CLASSIFICATION OF INBORN ERRORS OF METABOLISM

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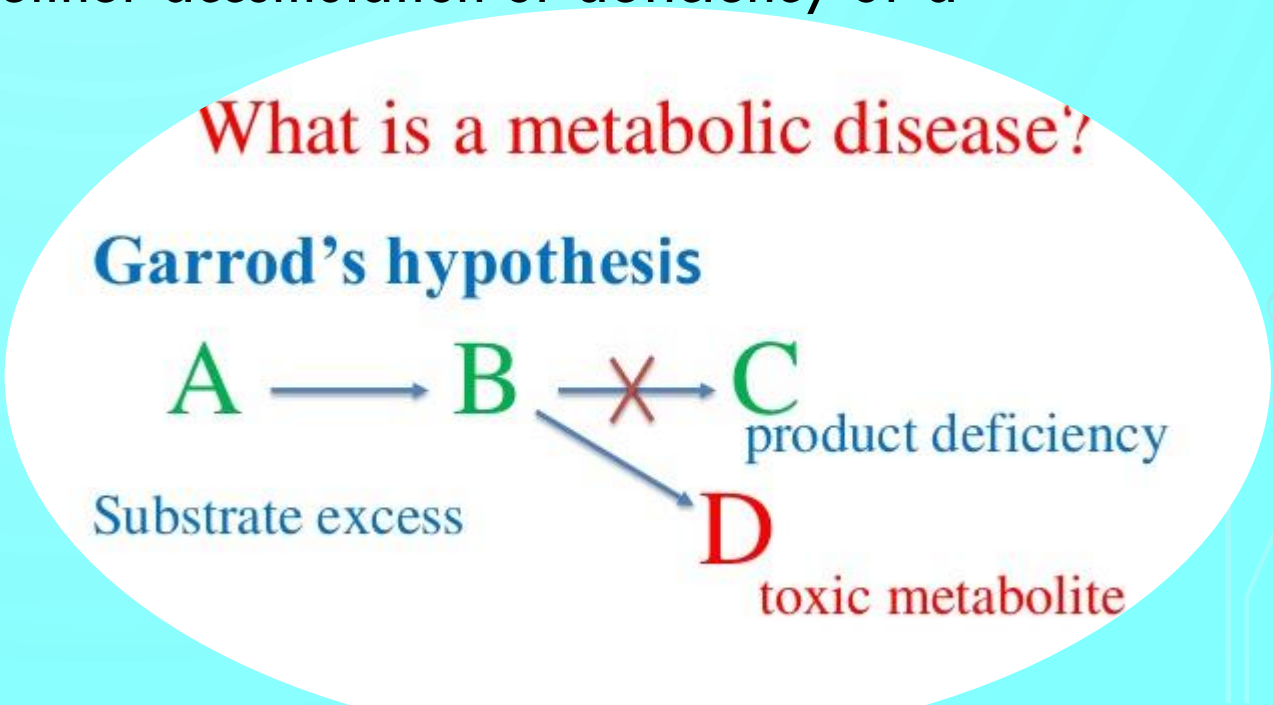
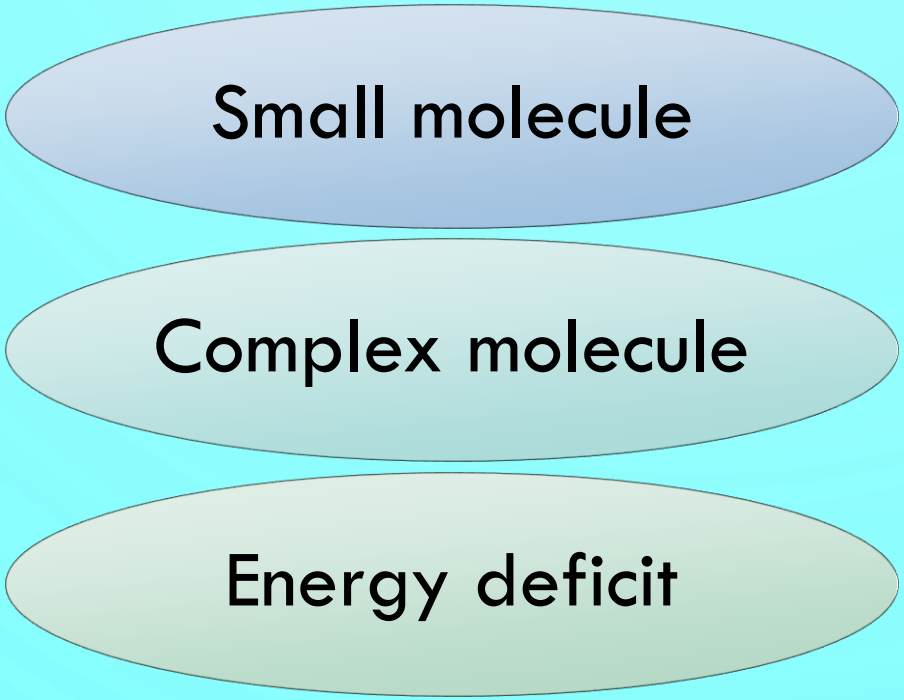
INTRODUCTION

