



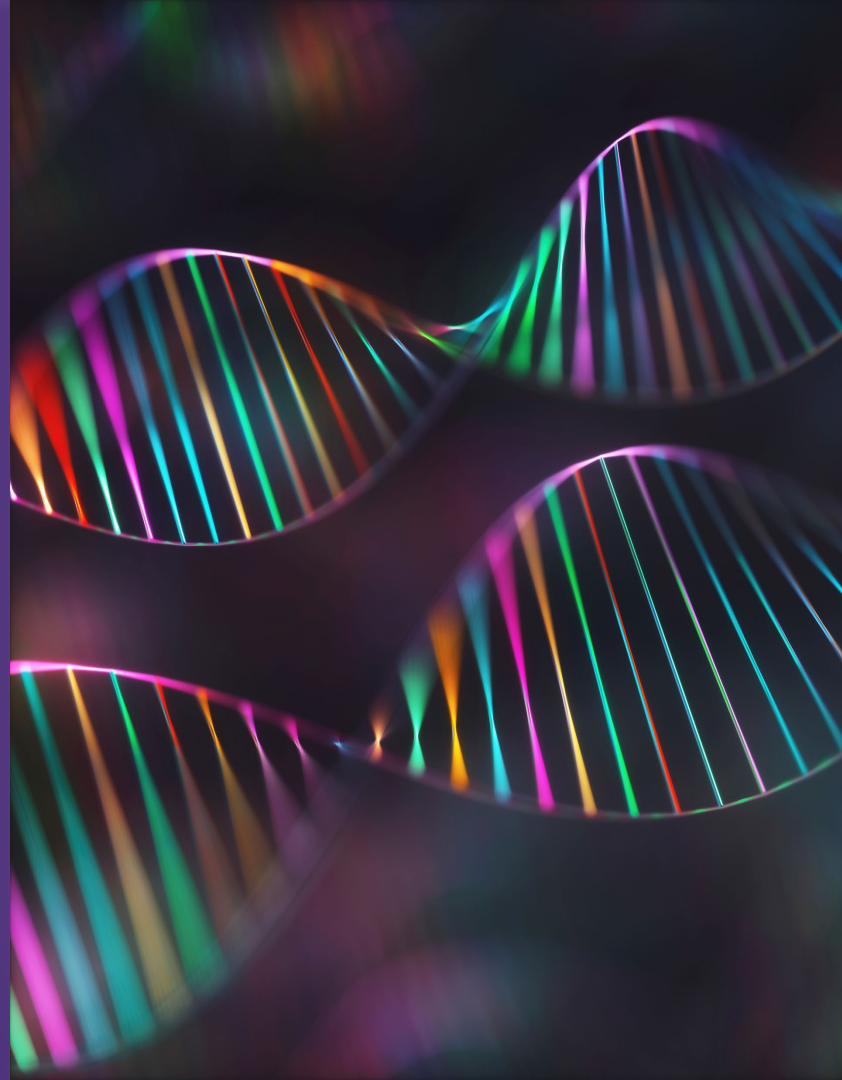
Nutrition 101 for Inborn Errors of Metabolism

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- Employee of Nutricia North America
- ***This does not pose any conflict of interest for this presentation***

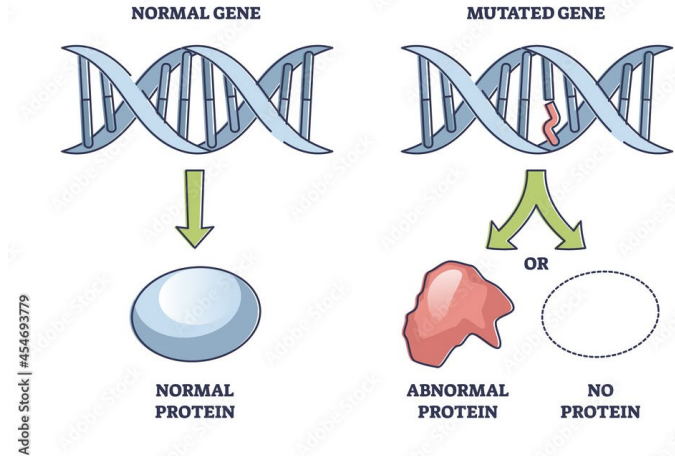
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Learning Objectives

- Participants will learn to:
 - Recall the basics of amino acid disorders, organic acidemias, and urea cycle disorders.
 - Explain the principles of dietary management for these IEMs.
 - Advocate for the nutritional needs of patients with these IEMs as you encounter them clinically.

What is an Inborn Error of Metabolism (IEM)?

- Genetically inherited (also known as inherited metabolic disorders)
- Caused by a change in a gene, affecting the metabolic pathway (typically the function of an enzyme)
- Present from birth



Discovering IEM Diagnoses

- ❑ Many IEMs are diagnosed by state-run Newborn Screening (NBS) Programs
 - ▣ Blood spot taken within 24-48 hours of birth
 - ▣ Results with 4-10 days
 - ▣ Referral to Genetics provider to begin management
- ❑ Some infants may be diagnosed clinically because they present in the hospital before NBS results are back



Protein-Related IEM included on the RUSP

RUSP =

Recommended Uniform Screening Panel
(from U.S. Secretary of HHS)

[Click here for
the full RUSP](#)

[Click here to
discover what is on
your state's NBS](#)

Core Conditions

3-Hydroxy-3-Methylglutaric Aciduria
3-Methylcrotonyl-CoA Carboxylase Deficiency
β-Ketothiolase Deficiency
Glutaric Acidemia Type I
Holocarboxylase Synthase Deficiency
Isovaleric Acidemia
Methylmalonic Acidemia (Cobalamin disorders)
Methylmalonic Acidemia (methylmalonyl-CoA mutase)
Propionic Acidemia
Carnitine Uptake Defect/Carnitine Transport Defect
Long-chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency
Medium-chain Acyl-CoA Dehydrogenase Deficiency
Trifunctional Protein Deficiency
Very Long-chain Acyl-CoA Dehydrogenase Deficiency
Argininosuccinic Aciduria
Citrullinemia, Type I
Classic Phenylketonuria
Homocystinuria
Maple Syrup Urine Disease
Tyrosinemia, Type I

