NIH Consensus Statement

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Phenylketonuria (PKU): Screening and Management

NATIONAL INSTITUTES OF HEALTH
Office of the Director

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Phenylketonuria (PKU): Screening and Management

This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge of the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

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Disclosure Statement

All of the panelists who participated in this 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. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on NIH consensus panels are selected specifically because they are not professionally identified with advocacy positions with respect to the conference topic or with research that could be used to answer any of the conference questions.

Abstract

Objective

To provide health care providers, patients, and the general public with a responsible assessment of currently available data regarding screening for, and management of, phenylketonuria (PKU).

Participants

A non-Federal, non-advocate, 14-member panel representing the fields of pediatrics, genetics, human development, public policy, nursing, molecular physiology, and including patient representatives. In addition, 19 experts in pediatrics, medical genetics, psychology, pediatric neurology, biochemical and molecular genetics, and gene therapy presented data to the panel and to a conference audience of more than 300.

Evidence

The literature was searched using MEDLINE and an extensive bibliography of references was provided to the panel. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus Process

The 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. The panel 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.

Conclusions

Genetic testing for PKU 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. Metabolic control is necessary across the lifespan of individuals with PKU. A comprehensive, multidisciplinary, integrated system is required for the delivery of care to individuals with PKU. Greatly needed are consistency and coordination among screening, treatment, data collection, and patient support programs. 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 PKU testing should be established. Research into the pathophysiology of PKU 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 PKU. Research on nondietary alternatives to treatment of PKU 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.

Introduction

Classical phenylketonuria (PKU) is a rare metabolic disorder (and orphan disease) that usually results from a deficiency of a liver enzyme known as phenylalanine hydroxylase (PAH). This enzyme deficiency leads to elevated levels of the amino acid phenylalanine (Phe) in the blood and other tissues. The untreated state is characterized by mental retardation, microcephaly, delayed speech, seizures, eczema, behavior abnormalities, and other symptoms. Approximately one of every 15,000 infants in the United States is born with PKU.

Because effective treatments exist to prevent symptoms, all states screen infants for PKU. The current treatment for this disorder involves strict metabolic control using a low-Phe diet that includes specialized medical foods. The newborn screening programs for PKU have been remarkably successful: infants, when 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.

Metabolic control of PKU can be difficult to achieve, and poor control can result in significant decline of mental and behavioral performance. Women with PKU must also maintain strict metabolic control before and during pregnancy to prevent fetal damage. Scientists are actively exploring nondietary treatments for PKU.

Research on PKU continues to broaden the knowledge base from which informed decisions regarding screening and treatment can be made. The National Institute of Child Health and Human Development and the NIH Office of Medical Applications of Research organized this conference to evaluate the scientific data on PKU screening and management. After a day and a half of expert presentations and public discussion of the biology and biochemistry of PKU, epidemiology and genetics, screening strategies, and treatment regimens, an independent, non-Federal panel weighed the scientific evidence and drafted a statement that was presented on the third day.

The consensus development panel's statement addressed the following questions:

- What are the incidence and prevalence of 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 is 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 PKU? 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?
- Based on this information, what are the recommended strategies for optimal newborn screening and diagnosis and lifelong management and followup of PKU?
- What research is needed to gather information that will optimize the outcomes for individuals with PKU and their families?

What are the Incidence and Prevalence of PKU and Other Forms of Hyperphenylalaninemias, and What is Known About the Genetic and Clinical Variability?

Hyperphenylalaninemia results from impaired metabolism of Phe due to deficient activity of the enzyme PAH. Persons with PKU have a complete absence or profound deficiency of enzyme activity, typically show very high elevations of blood Phe (>20 mg/dL), and accumulate phenylketones. A partial deficiency of PAH results in non-PKU hyperphenylalaninemia and a lower degree of blood Phe elevation without phenylketone accumulation. Both forms of hyperphenylalaninemia, which account for the vast majority of cases, are autosomal recessive disorders caused by mutations in the PAH gene. Rarely, mutations in other genes that are necessary for the synthesis or recycling of the tetrahydrobiopterin cofactor of PAH also result in hyperphenylalaninemia, but will not be addressed in this consensus statement.

