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REVIEW

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The Metabolic Treatabolome and Inborn Errors of Metabolism Knowledgebase therapy tool: Do not miss the opportunity to treat!

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Abstract

Inborn errors of metabolism (IEMs) are rare genetic conditions with significant morbidity and mortality. Technological advances have increased therapeutic options, making it challenging to remain up to date. A centralized therapy knowledgebase is needed for early diagnosis and targeted treatment. This study aimed to identify all treatable IEMs through a scoping literature review, followed by data extraction and analysis according to the Treatabolome principles. Knowledge of treatable IEMs, therapeutic categories, efficacy, and evidence was integrated into the Inborn Errors of Metabolism Knowledgebase (IEMbase), an online database encompassing all IEMs. The study identified 275 treatable IEMs, 18% of all currently known 1564 IEMs, according to the International Classification of Inherited Metabolic Disorders. *Disorders of fatty acid and ketone body metabolism* had the highest treatability (67%), followed by *disorders of vitamin and cofactor metabolism* (60%), and *disorders of lipoprotein*

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metabolism (42%). The most common treatment strategies were pharmacological therapy (34%), nutritional therapy (34%), and vitamin and trace element supplementation (12%). Treatment effects were most commonly observed in nervous system abnormalities (34%), metabolism/homeostasis abnormalities (33%), and growth (7%). Predominant evidence sources included case reports with evidence levels 4 (48%) and 5 (12%), and individual cohort studies with evidence level 2b (12%). Our study generated the Metabolic Treatabolome 2024. IEMs are the largest group of monogenic disorders amenable to disease-modifying therapy. With drug repurposing efforts and advancements in gene therapies, this number will expand. IEMbase now provides up-to-date, comprehensive information on clinical and biochemical symptoms and therapeutic options, empowering patients, families, healthcare professionals, and researchers in improving patient outcomes.

KEYWORDS

ICIMD, IEMbase, IMD, inborn error of metabolism, treatable IEM, Treatabolome

1 | INTRODUCTION

1.1 | Inborn errors of metabolism

Half a century ago, the first dedicated book on treating inborn errors of metabolism (IEMs) was published.[1] Given the rapid therapeutic advancements and digital opportunities, there is a growing need to systematically document and centralize therapeutic strategies for current IEMs in an accessible online format. IEMs represent a complex and heterogeneous group of rare disorders (prevalence <1 per 2000 persons in Europe[2]) stemming from alterations in biochemical pathways, resulting in various clinical manifestations and significant morbidity and mortality.[3] Presently, 1564 recognized IEMs exist, according to the International Classification of Inherited Metabolic Disorders (ICIMD) (June 2024).[4] This number is constantly expanding due to advancement in high-throughput analytical methods, which can elucidate the molecular and metabolic basis of previously undefined conditions.[5] While each disorder is rare on its own, their combined occurrence is significant, with an estimated incidence of 1 in 800–2000 live births.[6–8]

1.2 | Treatment advances

IEMs represent the largest category of treatable genetic disorders and are increasingly amenable to targeted interventions,[4,9–11] offering varying degrees of improvement. The effective management of cystinuria through a protein-free diet in 1905 marked one of the first successful interventions at the metabolic level.[12] Afterwards, diverse medical diets and cofactor treatments emerged, impacting the biochemical pathways for numerous IEMs. Notable therapies for lysosomal storage disease, such as enzyme replacement therapy, have been developed. Furthermore, an expanding array of IEMs now benefit from interventions such as solid organ transplants (i.e., liver and kidney), cell-based therapies such as stem cell transplantation, and targeted small molecules therapies that address subcellular molecular irregularities.[13] Presently, drug repurposing is gaining increasing importance.[14] Gene therapies (e.g., hematopoietic stem cell gene therapy in X-linked adrenoleukodystrophy[15]) and RNA therapies (e.g., volanesorsen in lipoprotein lipase deficiency[16,17]) are emerging as promising therapeutic interventions for patients with IEMs. These multifaceted treatments aim to prevent the onset of disease symptoms, alleviate existing symptoms, maintain disease stability, and slow symptom progression.

Evaluating the effectiveness of these therapies for IEMs is challenging due to limited numbers of patients, geographical dispersion, and clinical diversity.[18] Factors like incomplete understanding of disease progression, absence of validated measures for tracking disease advancement, and financial constraint further complicate treatment assessment.[18,19] Consequently, the evaluation of current therapeutic approaches for most IEMs suffers from a persistently low evidence level.[13,20] Researchers often face hurdles conducting traditional randomized controlled trials (RCTs) and resort to open-label studies, observational studies, and case reports to gather evidence of treatment efficacy.[21]

1.3 | The Metabolic Treatabolome

Due to the progressive character of most IEMs, early recognition and intervention are crucial to prevent irreversible organ damage and lifelong disabilities.[22] However, clinicians and geneticists often struggle to access accurate and timely treatment information when providing diagnoses. Addressing this challenge, we developed a treatment module, centralizing and disseminating up-to-date treatment information. Digital platforms such as Treatable ID (https://www.treatable-id.org/) and IEMbase (http://www.iembase.org/) play a pivotal role by providing clinicians with comprehensive resources, facilitating prompt initiation of treatment.[9,11,23] The Treatable ID app, encompassing 116 IEMs causally linked to intellectual developmental disability (IDD) and amenable to therapy, has been downloaded over 10 000 times, illustrating the widespread interest in accessible treatment-related data.

