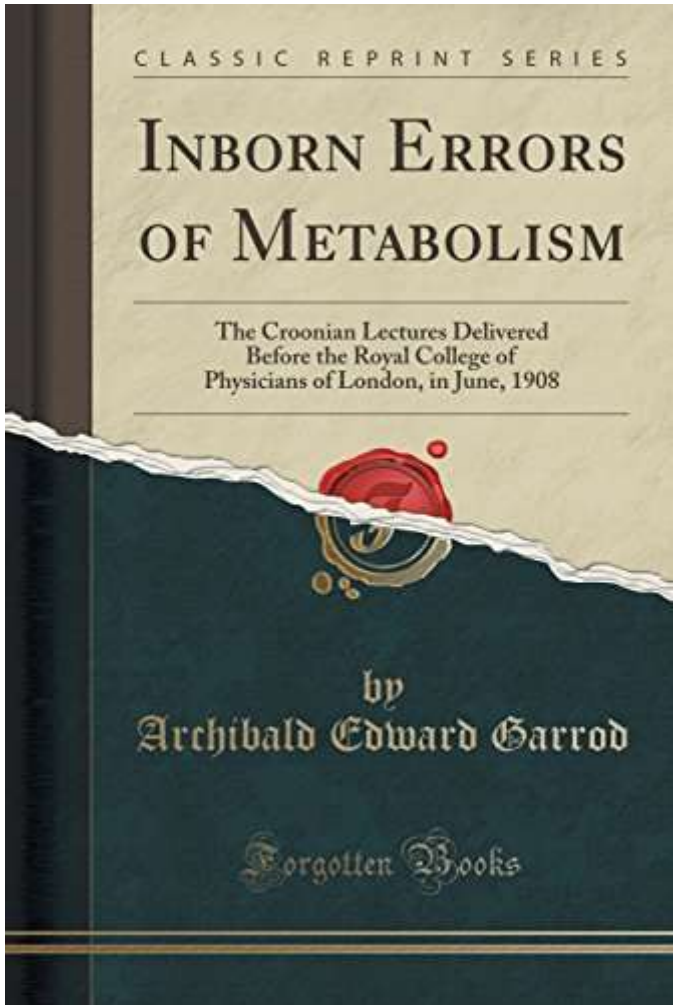
INBORN ERRORS OF METABOLISM

Dr Jayanth ·K,
Fellow in Pediatric Neurology,
MIMER Medical College

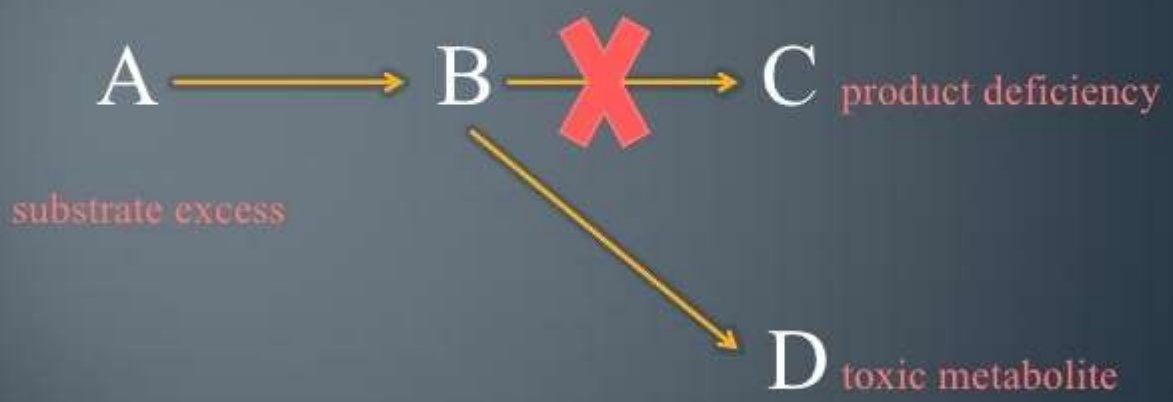
- Historic background of IEM
- Epidemiology
- Classification of IEM's
- Basics and approach to IEM's
- Some selected IEM's in detail

Dr Archibold Garrod

1908



Garrod's hypothesis



Dr Asbjorn Foling

1934

A great day for celebration!

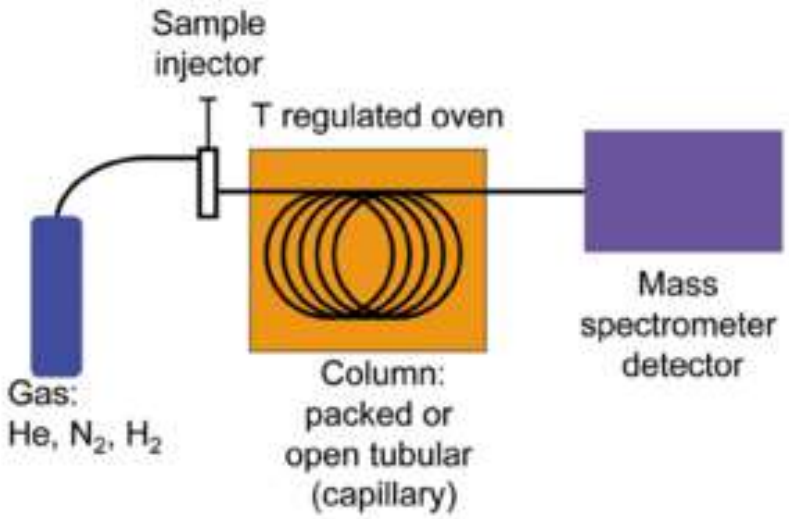
Dr. Horst Bickel
Pioneer in the treatment for PKU

1950's

INTERNATIONAL PKU-DAY 28TH JUNE

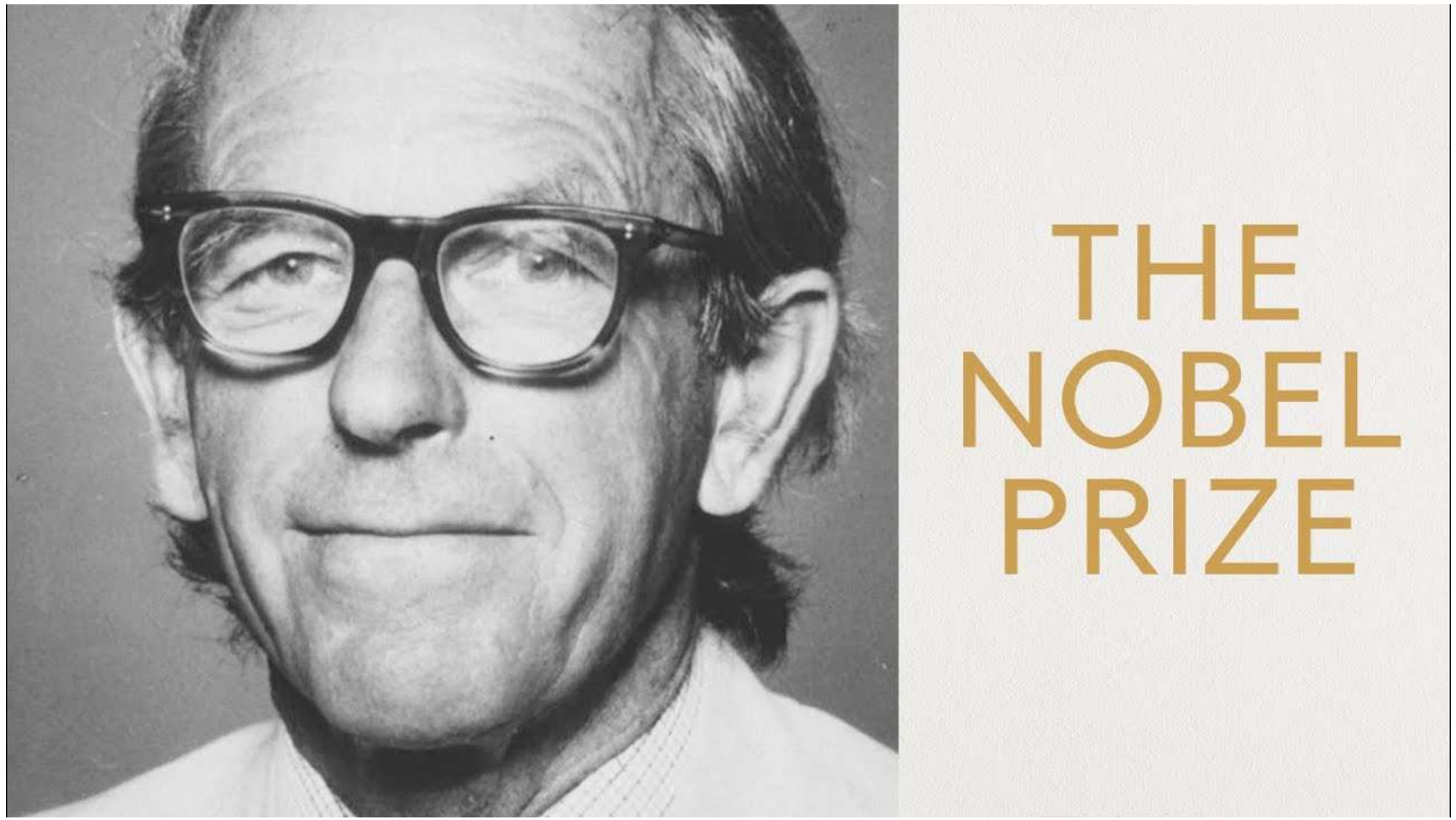
Dr. Robert Guthrie
Newborn Screening Pioneer

1960's


Sample injector
T regulated oven
Mass spectrometer detector
Gas: He, N_2, H_2
Column: packed or open tubular (capillary)

1955


TRACE GC



Dr Frederick Sanger

1960's

Next generation sequencing

2000's

The "-omics" revolution

EVOLUTION OF TREATMENT

Diverting abnormal metabolites / creating alternate pathways to eliminate potentially toxic metabolites (e.g., dialysis or ammonia scavenger drugs in urea cycle disorders or organic acidemias).

Supplementation of the enzyme's cofactor, tetrahydrobiopterin. A subset of responsive patients having residual enzyme activity had improved quality of life and dietary relaxation with this therapy. (e.g., B12 supplementation in some cases of methylmalonic acidemia, B6 in some cases of homocystinuria, and riboflavin for glutaric aciduria type 2)

Stem cell bone marrow transplantation can be therapeutic, particularly in some storage disorders (e.g., Hurler Syndrome)

Orthotopic liver transplantation is now a treatment of choice for a number of severe inborn errors of metabolism, particularly severe urea cycle defects.

Other therapies showing promise include chaperonins to optimize protein folding, enzyme replacement therapies, and therapeutic mRNA

Finally, the promise of gene therapy is on the very near horizon

WILSON AND JUNGNER CRITERIA

- ✓ The condition sought should be an important health problem.
- ✓ There should be an accepted treatment for patients with recognized disease.
- ✓ Facilities for diagnosis and treatment should be available.
- ✓ There should be a recognizable latent or early symptomatic stage.
- ✓ There should be a suitable test or examination.
- ✓ The test should be acceptable to the population.
- ✓ The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- ✓ There should be an agreed policy on whom to treat as patients.
- ✓ The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- ✓ Case finding should be a continuing process and not a ‘once and for all’ project.

INDIAN SCENARIO (IAP)

Considering the prevalence of these conditions and huge financial implications for universal screening for a developing country like India, a practical approach will be to categorise the conditions as follows:

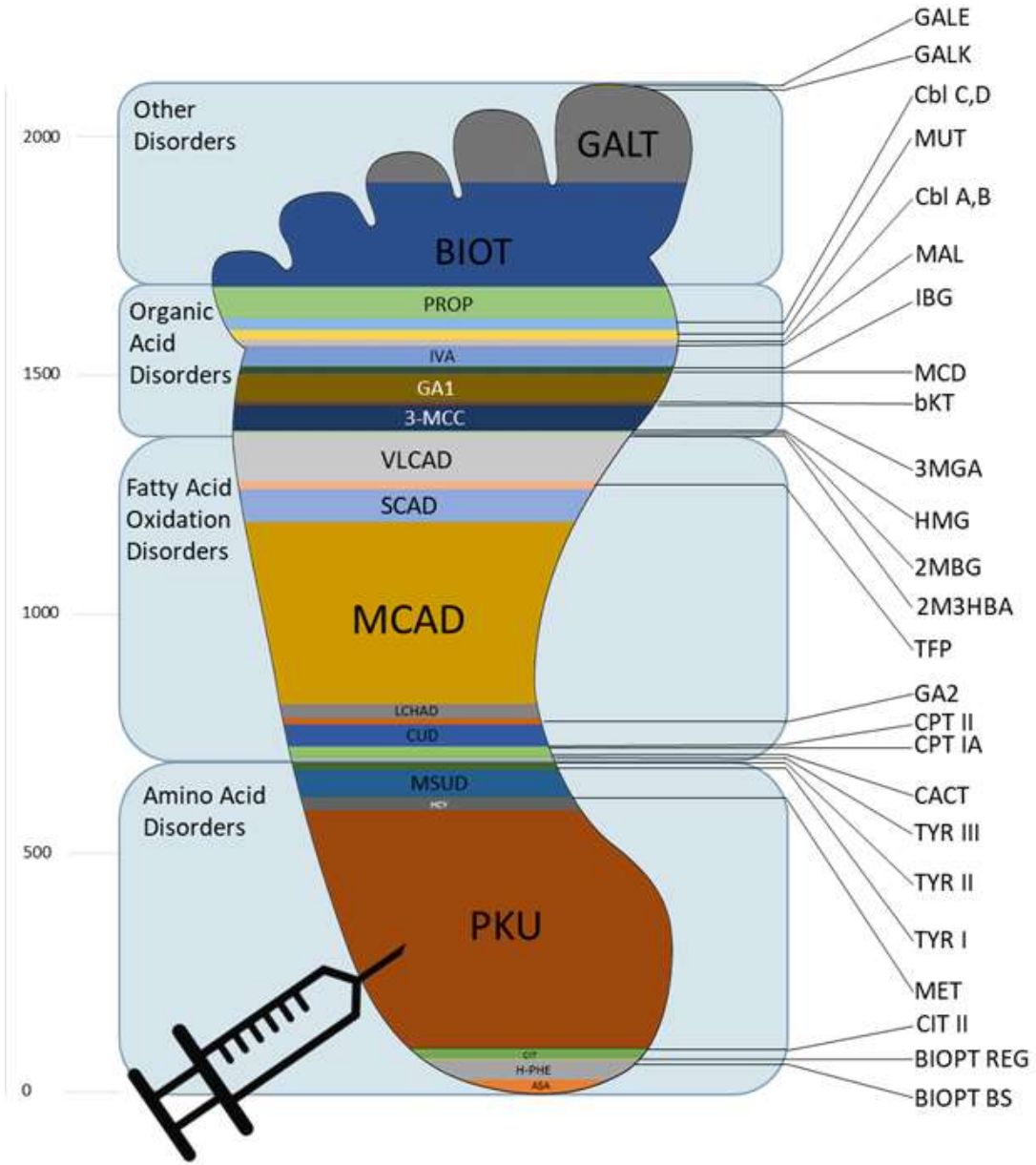
- ✓ *Category A (all newborns)*: Screening for congenital hypothyroidism and hearing should be a must in Indian scenario. Screening for CAH and G6PD deficiency may be added in a phased manner. G6PD screening should be done in Northern states of the country. Screening for Sickle cell disease and other hemoglobinopathies should be undertaken in pockets of high incidence.

- ✓ *Category B (High risk screening)*: Screening for the following disorders should be conducted in the high risk population (These conditions include phenylketonuria, homocystinuria, alkaptonuria, galactosemia, sickle cell anemia and other hemoglobinopathies, cystic fibrosis, biotinidase deficiency, maple syrup urine disease, medium-chain acyl-CoA dehydrogenase deficiency, tyrosinemia and fatty acid oxidation defects.

- ✓ *Category C*: Screening (in resource-rich setting/expanded screening) for 30-40 inherited metabolic disorders may be offered to ‘well-to-do’ families, especially in urban settings where facilities for sending sample to laboratory are available.

Epidemiology

Incidence – 1 in 800-2500 (depending on race, Ethnicity, Testing/Diagnosis & reporting)



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Original Article

Biochemistry Section

Prevalence of Inborn Errors of Metabolism in Neonates

PREETI SHARMA[1], PRADEEP KUMAR[2], MAYURIKA S TYAGI[3], RACHNA SHARMA[4], PS DHOT[5]

ABSTRACT

Introduction: Among the most advanced public health promotion and disease prevention programs, the newborn screening is of paramount importance, seeking timely detection, diagnosis and treatment of genetic disorders which may otherwise lead to serious consequences upon the health of newborn.

Aim: To evaluate the prevalence of Inborn Error of Metabolism (IEM) disorders among neonates of various ethnic or racial groups from east, west, north and south, zones of India through newborn screening.

Materials and Methods: A cross-sectional, population based prospective study was conducted at PreventiNe Life Care Laboratories, Navi Mumbai, Maharashtra, India. Study was conducted for a period of three years from October 2012 to November 2015. Mass screening of newborn blood samples was done via TMS/GCMS/Enzyme assay/HPLC/ELISA technique. The blood and urine samples were used for analysis. The samples have been collected from 150 locations through various hospitals across India. Samples obtained were categorised zone wise (east, west, north, south zones of India). For analysis of blood, samples were collected by heel prick method.

Results: In the present study, 2.9% prevalence (of the total 70,590 samples analysed, 2053 cases were found positive) of IEM was observed. Of these positive cases, 13% (279 of 2053 positive cases) cases belonged to eastern zone, 24% (493 of 2053 positive cases) were from northern zone, 38% (793 of 2053 positive cases) were from southern zone and 23% (488 of 2053 positive cases) were from western zone. Among these, the highest prevalent disorder was found to be G6PD deficiency, with 1.3% (923 positive of 70,590) cases reported followed by haemoglobinopathies, 0.5% (360 positive of 70,590) and congenital hyperplasia with 0.34% (239 positive of 70,590) cases of the total newborns, screened.

Conclusion: The newborn screening is expanding its wings throughout the world. The outcome of present data offers a unique opportunity to explore the birth prevalence of inborn metabolic disorders in the current population. Understanding the birth prevalence of these disorders in India from its various zones will definitely improve the short term and long term medical needs faced by affected communities.

