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### Title

An international classification of inherited metabolic disorders (ICIMD).

### Permalink

<https://escholarship.org/uc/item/60p0p666>

### Journal

Journal of inherited metabolic disease, 44(1)

### ISSN

0141-8955

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### Publication Date

2021

### DOI

10.1002/jimd.12348

Peer reviewed



# HHS Public Access

Author manuscript

*J Inherit Metab Dis.* Author manuscript; available in PMC 2022 April 21.

Published in final edited form as:

*J Inherit Metab Dis.* 2021 January ; 44(1): 164–177. doi:10.1002/jimd.12348.

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## An International Classification of Inherited Metabolic Disorders

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## Abstract

Several initiatives at establishing a classification of inherited metabolic disorders have been published previously, some focusing on pathomechanisms, others on clinical manifestations, while yet another attempted a simplified approach of a comprehensive nosology. Some of these classifications suffered from shortcomings, such as lack of a mechanism for continuous update in light of a rapidly-evolving field, or lack of widespread input from the metabolic community at large. Our classification – the International Classification of Inherited Metabolic Disorders, or ICIMD – includes 1,450 disorders, and differs from prior approaches in that it benefited from input by a large number of experts in the field, and was endorsed by major metabolic

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Details of the contributions of individual authors:

Carlos Ferreira, Shamima Rahman and Johannes Zschocke contributed pertinent aspects of the planning, conduct, and reporting of the work described in this article. Markus Keller has been active member of the ICIMD advisory group, created the sunburst chart – which included software programming to position fields according to the classification structure, not size –, and had a lead function in the creation of the website. All authors reviewed the manuscript and classification structure at various stages and consented to the final manuscript.

Conflict of Interest:

Carlos Ferreira, Shamima Rahman and Johannes Zschocke declare that they have no conflict of interest.

Informed Consent:

This article does not contain any studies with human or animal subjects performed by any of the authors.

societies around the globe. Several criteria such as pathway involvement and pathomechanisms were considered. The main purpose of the hierarchical, group-based approach of the ICIMD is an improved understanding of the interconnections between many individual conditions that may share functional, clinical and diagnostic features. The ICIMD aims to include any primary genetic condition in which alteration of a biochemical pathway is intrinsic to specific biochemical, clinical and/or pathophysiological features. As new disorders are discovered, we will seek the opinion of experts in the advisory board prior to inclusion in the appropriate group of the ICIMD, thus guaranteeing the continuing relevance of this classification via regular curation and expert advice.

## Introduction

The first attempt at classifying inherited metabolic disorders dates back to 1960, with the publication of the first edition of “The metabolic basis of inherited disease” (Stanbury et al. 1960). In that book, ten groups of disorders were defined, affecting the metabolism of carbohydrates, amino acids, lipids, steroids, purines and pyrimidines, metals, porphyrins, blood and blood-forming tissues, renal tubular transport, and plasma proteins, respectively. Several classification systems have been proposed since then, including a classification based on pathomechanisms, in four groups affecting transport, scavenging and secretion, synthesis, and intermediary metabolism, respectively (Sinclair 1982). A clinical classification is also available, dividing disorders into those involving single organ systems versus multisystemic presentations, the latter in turn subdivided into disorders of complex molecules, intoxication disorders, and energy deficiency disorders (Saudubray and Charpentier 2014). A hierarchical classification was established by the Society for the Study of Inborn Errors of Metabolism (SSIEM), with groups of disorders assigned according to the specific biochemical pathway involved (Zschocke 2014). A recently proposed nosology included greater than one thousand well-established diseases and more than 100 provisional ones, divided in 130 groups (Ferreira et al. 2019). A practical simplification of this nosology was subsequently suggested (Saudubray et al. 2019).

Why should one bother about structured disease classification at a time of complex electronic databases that allow easy access to, and plenty of interconnections between, a large number of entries? The primary aim of any classification is probably to structure one’s thoughts and approach in order to improve our understanding of large datasets. This is the reasoning behind the “International Classification of Inborn Metabolic Disorders” (ICIMD) presented here. It groups almost 1500 monogenic diseases whose underlying pathophysiology may be regarded as “metabolic” into a hierarchical structure that can serve as a basis for didactic purposes (including textbooks and seminars), electronic resources, other existing disease databases, patient registries, rare disease initiatives, and many other purposes. For registration of affected individuals and epidemiological studies it is very important to adhere to a uniform classification. An ontological system makes it much easier to understand and remember individual conditions through the knowledge of the common clinical features and diagnostic strategies for whole groups of disorders. The primary benefit of an ICIMD thus should be for teaching, understanding and clinical decision making with regard to inherited metabolic disorders. Given this, the target audience for this classification remains the group of physicians and researchers already working in the field of metabolism,

although practitioners in other fields might benefit as well; for example, we include approximately 70 disorders of neurotransmission and 50 endocrine metabolic disorders, the hierarchical inclusion of which could prove useful to neurologists and endocrinologists, respectively.

