



2000 NIH Consensus Development Conference: Some Conclusions

- 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 programs for screening, treatment, data collection and patient support.
- Continuity of care from infancy through adulthood is considered medically necessary for optimal outcomes of individuals with PKU
- There should be equal access to culturally sensitive, age appropriate treatment and support programs
- Ethically sound, specific policies for storage, ownership, and use in future studies of archived dried blood samples remaining from PKU testing should be established
- Research into the pathophysiology of PKU and the 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 (amino acid formulas) and modified low-protein, low-phe foods, as well as to provide access to support services required to maintain metabolic control in individuals with PKU.
- To achieve optimal statistical power, as well as cross-cultural applicability, it will be beneficial to use data acquired via national and international collaboration.
- For PKU women of child-bearing age, it is recommended that Phe levels below 360 $\mu\text{mol/L}$ (6 mg/dl) be achieved at least 3 months before conception
- Research on non-dietary alternatives to treatment of PKU is strongly encouraged
- Mutation analysis and genotype determination should be accomplished on all persons with PKU for initial diagnosis, genetic and management counseling, follow-up and long-term prognosis.
- Treatment guidelines should be established that are consistent across clinical facilities
- Mandated newborn screening for PKU implies a societal responsibility for comprehensive long-term follow-up and treatment. Equal access to treatment for all individuals with PKU is highly desirable
- Specialized medical foods and modified 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.
- Breastfeeding is encouraged along with medical food (amino acid formulas) in newborns.
- Maintenance of blood Phe concentrations between 120 -360 $\mu\text{mol/L}$ for neonates through 12 years of age seems to be medically necessary for ensuring optimal outcome.
- Blood Phe monitoring once weekly during the first year, twice monthly from 1-12 years, monthly after 12 years.
- Late-diagnosed Individuals with intellectual disabilities caused by PKU who are experiencing severe behavioral disturbances should be considered for nutrition management.

Summary of EPC (Evidence-Based Practice Center) Report, Vanderbilt University, commissioned by the Agency for Healthcare Research and Quality (AHRQ)

Support for Phe Control Beyond the Critical Period (< 6 years old) and Review of Non-Dietary Treatments for PKU

- For meta analysis:
 - Individual or mean/median Phe level and IQ data + measure of variance (e.g., standard deviation)
 - Studies of executive function had to provide correlation data, use appropriate control population, and same measure of executive function had to be used in at least 3 studies (no studies met criteria)

- Waisbren et al. (2007) Summary Points
 - Meta analysis of 40 studies
 - Goal to “assess the reliability of blood Phe levels as a predictive biomarker of clinical outcomes in the development of treatments for PKU“
 - Phe-IQ correlation found during critical period for early-treated PKU 100 $\mu\text{mol/l}$ increase =1.3 to 3.1 reduction of IQ
 - Phe-IQ correlation found for mean lifetime Phe 100 $\mu\text{mol/l}$ increase =1.9 to 4.1 reduction in IQ

- Key Points: Phe Levels and IQ
 - Standard of care target Phe <360 $\mu\text{mol/L}$ is supported
 - The predicted probability of IQ <85 exceeds the population probability (approximately 15%) at 400 $\mu\text{mol/L}$ and reaches a maximum of about 80% at 2000 $\mu\text{mol/L}$
 - Phe levels during the critical period are especially influential on later IQ, but Phe levels after the critical period continue to affect IQ as individuals get older
 - Time of measurement of phe levels influences ability to detect effects of Phe on IQ

- Key Findings of Sapropterin Studies: Phe Tolerance
 - Phe tolerance addressed in one Randomized Control Trial (Trefz 2009), one open label trial (Vernon 2010), & 3 case series (Burton 2010, Burlina 2009, Lambruschini 2005)
 - Tolerance increased from 0 to 20.9 mg/kg/day compared to 2.9 mg/kg/day in placebo group
 - Increase of average of 21-41 mg/kg/day for participants on Phe-restricted diet

- Key Findings of Sapropterin Studies: Phe Variability
 - Phe variability addressed in one retrospective case series (Burton 2010) (n=37 participants)
 - Individual variability lessened post-treatment

- Summary of Studies Addressing Sapropterin
 - 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
 - Harms were mild and not significantly different between treatment and placebo groups
 - Long term data to understand effects of sapropterin on cognition, quality of life, nutritional outcomes are not yet available
 - Potential modifiers of treatment effectiveness and treatment responsiveness not well understood
 - Data are unavailable to predict which individuals are likely to respond, even after initial responsiveness

