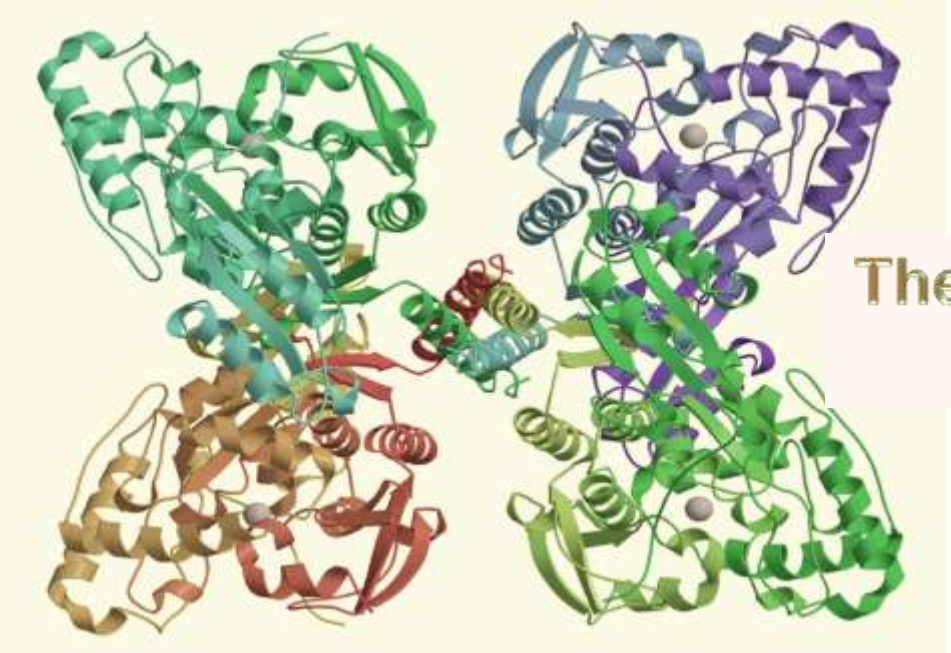
PHENYLKETONURIA

PKU

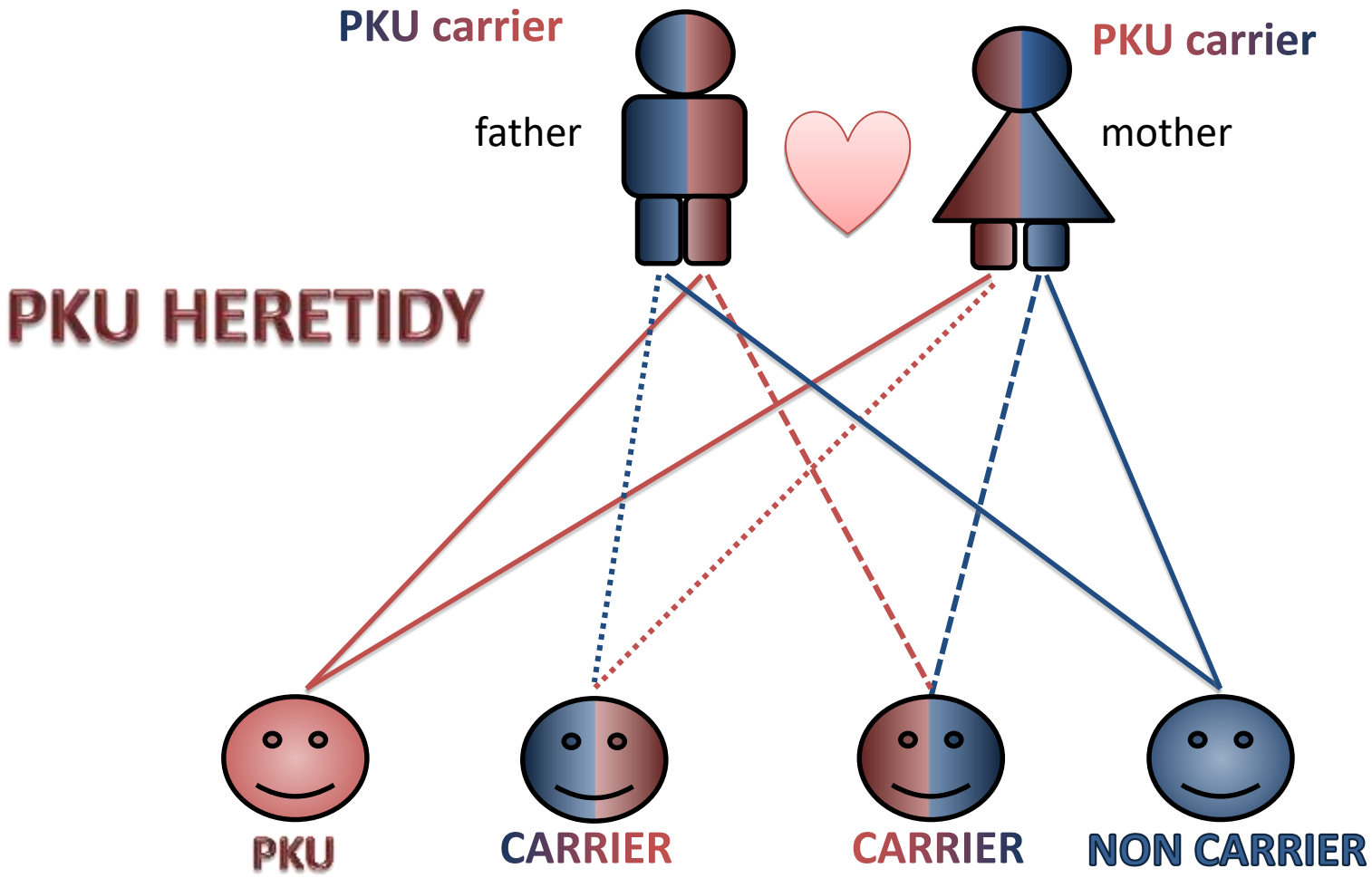
Astrinia Skapalezou BSc, MSc
Clin. Nutritionist-Metabolic Dietitian
National Neonatal Screening dept.-I.E.M.
Institute of Child Health, Athens, Greece

Phenylketonuria (PKU OMIM#261600) is an autosomal recessive inborn error of metabolism resulting from a deficiency of phenylalanine hydroxylase (PAH), an enzyme that catalyzes the hydroxylation of phenylalanine to tyrosine, the rate-limiting step in phenylalanine catabolism. If undiagnosed and untreated, phenylketonuria can result in impaired postnatal cognitive development resulting from a neurotoxic effect of hyperphenylalaninemia



