# Understanding the PKU Guidelines, 2025:

Essential Information for Patients and Health Professionals.

# TRACKING YOUR METABOLIC HEALTH!

**Individuals with PKU may be managed by dietary phenylalanine (Phe) restriction only, combined Phe restriction and drug therapy, or drug therapy only.**

## 4 PILLARS OF DIETARY TREATMENT

Protein substitutes must be taken **at least 3 times a day**

Fruits and vegetables containing Phe **up to 75 mg/100g** (except for potatoes) can be eaten without measurement

Individual **Phe tolerance** should be checked each year


Avoid the sweetener **aspartame (E951)**, a source of Phe commonly found in high amounts in "low-sugar" drinks

## BRAIN HEALTH CHECK-UPS

Neuropsychological testing should be offered to all people with PKU around age 5, 12, 18 years and thereafter every 5 to 10 years.

## DRUG TREATMENT OPTIONS

Ask your doctor if drug options such as sapropterin, sepiapterin or pegvaliase may help you.

## BLOOD PHE TARGETS

To protect brain health, individuals should aim for these therapeutic ranges:

Age 0 to <12 years: **120–360** µmol/L
Age 12 to 18 years: **120–600** µmol/L
Adults (over 18 years): **120–600** µmol/L

## BLOOD SPOT FREQUENCY

Regular dried blood spot testing is required a **minimum** of:
0–1 year: weekly
1–12 years: every two weeks
>12 years: monthly
Pregnancy pre-conception: weekly
Pregnancy: twice weekly


## PLANNING FOR A HEALTHY PREGNANCY

Reach target blood levels (**120–360 µmol/L**) before conception to protect the baby's development.

## UNIVERSAL NEWBORN SCREENING

Newborn screening for PKU should be considered a **national obligation.**

- Early detection is necessary for early treatment.
- Treatment should start **by 10 days of age.**

## GENETIC TESTING

- Patient genotyping is **recommended.**
- It distinguishes PAH deficiency from DNAC12 deficiency and defects in BH4 metabolism.
- It may help to predict **sapropterin-responsiveness** and define the **metabolic phenotype.**

## TARGETING VULNERABLE GROUPS

Screening for familial HPA/PKU in **unscreened mothers** of children with hyperphenylalaninemia or with signs of maternal PKU syndrome is recommended.

Routine screening for PKU is strongly recommended for immigrant or refugee children younger than 6y and selective at any age.

# NEWBORN

## SCREENING AND DIAGNOSIS OF PKU

### DIAGNOSTIC WORK-UP FOR ELEVATED BLOOD PHE

In the differential diagnosis of HPA, defects in **BH4 metabolism** and **DNAC12 deficiency** should be **excluded.**

BH4 deficiencies should be **investigated** by measurement of pterins in DBS or urine and dihydropteridine reductase activity in DBS.

**Genotyping** of DNAC12 should be performed in the case of normal pterins and DHPR activity, and when PAH genotyping is not indicative of 2 pathogenic or likely pathogenic variants.

# WHEN TO INITIATE TREATMENT AND TREATMENT GOALS

## TREATMENT GOALS

Lifelong follow-up in a specialist metabolic centre is recommended for any individual with PKU, including adults not on Phe lowering treatment.

In treated patients with PKU, the recommended therapeutic target blood Phe levels are:

Patients aged <12y:

**120–360 µmol/L**

Patients aged 12-18y:

**120–600 µmol/L**

Patients aged >18y:

**120–600 µmol/L**

## CRITERIA FOR INITIATING TREATMENT

**Are untreated blood Phe levels ≥360 µmol/L?**

**No**

### No treatment is recommended

Monitor blood Phe until a minimum of 6y to determine if levels rise above 360 µmol/L.

**Yes**

### Treatment should be initiated

In all children with untreated blood Phe levels >360 µmol/L treatment should be initiated.

## STARTING TREATMENT

Treatment should start as soon as possible, ideally **before 10 days of age.**

# MONITORING AND FOLLOW UP IN PKU


## METABOLIC TEAM

Access to a metabolic physician, a specialist dietitian, and a (neuro)psychologist is essential.


## LOST TO FOLLOW UP

Adult patients should be offered an open invitation to return to the clinic if they have previously disengaged from follow-up.

## MONITORING BONE HEALTH

Measurement of **Bone Mass Density (BMD)** by DXA should be first performed during early adolescence.

