

# Isovaleric acidemia

## Introductory information

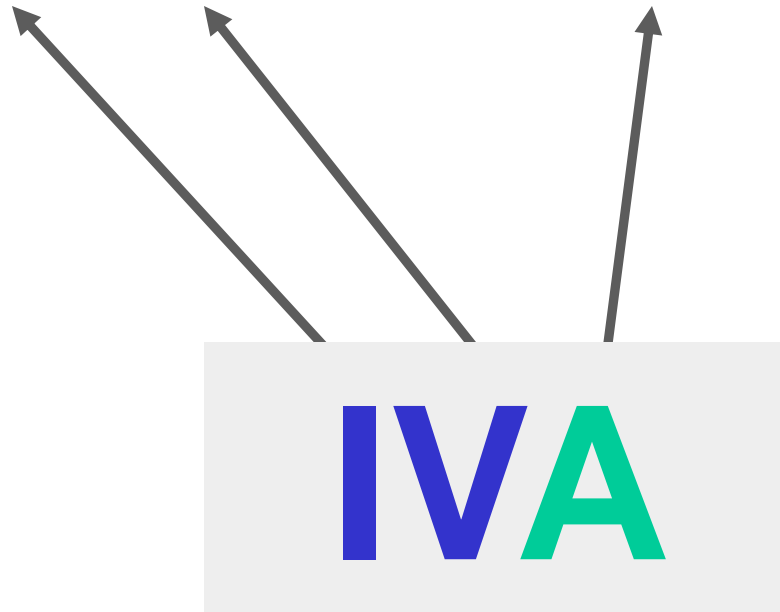
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# Isovaleric acidemia