The protein structure of PAH emzyme

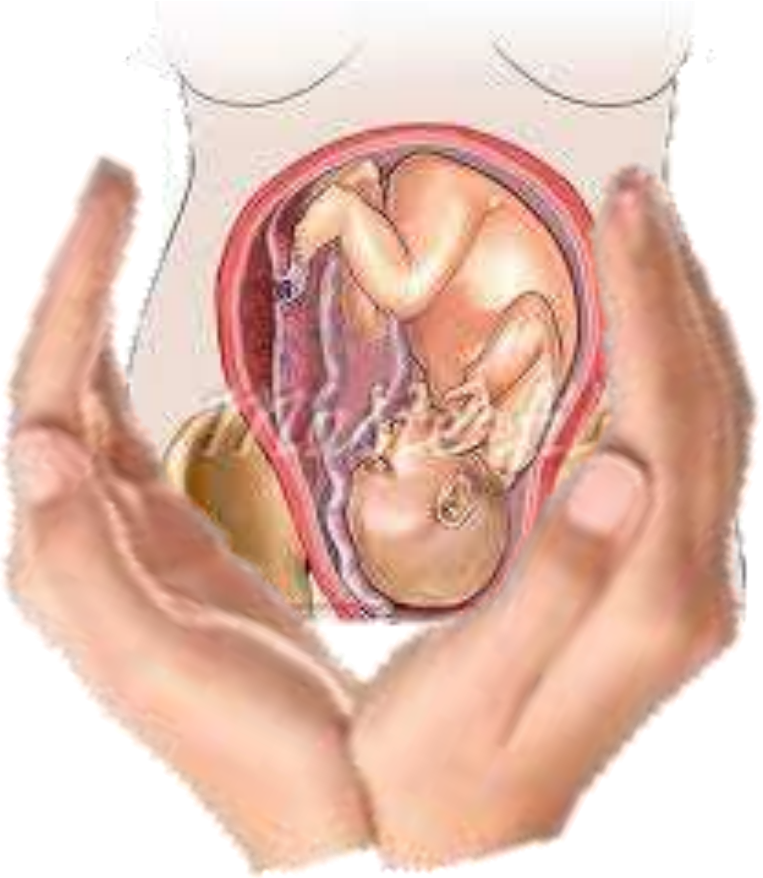
PKU IS AN INBORN ERROR OF HUMAN METABOLISM



PKU IS INHERITED TO THE CHILD BY BOTH PARENTS

EQUALLY

The PKU baby is protected during pregnancy…



…thanks to his/her mother's metabolism

PKU starts to appear after the 1st meal

The metabolic pathway of phenylalanine

Εμπλεκόμενα Ένζυμα

I.1 Phenylalanine-4-hydroxylase (PAH) deficiency (κλασσική μορφή PKU)

I.2 GTP cyclohydroxylase I (GTPCH) deficiency

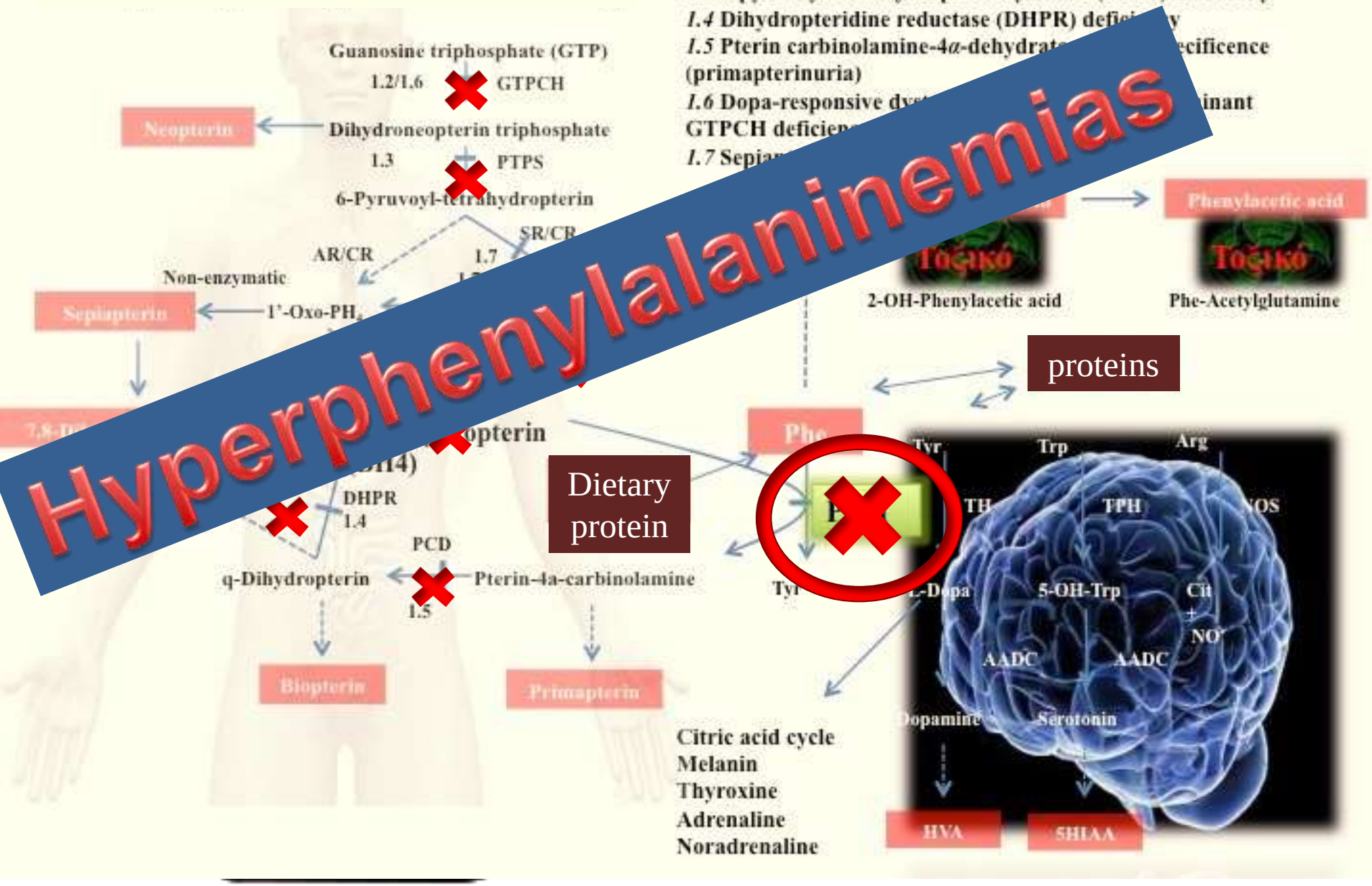
I.3 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency

I.4 Dihydropteridine reductase (DHPR) defici…y

I.5 Pterin carbinolamine-4*α*-dehydrat… …ecificence (primapterinuria)