- Key Findings of Studies Addressing LNAA
 - Blood Phe primary outcome measure
 - Greater reductions in blood Phe in treatment group compared with placebo
 - Reductions in Phe in open label trial including participants not on restricted diet
 - Evidence lacking for definitive conclusions about effects on Phe level, Phe tolerance, IQ, Executive Function, quality of life, harms

- Ongoing Research into Adjuvant Therapies
 - ~24 ongoing/recently completed studies of sapropterin

- Areas of focus include:
 - Assessment of **growth and neurocognitive development** with long-term use
 - Effects on executive function, behaviour, ADHD
 - Responsiveness testing
 - Safety and efficacy of sapropterin in younger children (age 0-4)
 - Safety and outcomes registry
 - Cardiac effects
 - Effects on amino acids and fatty acids
 - Effects on brain glucose metabolism, connectivity, and neurotransmitter concentration

- Areas for Future Research
 - Research consortium with public-private partnerships
 - Establish comprehensive long-term research agenda and registry
 - Larger trials including diverse populations (age, PKU type, level of dietary control, etc.) over longer time periods
 - Standardized tools and measures for outcomes including IQ, EF, quality of life, etc.
 - Standardized data collection and reporting, including of potential confounders such as familial IQ, Social Economic Status, maternal education, age at initial treatment, concurrent therapies, etc.
 - Measures to assess Phe control in addition to blood Phe
 - Understanding which outcomes are important to patients and their families
 - Clarifying effects of PKU type, including mild hyperphe, on cognition, behaviour, and other psychosocial issues
 - Understanding relationship between Phe reduction and cognitive and other outcomes
 - Understanding which measures of executive function are most appropriate for PKU population
 - Understanding psychological issues (e.g., anxiety, depression, mood swings, etc.) in PKU

- Areas for Future Research: Sapropterin
 - Observational or RCT data on populations not well studied (e.g. younger children, pregnant women, patients over 50 years of age)
 - Understanding variability in response to sapropterin and effects in subpopulations
 - Understanding effects of adherence to sapropterin regime and roles for adherence supports
 - Understanding long-term efficacy and safety outcomes of sapropterin
 - Understanding effects of diet liberalization/normalization on nutritional outcomes

- Areas for Future Research: LNAAs
 - Understanding LNAAs mechanisms of action
 - Larger, rigorously-conducted RCTs of LNAAs
 - Studies designed to include subgroup analyses (age, genotype, pregnant women, etc.)
 - Understanding effects of diet liberalization/normalization on nutritional outcomes

Overview of the NIH Working Group Process and Definitions

- Agreed Upon Definitions:

○ Mild HyperPhe, no treatment required	120-360 µmol/L
○ Mild HyperPhe, gray zone	360-600 µmol/L
○ Mild PKU	600-900 µmol/L
○ Moderate PKU	900-1200 µmol/L

- Classical PKU > 1200 $\mu\text{mol/L}$
- BH4 Deficiencies variable
- Maternal PKU – the state of having PKU and being pregnant
- Maternal PKU Syndrome – constellation of fetal abnormalities due to the teratogenicity of excessive Phe

PKU Working Group Presentations

Long Term Outcomes and Management across the Lifespan

- Universal newborn screening (NBS) a spectacular success
- NBS transformed PKU into a different kind of chronic condition
- Although profound neurological & cognitive impairment can be prevented, a host of more subtle yet critical issues of concern remain.
- Comprehensive, multidisciplinary approach to lifelong care for people with PKU
- “Mandated screening for PKU implies a societal responsibility for comprehensive long-term follow-up and treatment. Outcome monitoring should consist of periodic intellectual, neurological, neuropsychological, and behavioral assessment.”
- What domains of impairment can occur in PKU?
 - Medical: General health
 - Nutritional: See Working Group 1
 - Metabolic: Phenylalanine level
 - Neurological: Gait, strength, reflexes, tremor, seizure, etc.
 - Cognitive: General cognition/development, executive abilities, academic abilities
 - Behavioural, Emotional, Social: Psychiatric, social, emotional, behavioural, adaptive function.
- What are the current tools to screen for and measure impairments?
 - Medical
 - Medical examination
 - Medical history
 - Bone density (adolescence through later adulthood)
 - Nutritional
 - See Working Group 1
 - Metabolic
 - Serum phenylalanine
 - Neurological
 - Neurological examination
- Challenges in screening for and measuring impairments
 - Domains of impairment not yet recognized
 - When to refer for further evaluation
 - Availability of professionals to conduct further evaluation
 - Creation of multidisciplinary teams
 - Evidence for best screening & measurement tools in PKU
 - Ease, cost, reimbursement & interpretation of tools
 - Consistency in use of tools across clinics
 - Development of targeted remediation approaches in PKU
- What current approaches deliver interdisciplinary care across the lifespan?
 - This is important because:

- Emotional health, freedom from neuropsychological deficits, and a satisfying quality of life signify successful treatment in PKU as much as a “good” blood phenylalanine level and a “normal” IQ. No single health care professional can ensure these positive outcomes.
- What are the research needs and opportunities for improving outcomes?
 - Can the Uniform Assessment Method be implemented in metabolic clinics to identify individuals in need of further evaluation?
 - What is the long-term impact of social support programs for PKU?
 - Do youth and young adults with PKU who achieve a strong identity also attain better metabolic control during this period of transition to adult healthcare?
 - How effective and how well tolerated are psychotropic medications for ADHD, depression, and anxiety associated with PKU?

PKU & Pregnancy

- Conclusions from NIH 2000 Consensus Statement
 - Metabolic control is necessary across the lifespan of individuals with PKU
 - There is a strong relationship between maternal Phe levels during pregnancy and abnormalities in neonate, especially for phe levels >1200 $\mu\text{mol/L}$ (20 mg/dl)
 - If a woman discontinues dietary treatment it is difficult to achieve metabolic control prior to and during pregnancy
 - Variability for target levels for women during pregnancy:
 - USA: 60-360 $\mu\text{mol/L}$ (1-6 mg/dl)
 - UK & Germany: 60-240 $\mu\text{mol/L}$ (1-4 mg/dl)
 - Maintain blood phe level between 120-360 $\mu\text{mol/L}$ before conception and during pregnancy
- Sapropterin and Maternal PKU
 - Limited use during pregnancy to date
 - Koch et al, 2005 used sapropterin in conjunction with low-phe diet
 - Metabolic control was easily achieved
 - Normal offspring, no anomalies or dysmorphism and normal anthropometrics
 - Pridjian et al, 2009
 - Mild PKU, could not tolerate medical formula
 - Normal offspring, no anomalies or dysmorphism and normal anthropometrics
 - Child developing normal at 3 years of age; other pregnancies ongoing
 - FDA pregnancy risk category –C
 - No clear teratogenic activity noted in animals
 - Oral treatment in rats at dose ≥ 400 mg/kg/day
 - Oral treatment in rabbits at 600 mg/kg/day
 - (10x max human dose) –slight increase in holoprosencephaly
 - Not carcinogenic in mice, but an increase in benign pheochromocytoma in male rats (2x max human dose)
 - Not mutagenic in mice
 - No controlled human studies
 - Chemical composition suggests ability to cross placenta
 - Sapropterin crosses mouse placenta; unknown if crosses human placenta
 - Breastfeeding
 - Manufacturer has ongoing study
- Final considerations

- Initial reports of sapropterin use in pregnancy are encouraging –short-term outcome good
- Insufficient data available to recommend use in pregnancy. Sapropterin should only be given during pregnancy when benefits outweigh risks. Careful consideration of risks and benefits in each case
- Optimal dosing in pregnancy has not been established
- Women who are exposed to or take sapropterin during pregnancy are encouraged to enrol in the sapropterin patient registry through the manufacturer
- There is insufficient data available regarding breastfeeding while on sapropterin. Careful consideration of risks and benefits should be made in each case
- Current Interventions for obtaining metabolic control occur too late in fetal development
 - Mean entry into prenatal care occurs just before 13 weeks gestation
 - Critical development of fetus between 5 and 13 weeks gestation
 - 5 to 13 weeks gestation is most susceptible time for major malformation of Central Nervous System, Heart, Arms, Legs, Eyes, Teeth, Palate, Ear & External Genitalia
 - Diet is not always started before conception
 - UK: 44% start pre-conception
 - US: 33% start pre-conception
 - Germany: 46% start pre-conception
- Barriers to Adhering to Medical Recommendations
 - Poor access to medical care
 - Financial constraints
 - Unpaid time off work
 - Lack of coverage of medical formula, foods & clinic visits
 - Phe-restricted diet is time intensive
 - Frequent medical appointments are required
- Women with PKU are at risk for unplanned pregnancies
 - 35% of sexually active women use contraceptive sporadically
 - 19% never used birth control
 - Findings of Prevention of Unplanned Pregnancies Study
 - Women with PKU
 - Scored lower than comparison groups in knowledge of family planning
 - Had poorer impulse control than comparison groups
- Summary
 - Successful pregnancies occur when blood Phe levels are 120-360 $\mu\text{mol/L}$ (2-6 mg/dl) at least 3 months prior to conception
 - Best to transition responsibility of PKU care from parents to adolescent to promote an internal locus of control over their disorder
 - Preconception visit encouraged with a metabolic center as well as an obstetrician to initiate team care
 - No contraceptive methods contraindicated; long acting reversible contraception may be more successful
- Maternal PKU Diet: Protein & Energy
 - Adequate maternal protein and energy intake is needed to support fetal growth and development and prevent catabolism
 - Low intakes of protein and energy in MPKUCS (Maternal PKU Collaborative Study) were associated with poorer offspring birth measurements
 - Low intake of protein associated with increased risk of Congenital Heart Defects (CHD)
 - Primary source of protein is medical food (amino acid formulas)
 - Most medical foods use Phe free L-amino acids (incomplete protein) as protein source