The European project Solve-RD (solving the unsolved rare diseases) proposed a standardized methodology for conducting systematic literature reviews that contribute to the development of an innovative knowledge base for rare disease treatments.[24,25] The Treatabolome project aims to collect and freely provide information on gene-specific and variant-specific treatments for rare diseases. The process begins by selecting a disease (or disease group) of interest and conducting a systematic literature review to identify published treatments that are specific to genes and variants.[25] We selected IEMs as our disease group and developed our version of the Treatabolome, the "Metabolic Treatabolome," which we integrated into the existing Inborn Errors of Metabolism Knowledgebase (IEMbase) platform.[25] This initiative seeks to facilitate the identification of treatable IEMs for clinicians, and our objective is to provide immediate and readily accessible information on available therapies.

1.4 | Expanding the IEMbase

Rather than establishing a novel database, we have chosen to expand IEMbase with a treatment module. This decision enables us to leverage the existing infrastructure of IEMbase. IEMbase, established in 2018, functions as a centralized repository housing comprehensive knowledge on IEMs.[23,26] Initially focused on providing detailed information on disease names, prevalence rates, gene-related data, nosology codes, Online Mendelian Inheritance in Man references, clinical symptoms, and biochemical markers for known IEMs, IEMbase currently lacks information on treatment options for listed IEMs, so expansion to cover this topic would be advantageous to the global user community.

Rapid diagnosis is pivotal in preventing irreversible damage.[22] Yet, even after diagnosis, clinicians often encounter hurdles in ascertaining treatability, as mentioned in Atalaia et al.[25,27] The evolving treatment landscape adds complexity, necessitating clinicians to stay up to date. Expanding IEMbase provides clinicians direct access to information about available treatment options, reducing potential delays in care.

2 | AIMS AND METHODS

Our overarching goal is to establish the Metabolic Treatabolome. We defined the following aims: (1) To identify which IEMs are treatable; (2) to delineate available treatments and their correlation with human phenotype ontology (HPO) terms regarding their efficacy[28]; (3) to assess the impact of treatment on specific metabolites; (4) to determine the level of evidence supporting the efficacy of the treatment interventions; (5) to reference key studies detailing these treatments; and (6) to integrate these treatment data into the existing IEMbase platform.

The initial plan was to review all conditions listed in IEMbase.[26] However, in 2021, the ICIMD classification was released, and we found this to be the most suitable classification for IEMs to adopt.[4] Consequently, we decided to review all IEMs according to the ICIMD classification.

2.1 | Definition of a treatable IEM

IEMs were categorized based on the ICIMD classification.[4] In the context of a "treatable IEM," "treatable" refers to the availability of a disease-modifying therapy that specifically targets (an aspect of) the underlying genetic or biochemical defect responsible for the disorder, rather than simply managing the resulting clinical symptoms, with the aim of favorably modifying disease course. The "symptoms" represent the clinical manifestations that arise as a result of the underlying dysfunction. This therapy prevents, improves, or slows the disorder's progression, with a positive effect on measurable outcomes, while maintaining acceptable adverse effects (Table 1).

2.2 | Identification of treatable IEMs

We adhered to the Treatabolome principles, ensuring the dataset complies with the findable, accessible, interoperable, and reusable guidelines for easy translation into

TABLE 1 Definitions used in the literature review.

IEM	Any condition in which the dysfunction of a biochemical pathway is fundamental to the disease's pathophysiology, irrespective of the presence of abnormalities in currently available biochemical laboratory tests.[29]
Treatable IEM	A treatable IEM denotes a condition where a therapeutic approach specifically targeting the root cause of the disorder, rather than solely managing symptoms, is capable of preventing, improving, or slowing the decline associated with the IEM phenotype, while maintaining acceptable adverse effects. This targeted therapy aims to positively influence outcome measures.
Treatment strategies	• Enzyme replacement therapy • Gene-based therapy • Nutritional therapy • Pharmacological therapy • Solid organ transplantation • Stem cell therapy • Vitamin and trace element • Other (e.g., hemodialysis)
Levels of evidence[30]	• Level 1a = SR of RCTs and of prospective cohort studies • Level 1b = Individual RCT with narrow confidence interval, prospective cohort study = with good follow-up • Level 1c = All or none studies, all or none case series • Level 2a = SR (with homogeneity) of cohort studies • Level 2b = Individual cohort study • Level 2c = Outcome research, ecological studies • Level 3 = SR of case control studies • Level 4 = Case series/case report, poor quality cohort studies • Level 4–5 = 4, but if only one patient was reported • Level 5 = Expert opinion, bench research

