NIH PKU Conference: State of the Science and Future Research Needs

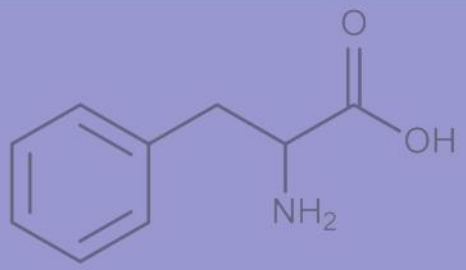
Melissa A. Parisi

Eunice Kennedy Shriver National Institute of Child Health and Human Development

NIH…Turning Discovery into Health

PHENYLKETONURIA SCIENTIFIC REVIEW CONFERENCE:

State of the Science and Future Research Needs



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

- Approach: Year-long Working Group process and Conference held Feb. 22-23, 2012

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

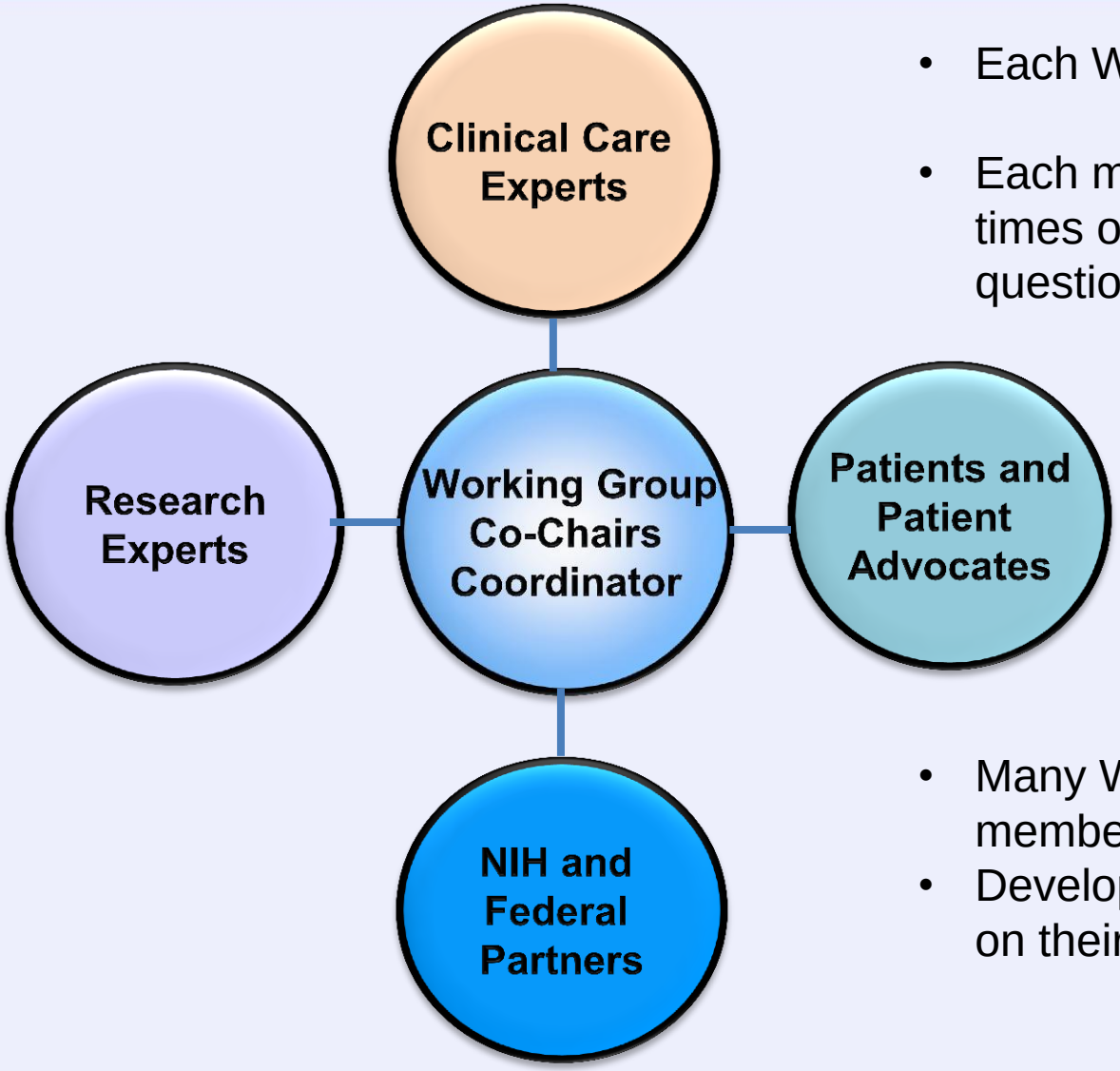
AHRQ conducted a formal evidence review of the scientific literature

- 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

AHRQ EPC Evidence Review: Key Points

- 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

- 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?