- Glycomacropeptide is a whey-based intact protein; not used yet in maternal PKU diet
 - Large Neutral Amino Acids
 - Contraindicated-blood Phe does not reach 120-360 $\mu\text{mol/L}$
 - Do not contain fat, vitamins and minerals, all essential AA
- Sapropterin supplementation may allow more intact protein in diets of women with PKU
- Tyrosine is a conditionally essential amino acid in maternal PKU diet
- Primary source of tyrosine is the amino acid formulas
- Fat, essential fatty acids and cholesterol are necessary for proper fetal brain development
 - Adequate sources of fat, cholesterol and DHA must be provided in the diet
 - Women with PKU of reproductive age-low DHA in Red Blood Cells
 - Women consuming a low-fat or fat-free medical food are at higher risk of deficiency
- Cholesterol
 - Necessary for membrane formation, DNA proliferation, steroid synthesis
 - Low plasma cholesterol was associated with increased incidence of spontaneous abortion
- Reasons for concern in MPKU diet:
 - Low intact-protein diet may be low in several nutrients
 - High blood Phe interferes with normal nutrient metabolism
 - Niacin, cholesterol
 - The additive effect of high plasma Phe and low nutrient intake has been shown to increase the risk of birth defects in Maternal PKU
 - Low Vitamin B12 intake associated with increased risk of Congenital Heart Defects
- Maternal PKU diet
 - Unpalatable and costly
 - Medical foods and low-protein foods
 - Third party payment throughout lifespan is a problem
 - Requires knowledge (tracking Phe intake) and skills (organization, low-protein cooking)
 - Socially limiting
 - Pregnancy-related issues
 - Nausea and vomiting
 - Increased energy demand on limited Phe allowance
 - Post-partum
 - Less contact and support from clinic
 - Difficult to manage newborn and special diet
- Post-Partum Period – Considerations
 - Several physiologic changes occur in the postpartum period:
 - Mean weight loss from delivery of the fetus, placenta, and amniotic fluid is about 13 pounds
 - Another 5-15 lbs weight loss may occur
 - What is the effect of these physiological changes on the serum Phe level?
 - The caloric demand of lactation is estimated at 640 kcal/day
 - The protein demand of lactation is estimated at 25 grams/day
 - Medical foods (formulas): dietary restriction of phenylalanine requires medical foods that are unpalatable and this remains a challenge
 - Sapropterin may be used as an adjunct to dietary restriction in individuals with PKU
 - Supplementation of nutrients (vitamins, minerals, fat, cholesterol, DHA) in woman with PKU is needed when:
 - Breast-feeding

- Medical food is not being consumed as prescribed
- Medical food is devoid of these nutrients
- Other Considerations:
 - Challenges of being a new mother and taking care of her own diet and that of the baby cannot be ignored
 - Loss of regular contact and support of metabolic clinic and dietitian after delivery add to the challenges of a PKU mom
 - In some cases, both the baby and the mother with PKU may be intellectually challenged and may require considerable social support

