



## Complete Summary

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### GUIDELINE TITLE

Phenylketonuria: screening and management.

### BIBLIOGRAPHIC SOURCE(S)

Phenylketonuria: screening and management. NIH Consens Statement Online 2000 Oct 16-18;17(3):1-27. [3394 references]

## COMPLETE SUMMARY CONTENT

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## SCOPE

### DISEASE/CONDITION(S)

Phenylketonuria (PKU) and other forms of hyperphenylalaninemia

### GUIDELINE CATEGORY

Management  
Screening  
Treatment

### CLINICAL SPECIALTY

Family Practice  
Internal Medicine  
Medical Genetics  
Nutrition  
Obstetrics and Gynecology  
Pediatrics  
Preventive Medicine

### INTENDED USERS

Advanced Practice Nurses  
Allied Health Personnel  
Dietitians  
Nurses  
Patients  
Physician Assistants  
Physicians  
Social Workers

## GUIDELINE OBJECTIVE(S)

To address the following key questions:

- What are the incidence and prevalence of phenylketonuria (PKU) and other forms of hyperphenylalaninemia and what is known about the genetic and clinical variability?
- What newborn screening strategies are available for diagnosis, what are the effectiveness of these strategies, and what cost-savings are generated by screening and treatment?
- What treatment regimens are used to prevent the adverse consequences of phenylketonuria? What is known about the effectiveness of these treatment and management strategies overall and with respect to variables such as time of initiation of medical nutritional therapy, levels of phenylalanine at various ages, methods for enhancing dietary compliance, duration of dietary management, and dietary regimens for women of childbearing age and other adults?
- What are the recommended strategies for optimal newborn screening and diagnosis and lifelong management and follow-up of phenylketonuria?
- What research is needed to gather information that will optimize the outcomes for individuals with phenylketonuria and their families?

## TARGET POPULATION

- All infants born in the United States
- Patients with classic phenylketonuria (PKU) or non-phenylketonuria hyperphenylalaninemia

## INTERVENTIONS AND PRACTICES CONSIDERED

### Screening/Diagnosis

1. Guthrie Bacterial Inhibition Assay (BIA)
2. Fluorometric analysis
3. Tandem mass spectrometry
4. Mutation analysis and genotype determination

### Management

1. Phenylalanine-restricted diet
2. Periodic measurement of blood phenylalanine levels
3. Review of nutritional intake and nutritional status

## MAJOR OUTCOMES CONSIDERED

### Diagnostic/screening outcomes

- Diagnostic efficacy
- Reliability
- Cost

### Treatment outcomes

- Therapeutic efficacy
- Intellectual, cognitive, and behavioral outcomes (e.g., IQ tests)
- Quality of life
- Treatment adherence
- Metabolic control

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature was searched through electronic databases including MEDLINE (National Library of Medicine [NLM]), and an extensive bibliography of references was provided to the panel and the conference audience.

### NUMBER OF SOURCE DOCUMENTS

Not stated

### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Scientific evidence was given precedence over clinical anecdotal experience.

### METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis  
Review of Published Meta-Analyses  
Systematic Review

### DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

#### METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

#### DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The National Institutes of Health (NIH) Consensus Development Panel, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference.

#### RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

#### COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

#### METHOD OF GUIDELINE VALIDATION

Peer Review

#### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The National Institutes of Health (NIH) Consensus Development Panel on Phenylketonuria: Screening and Management finalized the revisions within a few weeks after the conference. The draft statement was made available on the World Wide Web immediately following its release at the conference and was updated with the panel's final revisions.

## RECOMMENDATIONS

#### MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC):

#### Comprehensive Approach to Lifelong Care

A programmatic, multidisciplinary approach to lifelong care is required for the treatment of phenylketonuria (PKU) with sensitivity to the transition from screening to treatment. Continuity of care from infancy through adulthood is considered medically necessary for optimal outcomes for individuals with phenylketonuria. Treatment guidelines should be established that are consistent