Summary Points from the Working Groups

- 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

DOMAIN	Infant-Toddler (3 mo - 5 yr)	School Age (6 - 11 yr)	Adolescent/ Transition (12 - 17 yr)	Early Adulthood (18 - 25 yr)	Middle Adulthood (26 - 49 yr)	Later Adulthood (≥50 yr)
Medical	**Issue 1:** General health	**Issue 1:** General health	**Issue 1:** General health	**Issue 1:** General health	**Issue 1:** General health	**Issue 1:** General health
	Measure 1: Medical examination; medical history	**Measure 1:** Medical examination; medical history	**Measure 1:** Medical examination; medical history; bone density	**Measure 1:** Medical examination; medical history; bone density	**Measure 1:** Medical examination; medical history; bone density	**Measure 1:** Medical examination; medical history; bone density
Nutritional	Workgroup 1	Workgroup 1	Workgroup 1	Workgroup 1	Workgroup 1	Workgroup 1
Metabolic	**Issue 1:** Phe level	**Issue 1:** Phe level	**Issue 1:** Phe level	**Issue 1:** Phe level	**Issue 1:** Phe level	**Issue 1:** Phe level
	Measure 1: Serum Phe	**Measure 1:** Serum Phe	**Measure 1:** Serum Phe	**Measure 1:** Serum Phe	**Measure 1:** Serum Phe	**Measure 1:** Serum Phe
Neurological	**Issue 1:** Tremor; gait; strength; reflexes	**Issue 1:** Tremor; gait; strength; reflexes	**Issue 1:** Tremor; gait; strength; reflexes	**Issue 1:** Tremor; gait; strength; reflexes	**Issue 1:** Tremor; gait; strength; reflexes	**Issue 1:** Tremor; gait; strength; reflexes
	Measure 1: Neurological examination	**Measure 1:** Neurological examination	**Measure 1:** Neurological examination	**Measure 1:** Neurological examination	**Measure 1:** Neurological examination	**Measure 1:** Neurological examination

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Cognitive	**Issue 1:** General cognition	**Issue 1:** General cognition	**Issue 1:** General cognition	**Issue 1:** General cognition	**Issue 1:** General cognition	**Issue 1:** General cognition
	Measure 1a: Bayley III **Measure 1b:** WPPSI-III	**Measure 1:** WASI	**Measure 1:** WASI	**Measure 1:** WASI	**Measure 1:** WASI	**Measure 1:** WASI
	Issue 2: Executive abilities	**Issue 2:** Executive abilities	**Issue 2:** Executive abilities	**Issue 2:** Executive abilities	**Issue 2:** Executive abilities	**Issue 2:** Executive abilities
	Measure 2: BRIEF-P	**Measure 2:** BRIEF	**Measure 2:** BRIEF	**Measure 2:** BRIEF-A	**Measure 2:** BRIEF-A	**Measure 2:** BRIEF-A
	Issue 3: Academic Achievement	**Issue 3:** Academic Achievement	**Issue 3:** Academic Achievement	**Issue 3:** Academic Achievement	**Issue 3:** Academic Achievement	**Issue 3:** Academic Achievement
	Measure 3: Discuss early skills	**Measure 3:** Standard scores; discuss progress	**Measure 3:** Standard scores; discuss progress	**Measure 3:** Standard scores; discuss progress	**Measure 3:** Highest education level attained	**Measure 3:** Highest education level attained

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DOMAIN	Infant-Toddler (3 mo - 5 yr)	School Age (6 - 11 yr)	Adolescent/ Transition (12 - 17 yr)	Early Adulthood (18 - 25 yr)	Middle Adulthood (26 - 49 yr)	Later Adulthood (≥50 yr)
Behavioral, Emotional, Social	**Issue 1:** Behavioral, emotional, social	**Issue 1:** Behavioral, emotional, social	**Issue 1:** Behavioral, emotional, social	**Issue 1:** Behavioral, emotional, social	**Issue 1:** Behavioral, emotional, social	**Issue 1:** Behavioral, emotional, social
	Measure 1: BASC-2 or CBCL	**Measure 1:** BASC-2 or CBCL	**Measure 1:** BASC-2 or CBCL	**Measure 1:** BSI or BDI-2/ BAI	**Measure 1:** BSI or BDI-2/ BAI	**Measure 1:** BSI or BDI-2/ BAI
	Issue 2: Adaptive function	**Issue 2:** Adaptive function	**Issue 2:** Adaptive function	**Issue 2:** Adaptive function	**Issue 2:** Adaptive function	**Issue 2:** Adaptive function
	Measure 2: ABAS-II	**Measure 2:** ABAS-II	**Measure 2:** ABAS-II; discuss pregnancy with teens	**Measure 2:** ABAS-II; discuss pregnancy	**Measure 2:** ABAS-II; discuss pregnancy; discuss social issues	**Measure 2:** ABAS-II; discuss social issues

Novel Therapies for PKU-Cary Harding

- 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

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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.team-share.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

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