Keywords: Heel prick method, Metabolic errors, Neonatal disorders, Newborn screening

- ✓ With 2.9% prevalence of IEM, out of total 70,590 cases of neonates screened
- ✓ The most prevalent disorder was found to be G6PD deficiency f/b haemoglobinopathies and CAH.
- ✓ Amino acid disorders : Citrullinaemia-I, Homocysteinuria, Hypermethioninaemia, Maple Syrup Urine Disease (MSUD), Tyrosinaemia Type I, II, III, Phenylalaninaemia etc.,

Classification of IEM's

DISORDERS OF INTERMEDIARY METABOLISM

- ✓ Aminoacid metabolism and transport
- ✓ Fatty acid oxidation and ketogenesis
- ✓ Carbohydrate metablolism and transport
- ✓ Vitamin related (cobalamin,folate)
- ✓ Peptide metabolism
- ✓ Mineral metabolism
- ✓ Mitochondrial energy metabolism

DISORDERS OF BIOSYNTHESIS AND BREAKDOWN OF COMPLEX MOLECULES

- ✓ Purine and pyramidine metabolism
- ✓ Lysosomal storage
- ✓ Peroxisomes
- ✓ Sterol metabolism
- ✓ Bile acid and heme metabolism
- ✓ Glycosylation
- ✓ Lipoprotein metabolism

DISORDERS OF NEUROTRANSMITTTER METABOLISM

- ✓ Glycine and serine metabolism
- ✓ Pterin and biogenic amine metabolism
- ✓ GABA metabolism
- ✓ Other (pyridoxine dependent /folinic acid dependent seizures,sulfite oxidase deficiency

Lysosomal storage diseases

MUCOPOLYSACCHARIDOSIS

- ✓ Hurler syndrome
- ✓ Hunter syndrome
- ✓ Sanfillippo syndrome
- ✓ Morquio syndrome
- ✓ Maroteaux lamy
- ✓ Sly syndrome
- ✓ Natowicz syndrome

SPHINGOLIPIDOSIS

- ✓ GM-1
- ✓ GM-2 (Type-1 TAY SACHS)
- ✓ GM-2 (Type-2 SANDHOFF)
- ✓ Fabry
- ✓ Farber
- ✓ Gaucher
- ✓ Niemann picks
- ✓ Krabbe
- ✓ MLD

OLOIGSACCHARIDOSIS

- ✓ Galactosialidosis
- ✓ Fucosidosis
- ✓ Mannosidosis

MUCOLIPIDOSIS (1 -4)

Disorders of Carbohydrate metabolism

- ✓ Carbohydrate Intolerance
- ✓ GSDs

Disorders of protein metabolism

- ✓ Amino-acidopathies
- ✓ Urea cycle disorders
- ✓ Organic Acidemias

- ✓ Lysosomal Storage disorders
- ✓ Fatty acid oxidation defects
- ✓ Mitochondrial disorders
- ✓ Peroxisomal disorders

Large molecule diseases

- ✓ Lysosomal storage disorders
- ✓ Peroxisomal Golgi apparatus disorders Mucopolysaccharidoses.

- ▪ Insidious / Dementia/ Epilepsy/Movement/ disorders/Gradual blindness and spasticity
- ▪ Organomegaly and coarse facial features

'Small molecule' diseases

- ✓ Amino and organic acidemias
- ✓ Urea cycle disorders
- ✓ Fatty acid oxidation defects
- ✓ Carbohydrate metabolism defects
- ✓ Mitochondrial oxidative phosphorylation disorders
- ✓ Purine and pyrimidine metabolism disorders
- ✓ Pyruvate metabolism disorders

- ▪ More acutely/ acute encephalopathy.

Saudubray's classification

- ✓ ***Intoxication syndromes***
  Acute or progressive accumulation of toxic compound (Urea cycle defects ,Organic acidemias,Aminoacidopathies

- ✓ ***Energy deficiency syndromes*** (Gluconeogenic disorders,Glycogenosis disorders, Fatty acid oxidation defects)

- ✓ ***Metabolic diseases associated with Complex molecules*** (Disturbances in synthesis or catabolism of complex molecules) :Lysosomal disorders, Peroxisomal disorders,CDG

Neonatal Period–Early Infancy	Late Infancy–Childhood	Adolescence–Adulthood
Pyridoxine-dependent epilepsy		
PNPO deficiency	Creatine synthesis defects	Juvenile NCL
Folinic-acid responsive seizures	Late infantile NCL	Lafora body disease and
Biotinidase deficiency	Mitochondrial disorders	Unverricht–Lundborg disease
Holocarboxylase synthetase deficiency	Organic acidurias	Mitochondrial disorders: MELAS
GLUT-1 (Glucose transporter-1) deficiency	Sialidosis	(Mitochondrial
Serine biosynthesis defects	Gangliosidosis	encephalomyopathy, lactic
Molybdenum cofactor and	GLUT-1 deficiency	acidosis and stroke-like episodes),
Sulfite oxidase deficiency	Congenital disorders of	MERRF (Myoclonic epilepsy with
Menkes disease	glycosylation	ragged red fibers)
Non-ketotic hyperglycinemia	Purine metabolism defects	Lysosomal storage diseases: Late
Organic acidemias	Uridine responsive epilepsy	onset gangliosidosis,
Urea cycle defects	caused by CAD mutations	Niemann–Pick type C, Gaucher
Peroxisomal disorders	Disorders of methylation and	type III
Congenital disorder of glycosylation	folate metabolism	GLUT-1 deficiency
Congenital and early infantile Neuronal	Neurotransmitter defects	Porphyria
ceroid lipofuscinosis (NCL)	Congenital disorders of autophagy	Wilson's disease
Mitochondrial disorders		

Basics and approach to IEM's

Approach to an IEM

Ethnicity

Family history

Physical examination

Ethnicity

- ✓ **Gaucher disease**
- ✓ **Tay-Sachs disease**
- ✓ **Canavan disease**
- ✓ **Familial hyperinsulinism**
- ✓ **Maple syrup urine disease**
- ✓ **Niemann-Pick disease type A**
- ✓ **Mucolipidosis IV**

- ✓ Megalencephalic leukodystrophy with cysts
- ✓ PKAN
- ✓ LGMD 2A
- ✓ SCA12

Approach to an IEM

GENETIC INHERITANCE

AUTOSOMAL RECESSIVE.

X LINKED RECESSIVE

- ✓HURLER SYNDROME
- ✓FABRY DISEASE
- ✓LESCH NYHAN SYNDROME
- ✓G6PD
- ✓MENKES DISEASE
- ✓ADRENOLEUCODYSTROPHY

AUTOSOMAL DOMINANT.

- ✓PORPHYRIAS (AIP, HC, VP, PCT, EP)

CLINICAL HANDLE

- ✓CHERRY RED SPOT
- ✓CORNEAL CLOUDING
- ✓CATARACTS
- ✓FACIAL DYSMORPHISM
- ✓CUTANEOUS MARKERS
- ✓NEONATAL CHOLESTASIS
- ✓ACUTE ENCEPHALOPATHY
- ✓ACUTE SEPSIS LIKE CRISIS
- ✓CARDIOMYOPATHY
- ✓NEUROPATHY
- ✓SKELETAL MANIFESTATIONS
- ✓URINE ODOUR

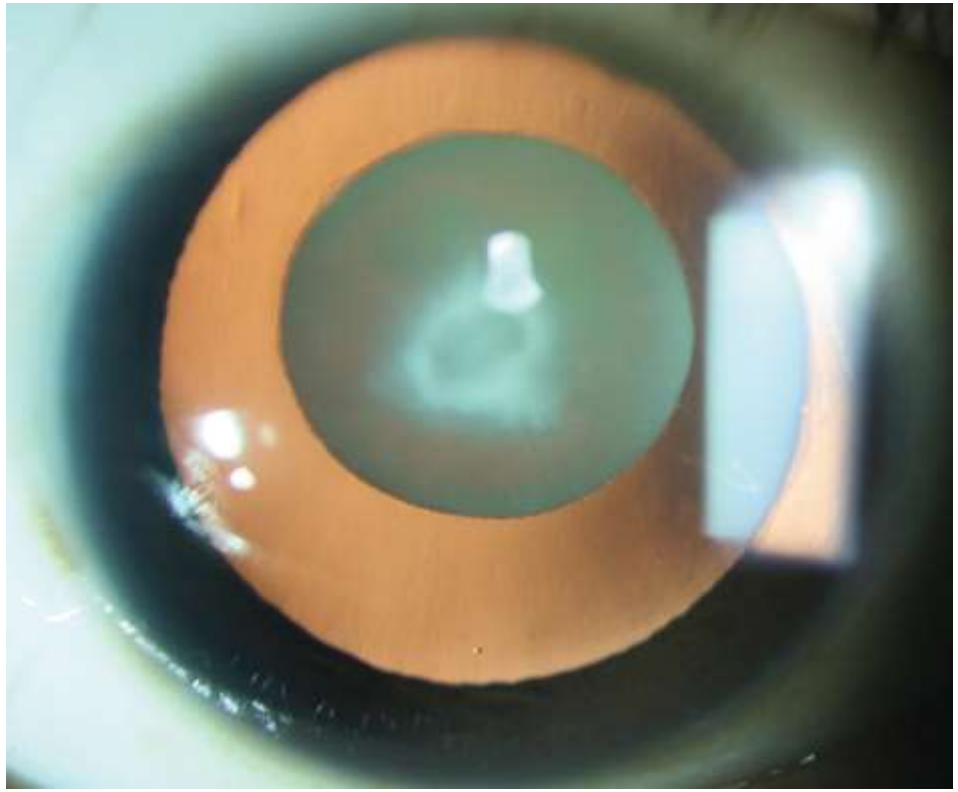
DIETARY TRIGGERS

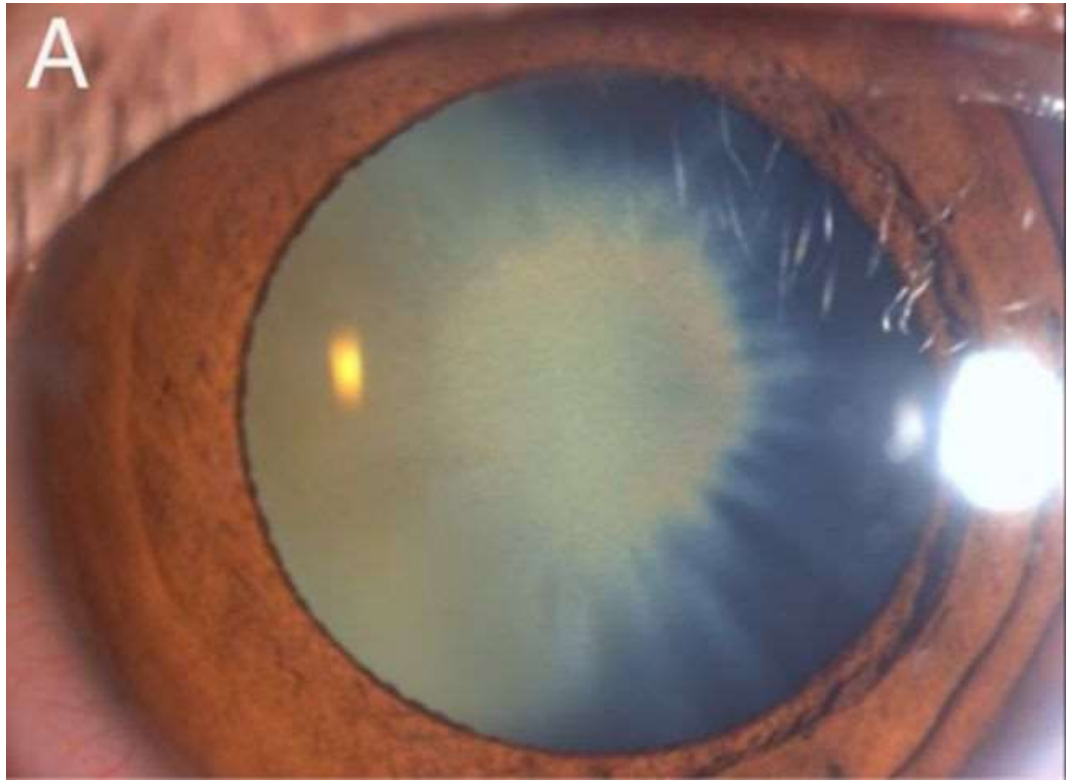
- ✓MILK
- ✓COMPLIMENTARY FEEDS
- ✓FRUITS/HF DRINKS
- ✓HIGH PROTEIN MEAL
- ✓FASTING HYPOGLYCEMIA

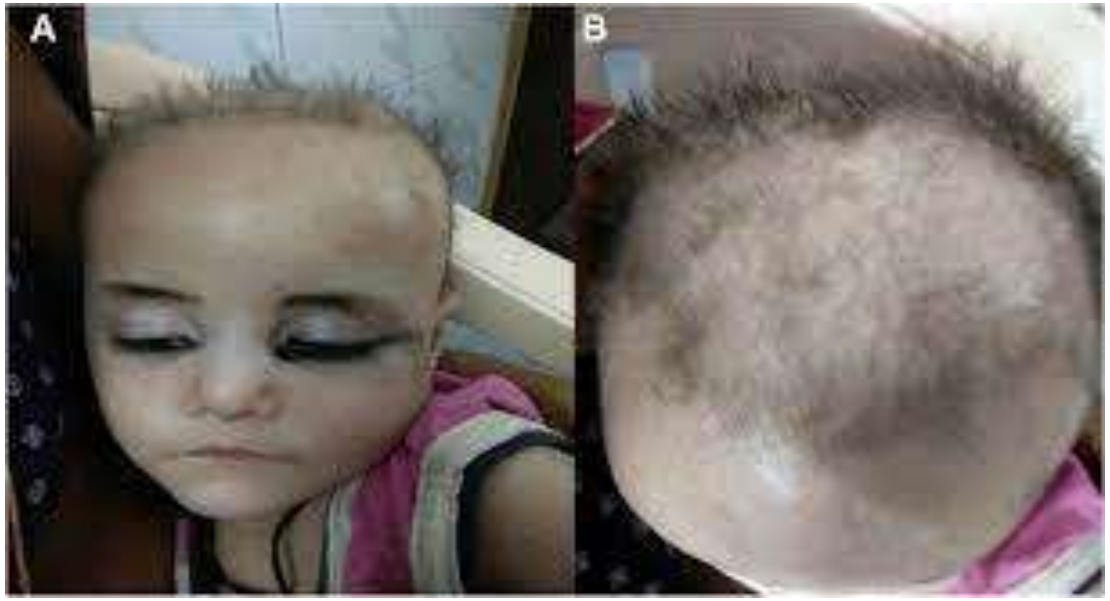
BIOCHEMICAL HANDLE

- ✓HYPOGLYCEMIA
- ✓KETOSIS
- ✓HYPERAMMONEMIA
- ✓ACIDOSIS
- ✓HYPERURICEMIA
- ✓HYPERLIPEDEMIA

CLINICAL HANDLE



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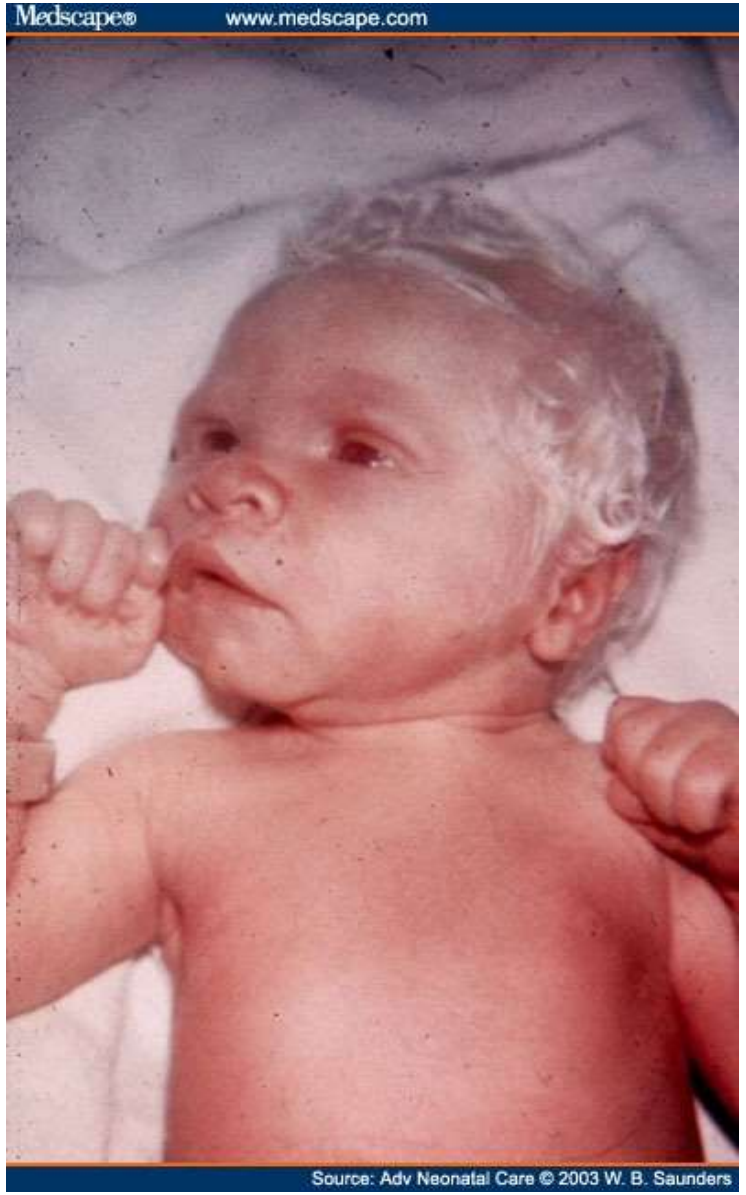
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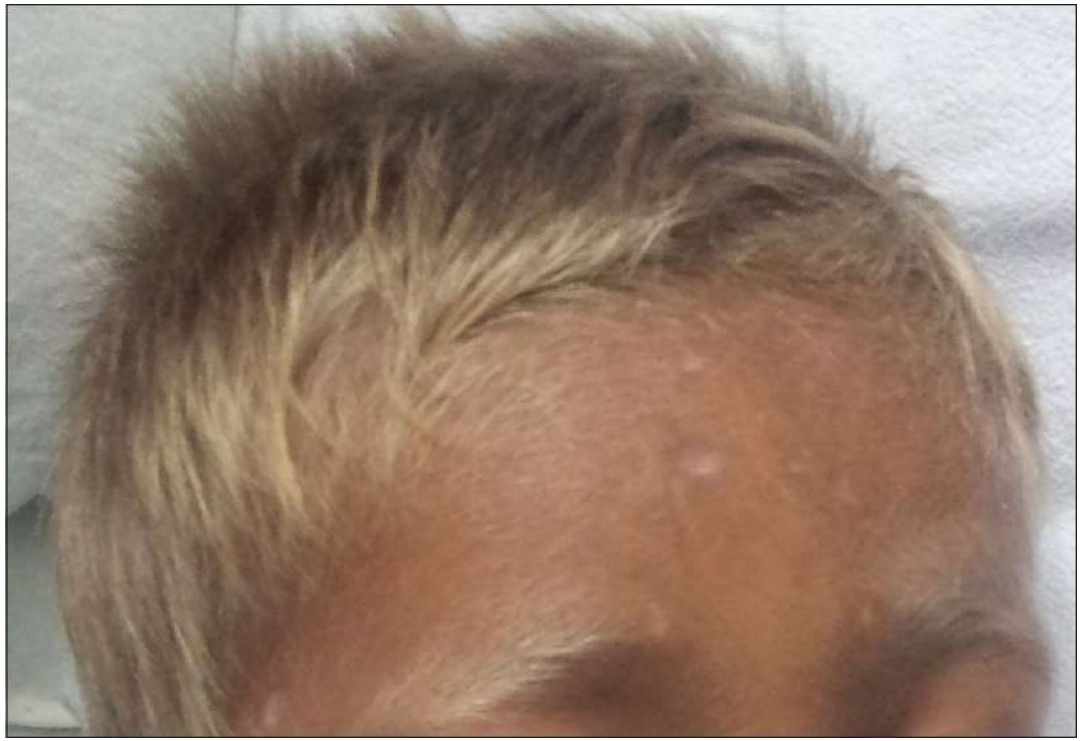

