Screening for Phenylketonuria: A Literature Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective
Phenylketonuria (PKU) is a clinical disorder resulting from an inborn error of metabolism. PKU, if untreated, results in neurological damage, including severe mental retardation. In order for the U.S. Preventive Services Task Force (USPSTF) to update its 1996 recommendation statement on screening for PKU, a literature search was performed to search for new evidence related to universal PKU screening of newborns.

Methodology
We performed a targeted search of the medical literature from January 1995 to May 2006 and consulted with subject matter experts. PubMed, the Cochrane Library, and the Centre for Reviews and Dissemination databases were searched in order to identify systematic reviews and randomized controlled trials.

Results
Recent reviews have focused on the effectiveness of early dietary interventions on development and intelligence quotient (IQ) scores.

Conclusions
There is no new and substantial evidence to change the current USPSTF recommendation on PKU screening.

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Introduction

Phenylketonuria (PKU) is a clinical disorder resulting from an inborn error of metabolism. A deficiency of the hepatic enzyme phenylalanine hydroxylase leads to accumulation of phenylalanine in the blood and tissues, which subsequently results in high urine levels of phenylketones. PKU, if untreated, results in neurological damage, including severe mental retardation and seizures. An affected newborn will usually appear normal during the first few months of life. However, by 6-12 months of age, signs of impaired development are present and irreversible. Treatment for PKU involves early dietary restriction of phenylalanine.(1)

The reported incidence of PKU in the United States ranges from 1 in 19,000 to 1 in 13,500 newborns.(2) This variation in reported incidence is due to differing definitions of hyperphenylalaninemia. Incidences vary by ethnic background, with a higher incidence of PKU seen in newborns of American Indian, Alaska Native, and Northern European descent. Other risk factors include genetic mutations affecting any of 400 possible genetic mutations of phenylalanine hydroxylase (PAH) locus on chromosome 12q24.1(2)

Newborn PKU screening in the U.S. is performed using one of three available tests: the Guthrie bacterial inhibition assay (BIA), fluorometric analysis, or tandem mass spectrometry (MS/MS). Screening tests are most accurate if performed after 24 hours of life but before the infant is 7 days old. Currently, all 50 states plus the District of Columbia require newborn PKU screening; however all but 2 permit parents to refuse the test.(3) A few states require a second screening if the initial screen was performed in the first 24 hours of life. (2)

In 1996, the U.S. Preventive Services Task Force (USPSTF) recommended screening for PKU in all newborns prior to discharge from the nursery.(4) In 2006, the USPSTF decided to update its recommendation statement on screening for PKU. Noting that its 1996 recommendation was made on a strong evidence base, and that it would take large, high-quality studies or evidence of substantial harms to overturn the current recommendation, the USPSTF chose to perform a reaffirmation update for this topic. The USPSTF performs reaffirmation updates for well-established, evidence-based standards of primary care practice that remain USPSTF priorities, are within the scope of the USPSTF, and for which there is compelling reason for the USPSTF to have a current recommendation statement. While the Task Force would like these recommendations to remain active and current as a part of its library of preventive services, it has determined

that only a very high level of evidence would change the recommendation. For this reason and to maximize resources, a limited review of the evidence is conducted.

Methods

To assist the USPSTF in updating the 1996 recommendation on Screening for PKU, staff at the Agency for Healthcare Research and Quality (AHRQ) performed a literature search and consulted content experts. The databases searched were PubMed, the Cochrane Library, and the Centre for Reviews and Dissemination. We used the following search terms: "phenylketonuria" and "screening," and limited the search to: newborns: birth-1 month, English, Publication Date from 01/01/1995 to 05/12/2006, and "core clinical journals." The search returned 52 titles, which were entered into an Endnote database. Twenty-four studies were excluded at the title stage; 9 studies were excluded at the abstract stage; and 17 were excluded at the full article stage. Exclusion criteria are listed in the Appendix. Numbers and reasons for exclusion were: 18 for "study design", 13 for "not PKU", 4 for "not newborn", 4 for "not screening", 4 for "too old", 3 for "no outcomes", 3 for "not English", and 1 for "other" (not published). Two studies met the inclusion criteria and are discussed below.

Results

A recent systematic review by Pandor and colleagues examined the evidence base for neonatal PKU screening in the United Kingdom; this review updated two previously published reviews by Pollitt and Seymour.(1, 5, 6) The Pandor review included two Cochrane systematic reviews and 5 other studies that provided information about the prevalence of PKU or evaluated the clinical effectiveness of different treatments for PKU. The Pandor review reported that early dietary interventions were effective in reducing the severity of developmental delay. Meta-analysis of 4 randomized controlled trials (RCT) from the included Cochrane review demonstrated significantly lower blood phenylalanine concentrations in patients with PKU who followed a phenylalanine-restricted diet compared to patients with less restricted diets. One of the studies in the review demonstrated a significantly higher intelligence quotient (IQ) score in patients who continued to follow a restricted diet compared to patients who did not (weighted mean difference of -5.0; 95% CI -9.595 to -0.405, $p = 0.03$). The report cited a lack of evidence regarding specific levels of phenylalanine restrictions or the appropriate time to lessen the dietary restrictions. Results from a cross-sectional study showed that delaying the termination of dietary restrictions until 10 years of age is adequate to prevent marked reductions in cognitive and motor abilities; however, the results also showed that there may be subtle intellectual deficiencies both during and after treatment.(1)

One study on harms was found. This study used the National Newborn Screening Reports of 1993 and 1994 from the Council of Regional Networks for Genetic Services (CORN) to evaluate the total number of false positives from the screening of PKU, galactosemia, biotinidase deficiency, congenital hypothyroidism, and congenital adrenal hyperplasia.(7) This Council collects and publishes annual tabulated data on newborn screening from all regions of the U.S. The positive predictive value for PKU screening was 2.7% and 3.2%

in 1993 and 1994, respectively. These values were calculated using reported “confirmed cases” as a gold standard, but no information was given about how cases were confirmed.(7)

Conclusions

In summary, there is no new and substantial evidence that would be of adequate weight and quality to change the current USPSTF recommendation on PKU screening.

Appendix
Exclusion Codes for the PKU Literature Search

Code	Description
High Risk	High risk population or special population
Study Design	Not appropriate study type (See Reaffirmation methods for types excluded – harms, benefits)
Not PKU	A study not on PKU
Not US	Study in a population not generalizable to the U.S.
Not Newborn	Studies in adults or older children
No Outcomes	Studies without information on appropriate PKU-specific harms or benefit outcomes
Not Screening	Studies of benefits of interventions other than screening
Not English	A study in a language other than English
Too Old	Published outside of search dates or newer update of study available
Other	

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