I.6 Dopa-responsive dy… …inant GTPCH deficien…

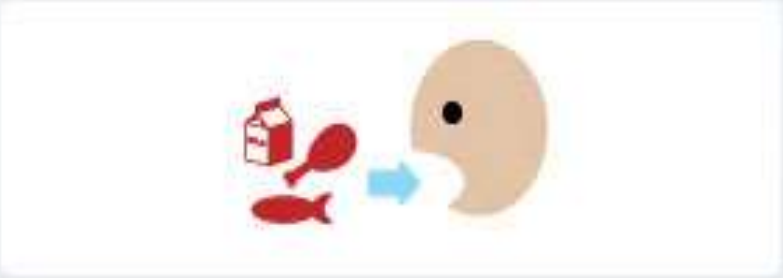
I.7 Sepia…



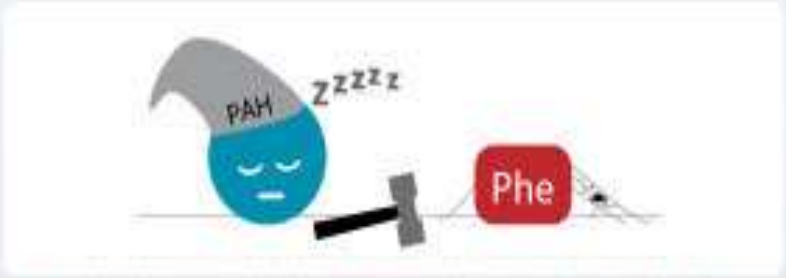
PEOPLE with classical PKU CAN NOT

. use PHE into their body
. convert PHE to tyrosine

LATE DIAGNOSED – OF DIET PKU PERSON



Foods with Phe are eaten



A defective enzyme (PAH) in the body fails to break down the Phe

This leads to high Phe levels in the blood

This leads to problems in thinking and behavior

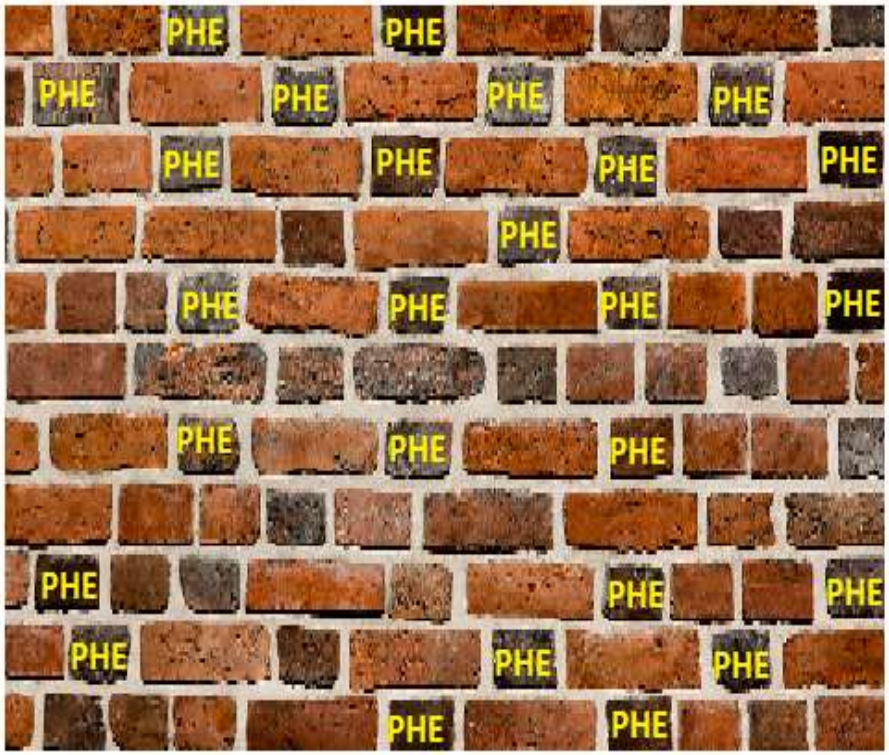
What is PHENYLALANINE?

