

Maple Syrup Urine Disease

Introductory information

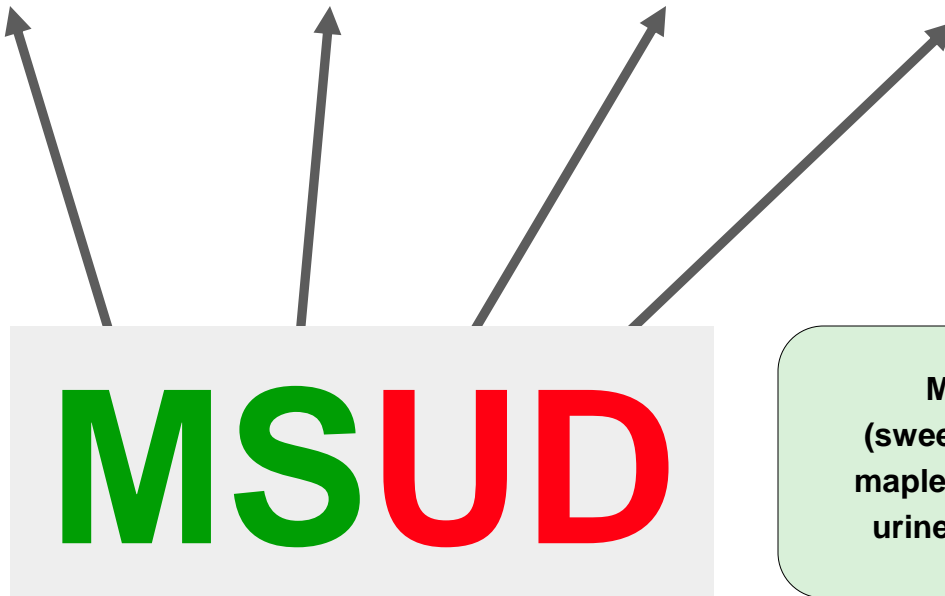
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TEMPLE 
Tools Enabling Metabolic Parents LEarning

Maple syrup urine disease



**MSUD refers to the
(sweet, malty, caramel-like)
maple-syrup-like odor of the
urine of untreated patients**

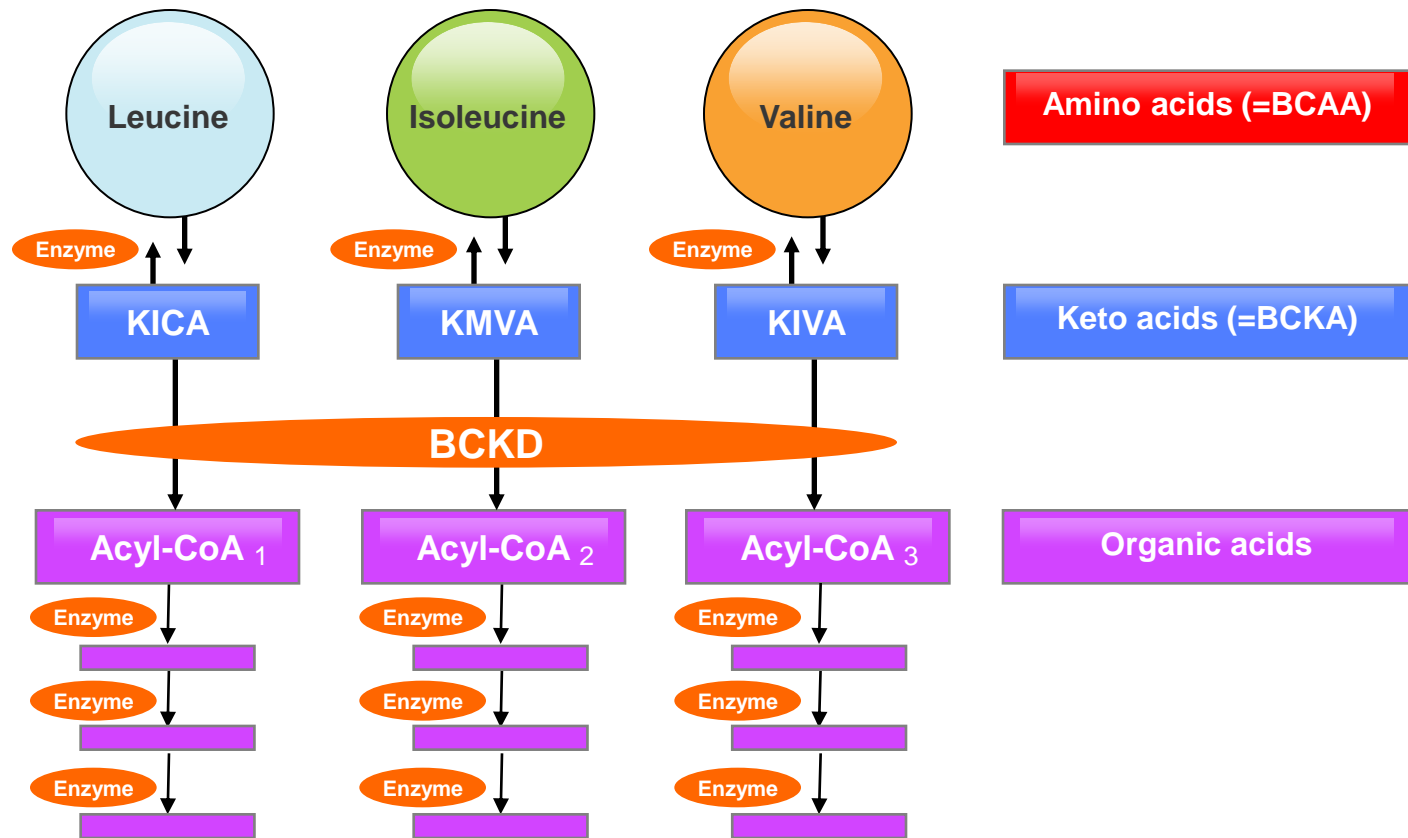
Enzymes

Enzymes are proteins that facilitate various chemical reactions in the body. They are involved in the biosynthesis (anabolism) and the degradation (catabolism) of all substances in the body. This is called “metabolism”.