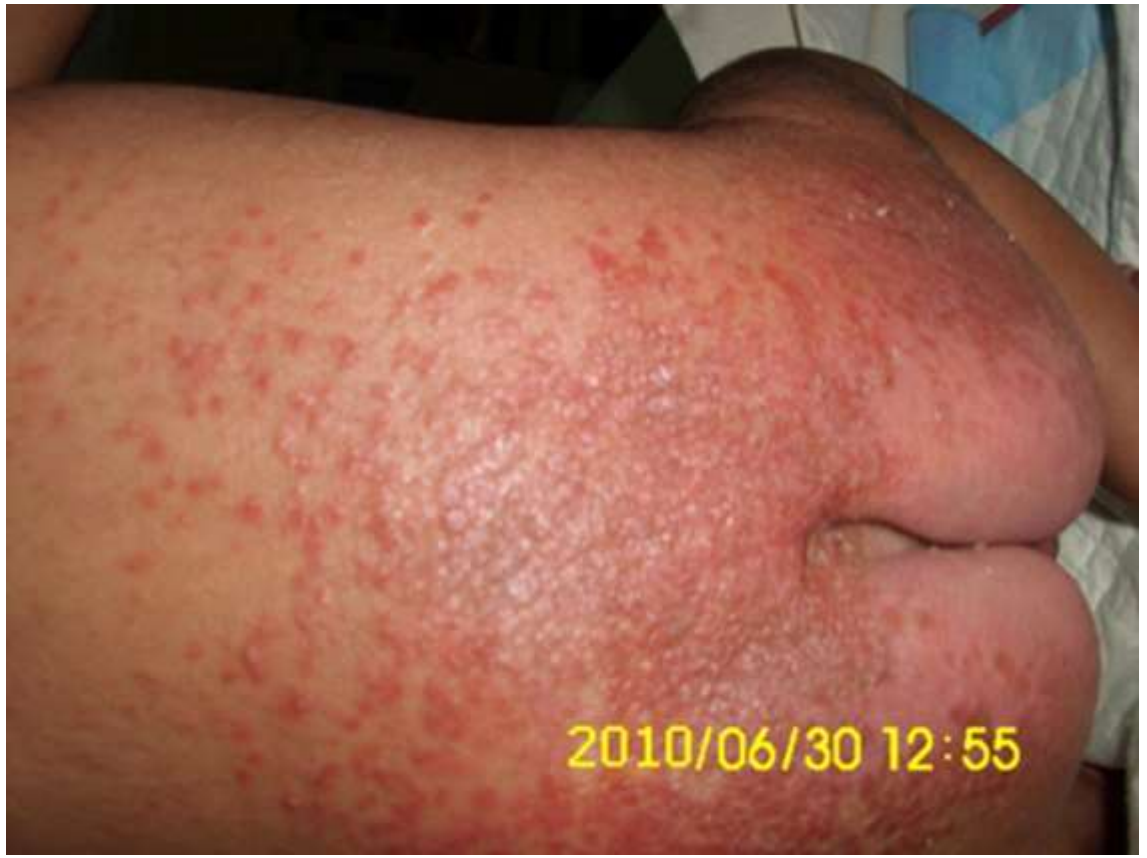
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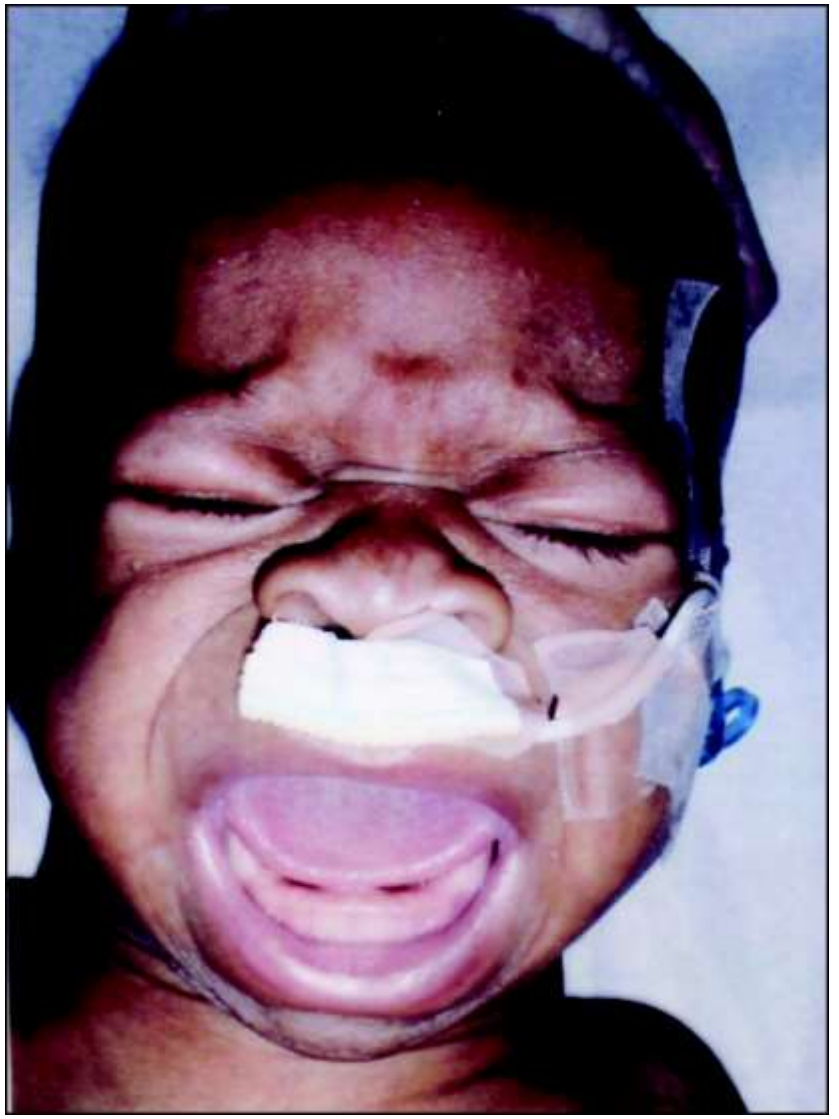