across clinical facilities in the United States that serve individuals with phenylketonuria and their families so they can expect consistent treatment. Equal access to treatment for all individuals with phenylketonuria is highly desirable. Current barriers to access include inconsistent policies on the part of third-party payers, Medicaid/Medicare, and other State and Federal entities concerning funding of medical foods and low-protein products, follow-up for metabolic control, and psychosocial support and educational programs. Mandated screening for phenylketonuria implies a societal responsibility for comprehensive long-term follow-up and treatment. Outcome monitoring should consist of periodic medical, nutritional, intellectual, neurological, neuropsychological, and behavioral assessment. Access to medical foods is essential for maintenance of metabolic control throughout life. Specialized medical foods and low-protein products are a medical necessity and should be treated as such. Reimbursement for these medical foods and products should be covered by third-party providers. Many State programs and third party payors have an age limit for counseling and funding of treatment, which deny access to treatment for life.

#### Age of Initiation of Treatment for Infants With Phenylketonuria

Treatment of neonates born with phenylketonuria should be initiated as soon as possible, but no later than 7 to 10 days after birth. Phenylalanine levels should be reduced as rapidly as possible. Breastfeeding is encouraged along with phenylalanine-free formula. Because of the need for early initiation of treatment, hospitals should ensure that screening samples are obtained within 12 hours of birth and sent for analyses within 24 hours of collection, and that results are returned to responsible parties within 7 days of an infant's birth.

#### Recommended Levels of Phenylalanine for Classical Phenylketonuria

Maintenance of phenylalanine levels between 2 to 6 mg/dL for neonates through 12 years of age appears to be medically necessary for ensuring optimal outcome. Furthermore, in light of findings that phenylalanine levels are related to cognitive function in adolescents and adults, it is recommended that phenylalanine levels be maintained between 2 to 15 mg/dL after 12 years of age. Considering the paucity of data on the relationship between phenylalanine level and brain function after 12 years of age, and the fact that brain development is ongoing during adolescence, even lower phenylalanine levels (between 2 to 10 mg/dL) are strongly encouraged during this age period. Related to achievement of these levels, treatment decisions need to consider factors related to individual differences in inherent metabolic control, gender, age, childbearing status, and behavioral and cognitive functioning.

#### Frequency of Phenylalanine Monitoring

The frequency of phenylalanine monitoring will vary according the individual's needs. Suggested guidelines are as follows:

- a. Once weekly during the first year
- b. Twice monthly from 1 to 12 years of age
- c. Monthly after 12 years of age
- d. Twice weekly during pregnancy of a woman with phenylketonuria

There should be increased emphasis on patient participation in monitoring programs with age, and recognition that individual factors, such as inherent metabolic control, age, and childbearing status, will influence decisions regarding frequency of monitoring. Development of a reliable home-testing method is recommended, as well as measures to increase adherence.

### Duration of Dietary Treatment

The goal in the treatment of phenylketonuria is to maintain metabolic control of phenylalanine for optimal adaptation and outcome. Treatment will vary to some extent depending on each individual's characteristics. To achieve optimal metabolic control and outcome, a restricted-phenylalanine diet, including medical foods and low-protein products, most likely will be medically required for virtually all individuals with classical phenylketonuria for their entire lifetimes. Although no definitive studies on the effects of dietary treatment in adults exist, data suggest that elevated phenylalanine levels in adolescents and adults adversely affect aspects of cognitive function, and individual case reports have documented deterioration of adult phenylketonuria patients after diet discontinuation. Persons who have discontinued the diet should contact their clinic or treating physician(s) to evaluate the need or advisability of resuming dietary treatment. It is also recommended that clinic personnel attempt to contact persons with phenylketonuria to advise them of current treatment guidelines and practices.

### Maternal Phenylketonuria

It is recommended that phenylalanine levels below 6 milligrams per deciliter (mg/dL) be achieved at least 3 months before conception. Therefore, outreach and educational programs for adolescents and women of childbearing age, which focus on social support, positive attitudes toward metabolic control of phenylalanine and its effectiveness, family planning, conscious reproductive choice, and information related to the management of maternal phenylketonuria, are strongly recommended. Participation in such programs should occur before planned pregnancy so that optimal metabolic control of phenylalanine can be obtained before conception. If conception occurs when the woman is not in metabolic control, counseling should be offered. Metabolic control should be achieved as soon as possible, and monitoring of phenylalanine levels should occur twice weekly, at a minimum, once per week. The recommended level is 2 to 6 mg/dL during pregnancy. Focusing on the overall nutritional status of the pregnant mother, including adequate intake of protein, fat, energy, minerals and vitamins, particularly folic acid and B<sub>12</sub>, and other nutrients is essential. Furthermore, a comprehensive approach that provides psychosocial support for the family as a whole and continuity of care for infants should be developed and followed. Parenting classes that focus on infant stimulation and maternal mental health (e.g., maternal depression) and adherence to dietary treatment may be indicated for high-risk mothers. Social support systems are especially important in such instances.