Branched Chain Keto Acid Dehydrogenase (BCKD) is the enzyme that breaks down the amino acids leucine, isoleucine and valine.

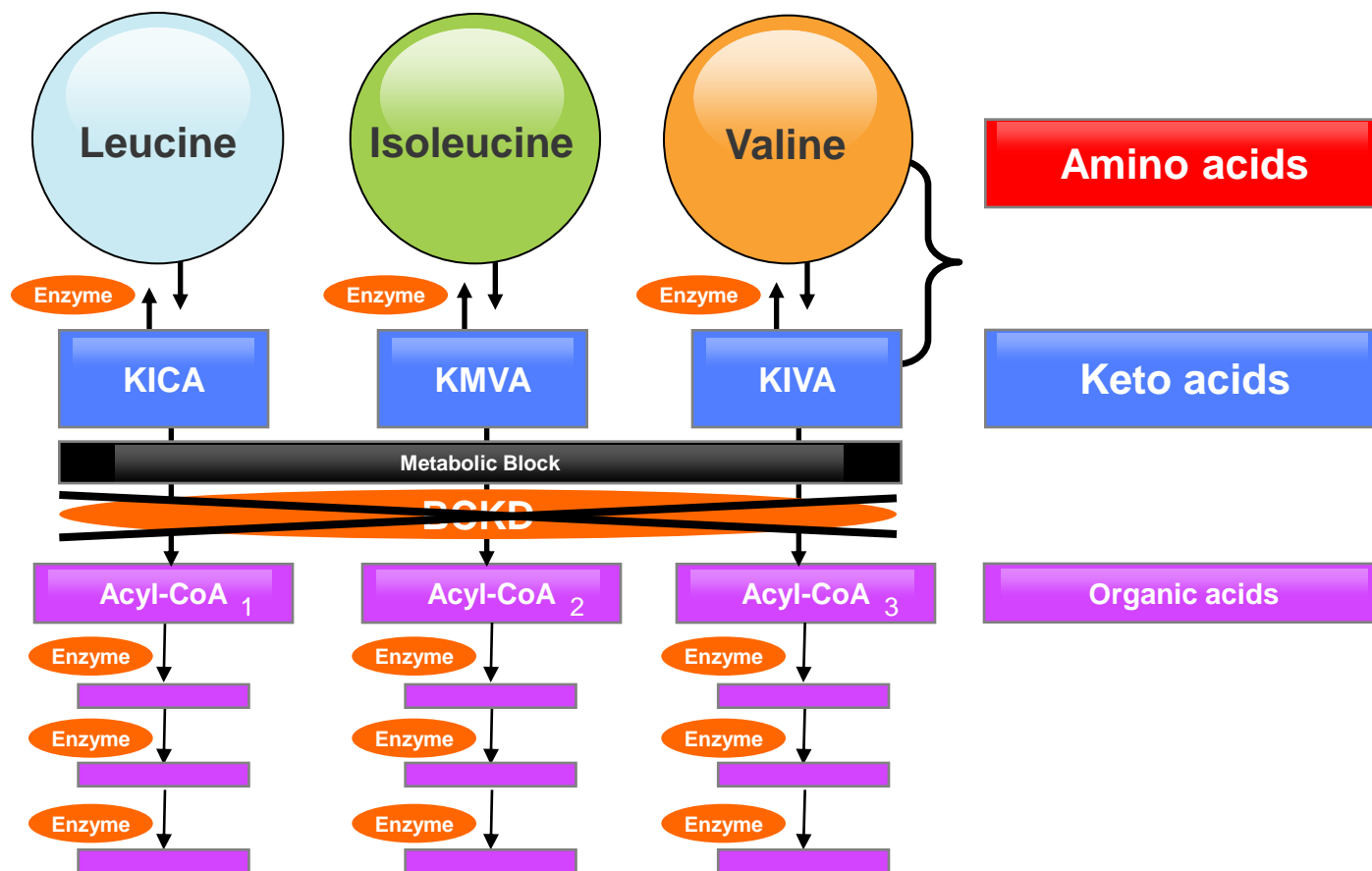
In MSUD, the activity of the **BCKD enzyme** is deficient.

In normal metabolism: **BCKD** works

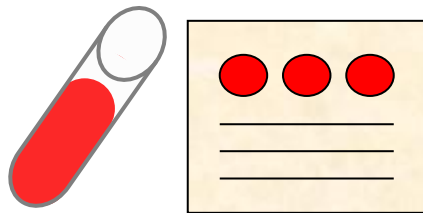


Leucine, isoleucine and valine are called Branched-Chain Amino Acids = BCAA
KICA, KMVA and KIVA are called Branched-Chain Keto Acids = BCKA

In MSUD: BCKD is deficient



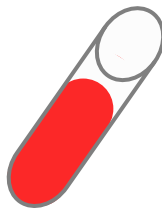
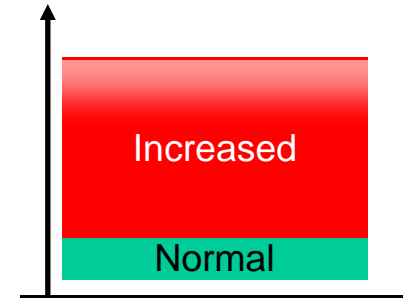
Diagnosis of MSUD



