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Proposal for a simplified classification of IMD based on a pathophysiological approach: A practical guide for clinicians

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Abstract

In view of the rapidly expanding number of IMD discovered by next generation sequencing, we propose a simplified classification of IMD that mixes elements from a clinical diagnostic perspective and a pathophysiological approach based on three large categories. We highlight the increasing importance of complex molecule metabolism and its connection with cell biology processes. *Small molecule disorders* have biomarkers and are divided in two subcategories: accumulation and deficiency. *Accumulation* of small molecules leads to acute or progressive postnatal "intoxication", present after a symptom-free interval, aggravated by catabolism and food intake. These treatable disorders must not be missed! *Deficiency* of small molecules is due to impaired synthesis of compounds distal to a block or altered transport of essential molecules. This subgroup shares many clinical characteristics with complex molecule disorders. *Complex molecules* (like glycogen, sphingolipids, phospholipids, glycosaminoglycans, glycolipids) are poorly diffusible. *Accumulation* of complex molecules leads to postnatal progressive storage like in glycogen and lysosomal storage disorders. Many are treatable. *Deficiency* of complex molecules is related to the synthesis and recycling of these molecules, which take place in organelles. They may interfere with fœtal development. Most present as neurodevelopmental or neurodegenerative disorders unrelated to food intake. Peroxisomal disorders, CDG defects of intracellular trafficking and processing, recycling of synaptic vesicles, and tRNA synthetases also belong to this category. Only few have biomarkers and are treatable. Disorders involving primarily *energy metabolism* encompass defects of membrane carriers of energetic molecules as well as cytoplasmic and mitochondrial metabolic defects. This oversimplified classification is connected to the most recent available nosology of IMD.

KEYWORDS

complex lipids disorders, complex molecules, inborn errors of metabolism classification, neurodegenerative disorders, neurodevelopmental disorders, trafficking disorders

1 | INTRODUCTION

Metabolism involves thousands of proteins, mostly enzymes, cofactors, receptors and transporters, the deficit of which

Abbreviations: CD, congenital disorders of glycosylation; GSD, glycogen storage disorders; IMD, inborn metabolic disorder; LSD, lysosomal storage disorders; NGS, next generation sequencing.

causes an IMD. According to Morava, the "classification of a disorder as an IMD requires only that impairment of specific enzymes or biochemical pathways is intrinsic to the pathomechanism".[1] Until recently, there was a tendency to mostly consider disorders affecting the catabolism of molecules while synthesis and transport defects were clearly underrepresented; in fact, they were almost ignored. In view of the rapid recognition of these new categories of IMD by next generation sequencing (NGS),[2] it is now of utmost importance to integrate them in the classification of IMD based on these biochemical categories (synthesis, remodeling, transport, catabolic and trafficking defects) rather than on an organelle-centric approach that splits arbitrarily metabolic pathways.

2 | TOWARD A NEW AND SIMPLIFIED PATHOPHYSIOLOGICAL CLASSIFICATION OF IMD

Using this extended definition of IMD, the most recent tentative of IMD nosology encompasses more than 1100 disorders, provisionally classified into 130 groups.[3] This is a useful and exhaustive list primarily based on biochemical considerations. It fulfills the critical requirements for database programming, and the possibility of linking to nomenclatures via MIM gene numbers. In fact, this nosology represents a framework in terms of nomenclature and "speaking a common language" within the metabolic community. Additionally, it is linked to an updated website www.iembase.org/nosology/index.asp. However, and in addition to this detailed and helpful nosology, there are several reasons why a simplified classification, based on a pathophysiological approach, is needed:

1. Guidelines to help clinicians to suspect, detect, understand and treat IMD are critical. The day-to-day clinical reasoning is far from being a list of disorders grouped in biochemical and organelle-based categories. In particular, such type of list has little in common with neurologists' clinical approach. By contrast, the number of new IMD affecting the brain is growing very quickly. Therefore a classification including both clinical phenotypes and mechanisms of disease, easy to understand and grouped into few categories, is more likely to be learnt and integrated in the clinical practice not only of metabolic physicians, but also general pediatricians, neurologists, internists, endocrinologists, etc.
2. The proposal of a simplified classification focuses also on pathophysiology-based treatments. Therefore it stimulates the clinical exercise of linking symptoms, pathophysiology and therapeutic management, particularly in emergency situations.
3. Exhaustive and accurate descriptions of each disease are essential to deepen the knowledge of metabolic diseases. However, a holistic, integrative approach is crucial in order to decipher the complexity of mechanisms and phenotypes in IMD. Our simplified classification is in line with a system biology practice, and combines *biochemistry* with *cellular biology* processes.

Accordingly, the following simplified classification is based on a number of basic principles:

- Whatever their size, metabolites involved in IMD may behave as signaling molecules, structural components and fuels, and many metabolites can play different roles during development.[4]

- The proposal for a simplified classification of IMD mixes clinical diagnostic and pathophysiological approaches into three large categories based on the size of molecules ("small" or "complex") and their implication in energy metabolism (Figure 1).

- This approach has been used for a long time in our clinical practice and has been partly exposed in classic pediatric[5] and metabolic textbooks[6–8] as well as recent review papers.[9,10]

- This proposal is organized into categories in order to facilitate the diagnosis and treatment of patients with IMD. However, patients have disorders in complex, overlapping, non-categorical biologic systems. Accordingly, the authors, and the readers, are faced with the classic dilemma of balancing the practicality of categorical thinking with the reality of biology complexity and individual clinical diversity. Compromises were made in seeking that balance and reflecting the core mechanism of each disease that correlates the most with clinical signs and biomarkers. This is the key to this simplified classification that, most of all, aims at transforming the enormous complexity of IMD into a useful tool for clinicians.

3 | CLASSIFICATION

3.1 | Group 1: 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, usually in one run (like amino acids, organic acids, acylcarnitines, porphyrins, fatty acid, purines, pyrimidines, etc.), or by using specific methods (like metals or galactose metabolites). These markers are also useful for therapy monitoring since most of these IMD are amenable to treatment. This group can be divided in 2 subcategories (Table 1).

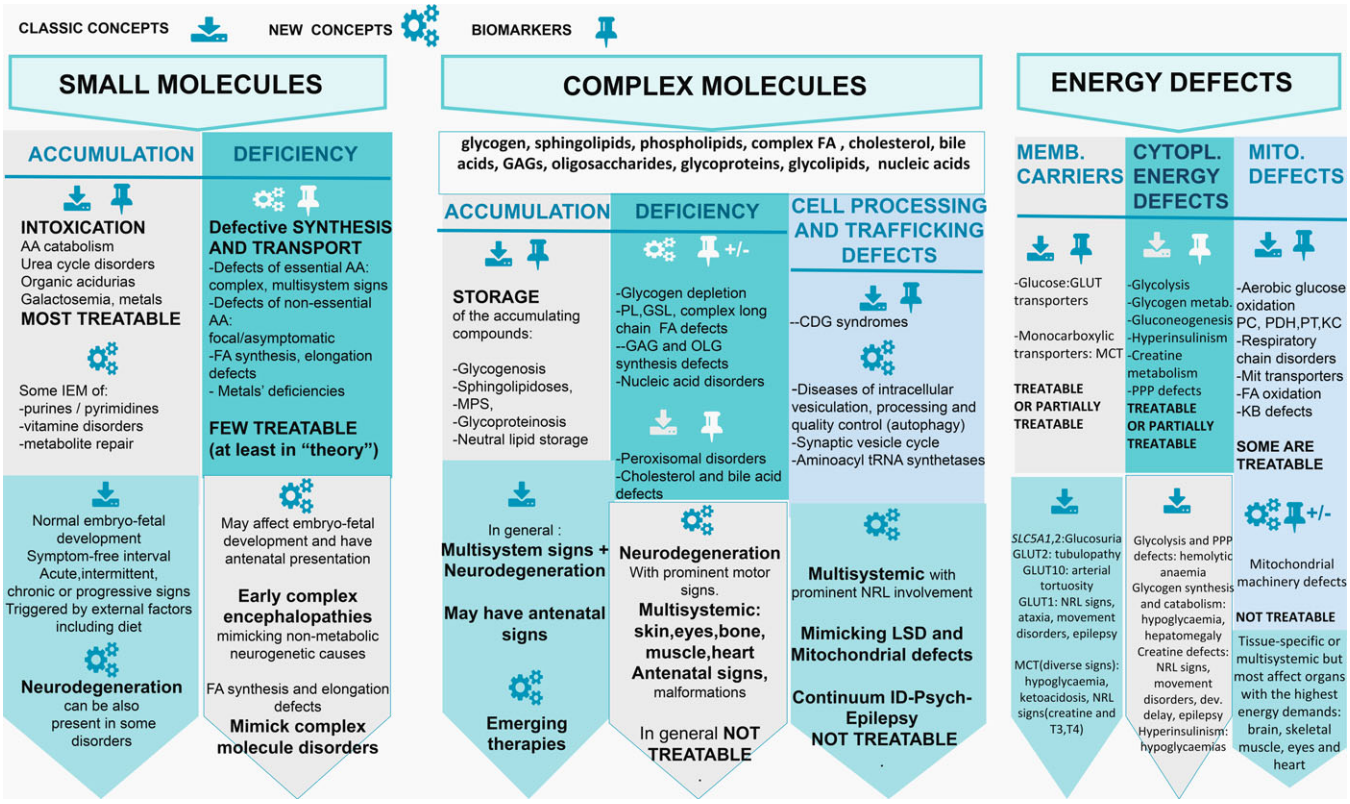

FIGURE 1 Simplified classification « at a glance ». AA, amino acids; CDG, congenital disorders of glycosylation; FA, fatty acids; GAG, glycosaminoglycans; GSL, glycosphingolipids; ID, intellectual disability; IEM, inborn errors of metabolism; KB, ketone bodies; KC, Kreb's cycle defects; LSD, lysosomal 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