Diet Control and Management

• Outcomes of Nutrition Management

- Amino acids in treatment ranges
 - Current target blood Phe: 120-360 $\mu\text{mol/L}$ (2-6 mg/dl) (AHRQ 2011)
 - Lifelong management to prevent adverse medical findings, cerebral MRI changes, and to promote normal cognitive development (Koch 2002, Azen 1996)
 - There is no evidence that blood Phe control in adolescents and adults can be relaxed (AHRQ 2011), especially during pregnancy and trimester before conception
 - There is insufficient evidence regarding optimal control for adolescents and adults, except for pregnancy
 - Tyrosine: > 1.0 mg/dL (60 $\mu\text{mol/L}$)
 - Other amino acid concentrations (Acosta 1999)
- Adequate Nutrition Status
 - May require intakes greater than the Daily Recommended Intake (DRI), especially for protein and minerals
 - Use of incomplete medical foods (formulas) increase risk of nutrient deficiencies
 - Monitoring:
 - Growth
 - Intake (diet records)
 - Biomarkers
 - Minerals and vitamins: iron, selenium, zinc, copper, vitamin A, vitamin B12, total homocysteine, and other minerals and vitamins as clinically indicated
 - Protein status: prealbumin
 - Red blood cell essential fatty acids
 - Clinical indicators
 - Bone health: vitamin D, DEXA
 - Hair, skin findings
 - Physical signs and symptoms reported in the literature resolve when blood Phe concentrations are within treatment range (Belloso 2003, Guillet 1983, Szczepanski 1995)
- Cognitive and Behavioural Function
 - Role(s) of nutrients noted below among individuals with PKU
 - Vitamin D –neurotransmission
 - B vitamins –energy metabolism
 - Vitamin B6 (Kennedy 2011) and other B vitamins –neurotransmitter synthesis
 - Selenium –cognitive function (Gassio 2008)

- Future Research
 - Monitoring tools
 - Additional methods to measure adherence to diet
 - Usefulness of ratio in blood of Phe:Tyr
 - Evaluation of lower blood Phe concentrations
 - Effects of other nutrients on overall nutrition status and outcome measures, eg.
 - Pre-and probiotics
 - Desirable blood Phe concentrations for adolescents and adults to promote optimal cognition, behavior, and mood
 - Role of nutrients and nutrient inadequacy on body composition, cognition, behaviour and mood
 - Treatment strategies and approaches to promote optimal outcomes
- **Sapropterin and Diet**
 - Benefits
 - Lower blood Phe and/or increased Phe tolerance
 - Diet liberalization/normalization may lead to improved nutritional status, compliance and quality of life (Blau 2009, Burlina 2009, Giovannini 2007)
 - Patients non-adherent to nutrition therapy –blood Phe controlled without further restriction
 - Nutrition therapy modified based on individual response may:
 - Liberalize diet Phe restriction
 - Decrease medical food (formula) requirements
 - Increase intact protein
 - ***While maintaining blood Phe control***
 - Phe challenge –systematic determination of maximum Phe tolerated and minimum medical food required while maintaining blood Phe within a therapeutic range (Singh 2008, 2011)
 - Add Phe incrementally (eg. dry milk powder added to medical food) until maximum tolerance is reached and has stabilized
 - Replace Phe used in challenge with Phe from food
 - Decrease medical food (formula) incrementally, ensuring total protein adequacy
 - Monitor blood Phe concentrations to guide all steps
 - Re-educate patients
- **LNAAs and Diet**
 - Effect: Elevated blood Phe competitively inhibits uptake of other LNAAs in the gut and transport across the blood brain barrier
 - Leads to deficient protein and neurotransmitter synthesis and increased myelin turnover in the brain
 - Current LNAAs product composition has improved based on functional effect –mimics natural affinity to amino acid transporter
 - Effect on blood Phe concentrations is not definitive
 - Potential Benefit: LNAAs may lower blood Phe and normalize protein and neurotransmitter synthesis in the brain
 - Potential Risk: Does not contain minerals and vitamins. Use requires frequent monitoring of relevant biomarkers and growth for nutritional adequacies
 - Some literature suggests beneficial use in adolescents and adults with elevated blood Phe concentrations who:
 - Do not follow dietary recommendations (Nielsen 1988, Lou 1985 and 1994, Schindeler 2007)
 - Are previously untreated or late treated (Kalkanoglu 2005)