Secondary Conditions

2-Methyl-3-hydroxybutyric aciduria
2-Methylbutyrylglycinuria
3-Methylglutaconic aciduria
Isobutyrylglycinuria
Malonic acidemia
Methylmalonic acidemia with homocystinuria
Argininemia
Benign hyperphenylalaninemia
Biopterin defect in cofactor biosynthesis
Biopterin defect in cofactor regeneration
Citrullinemia, type II
Hypermethioninemia
Tyrosinemia, type II
Tyrosinemia, type III

Infant Admissions pre-NBS Result

- For infants who present with IEMs clinically, symptoms can be vague and serious:
 - Lethargy progressing to coma
 - Poor feeding
 - Vomiting
 - Hypotonia
 - Rapid breathing
 - Seizures (typically a later finding)

- Prompt medical intervention with appropriate IV fluids, indicated medications, and nutrition management can be life-saving

- Once an IEM has been included in the differential diagnosis, ACMG [ACT Sheets](#) provide guidance on next steps (including diagnostic evaluation & clinical considerations)

Types of IEMs

The genetically-impaired enzymes prevent the body from breaking down a component of one of the 3 macronutrients:

Carbohydrates

e.g. Galactosemia or Glycogen Storage Disease

Fat

e.g. Very Long Chain Acyl Co-A Dehydrogenase Deficiency

Protein

e.g. Phenylketonuria, Maple Syrup Urine Disease, or Urea Cycle Disorders

Protein-Related IEM are classified in 3 categories

Amino Acid Disorders

- Phenylketonuria (PKU)
- Maple Syrup Urine Disease (MSUD)
- Homocystinuria (HCU)
- Tyrosinemia (TYR)

Organic Acidemias

- Glutaric Acidemia Type 1 (GA-1)
- Methylmalonic Acidemia (MMA)
- Propionic Acidemia (PA)

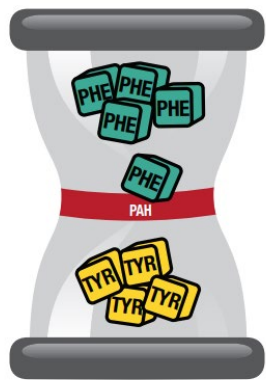
Urea Cycle Disorders

- NAGS
- CPS1
- OTC Deficiency
- Argininosuccinate synthase deficiency (ASS)
- Argininosuccinic aciduria (ASA)
- Arginase deficiency (ARG1)

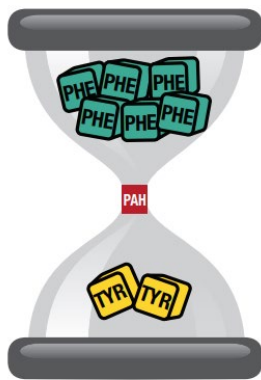
Understanding Protein-Related IEMs: PKU as an Example

- U.S. Incidence: 1:16,500 (approx. 220 births/year)
- U.S. PKU population \approx 12,000
- Enzyme impacted: Phenylalanine hydroxylase (PAH)

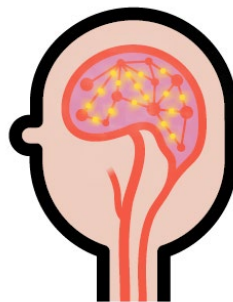
For someone without PKU, PAH converts PHE into TYR



For someone with PKU, there is not enough PAH to convert PHE into TYR



Without management, over time, the buildup of phenylalanine causes irreversible brain damage and poor intellectual development.



With management, the buildup of phenylalanine is controlled to support normal growth and development.



The Principles of Management

THE PROBLEM:

The body isn't able to break down the offending amino acid(s) (AAs) in dietary protein.

The AA(s) or their byproducts build up in the body, which is *toxic*.

THE SOLUTION:

Reduce intake of the offending AA(s) by restricting protein.

Provide adequate calories and other nutrients needed for growth, development, and to continue regular body functions while preventing catabolism.

→ Metabolic formula, protein-free modulars, certain AA or other supplements

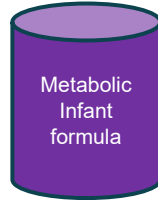
The Principles of Management

THE DIET:

INFANCY



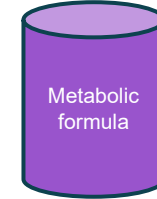
and/
or



PAST INFANCY



Foods naturally low in protein
and specialty low protein
foods, given in measured
amounts



Metabolic formulas contain “protein equivalent” or “modified protein”, meaning the offending AA(s) are omitted. The remaining protein needs are met through “intact” or “whole” protein.

*Some intact protein must be consumed to avoid essential AA deficiency.
Metabolic formulas are **not** suitable as a sole source of nutrition.*

Offending Amino Acid (AA) by Disorder

Phenylketonuria (PKU)	Phenylalanine
Glutaric Aciduria Type 1 (GA-1)	Lysine & tryptophan
Homocystinuria (HCU)	Methionine
Isovaleric Acidemia (IVA)	Leucine
Maple Syrup Urine Disease (MSUD)	Valine, leucine, and isoleucine
Methylmalonic Acidemia (MMA)	Methionine, threonine, valine and isoleucine
Propionic Acidemia (PA)	
Tyrosinemia (TYR)	Tyrosine and phenylalanine
Urea Cycle Disorders (UCD)	All AAs restricted; only PRO in formula is essential AAs

Percent of Protein from Metabolic Formula by Disorder

Phenylketonuria (PKU)	75-85%
Glutaric Aciduria Type 1 (GA-1)	50%
Homocystinuria (HCU)	Variable (60-80%)
Isovaleric Acidemia (IVA)	Up to 60%
Maple Syrup Urine Disease (MSUD)	80-90%
Methylmalonic Acidemia (MMA)	0-30%
Propionic Acidemia (PA)	
Tyrosinemia (TYR)	Variable (>50%)
Urea Cycle Disorders (UCD)	0-50%

What this looks like for a PKU patient

- Total protein target: 120-140% of the DRI
- On average, 75-85% of protein from metabolic formula
- Goal of management: Maintain plasma PHE levels between 120-360 mmol/L

Example Diet Prescription:

8 y.o. female with classical PKU, 26 kg

140% of DRI for protein: 35 g

$0.85 \times 35 \text{ g} = \mathbf{30 \text{ g PE from PKU formula}}$

Remaining **5 g protein from foods**



Daily formula prescription:

100 g powder mixed with

18 fl. oz. water

Provides: 370 kcal & 30 g PE

Meets 85% of protein needs & 33% of kcal needs

Daily intact protein prescription:

5 g of protein from foods

For Reference:



= 2 g protein



$\frac{1}{2}$ cup = 1.5 g protein



= 3 g protein



2 Tbsp. = 1 g protein



$\frac{1}{2}$ cup = 2 g protein

Intact Protein-Restricted Diets are *Restricted*



Not Permitted

- Meat
- Poultry
- Fish
- Eggs
- Cheese
- Milk
- Yogurt
- Beans
- Tofu
- Nuts



Permitted – Must be counted

- Bread
- Cereals
- Rice
- Crackers
- Starchy vegetables (potatoes, peas, corn)



Permitted - Uncounted

- Fruits
- Non-starchy vegetables
- Specialty low-protein foods

- Routine metabolic clinic visits to monitor growth, development, and diet adherence
 - Monthly during infancy; every 4-6 months during childhood; every 6-12 months in adulthood
- Plasma AA levels (and nutritional labs) consistently collected
- Dietary adjustments made based on growth, pertinent labs, and nutritional adequacy

For the patients who need it, metabolic formula *must* be taken daily

- For those who require metabolic formula, there is no way to replace it with standard foods.
- Following a low protein diet *without* metabolic formula could result in...
 - continuous feelings of hunger
 - protein deficiency
 - malnutrition
 - vitamin/mineral deficiencies (especially vit B12, iron, calcium, and vitamin D)
 - growth failure
- Some IEMs require less metabolic formula than PKU; certain patients may even be able to maintain metabolic control with a diet restricted in protein to the DRI only (without metabolic formula).
- Consequences of not taking metabolic formula as prescribed may be more critical, depending on the disorder, particularly for those where patients are at risk for a **metabolic crisis**.

Disorders at risk for a metabolic crisis

MSUD

Maple Syrup Urine Disease

MMA/PA

Methylmalonic or
Propionic Acidemia

GA-1

Glutaric Acidemia

IVA

Isovaleric Acidemia

UCD

Urea Cycle Disorders

- A *metabolic crisis* or *decompensation* is brought on in instances where there are rapidly rising levels of the offending AA or its byproducts
 - ▣ Prior to treatment (infancy)
 - ▣ Any circumstance that leads to catabolism (break down of the body's own muscle and tissues for energy)
 - Illness involving fever, vomiting, diarrhea
 - Surgery or trauma (i.e., car accident or broken bone)
 - Extreme or prolonged exercise
- Even minor illnesses can lead to a metabolic crisis, which can result in irreparable mental or physical disability
 - these patients have specific dietary and medical protocols for illness

Inpatient Admissions – What to look for

- For these disorders, expect the patient/caregiver to bring an **Emergency Protocol Letter** which will contain:
 - ▣ Their diagnosis
 - ▣ Genetics provider on-call number (get in contact immediately WHILE following letter protocol)
 - ▣ Immediate protocol to follow
 - Typically IV glucose (to quickly mitigate catabolism)
 - Lab values to be drawn ASAP

- Ideally, the patient/family will also bring their Diet Plans: “Well Day” and “Sick Day” – if not, contact the Genetic/Metabolic RD and read their most recent note in the EMR (search for “sick day” in the EMR)



Understanding “Sick Day” Diets

“Sick Day” Diets are individualized, but typically have the following characteristics:

- ❑ No intact protein
- ❑ Increase in protein equivalent (from metabolic formula)
- ❑ Increase in calories (from metabolic formula and/or a protein-free modular)
- ❑ Increase in fluids
- ❑ May include an increase in certain amino acid supplements or other medically-necessary supplements (depending on the disorder)

Metabolic Disorder Overview

Amino Acid Disorders

Phenylketonuria (PKU)

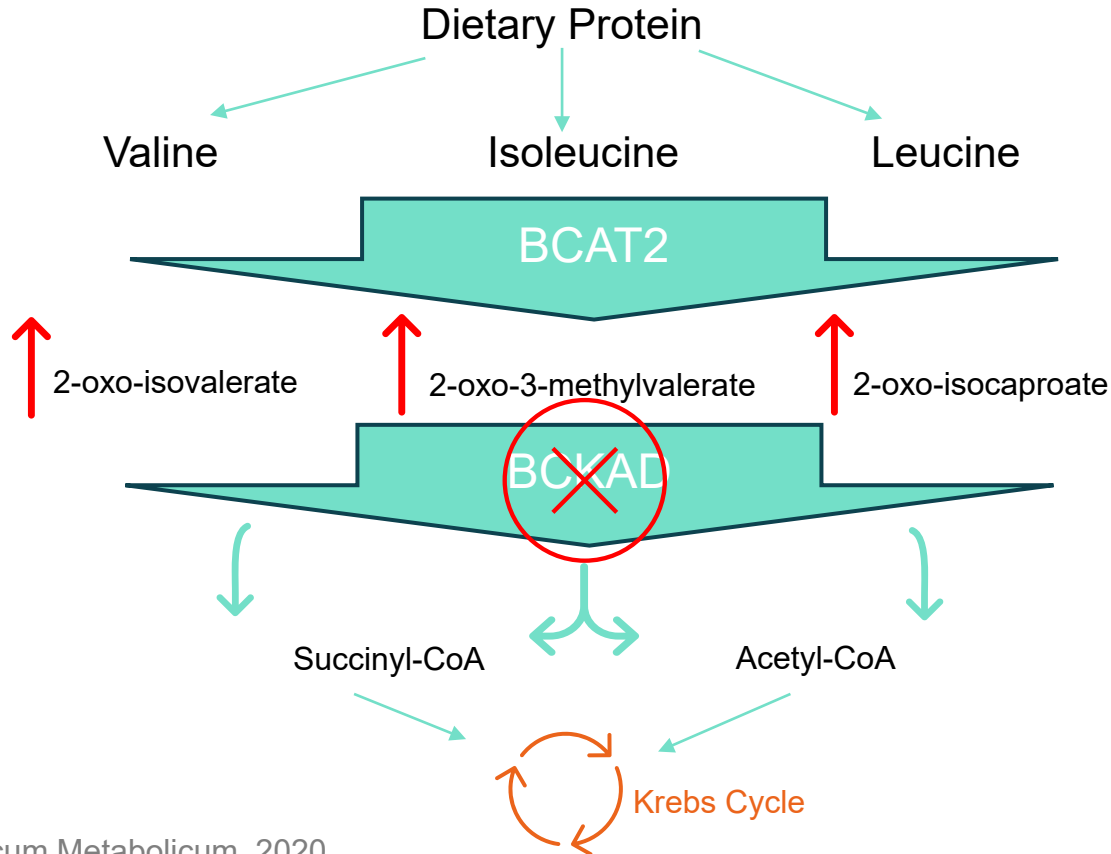


Phenylketonuria (PKU)

Offending (limited) AA	Phenylalanine (PHE)
Impaired enzyme	Phenylalanine hydroxylase (PAH) – converts PHE into TYR
Management Goal	Blood PHE: 120-360 mmol/L
Metabolic Formula	Low in or free of PHE 75-85% of total protein
System(s) Impacted	Brain (irreparable brain damage with prolonged high PHE levels; short-term high-PHE can lead to executive functioning impairment); seizures, eczema, “musty” odor, hypopigmentation
Other notes	Adults not on diet or not currently on formula may have poor memory and challenges with planning and organization as a side effect of their high PHE levels.