Starting with a kick-off meeting at the Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM) in Athens 2018, the strategy was to combine knowledge and opinions from a large number of stakeholders throughout the world and to seek endorsement by international professional societies. The proposed ICIMD was to be combined with existing databases and nosologies. A classification is irrelevant if there is no strategy for long-term maintenance, e.g., through support of the international scientific community. A broad process with general consensus, authorization and maintenance by international societies worldwide, was regarded as the best way to create a useful and lasting structure. The result of this process is presented here.

## Methods

### Definition of “inherited metabolic disorders”

We opted to use the nomenclature “inherited metabolic disorders”. Here, we use the term inherited to account for traits that have a *defined (or assumed) primary genetic cause*, regardless of whether the genetic material was inherited from a parent or appeared *de novo*. In the great majority of cases, these traits are also inborn, meaning they are present at the time of birth. However, in rare occasions we decided to also include somatic diseases, either when they can be associated with abnormalities in standard biochemical tests (as is the case with somatic mutations in *IDHI* [isocitrate dehydrogenase 1] leading to D-2-hydroxyglutaric aciduria), or when these diseases lead to clinical manifestations commonly encountered by metabolic physicians (such as for example in the setting of hyperinsulinism caused by somatic activating mutations in *AKT2* [AKT serine-threonine kinase 2]). The term “mutation” is used in this manuscript for genetic variants that have confirmed clinical consequences.

What defines metabolism? We decided to use an inclusive approach, covering any condition in which *primary alteration of a biochemical pathway is intrinsic to specific biochemical, clinical and/or pathophysiological features*, regardless of whether there are abnormalities in currently available biochemical laboratory tests (Morava et al. 2015).

We abstained from using the term “errors” in order to avoid negative connotations. The choice between diseases and disorders was somewhat more nuanced. The rather broad term “disorder” describes basically any deviation from normal physical function, whereas “disease” is usually thought to make assumptions about the causation of a clinical phenotype, in line with the notion, for example, of histidinaemia as a “non-disease” as lack of histidine ammonia-lyase has no known health consequences. However, the clinical consequences of some “diseases” are unclear or unproven (as is the case with *ACSF3* [Acyl-CoA Synthetase Family Member 3] deficiency causing combined malonic and methylmalonic aciduria, Levtova et al. 2019), whereas some apparently harmless traits may have clinical effects under specific conditions. Thus, basing the term “disease” on

purely clinical criteria is difficult. Another approach to the terms “disease” and “disorder” focuses on the knowledge of the specific aetiology of a condition. In this concept, any disturbance of the body’s normal homeostatic processes with a defined cause (such as mutations in a particular gene) is denoted a “disease”, whereas the term “disorder” is used for a more general functional abnormality that does not have a single precise cause. The metabolic syndrome, for example, is a disorder, not a disease. We have decided to combine these definitions for the ICIMD. In this context, “diseases” are defined as disturbances of metabolic functions that (a) are clinically significant, i.e., cause clinical symptoms and signs at least in certain circumstances, and (b) have a defined cause or pathogenesis, which in the context of the ICIMD mostly equates to known or presumed altered function of a single gene product. The term “disorder” covers any type of metabolic alteration, regardless of the cause or association with clinical manifestations.

In summary, the ICIMD aims to include any metabolic condition as defined above, *irrespective of its clinical consequences*. In the vast majority of cases the entries represent enzyme deficiencies caused by reduced function mutations in single genes, although some conditions are caused by activating mutations or by structural genomic alterations (e.g., in the mitochondrial genome).