### Screening and Treatment of Previously Untreated Patients

Individuals with mental retardation and/or severe behavioral disturbances of undetermined etiology, such as hyperactivity, aggression, self-injurious behavior, and pica, should be screened for phenylketonuria regardless of the individual's

age. Individuals with mental retardation due to phenylketonuria who are experiencing severe behavioral disturbances should be considered for dietary treatment lasting for at least 6 months, because metabolic control has been reported to improve behavior in such patients.

### Uniform Standards

States should adopt a uniform definition of the phenylalanine level for establishing the diagnosis of phenylketonuria and non-phenylketonuria hyperphenylalaninemia. Standardized reporting of data must include the number of individuals with phenylketonuria and non-phenylketonuria hyperphenylalaninemia, the number of individuals tested, and reports by gender and self-reported ethnicity.

### Genotyping

Mutation analysis and genotype determination should be accomplished on all persons with phenylketonuria for initial diagnosis, genetic and management counseling, follow-up, and long-term prognosis. Additional laboratories capable of performing genotype analysis will need to be developed. Optimal therapeutic management might in time require mutation analysis. Information about mutation frequency can be useful for calculating allele frequency and incidence of phenylketonuria.

### Storage and Use of Samples

States and others who store samples should develop a policy that addresses the following issues surrounding the storage and use of blood samples remaining after newborn screening:

- Length of time that all samples will be stored
- Ownership of samples
- Uses, other than the follow-up of newborn screening, which will be allowed and under what conditions
- Informed consent procedures

### Development of a Systems-Oriented Program for Screening

Newborn screening strategies should take a total systems approach. This system needs to include the following:

- A method for sending samples to the laboratory for analysis within 24 hours of collection.
- A standard approach nationwide of reporting abnormal results that leads to the referral of the newborn into appropriate care for diagnostic evaluation and management.
- Assurance that infants and families have access to the full complement of services necessary to treat the disorder (i.e., physicians, geneticists, dietitians, and other health care professionals with expertise in treatment of metabolic disorders, genetic counseling, nursing, psychological and social

- services, medical food protein sources, and age-appropriate low-protein modified products).
- Clinical services that meet the needs of the adolescent and adult individual with phenylketonuria.

### New Laboratory Technologies

Adoption of new laboratory technologies should be based upon benefits to the screened population, improvements in sensitivity and specificity of testing, and cost effectiveness. Instrumentation that quantitatively measures phenylalanine and tyrosine concentrations is beneficial in the early positive identification of phenylketonuria, while reducing the incidence of false-positive results. Any new laboratory technology must be thoroughly evaluated and carefully implemented to avoid temporary or long-term negative effects on established phenylketonuria screening programs.

### Regionalization

Often, especially for States with smaller populations, regional associations for phenylketonuria screening and therapeutic oversight will provide greater laboratory and patient care efficiencies and will promote common standards.

