

# NEWBORN SCREENING Provider Manual

**FOR THE COMMONWEALTH OF PENNSYLVANIA**



**NEWBORN SCREENING:  
A Special Time...A Special Test**



Division of Newborn Screening and Genetics  
Bureau of Family Health

July 2009

## **Our Mission**

The Department of Health's mission is to promote healthy lifestyles, prevent injury and disease and to assure the safe delivery of quality health care for all Commonwealth citizens.

The Bureau of Family Health's mission is to maintain and improve the health of pregnant women, infants, children and their families through education and health promotion, food benefits and improved access to quality health care to meet family's needs and provide services and benefits in a timely manner.

## **Acknowledgements**

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# I. Introduction

## **Public Health**

Public health can be broadly defined as the practice of protecting and improving the health of populations through preventing disease, health risk education, controlling communicable diseases, prolonging life and promoting health behaviors. The main goal of public health is to improve lives through the prevention and treatment of disease. The goal of the Commonwealth is to provide top-quality programs and services that benefit the health, safety and well-being of all Pennsylvanians and to assure the safe delivery of quality health care for all Commonwealth citizens. Maternal and child health is a component of public health focused on the special health needs of this segment of the population. The Maternal and Child Health Title V program is the nation's oldest Federal program to improve the health of all mothers and children, including children with special health care needs. Newborn screening helps reduce infant mortality. Integrating care from birth through adulthood supports a comprehensive approach to health care for all citizens, including children with special health care needs.

## **Newborn Screening**

Newborn screening saves lives.

Each year approximately 150,000 newborns are delivered in Pennsylvania. Virtually all receive a metabolic/genetic blood spot screening test and 98% receive a hearing screening test. Pennsylvania's Newborn Screening and Follow-Up Program (NSFP) strengthens the role of public health by fostering comprehensive genetic/metabolic and hearing screening testing through a broad network of stakeholders. The Commonwealth's NSFP directly serves the public health by being first and foremost preventive, supporting the long term goal to follow all infants born in the Commonwealth. Most birthing hospitals and birthing centers in Pennsylvania now test for more than the recommended guidelines of 28 conditions plus hearing promulgated by the American College of Medical Genetics. Act 36, which amends the Pennsylvania Newborn Child Testing Act effective July 1, 2009, now codifies the existing practice of supplemental screening currently being done in Pennsylvania.

NSFP has become highly efficient in not only identifying newborns who receive an abnormal metabolic/genetic or unacceptable hearing screen, but also in assisting the appropriate referral for diagnosis, treatment or early intervention. While these metabolic and genetic conditions are rare, with proper treatment the serious medical problems related to these conditions, including death or mental retardation, are often prevented.

The Newborn Screening and Follow-Up Program interacts with local, state, and federal partners to implement national recommendations on newborn blood spot and hearing screening. The Newborn Screening Technical Advisory Board and the Hearing Screening Technical Advisory Committee provide expertise and advice for their respective Programs.



# Provider Manual

This manual is intended to be a reference tool concerning blood spot and hearing screening for newborns within the Commonwealth of Pennsylvania. Primary care practitioners, pediatricians and midwives who are involved in the initial and postnatal care of newborns should find this manual helpful in coordinating further laboratory diagnosis and follow-up of infants with an abnormal or inconclusive newborn screen result.

Currently, the Pennsylvania Department of Health's Division of Newborn Screening and Genetics requires blood spot tests on all newborns per the Newborn Child Testing Act (35 P.S. § 621, et. seq.) and the regulations under (28 Pa. Code § 28.1, et. seq.) for the following conditions:

**Metabolic Disorders:**

- 1) Galactosemia
- 2) Maple syrup urine disease
- 3) Phenylketonuria

**Endocrine Disorders:**

- 4) Congenital adrenal hyperplasia
- 5) Congenital hypothyroidism

**Hemoglobinopathies:**

- 6) Sickle cell disease, thalassemia, and other hemoglobinopathies

Act 36 of 2008 amends the Newborn Child Testing Act and enables the Pennsylvania Department of Health, through the NSFP, to continue to provide for both screening and follow-up services for six mandated genetic and metabolic conditions for newborns and beginning July 1, 2009, establish a program for follow-up services for 22 additional genetic and metabolic conditions, listed below. The PerkinElmer Genetics, Inc. and University of Massachusetts Laboratories are under contract to the Commonwealth for the reporting of the screening test results for the current 6 mandated conditions and effective 7/1/09 the additional 22 conditions. Further description of the aforementioned mandated and additional conditions can be found in Appendix 1.

**The 22 Supplemental Conditions Mandated for Follow-up are:**

**Organic Acid Disorders**

- IVA Isovaleric Acidemia
- GA I Glutaric Acidemia Type I
- HMG 3-Hydroxy 3-Methyl Glutaric Aciduria
- MCD Multiple Carboxylase Deficiency
- MUT Methylmalonic Acidemia (Mutase Deficiency; MMA)
- 3MCC 3-Methylcrotonyl-CoA Carboxylase Deficiency
- Cbl A,B Methylmalonic Acidemia (Cbl A,B)
- PROP Propionic Acidemia (PA)
- BKT Beta-Ketothiolase Deficiency



### **Fatty Oxidation Disorders**

MCAD Medium-Chain Acyl-CoA Dehydrogenase Deficiency  
VLCAD Very Long-Chain Acyl-CoA Dehydrogenase Deficiency  
LCHAD Long-Chain L-3-Hydroxy Acyl-CoA Dehydrogenase Deficiency  
TFP Trifunctional Protein Deficiency  
CUD Carnitine Uptake Defect

### **Amino Acid Disorders**

HCY Homocystinuria  
CIT Citrullinemia  
ASA Argininosuccinic Acidemia  
TYR I Tyrosinemia Type I

### **Hemoglobinopathies**

Hb SC-Disease Sickle-C Disease  
Hb SA S-Beta Thalessemia

### **Others**

BIOT Biotinidase Deficiency  
CF Cystic Fibrosis

In addition, hearing screening is also performed on newborns in Pennsylvania to detect any hearing abnormality or impairment that would warrant further screening. The Pennsylvania Department of Health (Department) strongly recommends hearing screening, per the Infant Hearing Education, Assessment, Reporting and Referral (IHEARR) Act (11 P.S. § 876-1, et. seq.) of 2001.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program by calling 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).





## II. Blood Spot Screening Process (Overview)

All newborns in Pennsylvania are required to receive newborn genetic and metabolic screening pursuant to the Newborn Child Testing Act (35 P.S. § 621, et. seq.) and the regulations promulgated thereunder (28 Pa Code § 28.1, et. seq.)

Blood is collected on a filter paper specimen card. Filter paper specimen cards are available through the Department's Newborn Screening and Follow-Up Program's contracted laboratories to perform specimen card analysis. Collection from all infants should be completed as close to 48 hours as possible, but not before 24 hours or after 72 hours of age, by the birthing facility or by the healthcare provider attending the birth (including home or out-of-hospital births). The completed filter paper specimen card is then sent to one of the NSFP's contracted newborn screening laboratories.

Hospital providers, individual providers, midwives and other licensed practitioners within the Commonwealth are encouraged to conduct additional blood spot testing for additional genetic and metabolic conditions commonly referred to as supplemental screening. The American College of Medical Genetics (ACMG) currently recommends newborn screening for 29 disorders (28 genetic/metabolic conditions and hearing screening) for which treatment is available. This recommendation is based on an ACMG report commissioned by the U.S. Health Resources and Services Administration. Currently 99% of all birthing hospitals in the Commonwealth are screening for all ACMG recommended conditions. Of the approximately 150,000 annual births in the Commonwealth, 97.5% are hospital births, with approximately 3,800 (or 2.5%) out-of-hospital/midwife births. Effective 7/1/09 under Act 36, the screening laboratories are required to report the screening test results for all 22 additional conditions to the Department. Therefore, the labs will report all Tandem Mass Spectrometry (MS/MS) results to the Department, who will now follow the 22 additional conditions and any additional conditions added by the Department as approved by Newborn Screening and Follow-up Technical Advisory Board. See Appendix 10 for the flow charts summarizing the screening process.

### **Tandem Mass Spectrometry (MS/MS)**

A mass spectrometer is essentially a detector that measures the mass (molecular weight) of substances. If the mass of a molecule and its common fragments are known, the identity of the molecule can be deduced. Results from this analysis are then displayed in a graph called a mass spectrum. Tandem mass spectrometry (MS/MS) is an analytical method which involves the use of two mass spectrometers in sequence (tandem) to separate and analyze the content of an ionized mixture of interest. MS/MS newborn screening methodology detects various metabolic diseases by analysis of amino acids and/or acylcarnitine species present in a dried blood spot specimen. Many of the abnormal analyte increases found in MS/MS screening are not pathognomonic of a single disorder. Generalized elevations of medium and long chain acylcarnitine species are also seen in mitochondrial disorders. Prematurity and hyperbilirubinemia can also result in false positive MS/MS newborn screening results.





### III. Hearing Screening (Overview)

Between one and three children per thousand are born each year with some form of hearing loss. Early identification of hearing impairment, coupled with early intervention, helps children overcome impediments to speech and language development and can greatly improve their outlook for social, emotional and cognitive development.

While not currently mandated, hearing screening is performed on newborns prior to hospital discharge, consistent with the Infant Hearing Education, Assessment, Reporting and Referral (IHEARR) Act (11 P.S. § 876-1, et seq.), as well as the Health Resources and Services Administration's and Healthy People 2010 Objectives on Newborn Hearing Screening. The Department recommends that all Pennsylvania newborn hearing screening takes place within 30 days of birth. A confirmation of any hearing loss detected on such screening should be made by three months of age, with further audiologic assessment and possible early intervention services provided by the age of six months. The Department requires birthing facilities to submit aggregate data about hearing screening results to the Early Hearing Detection and Intervention Program at monthly intervals. Hospitals also refer the names of individual newborns not passing hearing screening to the Department of Health for follow-up.

Currently, Pennsylvania hospitals with a birthing center screen newborns for a hearing loss and approximately 98.5% of the infants born in these hospitals are screened. Approximately 3,800 annual births are performed out-of-hospital and/or by midwives, representing 2.5% of the annual births in the Commonwealth. Through a combination of federal and state funds, portable hearing screening units are made available through the Department of Health at no cost to free-standing birthing centers and midwives to screen newborns born outside of a hospital. However, a small percentage of infants continues to be lost to follow-up. Approximately 42% of the newborns delivered by midwives are screened for hearing loss. Our objective is to screen all infants and to provide appropriate follow-up services.

The Department's Newborn Hearing Screening Follow-up Program each year identifies approximately 250 infants with some form of hearing loss who are then linked to on-going medical treatment or to Early Intervention Services.

The Department of Health's Newborn Hearing Screening and Follow-up Program also administers infant hearing screening educational outreach and training workshops for nurses, audiologists, physicians, early intervention staff and other concerned professionals.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Hearing Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).





## IV. Blood Spot Screening Practices and Procedures as Specified in Regulations 28 Pa. Code § 28.1, et. seq.

### **i. Timing:**

Ideally, specimen collection should take place as close to 48 hours as possible, but not before 24 hours or after 72 hours of age. Unless medically contraindicated, specimens are required on all newborns prior to transfusion, hyperalimentation, upon transfer, or early discharge, even if the specimen has to be drawn prior to 24 hours of age. Under those circumstances, a repeat specimen will be necessary using the following timelines:

1. Initial sample collected prior to 24 hours of age: repeat sampling within 72 hours.
2. Initial sample collected prior to 24 hours of age with a subsequent transfusion of blood products: repeat sampling within 72 hours from last transfusion.
3. Initial sample collected after transfusion has taken place and there is no pre-transfusion specimen: repeat sampling at 90 days from last transfusion.
4. For infants placed on hyperalimentation, the Department of Health's guidelines recommends blood spot re-sampling within 48 hours after discontinuing hyperalimentation in order to accurately determine the infant's phenylalanine and leucine levels.

### **ii. Refusal of testing:**

No screening test shall be performed if a parent or legal guardian refuses on the grounds that the test conflicts with a religious belief or practice. The health care provider shall ensure that the recorded objection of the parent or guardian is entered into the medical record of the newborn child and is signed by the parent or legal guardian. The parent or legal guardian should retain a copy of such request.

**iii. Specimen collection method should be followed as recommended by the National Committee for Clinical Laboratory Standards (NCCLS):**

Specimens should always be collected by following instructions found on the back of the filter paper specimen cards (Appendix 2). When collecting a specimen regardless of hospital or outpatient clinic setting, follow these general guidelines:

1. Do not squeeze tissue to obtain blood.
2. Do not use devices that contain EDTA (ethylene-di-amine-tetra-acetic acid).
3. Do not apply specimen to both sides of specimen card.
4. Do not expose card to heat, moisture, or direct sunlight.
5. Do not hold specimens to form batches.
6. Make sure all information on specimen card is filled out completely and accurately. Correctly report the newborn's primary care provider.
7. Mail initial filter paper with 24 hours of collection to the correct testing laboratory.

The Department recommends that the blood spot on the filter paper is properly dry and that specimens are mailed the same day as collection other than Sundays. If possible, ask for an emergency contact for the mother.

The Department also requests that the NICU hospital physician or staff call the screening laboratory with a diagnosis of Meconium ileus and document that diagnosis on the filter paper prior to sending it to the lab.

The heel-stick is the usual practice in obtaining blood spot. Venipuncture may be attempted for complicated heel-stick. The following document may be used as additional reference: The National Committee for Clinical Laboratory Standards (NCCLS). *Blood Collection on Filter Paper for Newborn Screening Programs; Approved Standard – 5th edition*. NCCLS document LA4-A5 (2007), accessible at NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).



## V. Blood Spot Screening Results

### **i. Overview**

Newborn screening results are reported to the Department's Newborn Screening and Follow-up Program, the primary care provider, practitioner or midwife listed on the filter paper specimen card, and the facility of birth (or the filter paper submitter in the case of home or out-of-hospital birth). The primary care provider or submitter is responsible for contacting the parents/guardians of the newborn with the laboratory results; therefore, it is vital that the correct primary care provider is listed on the filter paper.

Completion of testing usually varies from seven to ten working days. If results are not received within two weeks following sample submission, contact the facility of birth or the Newborn Screening and Follow-Up Program. If an infant shows symptoms of one of the screened disorders prior to completion of the newborn screening test, the infant should immediately be clinically evaluated.

***If clinical signs suggest that one of the diseases screened is present in a child who has screened normal, do not assume the disease has been ruled out. A repeat screen may be necessary. Screening tests may produce false negative and false positive results. Report all encounters with false negative results to the Newborn Screening and Follow-up Program.***

For out-of-hospital births, the healthcare provider attending the birth is responsible for coordinating all repeat laboratory testing or referrals when necessary.

In regards to screening results of adopted infants, the organization/individual(s) with guardianship of the newborn may need to be involved in order for information to be released. The Department will work with the organization/individual to expedite release of the information.

### **ii. Normal screen:**

For newborns with a normal blood spot screen, results are reported directly from the screening laboratory to the submitting facility (or the filter paper submitter in the case of home or out-of-hospital birth), the primary care provider listed on the filter paper specimen card and to the Newborn Screening and Follow-Up Program.

Regardless of outcomes, test results can always be obtained from the screening laboratory or through the Newborn Screening and Follow-Up Program.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).

### **iii. Unacceptable screening result:**

All unacceptable specimens will require a repeat specimen to be sent to the appropriate reference laboratory within 72 hours of initial notification. A blood spot specimen collected within 24 hours of birth is unacceptable for some newborn screening tests. Other reasons leading to an unacceptable specimen would include:



1. Poor soak – circles on specimen card not filled or thoroughly saturated.
2. Specimen appears scratched or abraded.
3. Specimen not dry before transporting.
4. Specimen appears clotted or layered.
5. Specimen appears diluted or contaminated.
6. Quantity not sufficient.
7. No blood.
8. Insufficient demographic information to identify patient.

For newborns who require repeat testing due to unacceptable specimens, the screening laboratory will contact the submitting facility's hospital coordinator (or the filter paper submitter in the case of home or out-of-hospital birth) to facilitate a repeat specimen. That individual will in turn contact the parents of the newborn and/or the primary care provider listed on the filter paper specimen card to facilitate a repeat specimen. Results from the repeat screening will be reported by the screening laboratory to the submitting facility, the healthcare provider listed on the filter paper, and to the Department's Newborn Screening and Follow-Up Program (NSFP). Further questions or concerns regarding repeat testing due to unacceptable sampling should first be addressed to the hospital coordinator of the submitting facility. The NSFP can also provide additional assistance regarding repeat testing concerns.

#### **iv. Inconclusive screening result:**

For newborns with an inconclusive screening result for the six mandated conditions, the screening laboratory will contact the NSFP, who will in turn contact the hospital coordinator at the facility of birth or the filter paper submitter for at-home or out-of-hospital births. For all supplemental inconclusive screening results, the screening laboratory will directly contact the birth facility or submitter, and may contact the primary care provider listed on the filter paper specimen card. Most repeat screenings of the newborn will be required within 48-72 hours from the initial contact. For any repeat that is still inconclusive, it should be handled as a presumptive positive and the infant referred immediately to a treatment center or specialist for a consultation to determine further testing and follow-up services.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).

#### **v. Presumptive positive screening result:**

For all newborns that have a presumptive positive screening result, the Newborn Screening and Follow-Up Program and/or the reference laboratory will immediately contact the primary care provider listed on the filter paper specimen card and provide specific instructions on follow-up/referral planning and further diagnostic procedures.





Health care practitioners, including physicians, and health care facilities, birthing centers and hospitals, are required to report the diagnosis of certain diseases in the newborn child to the Pennsylvania Department of Health, Bureau of Family Health, Division of Newborn Screening (see 35 P.S. § 521.16; 28 Pa. Code § 27.1; 28 Pa. Code §27.30; 28 Pa Code § 27.21α, and effective July 1, 2009 35 P.S. § 623). Beyond this, the Department requests the cooperation of practitioners and facilities in sharing information relevant to the condition, follow-up, and treatment of diagnosed newborns, to ensure appropriate and timely interventions. Ongoing communication among all parties involved with the care and treatment of the infant, including the primary care provider, the specialist and the family, is vital for a comprehensive care plan. Please refer to the Medical Home section of this manual (Section VII) for more information.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).

## VI. Hearing Screening Results

Initial screening for hearing impairment should be performed prior to hospital discharge. Newborn hearing screening is usually performed by hospital staff, free-standing birthing centers and midwives either through otoacoustic emissions (OAE) or automated auditory brainstem response (AABR) technologies.