1st blood sample

Newborn/Metabolic
screening

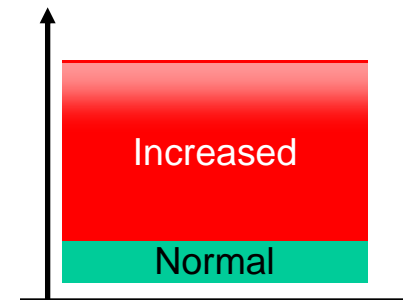
Leucine, isoleucine,
valine in blood



2nd blood sample

Confirmation
of diagnosis

Leucine, isoleucine,
valine in blood



Normal concentration of BCAA in blood

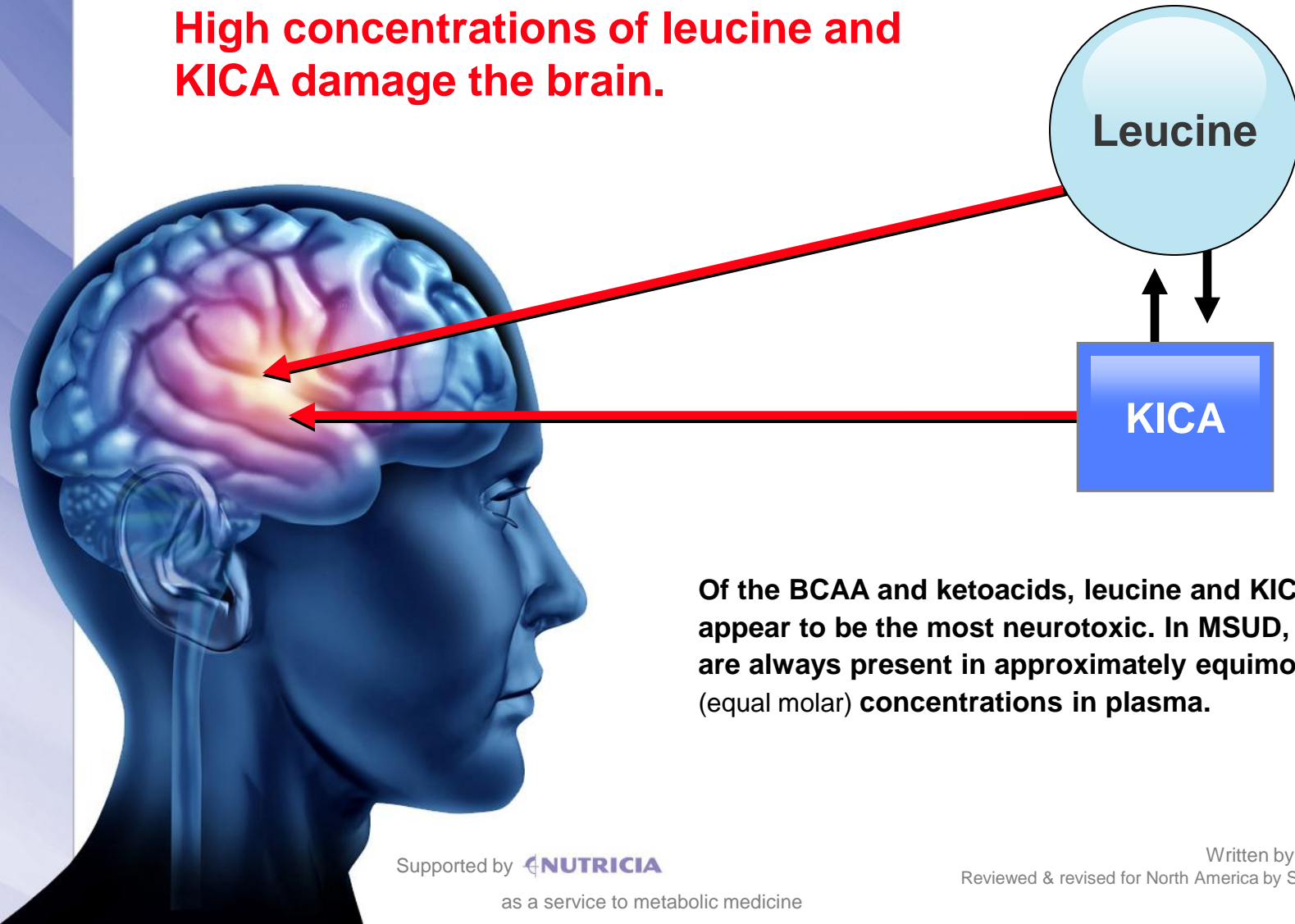
Leucine:	77-153 $\mu\text{mol/L}$	(1.0 - 2.0 mg/dl)
Isoleucine:	39-76 $\mu\text{mol/L}$	(0.5 - 1.0 mg/dl)
Valine:	135-260 $\mu\text{mol/L}$	(1.6 - 3.0 mg/dl)

At confirmation of MSUD:

Leucine concentration is elevated
800 - 4000 $\mu\text{mol/L}$ (10.5 - 52.0 mg/dl)

Pathogenesis of MSUD

High concentrations of leucine and KICA damage the brain.



Of the BCAA and ketoacids, leucine and KICA appear to be the most neurotoxic. In MSUD, they are always present in approximately equimolar (equal molar) concentrations in plasma.

Acute brain dysfunction

When the leucine level increases rapidly to high concentrations in blood.