Overarching HPO terms used to describe the phenotypes affected by treatment(s)[28]	• Abnormality of the genitourinary system (HP: 0000119)
	• Abnormality of the head or neck (HP: 0000152)
	• Abnormality of the eye (HP: 0000478)
	• Abnormality of the ear (HP: 0000598)
	• Abnormality of the nervous system (HP: 0000707)
	  ○ Cognitive function/developmental
	  ○ Movement disorder
	  ○ Muscle function
	  ○ Neuropathy
	  ○ Psychiatric/behavior
	  ○ Seizure/epilepsy
	  ○ Sensory deficit
	  ○ Other
	• Abnormality of the breast (HP: 0000769)
	• Abnormality of the endocrine system (HP: 0000818)
	• Abnormality of prenatal development or birth (HP: 0001197)
	• Growth abnormality (HP: 0001507)
	• Abnormality of the integument (HP: 0001574)
	• Abnormality of the voice (HP: 0001608)
	• Abnormality of the cardiovascular system (HP: 0001626)
	• Abnormality of blood and blood-forming tissues (HP: 0001871)
	• Abnormality of metabolism/homeostasis (HP: 0001939)
	• Abnormality of the respiratory system (HP: 0002086)
	• Neoplasm (HP: 0002664)
	• Abnormality of the immune system (HP: 0002715)
	• Abnormality of the digestive system (HP: 0025031)
	• Constitutional symptom (HP: 0025142)
	• Abnormality cellular phenotype (HP: 0025354)
	• Abnormality of the musculoskeletal system (HP: 0033127)

TABLE 1 (Continued)

	• Abnormality of the limbs (HP: 0040064) • Abnormality of the thoracic cavity (HP: 0045027)

Abbreviations: HPO, human phenotype ontology; IEM, inborn error of metabolism; RCT, randomized controlled trial; SR, systematic review.

machine-readable data. The dataset is freely accessible online and has been integrated into the existing IEMbase platform.[25] In line with these principles, we sought to comprehensively review the literature and knowledge bases to identify all IEMs that are treatable according to the mentioned definitions. First, six reviewers (EMMHvK, BdH, CvdM, BMB, CRF, and CDvK) assessed all IEMs listed in ICIMD to determine their treatability status. This was done in steps:

1. IEMs identified in the Dutch newborn screening or scheduled to be added to newborn screening were considered treatable (as this is a requisite to be included in the screening program).[31]
2. The IEMs presenting with intellectual disability and deemed treatable were extracted from the study conducted by van Karnebeek et al.,[11] and the update by Hoytema van Konijnenburg et al.[9]
3. Colleagues from the University Medical Center Groningen recently investigated which IEMs are potentially treatable within the context of IEM candidates for newborn screening.[32] This information was used to classify a subset of the IEMs as treatable.
4. The handbook "Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases 2-nd ed. 2022 Edition" was consulted for the evaluation of treatability among IEMs.[33]
5. For the remaining IEMs, a literature review was performed to investigate whether the remaining IEMs were treatable.

Only treatable IEMs were included in the Metabolic Treatabolome.

2.3 | Literature review and data extraction

For the treatable IEMs, four reviewers (EMMHvK, BdH, CvdM, and BMB) conducted a literature review to identify the available treatment(s), their treatment effect on symptoms classified according to HPO terms, involvement of specific metabolites, and the level of evidence supporting these treatments. This information was systematically documented for each IEM. CRF and CDvK supervised the results of the literature review. The reviewers engaged in regular consensus meetings, and final decisions on any disagreements were reached by a majority vote of the reviewers.

We searched PubMed with no restrictions on publication years, limited to English language and publication in peer-reviewed journals. If only symptomatic treatment was available for an IEM, the IEM was not classified as treatable. For instance, managing pain or controlling seizures without directly addressing the metabolic dysfunction would not be classified as treating the IEM.

CRF and CK were consulted in case of questions or discrepancies between reviewers.

2.4 | Treatments and levels of evidence

The treatments were categorized using generic terms for treatment strategies: (1) nutritional therapy; (2) vitamin and trace element; (3) pharmacological therapy; (4) enzyme replacement therapy; (5) hematopoietic stem cell transplant; (6) solid organ transplantation; (7) gene-based therapy; (8) other (Table 1). Additionally, the specific generic name of each treatment was documented. Levels of evidence were defined and applied according to Table 1. Evidence levels of available guidelines are used in a way that the level of evidence is defined by the guideline publications rather than by the underlying evidence of studies systematically evaluated by the guideline. For each treatment, the most recent and valuable reference was recorded.