### Conclusions

- Genetic testing for phenylketonuria has been in place for almost 40 years and has been very successful in the prevention of severe mental retardation in thousands of children and adults. Many questions, however, remain unanswered.
- Metabolic control is necessary across the lifespan of individuals with phenylketonuria.
- A comprehensive, multidisciplinary, integrated system is required for the delivery of care to individuals with phenylketonuria.
- Consistency and coordination among screening, treatment, data collection, and patient support programs is greatly needed.
- There should be equal access to culturally sensitive, age-appropriate treatment programs.
- Ethically sound, specific policies for storage, ownership, and use in future studies of archived samples remaining from phenylketonuria testing should be established.
- Research into the pathophysiology of phenylketonuria and relationship to genetic, neural, and behavioral variation is strongly encouraged.
- Uniform policies need to be established to remove from the individual and the family financial barriers to the acquisition of medical foods and modified low-protein foods, as well as to provide access to support services required to maintain metabolic control in individuals with phenylketonuria.
- Research on nondietary alternatives to treatment of phenylketonuria is strongly encouraged.
- To achieve optimal statistical power, as well as cross-cultural applicability, it will be beneficial to use data acquired via national and international collaboration.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The panel, answering predefined questions, developed their conclusions based on a comprehensive review of scientific evidence presented in open forum. Scientific evidence was given precedence over clinical anecdotal experience.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Infants who are diagnosed early in the newborn period and treated to achieve good metabolic control, have normal health and development and can likely expect a normal life span.

### POTENTIAL HARMS

Not stated

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

This statement is an independent report of the panel and is not a policy statement of the National Institutes of Health (NIH) or the Federal Government.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness  
Staying Healthy

### IOM DOMAIN

Effectiveness  
Patient-centeredness

BIBLIOGRAPHIC SOURCE(S)

Phenylketonuria: screening and management. NIH Consensus Statement Online 2000 Oct 16-18;17(3):1-27. [3394 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Oct 18

GUIDELINE DEVELOPER(S)

National Institute of Child Health and Human Development - Federal Government Agency [U.S.]  
National Institutes of Health (NIH) Consensus Development Panel on Phenylketonuria Screening and Management - Independent Expert Panel

GUIDELINE DEVELOPER COMMENT

National Institutes of Health (NIH) Consensus Statements are prepared by a non-advocate, non-Federal panel of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session; (2) questions and statements from conference attendees during open discussion periods that are part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the National Institutes of Health (NIH) or the Federal Government.

This conference was presented by the National Institute of Child Health and Human Development and the National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR). The co-sponsors included the National Human Genome Research Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute of Nursing Research, the National Institutes of Health (NIH) Office of Rare Diseases, and the Maternal and Child Health Bureau of the Health Resources and Services Administration.

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

National Institutes of Health (NIH) Consensus Development Panel on Phenylketonuria: Screening and Management

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: R. Rodney Howell, MD (Panel and Conference Chairperson); Aravinda Chakravarti, PhD; Geraldine Dawson, PhD; Claibourne I. Dungy, MD, MPH; Jack M. Fletcher, PhD; Desirée Jackson, PhD; Mark S. Kamlet, PhD; Felissa R. Lashley, PhD, RN; Bonnie S. LeRoy, MS; Mary Courtney Moore, PhD, RN, RD; Patti J. Patterson, MD, MPH; William B. Rizzo, MD; M. Anne Spence, PhD; Stephanie Stremer.

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All of the panelists who participated in the National Institutes of Health (NIH) conference and contributed to the writing of this consensus statement were identified as having no financial or scientific conflict of interest, and all signed conflict of interest forms attesting to this fact.

## ENDORSER(S)

Maternal and Child Health Bureau-Health Resources and Services Administration - Federal Government Agency [U.S.]  
National Human Genome Research Institute - Federal Government Agency [U.S.]  
National Institute for Nursing Research - Federal Government Agency [U.S.]  
National Institute of Diabetes and Digestive and Kidney Diseases (U.S.) - Federal Government Agency [U.S.]  
National Institute of Neurological Disorders and Stroke - Federal Government Agency [U.S.]  
Office of Rare Diseases (NIH) - Federal Government Agency [U.S.]

## GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

## GUIDELINE AVAILABILITY

Electronic copies: Available from the [NIH Consensus Development Conference Program Web site](#). Also available from the [National Library of Medicine Health Services/Technology Assessment Text \(HSTAT\) Web site](#).

Print copies: Available from the NIH Consensus Development Program Information Center, PO Box 2577, Kensington, MD 20891; Toll free phone (in U.S.), 1-888-NIH-CONSENSUS.

## AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- A complete bibliography prepared by the National Library of Medicine (NLM) is available at the [NLM Web site](#).

## PATIENT RESOURCES

None available

## NGC STATUS

This summary was completed by ECRI on May 23, 2001. The information was verified by the guideline developer as of October 23, 2001.

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