NORTH CAROLINA NEWBORN SCREENING PROGRAM

Amino acids: Phenylalanine elevation, with or without elevated phenylalanine to tyrosine ratio

Possible condition

- **Classic phenylketonuria (PKU)**
- **Other phenylalanine hydroxylase (PAH) deficiencies**
- **Pterin deficiencies**

Fact Sheet for Providers

What does phenylalanine elevation lead to?

Phenylalanine elevations result from a deficiency in the phenylalanine hydroxylase (PAH) enzyme or its cofactors. PAH is responsible for the conversion of phenylalanine into tyrosine. When absent, phenylalanine builds up in the brain, causing severe intellectual disability. Phenylalanine is found in varying amounts in most foods but is highest in protein-rich foods and aspartame, an artificial sweetener. Early diagnosis and treatment can prevent severe intellectual disability and other health concerns. The phenylalanine levels in the blood determine the severity of the deficiency and can be commonly reported as the following:

- Classic PKU: Untreated phenylalanine levels typically >1,200 µmol/L
- Moderate/mild PAH deficiency: Untreated phenylalanine levels typically ~600–1,200 µmol/L
- Hyperphenylalaninemia: Untreated phenylalanine levels typically 120–360 µmol/L
- Pterin deficiency disorders are due to deficits in the pterin synthesis pathway that make the cofactor for the PAH enzyme, causing high levels of phenylalanine.

What are the signs and symptoms of PKU and related diagnoses?

Symptoms may not be visible at birth. Common symptoms in the first months of life in those with untreated diagnoses include:

- Musty breath, urine, or body odor
- Skin rashes
- Developmental delays
- Intellectual delays
- Neurological symptoms (epilepsy, abnormal or involuntary muscle movement, tremors)

How are these conditions diagnosed?

Infants with a positive newborn screening result should have additional biochemical and molecular testing, including:

- Quantitative analysis of amino acids: should include phenylalanine and tyrosine levels
- Analysis of blood or urine pterins and dihydropteridine reductase enzyme assay
- A gene panel including *PAH* and genes for other disorders that can cause phenylalanine elevations.

Amino acids: Phenylalanine elevation, with or without elevated phenylalanine to tyrosine ratio—Fact Sheet for Providers

How are these conditions treated?

After a diagnosis is confirmed, the overall goal of treatment is to prevent toxic buildup of phenylalanine to reduce the risk of intellectual delay. Primary treatment may include:

- Routine monitoring of phenylalanine levels
- Lifelong low-phenylalanine diet and medical formula
- Tetrahydrobiopterin (BH4)or Sepiapterin supplementation, which can impact PAH activity
- Additional medications such as pegvaliase or other therapies, which are available for older children and adults

How do I handle an abnormal screening result?

Newborn screening measures the phenylalanine level on dried blood spots. If the phenylalanine level is above the cutoff, the result is considered abnormal and requires follow-up biochemical testing. If one of your patients has a positive newborn screening result, you will be contacted by the UNC Newborn Screening Follow-Up team housed within UNC Pediatric Genetics & Metabolism. Follow-up will likely include referring the patient to a pediatric metabolic specialist for follow-up testing.

Where do I go for more information?

Use your phone's camera to scan the QR codes below.

ACMG ACT Sheet

Gene Reviews

Where do I send parents for more information?

Use your phone's camera to scan the QR codes below.

Newborn Screening Information Center

Baby's First Test

National PKU Alliance

MedlinePlus

UNC Pediatric Genetics & Metabolism

NC DEPARTMENT OF HEALTH AND HUMAN SERVICES

State of North Carolina Department of Health and Human Services Division of Public Health

www.ncdhhs.gov

https://slph.dph.ncdhhs.gov/newborn/default.asp

NCDHHS is an equal opportunity employer and provider.

This fact sheet was supported by Health Resources and Services Administration (HRSA), Department of Health and Human Services (HHS) as part of a financial assistance award totaling $344,348, with 100 percent funded by HRSA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA/HHS or the U.S. Government.