depicting the human body as… a house

the **WALLS** play the role of the body **PROTEIN**

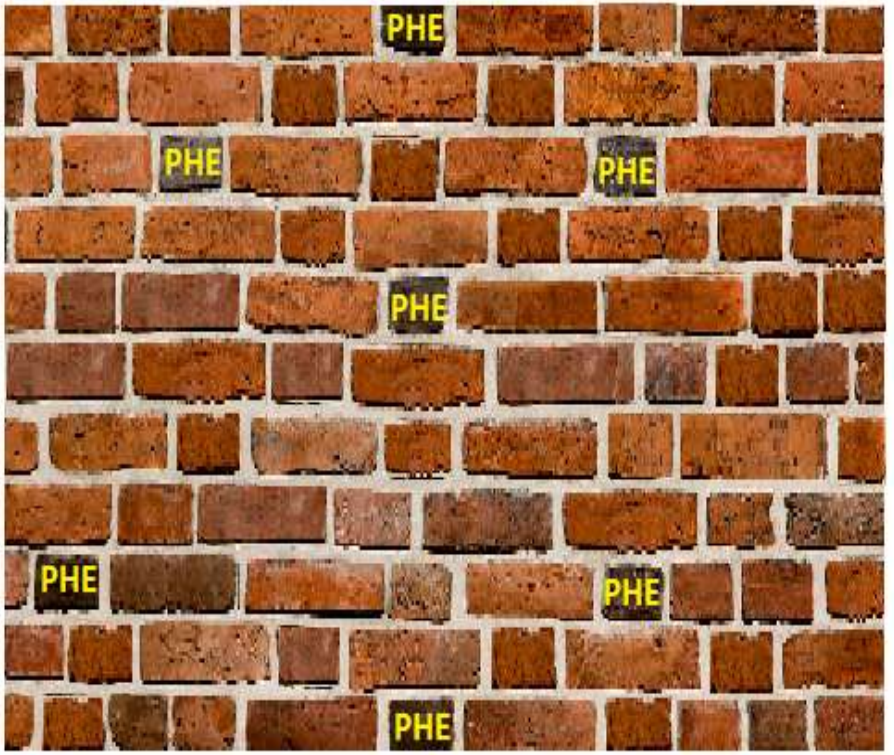
NON PKU wall

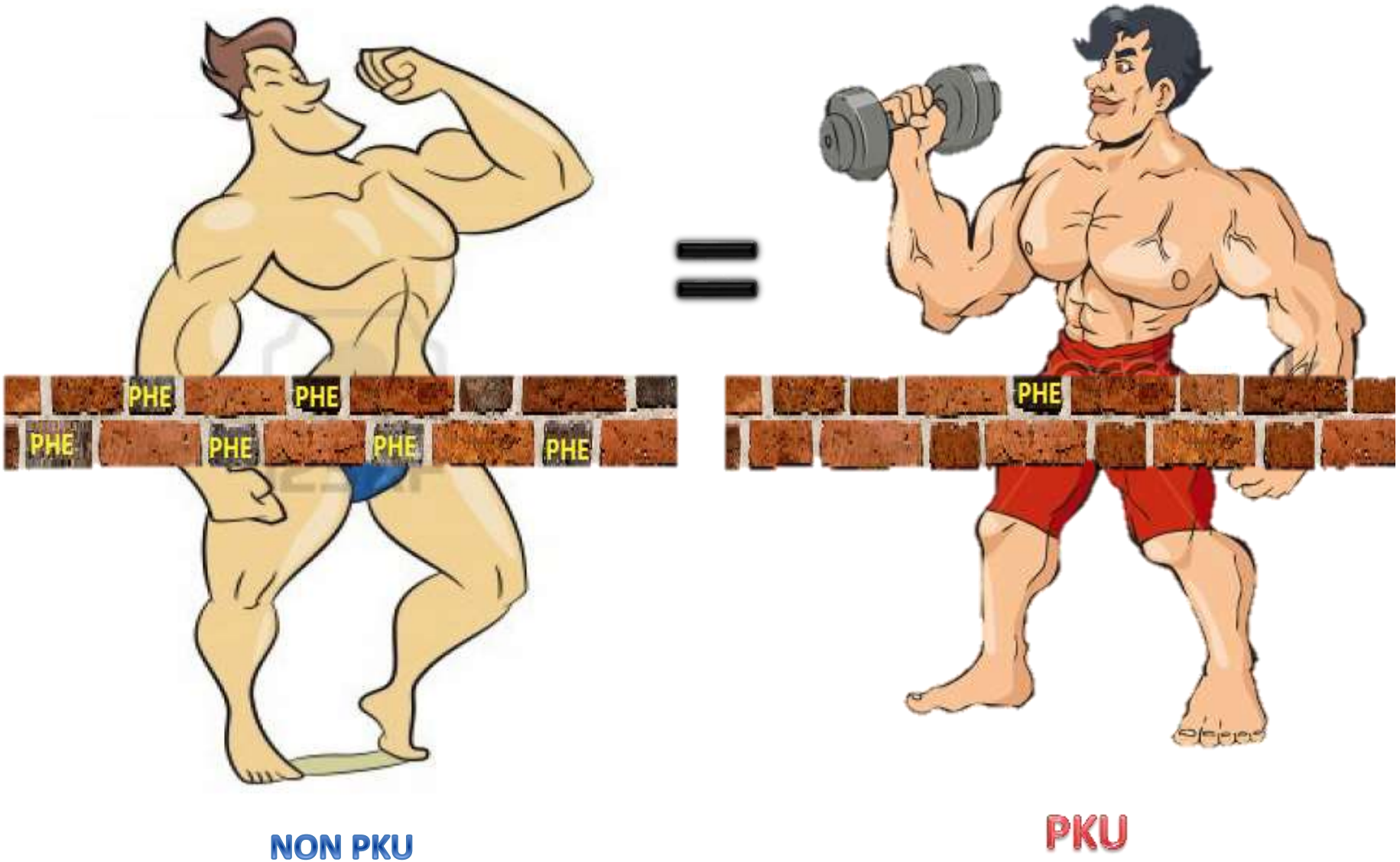
needs MORE PHE



PKU wall

needs LESS PHE

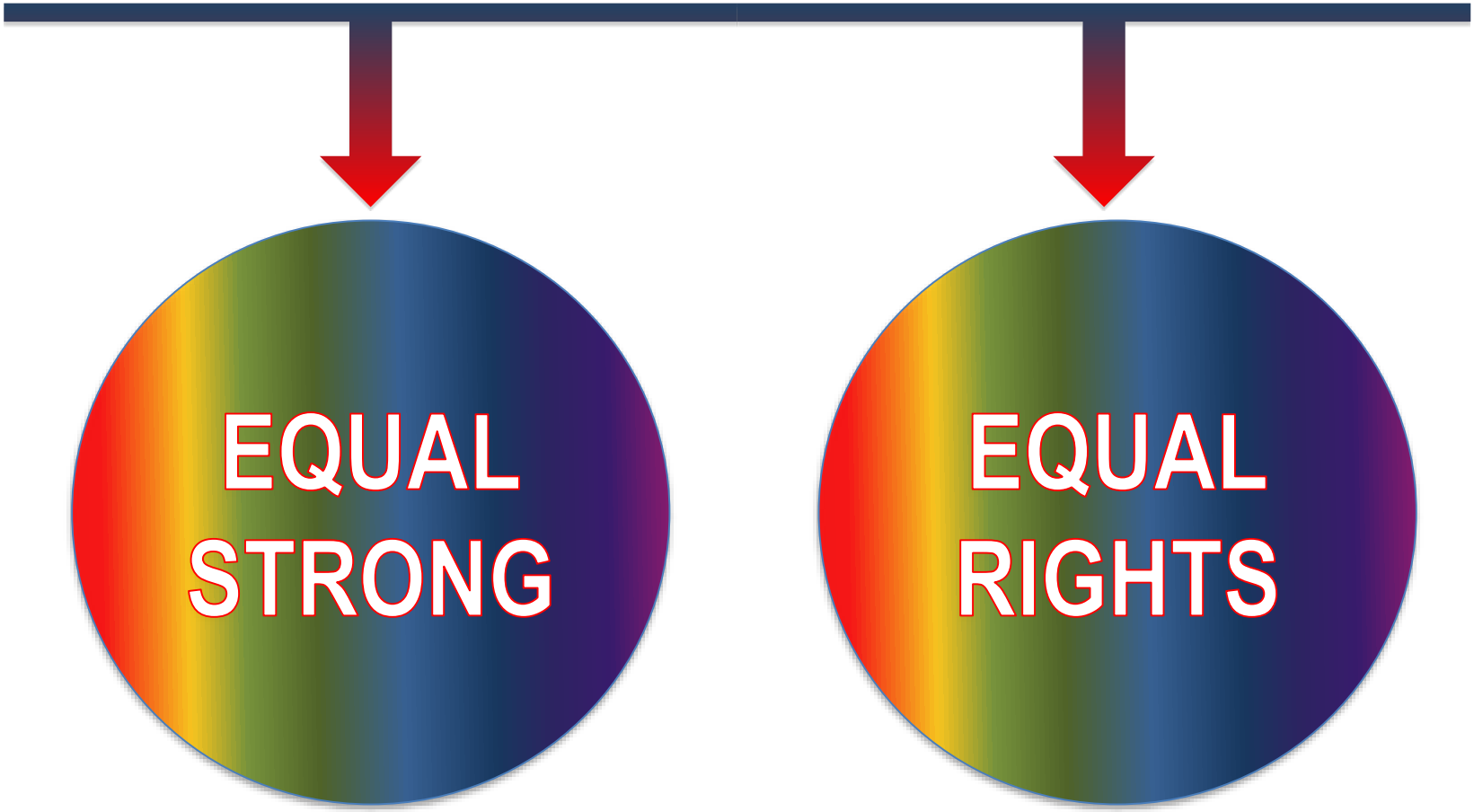




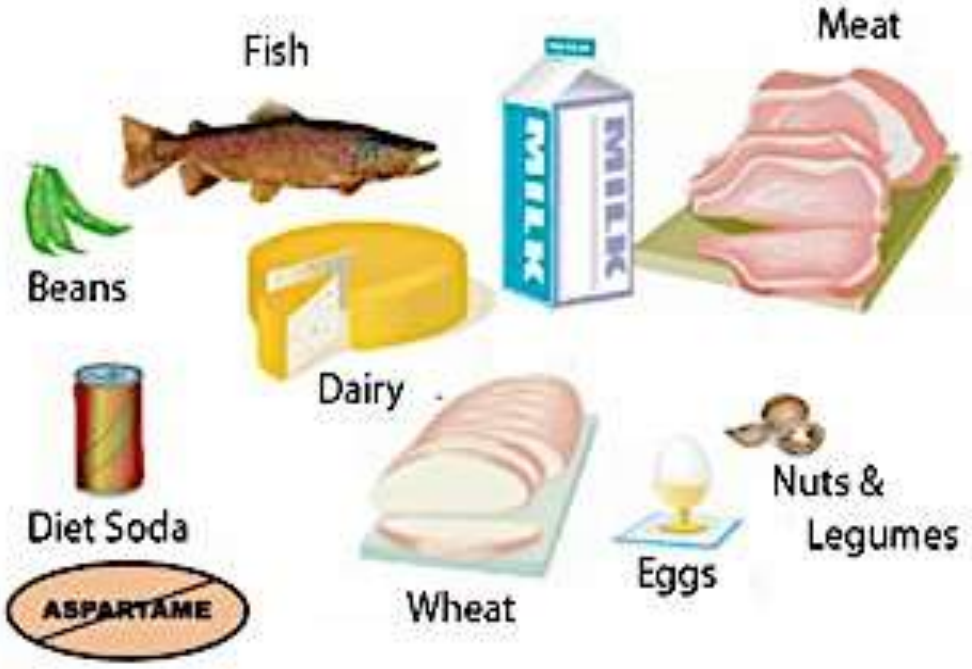
NON PKU

PKU

PKU DIET

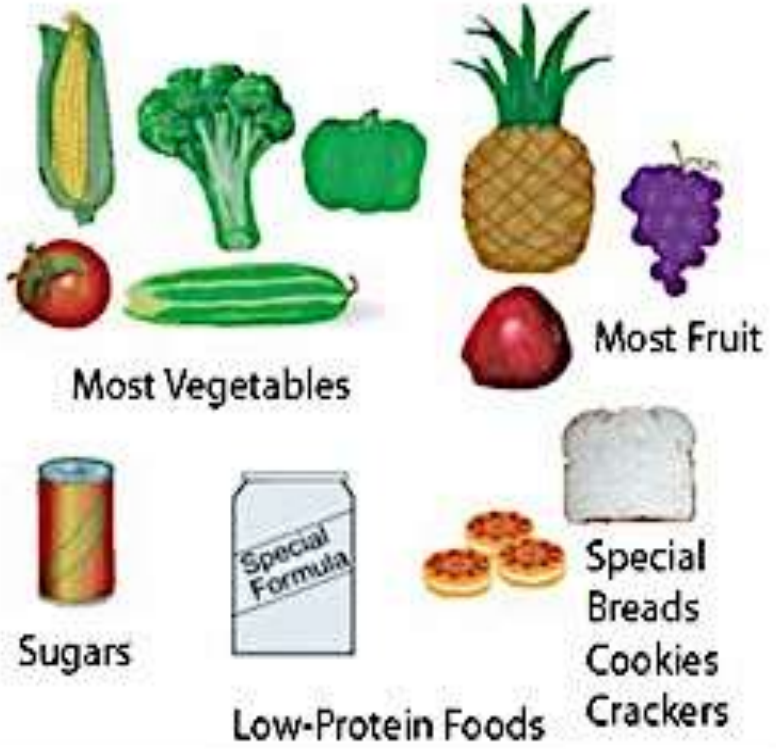


High Phenylalanine Foods:



High-Protein Foods

Low Phenylalanine Foods:



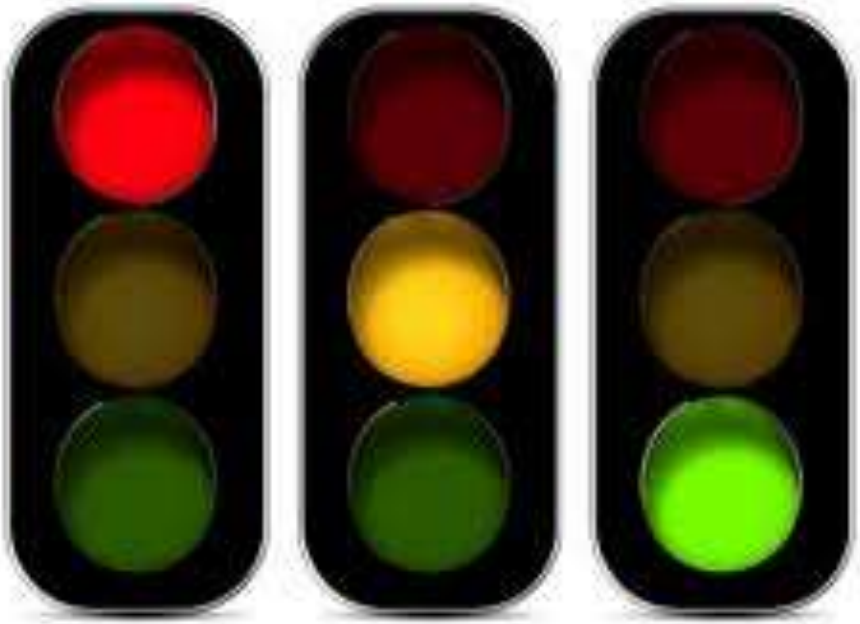
Low-Protein Foods

COMMON FOOD GROUPS

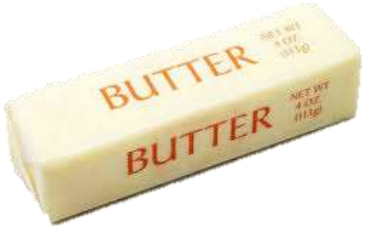
PKU FOOD GROUPS

PKU FOOD PYRAMID

TRAFFIC LIGHT SYSTEM



USE TRAFFIC LIGHT SYSTEM TO CHOOSE THE RIGHT FOODS FOR PKU DIET



+ special food


PHILADELPHIA
300g
PHILADELPHIA










ALL FAMILY MEMBERS MUST HAVE THEIR MEALS TOGETHER

INTERNET

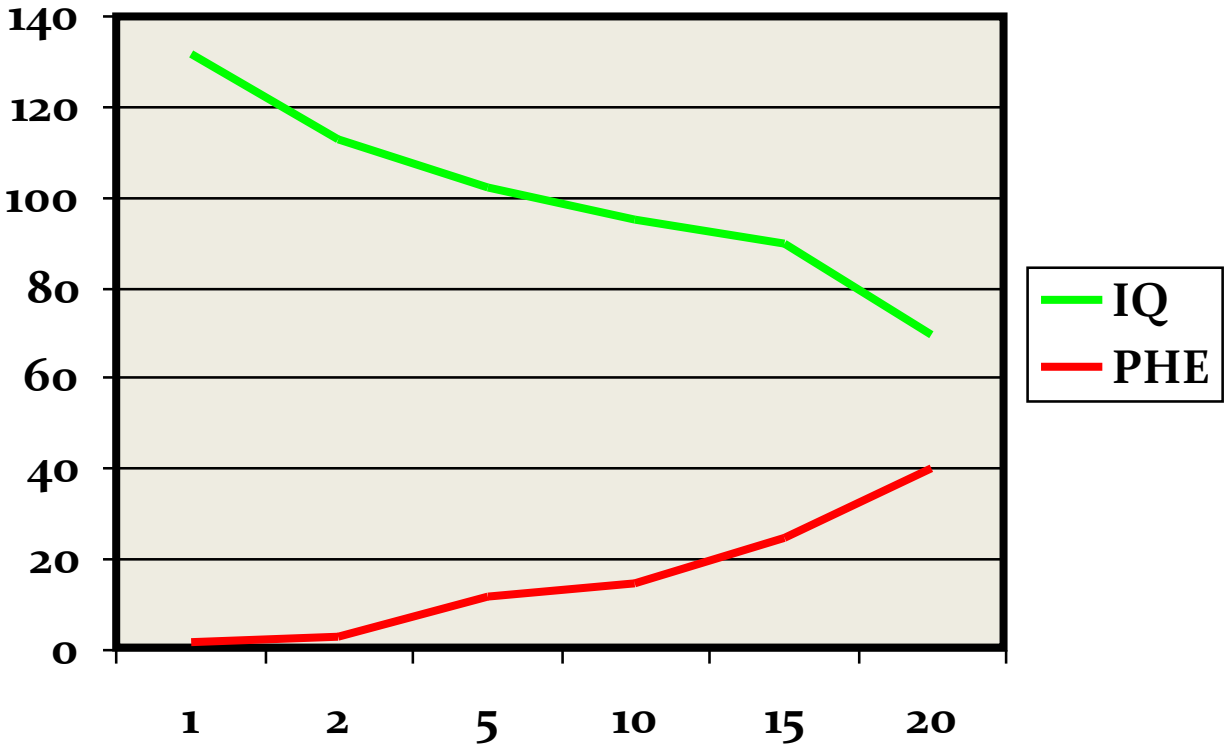
LOW PROTEIN FOOD

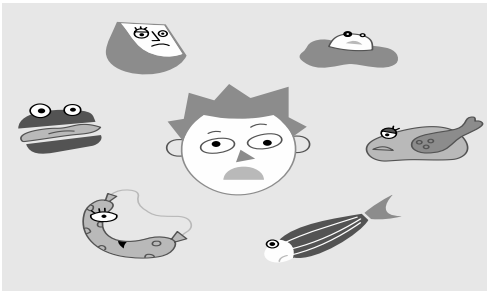
FOOD FOR ALLERGY

DIABETIC FOOD

GLUTEN FREE FOOD

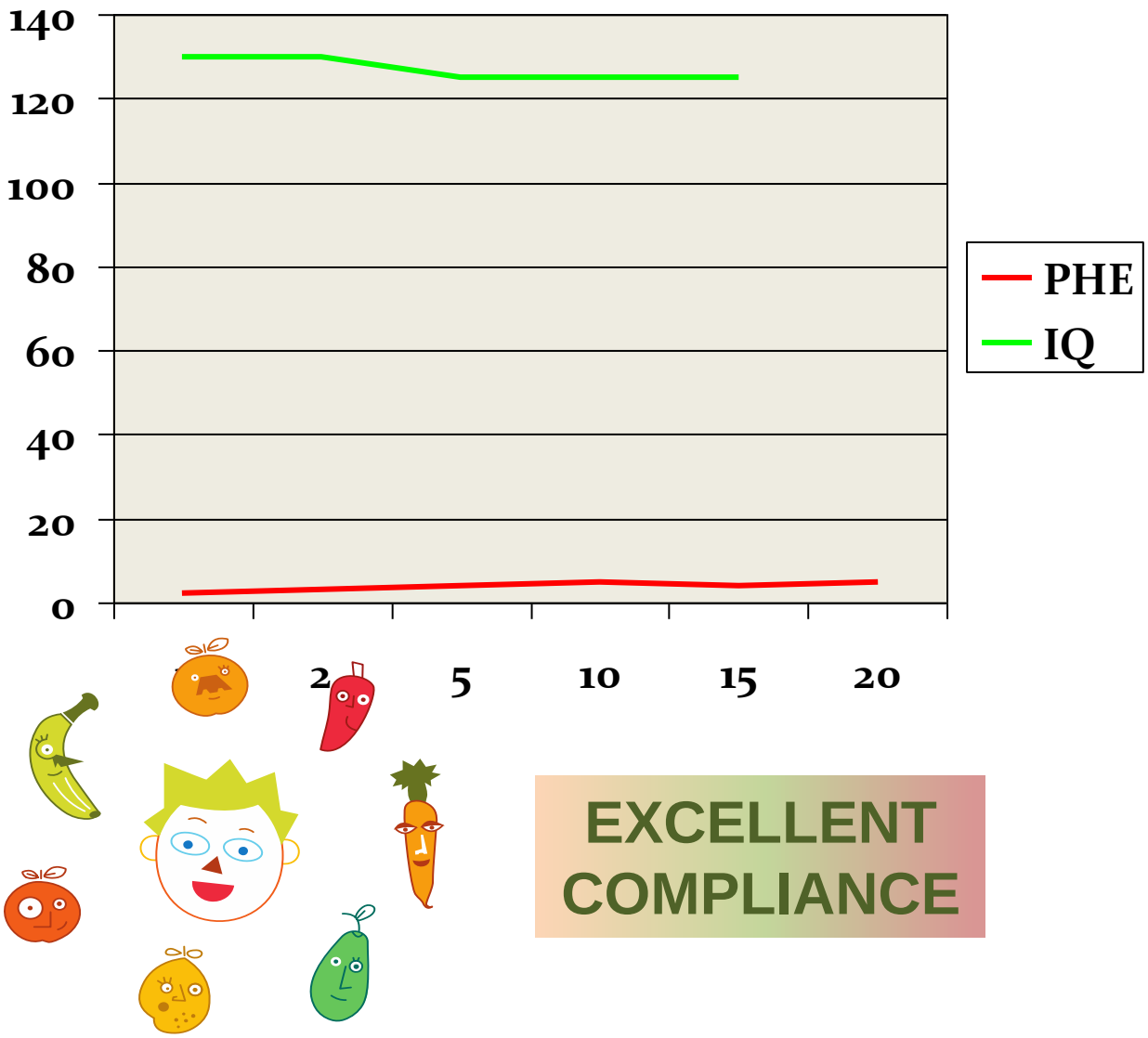
BLOOD PHE and IQ





Non compliance

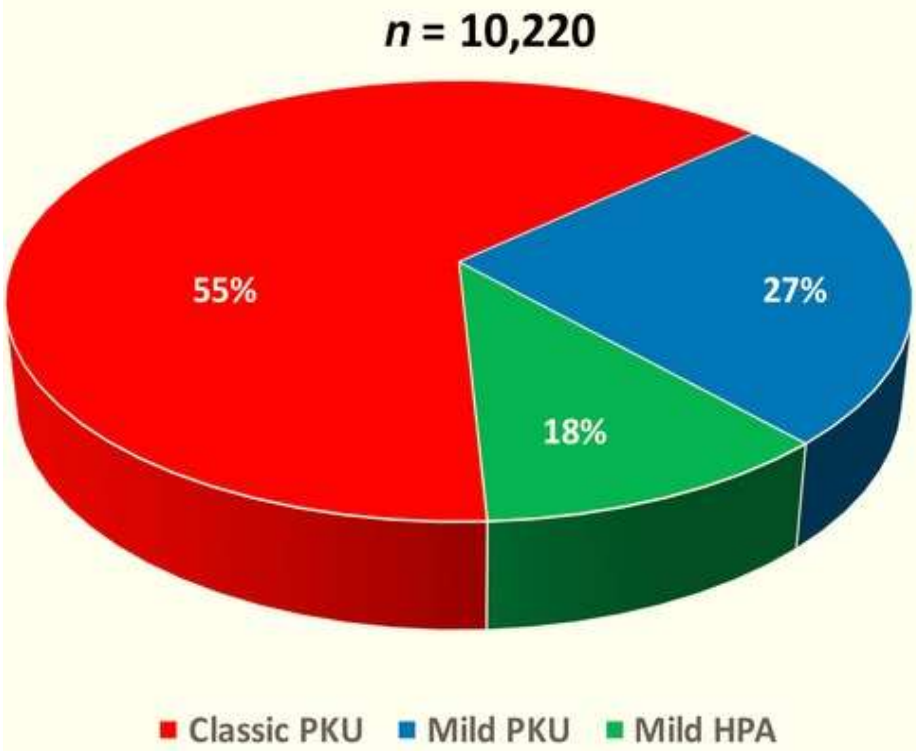
BLOOD PHE and IQ



PKU CLINICAL PHENOTYPES

