

## Newborn Screening ACT Sheet

### [Elevated Phenylalanine]

## Phenylalanine hydroxylase deficiency (PAH)

**Differential Diagnosis:** Classic phenylketonuria (PKU), mild hyperphenylalaninemia, bipterin 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.

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### **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.

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**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](#)

This practice resource is designed primarily as an educational resource for medical geneticists and other clinicians to help them provide quality medical services. Adherence to this practice resource is completely voluntary and does not necessarily assure a successful medical outcome. This practice resource should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this practice resource. Clinicians also are advised to take notice of the date this practice resource was adopted, and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

## State and Other Resources

### State Newborn Screening Program

Newborn Screening, State of Rhode Island Department of Health  
401-921-7619, [health.ri.gov/newbornscreening/](http://health.ri.gov/newbornscreening/)

### Genetics/Metabolic Consultants

Division of Genetics, Lifespan Physician's Group, Hasbro Children's Hospital  
401-444-4000, [www.lifespan.org/centers-services/childrens-neurodevelopment-center/genetics-and-dysmorphology](http://www.lifespan.org/centers-services/childrens-neurodevelopment-center/genetics-and-dysmorphology)

### Information for Clinicians and Families

Rhode Island Medical Home Portal (see Newborn Disorders and Parents & Families sections)  
[ri.medicalhomeportal.org/newborn/phenylketonuria](http://ri.medicalhomeportal.org/newborn/phenylketonuria)

### Parent/Family Support

National PKU Alliance  
[www.npkua.org](http://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](http://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/](http://medlineplus.gov/genetics/condition/3-methylglutaconyl-coa-hydratase-deficiency/)

Condition Information for Families-HRSA Newborn Screening Clearinghouse  
[newbornscreening.hrsa.gov/conditions/classic-phenylketonuria](http://newbornscreening.hrsa.gov/conditions/classic-phenylketonuria)

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Find a Genetics Clinic Directory  
[clinics.acmg.net](http://clinics.acmg.net)

Genetic Testing Registry  
[www.ncbi.nlm.nih.gov/gtr/](http://www.ncbi.nlm.nih.gov/gtr/)