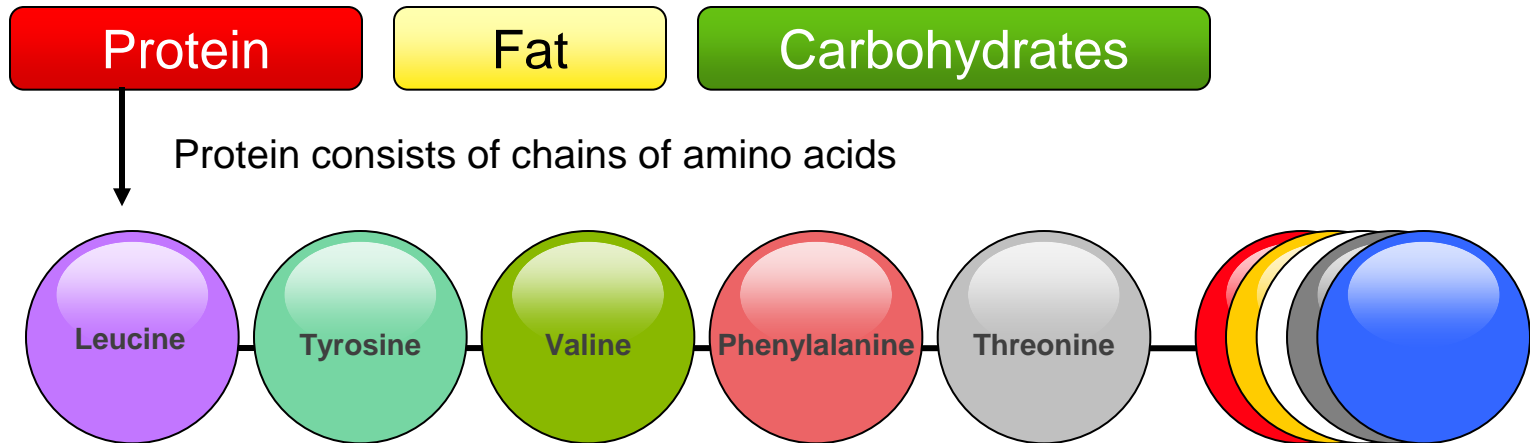
# Isovaleric acidemia

Isovaleric

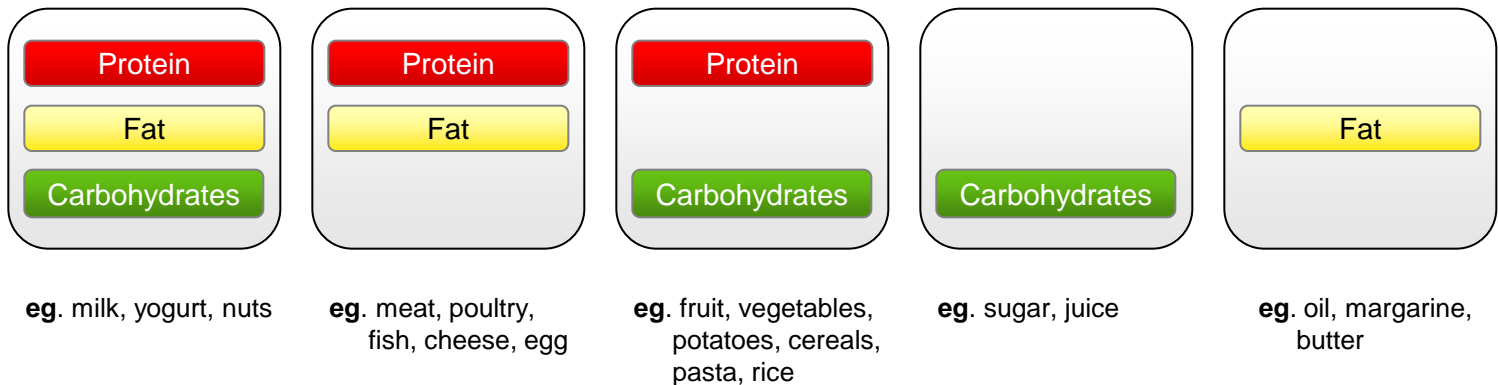
acid in blood

IVA

# Food – Components of a normal diet



## Natural Food



# Enzymes

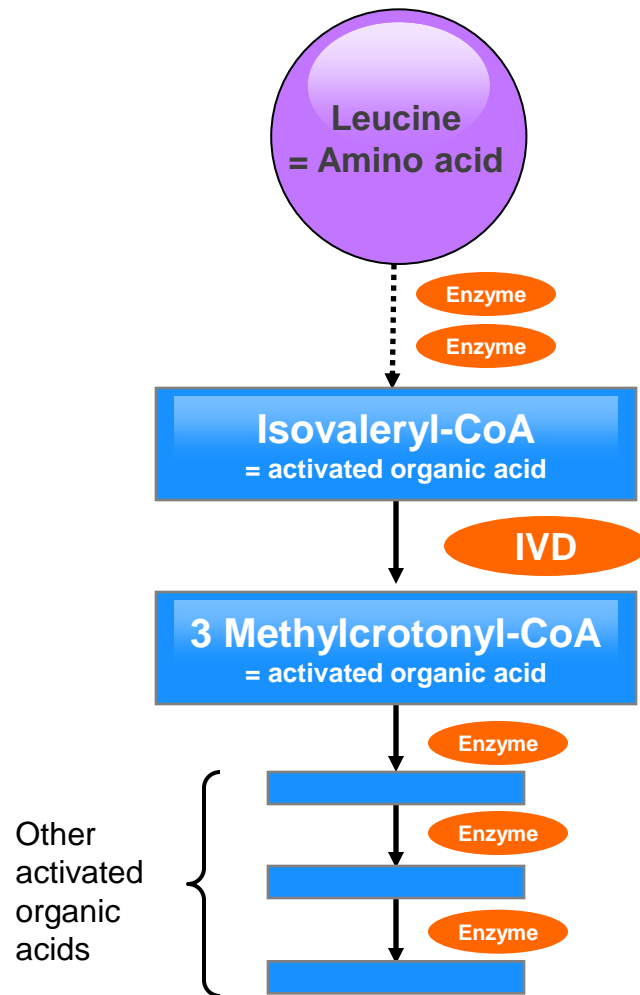
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**Enzymes** are proteins that facilitate various chemical reactions in the body. They are involved in the biosynthesis (anabolism) and the degradation (catabolism) of all substances in the body. This is called metabolism.

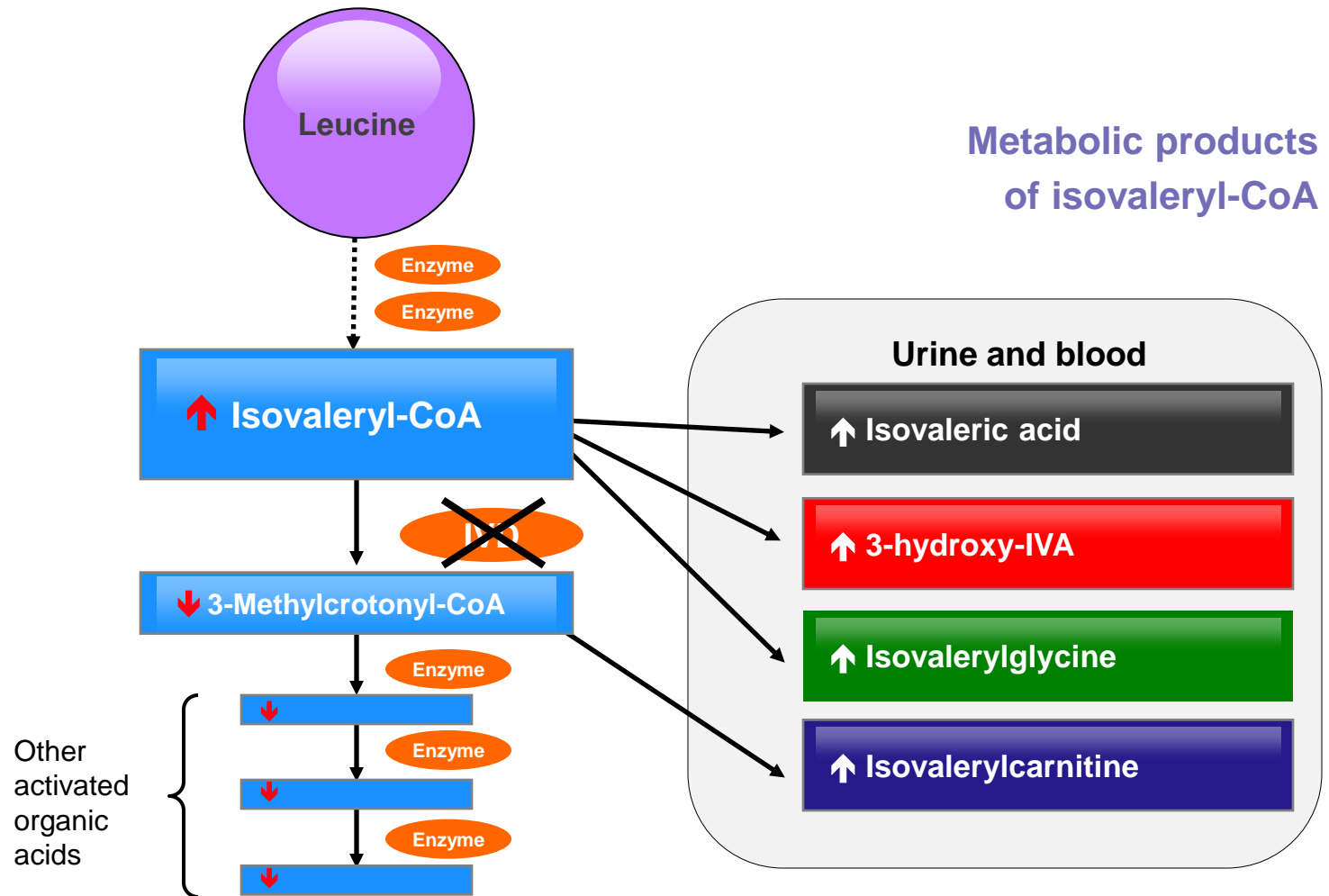
**Isovaleryl-CoA-dehydrogenase (IVD)** is an enzyme that is necessary for the metabolism of the amino acid leucine.