2.5 | Effect(s) of treatments on clinical outcome measures according to HPO terms

Effect of treatment outcomes were defined based on the HPO terms as shown in Table 1.[28] For simplicity, we used overarching HPO terms, except for neurological symptoms in which we felt more detail was valuable. If multiple treatments were available for an IEM, each treatment was individually assessed to determine its effect on the specific HPO terms. We included treatments that directly contributed to improvements in clinical outcomes, reductions in morbidity or mortality rates, or enhancements in the quality of life.

2.6 | Effect(s) of treatments on relevant metabolites

For each treatment, an assessment was made to determine if there was an effect on relevant metabolites that can be used for treatment monitoring. This is defined by evaluating meaningful alterations observed in specific metabolites tailored to the IEM and validated laboratory tests specific to the disorder's pathophysiology. These metabolites correlate with clinical improvements or disease progression, as outlined in relevant scientific literature and consensus guidelines for the particular IEM under evaluation. If an effect was observed, it was noted whether the treatment resulted in an increase or decrease in the metabolites.

All the extracted data was systematically recorded in a secure shared Google Docs Excel sheet. Table S1 displays all acquired data, including an example of a treatable IEM.

2.7 | Digital translation into IEMbase

In order to integrate the treatment module information into IEMbase, the schema of the existing database was updated to include the following tables: Treatment, DisorderTreatment, Effect, and Outcome (Table S2). The Treatment, Effect, and Outcome tables include new information relevant to the treatments themselves, whereas the DisorderTreatment table includes information relating the treatments to existing disorders in IEMbase.

Once the new schema was created, the changes were reflected in the existing database by running Django's "migrate" function.[34] Data from the curator generated .tsv format files were then imported into the newly created tables using custom import scripts to first add Treatments, then to find the unique disorder IDs in IEMbase and finally to import the associated Disorder, Treatment, Effect, and Outcome data.

After the new data was added to the database, the IEMbase interface was updated to present data from the new tables in the frontend. This involved adding a new section in the disorder page to display any treatment information relevant to that disorder.

3 | RESULTS

All treatment data are integrated and displayed on the disease-specific pages of IEMbase (Figure 1). The treatment data is available online at https://iembase.org/index.asp.

3.1 | Treatable IEMs

Our review identified 275 treatable IEMs, 17.6% of all IEMs ($n = 275/1564$) (Table S3). Among all treatable IEMs, the majority fell into the ICIMD category *disorders of vitamin and cofactor metabolism* ($n = 44/275$, 16.0%), followed by *disorders of amino acid metabolism* ($n = 41/275$, 14.9%), and *disorders of nucleobase, nucleotide, and nucleic acid metabolism* ($n = 32/275$, 11.6%). The smallest number of treatable IEMs belonged to the ICIMD categories *disorders of mitochondrial gene expression* ($n = 1/275$, 0.4%), *disorders of peptide and amine metabolism* ($n = 1/275$, 0.4%), and *miscellaneous disorders of intermediary metabolism* ($n = 1/275$, 0.4%) (Figure 2). The most treatable ICIMD category is *disorders of fatty acid and ketone body metabolism* (18 out of 27 disorders, 66.7%). This is followed by *disorders of vitamin and cofactor metabolism* (44 out of 74, 59.5%) and *disorders of lipoprotein metabolism* (13 out of 31, 41.9%). No treatable IEMs were found in categories *disorders of metabolite repair/proofreading* and *mtDNA-related disorders* (Figure 3).

3.2 | Treatment strategies

In total, 648 different treatments for 275 treatable IEMs were reported (Table 2). *Pharmacological therapy* and *nutritional therapy* were the most frequently used treatment strategy ($n = 217/648$, 33.5%), followed by *vitamin and trace element* ($n = 77/648$, 11.9%) (Table 2).

3.3 | Levels of evidence

Case series and case reports with an evidence level of 4 ($n = 311/648$, 48.0%) or 5 ($n = 79/648$, 12.2%) were most commonly used to report treatment in IEMs (Figure S1). Other frequent measures of reporting were individual cohort studies with an evidence level of 2b ($n = 78/648$, 12.0%). Level 1a was not reported. Table 2 shows the frequency of reported levels of evidence for each treatment strategy.