In newborns before starting management: poor feeding, drowsiness, neurologic signs, somnolence, convulsions, cerebral edema, coma

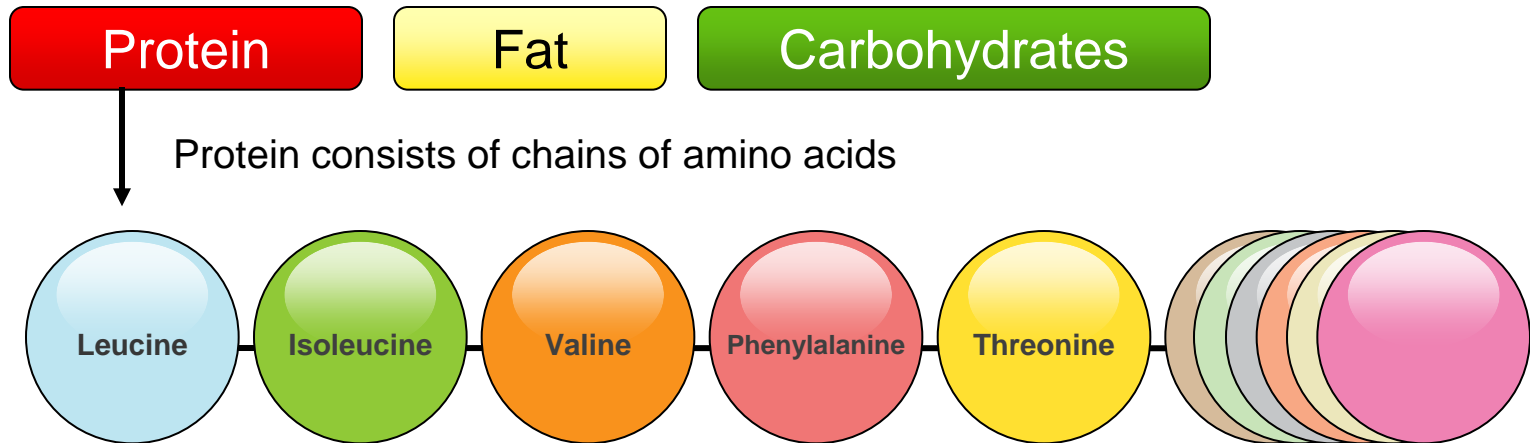
In infancy, childhood and adolescence during metabolic decompensations: apathy, ataxia, hallucinations, convulsions, cerebral edema, coma

Chronic brain damage

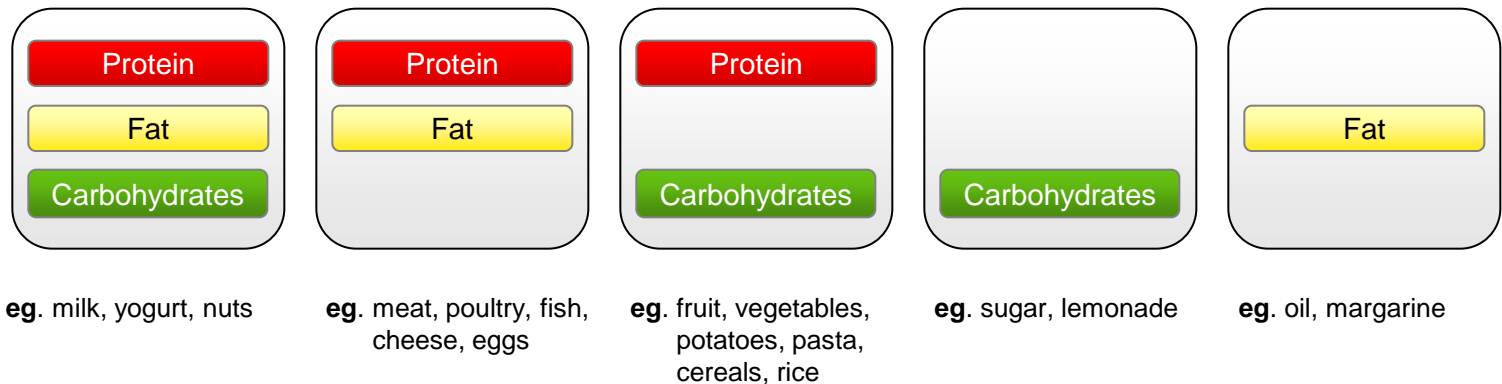
When the leucine concentrations are moderately but continuously increased

- Behavioral and intellectual disabilities
- Caused by dysmyelination of the white matter of the brain