### Method of generating the ICIMD

We chose certain criteria when designing our classification system. Different degrees of disease severity were considered as a single entity, and not broken down into subtypes. In cases of locus heterogeneity (multiple genes associated with the same phenotype) the involvement of each gene product was considered as the basis for inclusion. This has consequences for the nomenclature, as in these cases, diseases are named by the causative gene product, not by their clinical presentation. This is particularly relevant for the syndromic mitochondrial disorders. For example, the disease entity “mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes” (MELAS syndrome) is not listed in the ICIMD as such but rather by several mt-DNA encoded transfer RNA (tRNA) and respiratory chain subunits deficiencies. Leigh syndrome, the most frequently observed phenotype of mitochondrial disease in childhood, may be caused by approaching 100 different monogenic disorders involving mtDNA-encoded and nuclear genes (Rahman et al. 2017). Future revisions of the ICIMD may develop a system of including specific phenotype descriptions associated with variants in several genes in an ontological fashion. In cases of allelic heterogeneity (multiple phenotypes associated with the same gene), different pathomechanisms were considered necessary for separation into different entries. We decided to include disorders (143 in total) even if they remain provisional, i.e., have only been reported in a single family so far, or have not been confirmed at a molecular level. In many cases, diseases could easily be ascribed to more than one metabolic pathway or group; in such instances (about 10% of all disorders in the ICIMD), we selected the pathway which we judged most appropriate and cross-referenced diseases in the other group(s).

Whenever possible, we attempted to use already established metabolic databases (such as the KEGG Pathway Database) as the default basis for the ICIMD, but adapted it for clinical purposes where necessary. For example, the KEGG database (Kanehisa and Goto 2000) lists



the citric acid cycle under the category of carbohydrate metabolism, whereas we included it under the category of energy substrate metabolism, as this seems more appropriate for clinical and didactic purposes. Similarly, glycerol kinase deficiency has previously been included under the category of “disorders of glycolysis and the pentose phosphate pathway” (Saudubray et al. 2016), or disorders of glycerol metabolism included under the category of lipid disorders (Ferreira et al. 2019) or organic acidurias (McCabe 2019). Although each of the aforementioned approaches had their own rationale (glycerol is a polyol, it is a precursor for the synthesis of triglycerides and glycerophospholipids, and glycerol kinase deficiency can be detected by urine organic acid analysis), we decided to include this enzyme deficiency under the category of disorders of gluconeogenesis. This is because glycerol kinase participates in the conversion of glycerol into a gluconeogenic substrate, and this more easily explains the manifestations of hypoglycemia and metabolic acidosis seen in glycerol kinase deficiency. This example emphasizes once more our pursuit towards a clinical and didactic goal for the ICIMD.

A representative advisory group was established which included experts involved in previous classifications, senior members of international metabolic societies, metabolic journal editors, and others based on known expertise in specific disorders. They were asked to provide input on delineation of disorder groups at the initial stage of development, as well as to review entries in all groups towards the final stage of development of the ICIMD. Endorsement of the final classification was obtained from the elected representatives of all international metabolic societies.

## Results

The ICIMD includes 1,450 disorders divided in 24 categories comprising 124 groups (see figure 1). The full database can be viewed at [www.icimd.org](http://www.icimd.org). The first 13 categories comprise the *disorders of intermediary metabolism*. For the purpose of this classification, we defined intermediary metabolism as follows:

- a. the full set of reactions that transform nutritive material into energy storage compounds, reducing equivalents, and biosynthetic intermediates;
- b. the metabolites involved in these reactions are required to be of low-molecular weight, thus excluding macromolecules; and
- c. it is circumscribed to anabolism/catabolism of nutrient small molecules (excluding non-nutrient ones).

In other words, disorders of intermediary metabolism involve pathways that mediate the breakdown of low-molecular weight nutrient compounds belonging to one of the three major energy substrates (proteins, carbohydrates, and lipids) or convert them into substrates for the biosynthesis of complex molecules. Intermediary metabolism in the definition used here includes energy metabolism based on mitochondrial oxidative phosphorylation which covers categories 5–11 in the ICIMD. We have loosely followed the “rational genetic classification” of mitochondrial disorders originally proposed by Salvatore DiMauro (DiMauro 2011). This progressively evolved over the years with the discovery of new classes of mitochondrial disorders affecting mitochondrial DNA (mtDNA) maintenance and gene expression, import,

dynamics, cofactor biosynthesis and quality control. We decided to separate the mtDNA-related from the nuclear-encoded disorders impacting oxidative phosphorylation because of differences in genetic mechanisms, clinical presentation and diagnostic approaches.

Categories 14 and 15 represent *disorders of lipid metabolism and transport*, whereas the *disorders of heterocyclic compounds* (nucleotides and tetrapyrroles) are listed in categories 16 and 17. Categories 18–20 comprise *disorders affecting the metabolism of complex macromolecules and organelles*, they include disorders of glycan metabolism (including the congenital disorders of glycosylation but excluding disorders of glycogen metabolism), the biogenesis and interaction of organelles, and complex molecule degradation (including lysosomal disorders). In contrast to other metabolic classifications and textbooks, the ICIMD does not have a single chapter on peroxisomal disorders as the enzymes in this organelle have rather diverse functions leading to very different clinical presentations. Most peroxisomal disorders affect lipid metabolism and are located in category 14 whereas peroxisomal biogenesis disorders are listed in the respective category 19. Also in that category are the disorders of lysosome-related organelle biogenesis which mostly have a different clinical presentation to the other lysosomal disorders.

