Lab Report
Kansas Newborn Screening Program**

January 6, 2011

Dr. John Smith
100 Main St.
Anywhere, KS 66666

RE: Baby Girl Doe

DOB: 01/01/11

MOTHER'S NAME: Jane Doe

PHONE NUMBER: 785-111-1111

Specimen date: 01/02/11

Argininosuccinic acid: Result $\mu\text{mol/L}$
Expected range: $< 0.48 \mu\text{mol/L}$

The newborn screening result above is **highly suggestive** of argininosuccinic acidemia. This condition can present acutely in the newborn period with hyperammonemia, seizures, failure to thrive, lethargy and coma. Later signs include mental retardation.

The final newborn screening lab report will be sent when all testing is completed.

RECOMMENDATION:

Immediate consultation with the consultant listed below is essential for diagnostic testing and genetic counseling. Please call to arrange an immediate appointment.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

For consultation, please contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City
Office 913-588-6326
Pager 913-917-3647

PLEASE COMPLETE AND RETURN THE ENCLOSED PHYSICIAN REPORTING FORM WHEN FOLLOW UP IS COMPLETE.

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF MULTIPLE MS/MS RESULTS FIRST LETTER

**Multiple Elevated MS/MS Analytes Lab Report
Kansas Newborn Screening Program**

January 6, 2011

Dr. John Smith
100 Main St.
Anywhere, KS 66666

RE: Baby Girl Doe
DOB: 01/01/11

MOTHER'S NAME: Jane Doe
PHONE NUMBER: 785-111-1111

Specimen date: 01/01/11

The above infant has multiple MS/MS analyte results that are within the low-moderate risk range. The elevated results may be due to TPN or other supplements, but further testing is required to identify any true positive results.

Analyte	Result (µmol/L)	Expected Range (µmol/L)	Associated Disorder
Phenylalanine	Result	< 128	PKU
Leucine	Result	< 250	MSUD
Methionine	Result	< 79	HCY
Tyrosine	Result	< 276	TYR I
Argininosuccinic Acid	Result	< 0.48	ASA
Citrulline	Result	< 53	CIT
C8	Result	< 0.38	MCADD
C14:1	Result	< 0.66	VLCADD
C16-OH	Result	< 0.12	LCHAD/TFP
C0	Result	> 14.5	CUD
C5	Result	< 0.71	IVA
C5DC	Result	< 0.32	GA-1
C5-OH	Result	< 0.61	3MCC, HMG, BKT AND MCD
C3	Result	< 6.23 if ≤ 7 days old < 4.00 if > 7 days old	PROP, MUT, Cbl A&B

RECOMMENDATION:

Infant should be off TPN or other dietary supplements for 48 hours prior to retest. Repeat the newborn screening test and send the specimen to the State lab for analysis. (If the baby was transfused, repeat the screening on day 4 after transfusion). If the repeat screen is positive or indeterminate, additional testing and consultation with a specialist will be required.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.



Robert Moser, MD, Acting Secretary

Department of Health & Environment

Sam Brownback, Governor

EXAMPLE OF 2ND LOW OR MODERATE RISK AMINO ACID LETTER

**Elevated Argininosuccinic Acid Lab Report
Kansas Newborn Screening Program**

January 20, 2011

Dr. John Doe
100 Main St.
Anywhere, KS 66666

RE: Baby Girl Doe MOTHER'S NAME: Jane Doe
DOB: 01/01/11 PHONE NUMBER: 785-111-1111

Specimen date: 01/02/11	Argininosuccinic acid: Result $\mu\text{mol/L}$	Citruline: Result $\mu\text{mol/L}$
Specimen date: 01/15/11	Argininosuccinic acid: Result $\mu\text{mol/L}$	Citruline: Result $\mu\text{mol/L}$
	Expected range: < 0.48 $\mu\text{mol/L}$	< 53.0 $\mu\text{mol/L}$

The newborn screening results above are **suggestive** of argininosuccinic acidemia. This condition can present acutely in the newborn period with hyperammonemia, seizures, failure to thrive, lethargy and coma. Later signs include mental retardation.

The final newborn screening lab report will be sent when all testing is completed.

RECOMMENDATION:

The repeat newborn screen is elevated. Consultation with the consultant listed below is essential for diagnostic testing and genetic counseling. Please call to arrange an immediate appointment.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

For consultation, please contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City
Office 913-588-6326
Pager 913-917-3647

PLEASE COMPLETE AND RETURN THE ENCLOSED PHYSICIAN REPORTING FORM WHEN FOLLOW UP IS COMPLETE.

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF ASA/CIT REPORT FORM

**ELEVATED Citrulline (Possible ASA / CIT)
NEWBORN SCREENING
PHYSICIAN REPORTING FORM**

****Return this form When Follow-Up is Complete ****

February 20, 2011

Dr. John Smith
100 Main St.
Anywhere, KS 66666

If this infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.

RE: Baby Girl Doe
DOB: 01/01/11

Baby's name if different than listed

DIAGNOSIS EXCLUDED: Date Excluded: _____

Baby does **NOT** have Argininosuccinic Acidemia or Citrullinemia type I / type II

DIAGNOSIS CONFIRMED: Date Diagnosis Confirmed: _____

Baby has Argininosuccinic Acidemia or Citrullinemia (circle one)

Lab Results: (please fill in and attach a copy of specialist's report)

Plasma amino acids: _____

Urine amino acids: _____

Additional lab results: _____

Date treatment began: _____

Baby referred to specialist (please attach copy of specialist's report)

Name of specialist: _____

FORM CONTINUES ON BACK

Robert Moser, MD, Secretary

Department of Health & Environment

Sam Brownback, Governor

EXAMPLE OF HCY REPORT FORM

**ELEVATED METHIONINE (POSSIBLE HCY)
NEWBORN SCREENING
PHYSICIAN REPORTING FORM**

****Return this form When Follow-Up is Complete ****

February 20, 2011

Dr. John Smith
100 Main St.
Anywhere, KS 66666

If this infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.