In IVA, the activity of the **IVD enzyme** is decreased.

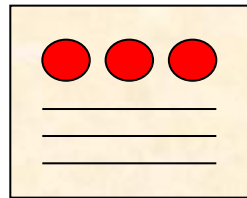
## In a person without IVA: **IVD** works



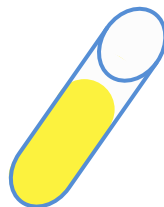
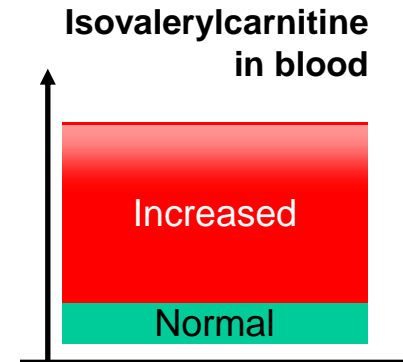
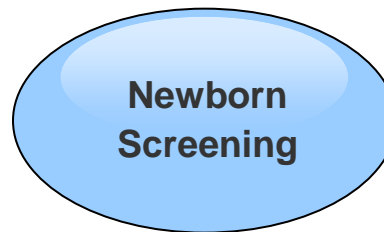
# Metabolism in a patient with IVA: **IVD deficiency**



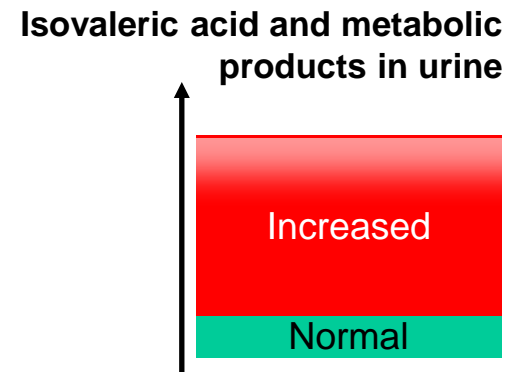
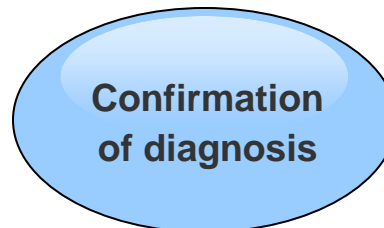
# Diagnostic investigations



Dried blood spots

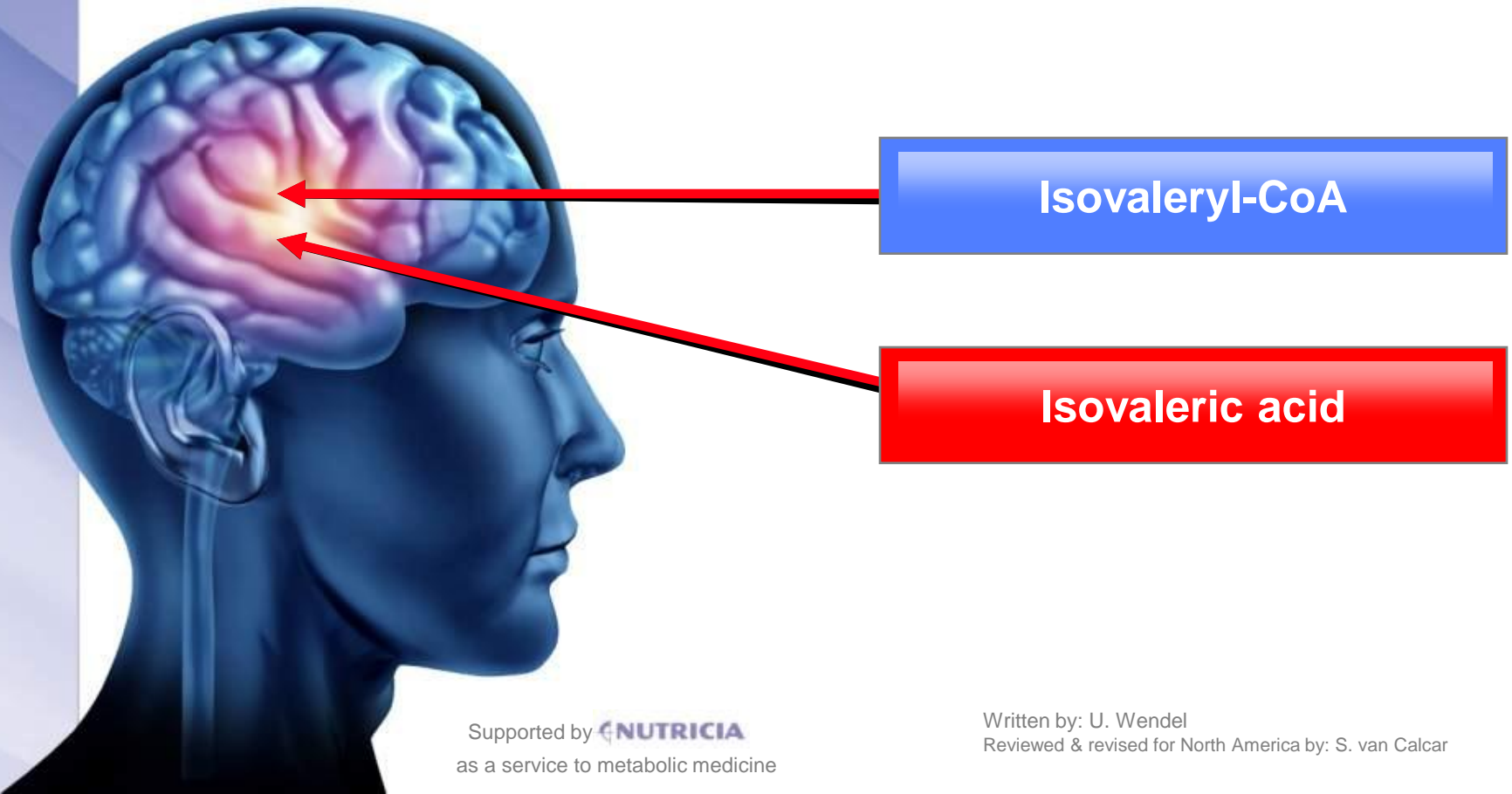


Urine sample



# Pathogenesis of IVA

Organic acids are toxic to the brain. **High concentrations of isovaleryl-CoA and isovaleric acid can damage the brain.**