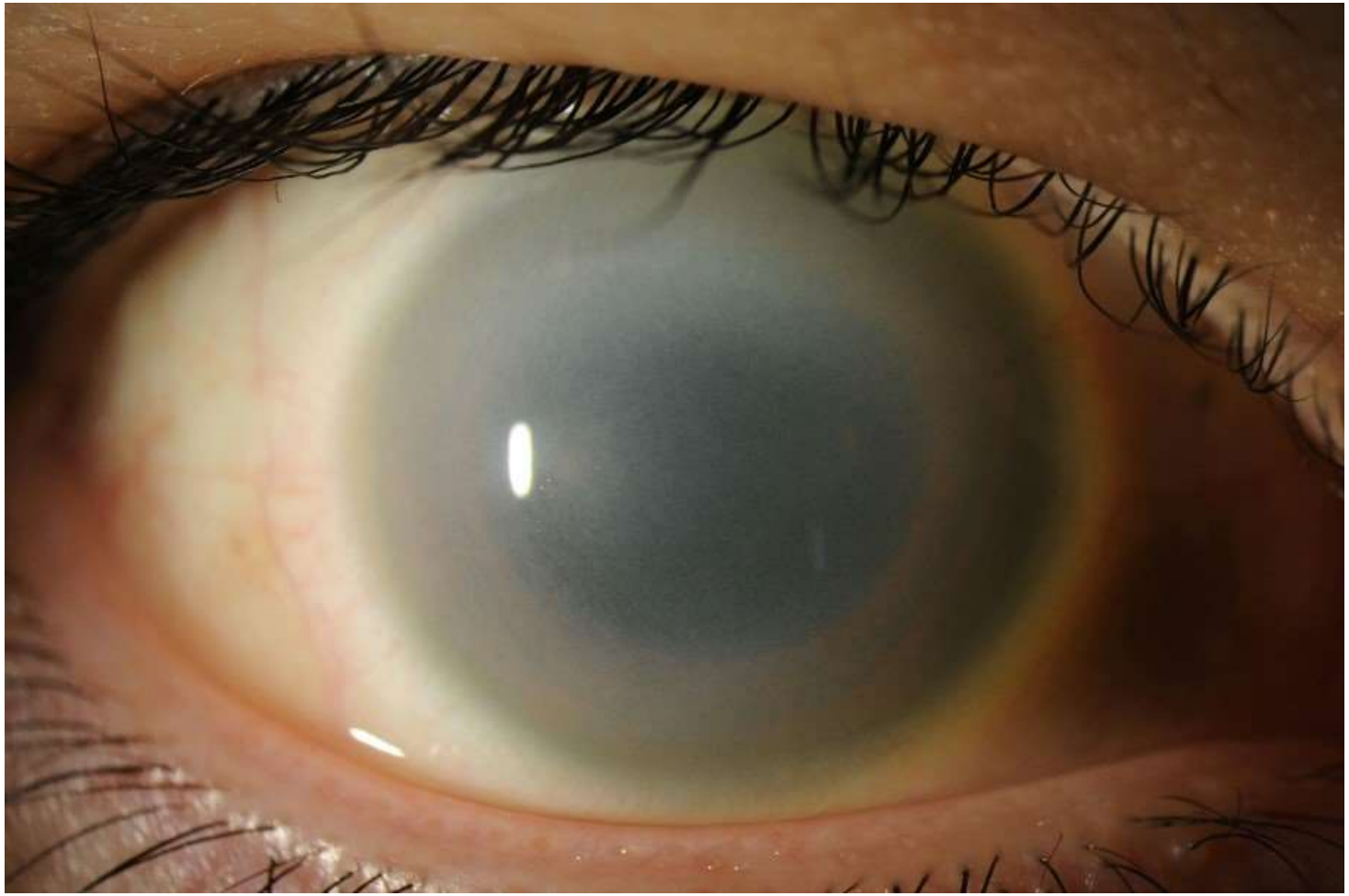

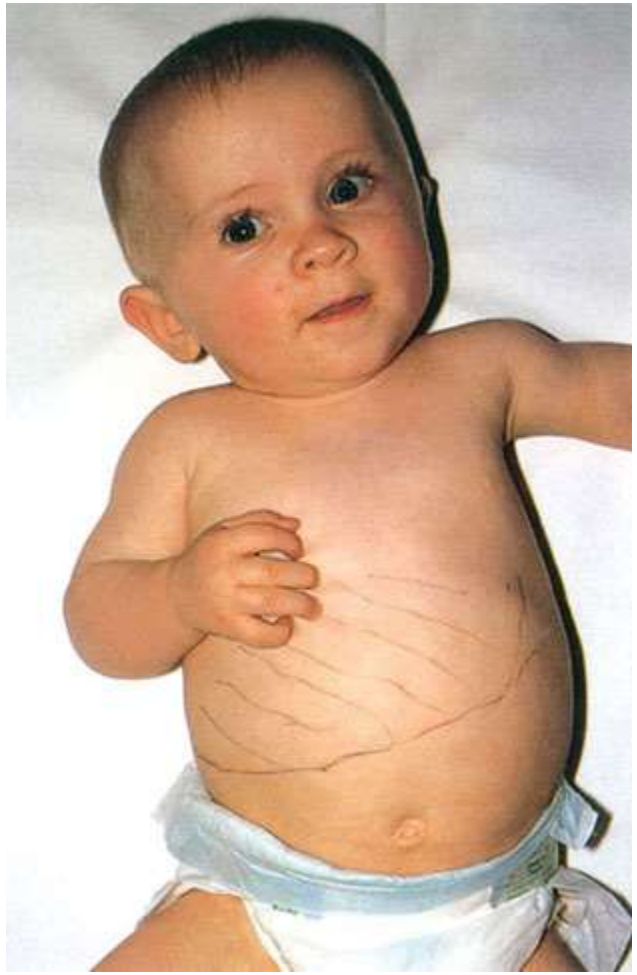

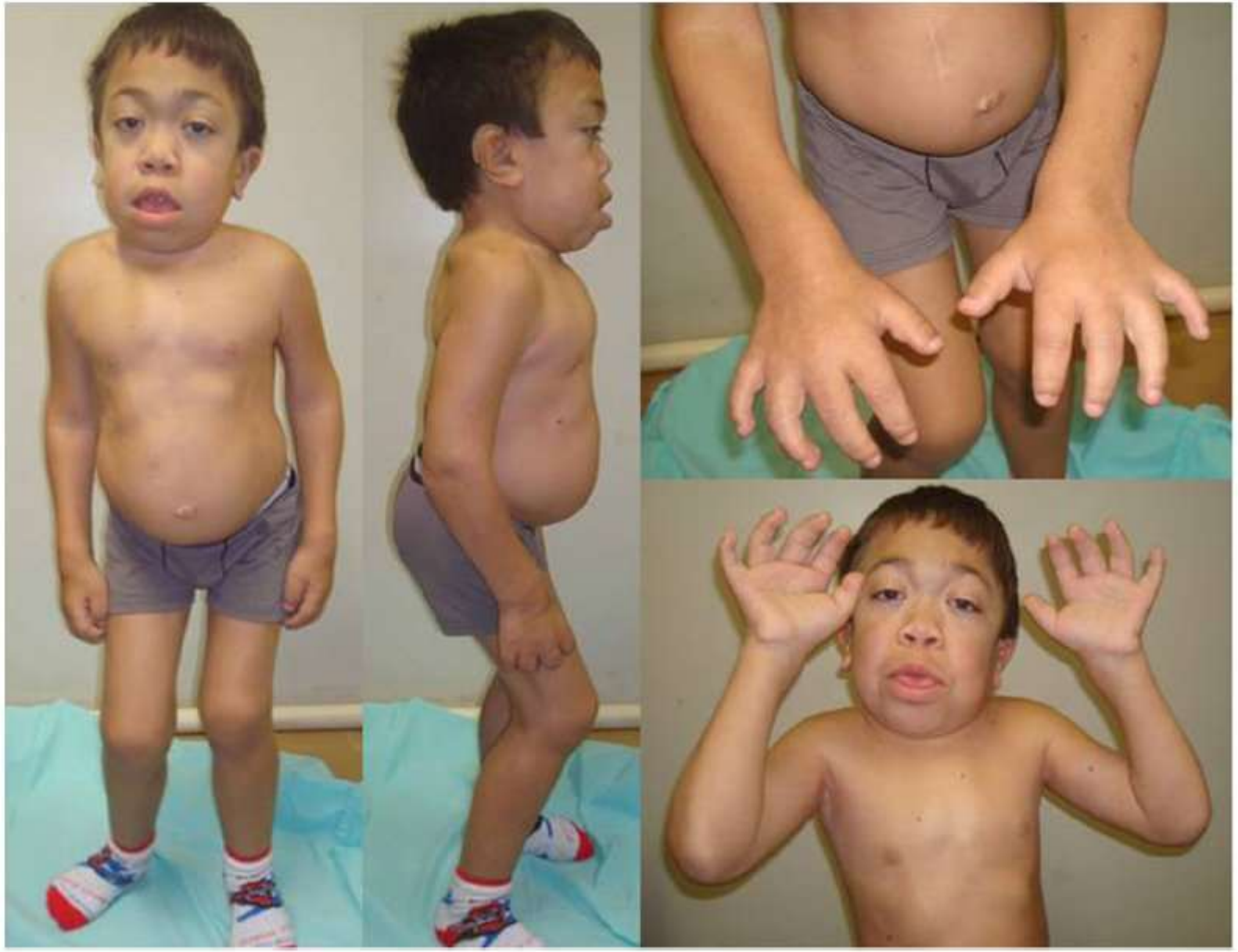

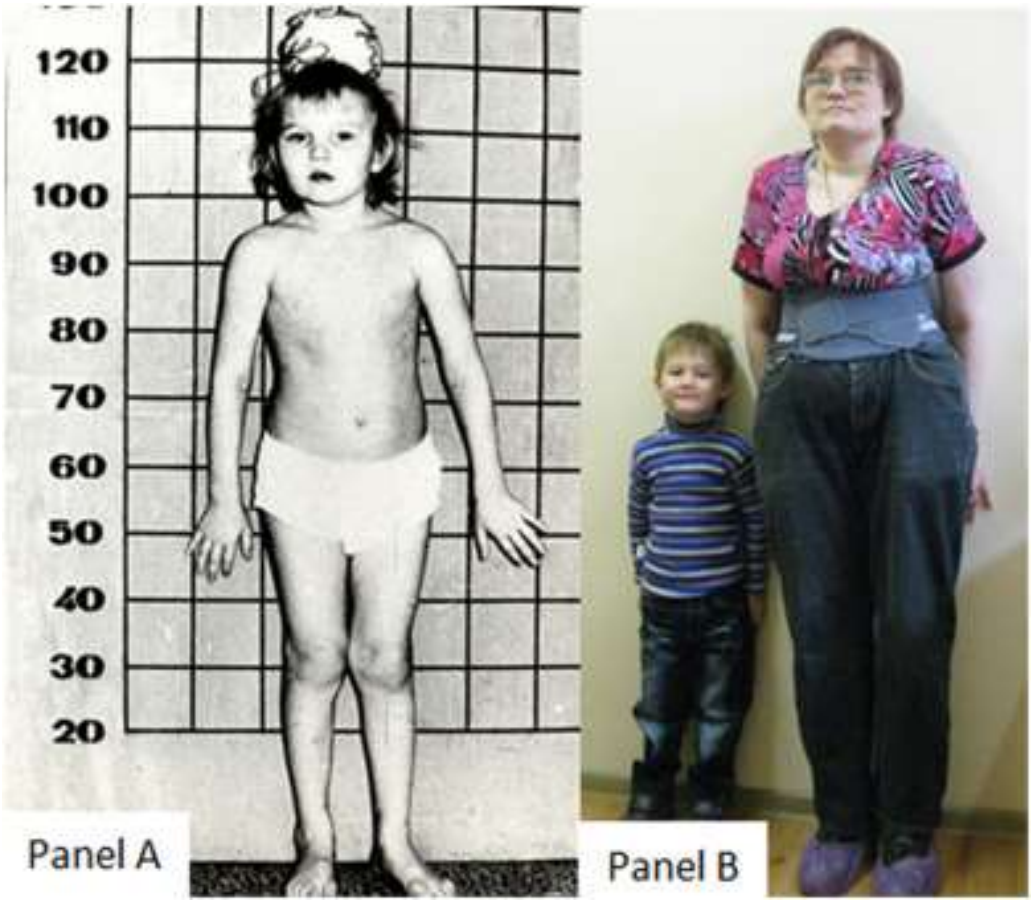
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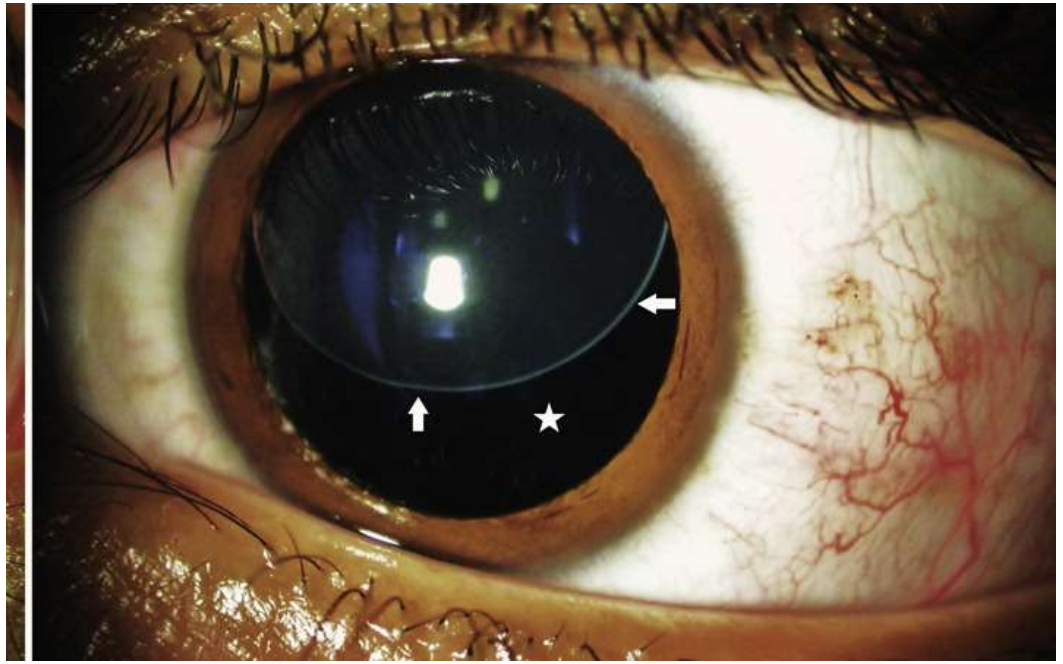
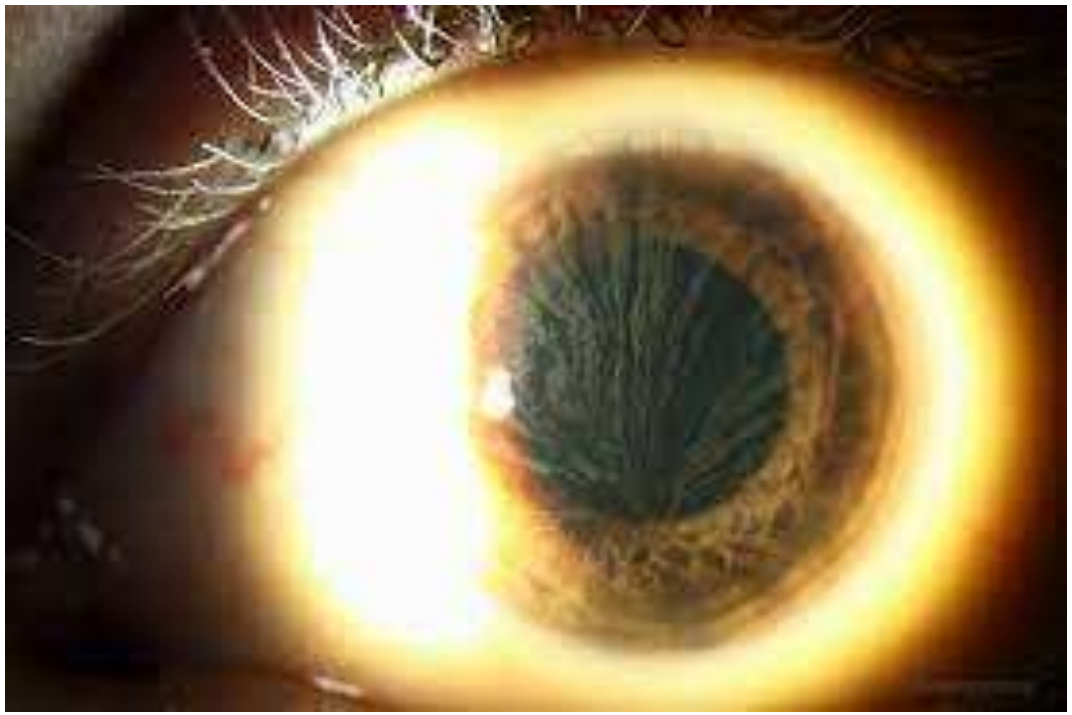
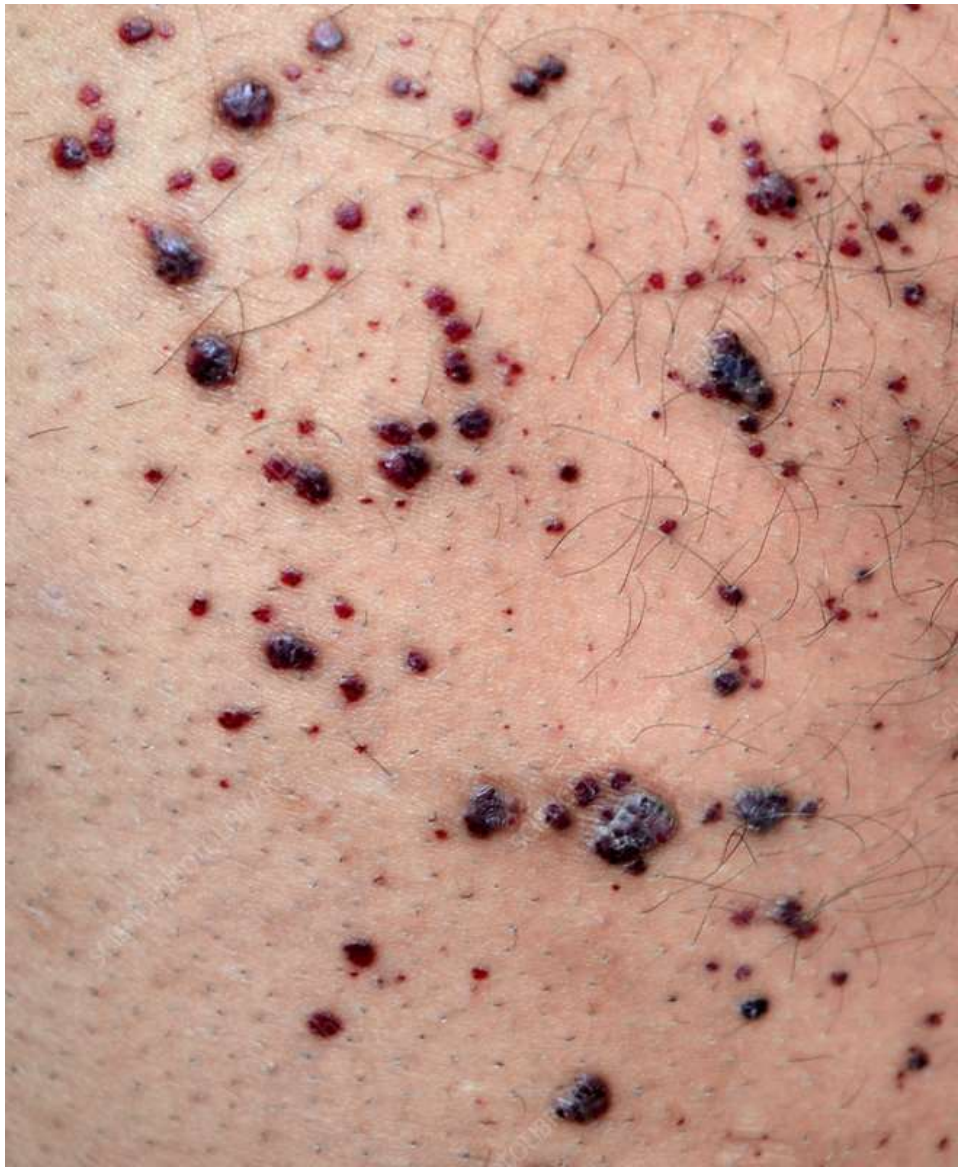
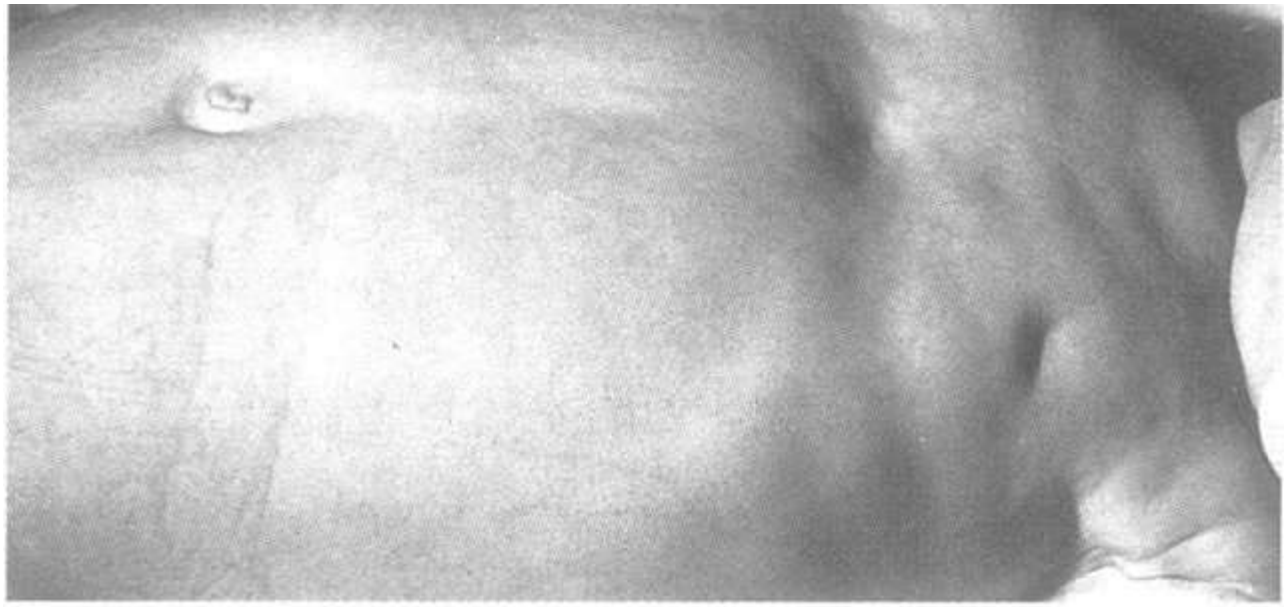
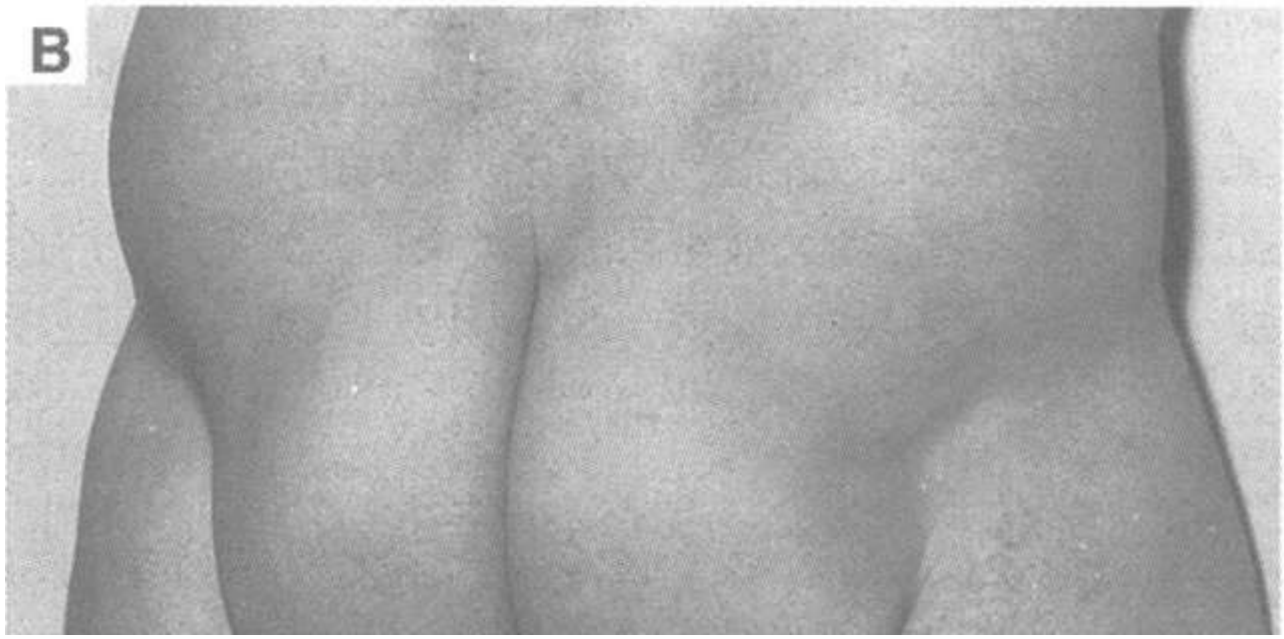
Panel A
Panel B







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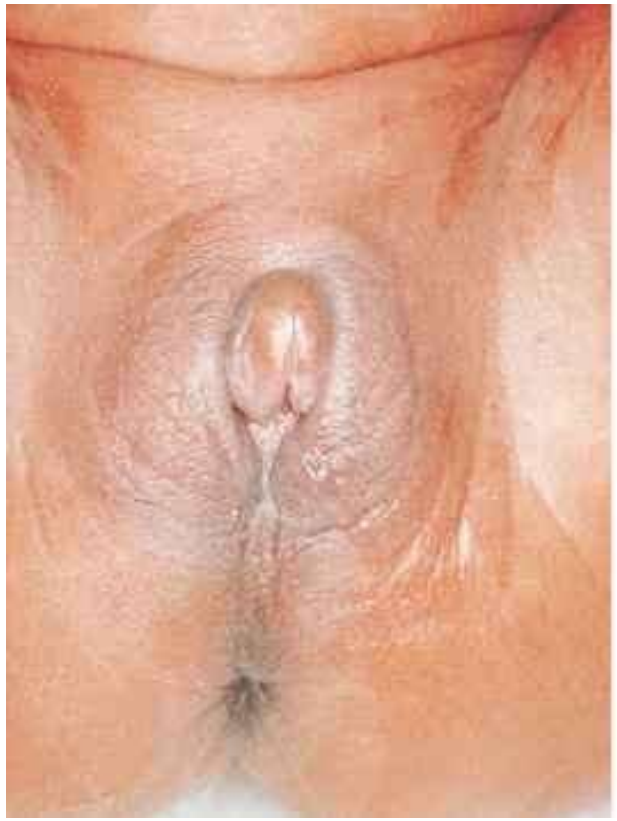

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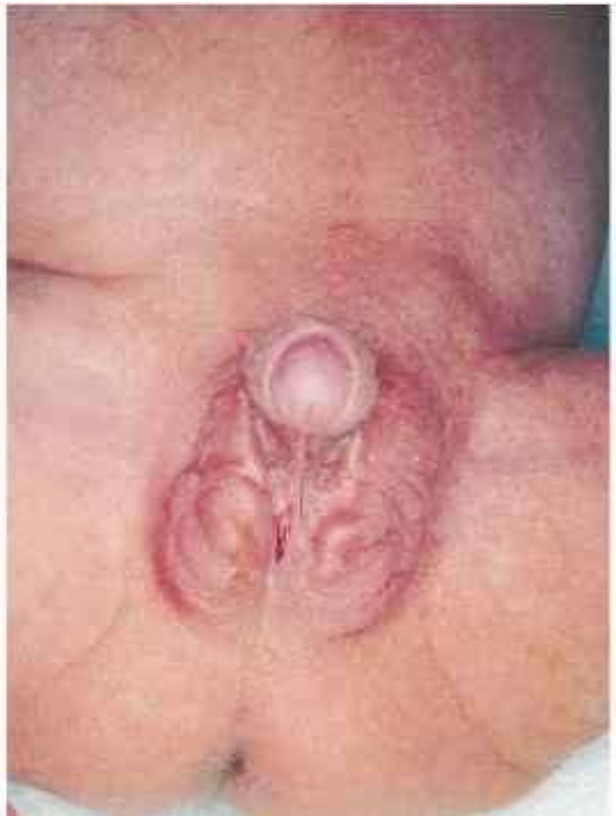

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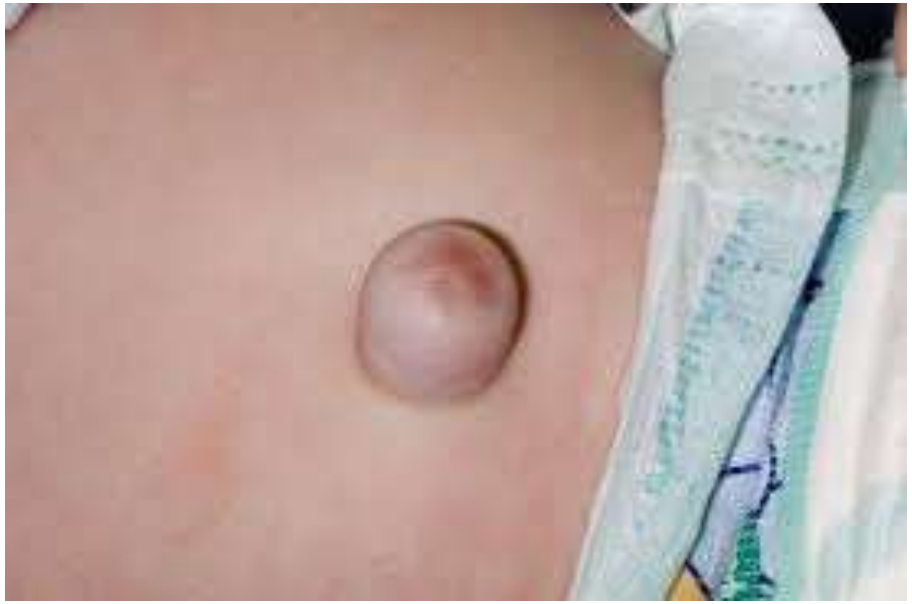