Incidence and Prevalence

Newborn screening has been under way for nearly 40 years in the United States. Nevertheless, little useful data are available regarding the incidence and prevalence of PKU and other forms of hyperphenylalaninemia. Data from the 1994 Newborn Screening Report of the Council of Regional Networks for Genetic Services (CORN) were used to address the incidence of this clinically heterogeneous metabolic disease. The nature of the data allows only an estimate of the PKU and non-PKU hyperphenylalaninemia incidence. For PKU, the reported incidence ranges from 1 per 13,500 to 1 per 19,000 newborns. For non-PKU hyperphenylalaninemia, a wide range of variation in reporting exists among states, resulting in a composite estimate of 1 per 48,000 newborns. The report also identified large variations in the incidence of PKU by ethnic group: a higher incidence in Whites and Native Americans, and a lower incidence in Blacks, Hispanics, and Asians.

The data available in the CORN report are limited, and there is nonuniformity concerning the blood Phe levels used by individual states for defining positive screening tests. Definitions of classical PKU and non-PKU hyperphenylalaninemia vary. Some states failed to report data by sex and ethnicity, and two failed to report the total number of newborns screened. Also, some state laboratories were noncompliant with regard to reporting newborn screening data. Instances where data from first screens were not reported separately from followup test results added to the dilemma. In contrast to incidence, composite data were unavailable on the prevalence of PKU and non-PKU hyperphenylalaninemias.

Genetic and Clinical Variability

Like all genetic disorders, PKU demonstrates extensive genetic and clinical variability. The PAH gene is a single locus with more than 400 identified different mutations, including deletions, insertions, missense mutations, splicing defects, and nonsense mutations. The fact that most individuals with PKU are compound heterozygotes generates the potential for numerous possible genotypic combinations and undoubtedly contributes to the clinical heterogeneity. These mutations also contribute to the biochemical heterogeneity and may be chiefly responsible for the biochemical phenotype. Genetic contributions to the phenotype are complex, consisting of documented allelic heterogeneity within the PAH gene. Certain PAH alleles are associated with non-PKU hyperphenylalaninemia and others with PKU. In addition, genes at other loci may influence Phe transport within the brain and the size and metabolic control of the Phe pool. This molecular heterogeneity for PKU results in wide phenotypic heterogeneity, contributing to biochemical individuality. In some cases, predicting enzymatic activity based on the PAH genotype may be possible. The relationship between the clinical phenotype and the genotype, however, is not always constant.

The existence of discordant phenotypes among siblings who share the same genotype at the PAH locus implies the existence of other genetic and environmental factors that influence clinical phenotype. The presence of modifier genes would be consistent with clinical variation, but modifier genes have not yet been identified. Indeed, a small number of individuals with PKU have no mental retardation even without dietary treatment. There is variation in the transport of Phe into the brain, which may explain, in part, different clinical symptoms and severity. The pathophysiologic mechanisms leading to mental retardation are undoubtedly complex. Evidence implicates Phe as the "toxic" agent in PKU. Hyperphenylalaninemia inhibits the transport of large, neutral amino acids (LNAA) into the brain. Reduction of LNAA in the brain is thought to cause inhibition of protein synthesis and neurotransmitter synthesis leading to deficient dopamine and serotonin levels. Studies are beginning to explore the relationship between specific genotypes and response to supplementation with tetrahydrobiopterin, the cofactor for PAH.

The observed clinical variability among individuals is partly due to these genetic factors, but environmental and lifestyle factors undoubtedly contribute to the variation. For example, age at diagnosis, age at commencement of metabolic control, and degree of metabolic control can explain the variation between two individuals with genetically identical mutations. Moreover, the variation observed depends on the specific trait examined, whether it is mental retardation in untreated cases, blood Phe level, neurological and neuropsychiatric deficits, or brain Phe concentration. There are no data yet on the clinical manifestations of PKU as early treated individuals age, because few are past 40 years of age. Consequently, new clinical features of PKU may become evident over time, and there is no scientific basis from which to predict future clinical outcomes.