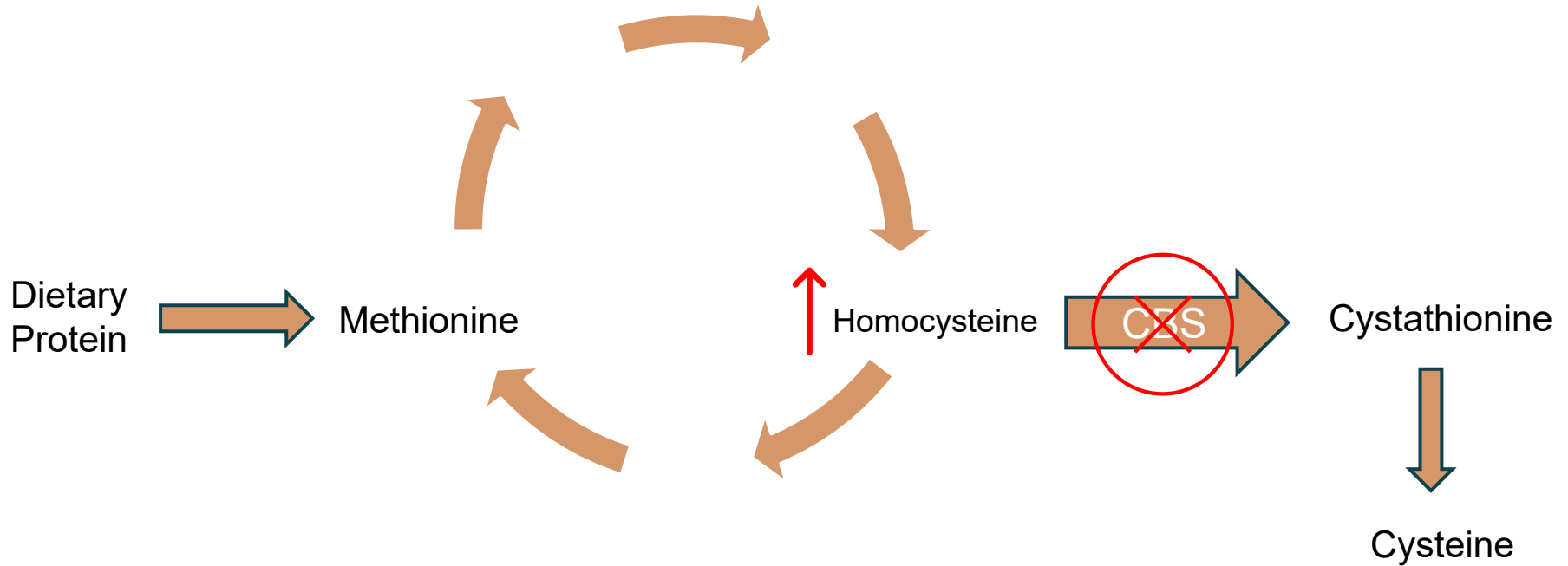
Maple Syrup Urine Disease (MSUD)



Maple Syrup Urine Disease (MSUD)

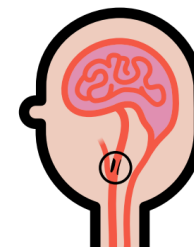
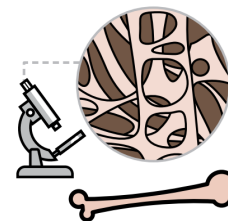
Offending (limited) AA	Leucine (LEU) & its ketoacid
Impaired enzyme	Branched-chain ketoacid dehydrogenase complex (BCKAD)
Management Goal	LEU: 75-200 mmol/L (for up to 5 yrs of age); 75-300 mmol/L (for over 5 yrs) ILE & VAL: 200-400 mmol/L
Metabolic Formula	Free of BCAAs (leucine, isoleucine, valine) 80-90% of total protein
Additional prescribed supplements	Isoleucine & valine
System(s) Impacted	Brain (Irreversible brain damage resulting in cognitive losses and/or movement disorders, coma)
Transplant	Liver transplant (typically) eliminates the high risk of metabolic crisis and removes diet restriction (& formula); however if transplant happens after cognitive losses, they will not be regained
Other notes	Even with consistent management, IQ levels of MSUD patients are below controls; adult patients may have a parent/care-person making the decisions regarding their care.

Homocystinuria (HCU)