*Disorders of the metabolism of cofactors and minerals* (including vitamins and trace elements) are collected in categories 21 and 22. These disorders have the potential to affect multiple aforementioned pathways, as they are necessary for a variety of enzymatic (and sometimes non-enzymatic) reactions. Vitamins and cofactors that are relevant for single pathways only (e.g., coenzyme Q<sub>10</sub> and lipoic acid in mitochondrial disorders) are positioned in the respective group. Finally, disorders of neurotransmitter and endocrine metabolism are provided as *disorders of metabolic cell signaling* in categories 23 and 24.

The categories are as follows:

#### 1) Disorders of amino acid metabolism

This rather large category comprises many of the traditional “metabolic disorders” which are identified by standard “metabolic investigations” such as amino acid and organic acid analysis and are often amenable to dietary treatment. Deficiencies of enzymes involved in amino acid metabolism frequently result in the accumulation of toxic substances and subsequent organ damage. Acute symptoms are often associated with catabolic states that lead to the breakdown of endogenous proteins. Most groups are based on (common) metabolic pathways of specific amino acids. An exception is the group of the organic acidurias which we define as deficiencies of mitochondrial enzymes required for the breakdown of coenzyme A (CoA)-activated small carboxylic acids mostly resulting from deamination of amino acids. Disorders of amino acid transport are also included here.

#### 2) Disorders of peptide and amine metabolism

This small but diverse category covers deficiencies of enzymes involved in the biosynthesis and regeneration of glutathione, as well as dipeptidase deficiencies and disorders of methylamine and polyamine metabolism.

### 3) Disorders of carbohydrate metabolism

This category includes the disorders of galactose and fructose metabolism; gluconeogenesis, glycogen metabolism, and glycolysis; pentose/polyol metabolism; and hexose transmembrane transport and absorption.

### 4) Disorders of fatty acid and ketone body metabolism

Clinically, mobilisation of stored triglycerides (lipolysis) during fasting results in the hepatic production of ketone bodies which serve as an energy source particularly for muscle and brain, the latter with a high energy demand but a limited ability to oxidise fatty acids. Consequently, this category includes the disorders of mitochondrial fatty acid oxidation, carnitine metabolism, and ketone body synthesis, breakdown and transport.

### 5) Disorders of energy substrate metabolism

The products of amino acid, carbohydrate, and lipid breakdown are transported into the mitochondria where they serve as substrates for adenosine triphosphate (ATP) synthesis by the process of oxidative phosphorylation. We have combined the disorders of pyruvate metabolism and the Krebs cycle as well as creatine metabolism under the term “energy substrate metabolism”; however, pyruvate carboxylate deficiency is positioned in the “disorders of gluconeogenesis” group because of biochemical functional and clinical reasons.

### 6) Mitochondrial DNA-related disorders

The first mitochondrial disorders defined genetically involved deletions and point mutations of the mtDNA. As the mtDNA has a different inheritance pattern to the nuclear genome, and clinical expression of pathogenic mtDNA variants is influenced by mtDNA heteroplasmy, biochemical threshold for the specific variant and its tissue segregation, we have elected to list the 37 mtDNA-encoded genes together as one category. Three groups encompass disorders associated with the 13 protein-coding genes, the genes encoding mitochondrial tRNAs and rRNAs, and the disorders associated with single large-scale mtDNA deletions.

### 7) Nuclear-encoded disorders of oxidative phosphorylation

This category includes deficiencies of nuclear-encoded subunit components as well as assembly factors of the five oxidative phosphorylation complexes, which are generally (although not invariably) associated with isolated deficiency of a single enzyme complex in affected tissue(s).

### 8) Disorders of mitochondrial cofactor biosynthesis

Here we have included disorders affecting the intramitochondrial biosynthesis of the following cofactors: coenzyme Q<sub>10</sub> (ubiquinone), lipoic acid, iron-sulphur clusters and cytochrome *c*. These disorders have been separated out from the main category of vitamin and cofactor metabolism deficiencies because they are expressed exclusively in the mitochondrion.

#### 9) Disorders of mitochondrial DNA maintenance and replication

In this category there are two groups: proteins needed for mitochondrial nucleotide pool maintenance and those essential for mtDNA replication and maintenance.