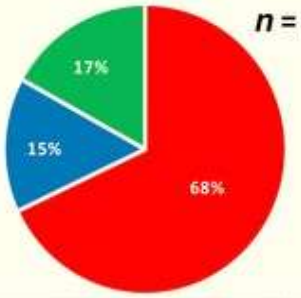
CLINICAL PHENOTYPE	OF DIET BLOOD PHE LEVELS	DIETETIC PHE TOLERANCE
Non PKU hyperphenylalaninemia (MHP)	<600 µmol/L < 10 mg/dl	>1000 mg /day
Mild or atypical phenylketonuria (mPKU)	600-1200 µmol/L 10-20 mg/dl	450 - 1000 mg/day
Classical or severe phenylketonuria (sPKU)	>1200 µmol/L >20 mg/dl	250 - 450 mg/ημέρα

GLOBAL DISTRIBUTION OF PKU PHENOTYPES + TWO EUROPEAN DISTRICT EXAMPLE



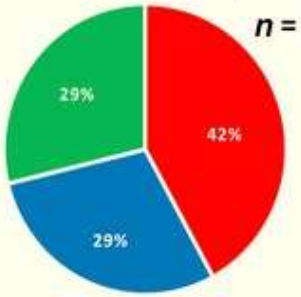
Variant	AF (%)	PAH (%)
p.R408W	22.6	2
p.Q355_Y356insGLQ	6.1	5
p.R261Q	8.1	44

Eastern Europe



Variant	AF (%)	PAH (%)
p.R408W	54.8	2
p.R158Q	4.0	10
p.Q355_Y356insGLQ	3.8	5

Southern Europe



Variant	AF (%)	PAH (%)
p.Q355_Y356insGLQ	13.5	5
p.R261Q	8.1	44
p.V388M	5.5	28

(Blau N. Human Mutation, 2016)