- Contraindicated in
 - Pregnancy
 - Unknown effects on fetus
 - Blood Phe concentration reduction is not adequate for pregnancy
 - Young children due to lack of safety and efficacy data
- How should treatment be altered when using LNAAAs?
 - LNAAAs may be supplemented with or replace medical food (formulas)
 - LNAAAs typically provide 20 percent of total protein; natural protein provides 80 percent
 - Level of tolerance to dietary protein tailored to each patient
 - Total protein should achieve but not exceed the Daily Recommended Intake of 0.8 to 1 g/kg
 - Clinician monitoring should continue
 - Blood amino acids to assure essential amino acid sufficiency
 - Neuropsych and measures of “mental wellness”
 - Nutrition status; adjust diet as for any individual with PKU
- **GMPs and Diet**
 - Alternative to amino acid based, Phe-free medical foods
 - Intact protein source naturally low in Phe
 - Purified and concentrated to further reduce residual Phe
 - AA profile
 - Must be supplemented with limiting amino acids
 - Thr and Ile 2-3 times higher than in other natural protein sources
 - Available in a medical food as Glytactin™
 - Possible Risks: All products may not contain all essential minerals and vitamins
 - Benefit: Increased palatability/compliance; improved nutritional status (van Calcar 2009)
 - Limited number of studies using GMP
 - Palatability among patients greater than 1 year who were diagnosed with PKU after abnormal newborn screen (Lim 2007, Ney 2009)
 - Growth and Phe concentrations in brain and plasma in mice (Ney 2008)
 - Insulin concentrations and ghrelin concentrations in short term human studies (MacLeod 2010)
 - Contains a small amount of Phe (2.5 to 5 mg/g protein) which needs to be accounted for in daily intake
- **Adults who refuse optimal diet therapy present a special dilemma: to treat or not to treat?**
 - Moral and ethical concerns suggest that there may benefit from any level of treatment that reduces plasma Phe concentrations and reduces behavioural problems, improves executive functions and reduces neurological dysfunction
 - Goal of treatment should be any benefit to the patient that can be achieved with a realistic level of compliance
 - Treatment should include consideration of sapropterin and/or LNAAAs
- **Summary:**
 - Diet for life
 - Current treatment goal of blood Phe concentrations between 120-360 µmol/L (2-6 mg/dL)
 - Higher protein intake than DRI's when consuming medical foods
 - Appropriate growth and development while
 - Avoiding underweight or obesity
 - Individualize treatment to maximize nutritional status, cognitive outcomes, behaviour, mood and quality of life

- Regular monitoring of blood Phe and Tyr and nutritional biomarkers to evaluate treatment adequacy and adherence
- Phe tolerance and genotype can each inform clinical expectations and design of effective treatment
- Assess appropriateness of additional treatment options
 - Especially for “off diet” or poorly adherent individuals
- **Summary of Future Research:**
 - Optimal blood Phe concentration goals across the lifespan
 - Nutritional status throughout the lifespan and its relationship to outcomes such as growth, cognition and behaviour
 - Long-term outcomes associated with the use of additional treatment options such as sapropterin, LNAAAs, and GMP
 - Utilizing new technologies to develop tools to measure and improve adherence to treatment

Pharmacologic Interventions

- **What is a positive response to sapropterin?**
 - Phenylalanine reduction?
 - What is significant (30%?)
 - Which phenylalanine levels are used?
 - Phe/Tyr ratio?
 - Increased Phe tolerance?
 - Definition variable
 - 300mg/day vs 2-3 x increase vs off diet
 - Psychological outcome?
 - Ultimately may be most important
 - Which tests to use?
 - Limited resources
- **Sapropterin loading protocols**
 - Short protocols
 - 8-72 hours: 48 hours superior to 8 or 24 hours
 - Often used in European centers
 - Advantages:
 - Less room for dietary manipulation
 - Less false positives
 - Disadvantages
 - Frequent blood tests
 - May miss slow responders
 - Long protocols
 - 4 days to 1 month
 - Frequently used in North America
 - Advantages
 - Detection of slow responders as first described by Shintaku
 - Disadvantages
 - Many testing protocols only use one-week testing
 - Variability
 - Illness
 - Dietary manipulation

- Placebo controlled ABAB design
 - Advantages
 - Eliminates much of variability seen in previous testing
 - Disadvantages
 - Additional cost of placebo
 - More complex for clinics/patients
 - Still room for variation with few samples
- Conclusions:
 - No gold standard test for sapropterin responsiveness
 - Short protocols will pick up majority of responders but will miss a few slow responders and demand on clinics is high
 - Long protocol easier but more prone to variability
 - Perhaps best option is placebo-controlled protocol
- **START Protocol (Sapropterin Therapy Actual Response Test) Dr. Chet Whitley of Minneapolis**
 - Sapropterin dose = 20 mg/kg day
 - Response defined as > 20% reduction in plasma PHE during 2 separate weeks of sapropterin therapy
 - Test duration = alternating 7 days on sapropterin with 7 days on placebo for 4 weeks (example of ABAB protocol)
 - Double-blind, placebo controlled test
 - Eighty-eight patients completed START
 - Responders: 42 (10 men, 10 women, 14 boys, 8 girls)
 - Non-responders: 46 (11 men, 19 women, 9 boys, 7 girls)
 - Response rate: 47.7%
 - Genotype known for 62 patients
 - 31 in the responder group
 - 31 in non-responder group
 - 46 different genotypes represented
- Future Research
 - What we know:
 - Sapropterin reduces blood phenylalanine levels for approximately half of PKU patients
 - Reduction of phenylalanine levels, and increased dietary phenylalanine tolerance, are significant and helpful for some patients often improving the quality of life
 - Increasing diversity of diet – more natural protein is beneficial
 - Reducing the out-of-pocket expense for medical foods (formulas)
 - The gaps:
 - Many patients have not been tested for sapropterin responsiveness due to
 - Access
 - Information
 - Fear
 - Future Directions:
 - Ensure the availability of sapropterin for all patients
 - Encourage accurate testing for sapropterin responsiveness for those PKU patients who receive the medication
 - Develop a comprehensive genotype-phenotype catalog
 - Explore new therapies that are:
 - More efficacious