What Newborn Screening Strategies Are Available for Diagnosis, What Is the Effectiveness of These Strategies, and What Cost-Savings Are Generated By Screening and Treatment?

Since the early 1960s, newborn infants in the United States have been screened for PKU through the collection of neonatal blood samples on special paper cards within the first days of life. Blood samples are evaluated for the presence of abnormally elevated levels of Phe, and those infants found to have high levels of Phe are referred for diagnostic evaluation and comprehensive treatment and care.

Screening Strategies

The three main laboratory methods used for population-based screening of newborns for PKU in the United States are the Guthrie Bacterial Inhibition Assay (BIA), fluorometric analysis, and tandem mass spectrometry. The Guthrie BIA is inexpensive, relatively simple, and reliable. Fluorometric analysis and tandem mass spectrometry are quantitative, can be automated, and produce fewer false positives than BIA. Tandem mass spectrometry has the ability to simultaneously obtain tyrosine levels that can be used to assist in the interpretation of Phe levels and the identification of numerous other metabolic disorders on a single sample.

Effectiveness

Effective screening of newborn infants for PKU requires competence in a number of complex, interrelated systems: specimen collection; specimen transport and tracking; laboratory analysis; data collection and analysis; locating and contacting families of infants with abnormal results; diagnosis; treatment; and long-term management, including psychological, nursing, and social services and medical nutritional therapy, genetic, and family counseling. Although the U.S. screening programs have been highly effective, there is concern that individuals with PKU could be missed. This could occur at any step in the process — in collection

of specimens, laboratory procedures, or initiation of treatment and clinical followup. Although missing an individual with PKU through screening is considered to be extremely rare, there are few recent data available to accurately determine the magnitude of the problem or to define the actual cause of the missed cases. Home births and early hospital discharge may contribute to missed cases.

All states include PKU testing in their newborn screening programs. Through these programs, the nation has been quite successful in identifying children affected with PKU and in preventing the mental retardation associated with PKU through comprehensive treatment and care. Nonetheless, there is great variation in practice in all areas of newborn screening protocols in the United States. All but four states permit parental refusal. Even criteria for defining a positive PKU screen varies among states. Some states have newborn screening advisory boards to guide policy decisions, while others rely on state health department staff. Some states fund their programs by charging fees; other programs are supported only by appropriated funds. For states that charge a fee, some bill patients, while others bill referring physicians, hospitals, or third-party payers. Funding sources and the services covered vary greatly. The levels of followup services also vary immensely. The availability of psychological nursing services, social services, genetic counseling, medical nutrition therapy, parent education about PKU, medical foods, and modified low-protein foods, and the resulting economic burden on families also show discrepancies. Many families require these and other ancillary services to address difficulties in school, family problems, and behavioral disorders. Because of this variation in practice, not all newborns and their families have access to the same level of care.

States also differ in policies relative to how information is provided to parents concerning test results and whether parents can decline testing of their children. In addition, there appears to be a lack of explicit policies regarding retention, ownership, and use of blood specimens for purposes other than PKU detection.

Cost Savings

Most economic analyses of PKU screening are more than 10 years old. Methodological approaches vary widely among the studies. All published studies, however, find that PKU screening and treatment represent a net direct cost savings to society, although the analyses assume 100 percent compliance, and typically exclude the costs of operating data systems and follow-up components of a newborn screening program.

What Treatment Regimens Are Used to Prevent the Adverse Consequences of PKU?

What Is Known About the Effectiveness of These Treatment and Management Strategies Overall and with Respect To Variables Such As Time of Initiation of Dietary Management, Levels of Phenylalanine at Various Ages, Methods for Enhancing Dietary Compliance, Duration of Dietary Management, and Dietary Regimens for Women of Child-Bearing Age and Other Adults?

Implementation of a Phe-restricted diet early in life can significantly reduce mental deficiencies associated with PKU. Professionals agree that infants with PKU who have blood Phe levels > 10 mg/dL should be started on treatment to establish metabolic control of Phe levels as soon as possible, ideally by the time the neonate is 7–10 days of age. Most physicians will begin medical nutritional therapy in newborns with levels between 7–10 mg/dL that persist more than a few days. Before starting treatment, however, tetrahydrobiopterin deficiency must be excluded.