2014

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

Requirements for a minimum standard of care for phenylketonuria: the patients' perspective

E.S.PKU

ALTER, Belgium – 20 January 2014 – the first ever pan-European patient/carer perspective on optimal care of the rare genetic disorder phenylketonuria (PKU) has been published in the Orphanet Journal of Rare Diseases

2015

ES PKU

EUROPEAN CONFERENCE BERLIN 2015

E.S.PKU

Key European Guidelines for Phenylketonuria

Review

Key European guidelines for the diagnosis and management of patients with phenylketonuria

Orphanet Journal of Rare Diseases

2017

The complete European guidelines on phenylketonuria: diagnosis and treatment

A. M. J. van Wegberg[1], A. MacDonald[2], K. Ahring[3], A. Bélanger-Quintana[4], N. Blau[5,6], A. M. Bosch[7], A. Burlina[8], J. Campistol[9], F. Feillet[10], M. Giżewska[11], S. C. Huijbregts[12], S. Kearney[13], V. Leuzzi[14], F. Maillot[15], A. C. Muntau[16], M. van Rijn[1], F. Trefz[17], J. H. Walter[18] and F. J. van Spronsen[19]*

Abstract: Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine metabolism caused by deficiency in the enzyme phenylalanine hydroxylase that converts phenylalanine into tyrosine. If left untreated, PKU results in increased phenylalanine concentrations in blood and brain, which cause severe intellectual disability, epilepsy and behavioural problems. PKU management differs widely across Europe and therefore these guidelines have been developed aiming to optimize and standardize PKU care. Professionals from 10 different European countries developed the guidelines according to the AGREE (Appraisal of Guidelines for Research and Evaluation) method. Literature search, critical appraisal and evidence grading were conducted according to the SIGN (Scottish Intercollegiate Guidelines Network) method. The Delphi method was used when there was no or little evidence available. Several consultants reviewed the guidelines. Using these methods 70 statements were formulated based on the highest quality evidence available. The level of evidence of most recommendations is C or D. Although study designs and patient numbers are sub-optimal, many statements are convincing, important and relevant. In addition, knowledge gaps are identified which require further research in order to direct better care for the future.

Keywords: European, Guidelines, Phenylalanine hydroxylase deficiency, PAH deficiency, Phenylketonuria, PKU, Hyperphenylalaninemia, Phenylalanine, Tetrahydrobiopterin, Management, Recommendations, Tetrahydrobiopterin, Sapropterin

Background

Phenylketonuria (PKU; McKusick #261600) is a rare autosomal recessive inborn error of phenylalanine (Phe) metabolism caused by variants in the gene encoding phenylalanine hydroxylase (PAH). PAH normally converts Phe into tyrosine (Tyr) requiring the cofactor tetrahydrobiopterin (BH4), molecular oxygen and iron (Fig. 1) [1]. PAH deficiency leads to accumulation of Phe in the blood and brain. Untreated, PKU is characterized by irreversible intellectual disability, microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behaviour and psychiatric symptoms. The precise pathogenesis of brain dysfunction is still unclear (Fig. 2) [2]. As high blood Phe concentrations are strongly related to neurocognitive outcome, existing treatments aim at decreasing blood Phe concentrations. PKU was identified in 1934 by Følling when he detected phenylketone bodies in the urine of affected individuals and in 1953, Bickel first reported the effectiveness of a low-Phe diet in a child with PKU. In the 1960's, Guthrie developed a simple test to detect hyperphenylalaninemia (HPA) in large populations. This led to PKU becoming the first disorder to benefit from newborn screening: its early detection and treatment prevented mental retardation. However, the NBS serves to list HPA and this is defined as any blood Phe >120 μmol/L. Therefore, in every positive NBS for Phe, primary phenylalanine hydroxylase deficiency should be

* Correspondence: f.j.van.spronsen@rug.nl
[19]Division of Metabolic Diseases, Beatrix Children's Hospital, University Medical Center Groningen, PO BOX 30001, 9700 RB Groningen, The Netherlands.
Full list of author information is available at the end of the article

E.S.PKU

Panel 3: Key recommendations for patients with phenylketonuria (PKU)

The grades range from ✓ (no possibility to assess the level of evidence because of a lack of any published work on this issue) to as high as B. The key recommendations were either based on evidence (if level of evidence was A or B using the SIGN method) or by consensus (using the Delphi method) if the level of evidence was C or D, or the so-called good practice points that are not based on any evidence if the level was ✓.

Statement 1

Grade of recommendation: ✓

To maintain blood phenylalanine concentrations in the recommended range, patients with phenylalanine hydroxylase (PAH) deficiency can be classified as either not requiring treatment, or requiring diet or tetrahydrobiopterin (BH4), or both.

Statement 2

Grade of recommendation: C*

In the differential diagnosis of hyperphenylalaninaemia, of any degree, BH4 deficiencies should be excluded by measurement of pterins in blood or urine and dihydropteridine reductase activity in dried blood spot.

Statement 3

Grade of recommendation: D/C

Patients with untreated blood phenylalanine concentrations less than 360 µmol/L do not require treatment. Patients with untreated blood phenylalanine levels more than 360 µmol/L should be treated. Patients with untreated phenylalanine levels between 360 µmol/L and 600 µmol/L should be treated until the age of 12 years. Patients with untreated phenylalanine levels more than 600 µmol/L should be treated for life.

Statement 4

Grade of recommendation: C

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

Statement 5

Grade of recommendation: B

In treated patients with PKU up to the age of 12 years, target

Statement 7

Grade of recommendation: B

In pregnant patients treated for PKU the target phenylalanine concetrations should be 120–360 µmol/L.

Statement 8

Grade of recommendation: B

Women with untreated blood phenylalanine concentrations less than 360 µmol/L do not require treatment to lower blood phenylalanine before or during pregnancy.

Statement 9

Grade of recommendation: C

An annual nutritional review is required for any patient who is on a prescribed low phenylalanine diet or is self-restricting high protein foods. Such review must include a clinical examination including the anthropometric parameters (weight, height, BMI). We also recommended that plasma aminoacids, plasma homocysteine or methylmalonic acid, haemoglobin, mean corpuscular volume, and ferritin are measured. All other micronutrients (vitamins and minerals including calcium, zinc, selenium) or hormones (parathyroid hormone) can be considered if clinically indicated.

Statement 10

Grade of recommendation: ✓

In patients younger than 12 years, when more than 50% of the phenylalanine concentrations are out of target range over a period of 6 months, consider: (1) increased frequency of blood phenylalanine monitoring and outpatient visits and re-education, (2) psychology consultation or social worker intervention, and (3) hospital admission. When around 100% of blood phenylalanine concentrations are out of target range over a period of 6 months and there are other signs of failure of adherence, such as lack of cooperation, clinic non-attendance, or unresolved issues outside PKU consider consultation with social services and child safeguarding measures.

*Level of evidence is chosen as C because of the high number of data notwithstanding that most included papers are of descriptive nature.

KEY RECOMMENDATIONS

Statement 3 Grade of recommendation: D/C Patients with untreated blood phenylalanine concentrations less than 360 µmol/L do not require treatment. Patients with untreated blood phenylalanine levels more than 360 µmol/L should be treated. Patients with untreated phenylalanine levels between 360 µmol/L and 600 µmol/L should be treated until the age of 12 years. Patients with untreated phenylalanine levels more than 600 µmol/L should be treated for life.