# Pathogenesis: Metabolic crises

Isovaleryl-CoA and isovaleric acid can be especially high during metabolic crises. The following situations can lead to a metabolic crisis in IVA:

- **Febrile illnesses**  
e.g. diarrhea, infectious disease, fever, etc.
- **Vaccinations**
- **Surgeries**
- **Malnutrition**

## In these situations **catabolism** develops

The term “catabolism” refers to the metabolic reactions leading to the breakdown of body tissues.

Isovaleryl-CoA and isovaleric acid are produced from body proteins, especially the breakdown of muscle!

Catabolism can lead to a metabolic crisis in the first days of life.

# What are the symptoms of a metabolic crisis?

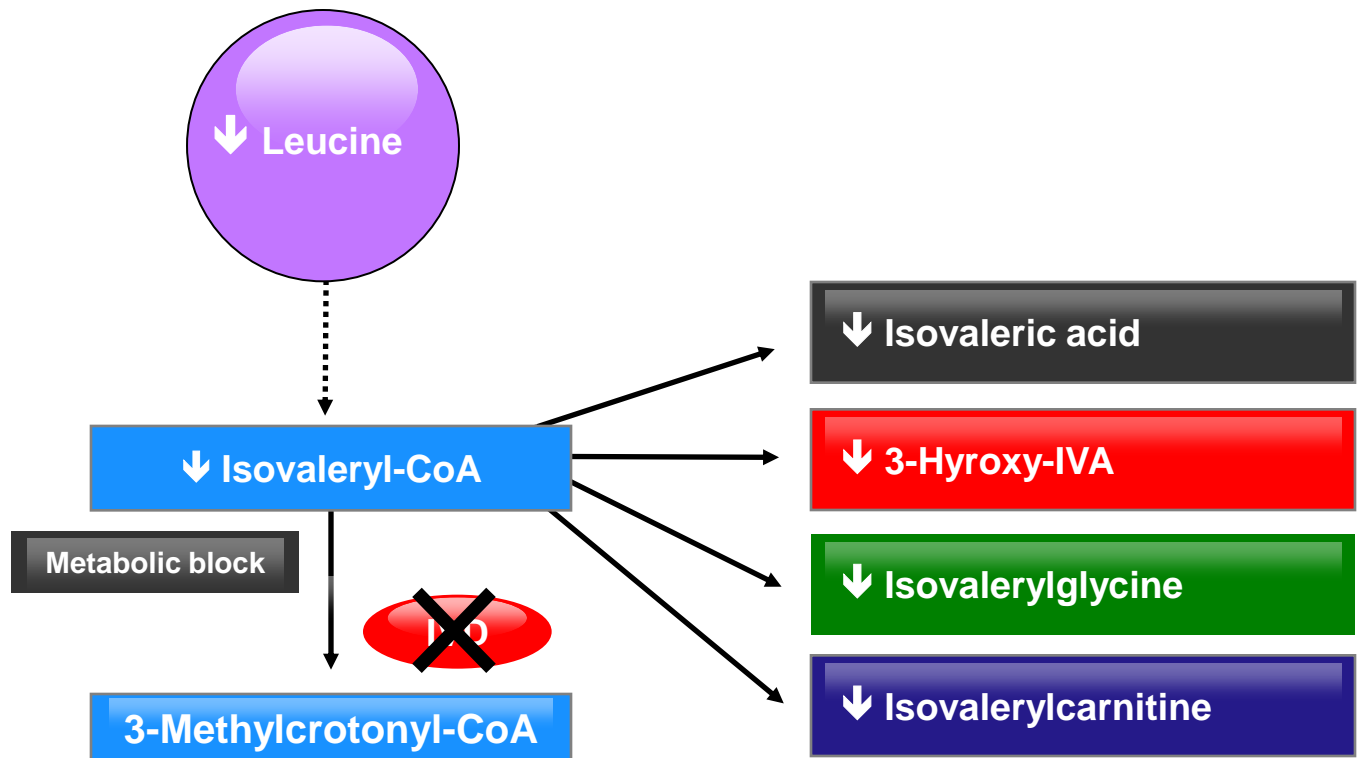
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- Unusual tiredness, unresponsiveness
- Loss of appetite, vomiting
- Movement disorders (the child cannot sit or stand anymore, becomes “floppy”, develops abnormal movements)
- Quick and deep breathing
- Sweaty feet odor
- The child is very difficult to wake up or you cannot get him to wake up at all (coma)