#### 10) Disorders of mitochondrial gene expression

This rapidly expanding category of now more than 60 conditions includes disorders of mitochondrial transcript processing and modification, aminoacyl-tRNA synthetases and the mitoribosome.

#### 11) Other disorders of mitochondrial function

In this category we have included disorders of mitochondrial shuttles and carriers (with cross-referencing to some mitochondrial carriers that are included elsewhere in our classification), disorders of mitochondrial protein import, disorders of mitochondrial protein quality control, and miscellaneous mitochondrial disorders that do not fit in the above groups, or whose function has not been established conclusively.

#### 12) Disorders of metabolite repair/proofreading

There is a growing number of diseases affecting metabolite repair or proofreading (Veigada-Cunha et al. 2020); enzymes deficient in these conditions do not have a function in a particular metabolic pathway but remove detrimental metabolites generated as side reactions of other enzymes. As the number of these diseases is expected to increase, we felt that they deserve “their own” category.

#### 13) Miscellaneous disorders of intermediary metabolism

In this category we included disorders of glyoxylate and oxalate metabolism as these can derive from a range of metabolites including amino acids (hydroxyproline, glycine, serine), ascorbic acid, and others. In addition, we created a group of unassigned disorders of intermediary metabolism that are difficult to locate in any other group.

#### 14) Disorders of lipid metabolism

For the classification of disorders of lipid metabolism, we tried to follow as closely as possible an already-established and well reputed classification system for lipids, LIPID MAPS® (Fahy et al. 2005, 2009). Thus, we include groups for disorders of the metabolism of fatty acyls (with peroxisomal fatty acid oxidation disorders as a distinct entity), glycerolipids, glycerophospholipids, sphingolipids, and sterol lipids (the latter including sterols and bile acids). Fatty acyls include fatty acids, fatty aldehydes, and eicosanoids. However, we decided to diverge from this previously established lipid classification for didactic purposes, as mitochondrial fatty acid oxidation disorders are better included under intermediary metabolism, glycolipids (glycosylphosphatidylinositol and glycosphingolipids) are included under the category of congenital disorders of glycosylation, and prenol lipids are included as ubiquinones (disorders of coenzyme Q<sub>10</sub> biosynthesis under mitochondrial cofactor biosynthesis in group 8), vitamin E and K are included under other disorders of

vitamin metabolism, and polyprenols in disorders of dolichol metabolism under congenital disorders of glycosylation.

#### 15) Disorders of lipoprotein metabolism

The disorders that affect lipid transport are divided into different groups based on the type of lipid anomalies manifest in the blood, and other functional aspects. They include the hypercholesterolemias, hypertriglyceridemias, mixed hyperlipidemias, disorders of high-density lipoprotein (HDL) metabolism, disorders with decreased low-density lipoprotein (LDL) and/or triglycerides, and other disorders of lipoprotein metabolism.

#### 16) Disorders of nucleobase, nucleotide and nucleic acid metabolism

The disorders of pyrimidine and purine metabolism disorders include disorders in the de novo synthesis, salvage and breakdown of nitrogenous bases, nucleosides and nucleotides. We then added disorders of ectonucleotides and nucleic acids (polymers of nucleotides) as well as non-mitochondrial tRNA and rRNA metabolism.

#### 17) Disorders of tetrapyrrole metabolism

Under this category we include disorders of porphyrins (heme biosynthetic disorders) as well as disorders involving the products of heme breakdown (biliverdin and bilirubin). Although corrin also represents a tetrapyrrole, disorders involving corrin metabolism are discussed elsewhere (as disorders of cobalamin metabolism).

#### 18) Congenital disorders of glycosylation

Many proteins and lipids require the attachment of carbohydrates to render them functional. The Congenital Disorders of Glycosylation (CDG) are divided into disorders affecting N-linked and O-linked protein glycosylation (including glycosaminoglycan synthesis), disorders of lipid glycosylation (including the disorders of glycosylphosphatidylinositol biosynthesis), and disorders with the potential to affect multiple glycosylation pathways (dolichol metabolism, Golgi transport and homeostasis, sialic acid metabolism, and others).

#### 19) Disorders of organelle biogenesis, dynamics and interactions

Disorders that affect the biogenesis and interaction of organelles are usually difficult to link to specific metabolic pathways and often cause diverse clinical manifestations. To address this, we decided to create a separate category which includes disorders of mitochondrial membrane biogenesis and remodelling, mitochondrial and peroxisomal dynamics, peroxisomal biogenesis (the peroxin-related peroxisomal disorders), lysosome-related organelle biogenesis, organelle interplay, and vesicular trafficking.