- Work for more patients

Molecular Testing, New Technologies and Epidemiologic Considerations

- **Should all patients with HPA receive genotyping?**
 - The genotype may be the most accurate determinant of the degree of PKU (classic, moderate, mild, MHP) today and this determination is important to inform medical treatment and parents or adult patients at beginning of therapy
 - Determining degree of PKU (Classic, Moderate, Mild, MHP)
 - Newborn Screening now leads to diagnosis and treatment of PKU/HyperPhe often in first week of life. Previously used determinants of degree of PKU not accurate
 - Confirmatory pre-treatment Phe level now often collected before peak Phe reached thus utilizing pre-treatment Phe to establish phenotype now unreliable
 - Dietary Phe tolerance as determinant of phenotype problematic since this takes time and may be misleading in outpatient setting
 - Protein/Phe loading of newly identified patients is no longer appropriate
 - Determining Treatment and Predicting BH4 Responsiveness
 - Mild HyperPhenylalaninemia (mild HPA) does not require diet but monitoring; PAH genotype can distinguish MHP from PKU in early infancy with great benefit to family and clinic
 - BH4 responsiveness not always obvious, especially when assessed in outpatient setting. Confounding factors include inaccurate diet record & infrequent Phe levels
 - When it is difficult to determine whether patient is BH4 responsive having a known BH4-responsive genotype can be very helpful
 - Summary:
 - Strong correlation between genotype (both mutations of a patient) and biochemical phenotype (degree of PKU)
 - Reliable PAH genotyping widely available
 - 95% of patients can be fully genotyped by gene sequencing
 - Cost now reasonable (\$1,100) and decreasing
 - Genotyping cost once in a lifetime, comparable to 3-4 amino acid analyses and may reduce frequency of amino acid analyses in mild HyperPhenylalaninemia
- **Correlations of Genotype-Phenotype**
 - Germany and Denmark: 40% of patients completely genotyped testing for only 8 PAH mutations. Strong genotype-phenotype correlation (Okano et al NEJM 1991)
 - Complete genotype correctly predicted biochemical phenotype in 80% of patients with European ancestry
 - One limiting factor in correlation is unreliable phenotyping. Therefore, actual correlation probably higher than reported.
 - Substantial number of PAH genotypes predict BH4 responsiveness (BIOPKU database)
 - Two databases inform about biochemical phenotype and BH4 responsiveness of PAH genotypes (mutation combinations of patient)
 - PAHdb (<http://www.pahdb.mcgill.ca/>)
 - BIOPKU (www.biopku.org)
 - Phenotypes associated with large numbers of genotypes (mutation combinations) catalogued
 - DNA diagnostic laboratory should include probable biochemical phenotype in report of PAH genotype
 - In heterogeneous populations (North America) specific genotypic changes have less impact
 - New mutations will continue to be observed albeit at a slow rate