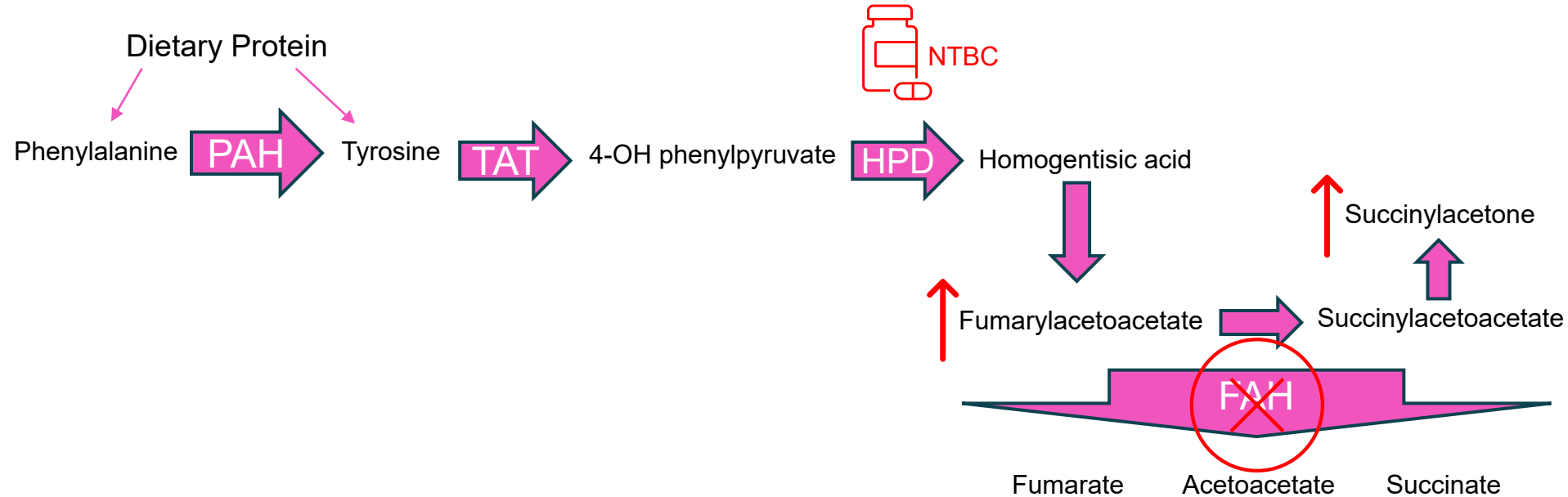


Homocystinuria (HCU)

Offending (limited) AA	Methionine (MET)
Impaired enzyme	Cystathionine beta-synthase (CBS)
Management Goal	Total Homocysteine (tHcy): <50 mmol/L for pyridoxine-responsive <100 mmol/L for pyridoxine-unresponsive Plasma MET: <1000 mmol/L
Metabolic Formula	Free of methionine Variable % of total protein
Additional prescribed drugs and/or supplements	Betaine, cystine, folic acid, B12, vitamin C Pyridoxine (B6) – responder or not
System(s) Impacted	Brain (similar to PKU), eye lens dislocation, osteoporosis, blood clots, seizures
Other notes	These patients are often missed on newborn screening, so its not uncommon for older children to be starting on formula for the first time if they've just been diagnosed.

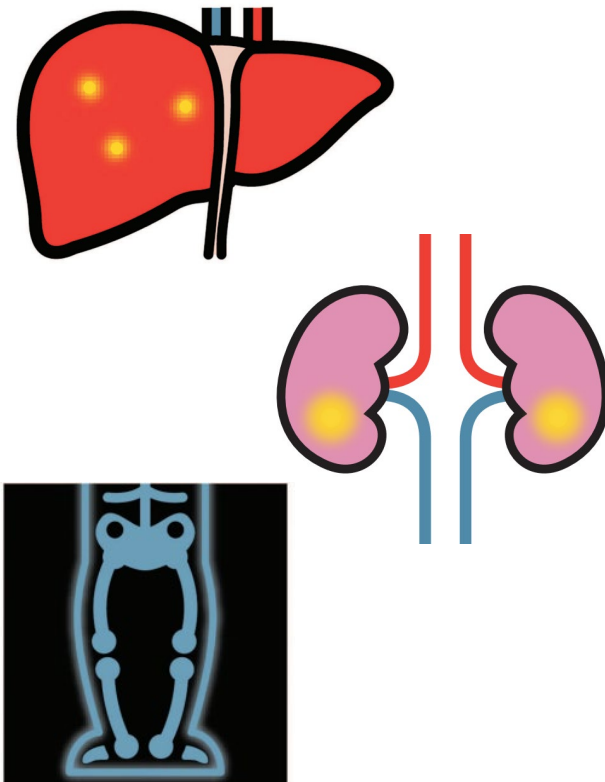


Tyrosinemia Type 1 (TYR)



Tyrosinemia Type 1 (TYR)

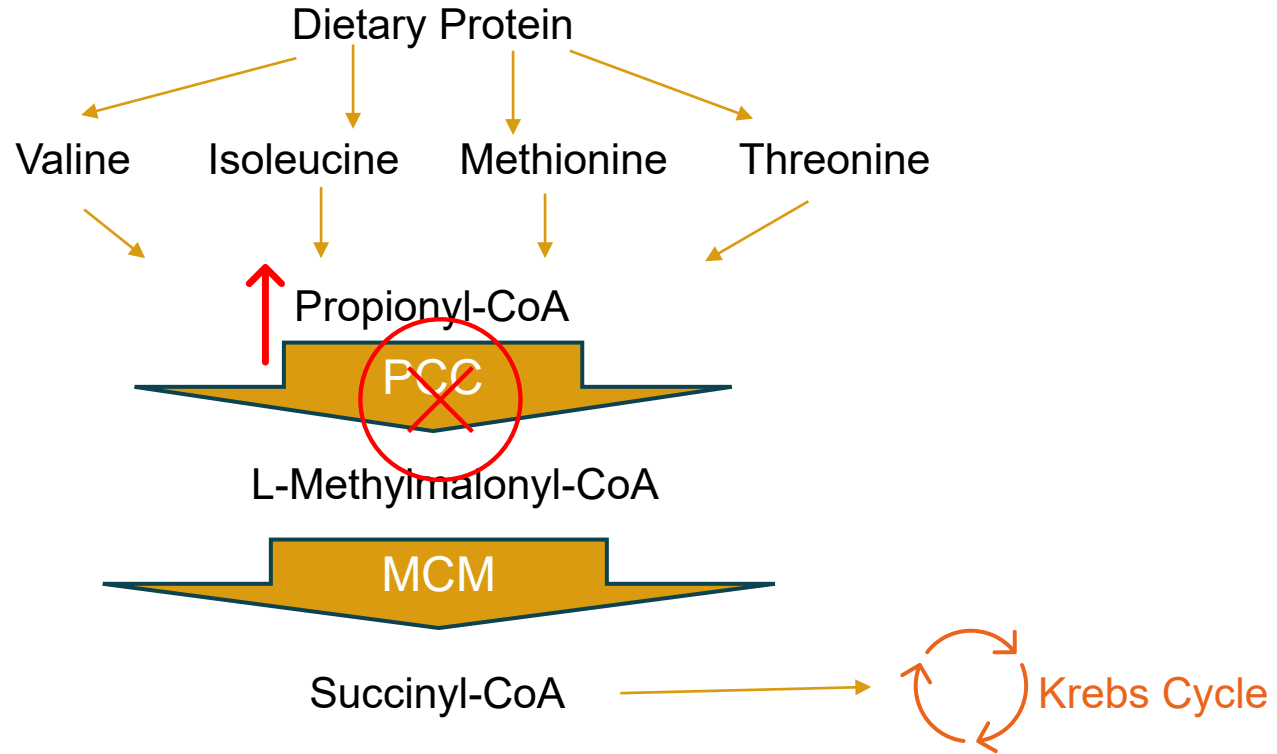
Offending (limited) AA	Tyrosine (TYR) and Phenylalanine (PHE)
Impaired enzyme	Fumarylacetoacetate hydrolase (FAH)
Management Goal	Plasma TYR: 200-600 mmol/L Plasma PHE: 20-80 mmol/L
Metabolic Formula	Low in or free of tyrosine & phenylalanine Variable % of total protein
Additional prescribed drugs and/or supplements	Nitisinone (NTBC)
System(s) Impacted	Liver and kidney failure, softening and weakening of bones; issues impacting the nervous system
Transplant	Liver transplant