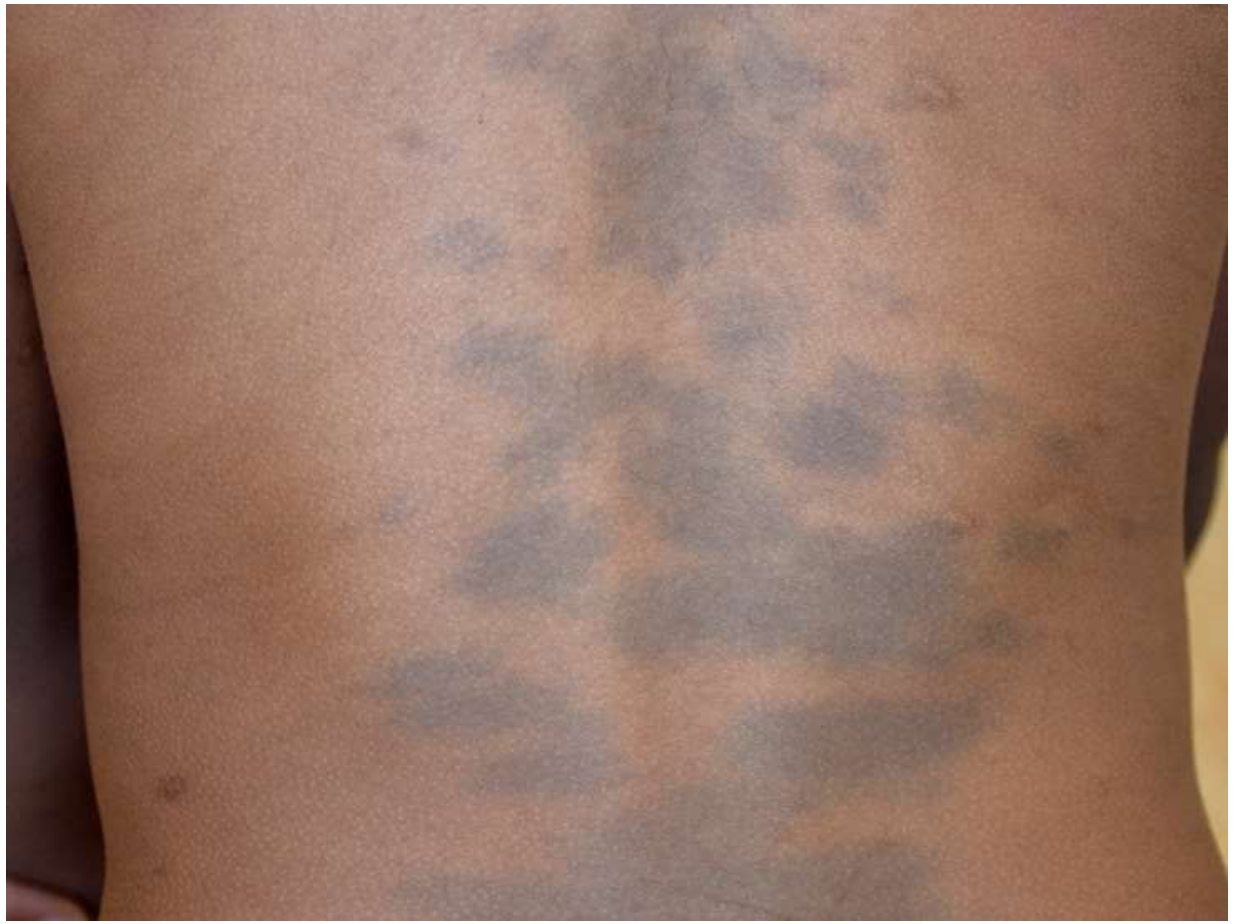

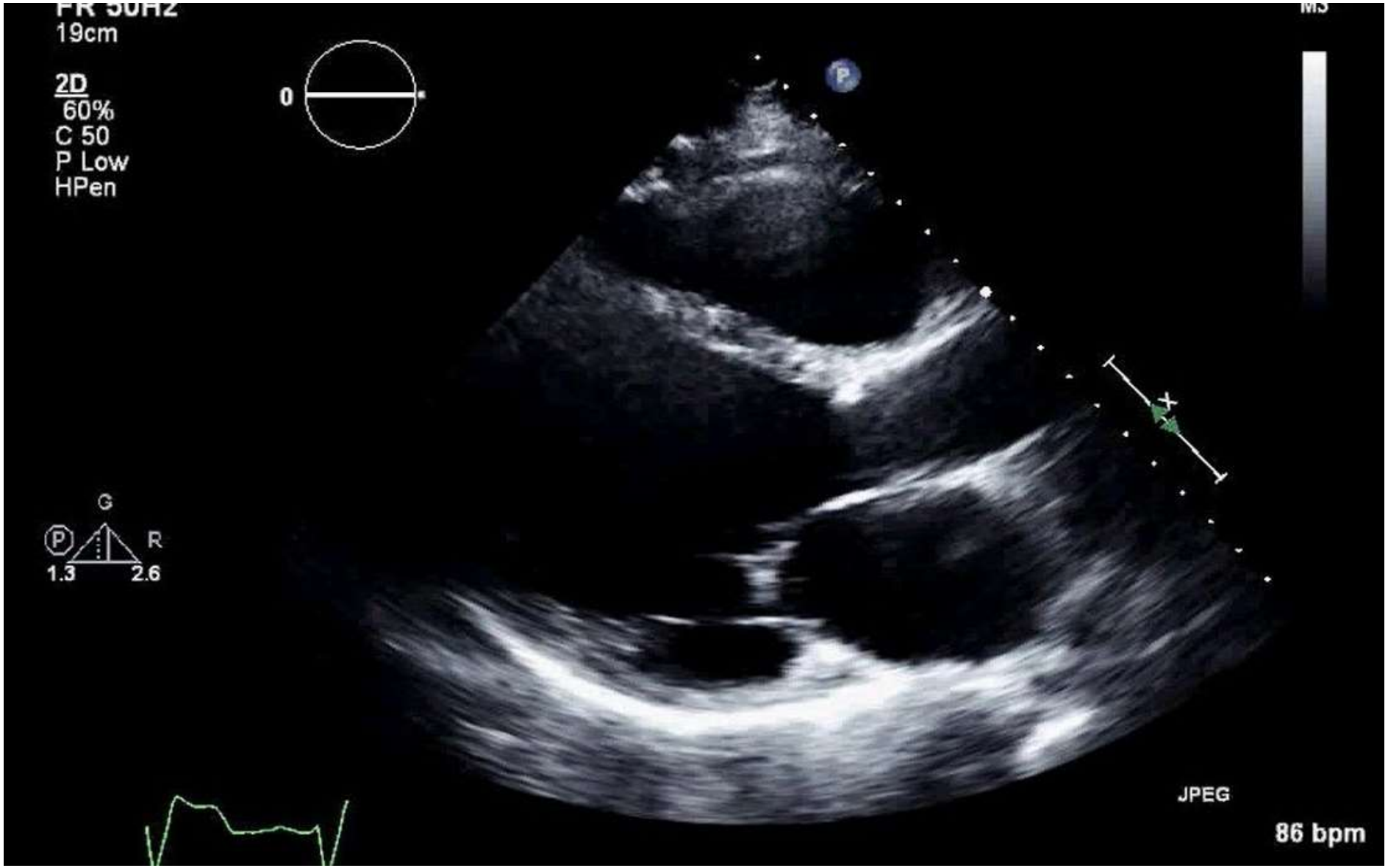
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1.3
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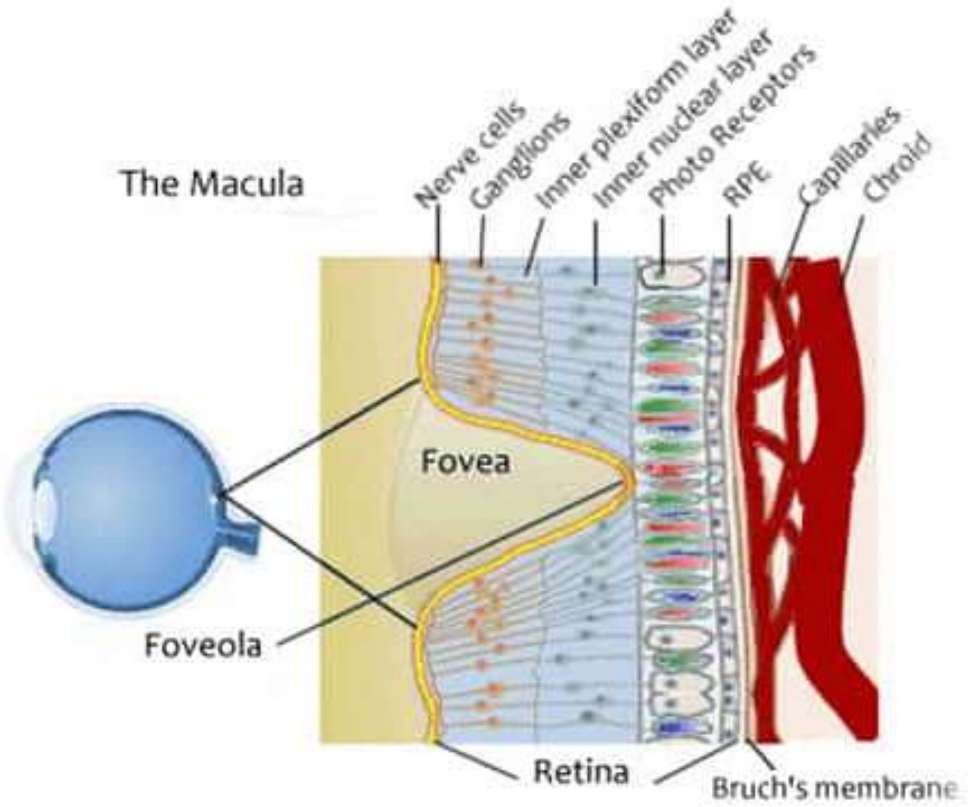
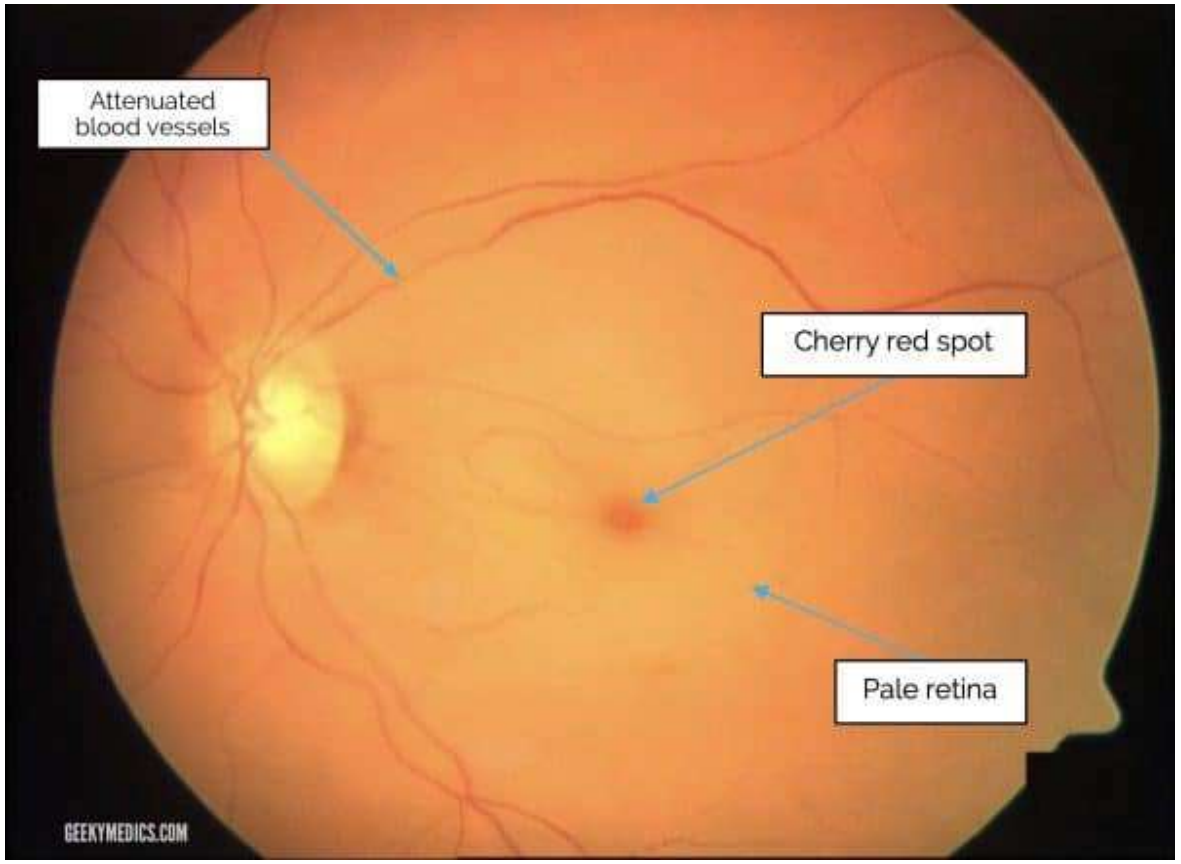
Urine odour	IEM
Musty /mousy	PKU
Maple syrup	MSUD
Sweaty feet	IVA,GA-II
Boiled cabbage	Tyrosenemia-1
Rancid butter	Tyrosenemia-1
Acid	MMA
Cat urine	MCD



Cherry red spot





- ✓ *Neimann Pick*
- ✓ *GM-1 gangliosidosis*
- ✓ *Tay sachs disease*
- ✓ *Sandhoff disease*

- ✓ *MLD*
- ✓ *Farbers*
- ✓ *Mucolipidosis*
- ✓ *Sialidosis*

Emergency management in an IEM

- ✓Stabilise –ABC
- ✓Correct Dyselectrolytemia
- ✓Dextrose bolus to maintain glucose levels @125-150mg/dl (prevents catabolism)
- ✓Avoid RL/hypotonic fluids
- ✓Sodium phenylacetate, sodium benzoate& arginine for hyperammonemia.
- ✓Nitisinone – Tyrsoinemia-1
- ✓Hemodialysis /PD/exchange tranfusion

Workup in an IEM

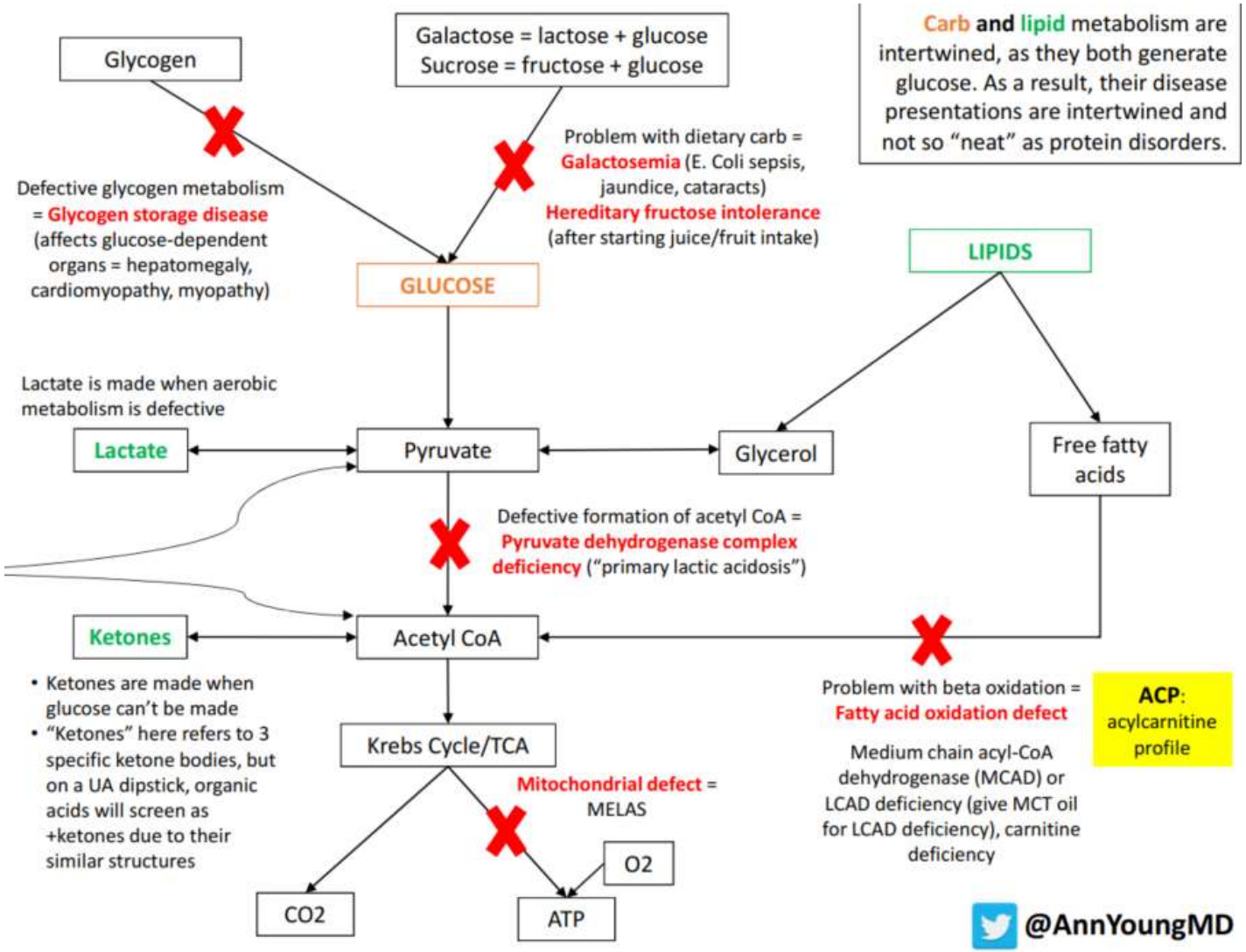
DBS/whole blood – TMS
Urine - GCMS

- ✓ CBC
- ✓ Electrolytes
- ✓ ABG
- ✓ Urine Ph
- ✓ LFT
- ✓ KFT
- ✓ Glucose
- ✓ Ketone bodies
- ✓ Ammonia
- ✓ Lactate
- ✓ LDH
- ✓ CPK
- ✓ Urinary GAG
- ✓ BMA/Biopsy

- ✓ Enzyme assay

Genetic testing

- ✓ Clinical exome segeuencing
- ✓ Whole exome sequencing
- ✓ Mitochondrial genome sequencing



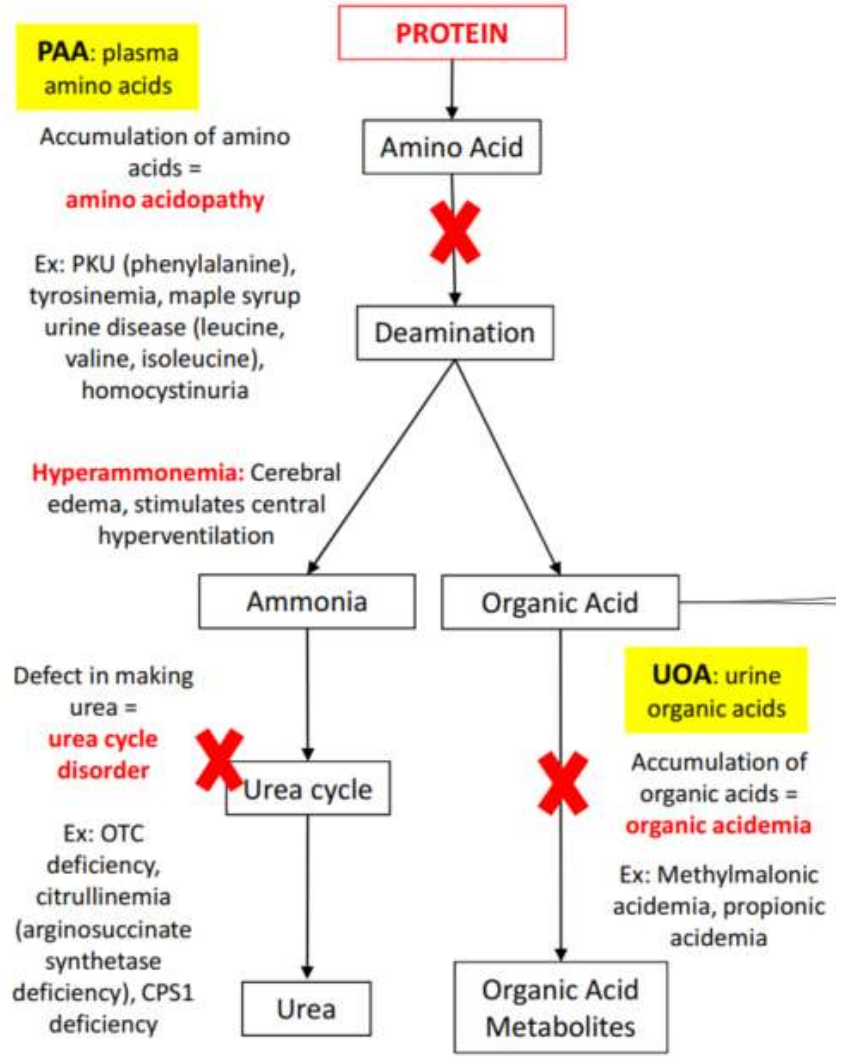
Anion Gap Metabolic Acidosis: AG>12

- What anions are present that can cause a gap?
- **Lactate**: Poor perfusion, mitochondrial defects, Primary lactic acidoses
- **Ketones**: Organic acidemia, Carb metabolism disorder

Hypoglycemia

- Ketones are expected in hypoglycemia
- (-) Ketones: Fatty acid oxidation disorder
- (+) Ketones: Organic acidemia, Carb metabolism disorder

Protein metabolism is relatively isolated from carb/lipids, thus its presentations of disease are a bit more straight forward



Hyperammonemia: Neos: > 50…> 100; Kids/Adults: >100…>150

- Level of hyperammonemia: 1) urea cycle defect 2) organic acidemia 3) amino acidopathy
- Central hyperventilation → respiratory alkalosis
- Why is it bad? Cerebral edema → herniation

Protein metabolism is relatively isolated from carb/lipids, thus its presentations of disease are a bit more straight forward

PAA: plasma amino acids

PROTEIN

Amino Acid

Accumulation of amino acids = **amino acidopathy**

Ex: PKU (phenylalanine), tyrosinemia, maple syrup urine disease (leucine, valine, isoleucine), homocystinuria

Deamination

Hyperammonemia: Cerebral edema, stimulates central hyperventilation

Ammonia

Organic Acid

Defect in making urea = **urea cycle disorder**

Urea cycle

Ex: OTC deficiency, citrullinemia (arginosuccinate synthetase deficiency), CPS1 deficiency

Urea

UOA: urine organic acids

Accumulation of organic acids = **organic acidemia**

Ex: Methylmalonic acidemia, propionic acidemia

Organic Acid Metabolites

Glycogen

Defective glycogen metabolism = **Glycogen storage disease** (affects glucose-dependent organs = hepatomegaly, cardiomyopathy, myopathy)

Galactose = lactose + glucose
Sucrose = fructose + glucose

Problem with dietary carb = **Galactosemia** (E. Coli sepsis, jaundice, cataracts)
Hereditary fructose intolerance (after starting juice/fruit intake)

GLUCOSE

Carb and lipid metabolism are intertwined, as they both generate glucose. As a result, their disease presentations are intertwined and not so "neat" as protein disorders.