3.4 | Effects of treatments on clinical outcome measures (HPO terms)

In total, 1.169 different outcomes (HPO terms) were measured for 648 treatments targeting 275 treatable IEMs (Figure 4). One treatment can affect multiple outcome measures. The outcome measure most frequently showing a treatment effect is *abnormality of the nervous system*

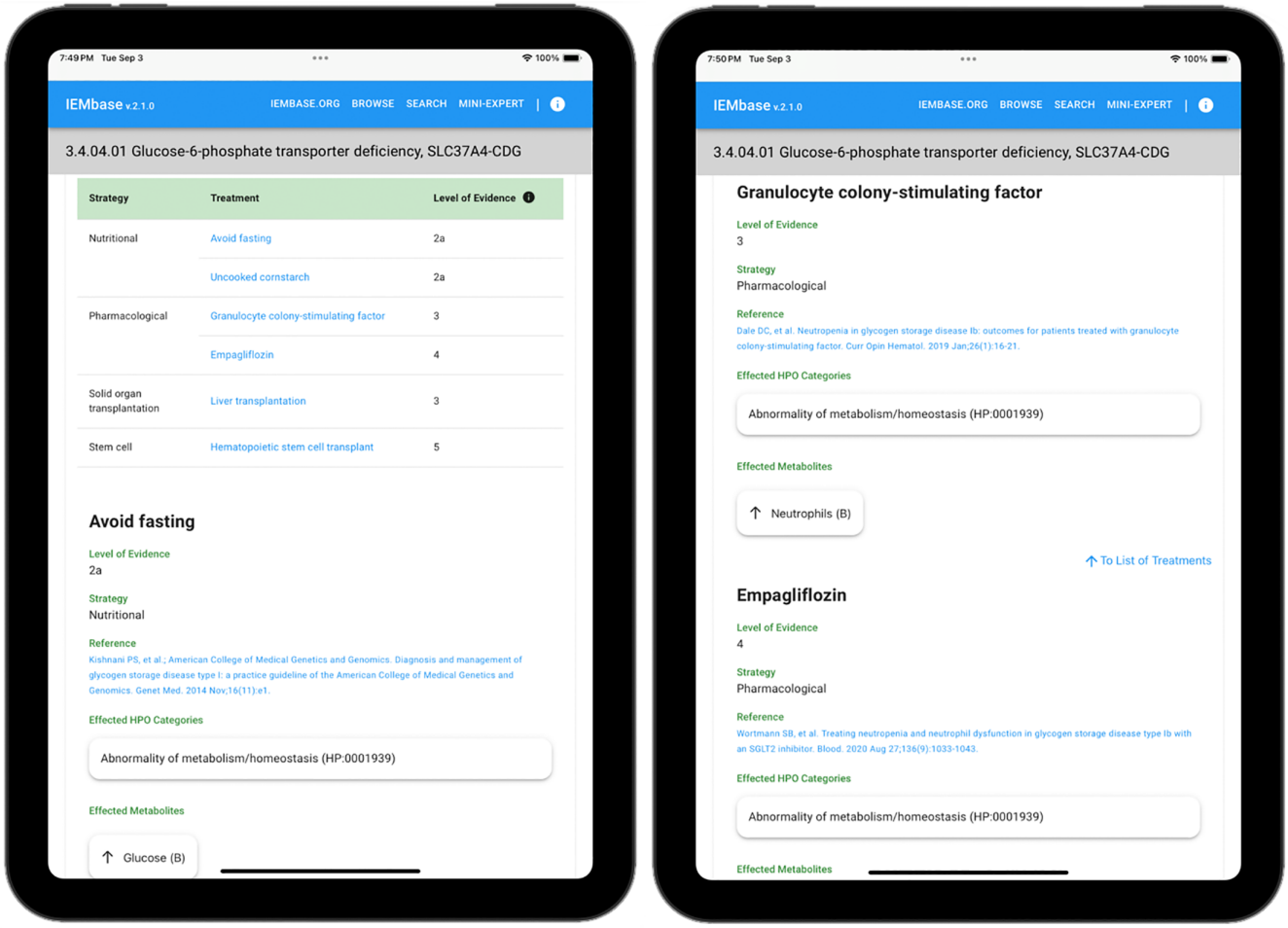

FIGURE 1 The integration and display of treatment data for glucose-6-phosphate transporter deficiency, SLC37A4-CDG on the disease-specific page of the Inborn Errors of Metabolism Knowledgebase.