- Metabolism involves thousands of proteins, mostly enzymes,cofactors, receptors and transporters.
- Congenital metabolic disorders result from the absence or abnormality of an enzyme or its cofactor, leading to either accumulation or deficiency of a specific metabolite.



CLASSIFICATION

- classification is in line with a system biology practice, and combines biochemistry with cellular biology processes.



SMALL MOLECULES

- Almost all these IMD have plasma and/or urine metabolic marker(s) (ie, small diffusible water-soluble molecules) , that can be easily and rapidly measured in emergency.
- like amino acids, organic acids, acylcarnitines, porphyrins, fatty acid, purines, pyrimidines, etc.), or by using specific methods (like metals or galactose metabolites).


accumulation
intoxication
Most treatable


deficiency
Defective syntheses and transport
Few treatable

SMALL MOLECULES: ACCUMULATION

- Cause acute or progressive intoxication
- Signs result primarily from accumulation of the compound and reverse
- Do not interfere with fetal development
- Present after a symptom-free interval
- Crisis by food and catabolism
- Most of them are treatable

- Amino acids catabolism: PKU ,MSUD,TYR,….
- Organic acids: MMA,PA,IVA,….
- B vitamins: homocystunuria ,organic aciduria
- Urea cycle defect
- Metal: willson
- Purine and pyrimidine
- Carbohydrate: galactosemia,HFI