LIPIDS

Glycerol

Free fatty acids

Lactate is made when aerobic metabolism is defective

Lactate

Pyruvate

Defective formation of acetyl CoA = **Pyruvate dehydrogenase complex deficiency** ("primary lactic acidosis")

Ketones

- Ketones are made when glucose can't be made
- "Ketones" here refers to 3 specific ketone bodies, but on a UA dipstick, organic acids will screen as +ketones due to their similar structures

Acetyl CoA

Problem with beta oxidation = **Fatty acid oxidation defect**

Medium chain acyl-CoA dehydrogenase (MCAD) or LCAD deficiency (give MCT oil for LCAD deficiency), carnitine deficiency

ACP: acylcarnitine profile

Krebs Cycle/TCA

Mitochondrial defect = MELAS

O2

CO2

ATP

@AnnYoungMD

Hyperammonemia: Neos: > 50…> 100; Kids/Adults: >100…>150

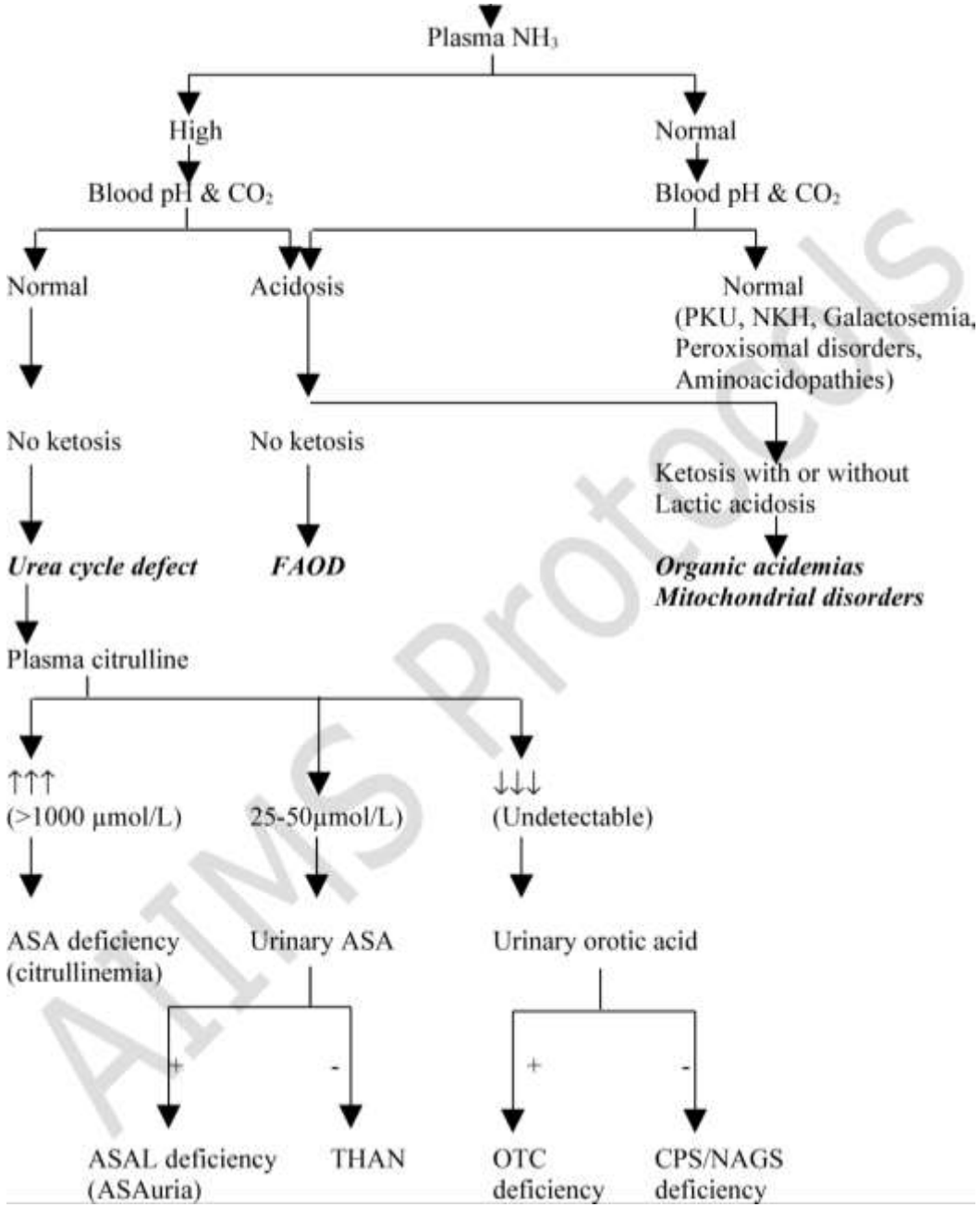
- Level of hyperammonemia: 1) urea cycle defect 2) organic acidemia 3) amino acidopathy
- Central hyperventilation → respiratory alkalosis
- Why is it bad? Cerebral edema → herniation

Anion Gap Metabolic Acidosis: AG>12

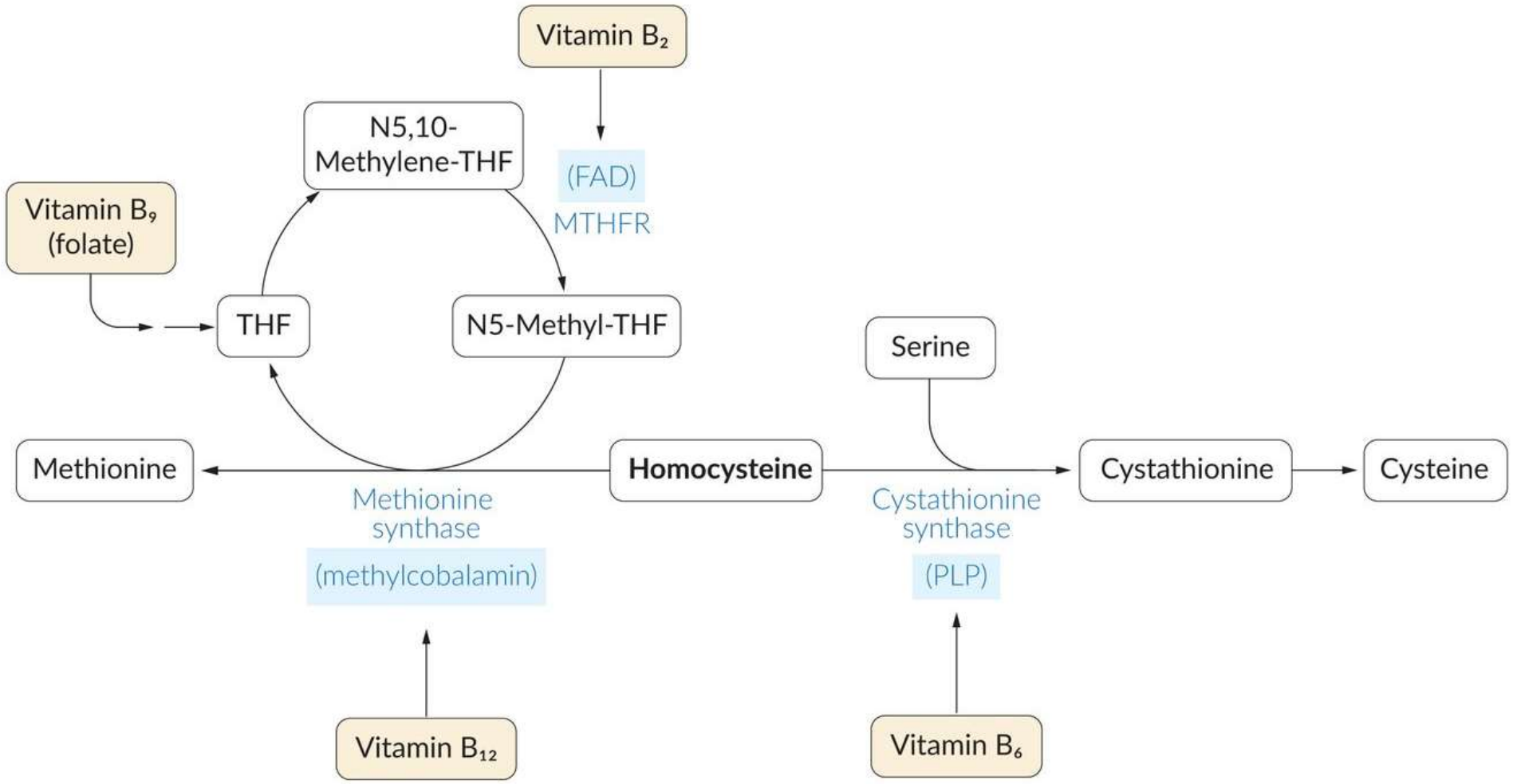
- What anions are present that can cause a gap?
- **Lactate**: Poor perfusion, mitochondrial defects, Primary lactic acidoses
- **Ketones**: Organic acidemia, Carb metabolism disorder

Hypoglycemia

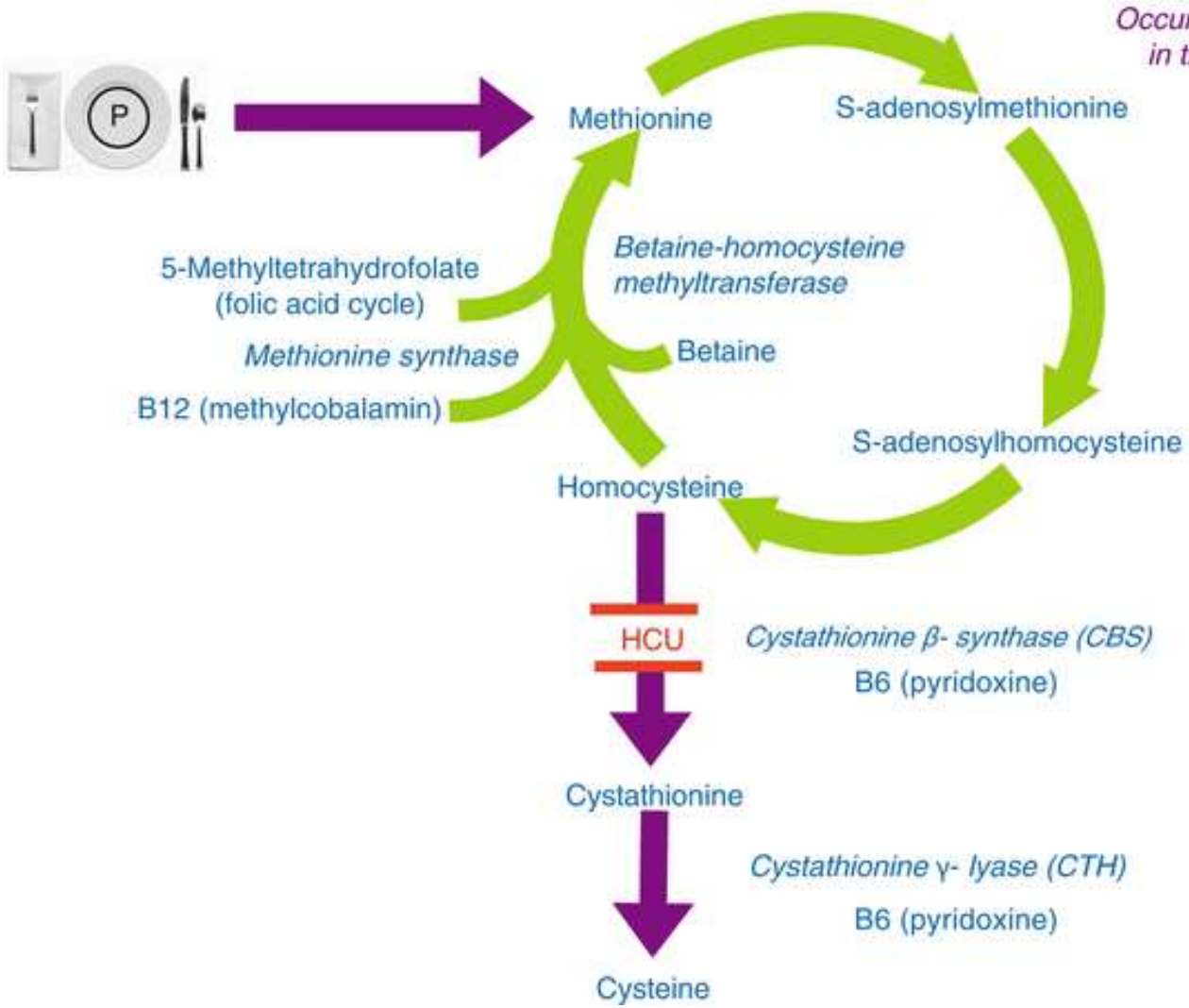
- Ketones are expected in hypoglycemia
- (-) Ketones: Fatty acid oxidation disorder
- (+) Ketones: Organic acidemia, Carb metabolism disorder



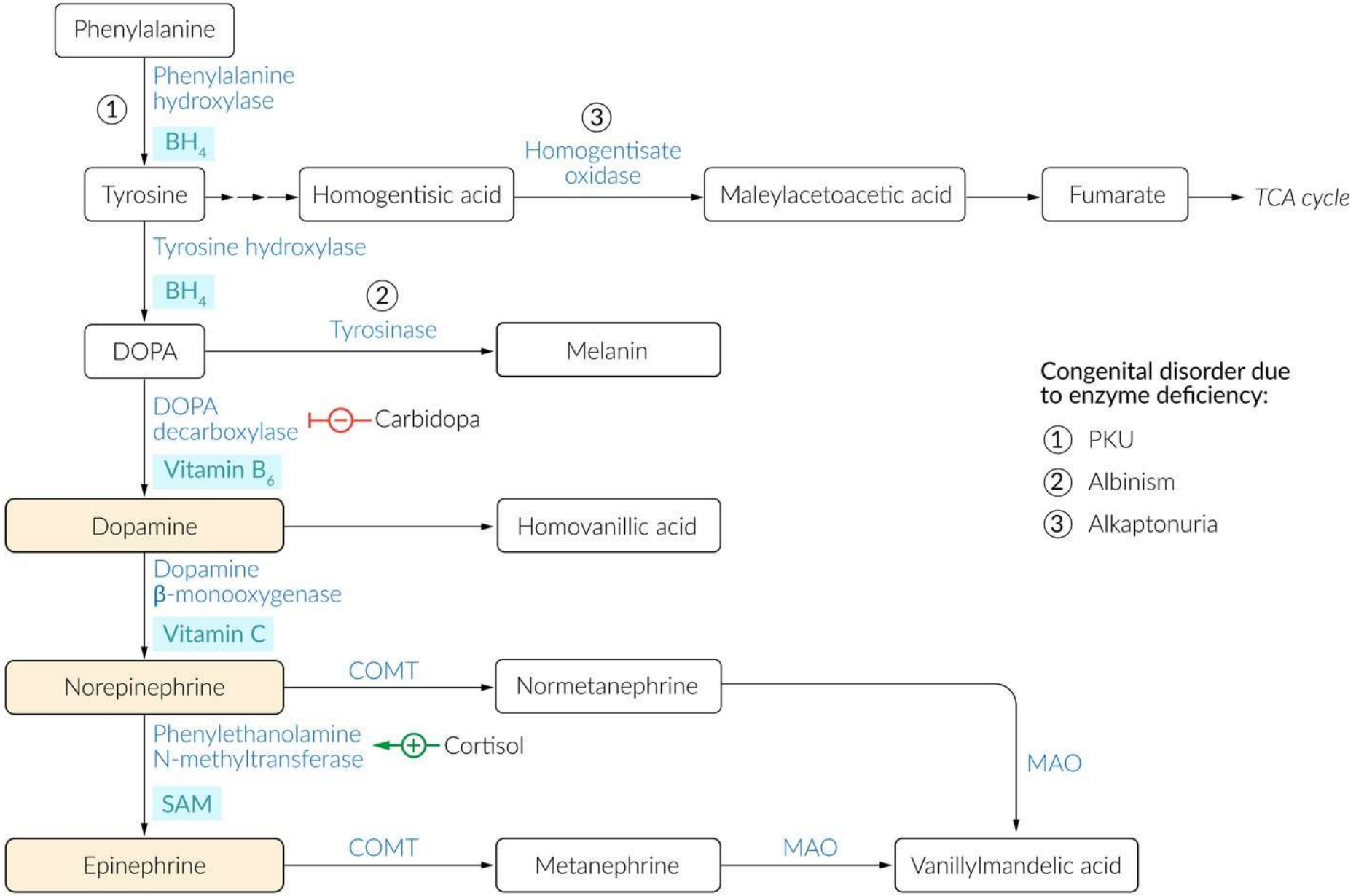
HOMOCYSTEINE METABOLISM



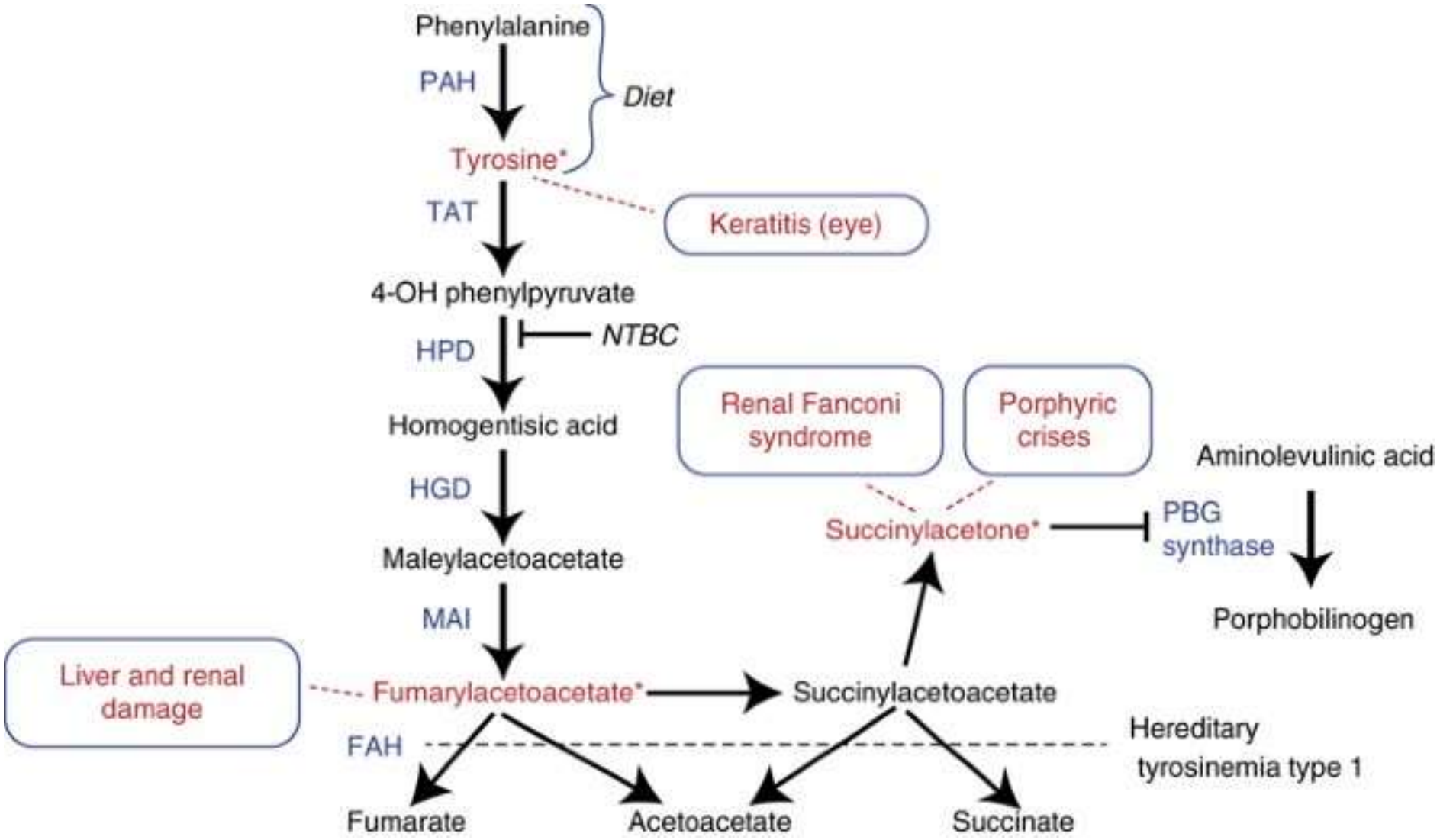
Homocystinuria (HCU)