Metabolic control via medical nutrition therapy involves the use of medical foods including medical protein sources and modified low-protein products in addition to the provision of required amounts of Phe through small amounts of natural protein. The response is monitored through periodic measurement of blood Phe levels in conjunction with analysis of nutritional intake and review of nutrition status. Metabolic control via dietary treatment, however, is only one component of a comprehensive treatment program.

There is no consensus concerning optimal levels of blood Phe, either across different countries or among treatment centers in the United States. The British policy for dietary treatment recommends that blood Phe levels in infants and young children be maintained between 2–6 mg/dL with relaxation of Phe levels after childhood. The British policy statement, however, acknowledges that these higher limits in older children may be associated with impaired cognitive

performance. The German Working Group for Metabolic Diseases recommended that Phe levels be maintained between 0.7–4 mg/dL until the age of 10 years, 0.7–15 mg/dL between 10 and 15 years, and 0.7–20 mg/dL after 15 years, along with a need for lifelong followup to evaluate for possible late sequelae. Criteria in France are similar. Formally recommended guidelines for blood Phe levels do not exist in the United States. The most commonly reported blood Phe recommendations in U.S. clinics are 2–6 mg/dL for individuals $\leq$ 12 years and 2–10 mg/dL for persons more than 12 years of age.

Frequent monitoring of blood levels of Phe is necessary especially during the early years of life, with less frequent monitoring as age increases. Current practices relative to the frequency of monitoring during the first year vary from once every week to once a month, with once a week being more common. Frequencies after 1 year of age range from once every month to once every 3 months, with monitoring occurring approximately once a month by 18 years of age in most U.S. clinics.

Surveys of clinical practices suggest that most clinics advocate lifelong dietary treatment for metabolic control of blood Phe levels. Reinstitution of diet after discontinuation is very difficult and requires expertise in issues of adherence. Issues pertaining to adherence, cost of treatment, independence, and pre-pregnancy management become salient during adolescence and young adulthood.

Somatic gene therapy for PKU is currently being explored in animal model studies and holds promise for the possible treatment for PKU in the future. Other avenues involving enzymes that degrade Phe in the digestive system also hold promise. Supplementation of diet with a variety of additives has not borne fruit, but is an active area of research.

Efficacy of Treatments for Early-Treated PKU

Questions remain concerning the extent to which individuals treated early for PKU demonstrate subtle problems involving cognitive functions, school achievement, behavioral adjustment, and quality of life. Related issues concern how early to begin treatment, effects of fluctuations in metabolic control, level of optimal metabolic control, and relaxation of metabolic control. Controversy surrounds these issues.

Many studies of intellectual, cognitive, and behavioral outcomes have attempted to address treatment efficacy. There are limitations to these studies, however, including small samples, inconsistent use of comparison groups, and excessive reliance on intelligence tests as the primary outcome measure. Given this situation, the panel carefully reviewed the literature and commissioned an empirical synthesis of these studies via meta-analysis.

Although many individuals with PKU manifest no cognitive and behavioral deficits, many comparisons of individuals with PKU to controls show lower performance on IQ tests, with larger differences in other cognitive domains. Children with PKU score somewhat lower than expected on IQ tests based on parent and sibling IQs, but their performance is still in the average range. Evidence for differences in behavioral adjustment is inconsistent despite anecdotal reports suggesting greater risk for internalizing psychopathology and attention disorders. The mechanism mediating this phenotypic variation is unknown, and current hypotheses are inadequate for accounting for this variation.

Age at treatment initiation and level of metabolic control clearly influence outcomes. There is an inverse relationship between age at treatment initiation and IQ even in early treated PKU. Moreover, new evidence suggests that high plasma Phe levels during the first 2 weeks of life can affect the structural development of the visual system. Although the visual deficits are mild, this warrants efforts at earlier treatment initiation.

The degree of metabolic control is related to the development of cognitive skills and behavioral adjustments. Those with poorer metabolic control, i.e., elevated Phe levels, show significantly lower scores on measures of IQ, attention, and reaction time. Similarly, levels of Phe show moderate relationships with performance on measures of cognitive functions and the presence of behavioral difficulties. These studies combine results from children and adults who vary widely in age, but the evidence suggests that good metabolic control is associated with better cognitive performance across the lifespan.