RE: Baby Girl Doe
DOB: 01/01/11

Baby's name if different than listed

DIAGNOSIS EXCLUDED: Date Excluded: _____

Baby does **NOT** have Homocystinuria

DIAGNOSIS CONFIRMED: Date Diagnosis Confirmed: _____

Baby has Homocystinuria

Lab Results: (please fill in and attach a copy of specialist's report)

Plasma Amino Acids: _____

Plasma Homocysteine: _____

Additional lab results: _____

Date treatment began: _____

Baby referred to specialist (please attach copy of specialist's report)

Name of specialist: _____

FORM CONTINUES ON BACK



Robert Moser, MD, Secretary

Department of Health & Environment

Sam Brownback, Governor

EXAMPLE OF MSUD REPORT FORM

**ELEVATED Leucine (Possible MSUD)
PHYSICIAN REPORTING FORM**

****Return this form When Follow-Up is Complete ****

February 20, 2011

Dr. John Smith
100 Main St.
Anywhere, KS 66666

If this infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.

RE: Baby Girl Doe
DOB: 01/01/11

Baby's name if different than listed

DIAGNOSIS EXCLUDED: Date Excluded: _____

Baby does **NOT** have Maple Syrup Urine Disease (MSUD)

DIAGNOSIS CONFIRMED: Date Diagnosis Confirmed: _____

Baby has MSUD

Lab Results: (please fill in and attach a copy of specialist's report)

Plasma amino acids: _____

Urine organic acids: _____

Additional lab results: _____

Date treatment began: _____

Baby referred to specialist (please attach copy of specialist's report)

Name of specialist: _____

FORM CONTINUES ON BACK



Robert Moser, MD, Secretary

Department of Health & Environment

Sam Brownback, Governor

EXAMPLE OF PKU REPORT FORM

PHENYLKETONURIA (PKU) NEWBORN SCREENING

PHYSICIAN REPORTING FORM

****Return this form When Follow-Up is Complete ****

February 20, 2011

Dr. John Smith
100 Main St.
Anywhere, KS 66666

If infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return form.

RE: Baby Girl Doe
DOB: 01/01/11

Baby's name if different than listed

DIAGNOSIS EXCLUDED: Date Excluded: _____

Baby does **NOT** have Phenylketonuria (PKU) or Variant

DIAGNOSIS CONFIRMED: Date Diagnosis Confirmed: _____

Baby has PKU

Lab Results: (please fill in and attach a copy of specialist's report)

o Phenylalanine level on plasma amino acids: _____

o Tyrosine level on plasma amino acids: _____

o Additional lab results: _____

o Date treatment began: _____

Baby has variant PKU

o (please circle one) Clinically significant / Not clinically significant

o Date treatment began, if indicated: _____

FORM CONTINUES ON BACK



Robert Moser, MD, Secretary

Department of Health & Environment

Sam Brownback, Governor

EXAMPLE OF TYR1 REPORT FORM

**ELEVATED Tyrosine (Possible TYR1)
NEWBORN SCREENING
PHYSICIAN REPORTING FORM**

****Return this form When Follow-Up is Complete ****

February 20, 2011

Dr. John Smith
100 Main St.
Anywhere, KS 66666

If this infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.

RE: Baby Girl Doe
DOB: 01/01/11

Baby's name if different than listed

DIAGNOSIS EXCLUDED: Date Excluded: _____

Baby does **NOT** have Tyrosinemia type I

DIAGNOSIS CONFIRMED: Date Diagnosis Confirmed: _____

Baby has Tyrosinemia type I

Lab Results: (please fill in and attach a copy of specialist's report)

Plasma amino acids: _____

Urine organic acids: _____

Additional lab results: _____

Date treatment began: _____

Baby referred to specialist (please attach copy of specialist's report)

Name of specialist: _____

FORM CONTINUES ON BACK

Argininosuccinic Acidemia Information for Health Professionals

Argininosuccinic acidemia is a urea cycle disorder in which the argininosuccinic acid lyase (ASAL) enzyme deficiency causes severe hyperammonemia.

✓ **Clinical Symptoms**

Hyperammonemia causes symptoms within the first few days of life which may include: feeding problems, lethargy, vomiting, and irritability. If untreated, high ammonia levels can cause muscle weakness, hypotonia, breathing problems, problems regulating body temperature, poor growth, enlarged liver, learning delays or mental retardation, seizures, swelling of the brain, and coma. Death typically occurs within the first few days/weeks of life if untreated.

✓ **Incidence**

Argininosuccinic acidemia occurs in less than 1 out of every 100,000 births with no increased incidence based on sex, race, or ethnicity.

✓ **Genetics of argininosuccinic acidemia**

Mutations in the ASL gene cause argininosuccinic acidemia. Mutations in this gene reduce or eliminate the activity of the enzyme argininosuccinic acid lyase, which is necessary in the urea cycle for the conversion of argininosuccinic acid into arginine. Mutations ultimately lead to an accumulation of ammonia in the blood causing the symptoms of this condition.