If a newborn does not pass the initial hearing screening process, a subsequent follow-up re-screen should be completed within thirty days of birth. Birthing facilities, free-standing birthing centers and midwives should send primary care providers the hearing screening results so that this information is available during the post-discharge clinic visit.

Currently, the Pennsylvania Department of Health's Newborn Hearing Screening and Intervention Program, receives information on newborns who have not passed the re-screening or who have not received a re-screening. Under these circumstances, the Newborn Hearing Screening and Intervention Program will contact the primary care provider to confirm that the provider is indeed the infant's Medical Home (see Medical Home section VII) and to offer further assistance in regards to follow-up planning and sub-specialty referral.

To increase awareness of the needs of families with newborns that have not passed their hearing screening the Department of Health sponsored the development of an online training program known as OnLi EHDI. To assist physicians in caring for infants who have not passed hearing screening they can now access this on-line CME course to learn more about early hearing detection and intervention and earn up to **2 free CME credits** through the University of Pittsburgh Center for Continuing Education in the Health Sciences. This course consists of case studies and information regarding the newborn hearing screening timeline, helping families obtain a follow-up re-screen, methods for finding an audiologist for referral, and information about hearing loss and parent-to-parent support groups. The website to this program can be found at:

**<https://cme.health.pitt.edu/index.asp?MI=000042>**

Then, click on "All Modules." Under the listed modules, click on "Early Hearing Detection and Intervention."

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).





## VII. Medical Home

A major effort supported by the Pennsylvania Department of Health is the medical home model, especially as related to the primary care of children and youth with special health care needs. Coordinating health care for all citizens of this Commonwealth, including integrating the specialty care provided for newborns and children with metabolic and genetic conditions into a comprehensive relationship with primary care providers including pediatricians, family care practitioners and midwives, is paramount. Medical home is a term used to describe a philosophy of ongoing children's healthcare which is comprehensive, coordinated, family-centered, and existent within the child's own community. Through the use of the medical home, specially trained medical practices can provide continuity of care to children and assure better patient outcomes. In particular, children with special healthcare needs (CSHCN) benefit from the proactive approach of the medical home in guiding patients and their families through the healthcare system. The family also plays an active, direct role in the management of the child's care needs.

A medical home as defined by the American Academy of Pediatrics is a practice that provides primary care that is:

- Accessible
- Continuous
- Comprehensive
- Family-centered
- Coordinated
- Compassionate
- Culturally effective

The Pennsylvania Department of Health, through funding provided by the Title V Maternal and Child Health Care Services Block Grant, has contracted with Educating Practices in Community Integrated Care (EPIC IC) to develop the medical home model throughout the Commonwealth. The project is a collaborative effort of the Pennsylvania Department of Health-Bureau of Family Health, family community organizations, and the PA Chapter of the American Academy of Pediatrics. EPIC IC is a statewide provider of education/quality improvement programs, using office-based change as the key to improving the care provided to children and youth with special health care needs. A map of the current medical home practices in Pennsylvania is found in Appendix 11.

### **Care Coordination in the EPIC IC Program**

EPIC IC primary care practices work with EPIC IC to meet many care coordination criteria. The criteria include:

- Identification of practice team members.
- Recruitment of Parent Partners to work with the practice team.
- Creating a comprehensive and continuously-updated patient registry of CSHCN.
- Submission of a brief monthly report.
- Collaboration with local, community-based organizations.
- Participation in EPIC IC monthly conference calls.
- Attendance at EPIC IC conferences.



While meeting the above criteria, EPIC IC works with practices to refine their model of care delivery so that successive quality measures are incorporated. Care coordination models within the practice include team members who implement care coordination as part of their job responsibilities. Care coordinators typically include: nurses, social workers, and office administrators. The scope of care coordination includes: care/medical management, self care, educational issues, linking to community resources, working with medical care and specialty providers and a variety of other activities.

**For more information, you can contact:**

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**The Role of the Primary Care Provider**

**OB/GYNs/midwives:**

- Prenatal education on newborn screening.
- Encourage pregnant mothers/parents to identify the infant's primary care provider pre-birth and to provide current contact information to birth facility/submitter for any follow-up contact.

**Newborn's Pediatrician/family practice/primary care provider or midwife (PCP):**

- Front line of care and contact with the parents.
- If identified as the newborn's PCP pre-birth, request mother to identify newborn's PCP as the PCP on the filter paper and encourage the mother to provide the submitter her most current contact information.
- Provide direct primary care services.
- Obtain screening results from the screening lab or the Department's Newborn Screening and Follow-Up Program (NSFP).
- Contact parents with results and provide them with instructions for repeat filter paper, interim care, referral to treatment center/specialist (TC) for confirmatory testing.
- Refer presumptive positive result to TC.
- Coordinate immediate care instructions with TC and parents.
- Obtain diagnosis from TC or NSFP.
- Coordinate & integrate ongoing primary care with TC (who will provide specific condition care) and with the family, as part of a team approach to care.



# Appendix 1:

## Genetic and Metabolic Conditions

## **i. Endocrine Disorders**

### **i. 1. Congenital Adrenal Hyperplasia**

Congenital adrenal hyperplasia (CAH) encompasses several autosomal recessive disorders that have in common complete or partial deficiency of an enzyme involved in cortisol and/or aldosterone synthesis. Manifestations of the disease relate to the degree of deficiency of cortisol, aldosterone, or both. Clinical presentations can range from asymptomatic to severe salt wasting and adrenal insufficiency in infants. Virilization or hypertension can also occur if there is an over-accumulation of precursor adrenocortical hormones. All forms of CAH are inherited in autosomal recessive fashion.

The most common form of congenital adrenal hyperplasia is due to CYP21 (also known as 21-hydroxylase) deficiency. This deficiency accounts for more than 90 percent of diagnosed cases. Mutations or partial deletions of CYP21 are common. Two copies of an abnormal gene are required for disease to occur, and not all mutations and partial deletions result in disease. CAH occurs with an overall prevalence of one case per 13,000 to one case per 16,000 births. 11-beta-hydroxylase deficiency accounts for five to eight percent of all patients with CAH. Severe forms of the disease are potentially fatal if unrecognized and untreated because of the cortisol and aldosterone deficiencies that result in salt wasting, hyponatremia, hyperkalemia, dehydration, and hypotension.

Females with some forms of CAH have ambiguous genitalia at birth or subsequently become virilized. Males with CYP21 deficiency are not generally identified in the neonatal period because their genitalia are normal. If the defect is severe, resulting in salt wasting, these male infants are seen at one-four weeks of age because of failure to thrive, recurrent vomiting, dehydration and shock. The diagnosis of congenital adrenal hyperplasia depends upon the demonstration of inadequate production of cortisol, aldosterone, or both in the presence of accumulation of excess concentrations of precursor hormones. For example, the distinguishing characteristic of 21-hydroxylase deficiency is a very high serum concentration of 17-hydroxyprogesterone. Elevated levels of 17-hydroxyprogesterone are also found in premature, low birth weight and sick infants. However, levels should return to normal within a few weeks after birth. False positives can also occur with samples collected from infants less than 24 hours of age. Dehydration, hyponatremia, hyperkalemia and salt wasting require immediate medical attention. Long term glucocorticoid and/or aldosterone treatment may also be warranted.

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**Common Symptoms in male patients with salt-wasting form:**

- Vomiting
- Circulatory collapse
- Hyponatremia
- Hyperkalemia
- Hypoglycemia
- Dehydration



These infants usually present in the neonatal period with acute adrenal crises and a life-threatening deficiency of both cortisol and aldosterone.

**Common Symptoms in female patients with salt-wasting form:**

- Prenatal masculinization characterized by ambiguous genitalia. Females with some forms of adrenal hyperplasia have ambiguous genitalia at birth or subsequently become virilized.

**Treatment: hormone replacement therapy.**

**Recommended Action by Primary Care Provider:**

- When contacted by the screening laboratory or the Department regarding an abnormal result, confirm your clear understanding of the recommendations.
- If contacted with a presumptive positive result **immediately** do the following:
  1. Advise the Department or laboratory which Specialist you are recommending.
  2. Contact that Specialist for a referral and additional information before contacting the family.
  3. Contact family and ascertain clinical status of newborn, and refer family to Specialist for confirmatory testing and management.
  4. Family may continue with their current practice of breastfeeding or bottle feeding.
- If infant is symptomatic, refer family immediately for urgent/emergency care.
- If another physician or primary care provider will be seeing this child, notify that provider promptly of the abnormal laboratory results and the needed follow-up steps.
- If initial result is inconclusive, refer family to the birthing facility to obtain a repeat filter paper screen test as soon as possible. If repeat screen is inconclusive, handle as a presumptive positive and contact the Specialist for a consultation to determine further testing and follow-up needs.

With an inconclusive or presumptive positive screening result, the screening laboratory or the Newborn Screening Follow-up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and assistance and/or subspecialty referral (Appendix 3).

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).

## **i. 2. Congenital Hypothyroidism**

Normal thyroid function is essential for the early and overall development of the central nervous system, growth, and metabolic homeostasis. Congenital hypothyroidism (CH) is defined by inadequate thyroid hormone production in newborn infants. This can occur because of an anatomic defect in the thyroid gland, an inborn error of thyroid metabolism, or iodine deficiency. Congenital hypothyroidism can lead to brain damage and developmental delay if not diagnosed early and treated throughout life.

The incidence of congenital hypothyroidism, as detected through newborn screening, is approximately one per 4,000. CH is one of the most common preventable causes of mental retardation. Disorders affecting the thyroid gland are the most common endocrinopathies in children. Females are affected twice as often as males. There is an increased incidence of CH in infants with Down syndrome. While percentages of specific etiologies vary from country to country, ranges are as follows:

- o Ectopic thyroid, 25-50%
- o Thyroid agenesis, 20-50%
- o Dyshormonogenesis, 4-15%
- o Hypothalamic-pituitary dysfunction, 10-15%

Infants with congenital hypothyroidism are usually born at term or after term. The clinical manifestations of congenital hypothyroidism are dependent on the time of onset of thyroid dysfunction. The presenting symptoms may be nonspecific and subtle and may not appear before the age of two months. Some infants may exhibit decreased activity, poor feeding, jaundice, hypotonia, or hoarse cry. Some physical features may include cardiac septal defects, macroglossia, large fontanelles, umbilical hernia, mottled/dry skin, pallor, myxedema, goiter, or coarse facial features. Profound mental retardation is the most serious effect of untreated congenital hypothyroidism. Affected infants whose treatment is delayed can also develop neurologic problems such as spasticity and gait abnormalities, dysarthria or mutism and autistic behavior.

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### **Common Symptoms:**

- Prolonged jaundice
- Large anterior fontanel
- Hypotonia
- Lethargy
- Constipation
- Feeding problems
- Umbilical hernia
- Macroglossia

**Treatment: thyroxine therapy.**

**Recommended Action by Primary Care Provider:**

- When contacted by the screening laboratory or the Department regarding an abnormal result, confirm your clear understanding of the recommendations.
- If contacted with a presumptive positive result **immediately** do the following:
  1. Advise the Department or laboratory which Specialist you are recommending.
  2. Contact that Specialist for a referral and additional information before contacting the family.
  3. Contact family and ascertain clinical status of newborn, and refer family to Specialist for confirmatory testing and management.
  4. Family may continue with their current practice of breastfeeding or bottle feeding.
- If infant is symptomatic, refer family immediately for urgent/emergency care.
- If another physician or primary care provider will be seeing this child, notify that provider promptly of the abnormal laboratory results and the needed follow-up steps.
- If initial result is inconclusive, refer family to the birthing facility to obtain a repeat filter paper screen test as soon as possible. If repeat screen is inconclusive, handle as a presumptive positive and contact the Specialist for a consultation to determine further testing and follow-up needs.

With a presumptive positive screening result, the screening laboratory or the Newborn Screening and Follow-Up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and assistance and/or subspecialty referral (Appendix 3).

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).





## **ii. Hemoglobinopathies**

### **ii. 1. Sickle Cell Disease (see also Appendix 4)**

Sickle cell disease (SCD) occurs when a combination of genes inherited from both parents results in the production predominantly of sickle hemoglobin (Hb S) in red blood cells. Hb S, when deoxygenated polymerizes into insoluble fibers. These fibers can force red cells to become distorted in shape (sickle cells), rigid, and adherent to vascular endothelium. Sickle cells cause two types of pathology: they hemolyze easily resulting in a chronic anemia and they obstruct small blood vessels and damage the walls of large blood vessels leading to various vasoocclusive complications. Sickle cell disease is a generic term used to include all clinical disorders resulting from the presence of Hb S.

Four genotypes account for most SCD in the United States. These are sickle cell disease SS (SCD-SS), sickle cell disease SC (SCD-SC), and two types of sickle  $\beta$ -thalassemia (SCD- $\beta^+$ -thal and SCD- $\beta^0$ -thal). The disease manifestations vary among patients and in the same patient from time to time. Also, the various genotypes are associated with a wide range of clinical severity. SCD-SS and SCD- $\beta^0$ -thal patients are the most severely affected while those with SCD- $\beta^+$ -thal are typically the mildest affected. The variable degrees of hemolysis and vasoocclusive complications in children with SCD place them at increased risk for severe morbidity and mortality especially during the first 5 years of life.

Hemoglobinopathy is the most frequent disorder identified by newborn screening. In newborn screening, detected hemoglobins are conventionally reported in order of decreasing quantity.

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#### **Common Symptoms for children under age 5:**

In infants, signs do not usually appear until the second six months of life. Most infants appear healthy at birth but may develop anemia, dactylitis (swollen hands and feet) and other pain episodes, and enlarged spleen by the end of their first year. The most serious complications and leading causes of death in infancy and early childhood are:

- Overwhelming invasive bacterial infection (especially by *Streptococcus pneumoniae*), due to splenic dysfunction;
- Acute chest syndrome, a pneumonia-like illness due to pulmonary vasoocclusion and/or infection;
- Acute anemia due to acute splenic sequestration or infection-induced transient red cell aplasia; and
- Septicemia.

Other common early childhood complications include:

- Frequent pain episodes (abdomen, extremities, lower back, ribs and sternum);
- Stroke and "silent" cerebral infarction;
- Abnormal neurocognitive performance;

- Poor growth and development;
- Jaundice and gallstones due to increased hemolysis;
- Acute chest syndrome;
- Proteinuria;
- Pulmonary hypertension.

**Treatment:** Includes prophylactic penicillin therapy; pain management; prompt evaluation and aggressive management (cultures, intravenous broad-spectrum antibiotics) of febrile illness and other signs of infection; red blood cell transfusions (when indicated); hydroxyurea therapy (for reduction in frequency of severe pain and acute chest syndrome); and good hydration. Hematopoietic stem cell transfusion is an option for a cure for patients with appropriate donor who meet clinical criteria.

**Recommended Action by Primary Care Provider:**

- When contacted by the screening laboratory or the Department regarding an abnormal result, confirm your clear understanding of the recommendations.
- If contacted with a presumptive positive result **immediately** do the following:
  1. Advise the Department or laboratory which Treatment Center/Specialist you are recommending.
  2. Contact that Treatment Center/Specialist for a referral and additional information before contacting the family.
  3. Contact family and ascertain clinical status of newborn, and refer family to Treatment Center/Specialist for confirmatory testing and management.
  4. Family may continue with their current practice of breastfeeding or bottle feeding.
- If infant is symptomatic, refer family immediately for urgent/emergency care.
- If another physician or primary care provider will be seeing this child, notify that provider promptly of the abnormal laboratory results and needed follow-up steps.
- If initial result is inconclusive, refer family to the birthing facility to obtain a repeat filter paper screen test as soon as possible. If repeat screen is inconclusive, handle as a presumptive positive and contact the Treatment Center/Specialist for a consultation to determine further testing and follow-up needs.

With a presumptive positive screen, the screening laboratory or the Newborn Screening and Follow-Up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and/or subspecialty referral (Appendix 3).

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).



## **ii. 2. Thalassemia (see also Appendix 4)**

Thalassemia is a hereditary condition affecting the production of red blood cells. Each molecule of adult hemoglobin is made up of two alpha chains and two beta chains. The predominant hemoglobin in newborns is composed of two alpha chains and two gamma chains.

Alpha thalassemia is caused by decreased production of alpha chains. Hemoglobin Barts (composed of four gamma chains) is produced by the fetus when there is insufficient production of alpha chains. The production of alpha chains is controlled by four genes on Chromosome 16. Deletion of one or two of these genes causes alpha thalassemia trait. Deletion of three genes causes Hemoglobin-H disease with moderate hemolytic anemia. In the absence of all four alpha genes, the fetus only produces hemoglobin Barts and usually dies in-utero.

Beta thalassemia is caused by decreased production of beta chains. Specific lab tests are required to detect this condition.

With a presumptive positive screen, the screening laboratory or the Newborn Screening and Follow-Up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and assistance. In general, newborns with thalassemia trait or disease are referred to one of the treatment centers (Appendix 3) for further testing, education, counseling services and treatment if indicated.

## **ii. 3. Other Hemoglobinopathies (see also Appendix 4)**

Hemoglobinopathies are inherited disorders of the hemoglobin molecule. Genetic alterations of hemoglobin (all of which are inherited as autosomal recessive traits), produce hemoglobin molecules with abnormal physical and chemical properties, some of which result in anemia. Collectively, the hemoglobinopathies are the most frequent single gene disorders in man. Sickle cell disease (due to a genetic defect in the  $\beta$ -globin chain) and thalassemias (due to genetic defects in which there is unbalanced  $\alpha$ - or  $\beta$ -globin production) are the most common hemoglobinopathies. These abnormal hemoglobins are differentiated by their electrophoretic mobility and are designated by letters. Individuals can inherit more than one hemoglobin variant with resulting hemoglobinopathies that are characterized by extremely complex clinical manifestations. Some of the hemoglobin variants have high frequencies in

some populations and consequently, different hemoglobin disorders can co-exist at a high frequency in many populations.

Hemoglobin-C trait is found in approximately two percent of African Americans. Persons with homozygous Hemoglobin-C disease usually have mild hemolytic anemia but are usually asymptomatic. Persons that are heterozygous for both Hemoglobin-C and -S will likely have a sickling disorder for which antibiotic prophylaxis is indicated.

Hemoglobin-E is common in persons of Southeast Asian origin. Patients with Hemoglobin-E trait are usually asymptomatic with mild microcytosis. Patients with homozygous Hemoglobin-E disease are usually mildly anemic with severe microcytosis. Patients with Hemoglobin-E/beta thalassemia can have severe anemia similar to thalassemia major.

Hemoglobin-O is a very rare hemoglobin variant which is asymptomatic in the heterozygous state. However, patients with both Hemoglobin-S and -O can have severe sickling similar to sickle cell disease.