## FROM PAEDIATRIC TO ADULT CARE

Young adults should be transferred from paediatric services to a specialized adult metabolic team to ensure **lifelong specialized follow-up.**

## FREQUENCY OF OUTPATIENT CLINIC VISITS

0–1 years: **every 2–3 months**

1–3 years: **three times per year**

3–18 years: **twice per year**

>18 years: **once to twice per year**

## BLOOD SPOT FREQUENCY

Regular dried blood spot testing is required a **minimum** of:

0–1 year: **weekly**

1–12 years: **every two weeks**

>12 years: **monthly**

Pregnancy pre-conception: **weekly**

Pregnancy: **twice weekly**

# DIETARY MANAGEMENT IN PKU


## CHECKING PHENYLALANINE TOLERANCE

**Phe intake** should be reassessed **annually**.

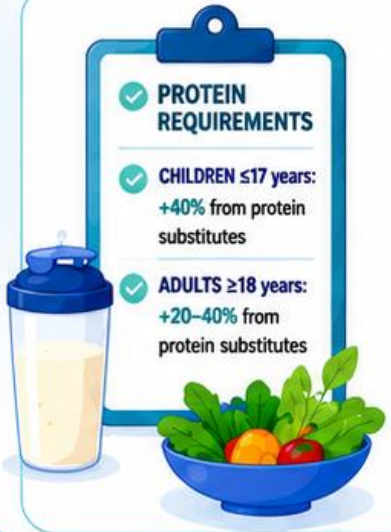
If blood Phe levels remain consistently within the therapeutic range, a controlled increase in dietary Phe can be considered.


## PROTEIN SUBSTITUTES

All countries should assure access to a wide variety of protein substitutes to ensure individualized patient care. They should be given at least 3 times throughout the day.


## GLYCOMACROPEPTIDE

GMP can be used as a protein substitute in patients with PKU **aged ≥4 years** if its **Phe** content is included in the daily **Phe allowance** and its amino acid profile meets requirements.




## PROTEIN REQUIREMENTS

Total protein intake should meet age-related safe levels (WHO/UNU/FAO 2007). Patients on dietary treatment require additional protein:

- Children ≤17 years: **+40%** from protein substitutes.
- Adults ≥18 years: **+20–40%** from protein substitutes.


## SPECIAL LOW PROTEIN FOODS

Special low-protein foods are an important energy source for people with PKU

Their energy, fat, sugar, and salt content should not **exceed** what is **normally** recommended for any food.

# DIETARY MANAGEMENT IN PKU

## NUTRITIONAL REQUIREMENTS

**Energy and nutrient intake** should meet standard requirements.

All age groups should aim for **balanced nutrition**, avoiding both deficiency and excess.

## FRUIT AND VEGETABLES

Fruits and vegetables (except potatoes) containing Phe ≤75mg/100 g can be given **without measurement.**


## ASPARTAME

Aspartame (E951) should be **avoided** in patients on a Phe-restricted diet, especially in beverages and tabletop sweeteners.


## BREAST FEEDING

Breastfeeding with a Phe-free L-amino acid formula should be **encouraged** for infants with PKU.

## GOVERNMENTS (HEALTH SYSTEMS)

Policies should ensure **reimbursement** for special **low-protein foods** and **low-Phe protein substitutes** for all people with PKU, regardless of age or dietary restriction.

# HEALTHY LIVING WITH PKU

## DENTAL HEALTH

Seek **early dental advice** and follow a strong prevention programme.

## PHYSICAL ACTIVITY

**Stay active** and maintain adequate nutrient and energy intake for good performance.

## HEALTH PROFESSIONAL SUPPORT

**Lifelong support** from your PKU team should be offered and tailored to each family's needs.

## SELF-CARE AND EDUCATION

**Effective** education is essential for lifelong self-care, good blood Phe control and social outcomes.

## OVERWEIGHT AND OBESITY

Lifestyle measures should be used to prevent overweight and related comorbidities.

## GENERAL WELL-BEING SURVEILLANCE

**Quality of life**, psychosocial functioning, wellbeing, and mental health should be reviewed at least annually in clinic.

## NUTRITIONAL REVIEW

An **annual nutritional review** is necessary and should include:

- Dietary assessment;
- Weight, height and BMI;
- Blood biochemistry [amino acids, vitamin B12 (homocysteine), hemogram, MCV and ferritin (iron status), and vitamin D].

## BRAIN HEALTH CHECK-UPS

Neuropsychological testing should be offered to all people with PKU around age 5, 12, 18 years and thereafter every (5 to) 10 years.

# MATERNAL PKU

## AVOID UNPLANNED PREGNANCIES

Avoid unplanned pregnancies through timely education and effective contraception.


## MONITORING OF BLOOD PHE

Monitor blood Phe at least weekly pre-conception and twice weekly during pregnancy.

## BLOOD PHE CONTROL

Pregnancy target Phe levels are 120–360µmol/L.
This should also be achieved pre-conception.
If already pregnant, dietary treatment should start within 24 hours.