3.1.1 | Accumulation of small molecules

The accumulation of small molecules causes acute or progressive "intoxication" disorders. Signs and symptoms result primarily from the abnormal accumulation of the compound(s) proximal to the block and can potentially reverse as soon as the compound(s) is (are) removed. They do not interfere with embryo and fetal neurodevelopment and they present after a symptom-free interval (days to years) with clinical signs of "intoxication" (acute, intermittent, chronic, and even progressive leading to neurodegeneration) provoked by fasting, catabolism, fever, intercurrent illness, and food intake. Most of these disorders are treatable and require the removal of the "toxin" by special diets, scavengers and cofactors (mostly vitamins).

This group encompasses IMD of *amino acid catabolism*—like phenylketonuria, maple syrup urine disease, or homocystinuria—, *urea cycle defects*, *organic acidurias*—like methylmalonic or glutaric aciduria type 1—, *galactosemia*, and *metal accumulation*—like Wilson disease, neuroferritinopathies and brain iron accumulation syndromes, or hypermanganesemia linked to *SLC30A10* and *SLC39A14* mutations.[15–17] Some small molecules accumulation may lead to visible crystals in diverse tissues like cystine in cystinosis (a lysosomal defect), oxalate in oxalosis (a peroxysomal defect) or homogentisic acid (ochronosis) in alkaptonuria.

Many *purine and a few pyrimidine disorders* may be classified in this group. Indeed, most disorders involving either nucleotide synthesis, catabolism or salvage pathways may be screened by plasma/urine purines and pyrimidines profiles. Clinical symptoms are very diverse and the pathophysiology is sometimes complex (linked to accumulation, deficiency or both) and still badly understood. Many enzymatic defects involve brain development by intricated mechanisms.[18] *Metabolite repair defects* are a new growing category in which symptoms are linked to the accumulation of a toxic compound like in L-2-hydroxyglutaric aciduria,[19] or *NAXE* mutations—NAXE catalyzes the epimerization of NAD(P)HX, thereby avoiding the accumulation of toxic metabolites.[20]

Vitamins (transport, and intracellular processing) interfere with many different metabolic pathways where they act as enzymatic cofactors, chaperones or signaling molecules. In most vitamin-responsive disorders, vitamin plasma levels are normal and treatment relies on pharmacological doses of

TABLE 1 Simplified classification of inborn errors of metabolism

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
I: Small molecules (water soluble diffusible)	**Almost all these IMD have plasma and urines metabolic marker(s) that can be easily and rapidly measured, making a metabolic signature easily accessible**				
Accumulation 1. Cause acute or progressive "intoxication" **2.** Signs result primarily from accumulation of the compound and can reverse as soon as it is removed. **3.** Do not interfere with foetal development **4.** Present after a symptom-free interval **5.** Crisis induced by food and catabolism 6. Most IMD are easily treatable but metabolite repair, many nucleic acids and fatty acid disorders	**« Intoxication » disorders (potentially reversible)**				
	Amino acids catabolism	PKU, MSUD, Tyr 1 and Tyr 2, OAT Homocystinurias. Glutathione	AAC, OAC	Toxin removal Special diets Vitamins Scavengers Drugs Supplement of distal product Organ transplantation	**A-Disorders of nitrogen-containing compounds:** 6-6-Disorders of glutathione metabolism 11-Disorders of phenylalanine 12-Disorders of tyrosine metabolism 13-Disorders of sulfur amino acid and sulfide metab. 14-Disorders of branched-chain amino acid metab. 15-Disorders of lysine metabolism 16-Disorders of proline and ornithine metabolism 18-Disorders of histidine metabolism 24-Disorders of glycine metabolism **B-Disorders of vitamins, cofactors, metals and minerals:** 39-Disorders of molybdenum metabolism
	Organic acids	MMA, PA, IVA Cerebral OA	OAC, acylcarnitines		**A-Disorders of nitrogen-containing compounds:** 9-Aminoacylase deficiencies 14-Disorders of branched-chain amino acid metab. 15-Disorders of lysine metabolism **B-Disorders of vitamins, cofactors, metals and minerals:** 26-Disorders of cobalamine metabolism
	B Vitamins	B6,B12,Folate Biotin (causing homocystinuria or organic acidurias)	AAC, OAC, acylcarnitines		**A-Disorders of nitrogen-containing compounds:** 15-Disorders of lysine metabolism (pyridoxine-dependent-epilepsy) **B-Disorders of vitamins, cofactors, metals and minerals**:

TABLE 1 (Continued)

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
					26-Disorders of cobalamin. 27-folate. 28-biotin 29-thiamine. 30-riboflavin. 32-pantothenate. 33-pyridoxine
	Urea cycle defects and related hyperammonaemias		AAC, OAC Orotic acid		**A-Disorders of nitrogen-containing compounds:** 7-Disorders of ammonia detoxification
	Metals	Copper (Wilson) Iron (NBIA) Manganese (*SLC39A14 SLC30A10*)	Specific metal tests T1-weighted brain MRI		**B-Disorders of vitamins, cofactors, metals and minerals**: 32-Disordes of pantothenate metabolism 40-Disorders of copper metabolism 41-Disorders of iron metabolism 42-Disorders of manganese metabolism
FA accumulation observed in peroxysome defects share many clinical similarities with complex lipid synthesis disorders suggesting that many other mechanisms than intoxication are involved	Carbohydrate	Galactosemias HFI	Gal-1P, GALT Molecular test		**C-Disorders of carbohydrates** 47-Disorders of galactose metabolism 48-Disorders of fructose metabolism
	Glycerol		Glycerol		**E. Disorders of lipids** 87-Disorders of glycerol metabolism
	Porphyrins	Porphyrias	Blood/urines porphyrins		**F-Disorders of tetrapyrroles** 98-Disorders of heme metabolism
	Metabolite repair	L-2-OH glutaric D-2-OH glutaric NAXE deficit	AAC, OAC	Not or poorly treatable	**D. Mitochondrial disorders of energy metabolism** 56-Disorders of metabolite repair
	Nucleic acids	Catabolic disorders of purines and pyrimidines and salvage pathway defects	purines/pyrimidines profile, uric and orotic acid	Low purine diet Allopurinol ERT, BMT and gene therapy in ADA, PNP and thymidine phosphorylase	**A. Disorders of nitrogen-containing compounds:** 1-Disorders of pyrimidine metabolism 2-Disorders of purine metabolism
I.2 Deficiency	**Mimic complex synthesis defects. Most but not all are irreversible**				
1. Symptoms result primarily from the defective synthesis or transportation of an essential molecule	AA synthesis	Serine, Glutamine, Asparagine, synthesis defects Glutathion	Plasma/CSF aminoacids	Not or poorly treatable (Serine?)	**A. Disorders of nitrogen-containing compounds:** 6-Disorders of glutathion metabolism 21-Disorders of glutamine metabolism 22-Disorders of asparagine metabolism 23-Disorders of serine metabolism 24-Disorders of glycine metabolism

TABLE 1 (Continued)