Hemoglobin-D is a rare sickling disorder if co-inherited with sickle hemoglobin.

Other variant hemoglobin traits can also be present. Most of the over 500 variants have no clinical significance. No follow-up is required unless indicated clinically.

With a presumptive positive screening result, the screening laboratory or the Newborn Screening and Follow-Up Program will contact the primary care provider listed on the filter paper specimen card to provide further guidance and assistance. In general, newborns with trait or disease are referred to one of the treatment centers (Appendix 3) for further testing, education, counseling services and treatment if indicated.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).



### **iii. Cystic Fibrosis**

Cystic Fibrosis (CF) is a multisystem disorder associated with life-long morbidity and premature mortality. It is the most common genetic disorder in Caucasians. The age of disease onset is variable, ranging from prenatal evidence of echogenic bowel to the onset of symptoms in late adolescence or adulthood. CF has a wide range of phenotypes and there is considerable variability in the clinical severity and course of the disease. Typical CF-related symptoms consist of chronic respiratory infections and gastrointestinal malabsorption, while atypical presentations include pancreatitis, congenital absence of the vas deferens, and nasal polyps. The pulmonary manifestations of CF are the principal determinant of the disease prognosis. Although improved supportive care has resulted in the current median life expectancy of an infant with neonatal diagnosis of CF being approximately 30 to 40 years, CF is still a chronic, debilitating disease with emotional and financial costs to individuals, families and society.

Early clinical diagnosis of CF is usually difficult unless there is neonatal bowel obstruction due to meconium ileus (approximately 10 - 25% of disease presentation). In the rest of CF patients, the disease can masquerade as persistent lower respiratory tract infections, failure to thrive, or diarrheal states. As a result, diagnosis can be missed or considerably delayed in children with CF when the disease identification is solely based on clinical presentation. In the absence of newborn screening, there is an average 15 month delay between onset of symptoms and CF diagnosis. Newborn screening of CF is typically by measurement of serum immunoreactive trypsinogen and this test has a high false positive rate. Benefits noted in individuals with the diagnosis of CF through newborn screening include the following: early treatment with improved disease outcome; improved growth; absent malnourishment; fewer hospitalizations; preservation of normal pulmonary function; and decreased risk of life-threatening complications or death from CF in infancy or early childhood.

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#### **Common Symptoms:**

##### **a). Chronic Sinopulmonary Disease:**

- o Persistent bronchopulmonary infection: chronic cough and chronic expectoration; airway obstruction with wheezing and air trapping; persistent abnormal radiologic chest images (bronchiectasis, atelectasis, infiltrates, hyperinflation).
- o Chronic sinus infection and abnormalities of the paranasal sinuses, nasal polyps; and
- o Digital clubbing.

##### **b) Gastrointestinal and Nutritional Abnormalities: These include:**

- o Intestinal: Meconium ileus, foul-smelling stools, diarrheal state, distal intestinal obstruction syndrome and rectal prolapse.
- o Pancreatic: Pancreatic insufficiency and recurrent pancreatitis.

- o Hepatic: Chronic hepatic disease with evidence of focal biliary cirrhosis or multilobular cirrhosis.
- o Nutritional: Protein-calorie malnutrition, hypoproteinemia and edema, complications from deficiency of fat soluble vitamins.
- c) **Salt-wasting Syndromes: Acute salt depletion & chronic metabolic alkalosis.**
- d) **Male Urogenital Abnormalities: Congenital bilateral absence of the vas deferens (obstructive azoospermia).**

**Treatment:** An interdisciplinary approach is needed for the management of CF since it is such a complex disorder with pulmonary and extrapulmonary complications. The standard therapeutic regimen for the pulmonary manifestations, depending on the severity of lung disease, and the nutritional issues consists of the following: antibiotic therapy, nutritional support (with pancreatic enzyme and vitamin supplementation for pancreatic insufficiency, extra calories and salt), airway clearance techniques and exercise, use of mucolytic agents, bronchodilators and anti-inflammatory agents, and oxygen supplementation. Ultimately the patient may require non-invasive ventilation and possibly lung transplantation.

**Recommended Action by Primary Care Provider:**

- When contacted by the screening laboratory or the Department regarding an abnormal result, confirm your clear understanding of the recommendations.
- When contacted with a presumptive positive result **immediately** do the following:
  1. Advise the Department or laboratory which CF Treatment Center/Specialist you are recommending from the list provided.
  2. Contact that CF center for a referral and additional information before contacting the family.
  3. Contact family and ascertain clinical status of newborn, and refer family to CF Treatment Center/Specialist for confirmatory testing (including sweat tests) and management.
  4. Family may continue with their current practice of breastfeeding or bottle feeding.
- If infant is symptomatic, refer family immediately for urgent/emergency care.
- If another physician or primary care provider will be seeing this child, notify that provider promptly of the abnormal laboratory results and the needed follow-up steps.

With an inconclusive or presumptive positive screening result, the screening laboratory or the Newborn Screening Follow-up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and assistance and/or subspecialty referral (Appendix 3). At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).



#### **iv. Galactosemia**

Galactose is an important simple sugar in humans and it is an essential source of energy in infants. The major organ of galactose metabolism is the liver. A deficiency in galactose metabolism causes classical galactosemia and it is the most common and the most severe (a potentially lethal disorder if untreated) of the three galactosemias. Classic galactosemia is due to a galactose 1-phosphate uridyl transferase deficiency. It is a serious disease with an early onset of symptoms. With newborns receiving as much as of 20 percent of their calorie intake as glucose and galactose, this enzyme deficiency renders infants unable to metabolize galactose 1-phosphate which then accumulates in the kidney, liver and brain, causing damage. Most affected individuals become very ill in the neonatal period after ingestion of galactose-containing milk and present with hyperbilirubinemia and septicemia. These and the other disease symptoms shown below usually resolve dramatically with early institution of treatment. Classical galactosemia often presents dramatically as a life-threatening crises in the neonatal period. Liver failure and sepsis in patients with untreated classical galactosemia are potentially fatal within days (approximately 5-10 days) of life. Widespread newborn screening for galactosemia has allowed early identification of infants with the disease allowing them to be placed on dietary restriction. Galactosemia screening will detect variant forms of galactosemia, some of which are mild and need no dietary intervention. In an otherwise asymptomatic infant, the primary care provider should discuss the screening results with a metabolic specialist before switching the infant to a lactose-free formula. This disease is inherited in an autosomal recessive pattern.

On long term follow-up, some of these patients present with ovarian failure manifest as primary or secondary amenorrhea, as well as developmental delay and learning disabilities, which increase in severity with age. Some also exhibit speech, motor function and balancing disorders.

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#### **Common Symptoms:**

- Poor feeding
- Hypotonia
- Vomiting
- Diarrhea
- Lethargy
- Bleeding
- Bulging fontanel
- Failure to thrive
- Cataracts
- Liver dysfunction and hepatomegaly
- Jaundice / Unconjugated hyperbilirubinemia
- Progressive liver dysfunction



- Seizures
- Overwhelming bacterial sepsis / neonatal E. coli sepsis
- Progression to death

**Treatment:** dietary restriction/elimination of galactose, which may need to be maintained for life. Complex plant carbohydrates often contain galactose and can be a significant quantity of unrecognized galactose intake.

**Recommended Action by Primary Care Provider:**

- When contacted by the screening laboratory or the Department regarding an abnormal result, confirm your clear understanding of the recommendations.
- If contacted with a presumptive positive result immediately do the following:
  1. Advise the Department or laboratory which Treatment Center/Specialist you are recommending from the list provided.
  2. Contact that treatment center for a referral and additional information before contacting the family.
  3. Contact family and ascertain clinical status of newborn, and refer family to Treatment Center/Specialist for confirmatory testing and management.
  4. Instruct family to contact the specialist regarding feeding instructions; in the interim continue with their current practice of breastfeeding or bottle feeding.
- If infant is symptomatic, refer family immediately for urgent/emergency care.
- If another physician or primary care provider will be seeing this child, notify that provider promptly of the abnormal laboratory results and the needed follow-up steps.
- If initial result is inconclusive, refer family to the birthing facility to obtain a repeat filter paper screen test as soon as possible. If repeat screen is inconclusive, handle as a presumptive positive and contact the Treatment Center/Specialist for a consultation to determine further testing, follow-up and dietary needs.

With an inconclusive or presumptive positive screening result, the screening laboratory or the Newborn Screening Follow-up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and assistance and/or subspecialty referral (Appendix 3).

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).

## **v. Amino Acid Disorders**

The defective metabolism of several amino acids (AAs) such as phenylalanine, tyrosine, leucine, isoleucine and valine result in quite distinctive inherited metabolic diseases. These disorders are characterized by specific metabolites in the blood (aminoacidemias) and in the urine (aminoacidurias). All amino acid disorders are inherited as an autosomal recessive trait.

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**Treatment common for AAs: protein restricted diet, supplementation.**

### **Recommended Action by Primary Care Provider:**

- When contacted by the screening laboratory or the Department regarding an abnormal result, confirm your clear understanding of the recommendations.
- If contacted with a presumptive positive result immediately do the following:
  1. Advise the Department or laboratory which Treatment Center/Specialist you are recommending from the list provided.
  2. Contact that treatment center for a referral and additional information before contacting the family.
  3. Contact family and ascertain clinical status of newborn, and refer family to Treatment Center/Specialist for confirmatory testing and management.
  4. Instruct family to contact the specialist regarding feeding instructions; in the interim continue with their current practice of breastfeeding or bottle feeding.
- If infant is symptomatic, refer family immediately for urgent/emergency care.
- If another physician or primary care provider will be seeing this child, notify that provider promptly of the abnormal laboratory results and needed follow-up steps.
- If initial result is inconclusive, refer family to the birthing facility to obtain a repeat filter paper screen test as soon as possible. If repeat screen is inconclusive, handle as a presumptive positive and contact the Treatment Center/Specialist for a consultation to determine further testing and follow-up needs.

With an inconclusive or presumptive positive screening result, the screening laboratory or the Newborn Screening Follow-up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and assistance and/or subspecialty referral (Appendix 3).

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).





A brief summary of the AA disorders followed by the Pennsylvania Department of Health are below. For specific and/or additional information about any of these conditions, contact the appropriate treatment specialist or screening laboratory (listed in Appendix 3).

#### **v. 1. Maple Syrup Urine Disease**

Maple syrup urine disease (MSUD) is an aminoacidopathy. An enzyme is defective in the catabolic pathway of leucine, isoleucine, and valine. Accumulation of these three branched amino acids and their corresponding ketoacid leads to brain damage. Early diagnosis and dietary intervention prevent further complications and may allow for normal intellectual and neurodevelopment. Multiple grades of MSUD have been recognized, but all children with MSUD are at increased risk for metabolic decompensation during periods of stress, regardless of underlying severity.

Affected infants are usually normal at birth, but within four to five days become lethargic, uninterested in feeding and develop ketosis. This may progress to seizures, changes in muscle tone and coma.

MSUD occurs in about one per 180,000 newborns in the United States but may be as frequent as one per 176 newborns in selected populations. As an autosomal recessive disorder, MSUD is more prevalent in populations with a high degree of consanguinity.

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#### **Common Symptoms:**

- Episodic vomiting
- Lethargy
- Poor feeding
- Failure to thrive
- Ketoacidosis
- Irritability
- Seizures

- Coma
- Odor of maple syrup in urine and cerumen
- Psychomotor retardation
- Hyperactivity
- Progressive CNS deterioration (cerebral edema → brain stem herniation → death)

**Treatment:** Includes a protein restricted diet low in branched-chain amino acids.

## **v. 2. Phenylketonuria**

Phenylketonuria (PKU) is an inborn error of phenylalanine metabolism that results from the autosomal recessive inherited deficiency of phenylalanine hydroxylase. Elevated phenylalanine levels negatively impact developmental function. Individuals with classical PKU are almost always mentally retarded unless levels are controlled through strict dietary treatment. Some patients have only a partial deficiency of phenylalanine hydroxylase and can tolerate higher dietary phenylalanine. Incidence of PKU is approximately one in 10,000 births.

A very small percentage of children with elevated phenylalanine levels exhibit normal phenylalanine hydroxylase but have a deficiency in synthesis or recycling of the enzyme's cofactor, tetrahydrobiopterin. This cofactor is also required for hydroxylation of tyrosine and tryptophan. Thus, patients with tetrahydrobiopterin cofactor deficiency have more significant neurological problems that are not fully corrected by dietary phenylalanine reduction. Late diagnosis and delayed introduction of treatment result in irreversible brain damage. The mechanism by which elevated phenylalanine levels causes mental retardation is not known, though restriction of dietary phenylalanine ameliorates this effect if initiated within a few weeks of birth. This also results in normal cognitive development. A strong relationship exists between control of blood phenylalanine levels in childhood and intelligence quotient (IQ).

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### **Common Symptoms:**

Affected neonates are usually clinically normal at birth.

- Microcephaly
- Neurocognitive impairment
- Neuromotor impairment
- Characteristic urine and body odor
- Hypertonia
- Seizures
- Autistic features
- Eczematous rash

**Treatment:** Includes a phenylalanine restricted diet / special formula, with monitoring for life. When neonates with PKU are placed on this restricted diet soon after birth, their neurological and intellectual development is normal. However, even with early treatment, children may



develop subtle neuropsychological deficits such as difficulties in problem solving, abstract reasoning, executive functioning, negative task orientation and increased hyperkinetic behavior if their Phe levels are not strictly controlled. With diligence and compliance in therapy, these findings do improve with age.

### **v. 3. Homocystinuria**

Homocystinuria is caused by genetic defects in cystathionine- $\beta$ -synthase (CBS) and several severe but rare disorders are caused by defects in folate and cobalimine metabolism. CBS deficiency causes "classical" homocystinuria, the most common disorder of sulfur-containing amino acid metabolism. There are also acquired causes of homocysteine metabolism disorders that result in homocystinuria. These include:

- Folic acid deficiency
- Vitamin B6 deficiency
- Vitamin B12 deficiency (elevated levels of homocysteine & methylmalonic acid)
- Renal failure

Homocystinuria due to CBS deficiency is a multisystem disorder with clinical manifestations in untreated severely affected patients of skeletal and ocular abnormalities, a predisposition to cerebral, coronary and peripheral vascular thromboembolic complications and mental retardation. Expression is extremely variable and includes asymptomatic individuals as well as some who present with apparently isolated thromboembolism in adulthood. Presentation within the same family is often variable. CBS deficiency may respond to supplementation with pyridoxine, the cofactor for CBS. Pyridoxine-responsive CBS deficiency is typically milder and progresses more slowly than the more severe non-responsive. Newborn screening based on the finding of elevated methionine in dried blood spots, detects almost exclusively patients with the severe, pyridoxine non-responsive form of the disease. Neonates are usually asymptomatic and not at risk for acute homocystinuria-induced symptoms, but prompt referral is still recommended. Diagnosis in milder patients typically is made only after the development of complications that are frequently irreversible.

### **v. 4. Tyrosinemia Type I**

Fumarylacetoacetate hydrolase (FAH), expressed mainly in liver hepatocytes and renal tubular epithelium, is the final enzyme in the tyrosine catabolic pathway. Deficiency of FAH causes hereditary tyrosinemia type I (hepatorenal tyrosinemia or HT1), the most severe disorder of the tyrosine metabolism. Early onset FAH deficiency presents in the first few months of life with progressive liver failure including coagulopathy, painful neurologic crises, rickets and hepatocellular carcinoma. If untreated, most patients rapidly deteriorate with death from hepatic failure before age two years. A more chronic course presenting later in childhood with survival to age 12 years is seen less frequently. Symptoms can vary within the same family. The risk of developing hepatocellular carcinoma early in life is as high as 37%. Many of the clinical problems related to FAH deficiency are related to the accumulation of an alternative metabolite, succinylacetone, which is diagnostic of the disorder. Most patients with tyrosinemia type I do not have elevated tyrosine levels in newborn blood spots. Thus, a normal newborn screen does not exclude tyrosinemia type I. In fact, significant elevation of tyrosine in the newborn bloodspot is most commonly due to causes other than FAH deficiency, especially transient tyrosinemia of the newborn.

## Urea Cycle Disorders

The urea cycle is a metabolic pathway through which waste nitrogen is converted to urea for renal excretion. Most individuals with a defective urea cycle present either in the neonatal period with significant hyperammonemia after initial protein intake, or later in life with episodic hyperammonemia often associated with intercurrent illness. Infants are normal at birth and present in first few days of life with non-specific signs and symptoms often mistaken as sepsis. Progression to coma can occur within hours of the onset of symptoms. Milder variants of urea cycle disorders may present at any age with hyperammonemia, respiratory alkalosis, and progressive encephalopathy resulting from cerebral edema, brain stem compression. The finding of tachypnea with respiratory alkalosis in a neonate is a key clinical sign of hyperammonemia and should trigger an immediate measurement of blood ammonia. Morbidity and mortality in individuals with a urea cycle disorder are directly correlated with the duration and severity of hyperammonemic episodes. The triad of hyperammonemia, encephalopathy and respiratory alkalosis is characteristic of all urea cycle disorders, except argininemia, which more frequently presents with late onset neurologic symptoms such as spasticity and seizures. Newborn screening does not reliably identify all disorders of the urea cycle but may show elevations in arginine or either an increased or decreased citrulline concentration depending on the disorder.

### v. 5. Citrullinemia

Citrullinemia type I (CTLN I) is caused by a generalized deficiency of the urea cycle enzyme argininosuccinate synthetase (ASS). ASS catalyzes the formation of argininosuccinate by the ligation of citrulline and aspartate. CTLN1 is a heterogeneous disorder with a neonatal onset form and an infantile onset form. The neonatal form classically presents in an initially well appearing newborn who, between age 24 and 72 hours, becomes increasingly lethargic, decreased feeding, vomiting, and hypothermic. Severe hyperammonemia develops with life threatening encephalopathy. Hepatomegaly may be present. Patients who survive a severe newborn hyperammonemic episode are often left with significant neurologic sequelae including seizures and mental retardation. The infantile/late onset form usually presents after age 5 months with a mild clinical course that includes hair and skin abnormalities, abnormal liver function and mental deficiency. In patients with residual ASS enzyme activity, the onset of symptoms may be gradual. ASS enzyme activity is deficient in all tissues.

