A total of 69 recommendations for PKU management have been formulated by the European Guidelines team and the 10 key guidelines have now been published. Scottish Intercollegiate Guidelines Network method and Delphi methods were used to assess evidence, grade it and form a consensus for best practice in areas of management with incomplete or equivocal evidence.

PKU is caused by a deficiency of the hepatic enzyme phenylalanine 4-hydroxylase (PAH) which converts excess phenylalanine to tyrosine. Classical PKU is characterised by phenylalanine levels >1200µmol/L. As well as high levels of phenylalanine, severe PAH deficiency may also result in a low tyrosine levels which is a semi-essential amino acid.

Untreated, PKU leads to irreversible brain damage; however, individuals with ‘early treated’ PKU (identified via newborn screening) show normal intellectual and motor development. There is evidence to suggest neuropsychological compromises do still occur in people with early treated PKU, which then lead to behavioural and social issues.

DIETARY TREATMENT - A RECAP

The only treatment for PKU in the UK is dietary treatment involving the restriction of natural protein in order to limit the amount of dietary phenylalanine. Phenylalanine is an essential amino acid and a controlled amount is needed to prevent deficiency. 50mg of phenylalanine is termed ‘one exchange’ and is equivalent to 1g natural protein. To achieve new target phenylalanine levels of 120-600µmol/L, an adult with classical PKU might be prescribed between six to 15 exchanges (roughly equivalent to 6-15g protein).

The diet is composed of:

- free foods - those naturally low in protein, or manufactured to be low in protein (often prescribed low protein foods);
- exchange foods - when measured portions provide the natural protein prescription; and
- regular protein substitute (usually amino acids which are phenylalanine free) daily in split doses.

The diet is highly restrictive - foods to be avoided are very high in protein such as meat, fish, cheese and eggs etc. However, the degree of protein restriction is such that a very wide range of foods is restricted, such as most cereals, bread, pasta, as well as some vegetables - notably white potatoes.

Taking protein substitute is essential to provide nutritional deficiencies which themselves could cause reduced brain functioning (and insufficient exogenous amino acids can cause increased endogenous phenylalanine release and thus a loss of metabolic control).
People with PKU were not always recommended lifelong dietary management due to a lack of consistent evidence. Adults with PKU currently attending metabolic clinics have different self-selected dietary approaches:

a) On a strictly controlled low phenylalanine diet and daily protein substitute.

b) On a diet with no restrictions at all, i.e. ‘off diet’, or self-imposed lower protein diet similar to a vegetarian diet, with or without protein substitute.

The body of evidence is significant and presented in three meta-analyses considered by the guidelines panel, as well as several well-designed studies which are scientifically robust. In some of the studies used, the evidence is slightly weakened by the presence of patients who have not been continuously treated through life, so deficits could be due to historically raised Phe levels; however, the volume of neuropsychology data and imaging studies (showing white matter changes >600umol/L), has led to the guideline of 600umol/L upper Phe level.

Evidence from people who have discontinued diet and returned to it, show that upon regaining metabolic control (i.e. reduced blood phenylalanine levels and improved nutritional status), the individuals experienced improvements, or even reversal of neurological symptoms (including vision loss).

This group of people also report an improvement in health-related quality of life upon returning to a Phe-controlled diet. Further information is needed about quality of life in continuously treated people with PKU and a validated PKU-specific quality of life questionnaire is now available online, so that this issue can be explored in more detail.

Individuals ‘off diet’

- All adults with PKU should have lifelong systematic follow-up in specialised metabolic centres because of specific risks that might occur during adulthood.

The evidence base to support diet for life is relatively new and continuing a Phe-restricted diet for life is burdensome. It is essential that
adults off diet are not lost to follow-up, so a non-judgmental approach in clinic is needed, whilst informing on the benefits of return to diet and annual clinical and nutritional monitoring.

**MONITORING & ANNUAL NUTRITIONAL REVIEW**

**Monthly blood spots**
Self-managed blood spots are for blood phenylalanine only and sent by individuals to laboratories directly. Blood spots are processed quickly, allowing prompt and remote dietary adjustments to achieve the desired blood levels of phenylalanine.

**Annual nutritional review**
Nutritional blood monitoring (taken in clinic) includes the full range of plasma amino acids, serum B12, homocysteine or methylmalonic acid, folate, ferritin, and full blood count (showing haemoglobin and mean corpuscular volume).

Serum homocysteine is strongly influenced by diet and raised homocysteine levels are found in people whose folate, B12 or B6 status is suboptimal - measuring homocysteine is recommended as serum B12 levels are not an accurate measure of functional deficiency. Serum methylmalonic acid concentrations are also raised when serum B12 concentrations are low.

**Diet history:** a three-day food record or a 24-hour recall should be done annually as a minimum. The diet assessment should also consider the spread of the exchanges through the day and protein substitute consumption including total daily dose, variation through the week, pattern of consumption through the day (split dosing is ideal for optimal serum phenylalanine stability through the day). Other aspects of metabolic diet history taking includes use of prescribable low protein foods.

**Anthropometry:** weight, height and BMI need to be measured and recorded.

Other micronutrients can be tested biochemically if clinically indicated, e.g. zinc, selenium, calcium, vitamin D, as well as hormones such as parathyroid hormone.

**Clinical reviews, neurocognitive assessments and psychosocial function review**
The guidelines recommend a yearly clinical neurological examination and a yearly clinical assessment of adaptive issues or functions - this means clinically relevant behavioural problems. Every year as a minimum, a clinic appointment must include an investigation into psychosocial functioning and wellbeing and health-related quality of life.

The guidelines recommend formal neurocognitive testing (IQ, perception and executive function - which includes inhibitory control, working memory and cognitive flexibility), at age 18 years old. Not all metabolic services have access to a psychologist to undertake the testing as recommended - the rationale for the recommendation is to have a baseline test at this stage, enabling identification of any deterioration in executive and cognitive performance in adult life. The transition to autonomous self-management of PKU by an individual might be complete by 18 years of age. The guideline authors acknowledge that major life events are occurring at this stage, such as moving out of home and/or starting paid employment.
The European Guidelines will bring a clear framework to people with PKU and those involved with their treatment, with the prospect of much improved outcome in thinking, behaviour, social function and (we propose) quality of life.

There will be challenges - historically, guidelines have higher permissible blood phenylalanine levels, so it is possible that adults with PKU may need to reduce natural protein intake to achieve the optimal metabolic control and, thus, optimal psychosocial outcomes.

All adults should have lifelong follow-up in specialised metabolic centres. Adults who choose not to follow optimal PKU dietary treatment need encouragement to attend for annual nutritional review. Lifelong dietary treatment for all those with PKU means that healthcare professionals need to provide continuous support to individuals in order for them to overcome difficulties in this challenging dietary treatment.

Information sources
1 Van Spronsen et al (2017). Key European guidelines for the diagnosis and management of patients with phenylketonuria; Lancet Diabetes & Endocrinology Available online 10 January 2017
4 www.nspku.org