ACMG American College of Medical Genetics and Genomics
Translating Genes Into Health®

ACT Sheet

Newborn Screening ACT Sheet

[Elevated Phenylalanine]
Phenylalanine hydroxylase deficiency (PAH)

Differential Diagnosis: Classic phenylketonuria (PKU), mild hyperphenylalaninemia, biopterin cofactor defects including dihydropterine reductase deficiency (DHPR), *DNAJC12*, transient hyperphenylalaninemia, parenteral nutrition, maternal PKU.

Condition Description: Elevated phenylalanine results from a deficiency of the enzyme phenylalanine hydroxylase (PAH) that converts phenylalanine to tyrosine from dietary protein. Hyperphenylalaninemia also results from a deficiency of tetrahydrobiopterin (BH4), a cofactor for PAH and other hydroxylases which is part of the pterin pathway. Defects in *DNAJC12*, which encodes a PAH co-chaperone protein, can present clinically as mild hyperphenylalaninemia. Maternal PKU refers to a pregnant individual with untreated PAH deficiency, which can cause fetal birth defects and developmental delay secondary to the teratogenic effects of increased levels of maternal phenylalanine.

You Should Take the Following Actions:

- Inform family of the newborn screening result.
- Ascertain clinical status (newborns are asymptomatic).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (newborns are asymptomatic).
- Initiate confirmatory/diagnostic testing and management, as recommended by the metabolic specialist.
- Provide the family with basic information about PKU, including dietary management.

- Report final diagnostic outcome to newborn screening program.

Diagnostic Evaluation: Plasma amino acids: Phenylalanine is markedly elevated in classic PKU, with less pronounced elevations in the milder hyperphenylalaninemia variants. The ratio of phenylalanine to tyrosine is also elevated. Urine pterins and DHPR activity from dried blood spots are evaluated to identify rare defects in pterin synthesis or recycling. Additional studies in CSF may also be warranted in rare cases. Molecular genetic testing may be required to clarify the diagnoses.

Clinical Considerations: Neonates with PKU are asymptomatic. If untreated, PKU leads to irreversible developmental delay, hyperactivity, autistic-like features, and seizures. Treatment can prevent these symptoms. Pterin defects cause early severe neurologic disease (developmental delay/seizures) and require specific therapy. Untreated maternal PKU can cause teratogenic birth defects such as cardiac malformations, microcephaly, and growth restriction in the newborn. Lifelong treatment aims to reduce phenylalanine levels to acceptable blood concentrations by dietary restriction of phenylalanine and cofactor supplementation or other emerging therapies. Breastfeeding can be continued under the guidance of a specialist. The clinical phenotype of *DNAJC12* varies from asymptomatic to development delay, autism, and parkinsonism.

Additional Information:

How to Communicate Newborn Screening Results
Emergency Protocols (New England Consortium of Metabolic Programs)
Gene Reviews
Medline Plus
Condition Information for Families- HRSA Newborn Screening Clearinghouse

Referral (local, state, regional, and national):

Find a Genetics Clinic Directory
Genetic Testing Registry

State and Other Resources

State Newborn Screening Program

Newborn Genetic Screening, New Mexico Department of Health
877-890-4692, www.nmhealth.org/about/phd/fhb/cms/nbgs/

Genetics/Metabolic Consultants

Michael Marble, MD
University of New Mexico Metabolic Clinic
505-272-6631, hsc.unm.edu/directory/marble-michael.html

Information for Clinicians and Families

New Mexico Medical Home Portal (see Newborn Disorders and Parents & Families sections)
nm.medicalhomeportal.org/newborn/phenylketonuria

Parent/Family Support

National PKU Alliance
www.npkua.org

National Resources (with web addresses)

Additional Information

How to Communicate Newborn Screening Results
www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/Resources/achdnc-communication-guide-newborn.pdf

Emergency Protocols (New England Consortium of Metabolic Programs)
https://www.newenglandconsortium.org/pku-open-page

Gene Reviews
https://www.ncbi.nlm.nih.gov/books/NBK1504/

Medline Plus
medlineplus.gov/genetics/condition/3-methylglutaconyl-coa-hydratase-deficiency/

Condition Information for Families-HRSA Newborn Screening Clearinghouse
newbornscreening.hrsa.gov/conditions/classic-phenylketonuria

Referral (local, state, regional and national)

Find a Genetics Clinic Directory
clinics.acmg.net

Genetic Testing Registry
www.ncbi.nlm.nih.gov/gtr/