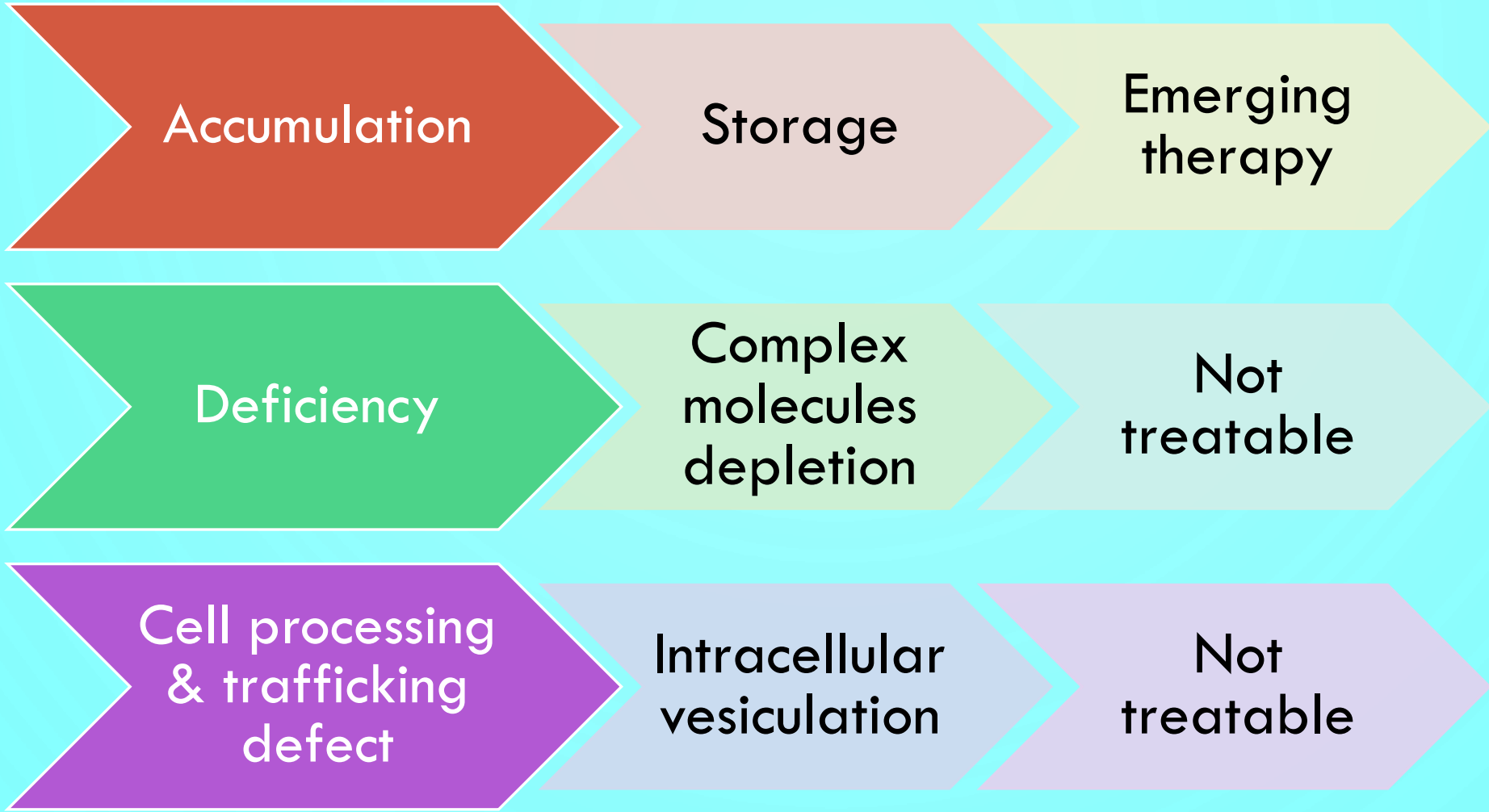
SMALL MOLECULES, DEFICIENCY

- Symptoms result primarily from the defective synthesis or transport of an essential molecule
- May cause neurodevelopment disruption, with congenital presentation
- Share many characteristics with complex group
- Metabolic markers are decreased
- Few of them are treatable

- Serine,glutamine,aspargine ,glutathione,glycine synthesis defect
- Disorder of AA,FA transport
- Disorder copper,Mg,Mn,Zinc,selenium metabolism
- Neurotransmitters synthesis & transport defect
- Disorder of purine and pyrimidine metabolism(nucleic acids)

COMPLEX MOLECULES

- Disturb the metabolism of complex molecules that are neither water soluble nor diffusible.
- Complex molecules are glycogen, triglycerides, sphingolipids (SPL), phospholipids (PL), bile acids, glycosaminoglycans, oligosaccharides, glycoproteins, glycolipids and nucleic acids
- very long chain FA and cholesterol, although they are simple molecules, because they can be a source of complex molecules
- Other complex molecules coagulation factors, liposoluble vitamins, hormones


Accumulation
Storage
Emerging therapy
Deficiency
Complex molecules depletion
Not treatable
Cell processing & trafficking defect
Intracellular vesiculation
Not treatable