✓ **How do people inherit argininosuccinic acidemia?**

Argininosuccinic acidemia is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition. Each pregnancy between carrier parents has a 25% chance of producing a child affected with argininosuccinic acidemia, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ **Treatment**

Immediate diagnosis and treatment of argininosuccinic acidemia in the neonatal period is critical to normal development and survival. Treatment is usually effective if started before ammonia levels are excessive. Hyperammonemia is a medical emergency that may require dialysis. Individuals should follow a life-long low-protein diet, which may require medical formulas and foods. Certain medications, such as sodium benzoate and/or sodium phenylacetate, as well as supplementation of arginine, may help prevent ammonia build-up. Episodes of high ammonia levels may require medications via IV or dialysis.

✓ **Screening Methodology**

Primary newborn screening for argininosuccinic acidemia utilizes tandem mass spectrometry to determine the level of citrulline. Individuals with a positive screen will have elevated levels of citrulline. False positive and false negative results are possible with this screening.

✓ **What to do After Receiving Presumptive Positive ASA Screening Results**

- 1) The clinician should immediately check on the clinical status of the baby.
- 2) Consultation with a metabolic specialist is essential.
- 3) The specialist may request confirmatory lab tests on the baby.
- 4) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
- 5) Report Clinical Findings to Newborn Screening Program at 785-291-3363.
- 6) Same birth siblings (twins, triplets) of infant diagnosed with argininosuccinic acidemia should be re-screened; addition testing of these siblings may be indicated.
- 7) Consider testing older siblings of affected individuals. Some people with mild or no symptoms may go undiagnosed.

✓ **Confirmation of Diagnosis**

The diagnosis of argininosuccinic acidemia can be confirmed by performing quantitative plasma ammonia and plasma and urine amino acid analysis. Individuals will have the presence of argininosuccinic acid in both blood and urine. Levels of orotic acid may be elevated in urine. Symptomatic individuals will have significantly elevated blood ammonia levels.

✓ **Communication of Results to Parents**

If a baby has a **presumptive positive argininosuccinic acidemia** newborn screening result, **additional testing needs to be performed to confirm a diagnosis.** In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If the baby is diagnosed with argininosuccinic acidemia, the following points should be conveyed to parents:

- ***Parents should understand that treatment for argininosuccinic acidemia will be life-long.***
- ***Parents should understand that treatment is not curative and that all morbidity cannot necessarily be prevented. Long-term management, monitoring, and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics, metabolic disease specialist, and dieticians. Regular blood analysis is needed.***
- ***Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation, contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
913-588-6326

05/20/11

Citrullinemia Information for Health Professionals

Citrullinemia type I (CTLN1) is a rare inherited disorder caused by a deficiency or lack of the enzyme argininosuccinate synthetase (ASS). Argininosuccinate synthetase is one of six enzymes that play a role in the urea cycle. The lack of this enzyme results in excessive accumulation of nitrogen, in the form of ammonia (hyperammonemia), in the blood.

Elevated citrulline is a marker for several urea cycle disorders including citrullinemia I [ASAS deficiency], citrullinemia II [citrin deficiency] and argininosuccinic aciduria [ASA lyase deficiency].

✓ **Clinical Symptoms**

There are two forms of citrullinemia type I; the common “classic/neonatal” form and a milder form. High ammonia levels in the blood cause symptoms to begin within the first few days of life in infants with the classic form. Symptoms include: feeding problems, lethargy, and irritability. If untreated, high ammonia levels can cause hypotonia, breathing problems, problems regulating body temperature, seizures, swelling of the brain, poor growth, enlarged liver, learning delays or mental retardation, and coma. Death typically occurs within the first few weeks of life if untreated.

In the milder form, symptoms begin in late infancy or childhood and include poor growth, hyperactivity, spasticity, learning problems or mental retardation, hair shaft abnormalities, and episodes of high levels of ammonia in the blood (often after periods of fasting, illness, or after high-protein meals). High blood ammonia levels in children can cause poor appetite, headaches, slurred speech, lethargy, ataxia, and vomiting. If untreated, high ammonia levels may lead to breathing problems, seizures, swelling of the brain, coma, and possible death.

Citrin deficiency is associated with neonatal intrahepatic cholestasis (NICCD) and citrullinemia type II (CTLN2). CTLN2 is characterized by adult-onset, recurring episodes of hyperammonemia and associated neuropsychiatric symptoms including nocturnal delirium, aggression, irritability, hyperactivity, delusions, disorientation, restlessness, drowsiness, loss of memory, flapping tremor, convulsive seizures, and coma. Death can result from brain edema.

✓ **Incidence**

Citrullinemia occurs in less than 1 out of every 100,000 births.

✓ **Genetics of citrullinemia**

Mutations in the ASS1 gene cause citrullinemia type I. Mutations in this gene reduce or eliminate the activity of the enzyme argininosuccinate synthetase 1. This enzyme is necessary in the urea cycle and the mutations prevent processing of nitrogen. By products of the urea cycle, particularly ammonia, accumulate in the blood causing the symptoms of this condition.

✓ **How do people inherit citrullinemia?**

Citrullinemia is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs or symptoms of the condition. Carrier parents have a 25% recurrence risk with each pregnancy to have an affected offspring.

✓ **Treatment**

Immediate diagnosis and treatment of citrullinemia, especially the classic form, in the neonatal period is critical to normal development and survival. Treatment is usually effective if started before ammonia levels are excessive. Individuals should follow a life-long low-protein diet, which may require medical formulas and foods. Certain medications, such as sodium benzoate and/or phenylbutyrate/phenylacetate, as well as supplementation of arginine may help prevent ammonia build-up. Episodes of high ammonia levels may require

medications via IV or dialysis.

✓ **Screening Methodology**

Primary newborn screening for citrullinemia utilizes tandem mass spectrometry to determine the level of citrulline. Individuals with a positive screen will have very elevated levels of citrulline. False positive and false negative results are possible with this screening.