Food – Components of a typical diet

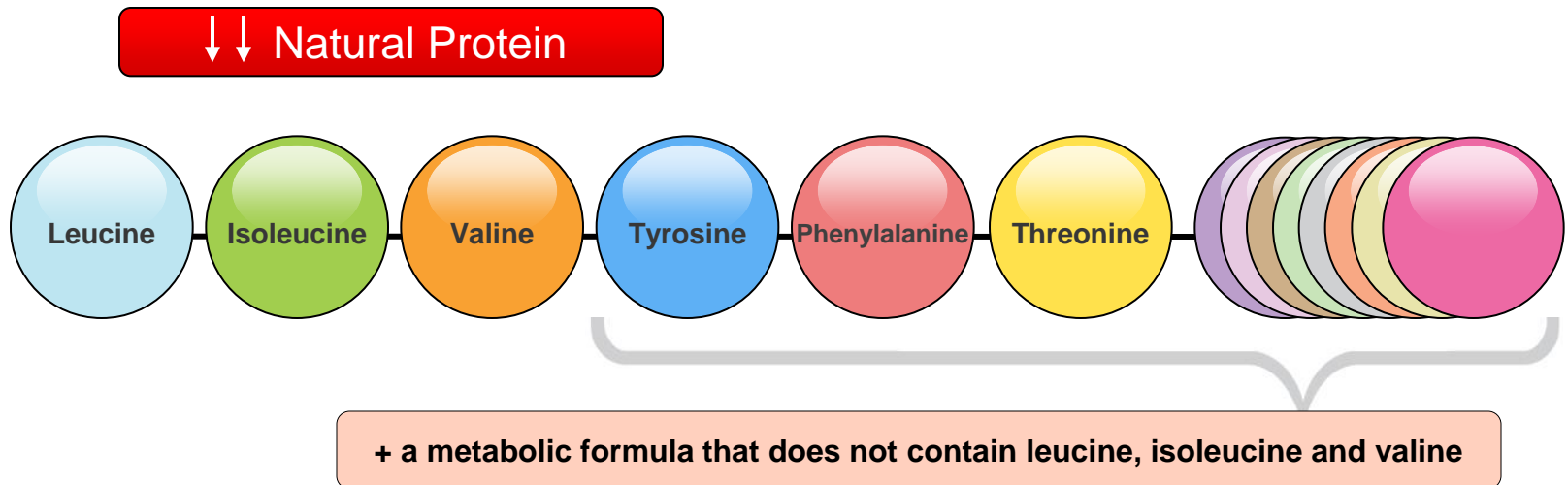


Natural Food

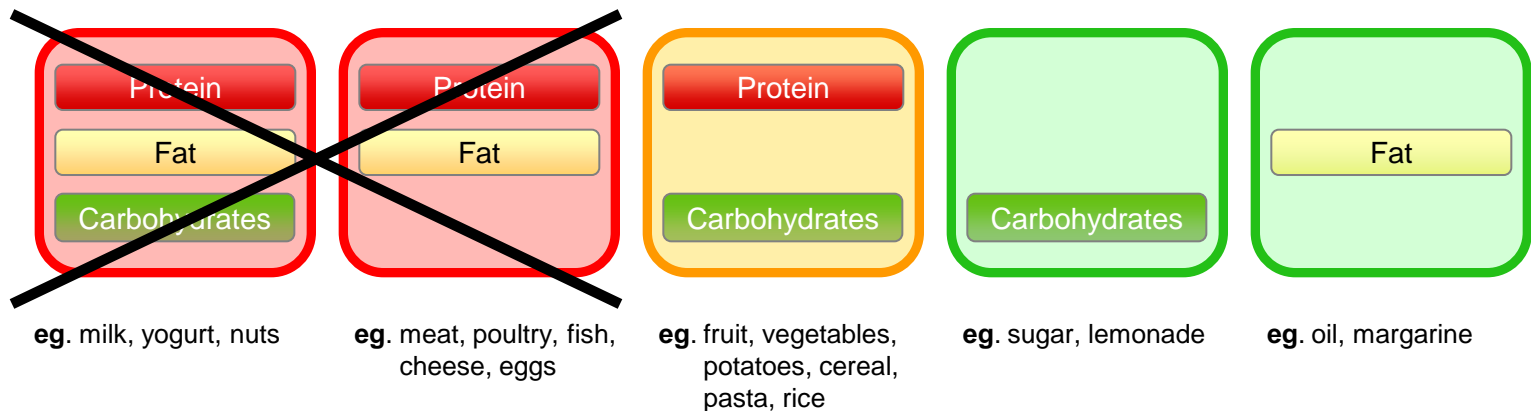


Principles of diet management

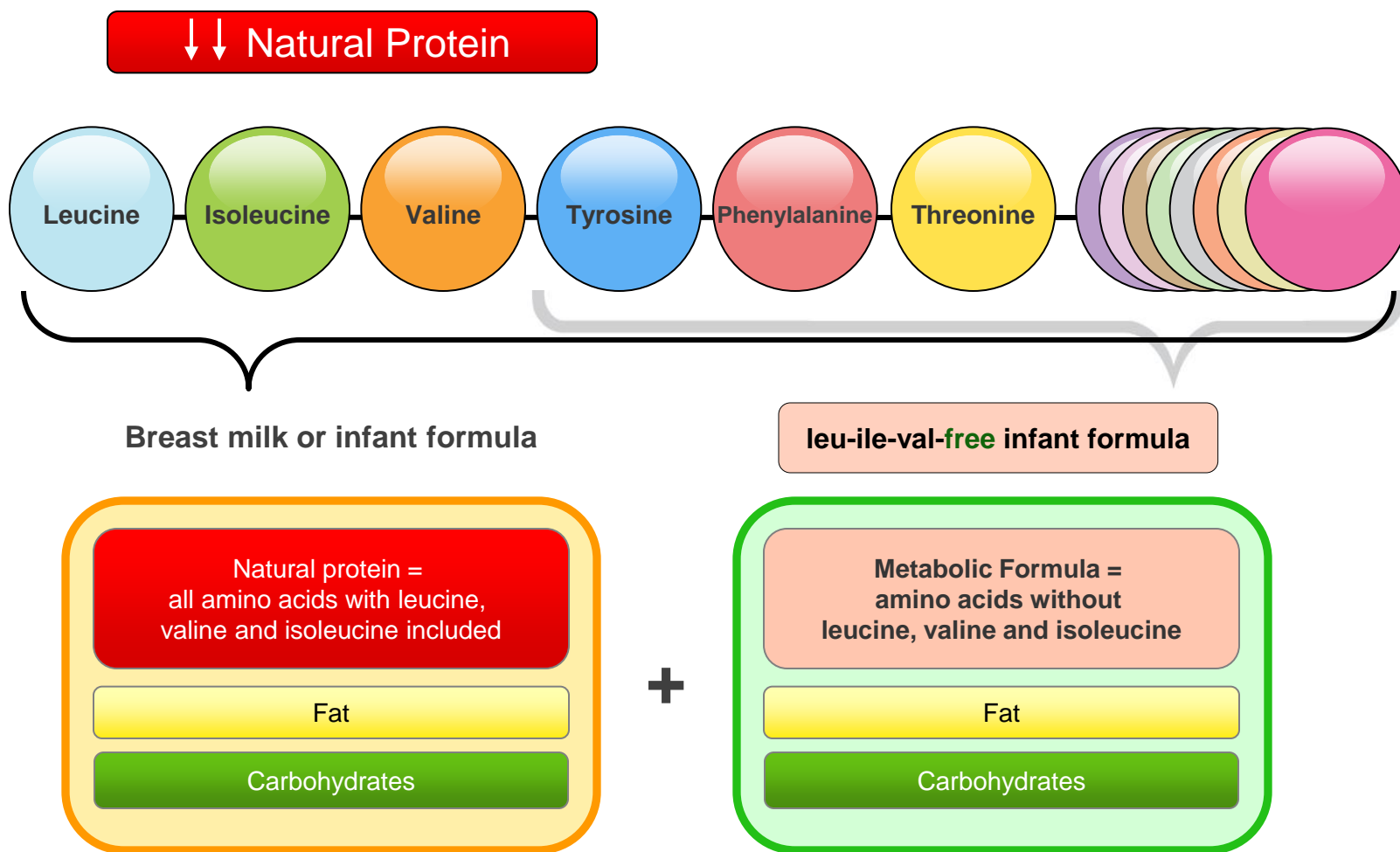
Very low natural protein diet + leucine–valine–isoleucine free metabolic formula