#### 20) Disorders of complex molecule degradation

This category comprises what is generally known as lysosomal disorders – such as the disorders of sphingolipid, glycosaminoglycan, or glycoprotein degradation and the neuronal ceroid lipofuscinoses – as well as the disorders of autophagy and some other disorders.

#### 21) Disorders of vitamin and cofactor metabolism

Vitamins and cofactors relevant for various metabolic pathways include tetrahydrobiopterin, thiamine (vitamin B<sub>1</sub>), riboflavin (vitamin B<sub>2</sub>), niacin and nicotinamide (vitamin B<sub>3</sub>), pantothenate (vitamin B<sub>5</sub>) and coenzyme A, pyridoxine (vitamin B<sub>6</sub>), biotin (vitamin B<sub>7</sub>), folate (vitamin B<sub>9</sub>), cobalamin (vitamin B<sub>12</sub>), molybdenum cofactor, and others. The cofactors coenzyme Q<sub>10</sub>, lipoic acid and iron-sulphur clusters are grouped under mitochondrial disorders.

#### 22) Disorders of trace elements and metals

We included disorders of the metabolism of copper, iron, manganese, and zinc.

#### 23) Neurotransmitter disorders

The ICIMD contains a specific category of disorders of neurotransmission, given the increased attention and scrutiny that these disorders have encountered in the metabolic community in recent years (Cortès-Saladelafont et al. 2016; Tristán-Noguero and García-Cazorla 2018). Well known “metabolic” neurotransmitter disorders that are recognized by the analysis of cerebrospinal fluid affect monoamines and gamma-aminobutyric acid. This category also includes disorders that affect the neurotransmitter function of specific amino acids (glutamate, glycine) and choline, as well as disorders of the synaptic vesicle cycle.

#### 24) Endocrine metabolic disorders

Our last category highlights the link between some metabolic and endocrine disorders. In this category we included disorders affecting insulin metabolism (because of the overlap with the clinical presentation, e.g., of fatty acid oxidation disorders) and disorders of steroid hormones (derived from sterol lipids).

## Discussion

Classifying a large number of metabolic diseases with a diverse genetic and pathogenic basis and almost any imaginable clinical presentation into a single hierarchical structure is an impossible task and can only be partially achieved, and only then by cutting many corners. The core unit of the ICIMD is the clinical or biochemical phenotype linked to a particular gene that defines a particular “monogenic” condition. The different genetically defined diseases are grouped according to metabolic pathways which usually share pathogenetic mechanisms and often give rise to related clinical presentations and are frequently recognized by the same biochemical-diagnostic strategies. Inherited metabolic disorders may be understood and learned by understanding the functional consequences of disturbances in different biochemical pathways, and identifying the individual disease in a second step. To aid this, we have also mapped ICIMD disorders onto 250 of the 255 inborn errors of metabolism captured in the Virtual Metabolic Human database (VMH.life) (Noronha et al. 2019) as well as to 767 of 3,288 (23%) genes present in the human metabolic reconstruction, Recon 3D (Brunk et al. 2018).

Clearly there are limits to this strategy as the concept of a “monogenic” inheritance pattern is often difficult to maintain. Disease manifestation may depend on more than one particular gene, there may be more than one causative gene for a clinically and biochemically defined condition, or different (e.g., loss-of-function vs. activating) mutations in the same gene may cause very different phenotypes. Nevertheless, there are ways to allow for these exceptions, e.g., by defining gene-based disease subtypes for conditions that may be caused by mutations in more than one gene. If a disease may have quite variable presentation in different patients it is generally regarded as a single condition in the ICIMD, regardless of the spectrum of associated severities.

The main reasoning behind this approach is that within the huge variety of “diseases” linked to specific “clinical presentations”, genes and their associated spectrum of clinical phenotypes are objective natural entities, reflected in, and linking to, many other genetic databases. Also, gene variants have become the main entry point into the diagnosis of rare diseases made by genome-wide sequencing technologies. In the new “reverse Medical Genetics” era, it is essential to understand the spectrum of clinical effects that variants in the same gene may cause. We therefore argue that a gene-/aetiology-centred scaffold logically intertwined with the clinical classification is essential for the success of a disease classification. With the ICIMD we have attempted to create a logical, hierarchical network of specific genes and specific diseases (encompassing clinical spectra and subtypes). In most instances this is a 1:1 relationship, but in some cases there is a 2/3/n:1 or 1:2/3/n relationship. This should not be considered a shortcoming of our classification, as long as classification users are aware of this approach. Genes, proteins or gene functions are part of hierarchical networks or pathways, and the same is true for diseases and disease groups. The presentation of these complex relationships should not constitute a problem, as long as the core units of “genes” and “disease” provide the essential scaffold.