✓ **What to do After Receiving Presumptive Positive Citrullinemia Screening Results**

- 1) **The clinician should immediately check on the clinical status of the baby.**
- 2) **Consultation with a metabolic specialist is essential.**
- 3) **The specialist may request blood or urine amino acid analysis on baby.**
- 4) **Call KS Newborn Screening Program at 785-291-3363 with questions about results.**
- 5) **Report Clinical Findings to Newborn Screening Program at 785-291-3363.**
- 6) **Same birth siblings (twins, triplets) of infant diagnosed with citrullinemia should be re-screened; additional testing of these siblings may be indicated.**
- 7) **Consider testing older siblings of affected individuals. Some people with mild or no symptoms may go undiagnosed.**

✓ **Confirmation of Diagnosis**

The diagnosis can be confirmed by performing quantitative plasma ammonia and amino acid analysis and urine amino acid analysis. Patients with citrullinemia will have greatly elevated blood citrulline levels, and may have elevated orotic acid levels in urine. Symptomatic individuals will have elevated blood ammonia levels.

✓ **Communication of Results to Parents**

If a baby has a presumptive positive citrullinemia newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If the baby is diagnosed with citrullinemia, the following points should be conveyed to parents:

- ***Parents should understand that treatment for citrullinemia will be life-long.***
- ***Parents should understand that treatment is not curative and that all morbidity cannot necessarily be prevented. Long-term management, monitoring, and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics, metabolic disease specialists, and dieticians. Regular blood analysis is needed.***
- ***Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
913-588-6326

05/20/11

Homocystinuria Information for Health Professionals

Homocystinuria is an amino acid disorder. Most individuals are lacking, or have low function, of the enzyme cystathionine beta-synthase, leading to a buildup of methionine and homocysteine in the body.

✓ **Clinical Symptoms**

Most newborns do not have symptoms. If the condition is left untreated, symptoms are usually recognizable between the ages of 1 and 3 and include growth delays, psychiatric disturbances, delayed developmental milestones, and learning disabilities or mental retardation. If untreated, homocystinuria can cause lens dislocation and glaucoma, osteoporosis, scoliosis, heart disease or stroke due to thrombi, or pancreatitis.

✓ **Incidence**

Homocystinuria occurs in less than 1 in 100,000 births. The incidence is higher in Caucasians from the New England region of the United States and in individuals of Irish ancestry.

✓ **Genetics of homocystinuria**

Mutations in the CBS, MTR (methionine synthase), MTRR (methionine synthase reductase), and MTHFR genes cause homocystinuria.

Most cases are caused by mutations in the CBS gene, which prevents or reduces the production of cystathionine beta-synthase. This results in a build-up of homocysteine and methionine in the blood and urine.

Mutations in other genes rarely cause homocystinuria. Mutations of the MTR, MTRR, or MTHFR gene prevent or reduce the conversion of homocysteine back into methionine. MTHFR deficiency is NOT detectable by current newborn screening since it is associated with decreased plasma methionine level.

✓ **How do people inherit homocystinuria?**

Homocystinuria is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition. Carrier individuals are more likely to be vitamin B12 and folic acid deficient than other individuals. Carrier parents have a 25% recurrence risk in each pregnancy to have an affected offspring.

✓ **Treatment**

Immediate diagnosis and treatment of homocystinuria is critical to normal growth and development. Treatment is very effective if started early. Recommended treatment is a low methionine diet. Individuals may also benefit from vitamin B6, betaine, vitamin B12, folic acid, or supplements. Even when treated, some people will develop lens dislocation.

✓ **Screening Methodology**

Primary newborn screening for homocystinuria utilizes tandem mass spectrometry. Individuals who screen positive for homocystinuria will have elevated levels of methionine. MTHFR deficiency causes low methionine level; therefore, it is not detected by current newborn screening. False positive and false negative results are possible with this screen.

✓ **What to do After Receiving Presumptive Positive Homocystinuria Screening Results**

- 1) The clinician should immediately check on the clinical status of the baby with attention to liver disease.
- 2) Consultation with a metabolic specialist is essential.
- 3) The specialist may request plasma amino acid analysis and plasma homocysteine on the baby.
- 4) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
- 5) Report Clinical Findings to Newborn Screening Program at 785-291-3363.
- 6) Same birth siblings (twins, triplets) of infants diagnosed with homocystinuria should be re-screened; additional testing of these siblings also may be indicated.

✓ **Confirmation of Diagnosis**

The diagnosis of homocystinuria is confirmed through quantitative plasma amino acid analysis to measure the levels of methionine and homocystine, as well as total plasma homocysteine. Urine testing may also be done.

✓ **Communication of Results to Parents**

If a baby has a presumptive positive homocystinuria newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with homocystinuria, the following points should be conveyed to parents:

- ***Parents should understand that treatment for homocystinuria will be life-long.***
- ***Parents should understand that treatment is not curative and that not all medical complications can necessarily be prevented. Long-term management, monitoring, and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended. Infants and children may need periodic evaluation with ophthalmology and orthopedics.***
- ***Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation, contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
913-588-6326

05/20/11

Maple Syrup Urine Disease (MSUD) Information for Healthcare Professionals

Maple Syrup Urine Disease (MSUD) is an inherited metabolic condition in which the branched-chain amino acids (leucine, isoleucine and valine) are ineffectively catabolized. The branched-chain alpha-ketoacid dehydrogenase (BCKD) complex in the mitochondrial membrane is responsible for breakdown of these three amino acids. A deficiency in one of the six enzymes forming the complex leads to high levels of leucine, isoleucine and valine in the plasma, cerumen, and urine. **Untreated, MSUD usually leads quickly to encephalopathy, spasticity, coma, seizures and death.**