Natural Food

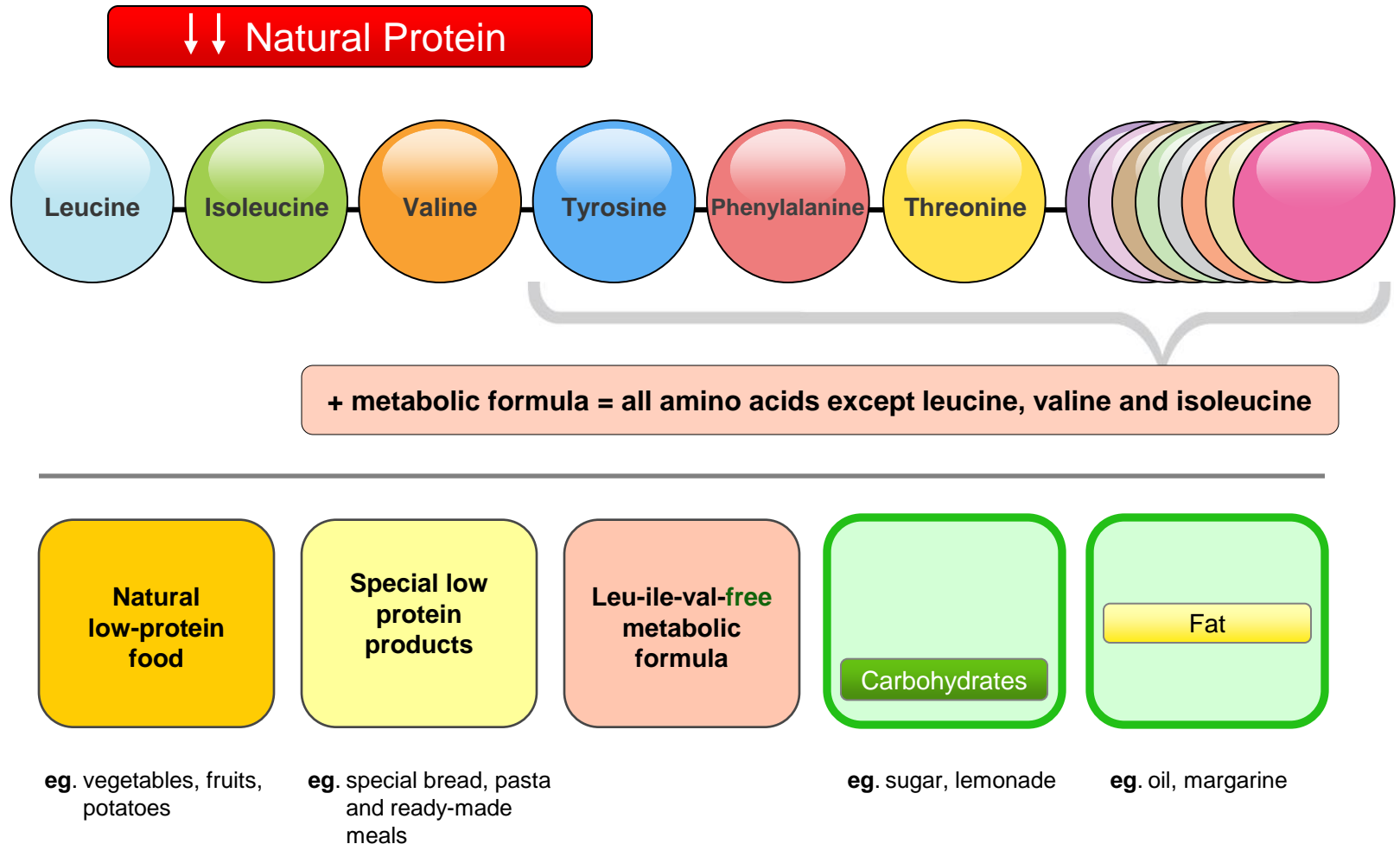


Diet management during the first 4 to 6 months of life



Foods + special low-protein products + metabolic formula

Nutritional components of a MSUD diet once the baby is weaned and solids are introduced



