Medical and Dietary Guidelines for the Treatment of PKU

Developed by the American College of Medical Genetics and Genomics (ACMG) and Genetic Metabolic Dietician's International (GMDI)[i]

The ACMG and GMDI recently released new guidelines to the medical community for the optimal treatment of PKU. Below is a list of the key recommendations on the new guidelines:

- The guidelines refer to PKU as phenylalanine hydroxylase deficiency.
- The treatment of PKU should be initiated as early as possible. Treatment is lifelong with a goal of maintaining blood phe levels in the range of 120-360 umol/l (2-6 mg/dl) in patients of all ages.
- There is no convincing evidence that levels about 360 umol/l and above are without clinical effect.
- Blood phe levels should be monitored at least weekly until age 1; biweekly to monthly in ages 1-12; and monthly in adolescents and adults who are stable and well controlled.
- Routine biochemical assessments (phe, tyrosine, plasma amino acids, prealbumin, total protein, complete blood count, ferritin, and vitamin D 25-OH should be monitored at regular intervals based on age.
- Plasma amino acids (full panel) should be considered when a formal nutritional assessment suggests it is needed.
- Patients treated within the early weeks of life with initial good metabolic control, but who lose that control in later childhood or as an adult, may experience both reversible and irreversible neuropsychiatric consequences.
- PAH genotyping (i.e. mutation analysis) is recommended for improved therapy planning.
- Medical foods (formula and foods modified to be low in protein) are medically necessary for people living with PKU and should be regarded as medications.
- Medical foods should be consumed throughout the day and divided into at least three servings because more frequent consumption is associated with better phe tolerance and improved plasma phe concentrations.
- Any combination of therapies (medical foods, sapropterin, large amino acids, etc) that improve a patient's blood phe levels is appropriate and should be individualized.
- Large amino acids may be used in adults who are not in good metabolic control and do not adhere to other treatment options.
- Experience with sapropterin under the age of 4 is limited.
- Response to sapropterin is not accurately predicted by a person's gene mutations and thus response should be documented by formal testing.
- Reduction of blood phe, increase in phe tolerance or improvement in clinical symptoms of PKU are all valid indications to continue a particular therapy.
- Genetic counseling should be provided as an ongoing process for individuals with PKU and their families.
- Due to an increased risk for neurocognitive and psychological issues, regular mental health monitoring is warranted. A number of screening tests are recommended to identify those in need of further assessment.

- Blood phe should be monitored at a consistent time during the day, preferably 2-3 hours after eating.
- Tyrosine levels should also be maintained in the normal range.
- Clinic visits should occur weekly- monthly for infants; every 6 months for children 1-7 years; every 6-12 months for 8 years old and up; and monthly to per trimester for maternal PKU.
- Maternal PKU recommendations:
    - Maternal phe levels should be maintained at 120-360 umol/l before conception and throughout pregnancy.
    - Large neutral amino acids should not be used during pregnancy
    - Women taking sapropterin who become pregnant should be offered the option of remaining on the medication
    - Women who may benefit from the lowering of blood phe levels with sapropterin should be offered it as an option during pregnancy
    - There are no contraindications to breastfeeding postpartum as infants not affected by PKU are able to metabolize the slightly higher phe levels in their mother's breast milk

Treatment of PKU will eventually be individualized with multiple medications and medical foods available to tailor therapy. The primary goal of therapy should be to lower blood phe, and any interventions, including medications, or combination of therapies that help to achieve that goal in an individual, without other negative consequences, should be considered appropriate therapy.

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[i] Vockley, Andersson, Antshel et al, Phenylalanine hydroxylase deficiency: diagnosis and management guideline, *Genetics in Medicine*, 2014, doi:10-1038/gim.2013.57 and Singh, Rohr, Frazier, etc al, Recommendations for the nutrition management of phenylalanine hydroxylase deficiency, Genetics in Medicine, 2014, doi:10-1038/gim.2013.179.