#### Citrullinemia Type II – Neonatal Intrahepatic Cholestasis due to Citrin Deficiency

Citrin is a mitochondrial aspartate-glutamate carrier protein primarily expressed in the liver, heart and kidney. Citrin deficiency is a recently recognized metabolic disorder that has two major age-dependent clinical phenotypes: adult onset type II citrullinemia (CTLN2) and neonatal intrahepatic cholestasis (NICCD) in infants. NICCD patients have a varied and transient clinical presentation that includes prolonged jaundice, idiopathic neonatal cholestasis and steatohepatitis. Symptoms in most patients resolve spontaneously by about 12 months of age without any special treatment. Patients with unresolved symptoms can progress to liver failure and require liver transplantation before age one year or progress to CTLN2 during adolescence and up to several decades later. It is presently unclear what determines the disease course and prognosis of the NICCD disorder. Some NICCD patients are asymptomatic. The MS/MS newborn screening profile of half of the children with NICCD



shows elevated galactose, methionine, phenylalanine and transient elevation of citrulline. Patients not detected during newborn screening present at approximately age 4 months with failure to thrive or hepatitis, biliary artresia and jaundice. NICCD is not always a benign condition, but when it is symptomatic it is not as severe as late-onset CTLN2. When an affected infant is switched from breast milk to formula feeding, there may be normalization of liver function and amino acid levels. Reintroduction of human breast milk after normalization of liver function and amino acid profile does not result in an immediate relapse of symptoms.

#### **v. 6. Argininosuccinic Acidemia**

Argininosuccinate lyase (ASL) has several roles in intermediary metabolism, one of which is the catalysis of the fourth step of the urea cycle. ASL also links the urea cycle to the tricarboxylic acid cycle by generating fumarate and is required for the endogenous synthesis of arginine. The enzyme is located in the cytosol of hepatocytes, renal cells and fibroblasts. ASL deficiency (argininosuccinic aciduria; ASA) is characterized by episodic hyperammonemia and the accumulation of argininosuccinic acid in body fluids, but the clinical picture is heterogeneous. Severe neonatal onset ASA is the most common phenotype. Newborns appear well for the first 24 to 72 hours of life, then develop progressive lethargy, hypothermia and apnea due to hyperammonemia. The disorder may progress to coma and death. Trichorrhexis nodosa (a hair abnormality) and brittle hair loss are seen mainly in these severe cases. The late onset or subacute form can manifest in infancy or childhood.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).





## vi. Organic Acid Disorders

Deficiencies of several enzymes that participate in amino acid metabolism result in organic acidemias. Many of these are inherited disorders of the metabolism of the branched chain amino acids valine, leucine and isoleucine. A defect in any of the enzymes that participate in the above pathways causes accumulation of organic acids proximal to the step catalyzed by the abnormal enzyme. These organic acidemias (OAs) include isovaleric acidemia (IVA), methylmalonic acidemia (MMA), 3-methylglutaconic aciduria, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, propionic acidemia (PA) and  $\beta$ -ketothiolase deficiency. These organic acidemias can be characterized by severe life-threatening episodes of metabolic acidosis, ketosis and hypoglycemia or progressive neurological involvement during the first few days of life. Management of many of these disorders remains difficult. The acute presentation of these disorders, both at the initial onset of symptoms and during subsequent episodes of metabolic decompensation, requires emergency management usually in intensive care units. This management may include exogenous protein restriction, inhibition of endogenous catabolism by adequate parenteral energy supply, medical therapy and maybe, removal of toxic metabolites by dialysis. Long-term therapeutic management protocol include low protein high energy diets with restriction of the non-metabolizable amino acid(s), removal of the corresponding enzyme substrate by conjugation or inhibition of endogenous synthesis of this substrate, use of co-factors (vitamins) at pharmacological doses, and L-carnitine supplementation. This treatment regimen has resulted in significant improvement in the prognosis of most of these disorders. Some individuals with these deficiencies remain asymptomatic. Each of the organic acidemias are inherited as autosomal recessive traits.

**The information contained in this manual is not intended to be a substitute for professional medical advice and should not be used for the diagnosis or treatment of any condition. A treatment specialist should be consulted for confirmatory testing, diagnosis and treatment of any condition.**

**Treatment for OAs:** protein restricted diet, formula, supplementation and medication, avoidance of fasting.

### **Recommended Action by Primary Care Provider:**

- When contacted by the screening laboratory or the Department regarding an abnormal result, confirm your clear understanding of the recommendations.
- If contacted with a presumptive positive result **immediately** do the following:
  1. Advise the Department or laboratory which Treatment Center/Specialist you are recommending from the list provided.
  2. Contact that treatment center for a referral and additional information before contacting the family.
  3. Contact family and ascertain clinical status of newborn, and refer family to Treatment Center/Specialist for confirmatory testing and management.
  4. Instruct family to contact the specialist regarding feeding instructions; in the interim continue with their current practice of breastfeeding or bottle feeding.

- If infant is symptomatic, refer family **immediately** for urgent/emergency care.
- If another physician or primary care provider will be seeing this child, notify that provider promptly of the abnormal laboratory results and the needed follow-up steps.
- If initial result is inconclusive, refer family to the birthing facility to obtain a repeat filter paper screen test as soon as possible. If repeat screen is inconclusive, handle as a presumptive positive and contact the Treatment Center/Specialist for a consultation to determine further testing, follow-up and dietary needs.

With a presumptive positive screen, the screening laboratory or the Newborn Screening and Follow-Up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and assistance and/or subspecialty referral (Appendix 3).

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).

**A brief summary of the OA disorders followed by the Pennsylvania Department of Health are below. For specific and/or additional information about any of these conditions, contact the appropriate treatment specialist or screening laboratory (listed in Appendix 3).**

#### **vi. 1. Isovaleric Acidemia**

Isovaleric acidemia (IVA) is a rare inborn error of leucine metabolism caused by a deficiency of isovaleryl-CoA dehydrogenase (IVD). Isovaleryl-CoA dehydrogenase deficiency results in the accumulation of isovaleric acid and its metabolites in body fluids. There are three forms of this disorder that in reality form a continuum of symptoms including an acute neonatal phenotype, a chronic phenotype, and an intermittent phenotype. Asymptomatic individuals have been identified through newborn screening and family studies. All patients are prone to episodes of chronic intermittent metabolic acidosis during intercurrent illness or at times of physiological stress. The acute neonatal form presents in the first two weeks of life and is characterized by vomiting and lethargy with overwhelming neonatal ketotic acidosis. If untreated, this may progress to coma and death often due to cerebral edema or hemorrhage. The chronic form has a less severe clinical presentation characterized by non-specific failure to thrive and/or developmental delay. Infants who survive the severe neonatal crisis are subsequently indistinguishable from patients with the more chronic later-onset form of the disease. With the advent of MS/MS newborn screening, the majority of IVA patients are diagnosed presymptomatically and many remain asymptomatic. Isovaleric acidemia is inherited as an autosomal recessive trait.

#### **vi. 2. Glutaric Acidemia Type I**

Glutaric acidemia type 1 (GA 1) is an inborn error of metabolism caused by a deficiency of the mitochondrial enzyme glutaryl-CoA dehydrogenase. GA 1 has a wide spectrum of

clinical presentation that ranges from acute onset in infancy to asymptomatic adults. Clinical manifestations of GA 1 can vary considerably even between siblings. Diagnosis of GA 1 can be difficult. Affected children are usually well in the first few months of life with only mild neurological symptoms. Macrocephaly, which is most pronounced during infancy, is found in 75-80% of patients. Clinical symptoms of GA 1 typically occur in an approximately 6 to 18 month old in whom an induced catabolic state (fever, a mild illness, routine immunizations, minor head injuries or pre-surgical fasting) precipitates an acute encephalopathic crisis with metabolic acidosis. Morbidity and mortality are high in patients that have had a crisis. If GA 1 is not diagnosed or treated in time, most patients will develop neurological disease in the period of brain development (age 3 -36 months) with resulting neurological problems (striatal damage, dystonia), secondary complications (feeding problems, recurrent aspirations, joint subluxations) and reduced life expectancy. Neurologic disease has been demonstrated in a few patients in the absence of any documented encephalopathic crises. Many patients now identified through expanded newborn screening by MS/MS and treated presymptotically with low lysine diet and rapid medical response to routine childhood illnesses, are doing well clinically. GA 1 is inherited as an autosomal recessive trait. GA 1 is particularly common in three genetic isolates including the Amish of Lancaster County, PA. A screening finding of low plasma carnitine could be due to a previously unidentified maternal GA 1 disorder.

Undiagnosed GA 1 should be suspected in a child presenting with a combination of nonspecific symptoms and the following:

- Subdural hematoma with no additional evidence of child abuse
- Subdural collections of different ages
- Retinal hemorrhages

Also, GA 1 should be included in the differential diagnosis of child abuse and in a child being evaluated for dystonia.

### **vi. 3. 3-Hydroxy-3-Methylglutaric Aciduria**

3-Hydroxy-3-methylglutaric aciduria is a rare inherited disorder of leucine catabolism and ketogenesis. It is caused by a deficiency of the mitochondrial enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase, which participates in the hepatic synthesis of ketone bodies. Ketone bodies are very important metabolically as they are a major alternate energy source for the brain, heart and kidney during fasting. HMG-CoA lyase deficiency is a clinically heterogeneous disorder. Approximately 30% of the patients have clinical manifestations in the neonatal period while 60% of the patients present by age one year. The clinical presentation of the neonatal form of HMG-CoA lyase deficiency includes hepatic encephalopathy with life-threatening illness that rapidly progresses to coma and death. It is fatal in approximately 20% of cases. Less frequently, HMG-CoA lyase deficient patients present with fatal cardiomyopathy (with arrhythmia) or sudden infant death syndrome. Fasting conditions usually precipitate the initial disease symptoms of metabolic acidosis and hypoketotic hypoglycemia. Untreated, the clinical manifestations may progress to coma and death or result in permanent neurologic damage with associated mental retardation, epilepsy and cerebral white matter changes.

#### **vi. 4. Multiple Carboxylase Deficiency**

Holocarboxylase synthetase (HCS), in the presence of biotin, is responsible for covalent linkage of biotin (biotinylation) to four different carboxylases. Holocarboxylase synthetase deficiency leads to decreased activity of all the four human enzymes and thus the resulting disorder is called multiple carboxylase deficiency (MCD). Clinical manifestations of holocarboxylase deficiency usually occur within the first few days of life (neonatal form) or within a few months of life (infantile/juvenile form). The most common presentation is that of an infant with breathing problems who also presents with vomiting, acidosis, dehydration, seizures, progressive loss of consciousness, coma and death. Severe erythematous eczema, when present, develops within the first few weeks of life. The eczema, a classic sign in this disorder, is an erythroderma-like dermatitis involving the eyebrows, eyelashes and scalp. It may also involve the perioral, perianal and flexural surfaces. Untreated, MCD is uniformly fatal. Early diagnosis and treatment results in the disappearance of most of the manifestations of the disorder although some children continue to have skin rashes and excrete abnormal organic acids. Some individuals can remain asymptomatic. A diagnosis of holocarboxylase synthetase deficiency needs to be excluded in a newborn with collodion membrane and severe metabolic acidosis.

#### **vi. 5. Methylmalonic Acidemia (Mutase Deficiency and Cbl A,B)**

Methylmalonic acidemia (MMA) is the most frequently observed organic aciduria. MMA is composed of a heterogeneous group of metabolic disorders that are biochemically characterized by the accumulation of methylmalonate in urine and other body fluids. Methylmalonic acidemia is most commonly caused by a primary defect (partial or complete) of methylmalonyl-CoA mutase, which requires a form of vitamin B12 as cofactor to be active. Eighty percent of patients with a complete deficiency of the mutase enzyme present in the first week of life and by the first month of life, 90% of these patients have disease manifestations. Infants with complete mutase deficiency most often present with life-threatening metabolic decompensation precipitated by stressors such as intercurrent illness. Most children survive the first acute metabolic crises MMA but long term complications are common. Children with late onset disease may still present with an overwhelming illness and therefore are likely to do better with early diagnosis. Defects in the metabolism of vitamin B12 can also lead to MMA (the cbl defects). Cbl A and B deficiency cause isolated MMA while other cbl defects can also lead to elevated homocystine. Cbl C and D also give MMA, but homocystine may or may not be elevated. Maternal B12 deficiency leads to a vitamin B12 deficiency in the neonate and this is a common cause of positive newborn screening test. The various forms of MMA are all inherited as autosomal recessive traits. Newborn screening may miss milder forms of MMA, but these variants are of unknown clinical significance. MS/MS does not discriminate between methylmalonic acid and propionic acid and thus newborn screening report indicates elevation of "C3-carnitine".

#### **vi. 6. 3-Methylcrotonyl-CoA Carboxylase Deficiency**

3-Methylcrotonyl-CoA carboxylase (3-MCC), one of the four human biotin-dependent carboxylases, is a mitochondrial enzyme that catalyzes the carboxylation of 3-methylcrotonyl-CoA to 3-methylglutaconyl-CoA. Isolated 3-methylcrotonyl-CoA carboxylase deficiency is a biotin-insensitive deficiency of 3-MCC that was initially detected in patients with

developmental delay or in patients that presented with a metabolic profile of ketoacidosis, hypoglycemia or Reye-like syndrome. It is presently one of the most frequent organic acidurias detected by MS/MS expanded newborn screening programs in North America, Europe and Australia. The clinical presentation of 3-MCC deficiency is extremely variable with the disease spectrum ranging from individuals who present with profound metabolic acidosis, seizures, cerebral ischemic event, coma and death in infancy to asymptomatic children and adults. Symptoms most often appear between the ages of 6 months and 3 years and patients usually present with an acute metabolic decompensation and sudden death, although an initial severe catabolic episode has been documented both in the neonatal period and in the second decade of life. Cardiomyopathy and leukodystrophy have been reported. Previously asymptomatic children can present in later years with profound ketoacidosis and hypoglycemia during acute catabolic stress such as fever, infections, fasting, or introduction of a protein rich diet. Asymptomatic patients and patients with severe disease have been described in the same family. Most affected infants detected by newborn screening appear clinically normal and remain healthy. In addition, a number of clinically healthy affected mothers have been ascertained through their infant's newborn screening profile. The disease state can be due to a complete enzyme deficiency ( $< 2\%$  of control) or a partial deficiency of the enzyme. It is unclear what determines the phenotypic severity of this metabolic disorder and clinicians are presently unable to predict which affected infants are at risk for serious sequelae. Consequently, 3-MCC deficiency should be considered a potentially severe disease with asymptomatic infants detected by newborn screening at risk for later onset disease.

## **vi. 7. Propionic Acidemia**

Propionic acidemia (PA) is a rare inborn error of the metabolism of branched chain amino acids, odd-chain fatty acids and cholesterol. It is caused by a deficiency of propionyl-CoA carboxylase (PCC), the enzyme that normally catalyzes the carboxylation of propionyl-CoA to methylmalonyl-CoA. The clinical manifestation of PA is variable and ranges from clinically normal PCC-deficient patients to patients with intermittent symptoms of vomiting, failure to thrive, ataxia, behavior problems, neurodevelopmental delay to very severely affected patients with life-threatening encephalopathy. Most patients with PA are well at birth but present in the neonatal period with 50% of affected infants showing symptoms by age 6 days. Affected individuals may have clinically symptom-free periods between episodes of relapse triggered by stressors such as infections, fever, starvation and high-protein intake. Viral infection in patients can lead to bone marrow suppression with neutropenia and thrombocytopenia. Mortality is high in the neonatal onset patients. In the short term, neurodevelopmental outcome is more favorable in patients detected by newborn screening and there is also decreased morbidity and early mortality. Long-term survival is associated with late disease manifestations of progressive immune suppression, recurrent infections and neurologic sequelae. Cardiomyopathy and pancreatitis may develop. Late onset disease may still present with an acute overwhelming illness and therefore children with this form of this disorder are likely to do better with early diagnosis. Propionic acidemia is also a component of multiple carboxylase deficiency and biotinidase deficiency as PCC requires biotin as a co-factor. PA is inherited as an autosomal recessive trait. False positives are a potential problem as minor elevations of propionylcarnitine are common especially in



sick or very low birth weight and jaundiced infants. MS/MS does not discriminate between methylmalonic acid and propionic acid and thus newborn screening report indicates elevation of "C3-carnitine".

#### **vi. 8. Beta-Ketothiolase Deficiency**

Mitochondrial acetoacetyl-CoA thiolase (T2) is the last enzyme in the isoleucine catabolism pathway. It catalyzes the reversible conversion of 2-methylacetoacetyl-CoA into propionyl-CoA and acetyl-CoA. The enzyme deficiency is commonly known as  $\beta$ -ketothiolase ( $\beta$ -KT) deficiency. The initial clinical presentation of T2 deficiency is that of acute ketoacidosis in a previously healthy child. The age of onset of the first metabolic episode is between 6 and 24 months. The acute episode is usually triggered by a febrile illness or gastroenteritis or by an increased protein intake. Episodic cyclic vomiting and dehydration are common. Onset in the neonatal period, though extremely rare, has been described. There are also some late childhood onset cases. T2 deficiency has a favorable outcome. Without treatment the disorder is characterized by intermittent ketoacidotic crises with no clinical symptoms between episodes. Most patients recover fully with normal growth and development but some patients have died or had long-term neurological sequelae especially with prolonged or recurrent acute crises. Occasionally, an asymptomatic affected sibling and parent have been identified in the same family as a manifesting patient.

#### **vi. 9. Biotinidase Deficiency**

Biotin, a member of the water-soluble vitamin B family, is an essential coenzyme for four human carboxylases. The biotin-dependent carboxylases play an important role in fatty acid synthesis, branched chain amino acid catabolism, and gluconeogenesis. The concentration of biotin in blood is dependent on dietary biotin intake and the recycling of endogenous biotin. Biotinidase cleaves biotin from the biocytin and biotinylpeptides derived from degradation of these carboxylases, thus recycling the biotin. Biotinidase deficiency results in loss of biotin due to excretion of biocytin in urine and leads to deficiency of all of the biotin-dependent carboxylases. Biochemical and clinical findings generally mirror those seen in holocarboxylase synthase deficiency. The clinical expression of biotinidase deficiency is highly variable. Affected children usually present during the first year of life with seizures, ataxia, hypotonia, stridor, sensorineural hearing loss and visual loss. Life threatening organic acidemia may be present. Without treatment patients are likely to show progressive encephalopathy. Later onset patients have been described with abnormalities of the skin and hair or milder neurologic signs. Biotinidase deficiency is classified as either profound or partial based on the residual amount of enzyme activity, less than 10% or 10 – 30% of mean normal enzyme activity in the serum respectively. In infants with profound biotinidase deficiency, the mean age of onset of symptoms is between 3 - 5 months (range = one week to two years). Biotinidase deficiency is inherited as an autosomal recessive trait. False positive screening results are rare but screening often cannot distinguish profound from partial defects.