The results presented here clearly represent a “work in progress” which presumably – and hopefully – will never end. For many metabolic pathways most of the “expected” monogenic conditions have by now been identified. However, there is a growing number of “metabolite repair” enzymes that do not function in a particular pathway but remove detrimental metabolites generated as side reactions of other enzymes (Veiga-da-Cunha et al. 2020). There are still more protein-coding genes in the human genome without an associated function or clinical phenotype than known disease-causing genes. Moreover, we have not even started to fully appreciate the range of possible clinical consequences of mutations in non-protein-coding genes. Every month novel inherited metabolic diseases are identified, and it can be expected that additional disease (sub-)groups will need to be created in the future. The ICIMD thus does not represent a fixed structure but the current agreement of a large number of individuals and international organizations which requires continuous discussion and update to make it truly useful.

The classification has been formally endorsed by the Society for the Study of Inborn Errors of Metabolism, SSIEM ([www.ssiem.org](http://www.ssiem.org)), the Society for Inherited Metabolic Diseases, SIMD ([www.simd.org](http://www.simd.org)), the Latin American Society of Inborn Errors of Metabolism and Neonatal Screening, SLEIMPN ([www.sleimpn.org](http://www.sleimpn.org)), the Australasian Society for Inborn Errors of Metabolism, ASIEM ([www.hgsa.org.au/asiem](http://www.hgsa.org.au/asiem)), and the Japan Society of

Inherited and Metabolic Diseases, JSIMD (<http://jsimd.net/>). The ICIMD has also been endorsed by the European Reference Network for Rare Hereditary Metabolic Disorders, MetabERN (<https://metab.ern-net.eu/>), is supported by Orphanet ([www.orpha.net](http://www.orpha.net)) and IEMbase ([www.iembase.org](http://www.iembase.org); Lee et al. 2018), and has been adopted by the Dutch Diagnosis Registration Metabolic Diseases (DDRMD) registry ([www.ddrmd.nl](http://www.ddrmd.nl)). It is also the basis of the latest edition of the Vademecum Metabolicum coat pocket book on the diagnosis and treatment of inherited metabolic disorders (Zschocke & Hoffmann 2020).

We plan to establish and maintain a long-term commission for the continuous revision and update of the ICIMD, linked to the international metabolic societies and other public stakeholders. This will entail the designation of (teams of) group editors who keep track of new developments for individual disease categories or groups, and a general ICIMD commission that confirms suggested extensions and decides on future developments. It is planned to designate two or more group editors for each of the 23 categories – or possibly individual groups – based on their expertise. Group editors will be selected on recommendation of the 75 current members of the ICIMD advisory board, the international societies, organisations and initiatives that support the ICIMD, and any interested person; suggestions can be sent by email to [mail@icimd.org](mailto:mail@icimd.org). The general ICIMD steering group that approves and integrates any changes shall be appointed or endorsed by the participating international societies and organisations. Updates to the ICIMD will be implemented in the dedicated website, [www.icimd.org](http://www.icimd.org), and made available in appropriate forms to the relevant databases such as IEMbase or Orphanet.

We hope that the ICIMD will find a range of uses not just for metabolic specialists but also for clinicians and scientists in associated fields as well as students, junior doctors and other professionals approaching this dynamic area of genetic medicine.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## References

- Brunk E, Sahoo S, Zielinski DC, et al. (2018) Recon3D enables a three-dimensional view of gene variation in human metabolism. *Nat Biotechnol* 36:272–281. 10.1038/nbt.4072 [PubMed: 29457794]
- Cortès-Saladefont E, Tristán-Noguero A, Artuch R, et al. (2016) Diseases of the Synaptic Vesicle: A Potential New Group of Neurometabolic Disorders Affecting Neurotransmission. *Semin Pediatr Neurol* 23:306–320. 10.1016/j.spen.2016.11.005
- Dimauro S (2011) A history of mitochondrial diseases. *J Inherit Metab Dis* 34:261–276. 10.1007/s10545-010-9082-x [PubMed: 20490929]
- Fahy E, Subramaniam S, Brown HA, et al. (2005) A comprehensive classification system for lipids. *J Lipid Res* 46:839–861. 10.1194/jlr.E400004-JLR200 [PubMed: 15722563]
- Fahy E, Subramaniam S, Murphy RC, et al. (2009) Update of the LIPID MAPS comprehensive classification system for lipids. *J Lipid Res* 50 Suppl:S9–14. 10.1194/jlr.R800095-JLR200 [PubMed: 19098281]
- Ferreira CR, van Karnebeek CDM, Vockley J, Blau N (2019) A proposed nosology of inborn errors of metabolism. *Genet Med* 21:102–106. 10.1038/s41436-018-0022-8 [PubMed: 29884839]