Statement 5 Grade of recommendation: B In treated patients with PKU up to the age of 12 years, target phenylalanine concentrations should be 120–360 µmol/L. Statement 6 Grade of recommendation: D In treated patients with PKU aged 12 years or older, the target phenylalanine concentrations should be 120–600 µmol/L.

Statement 4 Grade of recommendation: C All adults with PKU should have life-long, systematic follow-up in specialised metabolic centres, because of specific risks that might occur during adulthood

Statement 7 Grade of recommendation: B In pregnant patients treated for PKU the target phenylalanine concetrations should be 120–360 µmol/L

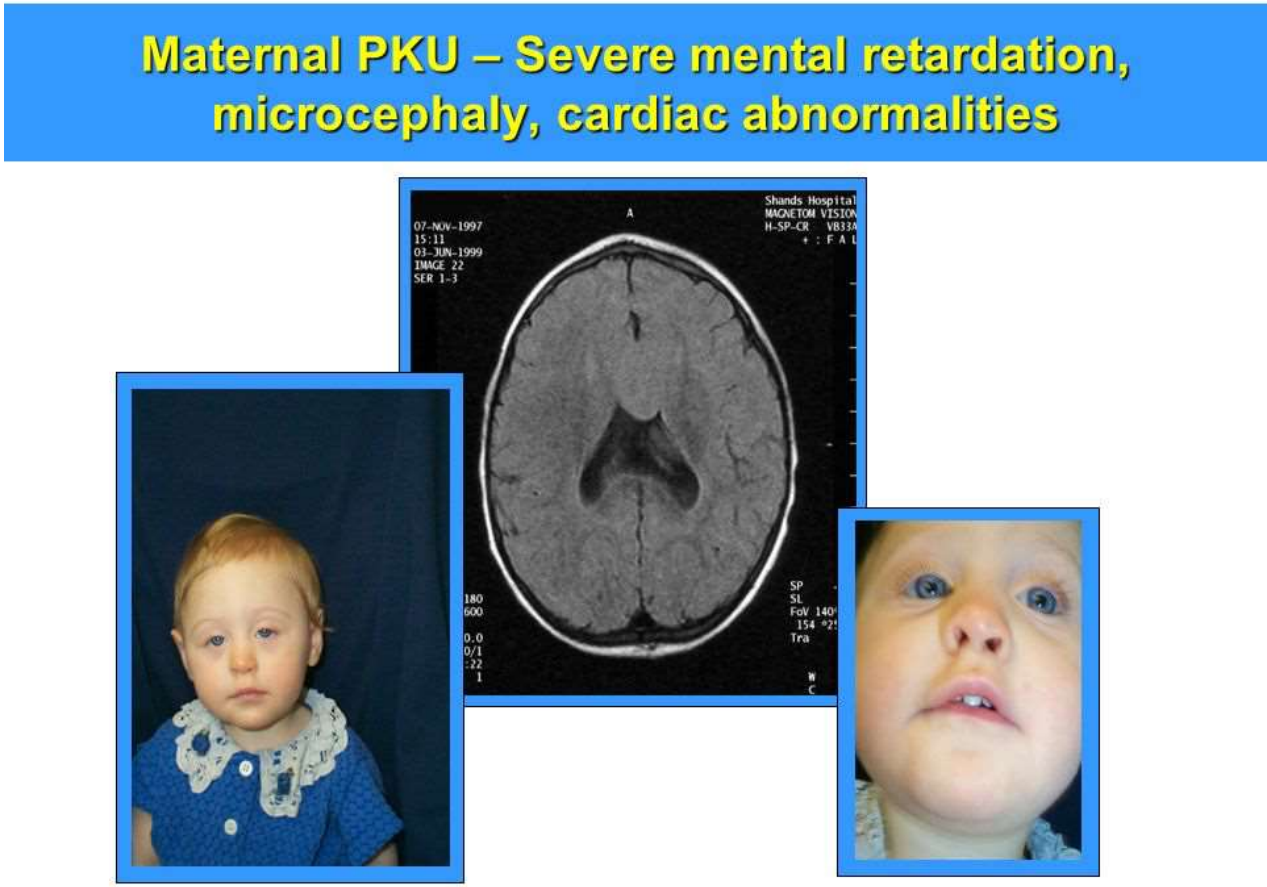
TARGET BLOOD PHE LEVELS

- **0-12 YEARS** → **2 – 6 mg/dl (120-360 µmol/L)**
  2 – 4 mg/dl = perfect levels
- **> 12 YEARS** → **6-10 mg/dl (360-600 µmol/L)**

GIRLS: IDEALLY < 6 mg/dl at all ages (MATERNAL PKU)

MATERNAL PKU SYNDROME

- Mental retardation
- Microcephaly
- Congenital Heart Disease
- Small for date



mother : fetus phe → 1:1,5 (1,1-2,9)

The fetus

- is exposed to higher phe concentration than the mother
- is at risk to be affected even by small blood phe fluctuations
- is at the highest risk of developing damages during the 1st trimester of pregnancy

EVERY PKU WOMAN
CAN DELIVER
A HEALTHY BABY.

JUST STAY ON DIET

Target blood phe : 2-6 mg/dl
(120 – 360 µmol/L)

2,5 – 4 mg/dl = perfect balance
(150 – 240 µmol/L)

KUVAN

- Synthetic form of BH4
- BH4 is natural compound of PAH
- First non dietetic successful therapeutic approach of PKU.

KUVAN

- Rresponsiveness depends mostly on genotype
- Some mutations respond better than others
- Null mutations do not respond

BUT

- Genotype – phenotype correlations sometimes show surprising or unexpected results.
- No genotype needed for PKU patients of diet for many years.

KUVAN

BH4 responsiveness In this Review we defined BH4 responsiveness as an increase of 100% or more in natural protein or improved biochemical control (>75% of phenylalanine levels in target range), or both, on a dose of BH4 that ranges between 10–20 mg/kg bodyweight (with a maximum dose of 1000 or 1400 mg per day in some countries).

- **Age > 4 yrs**
- **Responsiveness test starting dose: 10 mg/Kg BW**
- **20 mg/Kg BW is maximum dose**
- **Very strict dietetic control during the responsiveness test**
- **Target: ≥ 30% μείωση των επιπέδων phe αίματος και ≥ 50% dietetic phe tolerance**

Statement 1

***Grade of recommendation:* ✓**

To maintain blood phenylalanine concentrations in the recommended range, patients with phenylalanine hydroxylase (PAH) deficiency can be classified as either not requiring treatment, or requiring diet or tetrahydrobiopterin (BH4), or both.

New PKU patients' classification

- **No treatment**
- **Low phe diet**
- **BH4 supplemantation**
- **Low phe diet + BH4**


Support PKU Awareness
support our ribbons.com

What all countries need to do ???

Newborn screening!!!

INSTITUTE OF CHILD HEALTH

www.ich.gr

1969
Screening pilot phase

1972
Start of the Greek National Neonatal Screening Program

Births: ~ 100.000/year
PKU - HyperPHE: ~ 8-10 neonates/year
Diagnosis age: ~ 10-15 days

Routine Procedure after abnormal findings in PKU Guthrie Test

- Urgent invitation to the clinic (phone call)
- Confirmation of diagnosis –> Guthrie - Total blood amino acid profile – Phe:Tyr ratio
- Differential diagnosis –> Biopterines - DHPR activity in blood spots - 24h loading test with BH4
- Onset of treatment
- Genotyping

PKU

PKU

PKU

PKU

DIET

Thank you

Astrinia Skarpalezou BSc, MSc
Clin. Nutritionist-Metabolic Dietitian
National Neonatal Screening dept.-I.E.M.
Institute of Child Health, Athens
astrinia@ich.gr