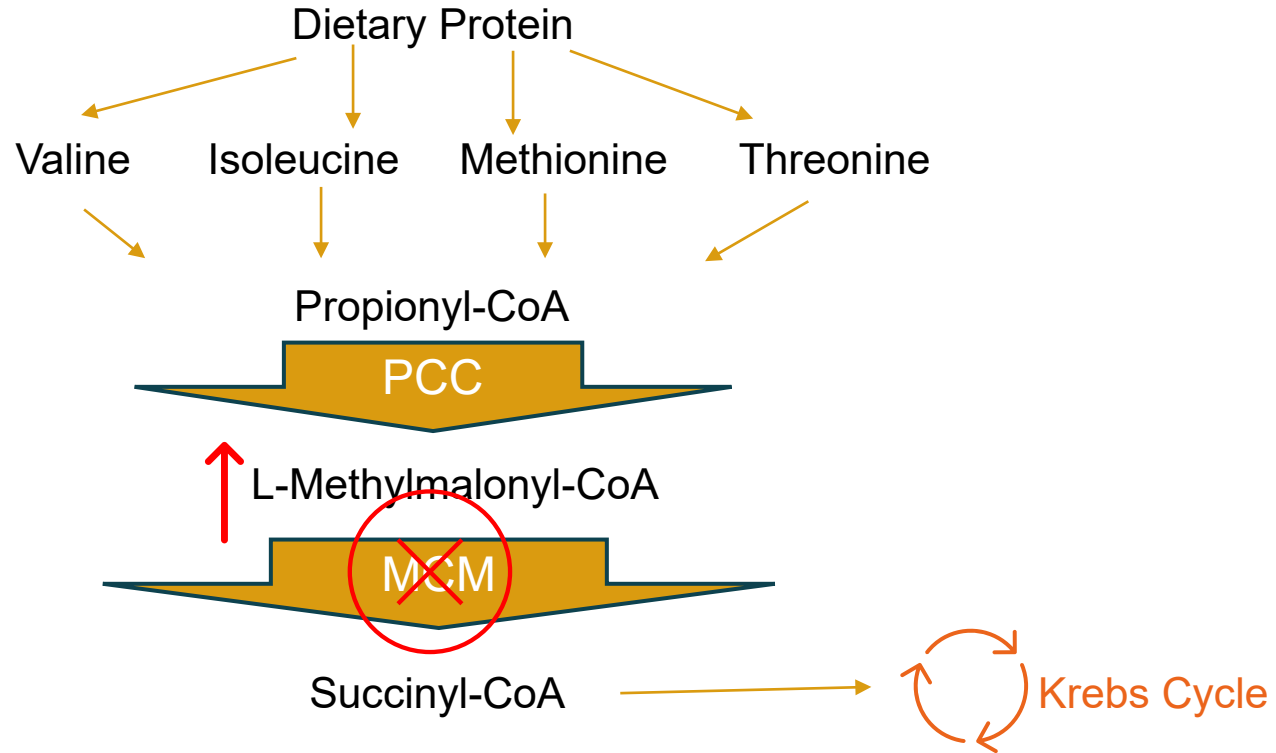
Metabolic Disorder Overview

Organic Acidemias

Altered Pathway for PA

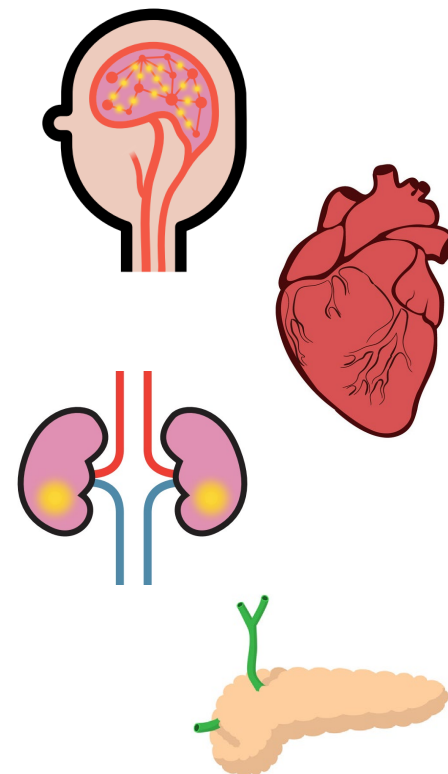


Altered Pathway for MMA

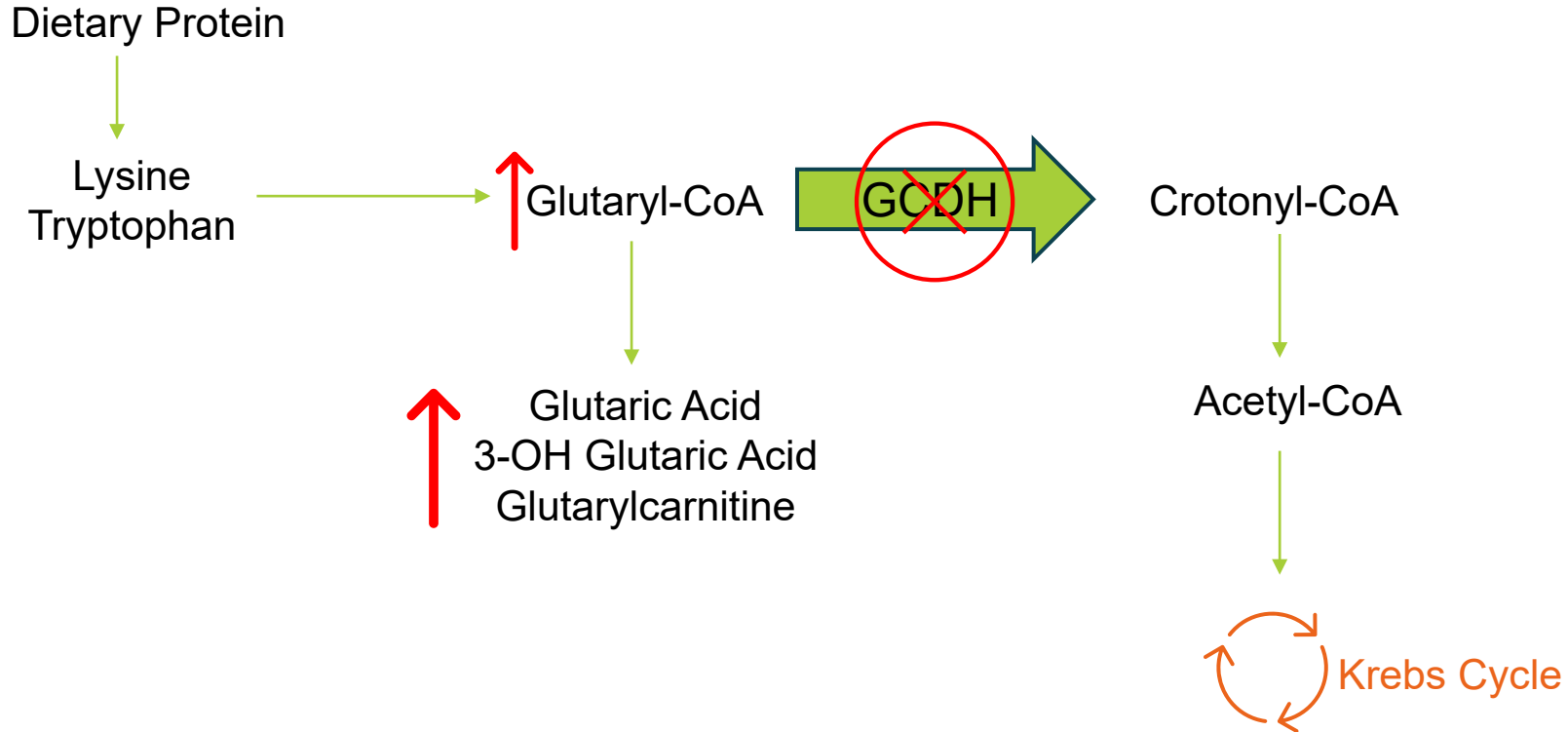


Methylmalonic & Propionic Acidemia (MMA & PA)

Offending (limited) AA	Isoleucine (ILE), Methionine (MET), Valine (VAL), and Threonine (THR)
Impaired enzyme	Methylmalonyl-CoA mutase (MCM – for MMA) Propionyl-CoA carboxylase (PCC – for PA)
Management Goal	Maintain plasma AAs WNL
Metabolic Formula	MET-, THR-, VAL-free, Low-ILE 0-30% of total protein
Additional prescribed drugs and/or supplements	Carnitine Nitrogen scavengers for hyperammonemia MMA: Hydroxycobalamin (B12) injections (responder or not)
System(s) Impacted	Both: Brain and heart MMA: kidneys, eyes PA: pancreas