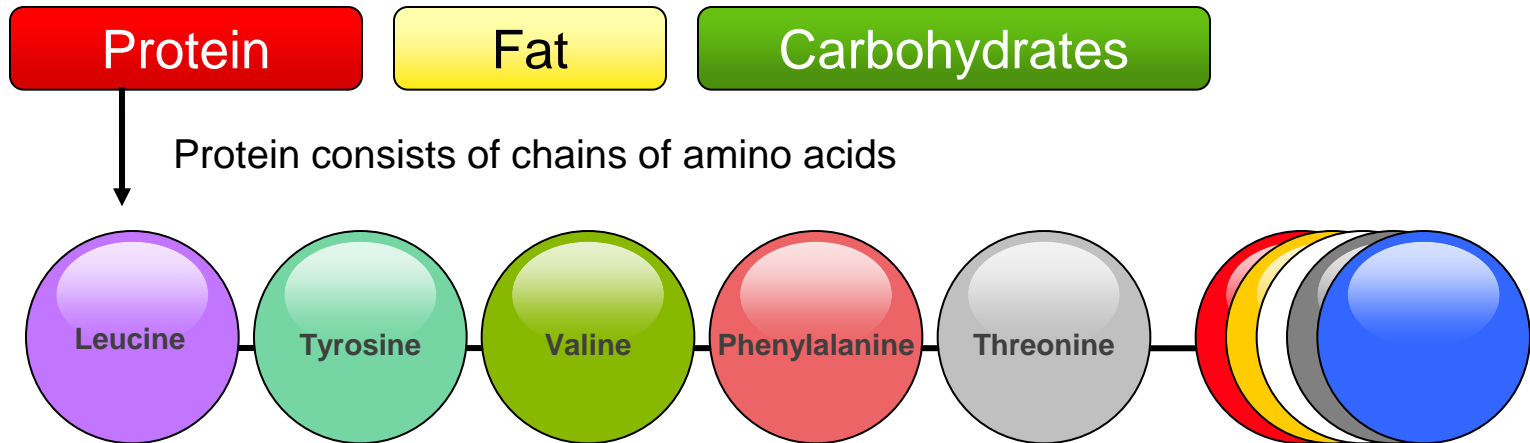
It is critical that management be started immediately to prevent the patient's condition from deteriorating. Metabolic crises can be fatal

# Principles of Management

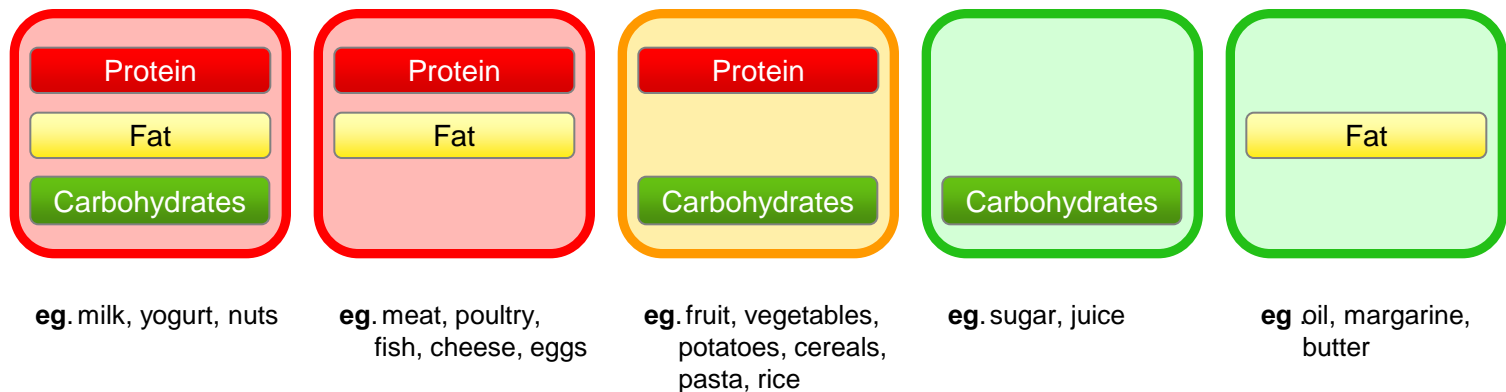
Diet management decreases intake of leucine