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
2. Defects may cause neurodevelopment disruption, with congenital presentation	AA brain or epithelial transport	*SLC7A5* *SLC7A7 (LPI)* *SLC6A19* (Hartnup disease)	Plasma/CSF AA Plasma/urines AA	BCAA? Citrulline. Lysine; Niacin	**A. Disorders of nitrogen-containing compounds**: 8-Disorders of amino acid transport 14-Disorders of branched-chain amino acid metab. 19-Disorders of tryptophan metabolism (Hartnup) **B. Disorders of vitamins cofactors, metals and minerals** 31. Disorders of niacin and NAD metabolism
3. Share many characteristics with disorders in the complex molecules group 4. Metabolic markers are decreased	BCKDH	BCAA	Plasma/CSF AA	BCAA and high protein diet	**A. Disorders of nitrogen-containing compounds**: 14-Disorders of branched-chain amino acid metab.
5. A few are or should be treatable by supplementing the missing product distal to the block like Niacin in tryptophan malabsorbtion (Hartnup disease) and catabolism defects	FA transport	MFSD2A deficiency FA transport protein 4 deficiency	plasma LPC VLCFA activation in fibroblasts	DHA? LPC?	**E. Disorders of lipids**: 83-Disorders of fatty acid oxidation and transport
	FA synthesis and recycling	ELOV 1,4,5, **other** Leukotriene defect	FA profile in fibroblasts Molecular tests	Not treatable	**E. Disorders of lipids**: 85-Disorders of fatty acid synthesis and elongation
	Metals	*SLC39A8 (Mn)* *ATP7A* (Cu) (Menkes disease) *AP1S1* (Cu) *SLC33A1* (Cu) (acetylCoA transporter: AT1)	Plasma Manganese Plasma Copper Ceruloplasmin	Chelation therapy Zinc acetate Metal supplementation	**B. Disorders of vitamins, cofactors, metals and minerals**: 40-Disorders of copper metabolism 42-Disorders of manganese metabolism 43-Disorders of zinc metabolism 44-Disorders of selenium metabolism 45-Disorders of magnesium metabolism
	« Classical » Neurotransmitters Synthesis Catabolism Transport Receptors	GABA Monoamines Glycine Serine Glutamate	Plasma, urine, CSF Monoamines AA, Neopterins Urines OA	L-DOPA + carbidopa Biopterins Others	**A. Disorders of nitrogen-containing compounds**: 10-Disorders of monoamine metabolism 11-Disorders of phenylalanine and tetrahydrobiopterin 17-Disorders of beta and gamma amino acids 20-Disorders of glutamate metabolism 23-Disorders of serine metabolism
	Nucleic acids disorders	Purine and Pyrimidine Synthesis defects	purine/pyrimidine profile, uric and orotic acid	Adenine Thiopurines	**A. Disorders of nitrogen-containing compounds:**

TABLE 1 (Continued)

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
				Allopurinol Uridine (CAD, UMPS)	1-Disorders of pyrimidine metabolism 2-Disorders of purine metabolism
II. Complex molecules (water insoluble poorly diffusible)	**Although considered as small molecules, fatty acids and cholesterol were added to this group because of similarities in clinical findings with complex lipids and molecules.** **IMD that disturb the metabolism of complex molecules; Pathways involve cellular trafficking and organelles, require protein transporters or vesicles.** **Symptoms are permanent, progressive and independent of undercurrent events, unrelated to food intake. Most diseases do not present with metabolic crises.** **May present like neurodevelopment and neurodegenerative disorders**				
II.1 Accumulation Catabolism or transport defects lead typically to storage of a visible compound like in classical LSD. or GSD. In general there is no antenatal manifestations. Neurological presentations display progressive disorders with neurodegeneration with or without obvious visceral « storage » signs.	**Progressive storage disease leading to loss of function. Potentially partially reversible on treatment**				
	Glycogen (GSD) (cytoplasmic) (lysosomal)	Glycogenosis (liver, muscle, heart, brain) Heart ,Muscle (Pompe)	Function tests Enzyme assays Molecular tests	Special diet Organ transplant ERT, BMT Gene therapy in clinical trials	**C. Disorders of carbohydrates**: 51-Glycogen storage diseases 53-Disorders of glycolysis
	GAG	MPS	Urinary GAGS Enzyme assays	ERT, SRT BMT	**G. Storage diseases**: 105-Mucopolysaccharidoses
	Fatty acids Prostaglandins	PZO biogenesis and FAO defects: X-ALD, X-AMN other PZO FAO, Refsum disease Sjogren-Larsson	Plasma/fibro VLCFA profile Enzyme testing Molecular tests	BMT, Gene therapy in X-ALD Diet in Refsum Zyleuton in SLS	**E-Disorders of lipids**: 86-Disorders of the fatty alcohol cycle **H. Disorders of peroxisomes and oxalate**: 110-Disorders of peroxisome beta-oxidation 111-Disorders of peroxisome alpha-oxidation 112-Disorders of peroxisomal biogenesis
Of note cystine and oxalate, although they are small molecules are presented in this section because they clinically present with progressive storage disorders leading to renal failure and multi systemic signs	Cholesterol	Niemann-Pick Wolman disease	Enzymatic, molecular tests	SRT: Miglustat, ERT	**G. Storage diseases**: 106-Disorders of lysosomal cholesterol metabolism
	Sphingolipids	Sphingolipidosis (nervous system)	Urinary Sulfatides Enzyme assays	ERT,SRT BMT	**G. Storage diseases**: 102-Sphingolipidoses
	Lipopigments	Ceroid lipofucinosis	Enzyme assays Molecular tests	Not treatable	**E. Disorders of lipids**: 92-Disorders of palmitoylation (CLN1)
	Oligosaccharides Glycoproteins Sialic acid Glucosamines	Oligosaccharidosis Glycoproteinosis Sialidosis Mucolipidoses	Urinary Oligosaccharides	Not or poorly treatable	**G. Storage diseases**: 102-Oligosaccharidoses 104-Mucolipidoses
	Neutral lipids (steatosis)	NLSD Many others	Jordan's anomaly Plasma Triglycerides Molecular test	Symptomatic	**E. Disorders of lipids**: 88-Disorders of cytoplasmic triglyceride metabolism

TABLE 1 (Continued)

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
	Cystine	Cystinosis	Leukocyte cystine	Cysteamine Kidney Transplant	**G. Storage diseases**: 107-Disorders of lysosomal transport or sorting
	Oxalate	Oxalosis PH1-PH3	Urinary Oxalate Molecular tests	Kidney Transplant B6 in PH1	**H. Disorders of peroxisomes and oxalate**: 113. Peroxisomal disorders not involving lipid metabolism 114-Disorders of oxalate metabolism
II. 2 Deficiency	**Defects of synthesis, recycling. No storage material. May interfere with fetal development. Most are irreversible disorders**				
Most of them are not treatable Only few have metabolic markers but peroxisome and cholesterol disorders. For all others the diagnosis is mostly based on NGS. Untargeted Metabolomics and lipidomics are promising methods Liposoluble vitamins A, and E defects may mimick some clinical findings of complex lipid and peroxisome disorders. Vitamin D and K defects display very specific presentations: Rickets and hemorrhagic syndromes respectively	Glycogen	GSD 0 0 A (liver) 0 B (muscle) Glycogenin	Molecular tests		**C-Disorders of Carbohydrate** 51. Glycogen storage diseases Muscle glycogenin 1, Muscle glycogen synthase deficiency, Hepatic glycogen synthase deficiency
	GAG	Many defects *SLC10A7* is the most recent	Molecular tests	None	**I. Congenital disorders of glycosylation** 117-Disorders of O-xylosylation and glycosaminoglycan synthesis
	FA transport	MFSD2A deficiency FA transport protein 4 deficiency	plasma LPC VLCFA activation in fibroblasts	DHA? LPC?	**E. Disorders of lipids**: 83-Disorders of fatty acid oxidation and transport
	FA synthesis and recycling. Arachidonic acid derivatives	ELOV 1,4,5, **other** Leukotriene defect CYP2U1	FA profile in fibroblasts Molecular tests	Not treatable	**E. Disorders of lipids**: 85-Disorders of fatty acid synthesis and elongation **E-Disorders of lipids**: 91-Disorders of eicosanoid metabolism
	Non mitochondrial FA metabolism (recycling, synthesis, catabolism ,transport)	Peroxysome biogenesis and FAO defects Refsum disease Sjogren-Larsson FA elongation	Plasma/fibro VLCFA profile Enzyme testing Molecular tests	BMT (X-ALD) Diet (Refsum) Zyleuton in SLS Many are not treatable	**E-Disorders of lipids**: 86-Disorders of the fatty alcohol cycle 37. Disorder of vitamin E metabolism **H. Disorders of peroxisomes and oxalate**: 110-Disorders of peroxisome beta-oxidation 111-Disorders of peroxisome alpha-oxidation 112-Disorders of peroxisomal biogenesis
	Ether phospholipids (Plasmalogens)	PZO Biogenesis plasmalogen synthesis defects (RCDP II-V) FAR	Plasma RBC, Plasmalogens Fibroblasts Enzymes Molecular tests	None	**H. Disorders of peroxisomes and oxalate**: 109-Disorders of plasmalogen synthesis

TABLE 1 (Continued)