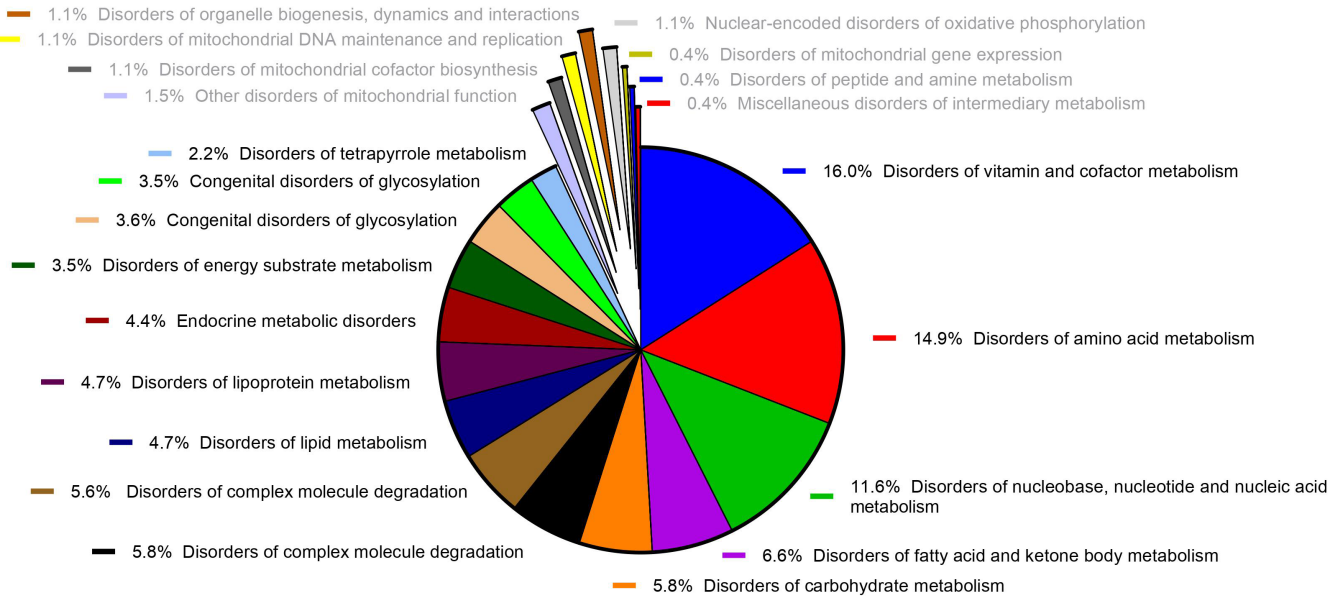

FIGURE 2 The distribution of the treatable inborn errors of metabolism ($n = 275$) across International Classification of Inherited Metabolic Disorders categories.