✓ Clinical Symptoms

Babies with classic MSUD usually appear normal at birth. Within the first few days of life, feeding difficulties, irritability and vomiting become apparent. This is often followed by failure to thrive and progressive neurological deterioration, characterized by lethargy, tachypnea, coma and seizures. A high-pitched cry is common, as is muscular rigidity, or alternating periods of hypo- and hypertonicity. There are three other forms of MSUD: intermediate, intermittent and thiamine-responsive. These alternate forms represent partial activity of the BCKA complex, and are generally less severe and of later onset than the classic neonatal form. **The intermittent form is not usually detected by newborn screening.**

✓ Incidence

MSUD occurs in less than 1 in 100,000 births. Some Amish and Mennonite populations in the United States, due to a founder mutation, may have an incidence as high as approximately 1 in 300. It is also more common in people of French-Canadian ancestry.

✓ Genetics of MSUD

Mutations are known in four genes that encode proteins of the branched-chain alpha-ketoacid dehydrogenase (BCKA) complex. The most common mutations are found in *BCKDHA*, the gene for the E1 α subunit of the BCKA complex. These mutations are most often associated with the classic (neonatal-onset) form of MSUD.

✓ Inheritance

MSUD is inherited in an autosomal recessive pattern. Parents of a child diagnosed with MSUD are unaffected. These individuals are carriers of the condition and have one normal copy of the gene coding for the BCKA complex and one abnormal copy. Each pregnancy between carrier parents has a 25% chance of producing a child affected with MSUD, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ Treatment

Emergency treatment consists of hemodialysis and/or administration of a specialized nutritional solution in order to quickly reduce serum levels of the branched-chain amino acids. Ongoing management involves dietary protein restriction of the branched-chain amino acids, supplementation with medical formula, and frequent monitoring of blood concentrations of branched-chain amino acids. Avoidance of fasting and a management plan for infection are important in preventing catabolic crisis. Prognosis is better the earlier treatment is begun. In the classic form of MSUD, prognosis is best when treatment is initiated before 14 days of life. Liver transplantation has been reported to successfully reverse symptoms.

✓ **Screening Methodology**

Newborn screening for MSUD is performed using tandem mass spectrometry. False positive and false negative results are possible with this screening. Infants with a presumptive positive screening test require prompt follow-up and, when notified of these results, the clinician should **immediately** check on the clinical status of the baby and **refer the infant to a metabolic disease specialist**.

False positives are possible and may occur if the specimen is drawn from pre-term infants, submission is delayed, or if the specimen has been exposed to heat. False negatives can result if an infant has had a blood transfusion. The newborn screen should be performed 90 days post-transfusion.

✓ **What to do After Receiving Presumptive Positive MSUD Screening Result**

- 1) **Consult with pediatric metabolic specialist.**
- 2) **Evaluate the newborn. Individuals should be evaluated for clinical symptoms including lethargy, feeding problems, vomiting, and tachypnea. If infant is symptomatic, initiate emergency treatment to reduce serum branched-chain amino acids.**
- 3) **Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.**
- 4) **Call KS Newborn Screening Program at 785-291-3363 with questions about results.**
- 5) **Report Clinical Findings to Newborn Screening Program at 785-291-3363.**

✓ **Confirmation of Diagnosis**

A positive newborn screening result requires immediate evaluation for symptoms of MSUD.

Diagnostic testing, including plasma amino acids and urine organic acids, should be undertaken in consultation with a metabolic disease specialist, to confirm the diagnosis. Patients should be followed at regular intervals by a metabolic specialist and a metabolic nutritionist.

✓ **Communication of Results to Parents**

If a newborn has a presumptive positive MSUD newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with MSUD, the following points should be conveyed to parents:

- ***Treatment is life-long. While effective, it does not prevent all medical problems.***
- ***Compliance with treatment is necessary for the best outcome.***
- ***Parents who have a child with MSUD have a 25% chance with each pregnancy of having another affected child.***
- ***Prenatal testing for pregnancies at 25% risk is available when both parents are confirmed carriers.***

For consultation, contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
913-588-6326

5/20/11



Phenylketonuria (PKU) Information for Healthcare Professionals

Phenylketonuria (PKU) is a disorder of amino acid metabolism that results in excess levels of phenylalanine in body fluids. Elevated levels of phenylalanine can become neurotoxic; early detection and treatment of hyperphenylalaninemia is necessary to prevent mental retardation.

✓ Clinical Symptoms

Infants with classic PKU appear normal until they are a few months old. Early symptoms can include skin rash, seizures, excessive restlessness, irritable behavior and a musty odor of the body or urine. Later signs include developmental delays, psychiatric disorders and mental retardation. Without treatment, these children develop permanent mental retardation. Children with classic PKU tend to have lighter skin and hair than unaffected family members due to low tyrosine levels, and are also likely to have skin disorders such as eczema.

✓ Incidence

In the United States, PKU occurs in 1 in 25,000 newborns. The incidence varies according to ethnic background of the child, with a higher incidence in White and Native American populations and lower incidence in African American, Hispanic, and Asian populations.

✓ Genetics of PKU

Mutations in the PAH gene cause phenylketonuria. The PAH gene codes for phenylalanine hydroxylase. Phenylalanine hydroxylase is responsible for the conversion of phenylalanine to tyrosine. PAH mutations reduce the activity of phenylalanine hydroxylase, preventing it from processing phenylalanine effectively. As a result, this amino acid can build up to toxic levels in the blood and other tissues. Because nerve cells in the brain are particularly sensitive to phenylalanine levels, excessive amounts of this substance can cause brain damage.