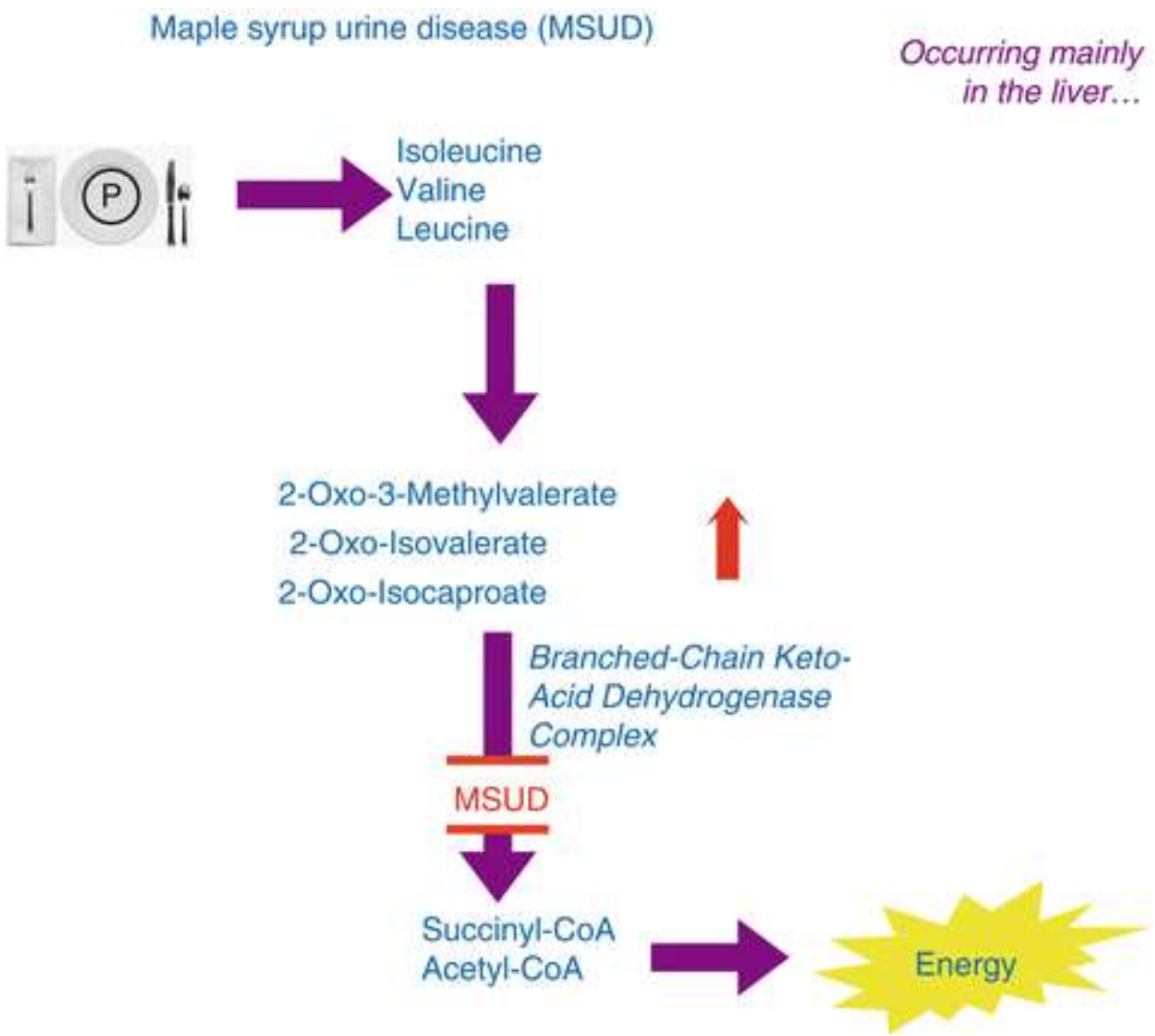
PHENYL ALANINE METABOLISM

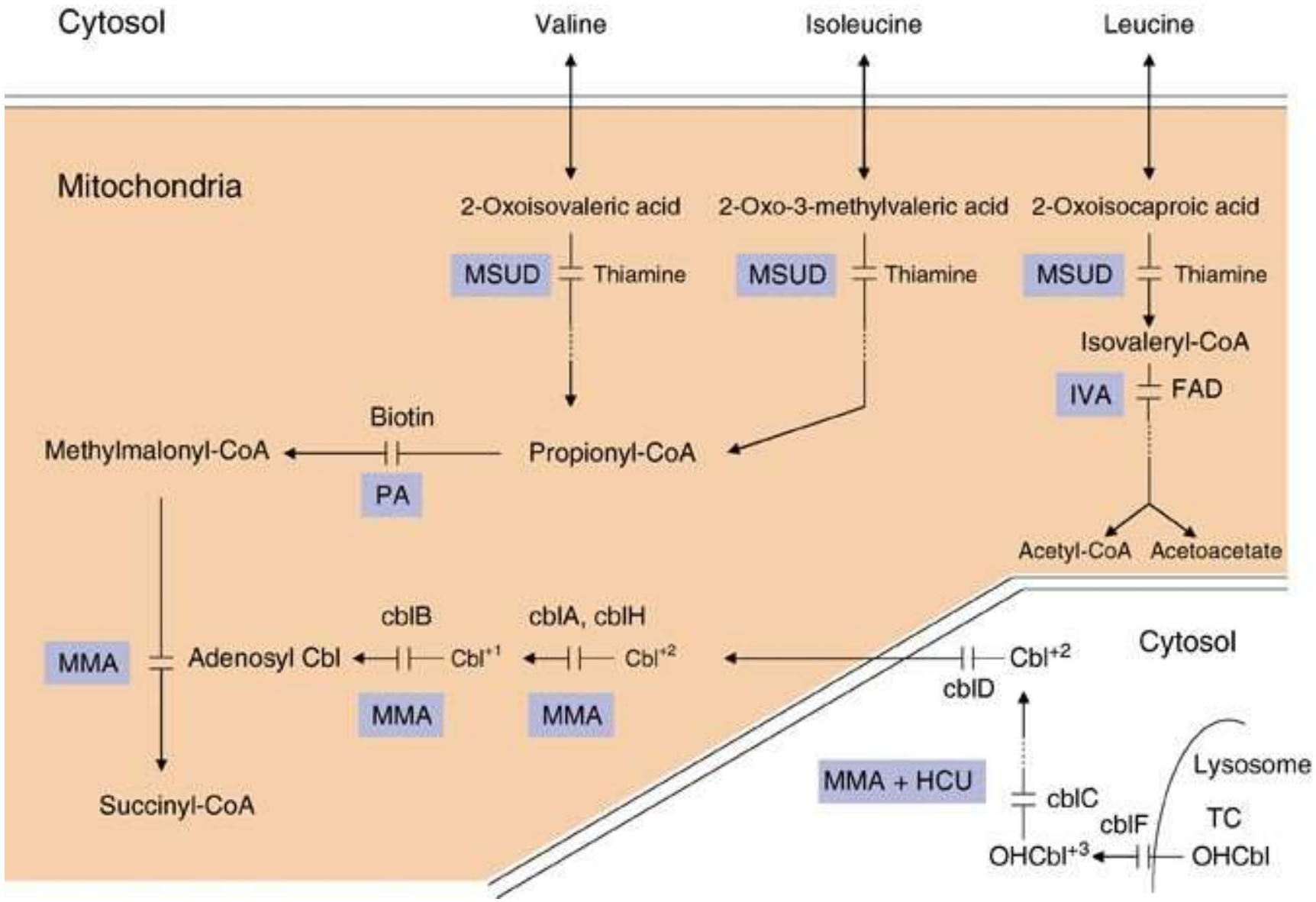


TYROSINE METABOLISM

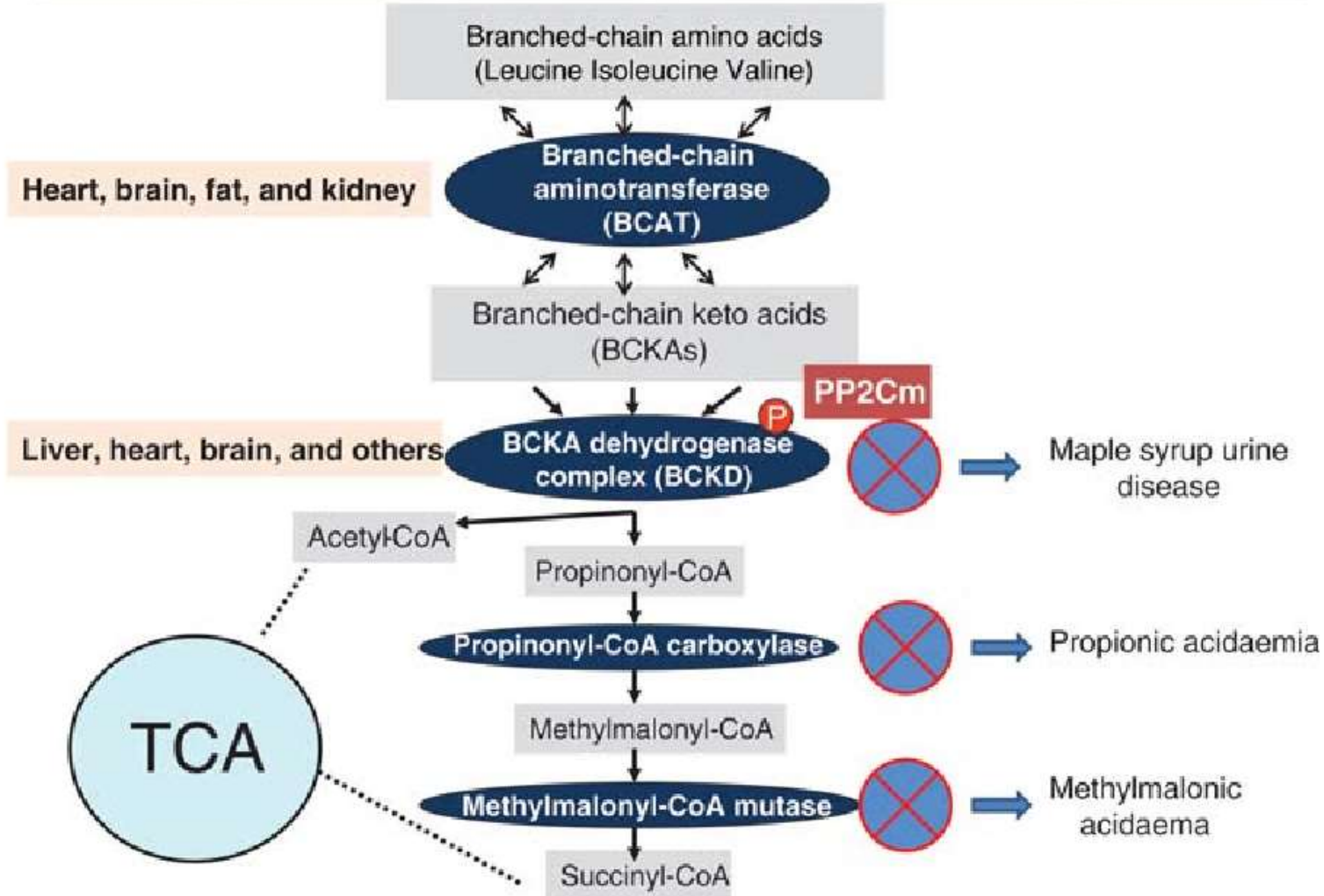


MAPLE SYRUP URINE DISEASE




Cytosol
Valine
Isoleucine
Leucine
Mitochondria
2-Oxoisovaleric acid
2-Oxo-3-methylvaleric acid
2-Oxoisocaproic acid
MSUD
Thiamine
MSUD
Thiamine
MSUD
Thiamine
Isovaleryl-CoA
IVA
FAD
Biotin
Methylmalonyl-CoA
Propionyl-CoA
PA
Acetyl-CoA
Acetoacetate
cblB
cblA, cblH
MMA
Adenosyl Cbl
Cbl+1
Cbl+2
Cbl+2
Cytosol
cblD
MMA
MMA
MMA + HCU
Lysosome
cblC
cblF
TC
OHCbl+3
OHCbl
Succinyl-CoA

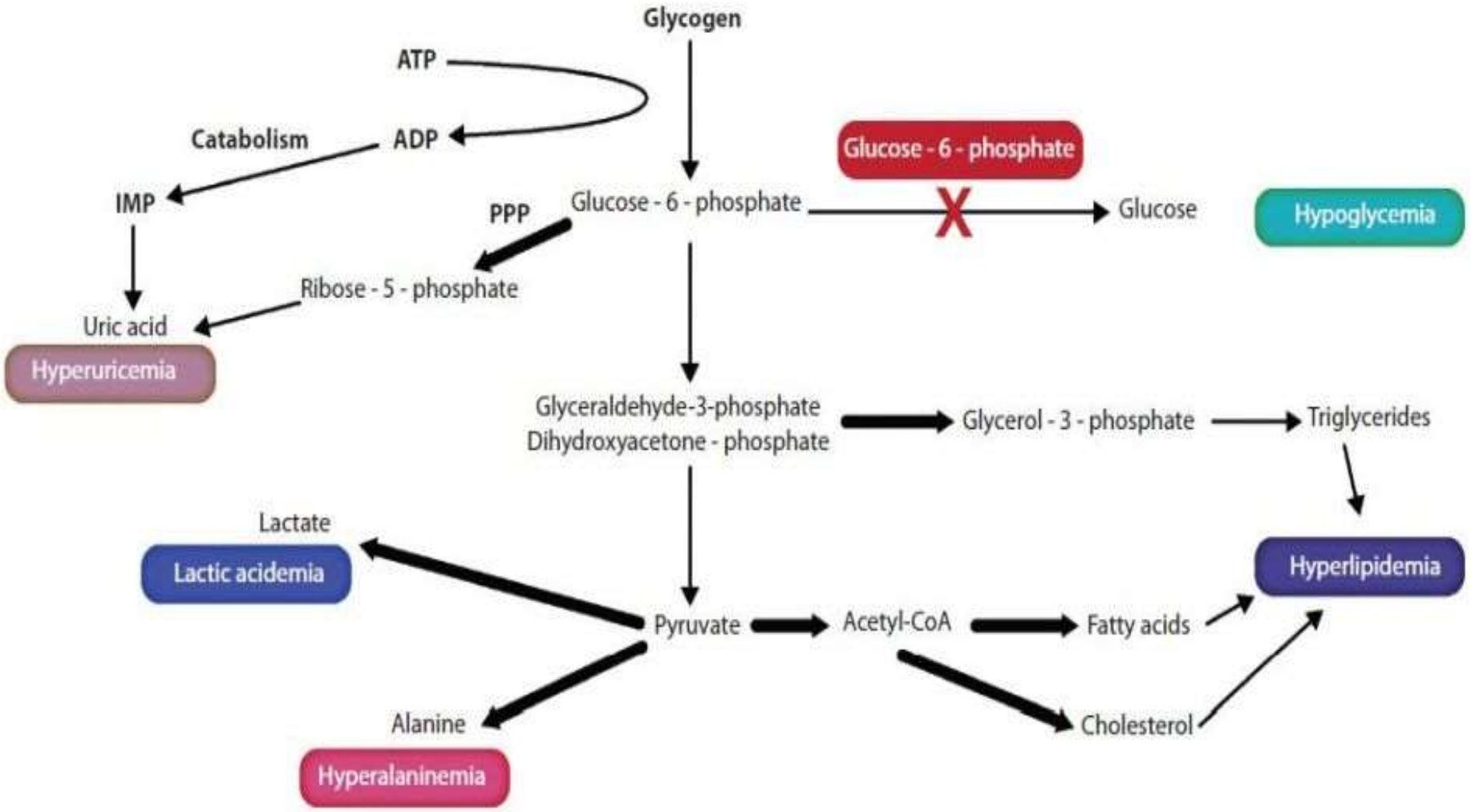
Catabolism of branched-chain amino acids



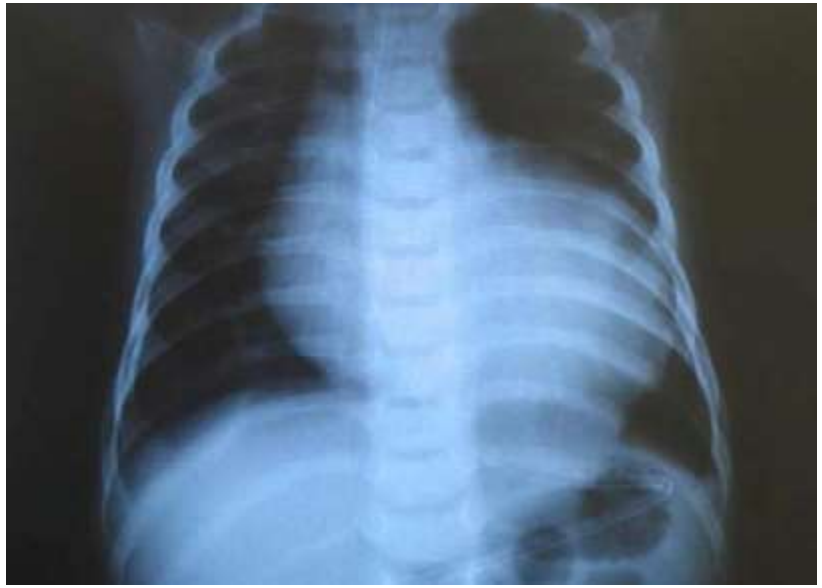
GSD's

Clinical handle/classical	IEM	Salient Features
GSD-1 **Von Gierke**	Glucose-6-phosphatase	Most common GSD Doll like facies, Hyperuricemia &lactic acidosis
GSD-2 **Pompe**	Alpha 1-4 glucosidase (Acid maltase)	Cardiomyopathy (large QRS complexes); Profound hypotonia ERT available
GSD-3 **Cori /Forbes** (limit dextrinosis)	Debrancher	
GSD-4 **Anderson**	Brancher	Liver cirrhosis
GSD-5 **McArdle's disease**	Muscle phosphorylase	Muscle involvement predominant
GSD-6 **Hers**	Hepatic phosphorylase	
GSD-7 **Tarui**	Phosphofructokinase	