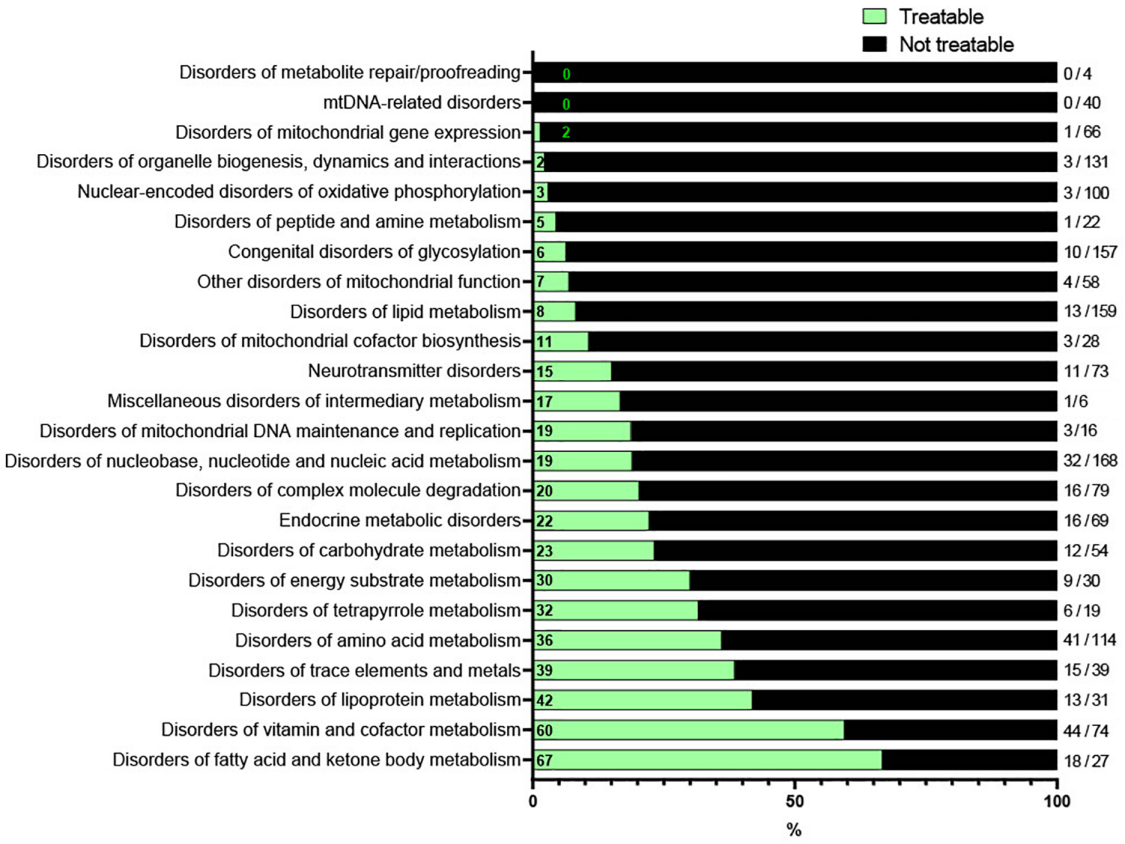

FIGURE 3 The percentage and frequencies of treatable inborn errors of metabolism (IEMs) within each International Classification of Inherited Metabolic Disorders (ICIMD) category. The percentages represent the proportion of treatable IEMs within each ICIMD category. The frequencies on the right indicate the number of treatable IEMs relative to the total number of IEMs in the corresponding ICIMD category. No treatable IEMs were found in disorders of metabolite repair/proofreading and mtDNA-related disorder.

($n = 398/1.169$, 34.1%), followed by *abnormality of metabolism/homeostasis* ($n = 380/1.169$, 32.5%), and *growth abnormality* ($n = 85/1.169$, 7.3%). The effect of the treatment on the nervous system was further divided into distinct categories to allow for specification (Table 1). The single clinical outcome measure *abnormality of the nervous system* could be divided into multiple subcategories. In total, 889 neurological subcategories were reported. The neurological manifestations most commonly affected by treatment were cognitive function/developmental ($n = 312/889$, 35.1%), followed by seizures/epilepsy ($n = 205/889$, 23.1%) and movement disorder ($n = 135/889$, 15.2%) (Table 3).

3.5 | Effects of treatments on metabolites

An overview is provided in Table S3 of the metabolites associated with specific IEMs. For 147 IEMs ($n = 147/275$, 53.5%), the effect of treatment on one or more metabolites was recorded. In total, 500 metabolites have been reported for these 147 IEMs. A change in the pertinent metabolite after treatment was most frequently found within the ICIMD category *disorders of amino acid metabolism*, followed by *disorders of vitamin and cofactor metabolism* and *disorders of trace elements and metals* and *endocrine metabolic disorders*. The most reported metabolites were ammonia, methylmalonic acid, low-density lipoprotein-cholesterol, glucose, and lactate.

4 | DISCUSSION

4.1 | Strengthening IEMbase with the Metabolic Treatabolome

This study identified and assessed treatable IEMs and their available treatment modalities and thereby created the Metabolic Treatabolome 2024. Through a comprehensive approach involving multiple steps, this research revealed a substantial number of IEMs ($n = 275$, 17.6%) amenable to treatment(s). While this is a significant portion of IEMs, it also highlights that much remains to be

TABLE 2 Frequencies of reported treatment strategies ($n = 648$ total, 100%) and their levels of evidence for 275 treatable inborn errors of metabolism (IEMs). A single IEM can be treated using several different strategies. The underlined level of evidence is the most frequently reported for the respective treatment strategy. If a level of evidence is not displayed in the table, it was not reported.

Treatment strategy	Levels of evidence	Treatment strategy	Levels of evidence
Nutritional therapy 217/648 (33.5%)	• Level 2a: 3.2% • Level 2b: 9.7% • Level 2c: 11.5% • Level 3: 9.2% • Level 4: 42.4% • Level 4–5: 11.1% • Level 5: 12.9%	Stem cell therapy 33/648 (5.1%)	• Level 1b: 3.0% • Level 1c: 3.0% • Level 2b: 6.1% • Level 3: 3.0% • Level 4: 66.7% • Level 4–5: 6.1% • Level 5: 12.1%
Pharmacological therapy 217/648 (33.5%)	• Level 1b: 3.7% • Level 2a: 0.9% • Level 2b: 20.3% • Level 3: 10.1% • Level 4: 41.0% • Level 4–5: 11.1% • Level 5: 12.9%	Solid organ transplantation 31/648 (4.8%)	• Level 2a: 6.5% • Level 2b: 3.2% • Level 3: 6.5% • Level 4: 71.0% • Level 4–5: 9.7% • Level 5: 3.2%
Vitamin and trace element 77/648 (11.9%)	• Level 2b:1.3% • Level 2c: 6.5% • Level 3:1.3% • Level 4: 58.4% • Level 4–5: 14.3% • Level 5: 18.2%	Enzyme replacement therapy 20/648 (3.1%)	• Level 1b: 35% • Level 1c: 5% • Level 2a: 5% • Level 2b: 35% • Level 3: 5% Level 4: 15%
Other 46/648 (7.1%)	• Level 3: 2.2% • Level 4: 80.4% • Level 4–5: 8.7% • Level 5: 8.7%	Gene-based therapy 7/648 (1.1%)	• Level 1b: 14.3% • Level 2b: 14.3% • Level 2c: 14.3% • Level 3:14.3% • Level 4: 28.6% • Level 4–5: 14.3%

done, as this represents only 17.6% of currently identified IEMs. This percentage does not directly correlate with the proportion of patients who can receive treatment, as certain diseases, like phenylketonuria compared to mitochondrial DNA disease, are more prevalent. Moreover, treatable diseases are often more frequently diagnosed, partly due to inclusion in newborn screening programs. Nevertheless, for the group of 1289 IEMs (82.4% of all IEMs), there is an urgent need for the development of therapeutic interventions, as effective treatments currently do not exist.