COMPLEX MOLECULES, ACCUMULATION

- Storage of a visible compound
- Multisystem signs
- Neurodegenerative
- May have antenatal signs
- Emerging therapy

Glycogen storage disease(cytoplasmic, lysosomal)

MPS

FA, prostaglandins (PZO biogenesis,X-ALD,Refsum,…)

Cholestrol (lysosomal: Niemann -Pick, wolman)

Sphingolipidosis

Lipopigments (lipofucinosis)

Oligosaccaridosis, glycoproteinosis,sialidosis,mucolipidosis

Neutral lipid storage disease

COMPLEX MOLECULES, DEFICIENCY

- Only few have metabolic markers
- Diagnosis based on NGS
- Neurodegenerative
- Multisystem
- Antenatal signs
- Most of them are not treatable

- Glycogen depletion(GSD 0)
- FA transport, synthesis, recycling, arachidonic derivatives
- Non mitochondrial FA metabolism
- Non lysosomal sphingolipid metabolism
- Phospholipids
- Cholesterol & bile acids(eg SLO), steroid disorders
- Disorders of vitamin D,E,K metabolism

CELLULAR PROCESSING & TRAFFICKING DEFECT

Finding similar to complex molecules deficiency

Intracellular vesiculation

Processing and quality control(autophagy)

Synaptic vesicle cycle

Aminoacyl tRNA synthetases

*CDG(congenital disorders of glycosylation)

