Background

- October 2000: NIH published guidelines for screening and management as the result of a Consensus Development Conference on PKU

- New therapies have emerged:
  - Sapropterin dihydrochloride, LNAAs, GMP
  - New data have been collected from additional studies
    ➔ The guidelines needed to be revisited

New Medication: Sapropterin dihydrochloride (Kuvan®)

• Synthetic form of BH4, the cofactor for the PAH enzyme
• FDA approval in December 2007 granted to BioMarin
  – Based on 4 studies in 579 patients, 4-49 yrs old
• Mechanism: increases activity of PAH enzyme in those with residual enzyme function
• Indications:
  – BH4-responsive PKU
  – No age restriction
  – For use in combination with a Phe-restricted diet
  – Requires frequent monitoring of blood Phe levels and recommended diet management with dietitian
NIH PKU Scientific Review Conference
February 22-23, 2012

Components:
• AHRQ Comparative Effectiveness Review
  • Adjuvant Treatments for PKU
• Five NIH Working Groups presented their findings
• Invited speaker presentations
• Advocacy, industry, and other interested parties

Conference goals:
• Provide a forum for identifying future research needs
• Provide data for the development of clinical practice guidelines by professional organizations
AHRQ conducted a formal evidence review of the scientific literature

- AHRQ received a public request to conduct a comparative effectiveness review of treatments for PKU, including diet, sapropterin, and LNAAs

- An Evidence-based Practice Committee (EPC) was identified

- This effort proceeded collaboratively with, but independently of, NIH process

- AHRQ draft report was posted September 2011, formally released at Conference
• Phe Levels and IQ
  – Standard of care target Phe <360 µmol/L is supported
  – Phe levels during the critical period (0-6 yrs) are especially influential on later IQ, but Phe levels after the critical period continue to affect IQ with age

• Dietary management remains the mainstay of treatment for PKU; however, some individuals may benefit from adjuvant therapy with sapropterin

• Sapropterin reduced Phe levels in 2 RCTs and 3 open label trials, significantly greater reductions seen in treated versus placebo groups

• Long term data to understand effects of sapropterin on cognition, quality of life, nutritional outcomes are unavailable

• Potential modifiers of treatment effectiveness and treatment responsiveness not well understood

• Need for large, rigorous RCTs of sapropterin and LNAAs
Preparation for the NIH Conference:
Working Groups

• Each WG had 10-14 members
• Each met via webinar at least 8 times over 1 year to discuss questions related to their topic

- Clinical Care Experts
- Working Group Co-Chairs Coordinator
- Research Experts
- Patients and Patient Advocates
- NIH and Federal Partners

• Many WG had international members
• Developed presentations based on their discussions
5 Working Groups were convened to address overarching themes

1. **Long-Term Outcomes and Management across the Lifespan**: What evidence and practices should inform management of individuals with PKU over their lifespan?

2. **PKU and Pregnancy**: What are the considerations for management for women of reproductive age, focusing on preconception care, conception planning, pregnancy, and the postpartum period?

3. **Diet Control and Management**: Should the dietary recommendations that emerged from the 2000 Consensus Statement be changed? If so, what current knowledge would inform development of new recommendations?

4. **Pharmacologic Interventions**: What is the role of sapropterin dihydrochloride in individuals with PKU?

5. **Molecular Testing, New Technologies, and Epidemiologic Considerations**: Should there be any changes to the 2000 Consensus Conference Statement regarding newborn screening and molecular testing for PKU?
Lifelong treatment for PKU is essential.

The critical elements of medical, nutritional, cognitive, emotional, behavioral, and social management of PKU throughout the lifespan, including pregnancy, were identified and refined.

Optimal management is essential to prevent maternal PKU syndrome.

Double-blind, placebo controlled studies have the greatest rigor for determining responsiveness to sapropterin.

Genotyping is valuable for categorization of severity of PKU and for prediction of responsiveness to sapropterin.

Insurance issues and psychosocial factors influence access to and compliance with nutritional and other therapies.

There is a critical need for more treatment options for individuals with no or minimal PAH enzyme activity.

Revised practice guidelines need to be developed.
## Screening for and Measuring Outcomes Across the Lifespan

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<th>DOMAIN</th>
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• Gene Therapy:
  – Current preclinical trials in mice
  – Need high doses of recombinant AAV-PAH
  – Integration into liver cells inefficient

• PEG-PAL (PEGylated Phenylalanine Ammonia Lyase):
  – No cofactor required
  – Relatively stable
  – Non-toxic metabolite is excreted in urine
  – PEGylation reduces but doesn’t eliminate immunogenicity
  – Current Phase 2 trials in humans are promising
Future Research Needs Identified during the Conference
Major Themes Identified

• Outcomes/Measures:
  • What measures can be used as screening tools and assessments (in all domains of function) across the lifespan for those with PKU?
  • What are appropriate and sensitive short-term and long-term outcome measures for identifying effects of interventions for individuals with PKU?

• Basic science/Neurological Effects:
  • What is the mechanism of neurotoxicity of elevated Phe levels?
  • Are there any promising biomarkers on the horizon that might be valuable for monitoring PKU, its neurological effects, and response to therapy?
Major Themes, cont’d.

- **Access/Social Supports:**
  - What are the social support systems that facilitate the best clinical outcomes for individuals with PKU?
  - What strategies can be used to overcome barriers and improve adherence to treatments in all phases of life?
  - What types of implementation research (e.g., comparative studies between countries) could demonstrate the value of treatments?

- **Clinical Trial Design:**
  - Which individuals should be eligible for new treatments for PKU, and what are the best methods to study responsiveness?
  - What should be the guiding principles when designing clinical trials for pharmacologic agents or combinations of therapies (including diet) to be used in PKU?
Major Themes, cont’d.

• Genotyping:

  Can genotyping be used to determine responsiveness to therapies? Should clinical trials for efficacy always incorporate genotype information?

• Given that PKU exhibits phenotypic variability, what is the role of modifier genes in PKU?

• Resources/Technology:

  Is there a role for a national PKU registry of individuals to inform future clinical trials and natural history studies?

  Can resources that have been developed for other rare diseases be used by the PKU community (e.g., Newborn Screening Translational Research Network, Common Data Elements)?

  Can the technology for home Phe monitoring be developed to facilitate disease management?
NIH PKU Scientific Conference: What’s Next?

- White paper in development
- Conference webcast available on NIH videocast site
- Conference summary documents available: https://www.teams hare.net/Phenylketonuria_Scientific_Review_Conference/Webcast.aspx
- For more information, contact:
  - Melissa Parisi at parisima@mail.nih.gov
Thank You!

If you have questions/comments about the conference, please send them to parisima@mail.nih.gov