Classical PKU occurs when phenylalanine hydroxylase activity is severely reduced or absent. People with untreated classic PKU have levels of phenylalanine high enough to cause severe brain damage and other serious medical problems. Mutations in the PAH gene that allow the enzyme to retain some activity result in milder versions of this condition, such as variant PKU or non-PKU hyperphenylalaninemia.

✓ Inheritance Patterns

PKU is inherited in an autosomal recessive pattern. Parents of a child diagnosed with PKU are unaffected. These individuals are carriers of the condition and have one normal PAH gene and one abnormal PAH gene. Each pregnancy between carrier parents has a 25% chance of producing a child affected with PKU, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ Treatment

Early diagnosis and treatment is essential to prevent developmental delays. Treatment is life-long and consists of a low phenylalanine diet, which includes a specialized medical formula, in combination with regular foods that are low in phenylalanine.

Tetrahydrobiopterin (BH₄) deficiency occurs in a subset of children with PKU due to defects in pterin metabolism. This causes early severe neurologic disease (developmental delay/seizures) and requires replacement therapy with tetrahydrobiopterin.

Babies born to mothers with poorly controlled PKU have a significant risk of mental retardation due to their exposure to very high levels of phenylalanine before birth. These infants may have a low birth weight and grow more slowly than other children. Other characteristic medical problems include heart defects, microcephaly, and behavioral problems. These babies have "Maternal PKU syndrome". Women with poorly controlled PKU also have an increased risk of miscarriage. Strict dietary control prior to conception and throughout pregnancy is essential to prevent the "Maternal PKU syndrome".

✓ Screening Methodology

Newborn screening for PKU is by tandem mass spectrometry. This technology allows for measurement of phenylalanine. Elevated phenylalanine levels in conjunction with an increased phenylalanine to tyrosine ratio is indicative of PKU. **Infants with a high risk positive screening test (significantly elevated phenylalanine level) require prompt follow-up.**

✓ What other conditions can cause elevated levels of phenylalanine?

Intermediate forms of hyperphenylalaninemia, in which the levels of phenylalanine are lower than what is usually found in classical PKU, can cause variable mental retardation and, in some cases, can be completely benign. Biopterin is a cofactor for PAH. Defects in biopterin metabolism can cause hyperphenylalaninemia and will also require treatment. Maternal PKU, hyperalimentation (TPN), and liver disease can also lead to the finding of increased phenylalanine levels in newborn screening blood spots.

✓ What to do After Receiving Presumptive Positive PKU Screening Results:

TAKE THE FOLLOWING IMMEDIATE ACTIONS:

- 1) **Contact family immediately to inform them of the newborn screening result.**
- 2) **Consult with pediatric metabolic specialist.**
- 3) **Evaluate the newborn and refer as appropriate.**
- 4) **Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.**
- 5) **Provide the family with basic information about PKU and dietary management.**
- 6) **Call KS Newborn Screening Program at 785-291-3363 with questions about results**
- 7) **Report Clinical Findings to Newborn Screening Program at 785-291-3363.**

✓ Confirmation of Diagnosis

Once the initial screen is positive, diagnostic tests must be performed:

- Plasma amino acid analysis which shows increased **phenylalanine** without increased **tyrosine** (increased phenylalanine: tyrosine ratio).
- Urine pterin analysis and red blood cell DHPR assay will identify pterin defects. Once these blood samples have been collected, a low phenylalanine diet is started.
- Consider PAH mutation testing.

✓ Communication of Results to Parents

If a baby has a presumptive positive PKU newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with PKU, the following points should be conveyed to parents:

- ***Parents should understand that treatment is life-long and that compliance with dietary management is imperative to the child's health, growth and development.***
- ***Infants and children with PKU or hyperphenylalaninemia should have regular follow-up appointments with a metabolic disease specialist.***
- ***Parents should understand that treatment is not curative. Long-term management, monitoring and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics, genetics, and nutrition.***
- ***Parents who have a child with PKU have a 25% chance with each pregnancy of having another affected child.***

For consultation, contact:

Dr. Leona Therou
KU Medical Center
Kansas City, KS
Office 913-588-5908

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
Office 913-588-6326

Dr. Brenda Issa
KU School of Medicine - Wichita
Wichita, KS
Office 316-962-7386

05/20/11

Tyrosinemia Type 1 Information for Health Professionals

Tyrosinemia type 1 is an amino acid disorder in which the enzyme fumarylacetoacetase (FAH) is missing or is not functioning correctly. This leads to a buildup of tyrosine and succinylacetone in the body, causing health problems including liver and kidney disease.

✓ **Clinical Symptoms**

There are two forms of tyrosinemia type 1; the common form in which symptoms develop in infants and the less common “chronic” form that develops in children and adults.

In the common form, symptoms develop within the first few months of life and may include diarrhea, bloody stools, failure to thrive, vomiting, lethargy, irritability, and a “cabbage-like” odor to the skin or urine. If untreated, liver problems such as hepatomegaly, jaundice, easy bleeding/bruising, and swelling of the legs/abdomen are common. Kidney problems can cause rickets and delays in walking. Without treatment, liver and kidney problems usually lead to death. Periodic episodes of pain/weakness (particularly in the legs), tachycardia, breathing problems, seizures, and coma may occur.

Both forms of tyrosinemia type 1 can lead to hepatocellular carcinoma.

✓ **Incidence**

Tyrosinemia type 1 occurs in less than 1 out of every 100,000 births. The incidence is increased in individuals with a French-Canadian background, particularly if they are from the Saguenay Lac Saint-Jean region of Quebec.