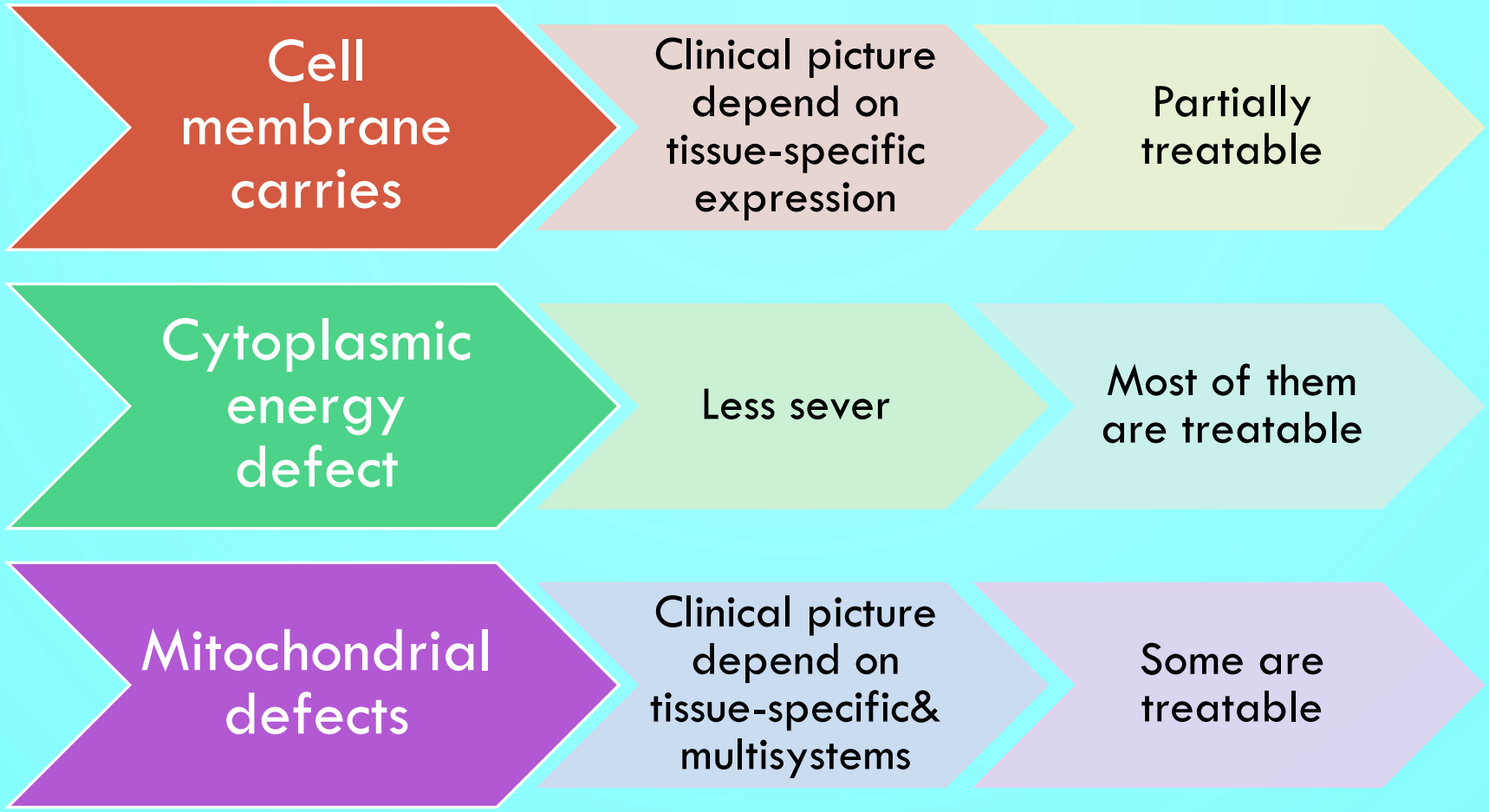
DISORDERS INVOLVING PRIMARILY ENERGY METABOLISM

- Deficiency in energy production or utilization within

  liver, myocardium, muscle, brain, and other tissues.

- Diagnosis can be oriented by function tests measuring glucose,lactate,ketones and other energy molecules(AA,OA,Acylcarnitines) in blood, CSF,urine

- Confirmed by enzyme assays and molecular testing


Cell membrane carries
Clinical picture depend on tissue-specific expression
Partially treatable
Cytoplasmic energy defect
Less sever
Most of them are treatable
Mitochondrial defects
Clinical picture depend on tissue-specific& multisystems
Some are treatable

ENERGY DEFECTS, MEMBRANE CARRIERS

- Glucose, lactate, pyruvate , ketone bodies are the most important molecules involved energetic carrier defects
- Glucose, monosaccharide transport(Na –glu transport)
- GLUT1(cerebral),GLUT2(hepatocyte,beta cell)
- MCT1(lactate,pyrovate ,ketone transport: EI hyperinsulinism),MCT12(creatine transport),MCT8(T3 transport)

MCT:Monocarboxylase

ENERGY DEFECTS, CYTOPLASMIC

- Glycolysis & pentose phosphate pathway defect
- Creatine defect
- GSD(Complex molecules)
- Insulin secretion