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**Common Symptoms:**

- Overwhelming illness
- Tachypnea/apnea
- Feeding difficulties
- Diarrhea
- Episodic vomiting
- Seizures
- Hypotonia
- Lethargy
- Conjunctivitis
- Hepatosplenomegaly
- Skin rash
- Partial or complete alopecia
- Seborrheic and atopic dermatitis
- Developmental delay
- Conjunctivitis
- Visual problems such as optic atrophy
- Sensorineural hearing loss

**Treatment:** biotin supplementation/therapy

With a presumptive positive screen, the screening laboratory or the Newborn Screening and Follow-Up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and assistance and/or subspecialty referral (Appendix 3). At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).

## vii. Fatty Acid Oxidation Disorders

Mitochondrial fatty acid  $\beta$ -oxidation is the main energy-producing pathway in skeletal and cardiac muscles, especially during fasting conditions. Muscle directly uses fatty acids as energy source while hepatic metabolism of fatty acids results in the synthesis of ketone bodies that can subsequently be used for energy by the brain. Fatty acids (usually  $< C_{20}$ ) are also the preferred fuel of the heart. Energy production from stored long-chain fatty acids is a complicated process requiring the coordinated action of over two dozen enzymes and transporters. Transport of fatty acids into mitochondrial matrix is accomplished via carnitine cycle and thus is carnitine-dependent. Once in mitochondria, fatty acyl-CoAs undergo a cyclic series of 4 enzymatic steps that results in the cleavage of one acetyl-CoA molecule and generates a fatty acyl-CoA with a carbon backbone that is two carbons shorter. Each step in this cycle is performed by enzymes optimized for substrates with a narrow range of primary backbone carbons. These include:

- Short chain acyl-CoA dehydrogenase (SCAD) acts on substrates  $C_4 - C_6$
- Medium chain acyl-CoA dehydrogenase (MCAD) acts on substrates  $C_6 - C_{12}$
- Very long chain acyl-CoA dehydrogenase (VCLAD) acts on substrates  $C_{14} - C_{20}$
- Long chain hydroxyacyl-CoA dehydrogenase (LCHAD) acts on substrates  $C_{10} - C_{18}$

Although SCAD can be detected by the MS/MS screening, unlike the other 3 conditions listed above, it is not one of the conditions the Department's Newborn Screening Follow-Up Program is following and therefore it is not further described below.

MCAD deficiency is by far the most common of the Fatty Acid Oxidation Disorders (FAODs) in the United States with a frequency similar to PKU. Mitochondrial fatty acid  $\beta$ -oxidation disorders are heterogeneous diseases both clinically and biochemically. The overall incidence of fatty acid  $\beta$ -oxidation defects is unknown. Affected individuals can present with a wide range of clinical symptoms though they can also be well. The most common symptoms in the newborn period include hypoglycemia, hyperammonemia, myopathy, cardiomyopathy, and liver dysfunction, all of which can be life threatening. Affected individuals may also be asymptomatic until undergoing a significant metabolic stress including fasting, illness, and injury. Again in this situation, life-threatening clinical problems similar to those seen in the newborn period may develop. These disorders are often the cause of infant deaths after a minor illness associated with fasting and they may account for some unexplained sudden infant deaths. MS/MS can identify many of the FAODs in the newborn bloodspot prior to the development of symptoms, but the characteristic acylcarnitine species may decrease over the first few days of life. Thus, abnormal screens suggestive of an FAOD should always be investigated carefully rather than just asking for a repeat sample. Fatty acid oxidation disorders are all inherited as autosomal recessive traits. Mothers carrying a fetus with an FAOD may develop the characteristic but non-specific complication of acute fatty liver of pregnancy and maternal hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome.

**The information contained in this manual is not intended to be a substitute for professional medical advice and should not be used for the diagnosis or treatment of any condition. A treatment specialist should be consulted for confirmatory testing, diagnosis and treatment of any condition.**

**Treatment common for FAODs: avoidance of fasting, special diet and supplementation.**

**Recommended Action by Primary Care Provider:**

- When contacted by the screening laboratory or the Department regarding an abnormal result, confirm your clear understanding of the recommendations.
- If contacted with a presumptive positive result immediately do the following:
  1. Advise the Department or laboratory which Treatment Center/Specialist you are recommending from the list provided.
  2. Contact that treatment center for a referral and additional information before contacting the family.
  3. Contact family and ascertain clinical status of newborn, and refer family to Treatment Center/Specialist for confirmatory testing and management.
  4. Instruct family to contact the specialist regarding feeding instructions; in the interim continue with their current practice of breastfeeding or bottle feeding.
- If infant is symptomatic, refer family immediately for urgent/emergency care.
- If another physician or primary care provider will be seeing this child, notify that provider promptly of the abnormal laboratory results and the needed follow-up steps.
- If initial result is inconclusive, refer family to the birthing facility to obtain a repeat filter paper screen test as soon as possible. If repeat screen is inconclusive, handle as a presumptive positive and contact the Treatment Center/Specialist for a consultation to determine further testing, follow-up and dietary needs.

With a presumptive positive screen, the screening laboratory or the Newborn Screening and Follow-Up Program will contact the primary care provider listed on the filter paper specimen card to provide further direction and assistance and/or subspecialty referral (Appendix 3).

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).

**A brief summary of the FAODs followed by the Pennsylvania Department of Health are below. For specific and/or additional information about any of these conditions, contact the appropriate treatment specialist or screening laboratory (listed in Appendix 3).**

### **vii. 1. Medium Chain Acyl-CoA Dehydrogenase Deficiency**

Medium chain acyl-CoA dehydrogenase (MCAD) catalyzes the first step in the  $\beta$ -oxidation of medium chain fatty acids with chain lengths of 6 to 12 carbon atoms. MCAD deficiency is the most frequent disorder of mitochondrial fatty acid  $\beta$ -oxidation and has a wide clinical spectrum. Most patients present in between 6-24 months of age and prior to the institution of newborn screening, there was high mortality (16% to 26%). Usually symptoms are precipitated by periods of catabolic stress such as febrile illness and by fasting. The acute symptoms are caused by hypoglycemia and include drowsiness, lethargy, coma and sudden death. Hyperammonemia may also be present. Additionally, there is considerable morbidity after an acute decompensation in undiagnosed patients. However, some patients develop symptoms within 48 hours of life, sometimes with a fatal outcome, and MCAD presentation in previously well adults has also been described. The clinical severity of MCAD deficiency varies more than anticipated from data derived from clinically ascertained populations. Most MCAD deficient patients appear healthy between acute episodes and some remain asymptomatic for decades and possibly throughout life. Expanded newborn screening detects 2 to 3 fold more cases of MCAD deficiency than clinical ascertainment. Early establishment of diagnosis and treatment of MCAD deficiency significantly improves the disease outcome.

### **vii. 2. Very Long Chain Acyl-CoA Dehydrogenase Deficiency**

Very long-chain acyl-CoA dehydrogenase (VLCAD) catalyzes the first step of mitochondrial long chain fatty acid  $\beta$ -oxidation spiral. As with most FOADs, VLCAD deficiency is heterogeneous with a disease spectrum ranging from a severe lethal infantile form to a mild form onset with onset in childhood or adolescence. The most severe form presents in the neonatal period with catastrophic metabolic acidosis, hypoketotic hypoglycemia, hypertrophic cardiomyopathy, life-threatening arrhythmias and Reye-like syndrome. Disease episodes are frequent and triggered by fasting or metabolic stress such as minor infections. Patients with this phenotype have no residual enzyme activity. Disease may also present in late infancy or early childhood with fasting or stress induced hypoketotic hypoglycemia, lethargy potentially leading to coma. Cardiomyopathy is uncommon and acute episodes may be less frequent than in the severe form. Late-onset disease presenting after adolescence typically includes myopathy, exercise-induced rhabdomyolysis and myoglobinuria. The milder presentation of the latter two forms is partially explained by the presence of some residual enzyme activity. Metabolic decompensation of VLCAD deficiency is associated with significant morbidity making early diagnosis crucial. Moreover, all patients with VLCAD deficiency have a normal outlook for development and intelligence if major sequelae of acute episodes are prevented. The majority of children identified by newborn screening have been asymptomatic at the time of diagnosis and most remain asymptomatic while on preventive measures such as fasting avoidance and high carbohydrate low fat diet supplemented with medium chain triglyceride oil.

### **vii. 3. Long Chain L-3-Hydroxy Acyl-CoA Dehydrogenase Deficiency**

Long-chain L-3-hydroxyacyl-CoA dehydrogenase (LCHAD) enzyme is one of the three enzymes that constitute membrane-bound mitochondrial trifunctional protein (MTP) complex. LCHAD has a chain-length substrate specificity of C10-C18. The majority of mitochondrial

trifunctional protein (MTP) deficient cases detected during metabolic crises have been due to isolated LCHAD deficiency. Isolated LCHAD deficiency results in a fatty acid  $\beta$ -oxidation disorder with considerable clinical heterogeneity. Children with isolated LCHAD deficiency have a higher incidence of prematurity, intrauterine growth retardation and intrauterine death. The onset of symptoms generally ranges from birth to three years of age but late onset symptoms in adolescence are possible. The disease phenotype ranges from a moderately severe form with multi-organ involvement and high morbidity and mortality, to long-term surviving patients who were identified and treated from an early age. The disorder can also present as a sudden unexplained infant death or as an infant with clinical findings of hepatic encephalopathy and cardiomyopathy. Individuals with a less severe form of LCHAD deficiency may present with hypotonia, vomiting, fasting nonketotic hypoglycemia, hypotonia, and hepatomegaly and seizures. LCHAD deficient patients can develop retinal atrophy, pigmentary retinopathy and recurrent muscle cramps. Peripheral neuropathy is less common than in MTP deficiency. Psychomotor development is normal but skills can be transiently lost during disease exacerbation. Mothers carrying a fetus with LCHAD deficiency have a higher incidence of developing acute fatty liver of pregnancy (AFLP), hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and pre-eclampsia during pregnancy. AFLP (prevalence of 1:7000 to 1:13,000 births) is a third trimester disorder associated with significant neonatal and maternal morbidity and mortality, while HELLP (1:1000 pregnancies), which is also a third trimester illness, has a better prognosis than AFLP. The clinical features of isolated LCHAD deficiency and complete MTP deficiency overlap though isolated LCHAD deficiency is typically milder.

#### **vii. 4. Trifunctional Protein Deficiency**

Mitochondrial trifunctional protein (MTP or TFD) is a membrane-bound multi-enzyme complex located in the mitochondrial matrix. The complex is associated with the inner mitochondrial membrane and catalyzes the last three reactions of the fatty acid  $\beta$ -oxidation spiral with specificity for the longer chain substrates. All three enzymatic activities may be deficient in patients, but most have an isolated deficiency of the LCHAD component. As with LCHAD deficiency, combined MTP leads to a wide clinical disease spectrum with symptoms ranging from severe neonatal/infantile cardiomyopathy and early death, to moderate/severe infantile presentation with hepatic manifestations, and a mild late onset disease form that presents with chronic progressive peripheral neuropathy and episodic rhabdomyolysis. Neonates may present with hypoglycemia, hyperammonemia, cardiomyopathy, Reye-like symptoms, rapid clinical decline and early death. A milder hepatic phenotype with recurrent hypoketotic hypoglycemia may also be seen both in infancy and later. Finally, a milder late onset presentation can be seen that includes episodic rhabdomyolysis with myoglobinuria and elevated creatine kinase. Neonatal/infantile deficiency typically includes fasting nonketotic hypoglycemia, hepatic encephalopathy and can also exhibit hypotonia, areflexia, rhabdomyolysis and cardiomyopathy resulting in sudden death. Most MTP deficient patients develop neuropathy and retinopathy. Prognosis for these patients is poor with most patients dying suddenly in early infancy without newborn screening, but outcome is still poor in patients identified by newborn screening. Mothers carrying an MTP deficient fetus also have a higher incidence of hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and acute fatty liver of pregnancy (AFLP). MTP is composed of multiple subunits encoded by genes, both of which are inherited autosomal. A normal profile from a repeat specimen does



not rule out isolated LCHAD deficiency or MTP deficiency. These infants should be referred immediately to a metabolic treatment center; do not wait to obtain a repeat specimen or urine for organic analysis.

#### **vii. 5. Carnitine Uptake (Transporter) Defect**

Carnitine plays an essential role in the transfer of long chain fatty acids from the cytosol into the inside of mitochondria for  $\beta$ -oxidation and in the removal of potentially toxic acyl-CoA metabolites, in the form of acyl-carnitines, from the inner aspect of the mitochondria. Seventy five percent of the daily human body carnitine is derived from diet and 25% is from de novo synthesis. Disorders of the carnitine cycle result in defective fatty acid oxidation and the impaired use of fat as a fuel during fasting and stress. Patients with this inability early in life can have the following manifestations:

- Acute metabolic decompensation
- Hepatic encephalopathy
- "Reye-like" syndrome
- Sudden infant death

There are two carnitine transporters. The first carnitine transporter is a low affinity, high capacity transporter located in the hepatocytes. No genetic defects in this transporter have been described. The second is the high affinity organic cation/carnitine transporter (OCTN2) expressed in the heart, muscle, kidney, lymphoblasts and fibroblasts. This transporter is very important in renal salvage of carnitine and consequently, in the maintenance of total body stores of carnitine. A defective high-affinity carnitine transporter causes primary systemic carnitine deficiency (SCD), also known as carnitine uptake deficiency (CUD). The primary defect in OCTN2 deficiency results in low serum carnitine levels, decreased intracellular carnitine accumulation and a severe reduction in active reabsorption of carnitine in the kidney with urinary excretion of carnitine. SCD is extremely variable and its presentation can be predominantly metabolic or predominantly cardiac. An early childhood-onset cardiomyopathic form presents before age 2 years and it is usually triggered by intercurrent illness. It is characterized by cardiac and skeletal myopathy, hypoketotic hypoglycemia, hyperammonemia and encephalopathy. If not promptly treated with intravenous glucose and carnitine, symptoms can rapidly progress to coma and death. The cardiomyopathy rapidly improves with carnitine therapy and it can actually be reversed with carnitine supplementation. Later onset symptoms are usually milder but still require therapy as there is continued risk for sudden death. An expanded newborn screening finding of low carnitine can be due to a primary carnitine deficiency in an asymptomatic mother. OCTN2 deficiency is probably the second most frequent fatty acid oxidation disorder after MCAD deficiency.





# Appendix 2:

## Blood Spot Filter Paper Specimen Card

## Blood Spot Filter Paper Specimen Card ( front side)

**TOP COPY FOR LAB: SUBMITTER MAY KEEP SECOND COPY**

**Pennsylvania Department of Health**  
Newborn Screening Specimen  
Phone: (717) 783-8143 TTY: (717) 783-6514

**PA085811212**

**DO NOT WRITE IN THIS SPACE**

**SUBMITTER KEEP THIS COPY**

**PENNSYLVANIA DEPT. OF HEALTH**  
10534503 Rev.1  
2011-02

Initial Specimen ☐ Repeat Specimen ☐ Initial Filter Paper # \_\_\_\_\_

Birth Facility Name ("HOME" if home) \_\_\_\_\_ CODE \_\_\_\_\_

Submitter Name \_\_\_\_\_ CODE \_\_\_\_\_

Address if no CODE given \_\_\_\_\_

**BABY'S Name (Last)** \_\_\_\_\_ **(First)** \_\_\_\_\_

**MOTHER'S Name (Last)** \_\_\_\_\_ **(First)** \_\_\_\_\_

Street (PO Box) \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

Phone \_\_\_\_\_ Mother's Social Security Number \_\_\_\_\_

Medical Asst. Number \_\_\_\_\_

Mother's Medical History: Thyroid Disease ☐ Diabetes ☐ On Cortisone ☐  
HEP Ag B: Positive ☐ Negative ☐ Unknown ☐

**BABY INFO** Female ☐ Male ☐  
Single Birth ☐ Multiple Birth ☐ A ☐ B ☐ C ☐ Other ☐

Birth Date: \_\_\_\_/\_\_\_\_/\_\_\_\_ Time \_\_\_\_:\_\_\_\_ AM PM  
Collection Date: \_\_\_\_/\_\_\_\_/\_\_\_\_ Time \_\_\_\_:\_\_\_\_ AM PM  
Birth Weight: \_\_\_\_ grams or \_\_\_\_ lbs or \_\_\_\_ oz  
Current Weight: \_\_\_\_ grams or \_\_\_\_ lbs or \_\_\_\_ oz  
Vesicle Gestation \_\_\_\_\_ Medical Record No. \_\_\_\_\_

**At Time of Collection:**  
Transfused? ☐ On Volume ☐ Exchange ☐ Drawn By: \_\_\_\_\_  
☐ Monitor for \_\_\_\_\_ Hyperstimulation ☐ NICU ☐

Baby's Race: Hispanic? Yes ☐ No ☐  
White ☐ Black ☐ Pac. Is. ☐ Asian ☐ Am. Ind. ☐ Other ☐

Medical Home - Physician / Healthcare Provider  
Phone \_\_\_\_\_  
Newborn Physician's Name (Last) \_\_\_\_\_ (First) \_\_\_\_\_  
Street (PO Box) \_\_\_\_\_  
City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

### Key Reminders:

- Complete the form in its entirety. Incomplete forms may cause the specimen to be unacceptable or delay testing and reporting of results.
- Do not hold specimens to form batches – mail daily, other than Sundays.
- Correctly obtain and report the newborn's primary care provider and the mother's contacts; if possible ask for an emergency contact.
- Document a diagnosis of Meconium ileus on the filter paper.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).