✓ **Genetics of tyrosinemia type 1**

Mutations in the FAH gene cause tyrosinemia type 1. Mutations in this gene reduce or eliminate the activity of the enzyme fumarylacetoacetate hydrolase which prevents the metabolism of tyrosine and phenylalanine. Fumarylacetoacetate accumulates and is converted into succinylacetone, which leads to elevated tyrosine levels and causes liver toxicity.

✓ **How do people inherit tyrosinemia type 1?**

Tyrosinemia type 1 is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition. Each pregnancy between carrier parents has a 25% chance of producing a child affected with tyrosinemia type 1, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ **Treatment**

Immediate diagnosis and treatment of tyrosinemia type 1 in the neonatal period is critical to normal development and survival. Treatment can prevent liver, kidney, and neurological symptoms if started immediately. Individuals should follow a life-long low-tyrosine and phenylalanine diet, which generally requires medical formulas and foods. Liver and kidney damage can be prevented with the medication nitisinone (NTBC). NTBC also stops neurological crises. This medication increases the level of tyrosine in patients, making adherence to the diet crucial. Regular blood and urine tests are needed to check amino acid levels, succinylacetone and nitisinone levels, and liver and kidney function. Liver transplantation is the only proven curative treatment.

✓ **Screening Methodology**

Primary newborn screening for tyrosinemia type 1 utilizes tandem mass spectrometry to determine the levels of tyrosine. Elevated tyrosine indicates the possibility of tyrosinemia type 1. False positives and false negatives are possible with this screen.

✓ **What to do After Receiving Presumptive Positive TYR 1 Screening Results**

- 1) **The clinician should immediately check on the clinical status of the baby.**
- 2) **Consultation with a metabolic specialist is essential.**
- 3) **The specialist may request urine organic acid or plasma amino acid analysis on baby.**
- 4) **Call KS Newborn Screening Program at 785-291-3363 with questions about results.**
- 5) **Report Clinical Findings to Newborn Screening Program at 785-291-3363.**
- 6) **Same birth siblings (twins, triplets) of infants diagnosed with TYR 1 should be re-screened; additional testing of these siblings also may be indicated.**

✓ **Confirmation of Diagnosis**

The diagnosis of tyrosinemia type 1 is confirmed through urine or plasma analysis revealing elevated succinylacetone or its metabolites. A lack of fumarylacetoacetase activity in lymphocytes or fibroblasts also confirms the diagnosis.

✓ **Communication of Results to Parents**

If a baby has a presumptive positive tyrosinemia type 1 newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with tyrosinemia type 1, the following points should be conveyed to the parents:

- ***Parents should understand that treatment for tyrosinemia type 1 will be life-long.***
- ***Parents should understand that treatment is not curative and that all morbidity cannot necessarily be prevented. Long-term management, monitoring and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics, metabolic disease specialist, dietician, hematologist, and hepatologist or gastroenterologist.***
- ***Periodic blood and urine analysis is needed.***
- ***Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation, contact:

Dr. Majed Dasouki
KUMC
Kansas City, KS
913-588-6326

05/20/11

EXAMPLE OF AMINO ACID PARENT LETTER

June 10, 2011

Jane Doe
600 Pleasant St.
Anywhere, KS 66666

RE: Baby Girl Doe DOB: 06/01/11

Dear Parent:

Best wishes on the birth of your baby! Shortly after your baby was born, a small blood sample was taken for a test called the Newborn Screen. This test helps parents find out if their baby has certain health problems. A baby can look healthy, but may have a harmful illness that can be found by doing this blood test.

The result of your baby's blood test shows that more testing needs to be done for an amino acid disorder. ***This does not necessarily mean your child is ill.***

THIS IS WHAT YOU NEED TO DO NOW:

1. Call your baby's doctor. Say that you have received a letter stating that your baby's Newborn Screen test was not normal. Set up a time for your baby to have a second test done as soon as you can.
2. We have Dr. John Smith listed as your baby's doctor, and we have notified him/her of your baby's test result. If this is NOT your baby's doctor, please call the Newborn Screening Program at 785-296-0109 so we can contact the right doctor.

DO NOT DELAY. YOUR BABY'S HEALTH DEPENDS ON YOU.

If your baby does not have a doctor, or if you have questions about this letter, please call Kansas Newborn Screening at 785-296-0109.

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

Sincerely,



Jamey Kendall BSN, RN
Kansas Newborn Screening
Follow-up Coordinator



Linda A. Williams, MT(ASCP)
Kansas Newborn Screening
Follow-up Coordinator

29 de junio de 2011

Jane Doe
600 Pleasant St.
Anywhere, KS 66666

RE: Baby Girl Doe Fecha de Nacimiento: 06/01/11

Estimado Padre:

¡Nuestros mejores deseos por el nacimiento de su bebé! Poco después de que su bebé nació, se le tomó una pequeña muestra de sangre para una prueba llamada Chequeo de Recién Nacido (*Newborn Screen*). La prueba ayuda a los padres a saber si su bebé tiene ciertos problemas de salud. Un bebé puede parecer muy saludable, pero podría tener enfermedades dañinas que pueden detectarse haciendo este análisis de sangre.

El resultado de la prueba de sangre de su bebé muestra que deben hacerse más pruebas para Trastornos de los Amino-Ácidos. ***Esto no significa necesariamente que su hijo está enfermo.***

ESTO ES LO QUE DEBE HACER AHORA:

1. Llame al médico de su bebé. Dígale que ha recibido una carta que dice que la prueba de chequeo de recién nacido de su bebé no fue normal. Haga una cita para que se le realice a su bebé una segunda prueba lo más pronto posible.
2. Tenemos a Dr. John Smith indicado como el médico de su bebé, y le hemos notificado los resultados de la prueba de su bebé. Si este NO es el médico de su bebé, por favor llame al Programa de Chequeo de Recién Nacido (*Newborn Screening Program*) al 785-296-0109 para que podamos contactar al médico correcto.