ENERGY DEFECTS, MITOCHONDRIAL

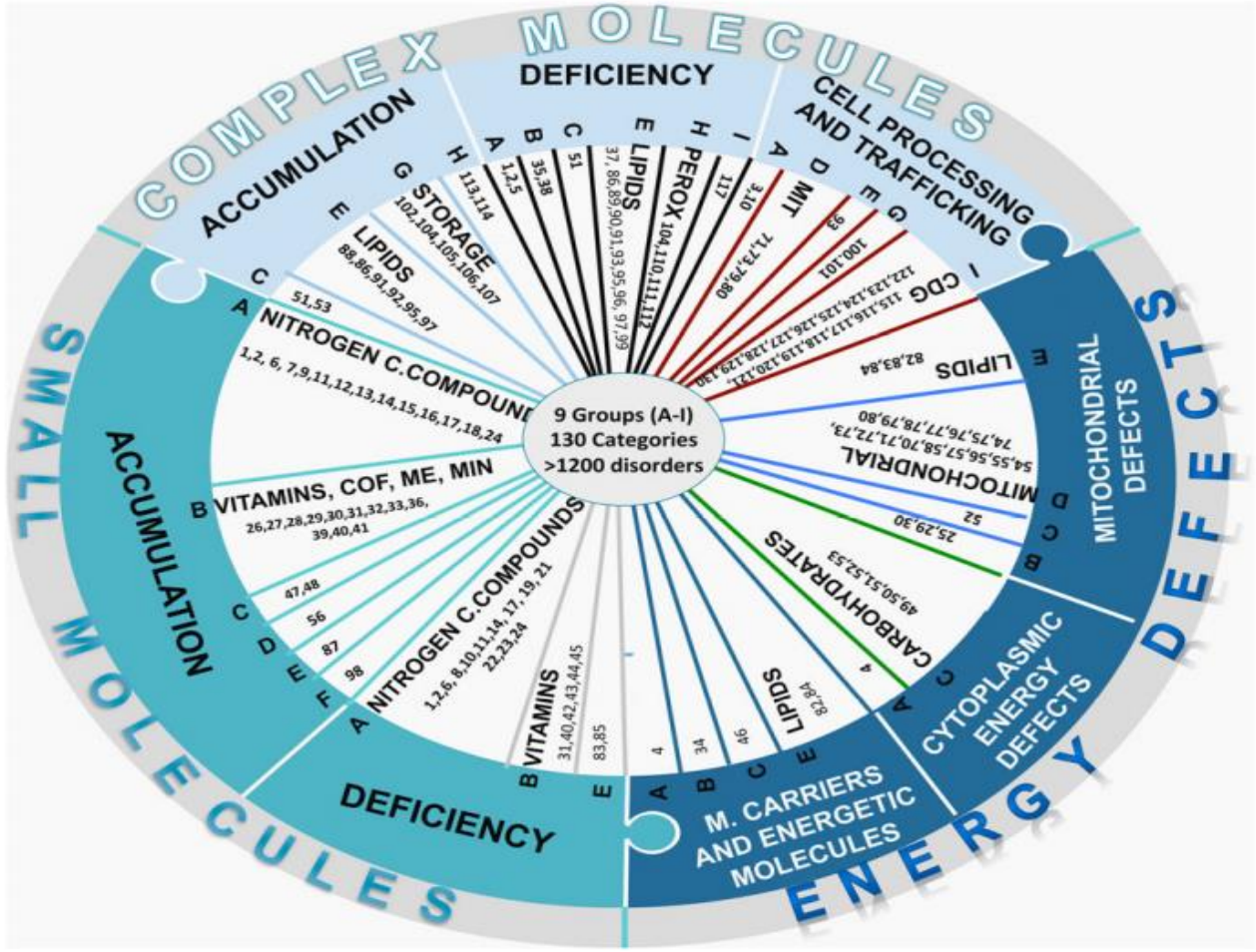
Fatty acid oxidation defect

Ketones metabolism

Pyruvate/lactate oxidation

Krebs cycle defect

Respiratory chain defect



Connection map between the simplified classification and the IMD updated nosology. A, NITROGEN containing compounds; B, VITAMINS, cofactors, metals, minerals; C, CARBOHYDRATES; D, MITOCHONDRIAL disorders; E, LIPIDS; F, TETRAPYRROLES; G, STORAGE disorders; H, PEROXISOME and oxalate; I, CDG