Transplant	Both: Liver transplant (not curative) MMA: Kidney transplant (not curative)
Other notes	Many patients have g-tubes



Glutaric Acidemia Type 1 (GA-1)



Glutaric Acidemia Type 1 (GA-1)

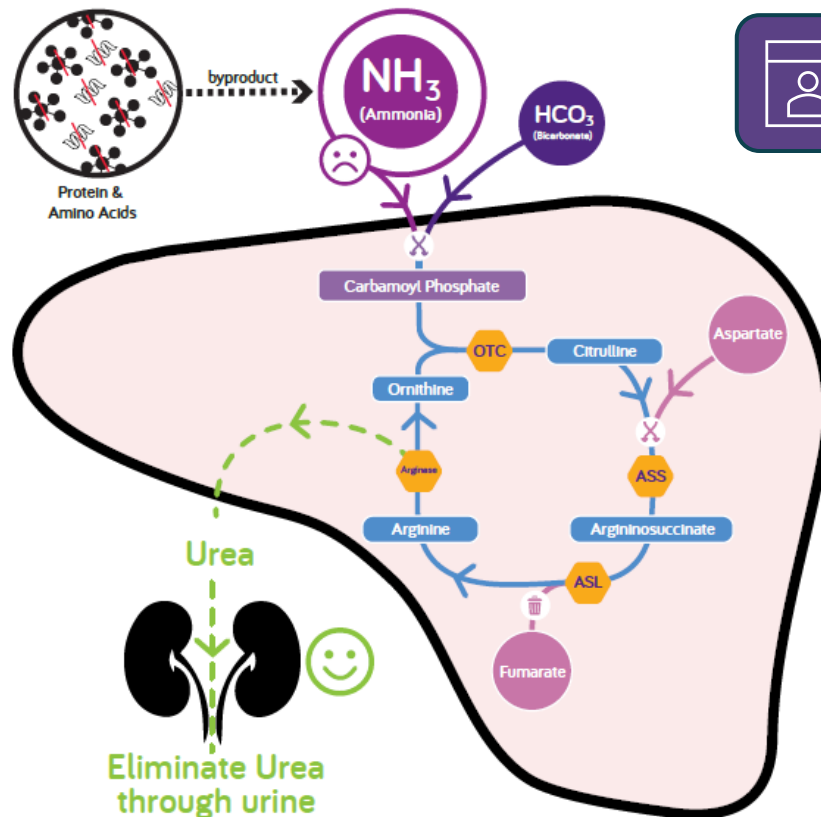
Offending (limited) AA	Lysine (LYS)
Impaired enzyme	Glutaryl-CoA dehydrogenase (GCDH)
Management Goal	Plasma LYS WNL (low end) Plasma free carnitine WNL
Metabolic Formula	LYS-free; low in or free of TRP 50% of total protein
Additional prescribed drugs and/or supplements	Carnitine
System(s) Impacted	Brain (risk of permanent striatal injury), microcephaly, dystonia, hypotonia
Other notes	Diet restriction (including metabolic formula) is typically liberalized after 6 years of age, but there is little consensus on practice