Dietary discontinuance before 8 years of age is associated with poorer performance on measures of IQ. The effects of dietary discontinuance at older ages (12 years and above) are less clear. Adults with PKU who are not on restricted diets show stable IQ scores, but also manifest poorer performance on measures of attention and speed of processing. Thus, European countries do not recommend complete discontinuance of the restricted diet. Higher levels of Phe are accepted with frequent monitoring. Evidence shows that the individual with PKU must be maintained on a lifelong restricted Phe diet, though some relaxation may be tolerable, in some cases, as the individual ages.

Adherence to Treatment Regimens

The treatment of PKU is complex, requiring regular collection of blood samples, recording of food intake, maintenance of a highly restrictive diet, and regular and frequent visits to a PKU clinic. Barriers to adherence include factors associated with the treatment regimen itself, as well as economic resources, psychosocial issues, social and emotional factors, and health care system issues.

A coordinated approach to the treatment of PKU is required, necessitating development of a comprehensive, multidisciplinary, integrated system for delivery of care. Crucial to achieving adherence to treatment is assurance of equal access to routine monitoring and care, including periodic monitoring; initial and ongoing patient and family education; patient follow-up by physicians, dieticians, nurses, social

workers, and other members of the health care team; and low- or no-Phe medical foods and modified low-protein foods. Adherence improves if individuals with PKU have a social support system, positive attitudes regarding the benefits of treatment, and a belief that PKU is manageable in their daily lives. Creative use of community and regional-based support mechanisms hold promise for improving adherence to the comprehensive PKU treatment regimen.

Metabolic Control in Women of Child-Bearing Age

Metabolic control in women planning conception and those whose pregnancies are unplanned is important because of the serious consequences to the fetus exposed to elevated Phe levels *in utero*. Most observed adverse consequences reflect processes that originate in the first trimester. The fetus is vulnerable to potentially serious sequelae, which include microcephaly, mental deficiency, and congenital heart disease.

There is a strong relationship between increasing levels of Phe and abnormalities in the neonate. Reports indicate that fetuses exposed to maternal Phe levels of 3–10 mg/dL had a 24 percent incidence of microcephaly, while those exposed to levels > 20 mg/dL had a 73 percent incidence. Similarly, congenital heart disease was not seen among offspring of women with Phe levels < 10 mg/dL but occurred in 12 percent of children exposed to maternal Phe levels > 20 mg/dL. Recent data indicate that levels of Phe above 6 mg/dL during pregnancy are associated with significant linear decrements in the IQ of the child through 7 years of age.

Unfortunately, few women who have discontinued dietary treatment achieve metabolic control before becoming pregnant and maintain it during pregnancy. The acceptable target levels vary among U.S. clinics, with some considering targets < 10 mg/dL acceptable, with others considering a more liberal target < 15 mg/dL acceptable. These levels are higher than the current United States Maternal Phenylketonuria Collaborative Study recommendation of 2–6 mg/dL. British and German standards set lower acceptable target ranges (1–4 mg/dL).

Several interventions have been used to increase adherence to diet, including mentoring by well-trained mothers of children with PKU and peer counseling. British guidelines for PKU management strongly recommend strategies to help children take responsibility for their own diets and blood testing by school age, thus preparing them to be more responsible for their own care when they are contemplating conception.

Based on This Information, What Are the Recommended Strategies for Optimal Newborn Screening and Diagnosis and Lifelong Management and Followup of PKU?

Comprehensive Approach to Lifelong Care

A programmatic, multidisciplinary approach to lifelong care is required for the treatment of 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 PKU. Treatment guidelines should be established that are consistent across U.S. clinical facilities that serve individuals with PKU and their families so they can expect consistent treatment. Equal access to treatment for all individuals with PKU 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 PKU implies a societal responsibility for comprehensive long-term followup and treatment. Outcome monitoring should consist of periodic 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.