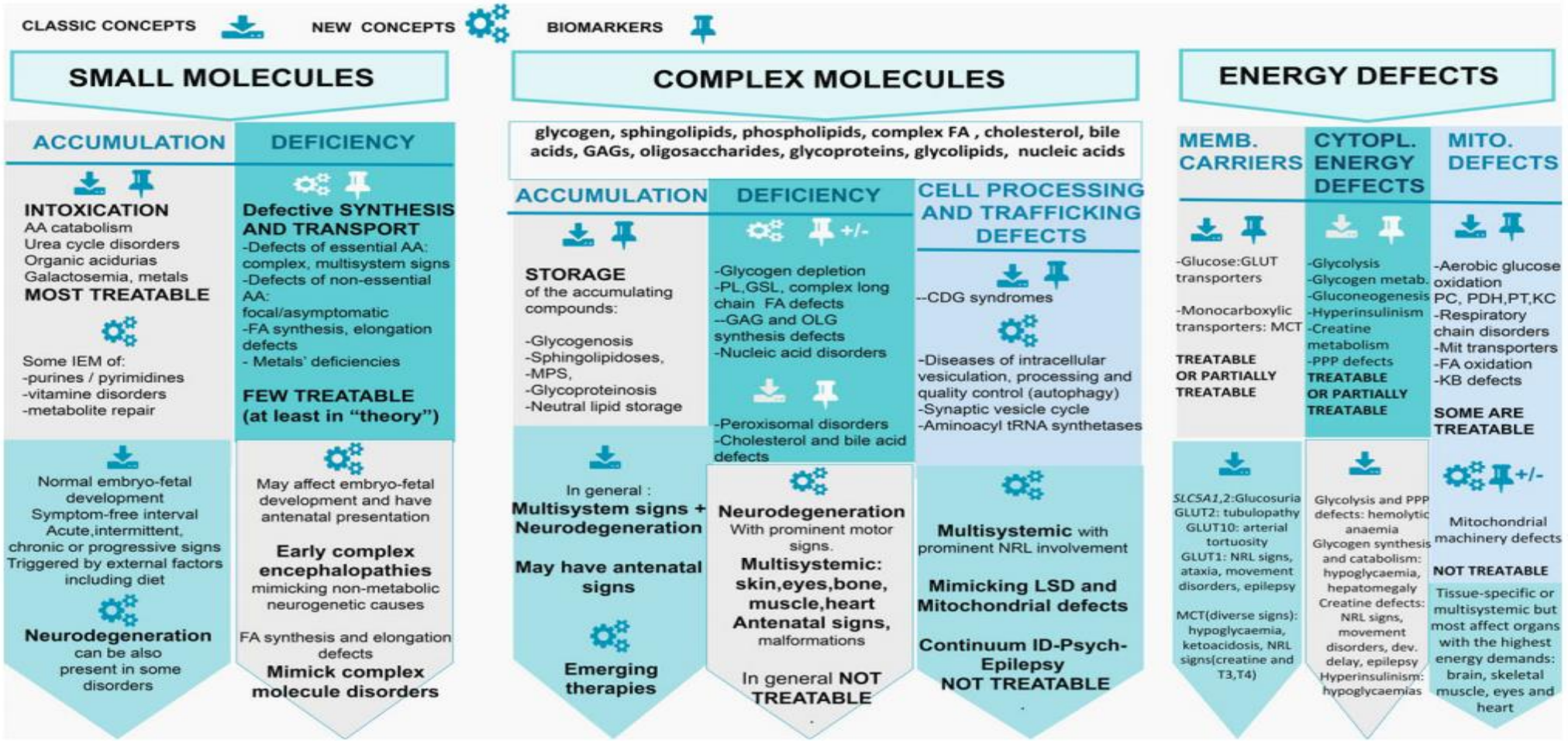


FIGURE 1 Simplified classification « at a glance ». AA, amino acids; CDG, congenital disorders of glycosylation; FA, fatty acids; GAG, glycosaminoglycans; GSL, glycosphingolipids; ID, intellectual disability; IEM, inborn errors of metabolism; KB, ketone bodies; KC, Kreb's cycle defects; LSD, lysosomal storage diseases; Mit, mitochondrial; MPS, mucopolysaccharidosis; NRL, neurological; OLG, oligosaccharides, PC, pyruvate carboxylase deficiency; PDH, pyruvate dehydrogenase deficiency; PL, phospholipids; PPP, Pentose phosphate pathway; PT, pyruvate transporter deficiency; Psych, psychiatric signs


Thanks for
your attention