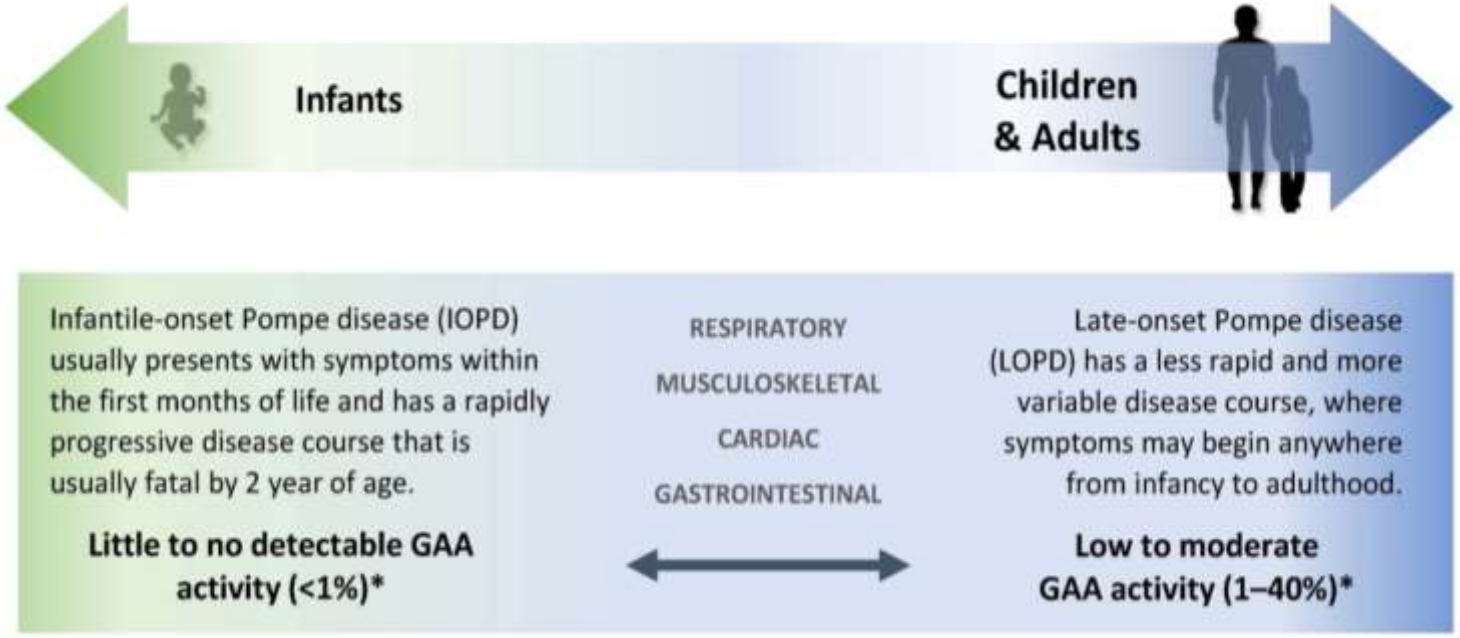
Von Gierke disease



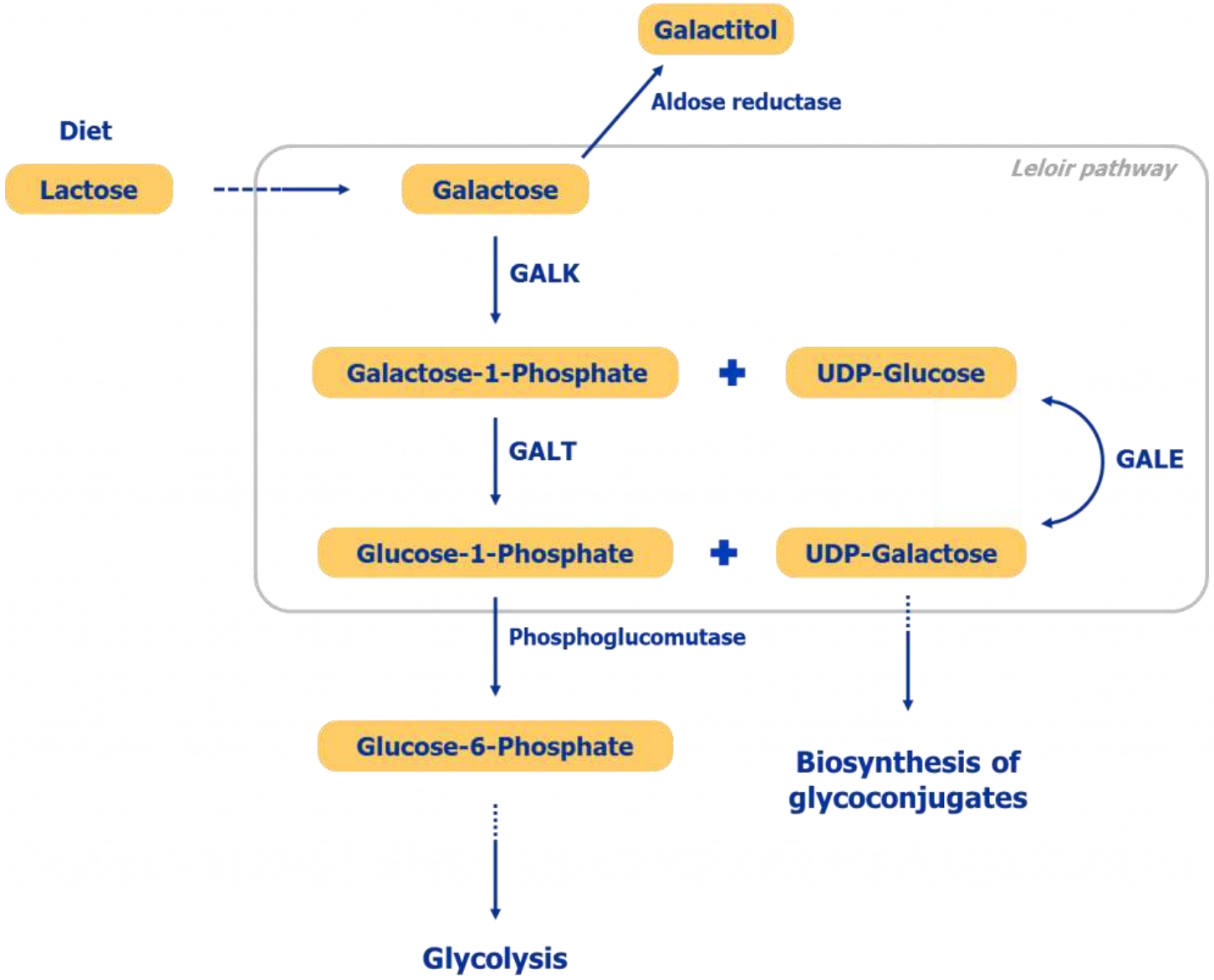
Pompe's disease

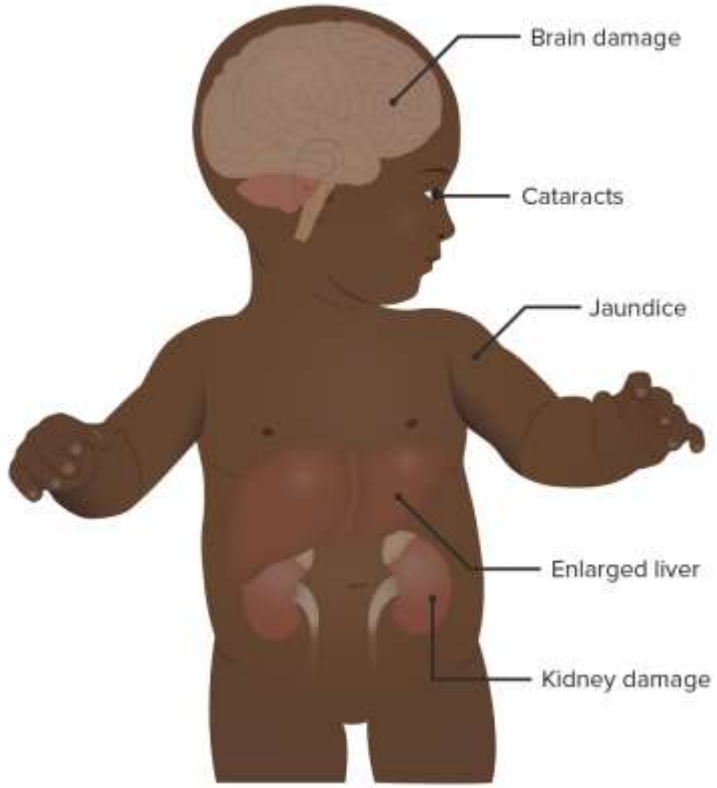


- ✓ Acid maltase (Alpha 1,4 glucosidase) deficiency
- ✓ Feeding difficulties
- ✓ Profound hypotonia
- ✓ Cardiomyopathy
- ✓ Hypoglycemia
- ✓ ERT

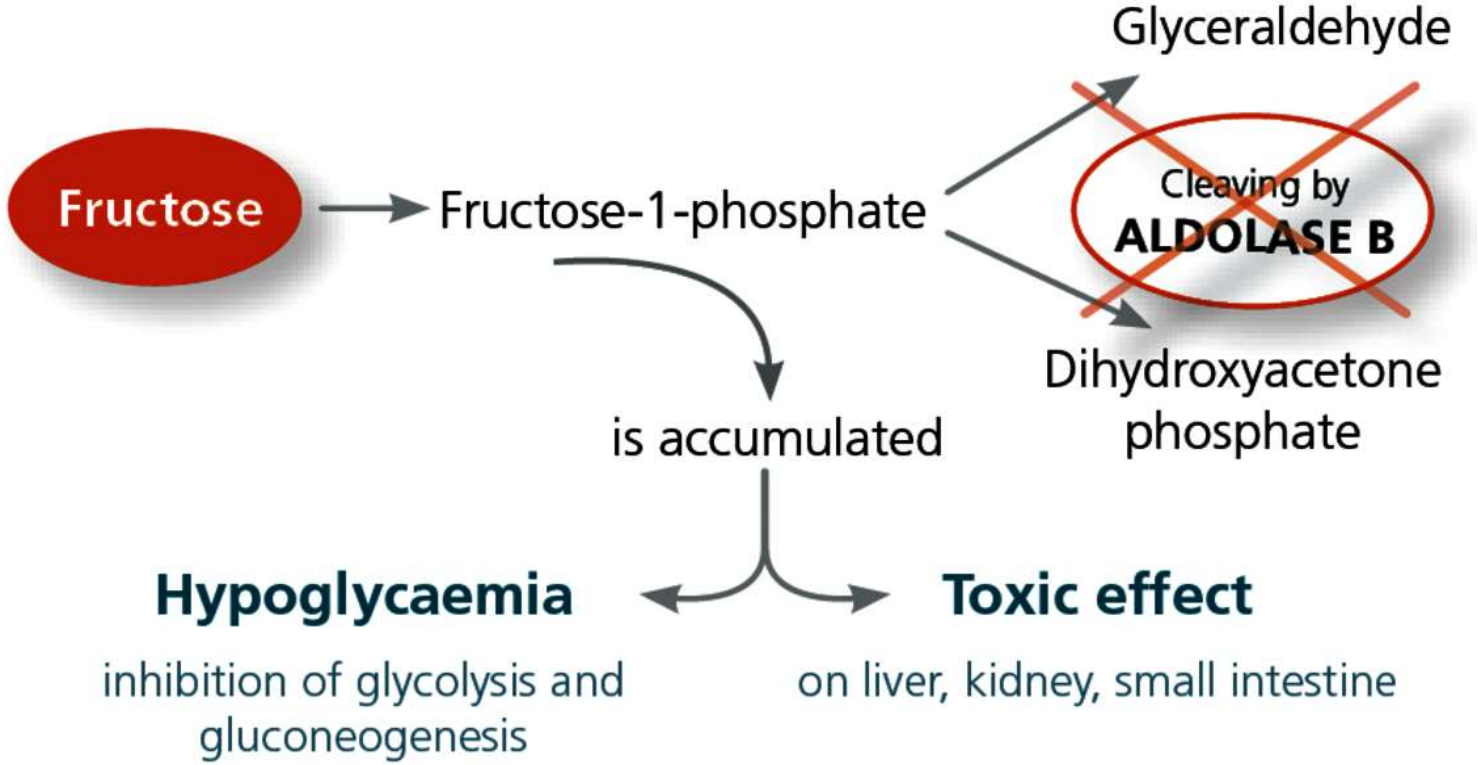


GALACTOSEMIA

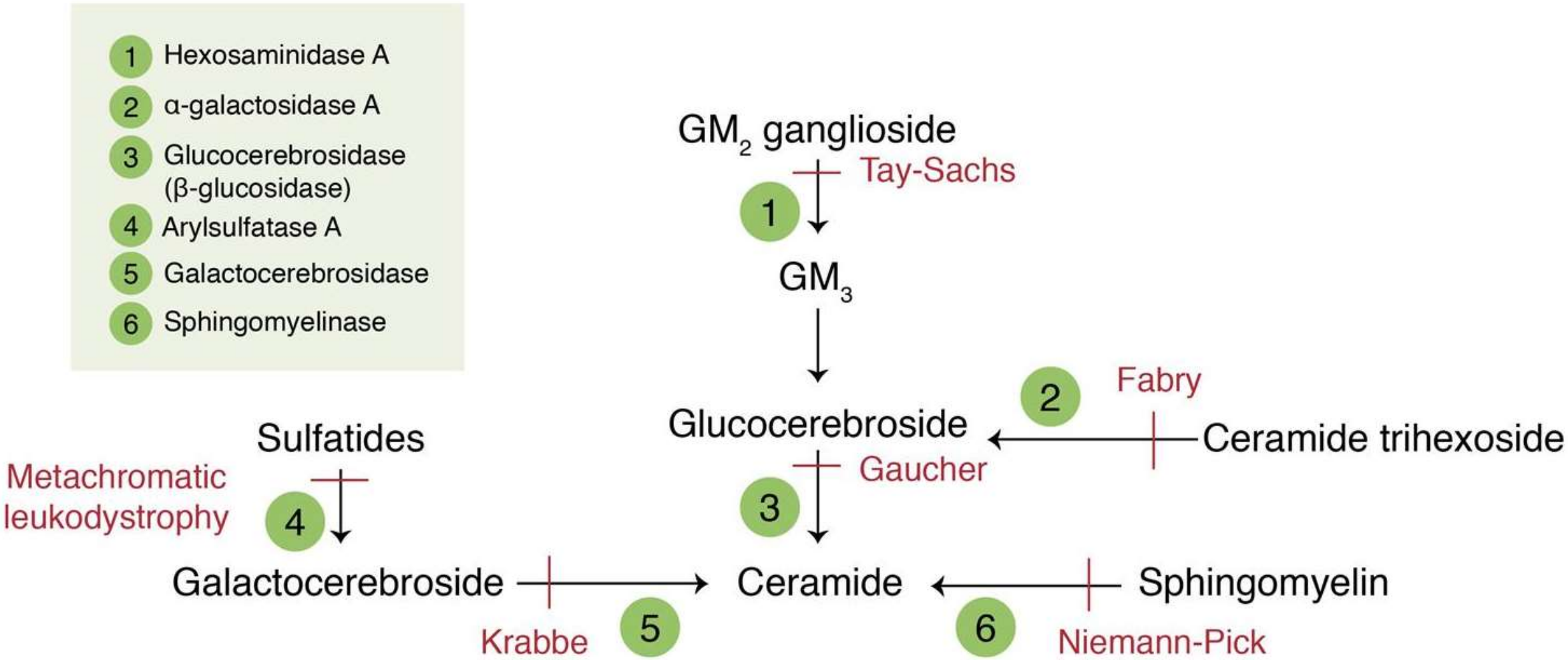




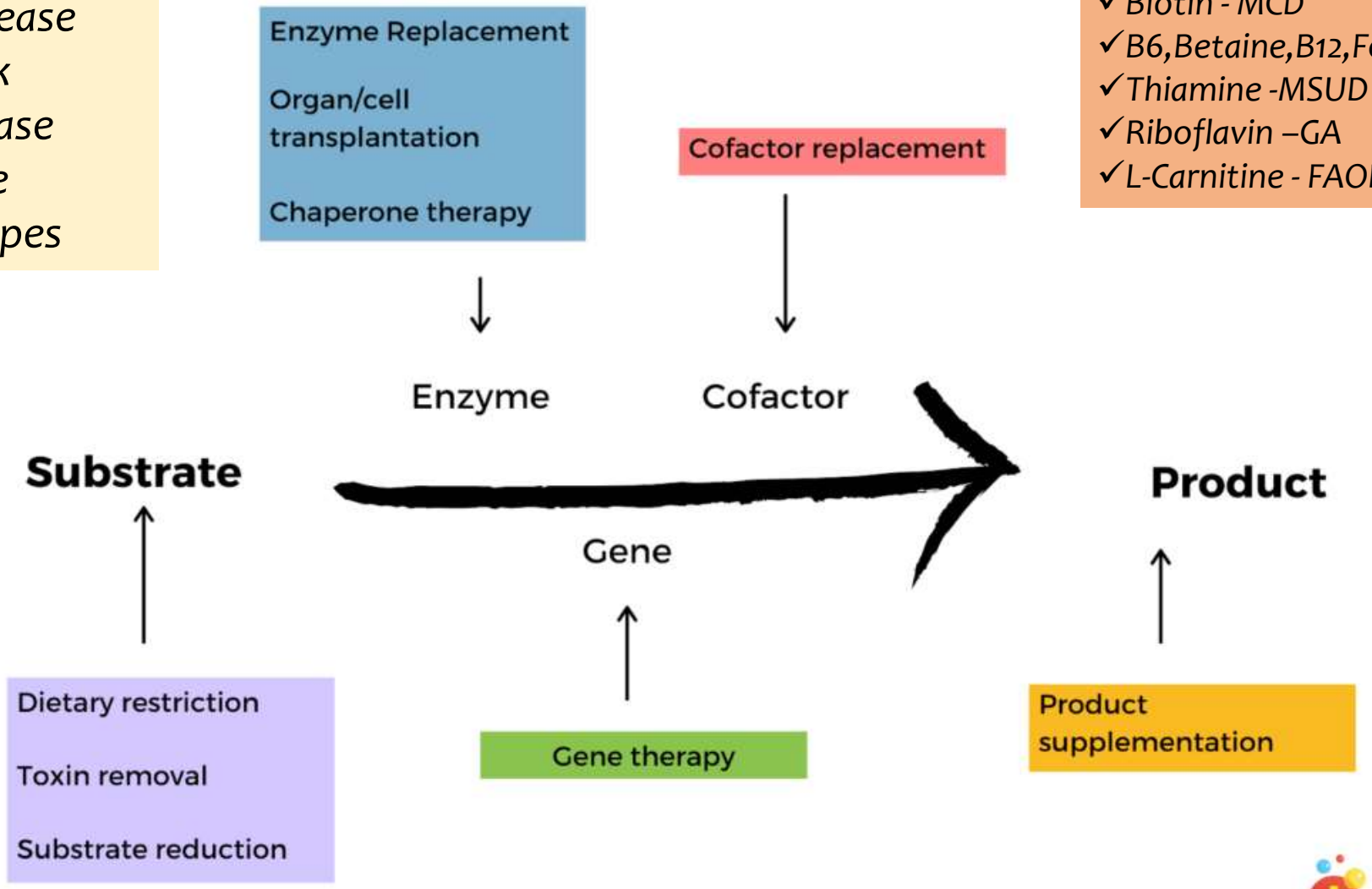
HEREDITORY FRUCTOSE INTOLERANCE



LYSOSOMAL STORAGE DISORDERS (LIPID)



- ✓ *Gauchers disease*
- ✓ *Neimann Pick*
- ✓ *Pompes disease*
- ✓ *Fabry disease*
- ✓ *MPS 1,2&6 types*



- ✓*THB (Sapropterin) -PKU*
- ✓*Biotin - MCD*
- ✓*B6,Betaine,B12,Folate - Homocystinuria*
- ✓*Thiamine -MSUD*
- ✓*Riboflavin –GA*
- ✓*L-Carnitine - FAOD*

THANK YOU