Age of Initiation of Treatment for Infants With PKU

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

Recommended Levels of Phe for Classical PKU

Maintenance of Phe levels between 2–6 mg/dL for neonates through 12 years of age appears to be medically necessary for ensuring optimal outcome. Furthermore, in light of findings that Phe levels are related to cognitive function in adolescents and adults, it is recommended that Phe levels be maintained between 2–15 mg/dL after 12 years of age. Considering the paucity of data on the relationship between Phe level and brain function after 12 years of age, and the fact that brain development is ongoing during adolescence, even lower Phe levels (between 2–10 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 Phe Monitoring

The frequency of Phe monitoring will vary according the individual's needs. Suggested guidelines are as follows: (a) once weekly during the first year; (b) twice monthly from 1–12 years of age; (c) monthly after 12 years of age; and (d) twice weekly during pregnancy of a woman with PKU. 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 child-bearing 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 PKU is to maintain metabolic control of Phe 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-Phe diet, including medical foods and low-protein products, most likely will be medically required for virtually all individuals with classical PKU for their entire lifetimes. Although no definitive studies on the effects of

dietary treatment in adults exist, data suggest that elevated Phe levels in adolescents and adults adversely affect aspects of cognitive function, and individual case reports have documented deterioration of adult PKU 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.

Maternal PKU

It is recommended that Phe levels below 6 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 Phe and its effectiveness, family planning, conscious reproductive choice, and information related to the management of maternal PKU, are strongly recommended. Participation in such programs should occur before planned pregnancy so that optimal metabolic control of Phe 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 Phe levels should occur twice weekly, but at least once per week. The recommended level is 2–6 mg/dL during pregnancy. Focusing on the overall nutritional status of the pregnant mother, including intake of vitamins (folic acid and vitamin B_{12}, in particular), 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 PKU regardless of the individual's age. Individuals with mental retardation due to PKU 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 Phe level for establishing the diagnosis of PKU and non-PKU hyperphenylalaninemia. Standardized reporting of data must include the number of individuals with PKU and non-PKU 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 PKU for initial diagnosis, genetic and management counseling, followup, 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 PKU.

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 PKU.

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 Phe and tyrosine concentrations is beneficial in the early positive identification of PKU, 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 PKU screening programs.

Regionalization

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

What Research Is Needed to Gather Information that Will Optimize the Outcomes for Individuals with PKU and Their Families?

- Studies are needed to determine the relationship between variations in the behavioral and neural phenotypes associated with blood phenylalanine concentrations. These phenotypes should be based on quantitative assessment of brain structure and function, and contemporary neuropsychological assessment. Research on basic pathophysiology is essential.
- What is the relationship between genetic mutation and phenotypic variation in PKU?
- What aspects of treatment programs are associated with optimal long-term outcomes? Potential factors that include genetic variation, sociodemographic predictors, age, duration of treatment, and Phe levels should be studied.
- Evaluation and analyses are necessary to measure the clinical utility, validation, and cost effectiveness of the use of tandem mass spectrometry for screening PKU. This evaluation should include awareness of broader issues of its application to neonatal screening for a variety of genetic disorders.
- Longitudinal studies of treated PKU individuals to study effects of aging on PKU persons should be performed.
- Evaluation of various modalities to increase dietary adherence in pre-conceptional and maternal PKU is indicated.
- Studies are needed to identify the factors that enhance maintenance of metabolic control throughout life, which could be used for program development. It will be important to evaluate the effects of variations in metabolic control on cognitive functions and behavioral adjustment, especially in adolescents and adults.
- Investigations should examine a wide range of potential new treatments other than medical nutritional therapy for PKU to include, at a minimum, enzymes that might degrade Phe in the intestine, the role of LNAA, tetrahydrobiopterin supplementation and the potential role of somatic gene therapy. PKU animal model(s) will be valuable in these studies.
- Research studies on individuals who did not receive early treatment for PKU, including those in institutions, would be valuable.

Conclusions

- Genetic testing for PKU 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 PKU.
- A comprehensive, multidisciplinary, integrated system is required for the delivery of care to individuals with PKU.
- Greatly needed are consistency and coordination among screening, treatment, data collection, and patient support programs.
- 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 PKU testing should be established.
- Research into the pathophysiology of PKU 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 PKU.
- Research on nondietary alternatives to treatment of PKU 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.