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
	Sphingolipids	already >15 Disorders	Molecular tests Deoxy-sphingolipids (MSMS)	None	**E-Disorders of lipids**: 90. Disorders of non-lysosomal sphingolipid metabolism
	Phospholipids (PL): Phosphatidylcholine, Phosphatidylserine Phosphatidyle-thanolamine Choline, Ethanolamine Retinol disorders	PL synthesis and recycling defects (>15) Retinol metabolism	Molecular tests	None	**E-Disorders of lipids**: 35-Disorders of vitamin A metabolism: 89. Disorders of non-mitochondrial phospholipid metabolism **A-Disorders of nitrogen-containing compounds**: 5-Disorders of choline metabolism
	Phospholipids: Phosphatidyl-inositides	Many types (OCRL, FIG4, INPP5K…) including mTor signaling pathway	Molecular tests	None	**E-Disorders of lipids**: 93-Disorders of phosphoinositides metabolism
	Cholesterol and bile acids Bilirubin metabolism Biliary transport	Cholesterol Bile acids	Plasma Oxysterols Plasma and urinary Bile acids profile Molecular tests	Bile acid replacement	**E-Disorders of lipids**: 95-Disorders of cholesterol biosynthesis 97-Disorders of bile acid synthesis 99. Disorders of bilirubin metabolism and biliary transport
	Steroid disorders and vitamin D disorders	Glucocorticoids Mineralocorticois Androgens Oestrogens	Hormone measurements in plasma	Hormonal substitution	96. Disorders of steroid metabolism 36. Disorders of vitamin D metabolism
	Coagulation factors Vitamin K		Investigations of coagulation	Factors supplementation Vitamin K	**B. Disorders of vitamins ,metals and minerals** 38. Disorders of vitamin K metabolism
II.3 Cellular processing and trafficking	**Nearly all the molecules reach their correct intracellular locations by virtue of sophisticated transport-and-delivery systems among which the intracellular membrane-transport apparatus is crucial.[11] A particular model of compartmentalized signaling and metabolism occurs at the synapse that uses an independent organelle, the synaptic vesicle[12]**				
Most these disorders share findings with disorders of II.2 1. Only few have metabolic markers 2. Many have multisystemic presentation	CDG syndromes (>100)	Protein N glycosylation O-Glycosylation Lipid glycosylation GPI anchor Multiple pathway Dolichol Deglycosylation	Serum tranferrin and ApolipoproteinC-III analysis Glycomics Molecular tests	Not treatable but MPI, DPAGT1, GFPT1, and PGM1-CDG	**I. Congenital disorders of glycosylation** From 115 to 130[3]

TABLE 1 (Continued)

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
3. Most involve nervous system 4. Almost all present as chronic or progressive diseases independent of food and intercurrent event 5. They are not treatable 6. Diagnosis is mostly based on exome/ genome sequencing	Trafficking Vesiculation Processing Quality Control Autophagy.	Many disorders *SNAP 29* *AP5Z1* *CHMP2B* Rabenosyn-5 Senda, Vici syndromes…	Exome /genome sequencing	Not treatable	**D-Mitochondrial disorders of energy metabolism**: 79-Disorders of mitochondrial protein quality control 80-Other disorders of mitochondrial homeostasis (ie, trafficking kinesin-binding protein 1 [TRAK1] deficiency) **G. Storage diseases:** 100-Disorders of autophagy **I. Congenital disorders of glycosylation** 128-Glycosylation disorders of vesicular trafficking 129-Disorders of Golgi homeostasis
	Synaptic vesicle (SV)	Many defects: Structure and composition of the SV, Exocytic and endocytic processes, Proteins/lipid interactions…..	Exome/genome sequencing	Not treatable	**A-Disorders of nitrogen-containing compounds**: 10-Disorders of monoamine metabolism (VMAT2, DNAJC12) **D-Mitochondrial disorders of energy metabolism**: 79-Disorders of mitochondrial protein quality control (PINK1) **E-Disorders of lipids**: 93-Disorders of phosphoinositide metabolism (ie, synaptojanin 1 deficiency) **G. Storage diseases**: 100-Disorders of autophagy (ie, SNX14, SPG11) 101-Neuronal ceroidlipofuscinosis: CLN4 (DNAJC5), ATP13A2
	t-RNA synthetases	Mito t-RNA Cyto t-RNA Mit/cyt t-RNA (KARS and GARS)	Exome /genome sequencing	Not treatable	**D-Mitochondrial disorders of energy metabolism**: 73. Disorders of mitochondrial tRNA
	Disorders of nucleotide metabolism	Ribosomopathies DNA repair and methylation	Exome /genome sequencing Interferon (AGS)	Not treatable	**A-Disorders of nitrogen-containing compounds**: 3-Disorders of nucleotide metabolism

TABLE 1 (Continued)

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
					D-Mitochondrial disorders of energy metabolism: 71. Mitochondrial ribosomopathies
III **Disorders involving primarily energy metabolism**	**Diagnosis can be orientated by function tests measuring glucose, lactate, ketones and other energetic molecules (AA, OA, Acylcarnitines) in blood, CSF and urines and confirmed by enzyme assays and molecular testing**				
III.1 **Cell membrane carriers of energetic molecules**	**Clinical picture and treatment depend on tissue-specific expression (enterocytes, hepatocytes, pancreatic beta cell, renal tubular cells, blood brain barrier, glia cells, thyroid…) and substrate specificity (glucose, lactate, ketones, creatine, carnitine….) of the affected transporter.**				
Glucose, lactate, pyruvate and ketone bodies are the most important molecules involved in energetic carrier defects The solute carrier (SLC) *SLC2* and *SLC5* gene family encodes for glucose carriers while *SLC16* gene family encodes for monocarboxylate transporters (MCTs)	Glucose monosaccharide transporter proteins	SGLT1*(SLC5A1)* SGLT2 *(SLC5A2)* (sodium dependent glucose transporter	Glucosuria,Melituria, monosaccharide, tolerance tests	Special diet	**C-Disorders of Carbohydrates** 34-Disorder of vitamin C metabolism: 46 Disorders of carbohydrate transport and absorption
		GLUT1 *(SLC2A1)* (Cerebral)	Low CSF Glucose	Special diet	
		GLUT2 (*SLC2A2)* (Hepatocyte, pancreatic βcells enterocyte)	Disturbed glucose homeostasis. Tubulopathy	Special diet	
	Monocarboxylic transporter	MCT1 *(SLC16A1)* Lactate, Pyruvate, Ketones transport	EI hyperinsulinism (Overactivity) Ketoacidosis Muscle injury (deficiency)	Diazoxide	**E-Disorders of lipids**: **84. Disorders of ketone body metabolism** Monocarboxylate transporter 1 deficiency and superactivity
		MCT12 (*SLC16A12*) Creatine transport	Low plasma creatine low U creatinine Low brain creatine peak (NMR)	Creatine	**A-Disorders of nitrogen-containing compounds**: 4-Disorders of creatinemetabolism: Creatine transporter deficiency
		MCT8/*SLC16A2* Triiodothyronine transporter	High T3,low T4 and TSH (Allan Herndon-Dudley syndrome	T3 analogues	Not included in Ferreira's nosology
III.2 Cytoplasmic energy defects	**Diagnosis is generally easy to suspect on a clinical basis and function tests in Glycolysis, and Glycogen defects and on brain H-NMR spectroscopy for creatine defects**				
	Glycolysis and Pentose Phosphate Pathway defects	All enzymes	Hemolytic anemia		**C-Disorders of Carbohydrates** 49-Disorders of the pentose phosphate pathway and polyol metabolism

TABLE 1 (Continued)

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
					53-Disorders of glycolysis
	Glycogen defects Synthesis and catabolism	(See complex molecules storage)	Glucose, lactate, Ketone Bodies, Creatine Kinase, uric acid	Special diet Corn starch	**C -Disorders of Carbohydrates** 51-Glycogen storage diseases 52-Disorders of gluconeogenesis Glucose-6-phosphatase deficiency
	Creatine defects	Creatine synthesis Creatine transport	Low plasma creatine low urinary creatinine low brain creatine peak (NMR spectro.)	Creatine	**A-Disorders of nitrogen-containing compounds**: 4-Disorders of creatine metabolism:
	Insulin disorders	Insulin secretion Insulin signaling	Glucose,lactate,KB NH3,AA,OA Insulin, peptide C	Glucagon Diazoxide Octreotide Surgery	**C-Disorders of carbohydrates** 50-Disorders of insulin secretion and signaling
III.3 Mitochondrial defects	**Mitochondrial diseases are clinically diverse and can present at any age. They can manifest in a tissue-specific or multisystemic manner, but most often affect organs with the highest energy demands such as brain, skeletal muscle, eyes and heart.**				
General oxidative metabolism: ability to generate energy components of the TCA cycle and PDC that feed into OXPHOS Thiamine (for oxdative decarboxylation), Biotin (for carboxylation) Riboflavin (for mitochondrial FA oxidation) are crucial cofactors in these processes	Fatty acid oxidation	Carnitine cycle β- oxidation defects Tango II MAD deficiency Riboflavin defects	Function tests Carnitine, AAC, OAC, Acylcarnitines Enzyme/molecular	Diet Carnitine Riboflavin	**E-Disorders of lipids**: 82. Disorders of carnitine metabolism 83. Disorders of fatty acid oxidation and transport **B-Disorders of vitamins, cofactors, metals and minerals**: 30-Disorders of Riboflavin metabolism
	Ketones metabolism	Ketogenesis Ketolysis	Anion Gap, Ketone bodies	Special Diet	**E-Disorders of lipids** 84-Disorders of ketone bodies metabolism
	Pyruvate/lactate oxidation	PC, PDC, MPC Thiamine defects Biotin defects	Lactate, pyruvate, amino acids, ketone bodies, organic acids, acylcarnitines	Special Diet	**D-Mitochondrial disorders of energy metabolism** 54. Disorders of pyruvate metabolism **C -Disorders of carbohydrates** 52-Disorders of gluconeogenesis: pyruvate carboxylase deficiency **B-Disorders of vitamins, cofactors, metals and minerals**: 29-Disorders of thiamin metabolism 28-Disorders of biotin metabolism
	Krebs cycle		Lactate, organic acids	None	**D-Mitochondrial disorders of energy metabolism**