# Food – Components of a normal diet



## Natural Food

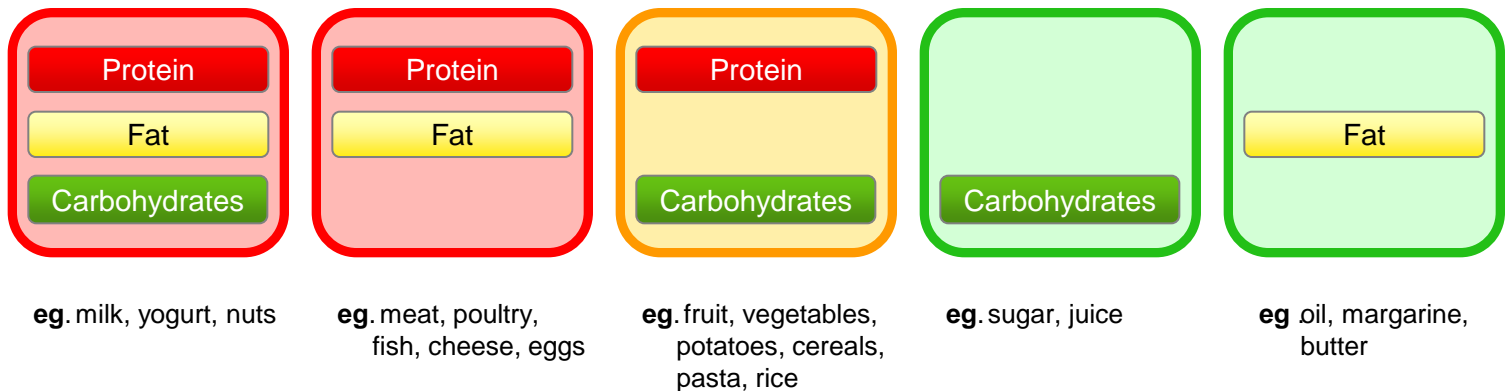


# Management:

## 1. Diet low in natural protein

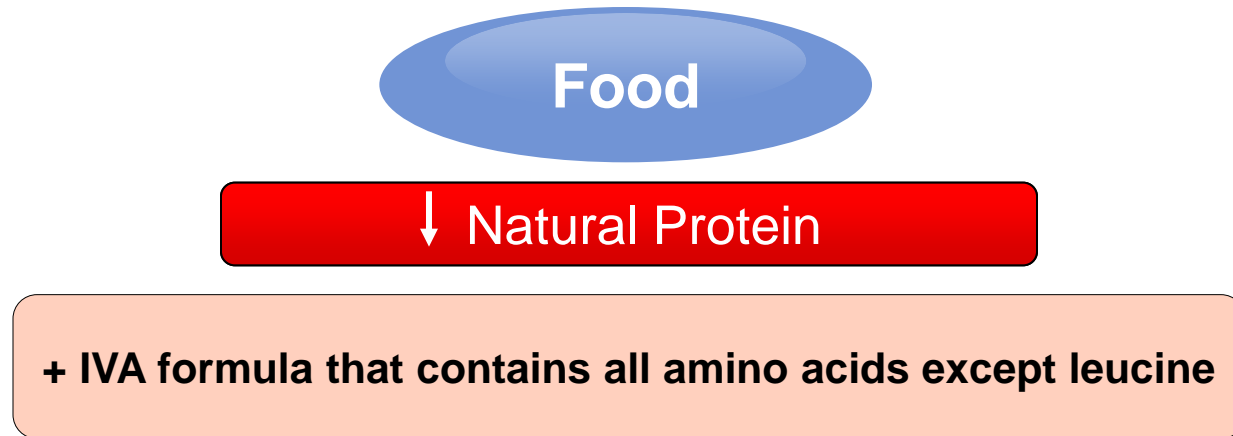


### Natural Food

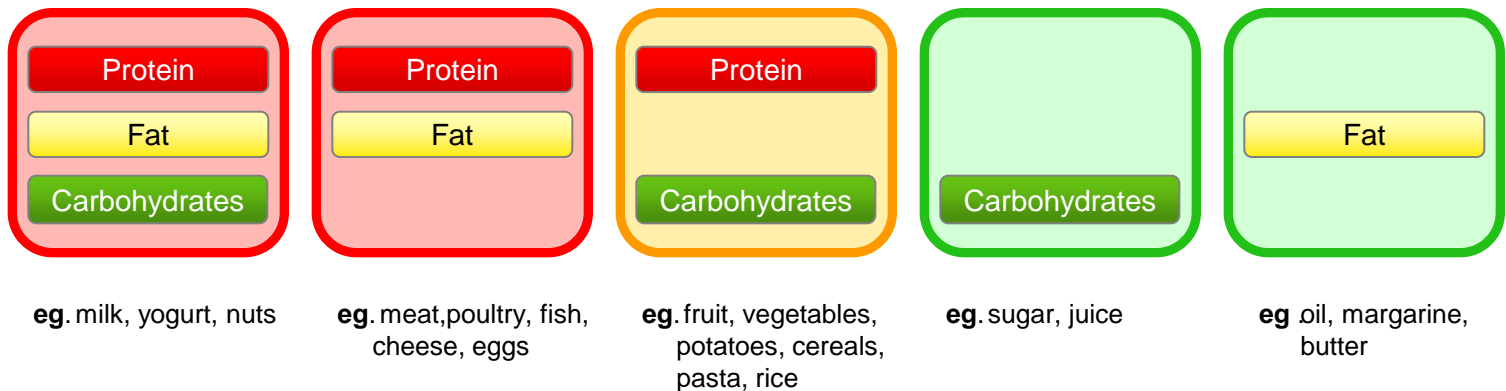


# Management:

## 2. Diet low in natural protein + a formula that does not contain leucine

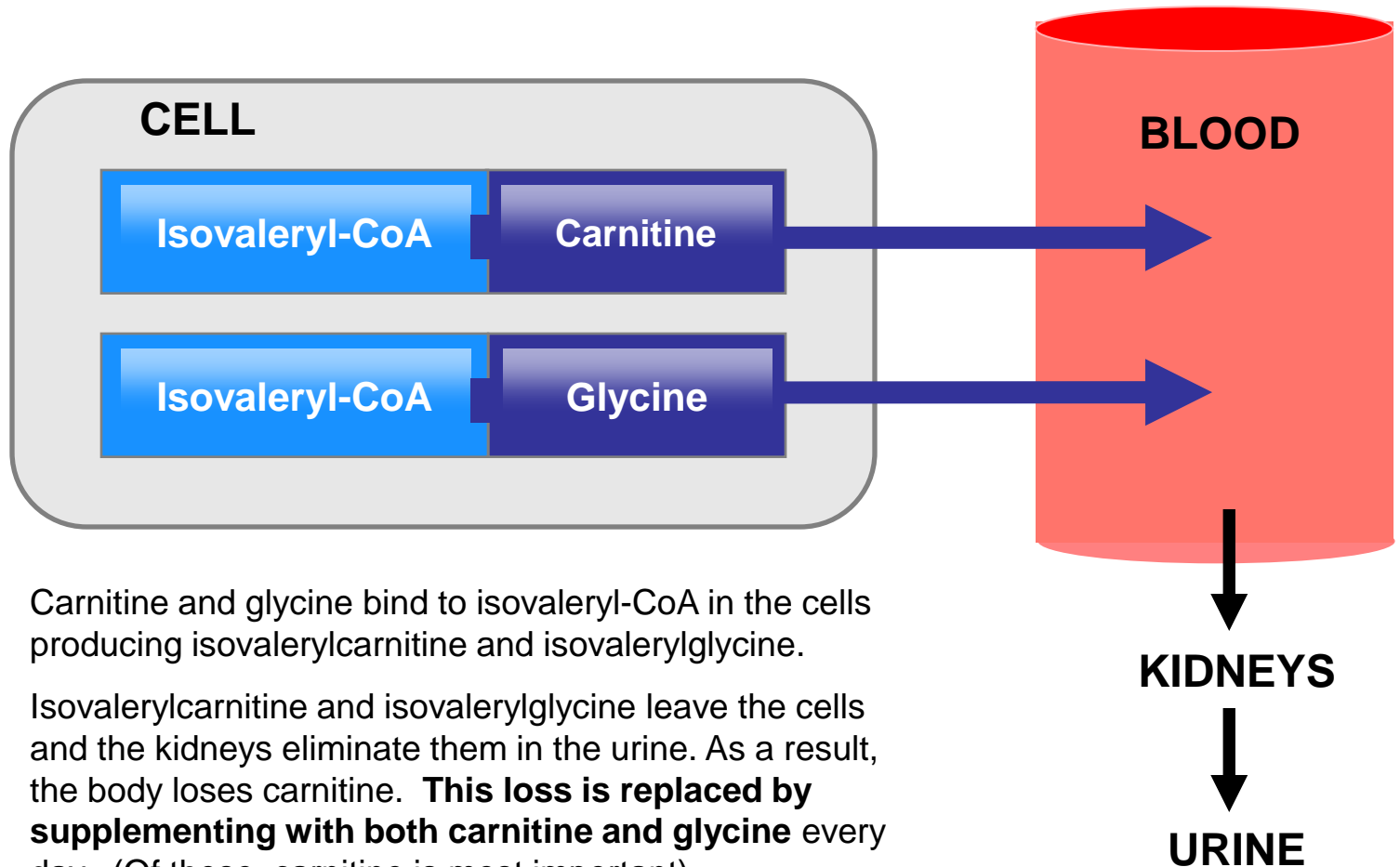


### Natural Food



# Management:

## 3. Carnitine and glycine supplementation



Carnitine and glycine bind to isovaleryl-CoA in the cells producing isovalerylcarnitine and isovalerylglycine.

Isovalerylcarnitine and isovalerylglycine leave the cells and the kidneys eliminate them in the urine. As a result, the body loses carnitine. **This loss is replaced by supplementing with both carnitine and glycine** every day. (Of these, carnitine is most important).

# Management:

## Emergency management during illness

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1. Frequent feedings of low in natural protein and high-carbohydrate foods and beverages.
2. If the child's condition deteriorates, contact the metabolic clinic for directions. A hospital admission may be necessary to provide adequate management.

**Emergency management should always be started promptly during any acute intercurrent illness!**

### **Important:**

All patients with IVA need an emergency protocol and plans for emergency management at the nearest children's hospital

# Follow-up in IVA

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Management with a diet low in natural protein, IVA formula, and carnitine and glycine supplementation requires regular laboratory tests!

These include:

1. Measuring the concentrations of amino acids and acylcarnitines in blood
2. Basic laboratory blood tests
3. Analysis of organic acids in the urine

# Chromosomes, Genes, Mutations

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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 **isovaleryl-CoA-dehydrogenase (IVD)** is produced constantly in the body following a specific recipe (**gene**). If the gene carries abnormal **mutations**, the **enzyme** cannot function properly or be properly produced.

# Inheritance of IVA

Both parents are carriers in autosomal-recessive inheritance

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Mother is a carrier of  
**IVA**