Consensus Development Panel

R. Rodney Howell, M.D.
Panel and Conference Chairperson
Professor and Chairman
Department of Pediatrics
University of Miami School of Medicine
Miami, Florida

Aravinda Chakravarti, Ph.D.
Henry J. Knott Professor and Director
McKusick-Nathans Institute of Genetic Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Geraldine Dawson, Ph.D.
Professor of Psychology
Center on Human Development and Disability
University of Washington
Seattle, Washington

Claibourne I. Dungy, M.D., M.P.H.
Professor and Director
Division of General Pediatrics and Adolescent Medicine
Department of Pediatrics
The Children's Hospital of Iowa
University of Iowa Health Care
Iowa City, Iowa

Jack M. Fletcher, Ph.D.
Professor
Department of Pediatrics
University of Texas-Houston Medical School
Houston, Texas

Desirée Jackson, Ph.D.
Assistant Professor
Department of Biology
Texas Southern University
Houston, Texas

Mark S. Kamlet, Ph.D.
Provost and Professor of Economics and Public Policy
Carnegie Mellon University
Pittsburgh, Pennsylvania

Felissa R. Lashley, Ph.D., R.N.
Dean and Professor
School of Nursing
Southern Illinois University Edwardsville
Edwardsville, Illinois

Bonnie S. LeRoy, M.S.
Director, Graduate Program in Genetic Counseling
Institute of Human Genetics
University of Minnesota
Minneapolis, Minnesota

Mary Courtney Moore Ph.D., R.N., R.D.
Research Assistant Professor
Department of Molecular Physiology and Biophysics
Vanderbilt University School of Medicine
Nashville, Tennessee

Patti J. Patterson, M.D., M.P.H.
Vice President for Rural and Community Health
Texas Tech University Health Sciences Center
Lubbock, Texas

William B. Rizzo, M.D.
Professor of Pediatrics and Human Genetics
Medical College of Virginia
Richmond, Virginia

M. Anne Spence, Ph.D.
Professor
Department of Pediatrics
University of California, Irvine
Orange, California

Stephanie Stremer
Student
University of Wisconsin-Madison
Madison, Wisconsin

Speakers

Véronique Abadie, M.D.
Service de Pédiatrie Générale
Hôpital Necker-Enfants Malades
Paris, France

Colleen Azen, M.S.
Coordinator, Biostatistics
Maternal PKU Collaborative Study
Division of Medical Genetics
Children's Hospital Los Angeles
Los Angeles, California

Peter Burgard, Ph.D.
Department of General Pediatrics
University of Heidelberg
Pediatric and Developmental Psychology
University Children's Hospital
Heidelberg, Germany

Forrester Cockburn, M.D.
Emeritus Professor of Child Health
University of Glasgow
Royal Hospital for Sick Children
Glasgow, Scotland

Flemming Güttler, M.D., Ph.D.
Head, Department of Inherited Metabolic Disease and Molecular Genetics
Associate Professor
University of Copenhagen
The John F. Kennedy Institute
Glostrup, Denmark

Richard Koch, M.D.
Principal Investigator
Maternal PKU Collaborative Study
Division of Medical Genetics
Children's Hospital Los Angeles
Los Angeles, California

Harvey L. Levy, M.D.
Senior Associate in Medicine and Genetics
Children's Hospital, Boston
Associate Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Michele A. Lloyd-Puryear, M.D., Ph.D.
Chief, Genetic Services Branch
Maternal and Child Health Bureau
Health Resources and Services Administration
Rockville, Maryland

Reuben Matalon, M.D., Ph.D.
Director
Biochemical/Molecular Genetics
University of Texas Medical Branch at Galveston
Galveston, Texas

Kimberlee Michals Ph.D., R.D., L.D.
Associate Professor of Nutrition
Department of Human Development and Consumer Sciences
College of Technology
Department of Pediatrics
University of Texas Medical Branch
University of Houston
Houston, Texas