- Future Research
 - Prospective multicentre study determining the appropriate pre-treatment Phe level for initiation of dietary therapy & genotyping all hyperphenylalaninemic infants with strict criteria for phenotyping
 - Need to establish new concentration ranges for pre-treatment Phe and their association with type of PKU taking age (days) and diet (breastmilk, formula) of patient into account
 - New concentration ranges prerequisite for determining genotype/phenotype correlation for newly identified genotypes
 - Need to educate about the value of genotyping in determining degree of PKU
- Ethical Considerations Regarding genotype/phenotype testing
 - Even if clear and directive recommendations about testing are developed, alternative approaches are acceptable for clinicians and families who weigh opportunities and challenges differently
 - Important to develop materials that explain the opportunities and challenges of the alternatives in clear language
- Sapropterin Treatment Decisions
 - Approaching Access/Cost Issues
 - Clarify what data are currently needed to inform decision making
 - Clinical data are necessary but not sufficient to make policy decisions
 - Value based decisions--different stakeholders have different values and interests
 - Important to have all stakeholders participate in policy decisions
 - Should costs be covered by payers?
 - High costs are generally justified by-production and surveillance costs; recovery of research and developments costs; and incentives for development of new treatments
 - Must be balanced with clinical value
 - What is a “fair cost” for society to bear?
 - Compare to individual costs for other conditions (Cystic Fibrosis = \$20-30K per year)
 - Compare to cost per population for other conditions (treating PKU population may be cheaper than treating CF population)
 - Compare to overall health care costs (even high costs for rare conditions are not large drivers of overall health care budget)
 - Social obligations towards vulnerable groups that lack political and/or economic power justifies coverage by payers
 - May be necessary to negotiate a fair “charge” with suppliers
 - Criteria should be established to guide which patients should have treatment reimbursed
- Emerging Technologies for PKU
 - In Progress:
 - Identification of non-Phe effects of sapropterin treatment
 - Post marketing sapropterin registry
 - Clinical trial for large neutral amino acids
 - Substitute and artificial protein sources contain no Phe
 - Peg-Pal Phase 2 clinical trial
 - Identify optimum dose and administration interval (eg. how many times a week)
 - 23 Adults enrolled with max >1 year
 - 7 Patients >1 mg/kg
 - Dosing up to 3 times/week
 - Phe response in longest treated 7 patients
 - Average response 1,293 $\mu\text{mol/L}$ to 527 $\mu\text{mol/L}$

- 2 Patients <5 $\mu\text{mol/L}$
- Adjusting dosing (daily to weekly)
- Side Effects:
 - Injection site reaction (43%)
 - Mild to moderate
 - Self limiting
 - Generalized skin reaction
 - 3 Patients
 - Managed with medical therapy or transient dose reduction
 - Systemic IgM reaction
- Liver Cell Transplant for PKU
 - Liver transplant is curative for metabolic liver disease
 - Immunosuppressive regimens are becoming less extensive
 - Some patients discontinue immunosuppression post- transplant
 - Hepatocytes protocol for metabolic rescue and urea cycle disorders
 - Other cell types (especially IPS cells) may eliminate need for immunosuppression
- Gene Therapy for PKU
 - Similar issues to, but longer history than, hepatocyte transplant
 - Current challenges
 - Vector type
 - Vector deliver
 - Prolonged gene expression

New Treatments on the Horizon for PKU

- Why do we need novel therapies for PKU?
 - Comparison of well-treated PKU patients with unaffected siblings
 - IQ 8-10 points lower on average in PKU
 - Higher incidence of learning disabilities
 - Visuospatial skills
 - Attention deficit/hyperactivity
 - Non-adherence to complicated, unpalatable diet
 - 75% of adolescents with blood Phe above recommended levels
 - Impaired executive functioning
 - Adult onset white matter degeneration
 - Spasticity
 - Ataxia
 - Seizures
 - Maternal PKU syndrome
 - Fetal teratogenesis
 - Microcephaly
 - Developmental delay
 - Congenital heart defects
- Gene Therapy and PEG-PAL research continues...

Transitions to Adult Health Care

- **Clarifying Expectations**
 - Health Care Providers
 - Pediatric Team - adults are not large children
 - Knowledge of adult comorbid diseases
 - Not just medical issues: social/economic
 - Adult Team – not adults
 - Well patient visits needed
 - Cannot cut out parents entirely
- **Communication**
 - Patients/families
 - Understand time and legal limitations of adult Health Care Provider
 - “3 sentence summary”
 - Knowledge of medications/allergies
 - Know which HCP is responsible for which problem
 - Be open to new means of health care delivery
 - Health Care Providers
 - Pediatric HCP
 - Direct communication with adult HCP
 - Schedule visits close to transition
 - Adult HCP
 - Flexible office practices
 - Multiple reminders
 - Motivational interviewing
 - Novel Communication Tools
 - Patient communicating with family
 - Clear definition of appropriate communication strategies
 - Social Media as a communication tool
 - Highly desirable by patients/families
 - HCP needs to recognize this and define communication that works
- **Sustainability**
 - Cost savings offset cost of transition resources
 - Cost of caring for one child affected by maternal PKU:
 - group home care:\$350/day
 - lifespan: 70 years
 - Total cost:\$8.9 million
 - Extensive data on transition planning for diseases with similar frequency
 - Shortage of trained metabolic physicians means that PKU will NEED to be cared for outside the narrow field of metabolic medicine
- **Summary**
 - Transition is a process rather than an event
 - Transition goals are not being met for the majority of individuals with chronic health conditions
 - Barriers to transition include expectations, challenges in communication, and sustainability of resources including health care providers
 - For patients with PKU, lack of data on hard outcomes hinders transition planning