TABLE 1 (Continued)

CATEGORIES Simplified classification	GROUPS OF DISORDERS	MAIN DISORDERS	DIAGNOSTIC TESTS	TREATMENT	CATEGORIES /GROUPS Updated Nosology[3]
					55. Disorders of the Krebs cycle
Respiratory chain (About 290 genes registered so far classified in 5 general categories according to Frazier[13] Recommendations for optimal diagnosis and treatment of this large evolving group are constantly reevaluated[13,14]	OXPHOS subunits, assembly factors and electron carriers mtDNA maintenance mtDNA expression mtaminoacyltRNA synthetases enzyme cofactors mitochondrial homeostasis and quality control	About 190 of the mitochondrial disease genes fall into one of these categories, with a primary role in OXPHOS biogenesis Pathogenic mutations have been reported in all 37 mtDNA genes and all tRNAsynthetases (19 genes)	Blood ,urines and CSF biochemical testing DNA testing (several strategies) Pathology and biochemical testing in tissues including functional assays (muscle and or liver biopsy, leukocytes, fibroblasts Neuroimaging	Only few are treatable so far: Vitamins CoQ …	**D-Mitochondrial disorders of energy metabolism** 58-68 Disorders of complex subunits and assembly 69-Disorders of mitochondrial DNA depletion, multiple deletion, or intergenomic communication 70-Disorders of mitochondrial transcription and RNA transcript processing 71-Mitochondrial ribosomopathies 72.-Disorders of mitochondrial translation factors 73-74 Disorders of mitochondrial tRNA 75-76 Disorders of mitochondrial fission and fusion 77-Disorders of mitochondrial phospholipid metabolism 78-80.Disorders of mitochondrial protein import quality control and homeostasis 81. Primary CoQ10 deficiencies **B-Disorders of vitamins, cofactors, metals and minerals** 25-Disorders of lipoic acid and iron–sulfur metabolism 29-Disorders of thiamine metabolism **D-Mitochondrial disorders of energy metabolism** 57. Disorders of mitochondrial carriers

Abbreviations: AA, Amino acid; AAC, Aminoacid chromatography; ADA, Adenosine deaminase; PNP, Purine nucleoside phosphorylase; BCAA, Branched chain amino acid; BCKDH, Branched chain keto acid dehydrogenase kinase; BMT, Bone marrow transplantation; CDG, Congenital disorder of glycosylation; CSF, Cerebrospinal fluid; DHA, Docosahexanoic acid; L-DOPA, 3,4 dihydroxyphenylalanine; EI, Exercise induced; ERT, Enzyme replacement therapy ER, Endoplasmic reticulum; FA, Fatty acid; FALDH, Fatty aldehyde dehydrogenase (deficient in Sjogren Larsson syndrome) FAR, Fatty acid oxidoreductase; GABA, gamma butyric amino acid; GAG, Glycosaminoglycans; Gal1P, Galactose-1-phosphate; GALT, Galactasose-1-phosphate uridilyltransferase; GPI, Glycophosphatidyl inositol; GSD, Glycogen storage disease; HFI, Hereditary fructose intolerance; IET, Isoelectrofocusing of transferrin; IVA, Isovalericacidemia; L-2-OH, 2 hydroxyglutaric aciduria; LPC, lysophosphatidyl choline; LPI, Lysinuric protein intolerance; MAD, multiple acylCoA dehydrogenase; MMA, Methylmalonicaciduria; MPS, mucopolysaccharidosis; MRI, Magnetic resonance imaging; MSUD, Maple syrup urine disease; mtDNA, mitochondrial DNA; mTOR, mechanistic target of rapamycin; NAXE, NADH Epimerase; NBIA, Neurodegeneration with brain iron accumulation; NLSD, Neutral lipid storage disease; NMR, Nuclear magnetic resonance; OAC, organic acid chromatography; OA, Organic acidurias; OAC, Organic acid chromatography; OAT, Ornithine amino tranferase; OXPHOS, Oxydative phophorylation; PA, Propionic acidemia; PDC, Pyruvate decarboxylase complex; PH, primary hyperoxaluria; P-ins, phosphatidyl-inositides; PL, phospholipids; PKU, Phenylketonuria; PZO, Peroxysome defect; RBC, red blood cell; SLS, Sjogren Larsson syndrome SRT, Substrate reduction therapy; T3, Triiodothyronine; TCA, Tricarboxylicacic cycle; tRNA, transfer RNA Tyr, Tyrosinemia; ULCFA, Ultralong chain fatty acid; VLCFA, very long chain fatty acids.

vitamin supplements (vitamin dependency). By contrast, some other vitamin-responsive defects linked to the absorbtion, or transport of the vitamin or its precursor—such as secondary niacin deficiency due to tryptophan malabsorbtion in Hartnup disease, folate deficiency in FOLR defects, or thiamine, riboflavine transport defects—are characterized by low vitamin plasma (or CSF) levels and respond to physiological doses of vitamin (vitamin deficiency). However, most of these IMD affecting vitamin metabolism may turn out as intoxication disorders. For example, both B12 malabsorbption and intracellular cobalamin defects lead to homocysteine and methylmalonic acid (MMA) accumulation.

Furthermore, the elevation of one specific neutral AA like phenylalanine in PKU or leucine in maple syrup urine disease can result in secondary transport defect of other essential AA. This observation has been used to treat PKU.[21]

Hyperglycinemias and dopamine transporter defect (accumulation of homovanillic acid in the synaptic cleft) behave more as neurotransmitter disorders and signaling molecules than as intoxication (see later). In fact, in the brain, molecules that accumulate can behave as signaling molecules that activate biological pathways related to neuronal plasticity, excitability and survival.

3.1.2 | Deficiency of small molecules

Symptoms result primarily from the defective synthesis of compounds that are distal to the block or from the defective transport of an essential molecule through cellular or organelle membranes. Clinical signs are, at least in theory, treatable by providing the missing compound. Most of these defects affect neurodevelopment, have a congenital presentation (antenatal), and may present with birth defects. They share many characteristics with disorders from the complex molecules group (see later).

This group encompasses all carrier defects of *essential* molecules that must be transported through cellular membranes, inborn errors of *non essential AA and FA synthesis* and several pyrimidine disorders that affects the synthesis of cytidine, uridine and thymidine nucleosides and are treatable, like CAD deficiency,[22] or the congenital orotic aciduria. The most paradigmatic IMD linked to brain carrier defects are *SLC7A5* mutations, resulting in the defective transport of branched chain AA (BCAA),[23] and MFSD2A deficiency resulting in the defective transport of essential FA such as docosahexanoic acid (DHA).[24] Interestingly, branched chain dehydrogenase kinase deficiency, which overactivates BCAA oxidation and leads to very low levels of BCAA as in *SLC7A5* mutations, presents with a similarly severe neurodevelopmental disease.[25] Other transepithelial *essential AA transport defects* are linked to mutations in *SLC7A7*[26] and *SLC6A19*,[27,28] which are responsible for lysinuric protein intolerance (lysine and dibasic amino acids) and Hartnup disease (neutral aminoacids with secondary niacin deficiency), respectively. Both diseases display low plasma amino acid levels and may present with postnatal multisystemic manifestations.[29] By contrast, transepithelial *non-essential AA transporter defects* (*SLC3A1, SLC7A9, SLC1A1*) involving cystine, glycine, proline, hydroxyproline, dicarboxylic acids present only with hyperaminoaciduria and remain mostly asymptomatic or with only « local » symptoms (urolithiasis).

Non-essential AA synthesis defects may present also antenatally with neurodevelopmental defects. All severe forms of serine synthesis defects cause Neu Laxova syndrome.[30] Glutamine synthetase[31] and asparagine synthetase[32] deficiencies display an almost complete agyria and clinically manifest as severe congenital epileptic encephalopathies.