Mary Kay Z. Pelias, Ph.D., J.D.
Professor of Genetics
Department of Biometry and Genetics
Louisiana State University Medical Center
New Orleans, Louisiana

Joachim Pietz, M.D.
Department of Pediatric Neurology
University of Heidelberg
Heidelberg, Germany

Charles R. Scriver, M.D.
Alva Professor of Human Genetics
McGill University—Montreal Children's Hospital Research Institute
Montreal, Quebec, Canada

Margretta R. Seashore, M.D., FAAP, FACMG
Director, Genetics Consultative Services
Professor of Genetics and Pediatrics
Yale University School of Medicine
New Haven, Connecticut

Friedrich K. Trefz, M.D.
Head, Children's Hospital Reutlingen
University of Tubingen School of Medicine
Reutlingen, Germany

Susan E. Waisbren, Ph.D.
Senior Psychologist
Inborn Errors of Metabolism Service
Associate Professor of Psychology
Department of Psychiatry
Harvard Medical School
Boston, Massachusetts

Marilyn C. Welsh, Ph.D.
Professor
Department of Psychology
University of Northern Colorado
Greeley, Colorado

Keith F. Widaman, Ph.D.
Professor
Department of Psychology
University of California, Davis
Davis, California

Savio L.C. Woo, Ph.D.
Professor and Director
Institute for Gene Therapy and Molecular Medicine
Mount Sinai School of Medicine
New York, New York

Planning Committee

Duane Alexander, M.D.
Planning Committee Chairperson
Director
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

John A. Bowersox
Communications Specialist
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Marie Bristol-Power, Ph.D.
Health Scientist Administrator
Mental Retardation and Developmental Disabilities Branch
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Felix de la Cruz, M.D., M.P.H.
Chief
Mental Retardation and Developmental Disabilities Branch
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Franklin Desposito, M.D.
Director
Center for Human and Molecular Genetics
UMDNJ-New Jersey Medical School
Newark, New Jersey

Jerry M. Elliott
Program Analysis and Management Officer
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

John H. Ferguson, M.D.
Director (Retired)
Office of Medical Applications of Research
Potomac, Maryland

Karin F. Helmers, Ph.D.
Program Director
Division of Extramural Activities
National Institute of Nursing Research
National Institutes of Health
Bethesda, Maryland

Richard Koch, M.D.
Principal Investigator
Maternal PKU Collaborative Study
Division of Medical Genetics
Children's Hospital Los Angeles
Los Angeles, California

Cara J. Krulewitch, Ph.D., C.N.M.
Program Director
National Institute of Nursing Research
National Institutes of Health
Bethesda, Maryland

Harvey L. Levy, M.D.
Senior Associate in Medicine and Genetics
Children's Hospital, Boston
Associate Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Edward R.B. McCabe M.D., Ph.D.
Professor and Executive Chair
Department of Pediatrics
Physician-in-Chief
Mattel Children's Hospital at UCLA
UCLA School of Medicine
Los Angeles, California

Catherine McKeon, Ph.D.
Senior Advisor for Genetic Research
Division of Diabetes, Endocrinology, and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Kathryn D. Moseley, M.S., R.D.
Metabolic Dietitian
Children's Hospital Los Angeles
Los Angeles, California

Margretta R. Seashore, M.D., FAAP, FACMG
Director, Genetics Consultative Services
Professor of Genetics and Pediatrics
Yale University School of Medicine
New Haven, Connecticut

Philip H. Sheridan, M.D.
Program Director, Neurodevelopment and Pediatric Neurology
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland

Elizabeth J. Thomson
R.N., M.S., C.G.C.
Program Director
Ethical, Legal, and Social Implications (ELSI Research)
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland

Judith M. Whalen, M.P.A.
Associate Director for Science Policy, Analysis, and Communication
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

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NIH Office of Rare Diseases
Stephen C. Groft, Pharm.D.
Director

Maternal and Child Health Bureau of the Health Resources and Services Administration
Peter C. van Dyck, M.D., M.P.H.
Associate Administrator

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U.S. DEPARTMENT OF HEALTH
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Public Health Service
National Institutes of Health
Office of Medical Applications of Research
Building 31, Room 1B03
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