Goals of diet management

MSUD diet

Very low-protein natural foods

+ special low-protein products

+ leucine-isoleucine-valine-free metabolic formula

+ supplement with isoleucine and/or valine to prevent low blood levels

Management goals (can vary by clinic)

Long-term plasma concentrations should be

Leucine: 100 – 300 $\mu\text{mol/L}$ (1.3 - 3.9 mg/dl)

Isoleucine: 200 - 400 $\mu\text{mol/L}$ (2.6 – 5.2 mg/dl)

Valine: 200 - 400 $\mu\text{mol/L}$ (2.4 – 4.8 mg/dl)

Conversions

Leucine: 1 mg/dl = 76 $\mu\text{mol/L}$ 100 $\mu\text{mol/L}$ = 1.3 mg/dl

Isoleucine: 1 mg/dl = 76 $\mu\text{mol/L}$ 100 $\mu\text{mol/L}$ = 1.3 mg/dl

Valine: 1 mg/dl = 85 $\mu\text{mol/L}$ 100 $\mu\text{mol/L}$ = 1.2 mg/dl

Monitoring BCAA and other labs

Remember!

The MSUD diet requires frequent monitoring of BCAA levels to prevent nutritional deficiencies.

The diet needs to be evaluated often to ensure that all nutrients (natural and metabolic formula protein, energy, vitamins and minerals) meet the recommendations for normal growth of the child.

Metabolic Emergencies

During the following conditions, a metabolic episode may occur with rapidly rising concentrations of leucine and KICA

- **Febrile illnesses**, e.g. vomiting and diarrhea, infectious diseases
- **Vaccinations**
- **Surgeries**

These conditions can cause an increase in catabolism

During catabolism, body tissue is broken down and leucine and KICA (and all other amino acids) are released from muscle protein! The accumulation of leucine and KICA can cause rapid neurologic deterioration!

Catabolism during the first few days of life results in a neonatal metabolic episode

- **Very high amounts of protein in the diet can also increase leucine**

What are the signs of a metabolic crisis?

- Apathy
- Anorexia, vomiting
- Abnormal movements (ataxia)
- Hallucinations
- Reduced response to stimuli
- Lethargy and coma

The urgent initiation of an emergency protocol is necessary in order to stop a metabolic crisis !

Emergency management during catabolism

1. Manage according to an emergency plan. Metabolic clinics may....
 - Start frequent feeding of carbohydrate-rich meals
 - Temporarily reduce natural protein in the diet
 - Continue intake of the leucine-isoleucine-valine-free metabolic formula.
2. A child may need to visit the metabolic clinic to monitor plasma amino acid levels
3. In cases of deterioration, inpatient management may be necessary

Emergency management has to start immediately after the first signs of illness !

Chromosomes, Genes, Mutations

A **chromosome** is like a cookbook.

A **gene** is like a recipe in the cookbook.

A **mutation** is like an error in the recipe or even a complete lack of a recipe.

The **enzyme** **BCKD** is produced constantly in the body following a specific recipe (**gene**). If the gene contains abnormal **mutations**, the **enzyme** cannot function correctly or be properly produced.