FA, either derived from dietary sources or synthesized de novo, can be converted into longer chain FA either saturated, mono- or poly-unsaturated to be further incorporated into complex lipids.[33] Elongases ELOVL5 and ELOVL4 deficiencies cause adult dominant spinocerebellar ataxia, SCA38 and SCA34, respectively.[34,35] Autosomal recessive ELOVL4,[36] and ELOVL1 deficiencies[37] may present early in infancy with neurodevelopmental arrest and ichthyosis similar to Sjogren-Larsson syndrome. FA synthesis/elongation defects share many similarities with peroxysomal very long chain FA catabolic disorders and complex lipid synthesis and remodeling deficiencies (see later). Leukotriene defects are due to deficiencies of an eicosanoid, and the much more common prostaglandin defects are associated with prostaglandin accumulation.

In addition to AA and FA defects, the group of small molecule defects also encompasses *IMD affecting neurotransmitters and metal deficiency.* The manganese transporter deficiency syndrome, caused by *SLC39A8* mutations, displays severe late-onset neurodegeneration with low plasma manganese.[38,39] Copper deficiency syndromes with low plasma copper and ceruloplasmin include Menkes disease related to *ATP7A* mutations affecting a copper transporter, MEDNIK syndrome due to the deficiency of the copper regulator AP1S1[40] and the acetyl-CoA transporter (AT-1) deficiency related to *SLC33A1* mutations.[41] Classic inborn errors of neurotransmitters encompass monoamine transport and synthesis, gamma amino butyric acid (GABA) synthesis and GABA receptor deficiency, glycine cleavage and transport defects and glutamate defects. The diagnosis of monoamine disorders is based on CSF monoamine and neopterin analysis. Glycine and GABA defects are in general detected by means of AA quantification in plasma and urine, and CSF for glycine related disorders.[42]

In summary, most disorders related to small molecule deficiencies produce major neurodevelopmental alterations, thereby leading to severe global encephalopathies where almost all neurological functions are chronically altered. In early-onset presentations, patients display severe psychomotor delays affecting both motor and cognitive milestones. These defects mimic early "non-metabolic" genetic encephalopathies that affect crucial neurodevelopmental functions. For instance, mutations in genes coding for tubulin subunits (*TUBA1A*, *TUBB2B*, *TUBG1*) and molecular motor proteins (*KIF2A*, *KIF5C*, *DYNC1H1*) can produce cortical migration defects and lead to severe complex encephalopathies[43] in a similar way than AA synthesis defects. This is because these small molecules contribute to antenatal brain "construction" in terms of signaling, cytoskeleton guidance, synapse formation and later on in experience-dependent synapse remodeling.[12] Interestingly, late-onset forms present as neurodegenerative disorders, reflecting the different roles of metabolism as the brain ages.

3.2 | Group 2: complex molecules

This expanding group encompasses diseases that disturb the metabolism of complex molecules that are neither water soluble nor diffusible. Such ubiquitous complex molecules are *glycogen, triglycerides, sphingolipids (SPL), phospholipids (PL), bile acids, glycosaminoglycans, oligosaccharides, glycoproteins, glycolipids and nucleic acids.* To this group, we added very long chain FA and cholesterol, although they are simple molecules, because they can be a source of complex molecules, such as triglycerides, glycolipids, PL, SPL and cholesterylesters—the deficiency of which share many clinical similarities with complex lipids.

Other specific circulating complex molecules like coagulation factors, liposoluble vitamins, or hormones synthesized in very specialized endocrine glands can be also classified in this group. However, they display very uniform clinical expression such as hemorragic syndromes, rickets, or adrenal failure and diagnosis is easy to reach. The complex metabolic processes of synthesis and recycling of complex molecules take place in organelles (mitochondria, lysosomes, peroxisomes, endoplasmic reticulum, Golgi apparatus and synaptic vesicles) and most pathways involve several organelles and require protein transporters or vesicles. Congenital disorders of glycosylation and trafficking, processing and quality control disorders belong to this category. In fact, *complex molecule defects exemplify the new paradigm of connections between metabolic pathways and subcellular organelles.* Moreover, multiple pathophysiological mechanisms may be present within a single disease. As an example, *SLC10A7* mutation is a disorder of N-glycosylation giving rise to a biosynthesis defect of glycosaminoglycans and a skeletal dysplasia with amelogenesis imperfecta.[44]

In this group, clinical symptoms are permanent, very often progressive, and independent of intercurrent events, unrelated to food intake. Most diseases do not present with metabolic crises. Similarly to the group of small molecules, there are also two subcategories of complex molecule disorders.

3.2.1 | Accumulation of complex molecules

Catabolism defects lead typically to storage of a visible compound that accumulates in the cytoplasm (eg, glycogenosis, steatosis), or in lysosomes (eg, LSD). They are the most typical and historical group (such as sphingolipidoses, mucopolysaccharidoses or glycoproteinopathies) in which signs and symptoms primarily result from the abnormal accumulation of compound(s) proximal to the block and potentially reverse as soon as the accumulation is removed. In general, there is no antenatal manifestation although, in some severe forms, this is possible such as hydrops or malformations.[45] Neurological presentations display progressive disorders with late-onset neurodegeneration with or without obvious « storage » signs**.** Diagnosis is mostly based on urine screening (mucopolysaccharides, oligosaccharides, sulfatides, sialic acid) and leukocytes enzyme analysis. A growing number of disorders that involve trafficking and autophagy may mimick classical LSD (see below). Intracellular cytoplasmic phosphoglyceride disorders display non-cerebral presentations including hepatic steatosis with hypertriglyceridemia, neutral lipid storage disorders (such as Chanarin Dorfman syndrome), and congenital lipodystrophy with insulin resistance and diabetes and several other tissue specific disorders.[33] Glycogen catabolism defects present with hepatic, muscular/cardiac or cerebral glycogenosis.

3.2.2 | Deficiency of complex molecules

Glycogen depletion syndromes with no visible glycogen are arbitrarily classified like glycogenosis type 0a and 0b (glycogen synthase liver and muscle type, respectively), or linked to *GYG1*/2 mutations encoding for glycogenin.[46] This group is also related to energy depletion.

Phospholipids (PL), glycosphingolipids (GSL) and FA (long, very long, ultra long chain FA) synthesis and remodeling defects represent a rapidly expanding new group.[33,47] PL and GSL synthesis and remodeling defects lead to a variety of progressive neurodegenerative symptoms, myopathy and cardiomyopathy (like in Barth or Sengers syndrome), orthopedic signs (bone and chondrodysplasia, malformation), syndromic ichthyosis, and retinal dystrophy. Phosphatidylinositides (P-ins) are PL synthesized from cytidyl

diphosphate diacylglycerol and inositol, and are highly regulated by a set of kinases and phosphatases. The P-ins 3Kinases are a family of signaling enzymes that regulate a wide range of processes including cell growth, proliferation, migration, metabolism and brain development.[48] Many mutations affecting this system are responsible for neurodevelopment and neurodegenerative disorders such as several congenital ataxias related to mutations in the inositol 1,4,5-triphosphate (IP_3) receptor (IP_3R),[49] or Joubert or MORM syndromes.[50] Overall, given the very short half-life of phosphatidylinositides, there are no easy metabolic marker for these diseases and diagnosis relies on NGS tools.

Peroxisomal disorders encompass a number of molecular defects affecting either the peroxisome biogenesis or a specific matrix enzyme involving the catabolism of very long chain, and branched chain fatty acids (phytanic acid), or complex molecule synthesis like bile acids or plasmalogens. All these defects imply complex lipids and metabolic pathways that are not limited to peroxisomes but rather cross over several other cellular compartments. They should be reclassified as non-mitochondrial FA metabolism in a vast complex lipid category. Many present at birth with a polymalformative syndrome, like Zellwegger syndrome. Others present later between the 1st and 2nd decade of life, or in adulthood, with neurodegenerative disorders (Refsum disease, X-ALD/AMN or a peroxisomal biogenesis defect) very similar to complex lipid synthesis and remodeling defects.[33,47] Plasmalogens synthesis (a subcategory of PL) involve several compartments: not only peroxisomes but also the endoplasmic reticulum (ER). As an example, ACBD5 deficiency disrupts lipid transfer between the ER and the peroximes and produces decreased synthesis of plasmalogens associated with a progressive leukodystrophy with ataxia and retinal distrophy.[51]

Diagnosis is first performed using blood tests measuring VLCFA, phytanic, pristanic and pipecolic acids in plasma, and plasmalogens from erythrocytes. Non-mitochondrial FA homeostasis defects share many similarities with Sjogren-Larsson syndrome or deficiencies in Elongase ELOV1, 4 and 5.