# Appendix 3:

## Referral and Treatment Centers and Screening Laboratories for Pennsylvania

# Referral and Treatment Centers

## **Sickle Cell disease, Thalassemia, and other Hemoglobinopathies \*:**

### **Hospital Providers:**

1. Children's Hospital of Philadelphia ..... 215-590-4173
2. Children's Hospital of Pittsburgh..... 412-692-5055
3. St. Christopher's Hospital for Children of Philadelphia ..... 215-427-5096
4. UPMC, Pittsburgh ..... 412-648-6575
5. Thomas Jefferson University, Philadelphia..... 215-955-8485

### **Community Providers:**

1. Shenango Valley Urban League, Farrell ..... 724-981-6154
2. Sickle Cell Disease Assoc. of America, Philadelphia ..... 215-471-8686
3. Sickle Cell Society, Pittsburgh ..... 412-371-0628
4. South Central Pennsylvania Sickle Cell Council, Harrisburg ..... 717-234-3358
5. United Neighborhood Facilities Health Care Corp, Erie. .... 814-898-0400
6. Susquehanna Rehabilitation Services, Mechanicsburg ..... 717-766-1967

\* Note: these providers are under contract with the Department to provide sickle cell services; other treatment centers may also offer services

### **Galactosemia:**

1. Children's Hospital of Philadelphia ..... 215-590-3376
2. Children's Hospital of Pittsburgh..... 412-692-8631  
.....(412-692-5325 after 5 PM & weekends)
3. Clinic for Special Children, Strasburg ..... 717-687-9408

### **Maple Syrup Urine Disease:**

1. Children's Hospital of Philadelphia ..... 215-590-3376
2. Children's Hospital of Pittsburgh..... 412-692-8631  
.....(412-692-5325 after 5 PM & weekends)
3. Clinic for Special Children, Strasburg ..... 717-687-9408

### **Phenylketonuria:**

1. Children's Hospital of Philadelphia ..... 215-590-3376
2. Children's Hospital of Pittsburgh..... 412-692-8631  
.....(412-692-5325 after 5 PM & weekends)
3. St. Christopher's Hospital for Children of Philadelphia ..... 215-590-3376
4. Penn State Milton S. Hershey Medical Center, Hershey..... 717-531-8006



### **Congenital Hypothyroidism:**

Follow-up appointment with a Pediatric Endocrinologist will be decided on between the provider and the patient's family. The Department's newborn screening program will also be able to provide a list of local specialists.

### **Congenital Adrenal Hyperplasia:**

Follow-up appointment with a Pediatric Endocrinologist will be decided on between the provider and the patient's family. The Department's newborn screening program will also be able to provide a list of local specialists.

### **Cystic Fibrosis – CF Foundation-Accredited Pediatric Care Centers:**

1. St. Christopher's Hospital for Children of Philadelphia	215-427-5183
2. Children's Hospital of Pittsburgh	412-692-5661
3. Children's Hospital of Philadelphia	215-590-3749
4. Hershey Medical Center, Hershey	717-531-5338
5. Geisinger Medical Center, Danville	570-271-7910
6. Lehigh Valley Hospital & Health Network, Bethlehem	484-884-3333
7. Saint Luke's Hospital North, Bethlehem	215-427-5183
(Outreach clinic for St. Christopher's Hospital: call St. Chris for appointments)	

### **Remaining of the 22 Supplemental Conditions: MS/MS & BIOT**

1. Children's Hospital of Philadelphia	All	215-590-3376
2. St. Christopher's Hospital for Children	Most (Others to CHOP)	215-427-5485
3. Children's Hospital of Pittsburgh	All	412-692-8631
		(412-692-5325 after 5 PM & weekends)
4. Penn State Milton S. Hershey Medical Center, Hershey	FOAD, HCY, CIT, ASA, BIOT, OAD (once stabilized)	717-531-8006

### **Screening Laboratories**

PerkinElmer Genetics, Inc.  
P.O. Box 219  
90 Emerson Lane  
Bridgeville, PA 15017  
866-463-6436  
Fax: 412-220-0784  
[www.perkinelmergenetics.com](http://www.perkinelmergenetics.com)

New England Newborn Screening Program  
University of MA Medical School (UMASS)  
305 South Street  
Jamaica Plain, MA 02130  
617-983-6300  
Fax: 617-522-2846  
[www.umassmed.edu/nbs/](http://www.umassmed.edu/nbs/)

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or go to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).





# Appendix 4:

## Hemoglobin and Hemoglobinopathy Result Interpretation Table



### Hemoglobin Variants:

Letter	Hemoglobin
F	Fetal hemoglobin, present in declining amounts until 6 months of age
A	Normal adult hemoglobin
S	Hemoglobin-S (sickle hemoglobin)
B	Hemoglobin Barts, indicating alpha thalassemia trait
H	Hemoglobin-C (Harlem) or Hemoglobin-O (Arab). Both traits are clinically asymptomatic, but can cause severe sickling when inherited with sickle cell trait
C	Hemoglobin-C
E/O	Hemoglobin-E or Hemoglobin-O

### Hemoglobinopathy Result Interpretation Table:

Letter	Hemoglobin
F	Fetal hemoglobin with no normal adult hemoglobin may indicate a delay in formation of adult hemoglobin or beta thalassemia. Further testing is needed
FS	Fetal hemoglobin and Hemoglobin-S, with no normal adult hemoglobin. Consistent with Hemoglobin-S disease
FC	Fetal hemoglobin and Hemoglobin-C, with no normal adult hemoglobin. Consistent with Hemoglobin-C disease
FSC	Fetal hemoglobin, Hemoglobin-S, and Hemoglobin-C, with no normal adult hemoglobin Consistent with Hemoglobin SC disease
FE/O	Fetal hemoglobin and Hemoglobin-E, with no normal adult hemoglobin. Consistent with Hemoglobin-E or Hemoglobin-O disease
FB	Fetal hemoglobin and Hemoglobin Barts (>30%) with no normal adult hemoglobin Consistent with Hemoglobin-H disease
FV	Fetal hemoglobin and anomalous variant hemoglobin, with no normal adult hemoglobin. Clinical significance determined by further investigation
FSA	Double heterozygous S/Beta thalassemia. Clinically significant disorder
FSB	Fetal hemoglobin, Hemoglobin-S, and Hemoglobin Barts, with no normal adult hemoglobin. Consistent with Hemoglobin-S disease with alpha thalassemia
FCB	Fetal hemoglobin, Hemoglobin-C, and Hemoglobin Barts, with no normal adult hemoglobin. Consistent with Hemoglobin-C disease with alpha thalassemia
FSCB	Fetal hemoglobin, Hemoglobin-S, Hemoglobin-C, and Hemoglobin Barts, with no normal adult hemoglobin. Consistent with Hemoglobin SC disease with alpha thalassemia
FE/OB	Fetal hemoglobin, Hemoglobin-E, and Hemoglobin Barts, with no normal adult hemoglobin. Consistent with Hemoglobin-E or Hemoglobin-O disease with alpha thalassemia

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).



# Appendix 5:

Pennsylvania Administrative Code,  
Title 28, Part III  
Chapter 28 (Selection)

# CHAPTER 28. SCREENING AND FOLLOW-UP FOR DISEASES OF THE NEWBORN

## **GENERAL PROVISIONS**

Sec.

- 28.1. Definitions.
- 28.2. Newborn diseases listed.
- 28.3. [Reserved].
- 28.4. [Reserved].
- 28.5. Confidentiality.

## **PURPOSE ADMINISTRATION OF TESTS**

- 28.11. Informing the parent or guardian.
- 28.12. Religious objections.

## **SPECIMEN COLLECTION AND FOLLOW-UP**

- 28.21. Responsibility for collecting and testing initial and repeat specimens.
- 28.22. Timing of initial specimen collection and handling in health care facilities.
- 28.23. Timing of initial specimen collection by health care practitioners.
- 28.24. Normal test results.
- 28.25. Circumstances require repeat specimens.
- 28.26. Timing of repeat specimen collection.
- 28.27. Abnormal screening test results.
- 28.28. Followup of symptoms consistent with newborn diseases.
- 28.29—28.31 [Reserved].

## **RECORDS**

- 28.41. Recordkeeping requirements.



For Authority, Source and Cross References as  
related to each section of the regulation  
see PA Code online at [www.pacode.com](http://www.pacode.com)

## GENERAL PROVISIONS

### § 28.1. Definitions.

The following words and terms, when used in this chapter, have the following meanings, unless the context clearly indicates otherwise:

*Abnormal confirmatory test result*—A test result obtained from a specimen of blood, serum or plasma which is diagnostic of the newborn disease under investigation.

*Abnormal screening test result*—A test result obtained from a specimen collected on a specimen collection form which is outside the parameters for a normal test result according to testing criteria applicable to the screening test result.

*Admission*—The formal acceptance of custody or care by a birth center or hospital of a newborn child who is provided with bassinet or incubator, nutrition and continuous nursing service.

*Birth center*—As defined in section 802a of the Health Care Facilities Act (35 P. S. § 448.802a).

*Days of age*—The measurement of age of the newborn child in 24-hour periods so that a newborn child is one day of age 24 hours after the hour of birth.

*Department*—The Department of Health of the Commonwealth.

*Discharge*—The release of the newborn child from care and custody within and by birth center or hospital to the care and custody of the parent or guardian.

*Health care practitioner*—A licensed physician or a practitioner licensed to deliver and care for pregnant women and newborn children.

*Health care provider*—A birth center, hospital or health care practitioner.

*Hemoglobin diseases*—Sickle cell (SS, SC, S + other variant, S β Thalassemia, S O Arab) disease or trait or other clinically significant hemoglobin (CC, EE, F, H) disease or trait.

*Hospital*—As defined in section 802a of the Health Care Facilities Act.

*Inconclusive screening test result*—A test result obtained from a specimen collected on a specimen collection form that is equivocal according to criteria applicable to the screening test result and which indicates the need for a repeat specimen and repeat testing.

*Initial specimen*—The first sample of blood collected from the newborn child and submitted for testing purposes on a specimen collection form.

*Newborn child*—An infant less than 28 days of age.

*Newborn screening program*—The association of the Department, the testing laboratory and the health care provider to ensure that every newborn child born in this Commonwealth has a blood specimen collected and screened for the newborn diseases in § 28.2 (relating to newborn diseases listed).



*Presumptive abnormal test result*—An abnormal screening test result which is sufficiently abnormal to indicate the probable presence of a newborn disease listed in § 28.2.

*Repeat specimen*—A specimen collected from a newborn child on a specimen collection form after the initial specimen.

*Repeat test*—The laboratory testing performed on a repeat specimen.

*Specimen collection form*—The official newborn screening program specimen form that includes both a multipart section for providing required information about the newborn child and a filter paper tab for application of blood.

*Testing laboratory*—The licensed clinical laboratory under contract with the Department to perform testing for the newborn diseases listed in § 28.2.

*Transfer*—The release of the newborn child from care and custody within and by a birth center or hospital and subsequent admission to another hospital.

*Treatment center*—A center under contract with the Department to provide expert consultation, diagnosis and treatment for children with a presumptive abnormal test result.

*Unacceptable specimen*—A blood specimen collected from a newborn child on a specimen collection form which is found to be unsuitable for testing in accordance with accepted laboratory testing standards as determined by the Department.

### **§ 28.2. Newborn diseases listed.**

A newborn child born in this Commonwealth shall be screened for the following diseases which may cause mental retardation, physical defects or death if not detected and treated soon after birth:

- (1) Congenital adrenal hyperplasia (CAH)
- (2) Galactosemia
- (3) Hemoglobin diseases
- (4) Maple syrup urine disease (MSUD)
- (5) Phenylketonuria (PKU)
- (6) Primary congenital hypothyroidism

### **§ 28.3. [Reserved].**

### **§ 28.4. [Reserved].**

### **§ 28.5. Confidentiality.**

(a) A health care provider, testing laboratory, the Department or any other entity involved in the newborn screening program may not release any identifying information relating to any newborn child screened in the newborn screening program to anyone other than a parent or guardian of the newborn child or the health care provider for the newborn child designated by a parent or the guardian except as follows:

- (1) As may be necessary to provide services to the newborn child.
- (2) With the consent of the newborn child's parent or guardian.

- (3) With the child's consent when the child is 18 years of age or older, has graduated from high school, has married or has been pregnant.
- (b) Only the Department will have the authority to release or authorize the release of nonidentifying information concerning the newborn screening program.

## **PURPOSE AND ADMINISTRATION OF TESTS**

### **§ 28.11. Informing the parent or guardian.**

Prior to specimen collection, the health care provider shall provide the pregnant woman, prior to the infant's birth, or the mother or guardian, after the infant's birth, with a pamphlet supplied by the Department to explain the nature of the newborn screening blood tests for the diseases in § 28.2 (relating to newborn diseases listed).

### **§ 28.12. Religious objections.**

- (a) A health care provider may not collect or cause to be collected, a specimen from a newborn child if the parent or guardian of the newborn child objects on the ground that the specimen collection conflicts with religious beliefs or practices held by the parent or guardian.
- (b) If the parent or guardian of the newborn child objects to the collection of the specimen for screening on the ground that the specimen collection conflicts with religious beliefs or practices held by the parent or guardian, the health care provider shall ensure that the recorded objection of the parent or guardian is entered into the medical record of the newborn child. The entry shall include a written statement of the objection signed by the parent or guardian.

## **SPECIMEN COLLECTION AND FOLLOW-UP**

### **§ 28.21. Responsibility for collecting and testing initial and repeat specimens.**

- (a) A birth center or hospital shall collect or cause to be collected from each newborn child delivered in that birth center or hospital, in accordance with instructions for newborn screening specimen collection in subsection (d), the initial and repeat specimens necessary to conduct the tests necessary for the detection of the newborn diseases specified in § 28.2 (relating to newborn diseases listed).
- (b) When a newborn child is delivered other than in a birth center or hospital, the health care practitioner who delivered the newborn child shall collect or cause to be collected from the newborn child, in accordance with instructions for newborn screening specimen collection in subsection (d), the initial and repeat specimens necessary to conduct the tests necessary for the detection of the newborn diseases specified in § 28.2.
- (c) The health care provider shall designate a newborn screening coordinator to do the following:
  - (1) Ensure that a specimen collection form contains correct and complete information.



- (2) Ensure that the individual who collected the specimen records that act in the newborn child's medical record.
- (3) Send all specimens collected by first class mail to the testing laboratory within 24 hours of collection.
- (4) Record the laboratory screening results in the newborn child's medical records.
- (5) Check each newborn child's record prior to discharge or release to ensure that a specimen has been collected.
- (6) Ensure, in the event of transfer of the newborn child prior to 48 hours of age, that the receiving health care provider has been notified that it has the responsibility to collect the initial specimen.
- (7) Assist the Department in follow-up of an abnormal or presumptive abnormal test result.
- (8) Follow-up inconclusive test results.
- (9) Receive notification from the testing laboratory or from the Department of the need for a repeat specimen.

(d) The health care provider shall ensure that the individual responsible for specimen collection shall collect the specimen necessary to conduct tests in accordance with consensus standards developed by the National Committee for Clinical Laboratory Standards (NCCLS) and accepted by the Department. The Department will publish these standards, and any revisions thereto, in a notice in the Pennsylvania Bulletin.

**§ 28.22. Timing of initial specimen collection by birth centers or hospitals.**

(a) A birth center or hospital shall collect the initial specimen from each newborn child regardless of feeding history or medical condition, as close to 48 hours of age as possible but not later than 72 hours of age unless the newborn child falls into one of the following categories:

- (1) Transfer. If the newborn child is transferred to another hospital for continuing care prior to 48 hours of age, the hospital to which the newborn child has been transferred shall collect a specimen from the newborn child, regardless of feeding history or medical condition, as close to 48 hours of age as possible but not later than 72 hours of age.
- (2) Exchange transfusion. If the newborn child is to undergo an exchange transfusion, the birth center or hospital shall collect the initial specimen for testing immediately prior to the exchange transfusion.
- (3) Early discharge. If the newborn child is discharged from the birth center or hospital before 24 hours of age, the birth center or hospital shall collect the initial specimen from the newborn child as close to the time of discharge as is practicable, regardless of feeding history or medical condition. The birth center or hospital shall give the parent or guardian in whose care and custody the newborn child is discharged written notification of the need for a repeat specimen and shall also provide instructions to the parent or guardian for obtaining a repeat specimen from the newborn child as described in § 28.26 (relating to timing of repeat specimen collection).

(b) When a newborn child, who was delivered other than in a birth center or hospital, is admitted to a hospital within the first 27 days of age and the hospital has received no record

of results of an approved screening test for the newborn diseases in § 28.2 (relating to newborn diseases listed), the hospital to which the newborn child is admitted shall collect the initial specimen within 48 hours of admission to the hospital and shall send the specimen to the testing laboratory specified by the Department within 24 hours of collection.

**§ 28.23. Timing of initial specimen collection by health care practitioners.**

A health care practitioner who delivers a newborn child other than in a birth center or hospital shall collect or cause to be collected the initial specimen from the newborn child, regardless of feeding history or medical condition, as close to 48 hours as possible but not later than 72 hours of age.

**§ 28.24. Normal test results.**

- (a) Within 7-calendar days following the day when the testing laboratory obtains the normal test results, the testing laboratory shall send those results to the health care provider that collected the specimen from the newborn child.
- (b) The health care provider to whom the normal test results are reported shall record the test results in the medical record of the newborn child.

**§ 28.25. Circumstances requiring repeat specimens.**

- (a) The health care provider responsible for collecting the initial specimen shall collect or cause to be collected and submit for testing a repeat specimen if the initial specimen collected is either of the following:
  - (1) Unacceptable for testing.
  - (2) Yields an inconclusive screening test result.
- (b) If a birth center or hospital collects the initial specimen from a newborn child prior to 24 hours of age because the newborn child is discharged from the birth center or hospital prior to 24 hours of age, the birth center or hospital shall collect or cause to be collected a repeat specimen.
- (c) If the initial specimen collected yields an abnormal screening test result, the Department may require the health care provider responsible for collecting the initial specimen to collect a repeat specimen.

**§ 28.26. Timing of repeat specimen collection.**

- (a) When the newborn child has been discharged from a birth center or hospital before 24 hours of age, the birth center or hospital shall collect or cause to be collected a repeat specimen from the newborn child, regardless of feeding history or medical condition, as close to 48 hours of age as possible but not later than 72 hours of age.
- (b) When the initial specimen is unacceptable or when the initial specimen yields an inconclusive screening test result, the Department or testing laboratory will notify the health care provider that collected the initial specimen. Within 72 hours of receipt of notice from the Department or testing laboratory, the health care provider that collected the initial specimen shall collect or cause to be collected from the newborn child a repeat specimen.

(c) If the health care provider cannot locate a parent or guardian of the newborn child within 4 days of notification of need for a repeat specimen, the health care provider shall contact the Department for consultation regarding additional means for locating a parent or guardian.

**§ 28.27. Abnormal screening test results.**

(a) When testing of the initial or repeat specimen yields an abnormal screening test result, the Department will notify the health care provider that collected the specimen. The health care provider shall promptly notify a parent or guardian of the newborn child.

(b) If the health care provider cannot locate the newborn child's parent or guardian within 48 hours of receiving notice from the Department, the health care provider shall contact the Department for consultation regarding additional means for locating a parent or guardian.

(c) The Department will assist the health care provider with and make available confirmatory testing.

(d) If the result of the confirmatory test is abnormal, the Department will assist with referral for diagnosis, treatment, and other follow-up services for the newborn child through designated treatment centers or clinical specialists.