Inheritance of MSUD

Parents are carriers in autosomal-recessive inheritance

Mother is a carrier of
MSUD

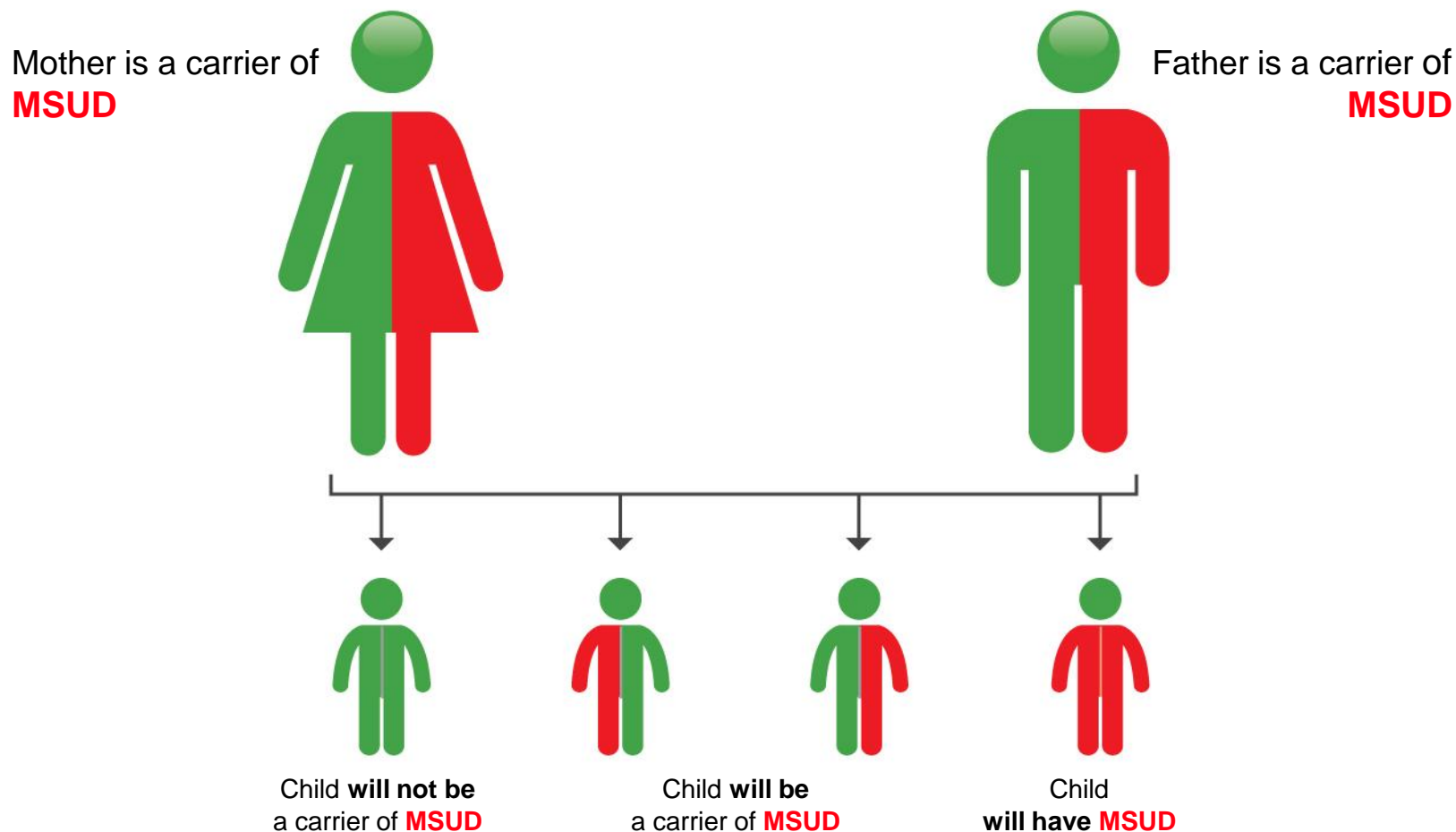


Father is a carrier of
MSUD



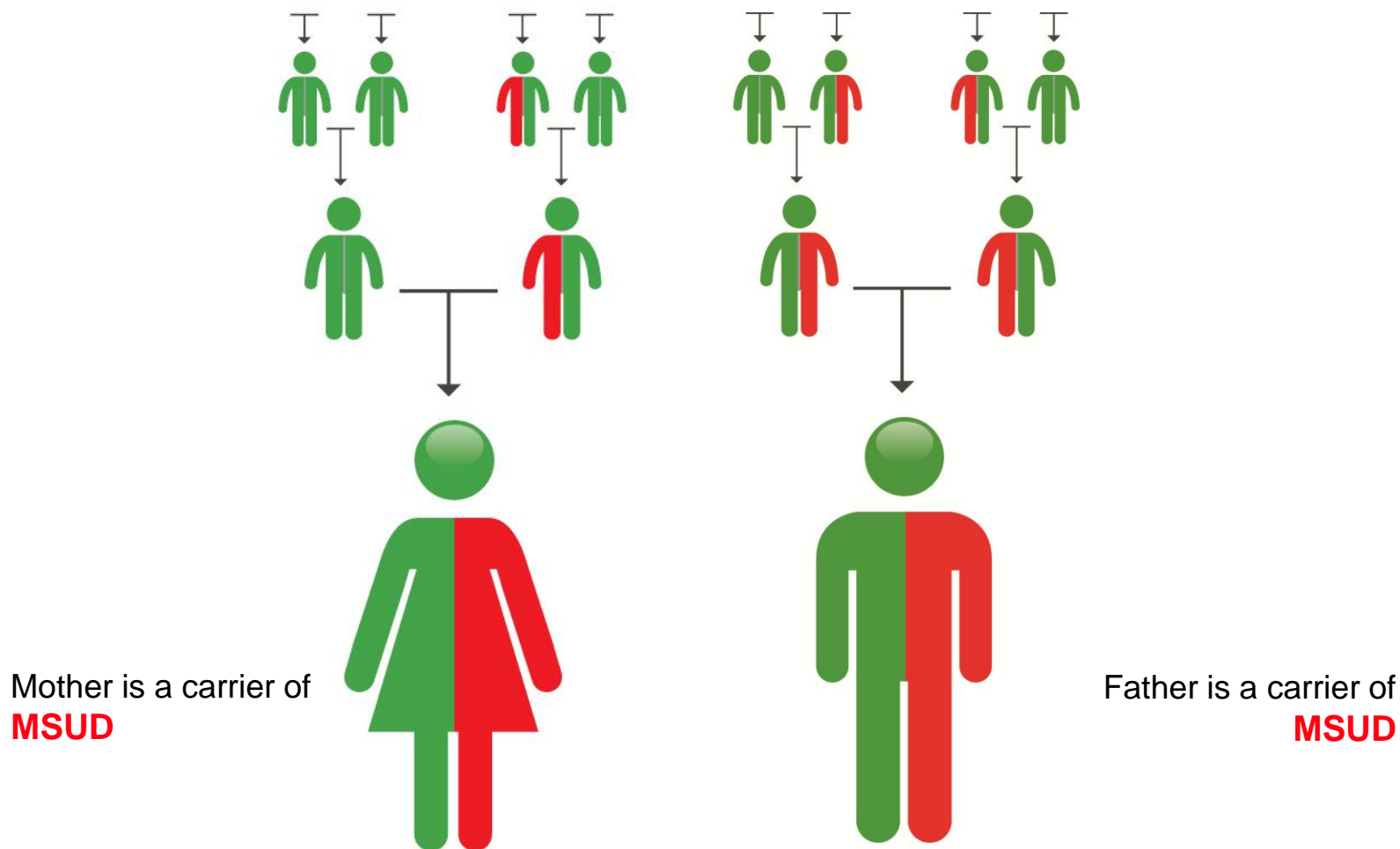
Inheritance of MSUD

Possible combinations



Inheritance of MSUD

Where does MSUD come from?



Summary