Cholesterol and bile acid synthesis defects present either with polymalformative syndromes—such as in Smith-Lemli-Opitz (SLO) syndrome—, neonatal cholestasis, or with late-onset neurodegenerative disorders—such as cerebrotendinous xanthomatosis treatable by chenodeoxycholic acid.[52] The pathogenesis of sterol disorders is complex and may result from cholesterol deficiency during embryonic development, accumulation of toxic sterol intermediates proximal to each enzymatic block, abnormal feedback regulation, generation of abnormal bioactive oxysterols, and/or abnormal signaling by hedgehog proteins that normally contain bound cholesterol.[53] Diagnosis is first performed using blood tests measuring cholesterol and oxysterols profile. Squalene synthase deficiency is a recently described cholesterol synthesis defect. Patients present with facial dysmorphy (SLO-like), and severe neurological involvement. Plasma cholesterol levels are low but there is also an accumulation of methylsuccinic acid, mevalonate lactone, mesaconic acid and 3-methyladipic acid.[54]

Glycosaminoglycans (GAG) synthesis disorders have been recently reviewed (56) GAGs are constructed through the stepwise addition of respective monosaccharides by various glycosyltransferases and maturated by epimerases and sulfotransferases. GAGs play a wide range of biological activities. Mutations in the human genes encoding glycosyltransferases, sulfotransferases, and related enzymes responsible for the biosynthesis of GAGs do not present with preponderant neurological symptoms. GAG synthesis defects should be suspected in patients with a combination of characteristic clinical features in more than one connective tissue: bone and cartilages (short long bones with or without scoliosis), ligaments (joint laxity/dislocations) and the subepithelium (skin, sclerae). Some of these defects produce distinct clinical syndromes, some share characteristics with CDG. The commonest laboratory tests used for this group of diseases, are molecular testing while analysis of GAGs and enzyme assays are rather for specialized labs and research setting.[55] Oligosaccharide synthesis disorders are classified with congenital disorders of glycosylation (see below).

Finally, nucleic acid disorders are much more than the classic purine and pyrimidine defects if we consider cytoplasmic and mitochondrial tRNA synthetases defects,[56,58] ribosomopathies,[57] diseases affecting mechanisms of DNA/RNA damage reparation such as subtypes of Aicardi-Goutières syndrome and disorders related to DNA methylation (DNAm) such as CHARGE and Kabuki syndromes in which highly specific and sensitive DNAm signatures have been recently identified.[58]

3.2.3 | Cellular trafficking and processing disorders

Congenital disorders of glycosylation (CDG) syndromes have become one of the largest group of IEM CDG should be considered in any unexplained clinical condition particularly in multiorgan disease with neurological involvement but also in non-specific developmental disability.[59] Many CDG interfere with neurodevelopment in the fœtal life, mostly disorders of protein O-glycosylation, lipid O-glycosylation and glycosylphosphatidylinositol.[60] Screening methods are limited to serum transferrin and serum apolipoprotein C-III analysis. Clinical glycomics may confirm to be a very efficient diagnostic system.[61] NGS is increasingly used in the diagnostic workup of patients with CDG-X.

Detailed classification of this vast and complex growing group is beyond the scope of this simplified paper.

Many other defects affecting systems involved in *intracellular vesiculation, trafficking, processing of complex molecules, and quality control processes* (like protein folding and autophagy) can be anticipated. This is illustrated for example by (i) the CEDNIK neurocutaneous syndrome due to mutation in *SNAP 29* coding for a SNARE protein implicated in intracellular vesiculation,[62] (ii) mutations in *AP5Z1* that encodes a protein facilitating specialized cargo sorting in vesicular-mediated trafficking, causing hereditary spastic paraplegia, and the cellular phenotype of which bears striking resemblance to features described in a number of LSDs,[63] (iii) mutations in *CHMP2B* and *GRN*, which encode the charged multivesicular body protein and progranuline, respectively, are characterized by neuronal lysosomal storage pathology presenting with familial frontotemporal dementia,[64,65] (iv) similarly, a single point mutation in *ZFYVE20* coding for Rabenosyn-5 (with evidence of defective endocytotic trafficking) presents with a complex phenotype including intractable seizures.[66] Congenital disorders of autophagy are another emerging class of IMD presenting as complex neurometabolic disorders like SENDA or Vici syndrome.[67,68] These new defects, all identified by NGS without obvious metabolic markers, raise the question of a broader definition of LSDs with the accumulation of indigestible material in the endosomal/lysosomal system.

Synaptic vesicle cycle disorders form a new group of IMD that has been very recently individualized (72) The synapse is a highly specialized cell junction that connects a presynaptic transmitting neuron with a postsynaptic receiving neuron. The concept of « synaptic metabolism » has been recently introduced and could be defined as the specific chemical composition and metabolic functions occurring at the synapse.[12] The synaptic vesicle (SV) is an independent complex and specialized organelle. Vesicular glycolysis was recently discovered to be capable of providing a constant intrinsic source of energy, independent of mitochondria, for the rapid axonal movement of vesicles over long distances.[69] Mutations coding for many different proteins that regulate the SV exocytic-endocytic pathway have been described as responsible of a variety of disorders that share general characteristics of complex molecule disorders.[70,71] In particular, trafficking, intracellular vesiculation, chaperon proteins (folding, unfolding and disaggregation), protein-protein, protein-lipid, and lipid-lipid interaction compose the main mechanisms of this group of diseases.[71]

Aminoacyl tRNA synthetases deficiencies compose a group of already more than 30 disorders With the exception of GARS and KARS, mitochondrial and cytoplasmic aaRSs are encoded by distinct nuclear genes.[72,73] Aminoacyl-tRNA synthetases deficiencies present with a broad clinical spectrum with many neurological phenotypes. Mitochondrial aaRSs deficiencies may mimick OXPHOS disorders with hyperlactatemia.[74] Diagnosis should be facilitated by aminoacylation assays as shown recently for patients with *LARS2* and *KARS* mutations.[75] Mutations in *KARS* and *GARS*, which act in both the mitochondria and the cytosol, as well as several cytosolic aminoacyl tRNA synthetases open a new field of IMD since cytoplasmatic tRNA synthetases are necessary for all proteins of the cell and therefore all organelles. The same occurs for other factors related to cytoplasmatic protein synthesis (eg, regulatory factors like EIF2AK3, etc.), nuclear factors related to gene expression and splicing.

3.3 | Disorders involving primarily energy metabolism

These consist of IMD with symptoms due, at least in part, to a deficiency in energy production or utilization within the liver, myocardium, muscle, brain, and other tissues. Diagnosis can be orientated by functional tests measuring glucose, lactate, ketones and other energetic molecules (AA, organic acids, acylcarnitines) in blood, CSF and urines and confirmed by enzyme assays and molecular testings. Energy-generating processes are master regulators of cell life. In particular, the mitochondrion is both origin and target of several metabolic signals which orchestrate cellular function and homeostasis. Mitochondrial diseases are the most common group of IMD and are among the most common forms of inherited neurological disorders. Mitochondrial medicine has largely developed to the extent of becoming a subspecialty of IMD. Because of its complexity, we will just briefly highlight the basic subgroups and core concepts related to energy metabolism (Table 1 part III).

3.3.1 | Membrane carriers of energetic molecules

Glucose, lactate, pyruvate and ketone bodies are the most important molecules involved in energetic carrier defects. The solute carrier (SLC) *SLC2* and *SLC5* gene families encode glucose carriers, GLUT and SGLT, respectively, while the *SLC16* gene family encodes for monocarboxylate transporters (MCT) for FA, ketone bodies, and monocarboxylic acids.[85,86] GLUT and MCT display many tissue specific isozymes such as GLUT1 (the glucose cerebral transporter),[76] GLUT2 (the glucose hepato-intestinal transporter) or MCT1[77] (Table 1 III.1).