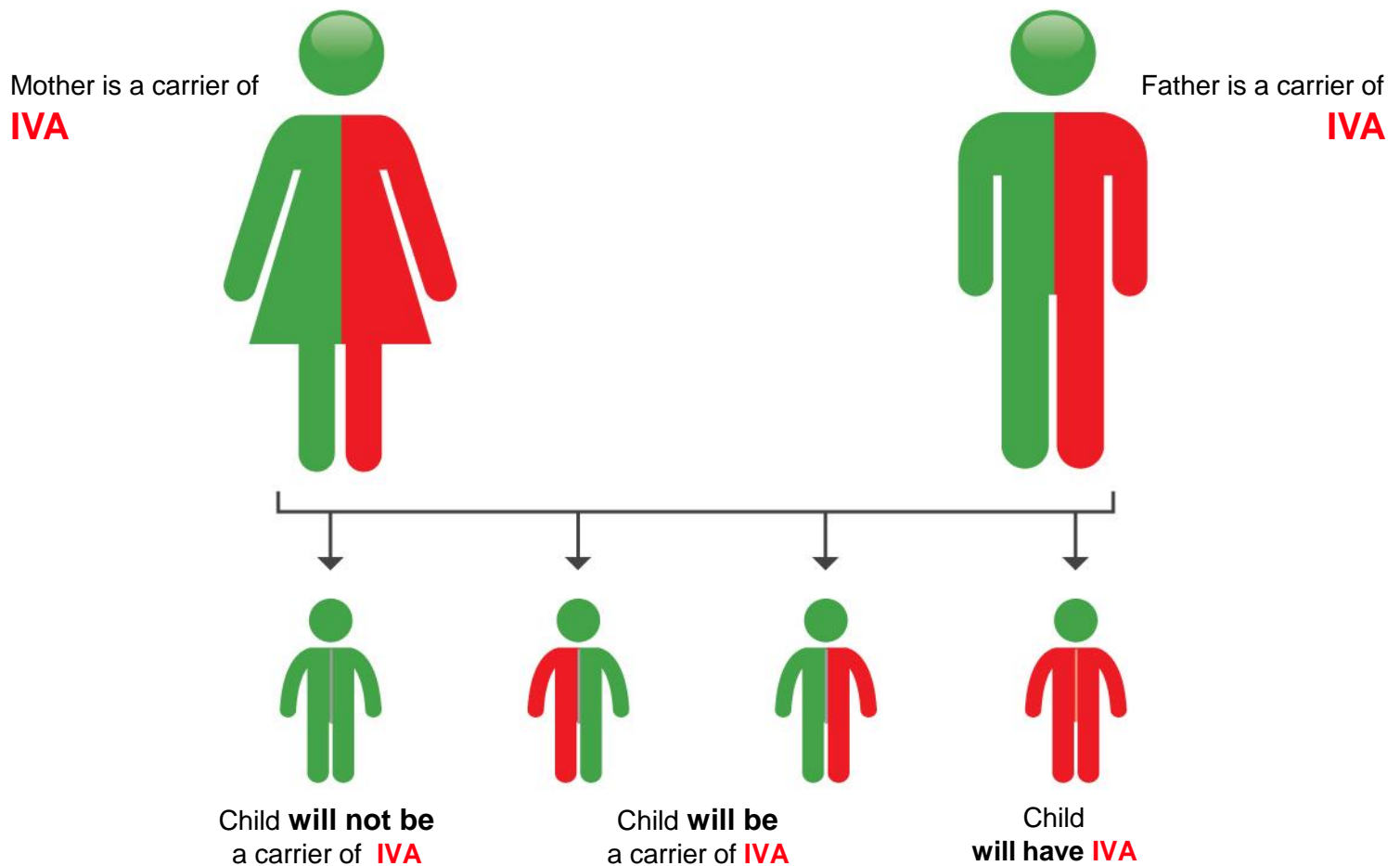


Father is a carrier of  
**IVA**



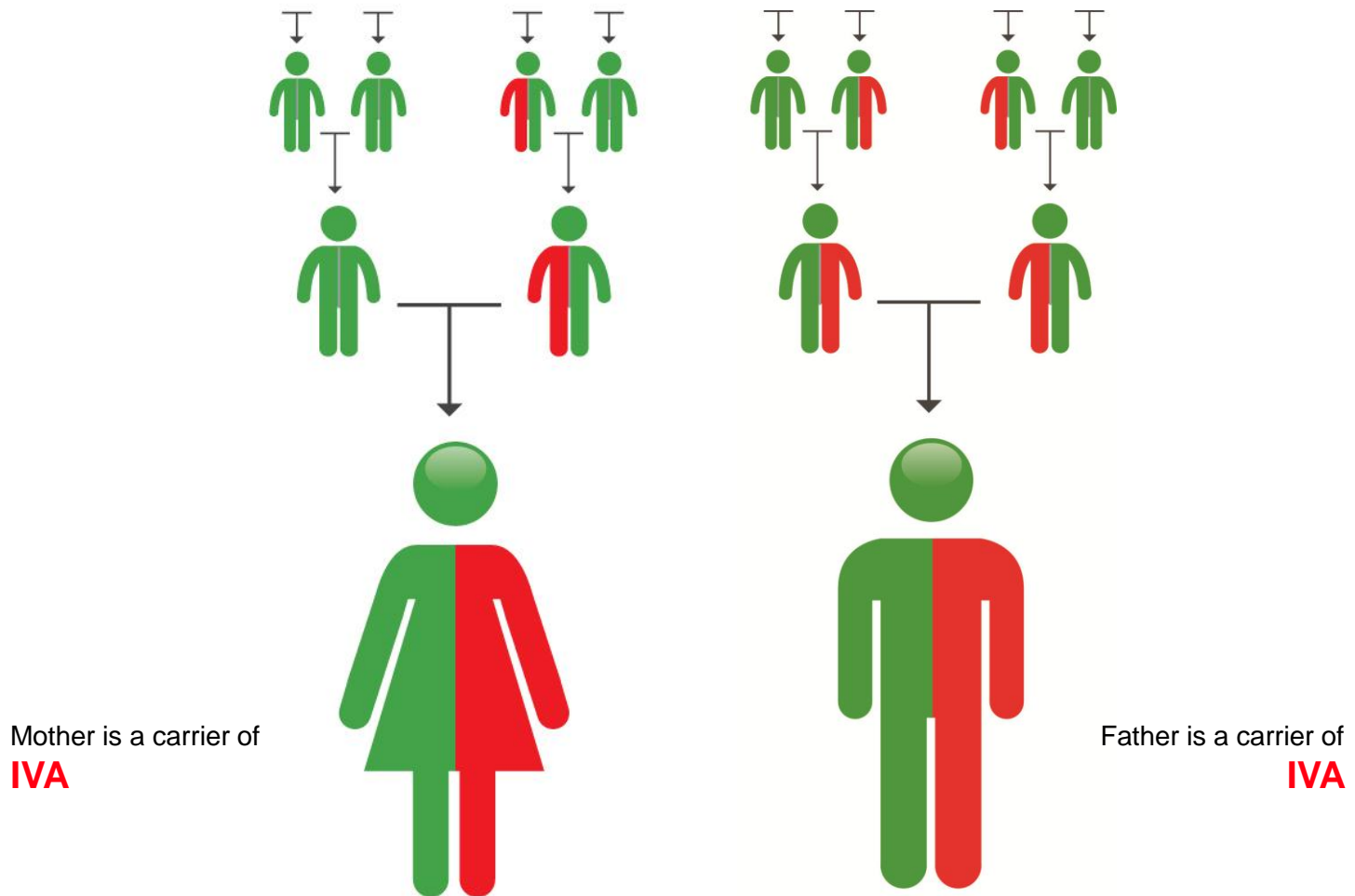
# Inheritance

There are 4 possible combinations for any child born to parents who are carriers



# Inheritance

How **IVA** is inherited in families



# Summary

<b>What is IVA?</b>	<b>Disorder of leucine metabolism</b>
	↑ Isovaleryl-CoA, ↑ Isovaleric acid, ↑ 3-Hydroxy-IVA

## Optimal management

1. Diet low in natural protein & IVA formula without leucine
2. Early and effective management of metabolic crises during illness
3. Pharmacological treatment with the use of carnitine, and glycine

## Management results

- Normal intellectual and neurologic development

## Follow-up

### Laboratory tests

#### Special tests

- Amino acids, acylcarnitines, organic acids

#### Routine tests

#### Physical development

- Body height and weight, head circumference

#### Psychomotor development

- Neuropsychological tests
- Intelligence (IQ)

## Management results in case of insufficient therapy

- Developmental delay
- Neurological symptoms, movement disorders
- Psychological and intellectual deficits
- Severe and late-managed metabolic crises can result in brain damage!