## AVOID VERY LOW PHE LEVELS

Low Phe levels (<120 µmol/L) should be managed cautiously during pregnancy.


## NEED FOR TREATMENT

No treatment is recommended when untreated Phe levels stay consistently <360µmol/L before or during pregnancy.

## DRUG TREATMENT

**Pre-conception:** Consider testing for saproterin responsiveness, if target Phe levels are not achieved on diet alone.
**During pregnancy:** Responsive patients already on sapropterin may continue treatment.

# MATERNAL PKU: NUTRITIONAL ASPECTS

## AVOID WEIGHT LOSS

In maternal PKU, **avoid weight loss** to prevent **Phe toxicity**, particularly in the first trimester.

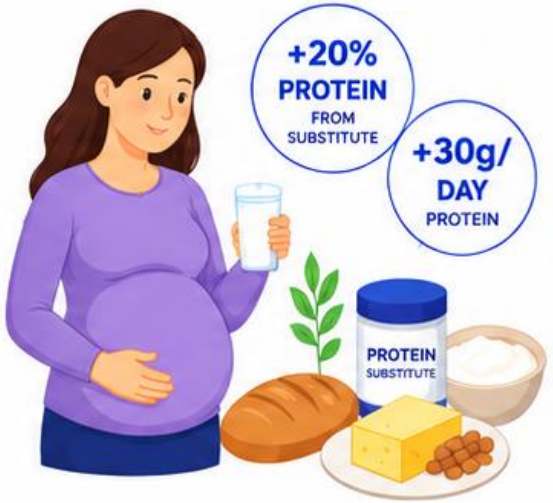
At the same time, women should maintain a **healthy** preconception weight and avoid excess maternal weight.

## TREATING NAUSEA AND VOMITING

Treat nausea and vomiting promptly to prevent reduced intake, poor Phe control, inadequate weight gain, and increased infant risk.


## FOLIC ACID SUPPLEMENTATION

Provide at least **400 µg/daily** folic acid pre-conception and through the first 12 weeks.




## PROTEIN REQUIREMENTS

In trimester 1 and 2, give an additional **20% of protein from protein substitute.**

In the third trimester, add a further **additional 30 g/day protein.**

In most pregnancies, because of improved protein tolerance this should also be provided by **natural protein.**


## DHA SUPPLEMENTATION

Provide **≥200 mg/day** DHA (n-3) for all women pre-conception and throughout pregnancy.

# LATE DIAGNOSED / UNTREATED PKU

## DIAGNOSIS IN UNSCREENED PEOPLE WITH PKU

Intellectual disability or neurological issues should prompt **PKU diagnostic testing** in unscreened children and adults.

## TREATMENT AIMS

In late-diagnosed **children** and **adolescents**, start treatment and keep Phe within target range.

## TREATMENT CONSIDERATIONS

In untreated **adults** with PKU, treatment can be beneficial, but decisions should be **individualised**; consider a >6-month treatment trial to assess effect.

## TREATMENT OPTIONS

Late-diagnosed or untreated PKU patients should have access to **all treatment options**, with decisions made individually.

# DRUG TREATMENT AND PKU


## SAPROPTERIN – SUITABILITY CRITERIA

Perform a sapropterin response test for all PAH-deficient patients **except those with two null variants.**


## SEPIAPTERIN

This is a new oral formulation that has not yet been evaluated within the formal European PKU Guideline process. However, it has been approved by the EMA and FDA.

## LONG TERM SAPROPTERIN RESPONSE

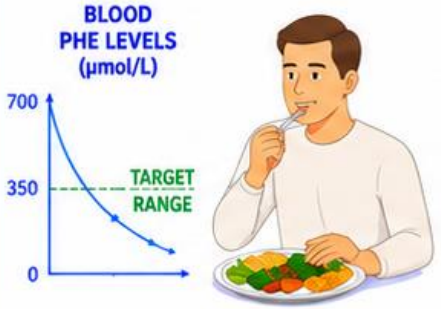
Demonstrate long-term response by adjusting sapropterin dose, natural protein, and Phe-free substitute intake.

Long-term benefit = **≥100% increase in natural protein** with blood Phe in range, or **improved biochemical control (≥75%** of levels within target).

## PEGVALIASE – SUITABILITY CRITERIA

Patients **>16 years** of age who are unable to achieve metabolic control may be offered treatment with pegvaliase, if sapropterin has been considered first.

Close follow-up with **clearly explained safety measures** is essential.




## GOAL OF PEGVALIASE TREATMENT

Achieve at least **0.8 g/kg/day of natural protein** from a mix of foods containing high and low biological protein, without the use of protein substitute or to **decrease blood Phe levels** in those that are not on a protein restricted diet.

Avoid persistently very low Phe levels (less than 35 micromols/L).