3.3.2 | Cytoplasmic energy defects

They are generally are generally less severe. They include *glycolysis, glycogen metabolism, gluconeogenesis, hyperinsulinism*, which are all treatable, *creatine metabolism* disorders, which are partially treatable, and inborn errors of the

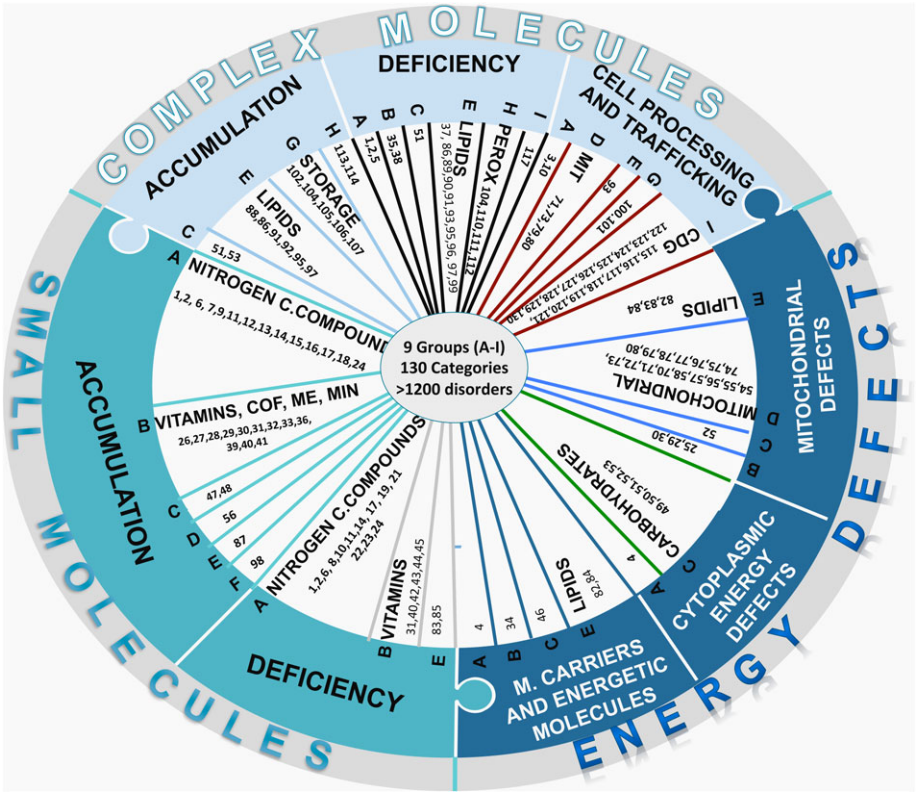

FIGURE 2 Connection map between the simplified classification and the IMD updated nosology. A, NITROGEN containing compounds; B, VITAMINS, cofactors, metals, minerals; C, CARBOHYDRATES; D, MITOCHONDRIAL disorders; E, LIPIDS; F, TETRAPYRROLES; G, STORAGE disorders; H, PEROXISOME and oxalate; I, CDG

pentose phosphate pathways, untreatable, with a phenotype mostly linked to defective NADP/NADPH production.[78] Diagnosis is generally easy to suspect on a clinical basis plus functional tests in glycolysis, and glycogen defects, and on urine creatine/creatinine ratio and brain ^{1}H-NMR spectroscopy for creatine defects.

3.3.3 | Mitochondrial defects

They encompass aerobic glucose oxidation defects presenting with congenital lactic acidemia (pyruvate transporter, pyruvate carboxylase, pyruvate dehydrogenase system, and Krebs cycle defects), mitochondrial respiratory-chain disorders, mitochondrial transporters of energetic and other indispensable molecules, coenzyme Q biosynthesis, FA oxidation, and ketone body defects. Some of thiamine and riboflavin defects may also be included in this group given that these vitamins serve as cofactors for oxidative decarboxylation and fatty acid beta-oxidation, respectively. A large and growing group of already >110 disorders involves the mitochondrial machinery (mitochondrial fusion, fission, replication, mitochondrial protein import and protein quality control, ribosomopathies, mitochondrial DNA depletion and intergenomic modification, mitochondrial tRNA synthetases and tRNA modification, and phospholipid membrane metabolism).[13] Mitochondrial diseases are clinically diverse and can present at any age. They can manifest in a tissue-specific or multisystemic manner, but most often affect organs with the highest energy demands such as brain, skeletal muscle, eyes and heart. About 290 genes registered so far are classified in five general categories according to Frazier et al.[13] Recommendations for optimal diagnosis and treatment of this large evolving group are constantly reevaluated.[13]

4 | DISCUSSION AND CONCLUSION

The oversimplified classification proposed here does not pretend to take into account the diversity of cellular biology nor the totality of disorders listed in the updated nosology. Likewise, the pathophysiology based on distinction between disorders with an accumulation vs a deficiency of compounds is not always clear. Both accumulation and deficiency may coexist in a single disease like for example in cholesterol synthesis or purines/pyrimidines defects.

The connection map between our three categories and the nine groups from the nosology classification allows to highlight several main « Highways » (Figure 2): (1) Group1 (small molecules) is strongly linked to A (nitrogen compounds), B (vitamin, metals and cofactors), and also F (tetrapyrroles) and C (carbohydrate) but not to groups D (mitochondrial disorders) and I (CDG). (2) By contrast group 2 (complex molecules) is strongly linked to G (storage disorders), E (lipids), I (CDG) and H (peroxisome) but also with A and D, while there is almost no connection with B. (3) Group 3 (energy) is strongly correlated to D (mitochondrial) and with C and E.

Rather than analytical approaches focusing only on genotype-phenotype correlations, this classification claims for exploring pathophysiological mechanisms based on an integrated approach that takes into account changes in metabolic pathways and substrates. In this respect, our simplified classification highlights the increasing relevance of complex molecules in the whole scenario of IMD. They contribute to explain the interconnection between cellular organelles and open new windows of differential diagnosis in complex neurological and multisystem presentations. In fact, in those clinical pictures we should now consider not only the « classical groups » of lysosomal, mitochondrial, peroxisomal and CDGs, but also disorders of autophagy, vesiculation, trafficking, complex lipid synthesis and remodeling defects, among others. Accordingly, this underscores the need for maintaining and further developing a strong capacity for metabolic investigations in biochemical genetic labs (eg, metabolomics, lipidomics) besides their increasing access to NGS. Indeed, metabolomics and lipidomics stand out among omics as the study of the end products of cellular processes, therefore are more likely to be representative of clinical phenotypes than genetic variants or changes in gene expression.[89]

Many clinical presentations remain difficult to foresee:

1. For example, the deficiency of adenylate kinase 2, an enzyme that is expressed in many tissues, presents with reticular dysgenesia syndrome, severe combined immune-deficiency and sensory neural deafness.[79]
2. Clinical consequences of compounds accumulated proximal to an enzymatic block can be unexpected. For example, thymidine accumulation in thymidine phosphorylase deficiency results in impaired mtDNA maintenance with accumulation of multiple mtDNA deletions and mtDNA depletion responsible for MNGIE syndrome. Abnormal accumulation in the fetus of polyols, osmolyte substances implicated in fetal water metabolism is responsible for hydrops fetalis with the oligohydramnios observed in transaldolase deficiency.[80]
3. Ubiquitous dominant activating mutations can lead to unexpected organ specific manifestations like hyperinsulinism associated with hyperammonemia, or induced by exercise,[87] in glutamate dehydrogenase and monocarboxylate transporter 1, respectively, with apparent clinical consequences in pancreatic beta cells only.[81]
4. Some mitochondrial enzymes such as those implicated in the urea synthesis (carbamyl phosphate-synthetase I, ornithine-transcarbamylase, glutamate dehydrogenase) are regulated by sirtuins (SIRT), proteins that are induced by nutritional state (protein intake, fast, catabolism) and able to activate these enzymes through an acetylation/deacetylation process. *SIRT3* and *SIRT5* mutations could be responsible for hyperammonemia without defects of the urea cycle enzymes, although it has never been observed in human so far.[82] SIRT4, a lysine deacylase, has been recently found to control leucine metabolism at the methylcrotonyl carboxylase step and insulin secretion.[83]
5. Finally, an increasing number of adult-onset IEM has now been recognized, as new metabolomics and molecular diagnostic techniques have become available. Mechanisms underlying pediatric vs adult phenotypic differences are numerous and still not well understood. Indeed, the phenotype is the net sum of hereditary and environmental factors. It depends on phenotypic plasticity (modulations in response to changes in the environment) and is age-dependent (ontogenic changes and aging). A greater understanding of phenotypic variability will be critical to personalize, or at least weigh in, the initiation of long-term, sometimes burdensome, therapies in diseases detected by expanded newborn screening but that can manifest only in adulthood.[84]

To conclude, this simplified classification aims to provide basic and practical rules to orientate the clinical thinking in an increasingly complex field. Nowadays, physicians are faced with a rapidly growing number of new diseases and pathophysiological categories that challenge our previous knowledge. However, large amounts of information do not necessarily imply a better understanding. In fact, there is a risk of being lost in exhaustive lists of genes and diseases unless they are associated to a structure that links both clinical signs and pathophysiology. Although every disease is unique in terms of clinical peculiarities, specific signs, and natural history, similar pathophysiological mechanisms tend to have similar spectrum of symptoms. Therefore there is a necessity of combining both in-depth knowledge of individual diseases with an integrative overview, in order to understand the global interconnected field of IMD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

Author contributions

J.M.S. has contributed the original idea and is the intellectual author of the article. A.G.C. has contributed to the neuropaediatric and neurobiological aspects, and together with J.M.S. have drafted, conducted and supervised the

manuscript. F.M. and F.L. provided informations on adult neurometabolic presentations and complex lipids classification respectively and contributed to the criticism, discussions and revision of the manuscript.

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