- Kanehisa M, Goto S (2000) KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res* 28:27–30. 10.1093/nar/28.1.27 [PubMed: 10592173]
- Lee JY, Wasserman WW, Hoffmann GF, et al. (2018) Knowledge base and mini-expert platform for the diagnosis of inborn errors of metabolism. *Genet Med* 20:151–158. 10.1038/gim.2017.108 [PubMed: 28726811]
- Levtova A, Waters PJ, Buhas D, et al. (2019) Combined malonic and methylmalonic aciduria due to ACSF3 mutations: Benign clinical course in an unselected cohort. *J Inher Metab Dis* 42:107–116. 10.1002/jimd.12032 [PubMed: 30740739]
- McCabe ERB (2019) Disorders of Glycerol Metabolism. In: Valle DL, Antonarakis S, Ballabio A, et al. (eds) *The Online Metabolic and Molecular Bases of Inherited Disease*. McGraw-Hill Education, New York, NY
- Morava E, Rahman S, Peters V, et al. (2015) Quo vadis: the re-definition of “inborn metabolic diseases”. *J Inher Metab Dis* 38:1003–1006. 10.1007/s10545-015-9893-x [PubMed: 26420281]
- Noronha A, Modamio J, Jarosz Y, et al. (2019) The Virtual Metabolic Human database: integrating human and gut microbiome metabolism with nutrition and disease. *Nucleic Acids Res* 47:D614–D624. 10.1093/nar/gky992 [PubMed: 30371894]
- Rahman J, Noronha A, Thiele I, Rahman S (2017) Leigh map: A novel computational diagnostic resource for mitochondrial disease. *Ann Neurol* 81:9–16. 10.1002/ana.24835 [PubMed: 27977873]
- Saudubray J-M, Baumgartner M, Walter J (eds) (2016) *Inborn Metabolic Diseases: Diagnosis and Treatment*, 6th edn. Springer-Verlag, Berlin Heidelberg
- Saudubray J-M, Charpentier C (2014) Clinical Phenotypes: Diagnosis/Algorithms. In: Beaudet AL, Vogelstein B, Kinzler KW, et al. (eds) *The Online Metabolic and Molecular Bases of Inherited Disease*. The McGraw-Hill Companies, Inc., New York, NY
- Saudubray J-M, Mochel F, Lamari F, Garcia-Cazorla A (2019) Proposal for a simplified classification of IMD based on a pathophysiological approach: A practical guide for clinicians. *Journal of Inherited Metabolic Disease* 42:706–727. 10.1002/jimd.12086 [PubMed: 30883825]
- Sinclair L (1982) A new look at the inborn errors of metabolism. *Ann Clin Biochem* 19 (Pt 4):314–321. 10.1177/000456328201900423 [PubMed: 6812485]
- Stanbury JB, Frederickson DS, Wyngaarden JB (1960) *The metabolic basis of inherited disease*. McGraw-Hill Book Company, New York, NY
- Tristán-Noguero A, García-Cazorla À (2018) Synaptic metabolism: a new approach to inborn errors of neurotransmission. *J Inher Metab Dis* 41:1065–1075. 10.1007/s10545-018-0235-7 [PubMed: 30014210]
- Veiga-da-Cunha M, Van Schaftingen E, Bommer GT. Inborn errors of metabolite repair. *J Inher Metab Dis*. 2020;43:14–24. [PubMed: 31691304]
- Zschocke J (2014) SSIEM Classification of Inborn Errors of Metabolism. In: Blau N, Duran M, Gibson KM, Dionisi Vici C (eds) *Physician’s Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases*. Springer Berlin Heidelberg, Berlin, Heidelberg, pp 817–830
- Zschocke J, Hoffmann GF (2020) *Vademecum Metabolicum – Diagnosis and Treatment of Inherited Metabolic Disorders*. 5th Edition. Stuttgart: Thieme



**Figure 1.** Sunburst chart depicting the hierarchical nature of the International Classification of Inherited Metabolic Disorders. The size of each section of the chart is directly proportional to the number of disorders in that group. For an interactive version of the chart incorporating a zoom function, please refer to [www.icimd.org](http://www.icimd.org).