**§ 28.28. Follow-up of symptoms consistent with newborn diseases.**

When a sick child exhibits symptoms suggestive of a newborn disease listed in § 28.2 (relating to newborn diseases listed) and has not already been determined to have one of those newborn diseases, the health care provider to whom care of the sick child has been entrusted by the parent or guardian shall collect and submit a blood specimen for newborn disease testing in accordance with standard diagnostic procedures.

**§ 28.29—28.31. [Reserved].**

## **RECORDS**

**§ 28.41. Recordkeeping requirements.**

A health care provider offering maternity and newborn services shall collect and forward data semiannually to the Department on the number of patients for whom specimens for newborn disease testing have been collected and the number of patients for whom the specimens have not been collected, together with the reason in each instance for the failure to collect.

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## Appendix 6:

Newborn Child Testing Act as  
ammended by Act 36 of 2008

## **Newborn Child Testing Act (as amended by Act 36 of 2008 effective 7/1/2009)**

35 P.S. § 621, et. seq.

### **§ 621. Short title**

This act shall be known and may be cited as the "Newborn Child Testing Act."

### **§ 622. Definitions**

The following words and phrases when used in this act shall have the meanings given to them in this section unless the context clearly indicates otherwise:

"BOARD." The State Advisory Health Board in the Department of Health.

"DEPARTMENT." The Department of Health of the Commonwealth.

"DISEASE." Diseases listed by the Department of Health by regulation which lead to mental retardation or physical defects, including, without limitation, Phenylketonuria (PKU), maple syrup urine disease (MSUD) and sickle-cell disease (hemoglobinopathies).

"HEALTH CARE PROVIDER." A health care facility or health care practitioner as defined by regulations of the Department of Health.

"NEWBORN CHILD." A child less than 28 days of age.

"PROGRAM." The Newborn Child Screening and Follow-up Program administered by the Department of Health.

"REPEAT SPECIMEN." A second or subsequent blood specimen collected from a newborn child for the same purpose.

"UNACCEPTABLE SPECIMEN." A newborn child's blood specimen which is not suitable in quality or quantity to perform newborn screening or confirmatory testing for one or more of the diseases covered by this act or the regulations promulgated thereunder.

### **§ 623. Newborn Child Screening and Follow-up Program**

(a) In order to assist health care providers to determine whether treatment or other services are necessary to avert mental retardation, permanent disabilities or death, the department, with the approval of the Newborn Screening and Follow-up Technical Advisory Board, shall establish a program providing for:

- (1) The screening tests of newborn children for the following diseases:
  - (i) Phenylketonuria (PKU)
  - (ii) Maple syrup urine disease (MSUD)
  - (iii) Sickle-cell disease (hemoglobinopathies)
  - (iv) Galactosemia
  - (v) Congenital adrenal hyperplasia (CAH)
  - (vi) Primary congenital hypothyroidism



- (2) Follow-up services relating to case management, referrals, confirmatory testing, assessment and diagnosis of newborn children with abnormal, inconclusive or unacceptable screening test results for the following diseases:
- (i) Phenylketonuria (PKU)
  - (ii) Maple syrup urine disease (MSUD)
  - (iii) Sickle-cell disease (hemoglobinopathies)
  - (iv) Isovaleric acidemia/Isovaleryl-CoA dehydrogenase deficiency (IVA)
  - (v) Glutaric acidemia Type I/Glutaryl-CoA dehydrogenase deficiency Type I (GA 1)
  - (vi) 3-Hydroxy 3-methylglutaryl-CoA lyase deficiency (HMG)
  - (vii) Multiple carboxylase deficiency (MCD)
  - (viii) Methylmalonic acidemia (mutase deficiency) (MUT)
  - (ix) Methylmalonic acidemia (Cbl A,B)
  - (x) 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
  - (xi) Propionic acidemia/Propionyl-CoA carboxylase deficiency (PROP)
  - (xii) Beta-ketothiolase deficiency (BKT)
  - (xiii) Medium chain acyl-CoA dehydrogenase deficiency (MCAD)
  - (xiv) Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
  - (xv) Long-chain L-3-OH acyl-CoA dehydrogenase deficiency (LCHAD)
  - (xvi) Trifunctional protein deficiency (TFP)
  - (xvii) Carnitine uptake defect (CUD)
  - (xviii) Homocystinuria (HCY)
  - (xix) Tyrosinemia type I (TYR I)
  - (xx) Argininosuccinic acidemia (ASA)
  - (xxi) Citrullinemia (CIT)
  - (xxii) Hb S/Beta-thalassemia (Hb S/Th)
  - (xxiii) Hb S/C disease (Hb S/C)
  - (xxiv) Congenital hypothyroidism (HYPOTH)
  - (xxv) Biotinidase deficiency (BIOT)
  - (xxvi) Congenital adrenal hyperplasia (CAH)
  - (xxvii) Galactosemia (GALT)
  - (xxviii) Cystic fibrosis (CF)



(b) Deleted effective July 1, 2009.

(b.1) All laboratories performing the screening tests for newborn children shall report the results to the department for follow-up activities.

(c) No screening test shall be performed if a parent or guardian dissents on the ground that the test conflicts with a religious belief or practice.

(d) The department, with the approval of the Newborn Screening and Follow-up Technical Advisory Board, shall establish, by periodic publication in the *Pennsylvania Bulletin*, changes to the lists under subsection (a)(1) and (2) of those diseases for which newborn children shall be screened and laboratory screening results reported.

(e) Notwithstanding any provisions of this act or the act of April 23, 1956 (1955 PL. 1510, No. 500), known as the "Disease Prevention and Control Law of 1955," to the contrary, test results and diagnoses based upon screening tests for the diseases listed in this section for newborn children shall be reported to the department. The department shall establish, by periodic publication in the *Pennsylvania Bulletin*, the method for reporting test results to the department.

(f) Test results for genetic diseases listed in this section and any diseases subsequently added by the department under subsection (d) shall be subject to the confidentiality provisions of the "Disease Prevention and Control Law of 1955."

#### **§ 624. Procurement of specimens by health care providers**

(a) Health care providers shall cause to be procured blood specimens of newborn children for required screening and confirmatory tests and send such specimens to a testing laboratory designated by the department.

(b) If the initial specimen is an unacceptable specimen or as otherwise required by the department by regulation, the health care provider shall collect a repeat specimen for screening and confirmatory tests.

#### **§ 625. Regulations**

The department, with the approval of the board, shall have the authority to promulgate regulations for the implementation and administration of this act.





# Appendix 7:

## State Community Health District Map and Contact Information

**Contact Information by Community Health Districts/Counties**  
**For further information regarding services available in your health district:**

<b>State Health district</b>	<b>Counties</b>	<b>Contact information</b>
Northwest District	Erie, Warren, McKean, Crawford, Forest, Elk, Cameron, Clearfield, Mercer, Lawrence, Clarion, Venango, Jefferson	19 McQuiston Drive Jackson Center, PA 16133 Phone: 724-662-6068 Fax: 724-662-6086
Northeast District	Susquehanna, Wyoming, Wayne, Pike, Luzerne, Monroe, Carbon, Lehigh, Northampton, Lackawanna	665 Carey Avenue Wilkes-Barre, PA 18706-5485 Phone: 570-826-2062 Fax: 570-826-2238
North Central District	Potter, Tioga, Bradford, Clinton, Lycoming, Union, Sullivan, Columbia, Snyder, Centre, Northumberland, Montour	Water Tower Square 1000 Commerce Park Drive Suite 109 Williamsport, PA 17701 Phone: 570-327-3400 Fax: 570-327-3748
Southeast District	Schuylkill, Berks, Bucks, Delaware, Lancaster	Reading State Office Bldg Room 442 625 Cherry Street Reading, PA 19602 Phone: 610-378-4352 Fax: 610-378-4527
Southwest District	Beaver, Butler, Armstrong, Indiana, Cambria, Greene, Washington, Westmoreland Fayette, Somerset	514 Pittsburgh State Office Bldg 300 Liberty Avenue Pittsburgh, PA 15222 Phone: 412-565-5085 Fax: 412-565-7582
South Central District	Blair, Bedford, Huntingdon, Mifflin, Fulton, Juniata, Perry, Cumberland, Adams, York, Dauphin, Lebanon, Franklin	30 Kline Plaza Harrisburg, PA 17104 Phone: 717-787-8092 Fax: 717-772-3151

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).



## County Health Departments

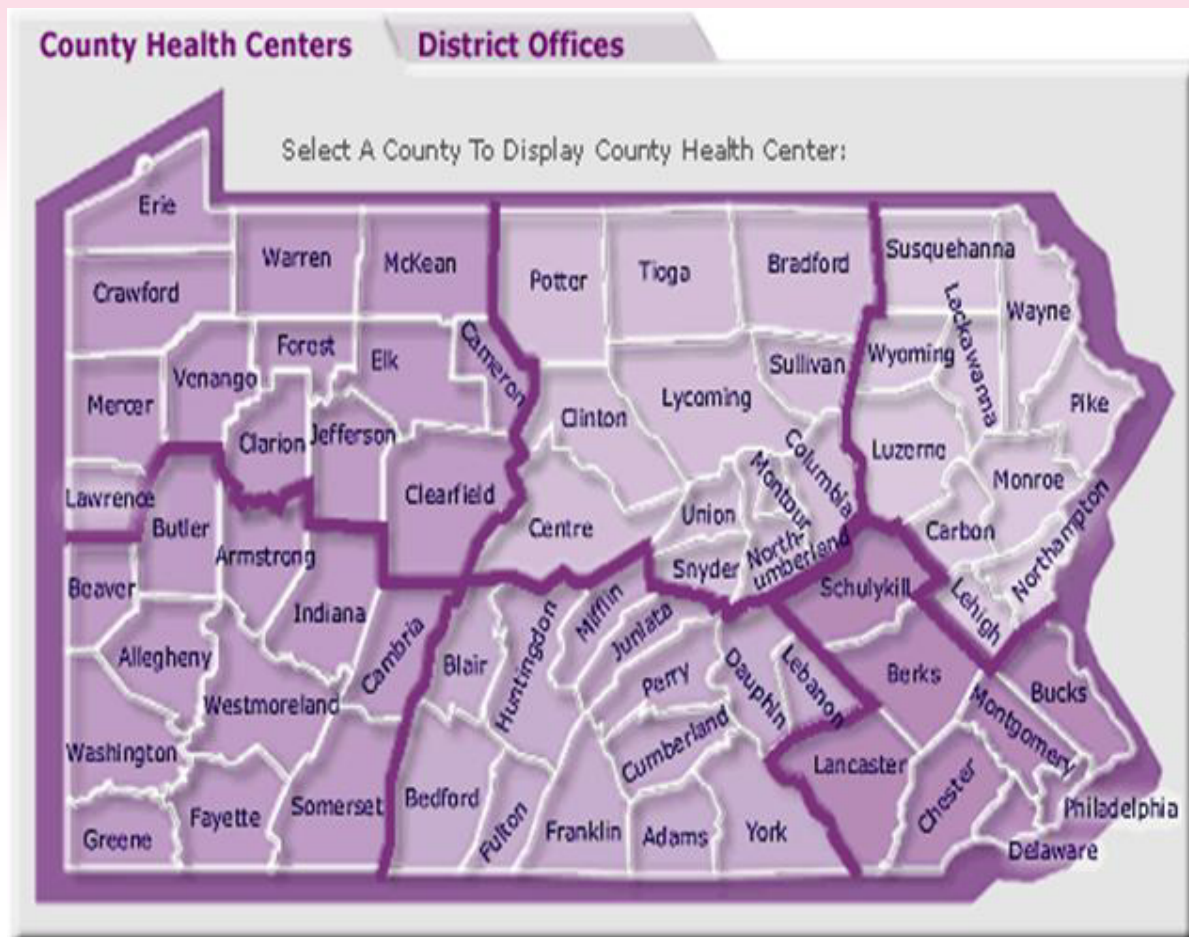
Counties	Contact information
Allegheny County	3333 Forbes Avenue Pittsburgh, PA 15213 Phone: (412)578-8026 Fax: (412)578-8325
Bucks County	Neshaminy Manor Center Doylestown, PA 18901 Phone: (215)345-3318 Fax: (215)345-3833
Chester County	Administrative Department 601 Westtown Road, Suite 290 West Chester, Pa 19382-4542 Phone: (610)344-6225 Fax: (610)344-6727 Web: <a href="http://www.chesco.org/health/">http://www.chesco.org/health/</a>
Montgomery County	1430 DeKalb Street P.O. Box 311 Norristown, PA 19404 Phone: (610)278-5117 Fax: (610)278-5167 Web: <a href="http://health.montcopa.org">health.montcopa.org</a>
Philadelphia County	1101 Market Street, 8th floor Philadelphia, PA 19107 Phone: (215)686-5000 Fax: (215)685-5398

For further information on finding a County Health Department location near you alphabetically by county, please go to [www.health.state.pa.us](http://www.health.state.pa.us) and click on Local Health Centers located on the left-hand side of the screen.

At any time, questions and concerns can be addressed to the Department of Health's Division of Newborn Screening and Genetics-Newborn Screening and Follow-up Program at 717-783-8143 or toll free 1-877-724-3258 or by going to our website at [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).



## Community health district/county map of Pennsylvania



<http://www.dsf.health.state.pa.us/health/site/default.asp>



# Appendix 8:

## Additional Resources For Providers and Parents



## **Additional Resources for Providers**

### **Newborn Screening and Genetic/Metabolic Conditions Resources**

<http://genes-r-us.uthscsa.edu>

National newborn screening and genetics resource center (NNSGRC) provides information and resources in the area of newborn screening and genetics to benefit health professionals, the public health community, consumers and government officials

<http://www.infanthearing.org>

National Center for Hearing Assessment and Management

[www.acmg.net](http://www.acmg.net)

Website for information on the American College of Medical Genetics and on genetic and metabolic conditions and resources

[www.cff.org](http://www.cff.org)

Website for information on the Cystic Fibrosis Foundation and cystic fibrosis

[www.sicklecelldisease.org](http://www.sicklecelldisease.org)

Website for information on the Sickle Cell Disease Association of America and sickle cell disease

[www.perkinelmergenetics.com](http://www.perkinelmergenetics.com)

Website for information on PerkinElmer screening lab and for condition fact sheets

[www.umassmed.edu/nbs/](http://www.umassmed.edu/nbs/)

Website for UMass screening lab and for condition fact sheets

[www.marchofdimes.com](http://www.marchofdimes.com)

Website for information and videos on newborn screening

<http://www.ncbi.nlm.nih.gov/omim>

Website for information on Online Mendelian inheritance in Man (OMIM) – compendium of human genes & genetic phenotypes; Johns Hopkins University

<http://www.genetests.org>

Website for information on medical genetics, resources for healthcare providers, reviews, clinic and laboratory directories; funded by NIH

[www.wadsworth.org/newborn/nymac](http://www.wadsworth.org/newborn/nymac)

Website for New York – Mid-Atlantic Consortium for Genetics and Newborn Screening Services (NYMAC), funded by HRSA to develop a regional approach to address the maldistribution of genetic resources in the New York-Mid-Atlantic region; Wadsworth Center, New York State Department of Health is the lead institution for this project

<http://www.rarediseases.org>

Website for National Organization for Rare Diseases (NORD) & rare disease database

Update of Expanded Newborn Screening – United States, 2006, MMWR Weekly, September 19, 2008 / 57 (37); 1012-1015



Blau N, Duran M, Blaskovics, et al. Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases, 2nd edition. Springer-Verlag Berlin Heidelberg, 2002

Fernandes J, Saudubray J, and Berghe G. Inborn Metabolic Diseases: Diagnosis and Treatment, 3rd edition. Springer-Verlag Berlin Heidelberg, 2000

Scriver CR, Beaudet AL, Valle D, et al. The Metabolic and Molecular Bases of Inherited Disease, 8th edition. McGraw-Hill 2000

Hay WW, Levin MJ, Sondheimer JM, et al. Current Pediatric Diagnosis and Treatment, 17th edition. McGraw-Hill, 2004

### **General Health Resources for Providers**

<http://www.health.state.pa.us>

Official site of the Pennsylvania Department of Health (DOH)

<http://www.health.state.pa.us/newbornscreening>

Official site of the PA DOH's Newborn Screening & Follow-up Program

[www.familydoctor.org](http://www.familydoctor.org)

Website for information on the American Academy of Family Physicians

[www.acog.org](http://www.acog.org)

Website for information on the American College of Obstetrics and Gynecologists

[www.aap.org](http://www.aap.org) and [www.paaap.org](http://www.paaap.org)

Websites for information on the American Academy of Pediatrics and the PA Chapter

<http://www.boystownhospital.org>

Boystown National Research Hospital conducts clinical and research programs focusing on childhood deafness, visual impairment and related communication disorders

[www.pamedicalhome.org](http://www.pamedicalhome.org)

Website for the PA Medical Home Initiative and for EPIC IC, Educating Practices in Community-Integrated Care

[www.commonwealthfund.org](http://www.commonwealthfund.org)

Website for information on the Commonwealth Fund Commission, and on research, publication, grants and programs for high performance healthcare

### **Additional Resources for Parents**

#### **Newborn Screening Resources**

[www.newbornscreening.info](http://www.newbornscreening.info)

Website from HRSA with information & genetic and metabolic condition fact sheets for Parents

[www.ghr.nlm.nih.gov](http://www.ghr.nlm.nih.gov)

Website of the National Institute of Health for general consumer-friendly information about the effects of genetic variation on human health & genetic/metabolic conditions

[www.geneticalliance.org](http://www.geneticalliance.org)

Website that provides assistance and tools to advocacy organization for patients with genetic conditions

<http://www.rarediseases.org>

Website for National Organization for Rare Diseases (NORD) & rare disease database

<http://www.magicfoundation.org>

Website with information on a wide variety of syndromes and disorders

<http://www.oaanews.org>

Website with information on organic acidemias

<http://www.ascaa.org>

Website with information on sickle cell disease

<http://www.galactosemia.org>

Website with information on galactosemia

<http://www.savebabies.org>

Website of Save Babies, non-profit organization, designed to inform parents about newborn genetic diseases diagnosed through newborn screening and support groups

<http://www.caresfoundation.org>

Cares Foundation Research, education, and support for CAH

[www.cff.org](http://www.cff.org)

Website for information on cystic fibrosis

[www.4woman.gov](http://www.4woman.gov) for information on breastfeeding

[www.acog.org](http://www.acog.org) for information on the American College of Obstetrics and Gynecologists

[www.dli.state.pa.us](http://www.dli.state.pa.us)

Website for information on Pennsylvania's Office for the Deaf and Hard of Hearing, with resources, service information and links

[www.aap.org](http://www.aap.org) for information on the American Academy of Pediatrics and for additional resources and website links for metabolic, genetic and hearing conditions

[www.marchofdimes.com](http://www.marchofdimes.com) for information and videos on newborn screening

[www.familydoctor.org](http://www.familydoctor.org) for information on the American Academy of Family Physicians

### **General Health Resources for Parents**

<http://www.health.state.pa.us/newbornscreening>

Official site of the PA DOH's Newborn Screening & Follow-up Program

<http://www.health.state.pa.us>

Website with information on Department of Health programs

<http://www.ins.state.pa.us>

Website with information on Pennsylvania Insurance Department's CHIP and adult basic Healthcare coverage programs



<http://www.dpw.state.pa.us>

Website with information on Pennsylvania Department of Public Welfare's Medicaid Healthcare coverage program

<http://www.compass.state.pa.us>

Website information on how to apply for state social service programs on line

[www.medlineplus.gov](http://www.medlineplus.gov)

Website for health information from the National Institutes of Medicine and Health

[www.healthfinder.gov](http://www.healthfinder.gov)

Website for health information from HHS, Office of Disease Prevention/Health Promotion

### **Phone numbers for parents to call for more information**

**1-877-724-3258** for Pennsylvania Department of Health Newborn Screening and Follow-up Program

**1-800-986-INFANT (2229)** for information on finding a health care provider, getting healthcare coverage, immunizations and tests for infant

**1-800-986-KIDS (5437)** for information on finding a health care provider, getting healthcare coverage, immunizations, or tests for your children

**1-800-WIC-WINS (942-9467)** to obtain supplemental foods, nutrition education and breastfeeding information

**1-800-986-4550** for information on services available for children with special needs

**1-800-4-A-CHILD (422-4453)** 24-hour crisis hotline to offer support, information and referrals on coping with a crying infant and preventing child abuse

Updates to the manual will be made periodically and can be found at the Department of Health website, [www.health.state.pa.us/newbornscreening](http://www.health.state.pa.us/newbornscreening).