Metabolic Disorder Overview

Urea Cycle Disorders

Urea Cycle Disorders



Watch a recent webinar
on the management of
infants & toddlers with UCDs

Urea Cycle Disorders

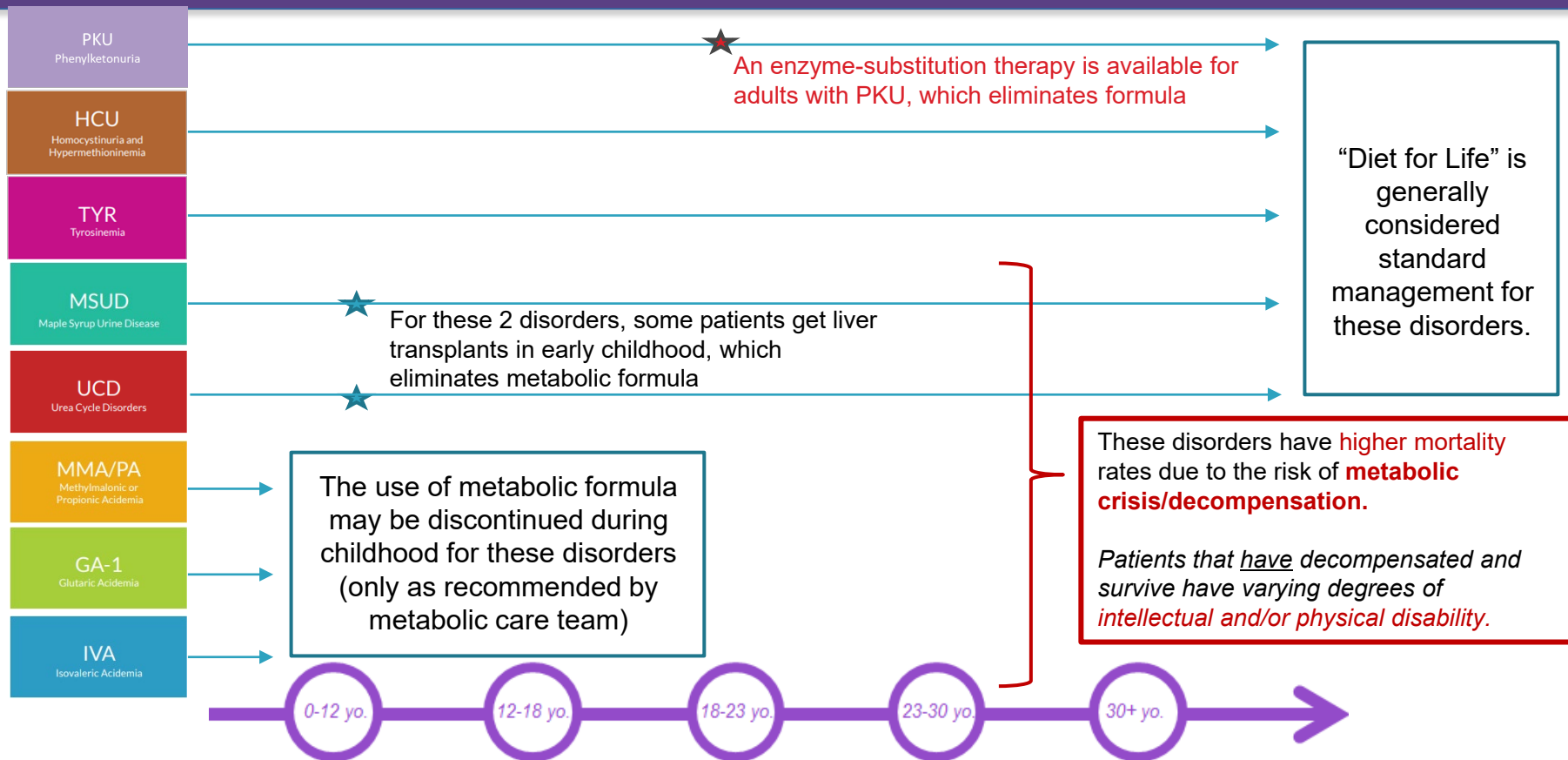
Offending (limited) AA	All Protein (all AAs); toxic metabolite is ammonia
Impaired enzyme	One of the 6 in the urea cycle disorder (see next slide)
Management Goal	Plasma AAs WNL Normal ammonia (<35 mmol/L)
Metabolic Formula	Essential AA containing 0-50% of total protein
Additional prescribed drugs and/or supplements	Nitrogen scavengers for hyperammonemia See next slide for supplemental AAs
System(s) Impacted	Brain, seizures, coma
Transplant	Liver transplant
Other notes	UCD severity varies considerably by patient; some are not diagnosed until later in life

Types of UCDs

Diagnosis	Level of Protein Restriction	Supplements
CPS1* Carbamoyl phosphate synthase 1 deficiency	High	Citrulline
OTC* Ornithine transcarbamylase deficiency	High	Citrulline
ASS Argininosuccinate synthase deficiency / Citrullinemia	High	Arginine
ASA / ASL Argininosuccinic aciduria / Argininosuccinate lyase deficiency	Moderate	Arginine
ARG1 Arginase deficiency	High	None
NAGS* N-acetyl glutamate synthase deficiency	None	Citrulline

*Not included on Recommended Uniform Screening Panel (RUSP) for NBS – typically diagnosed clinically

Protein Disorder Management Overview



Key Take-Aways

- Principle of diet is to restrict offending AA(s) to prevent undesired outcomes, but enough to ensure growth and regular functions.
 - The remaining protein/calories/nutrients are fulfilled with metabolic formula.
- Patients with protein-related IEMs who present to the hospital require prompt intervention
 - Always follow the instruction of the patient's metabolic healthcare team
 - Protein-free calories
 - “Sick Day” Diet

Helpful Resources

- ❑ [Nutricia Learning Center \(NLC\)](#)
- ❑ Nutricia Metabolics [Patient Education and Support](#) (including TEMPLE books & videos)
- ❑ GMDI/SERN [Nutrition Management Guidelines & Toolkits](#) (for PKU, MSUD and PA)
- ❑ Met Ed [“At a Glance” Series](#)
- ❑ [Genetic Metabolic Dietitians International \(GMDI\)](#)
- ❑ ACMG [ACT Sheets](#) & Algorithms
- ❑ [MetabolicPro](#) Nutrient Analysis Program

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