NO DEMORE. LA SALUD DE SU BEBÉ DEPENDE DE USTED.

Si su bebé no tiene un médico, o si tiene alguna pregunta acerca de esta carta, por favor llame a Chequeo de Recién Nacido de Kansas (*Kansas Newborn Screening*) al 785-296-0109.

Información adicional del Chequeo de Recién Nacido de Kansas está disponible en la página Web en: http://www.kdheks.gov/newborn_screening/info_professionals.htm.

Atentamente,



Jamey Kendall BSN, RN
Kansas Newborn Screening
Coordinadora de Seguimiento



Linda A. Williams, MT(ASCP)
Kansas Newborn Screening
Coordinadora de Seguimiento



EXAMPLE OF PKU PARENT LETTER

June 29, 2011

Jane Doe
600 Pleasant St.
Anywhere, KS 66666

RE: Baby Girl Doe DOB: 06/01/11

Dear Parent:

Best wishes on the birth of your baby! Shortly after your baby was born, a small blood sample was taken for a test called the Newborn Screen. This test helps parents find out if their baby has certain health problems. A baby can look healthy, but may have a harmful illness that can be found by doing this blood test.

The result of your baby's blood test shows that more testing needs to be done for phenylketonuria or PKU. ***This does not necessarily mean your child is ill.***

THIS IS WHAT YOU NEED TO DO NOW:

3. Call your baby's doctor. Say that you have received a letter stating that your baby's Newborn Screen test was not normal. Set up a time for your baby to have a second test done as soon as you can.
4. We have Dr. John Smith listed as your baby's doctor, and we have notified him/her of your baby's test result. If this is NOT your baby's doctor, please call the Newborn Screening Program at 785-296-0109 so we can contact the right doctor.

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If your baby does not have a doctor, or if you have questions about this letter, please call Kansas Newborn Screening at 785-296-0109.

Additional information is available on the Kansas Newborn Screening Website at:
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Sincerely,

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El resultado de la prueba de sangre de su bebé muestra que deben hacerse más pruebas para Fenilketonuria. ***Esto no significa necesariamente que su hijo está enfermo.***

ESTO ES LO QUE DEBE HACER AHORA:

1. Llame al médico de su bebé. Dígale que ha recibido una carta que dice que la prueba de chequeo de recién nacido de su bebé no fue normal. Haga una cita para que se le realice a su bebé una segunda prueba lo más pronto posible.
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NO DEMORE. LA SALUD DE SU BEBÉ DEPENDE DE USTED.

Si su bebé no tiene un médico, o si tiene alguna pregunta acerca de esta carta, por favor llame a Chequeo de Recién Nacido de Kansas (*Kansas Newborn Screening*) al 785-296-0109.

Información adicional del Chequeo de Recién Nacido de Kansas está disponible en la página Web en: http://www.kdheks.gov/newborn_screening/info_professionals.htm.

Atentamente,



Jamey Kendall BSN, RN
Kansas Newborn Screening
Coordinadora de Seguimiento



Linda A. Williams, MT(ASCP)
Kansas Newborn Screening
Coordinadora de Seguimiento



Amino Acid Disorders Information for Parents

➤ Overview

Amino acid disorders are a group of rare, inherited conditions that affect infants from birth. They are caused by enzymes that do not work properly. Protein is made up of smaller building blocks, called amino acids. A number of different enzymes are needed to process these amino acids for use by the body. Because of missing or non-working enzymes, people with amino acid disorders cannot process certain amino acids. These amino acids, along with other toxic substances, then build up in the body and cause problems.

➤ Kansas Newborn Screening for amino acid disorders

The newborn screening program in the State of Kansas is designed to screen for six different amino acid disorders. These disorders include:

Phenylketonuria (PKU)	Maple Syrup Urine Disease (MSUD)
Homocystinuria (HCY)	Tyrosinemia, type I (TYR I)
Argininosuccinate Lyase Deficiency (ASA)	Citrullinemia (CIT)

➤ Why is newborn screening done for amino acid disorders?

Newborn screening is done for amino acid disorders so that babies with these conditions can be diagnosed and treated quickly. Immediate diagnosis and treatment of amino acid disorders is important for normal development and health. Without prompt diagnosis and treatment, infants with amino acid disorders will develop varying degrees of developmental delay or mental retardation, medical complications and may even experience death.

➤ Does a positive result from the Kansas Newborn Screening Lab mean that my baby has an amino acid disorder?

No, not necessarily. Newborn screening identifies babies at increased risk for having one of these disorders. Additional tests will need to be done to determine if the baby actually has an amino acid disorder.

➤ What are the signs and symptoms of amino acid disorders?

The age that symptoms start and the types of symptoms that a person has vary. Many babies with these conditions will appear normal at birth. Some of the disorders will cause developmental delay or mental retardation if not treated promptly. Other newborns may develop symptoms such as poor appetite, sleepiness, vomiting, or irritability. If the condition is not treated promptly, babies can develop more serious problems including breathing problems, seizures, swelling of the brain, or even coma or death.

➤ Is there a cure for amino acid disorders?

No, there is no cure for amino acid disorders. However, the outcome is best in infants who are treated early and continue with life-long treatment. Treatment usually consists of a special diet and sometimes medications or supplements.

➤ Where can I get additional information?

Kansas Newborn Screening at www.kdheks.gov/newborn_screening/info_parents.htm
Save Babies Through Screening Foundation at www.savebabies.org
Screening, Technology and Research in Genetics at www.newbornscreening.info

05/20/11

Kansas Newborn Screening Program