## Appendix 9:

National and Pennsylvania Incidence  
Rates for 28 Disorders

## NATIONAL ECONOMIC COSTS AND INCIDENCE RATES FOR NEWBORN SCREENING

Source: Economic Costs Associated with Mental Retardation Articles:

1. CDC, MMWR Weekly, January 30, 2004/ 53 (03); 57-59
2. CDC, Mental Retardation

The average lifetime costs for a person with mental retardation is \$1,014,000 over and above the costs for an individual who does not have a disability.

National incidence rates for current 6 PA state-mandated conditions:		Burden if untreated:
1. Phenylketonuria (PKU)	1 in 10,000-15,000	Mental Retardation
2. Maple Syrup Urine Disease (MSUD)	1 in 100,000	Death
3. Galactosemia	1 in 50,000	Death
4. Sickle Cell	1 in 400 for African Americans 1 in 10,000 for others	Death
5. Hypothyroidism	1 in 3,500	Mental Retardation
6. Congenital Adrenal Hyperplasia (CAH)	1 in 15,000	Death

National incidence rates for 22 additional recommended conditions:		Burden if untreated:
1. Argininosuccinic Acidemia (ASA)	1 in 100,000	Death
2. Beta-ketothiolase (BKT) Deficiency	1 in 100,000	Mental Retardation/ Death
3. Biotinidase Deficiency	1 in 75,000	Death
4. Carnitine Uptake Defect (CUD)	1 in 100,000	Death
5. Citrullinemia	1 in 100,000	Death
6. Cystic Fibrosis	1 in 2,500 Caucasians 1 in 15,000 African Americans	Death
7. Glutaric Acidemia Type I (GA I)	1 in 50,000	Death
8. 3-OH 3 CH3 Glutaric Aciduria (HMG)	1 in 100,000	Death
9. Hb S/Beta Thalassemia	1 in 10,000	Death
10. Hb S/C Disease	1 in 10,000	Death
11. Homocystinuria (HCY)	1 in 100,000	Mental Retardation
12. Isovaleric Acidemia (IVA)	not available	Mental Retardation/ Death
13. Long-Chain 3-hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency	1 in 75,000	Death
14. Methylmalonic Acidemia (Cbl A,B)	1 in 48,000	Death
15. Methylmalonic Acidemia (Mutase deficiency) (MUT)	1 in 48,000	Death
16. 3-Methylcrotonyl-CoA Carboxylase (3MCC) Deficiency	1 in 50,000-75,000	Death
17. Multiple Carboxylase Deficiency (MCD)	1 in 100,000	Death
18. Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency	1 in 75,000	Death
19. Propionic Acidemia (PROP)	1 in 75,000	Death
20. Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency	1 in 10,000-15,000	Death
21. Trifunctional Protein Deficiency (TFP) Deficiency	1 in 100,000	Death
22. Tyrosinemia	1 in 100,000	Death



## **PENNSYLVANIA DIAGNOSED CONDITIONS FOR SIX MANDATED NEWBORN SCREENING CONDITIONS**

**2007**

### **Diagnosed Cases\*:**

Congenital Adrenal Hyperplasia (CAH)	3
Congenital Hypothyroidism (CH)	62
Galactosemia	17
Maple Syrup Urine Disease (MSUD)	6
Phenylketonuria (PKU)	20
Sickle Cell and Other Hemoglobinopathies	92
<b>Total Diagnosed:</b>	<b>200</b>

### **Data Summary:**

#### **6 mandated conditions:**

- The number of initial filter papers screened in Pennsylvania has risen from 143,360 in 2005 to 149,367 in 2007, corresponding with an increase in the number of births occurring in Pennsylvania from 2005-2007.
- Annually, an estimated 3,000 abnormal newborn screening results are identified for the six mandated conditions, resulting in approximately 200 diagnosed cases.
- Historically, the Department's Newborn Screening and Follow-Up Program (NSFP) has observed a high rate of false positive screening results for CAH and MSUD.

#### **22 supplemental conditions:**

- The NSFP estimates that 1,600-1,700 abnormal results are identified annually in Pennsylvania for the 22 additional conditions.
- Starting July 1, 2009, the NSFP will collect and analyze the data for abnormal results and the diagnosis of the additional 22 conditions

\* PA 2007 diagnosed data source: confirmed from referral specialists/treatment centers

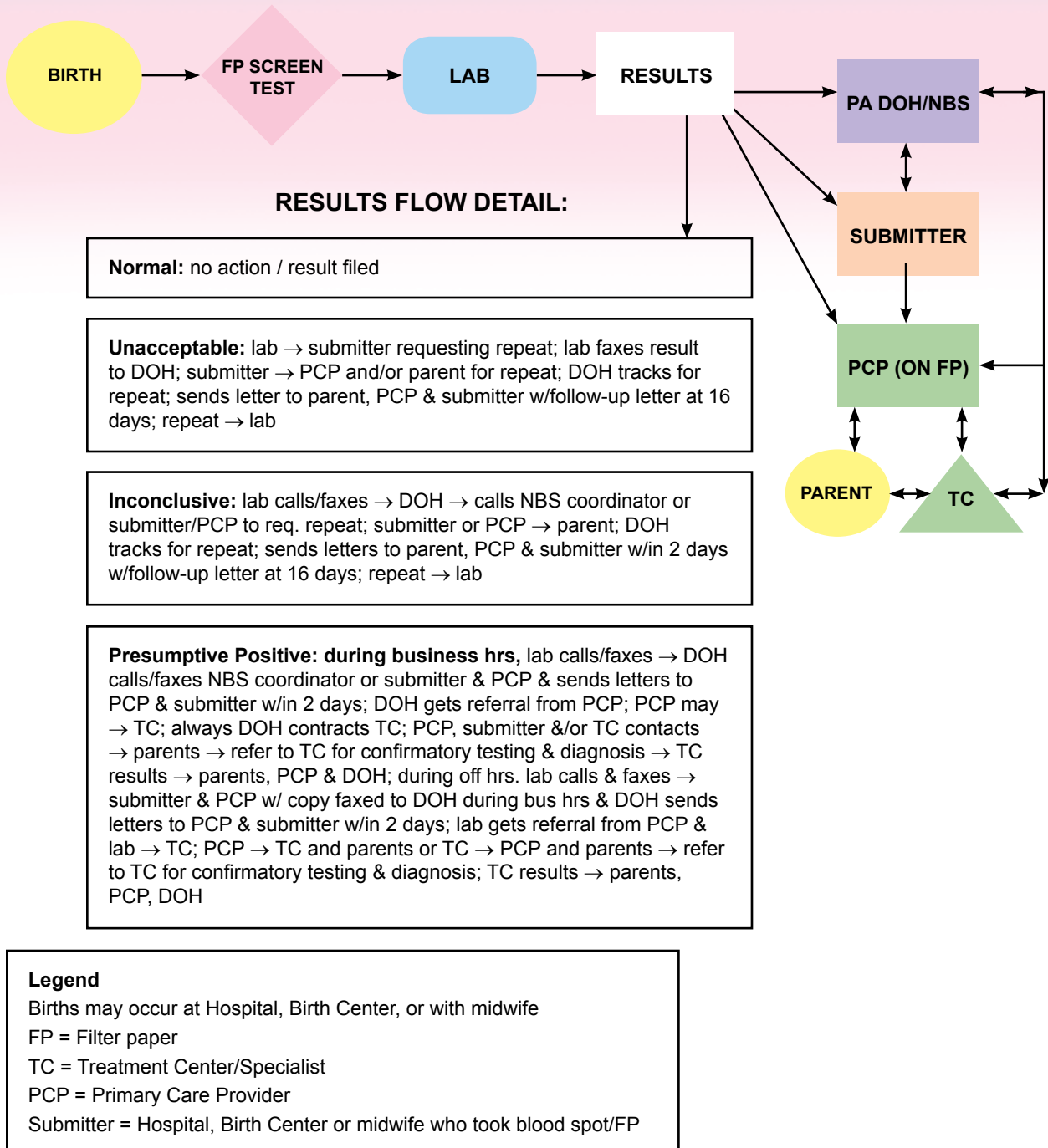


# Appendix 10:

## Newborn Screening & Follow-up Program Process Flow Charts

## NEWBORN SCREENING AND FOLLOW-UP PROGRAM FLOW CHARTS

Current 6 mandated conditions:

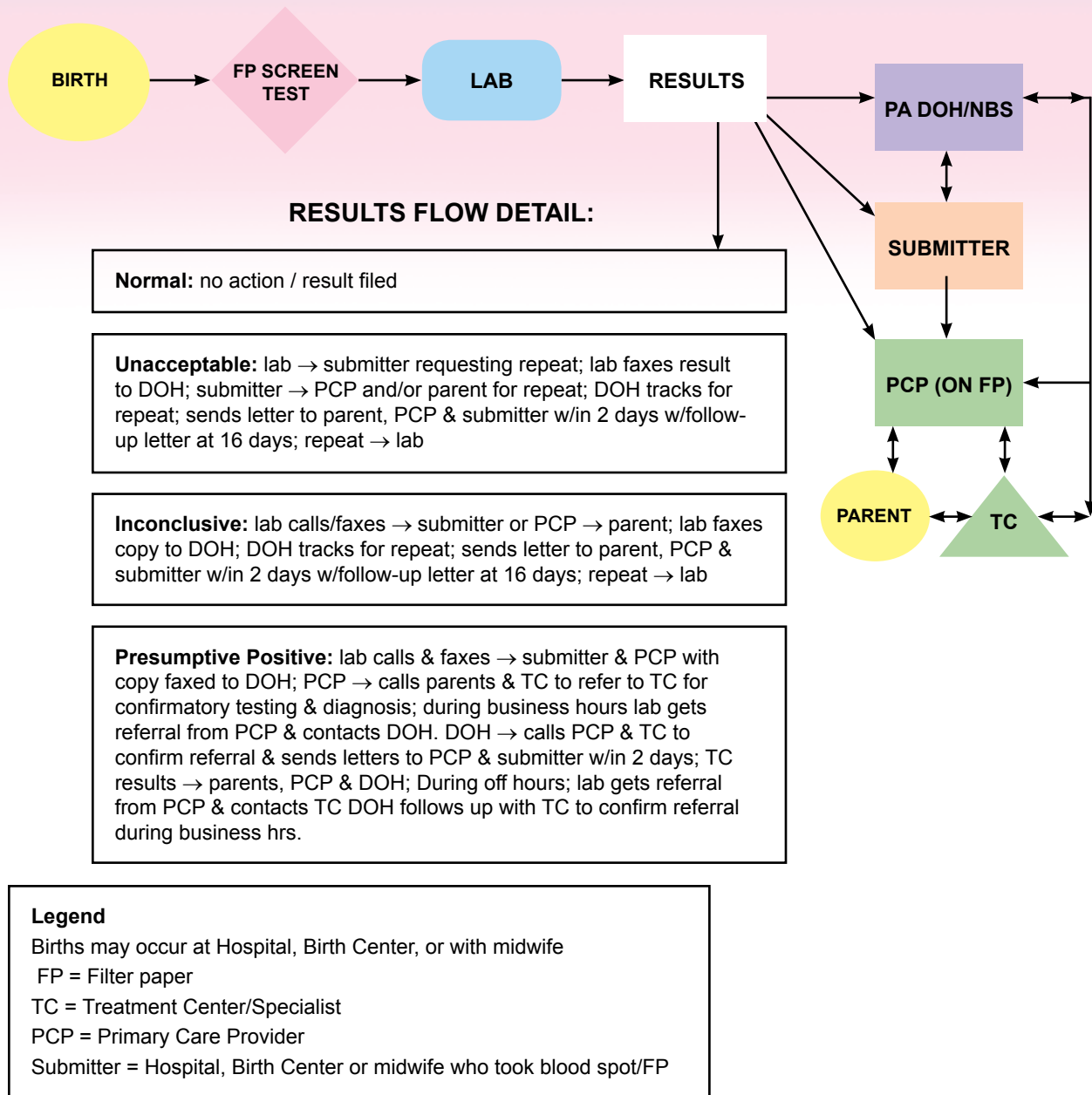


Note: Off hours includes after hours, weekends & holidays

4/1/09

## NEWBORN SCREENING AND FOLLOW-UP PROGRAM FLOW CHARTS

Additional 22 conditions as of 7/1/09



Note: Off hours includes after hours, weekends & holidays

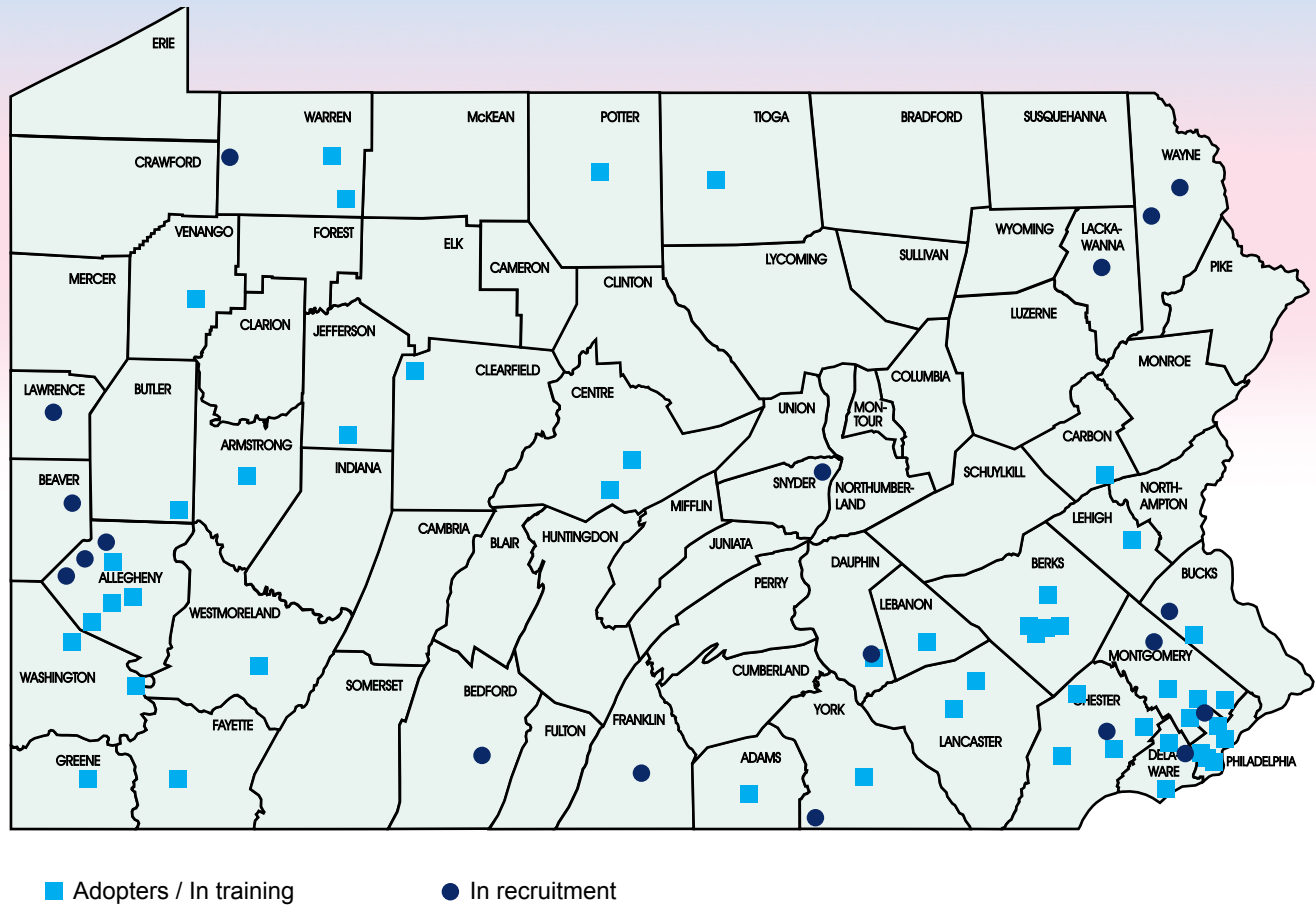
4/1/09



# Appendix 11:

## Medical Home Practices in Pennsylvania Map

## EPIC IC MEDICAL HOME SITES



### Notes

- Some of the pushpins denoting a medical home site overlap where sites are in close geographical proximity. Counties where pushpins overlap are: Washington (3 sites), Lehigh (2), Allegheny (8), Dauphin (2), Lancaster (4), and Philadelphia (14)
- There are 85 medical home sites marked on this map, as of 5/4/09
- For updated information on this map and EPIC IC medical home practices, visit website: [pamedicalhome.org](http://pamedicalhome.org)