4.2 | Use of the Metabolic Treatabolome database in the management of patients with an IEM

4.2.1 | For which ICIMD categories should treatment be considered?

Disorders of fatty acid and ketone body metabolism, *disorders of vitamin and cofactor metabolism, and disorders of lipoprotein metabolism* emerge as the most treatable ICIMD categories. Patients with an IEM in these categories have the highest probability of treatability. However, given the treatable IEMs within each ICIMD category, the physician should always consider whether a therapy is available. In the categories of *disorders of metabolite repair/proofreading* and *mtDNA-related disorders*, no treatable IEMs were identified. However, the landscape of medical research can change rapidly, and it would be premature to advise against further exploration for potential therapies in these areas.

4.2.2 | What symptoms are most amenable to treatment?

Therapy most frequently affected nervous system abnormalities (specify), followed by metabolism/homeostasis and growth abnormalities. However, this does not imply these symptoms are the most treatable. Assessing the treatability of symptoms across all 1564

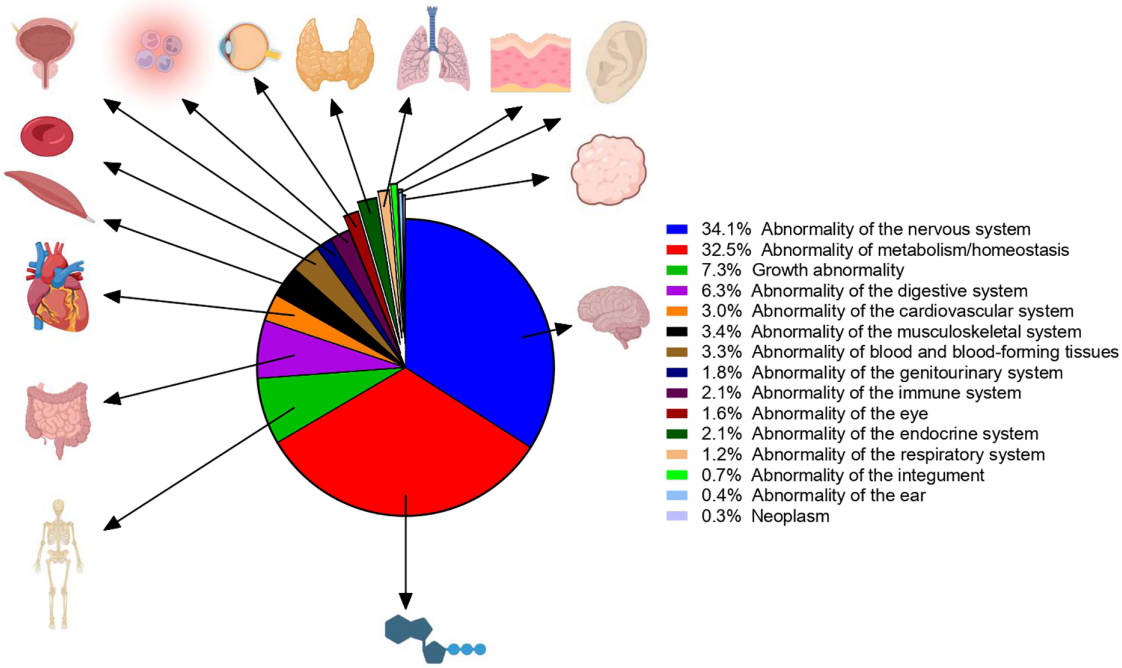

FIGURE 4 The distribution, in percentage, of the 1.169 outcome measures/human phenotype ontology (HPO) terms affected by the 648 treatments. One treatment can affect multiple outcome measures/HPO terms. This is shown for all 275 treatable inborn errors of metabolism.

TABLE 3 Specification of the clinical outcome measure "abnormality of the nervous system" divided into subcategories.

Subcategory	Count (total $n = 889$)	Percentage of total ($n = 889$)
Cognitive function/ developmental	312	35.1
Seizures/epilepsy	205	23.1
Movement disorder	135	15.2
Psychiatric/behavior	113	12.7
Neuropathy	63	7.1
Muscle function	39	4.4
Sensory deficits	19	2.1
Muscle tone	3	0.3

IEMs within a specific organ system is beyond this study's scope. Future research should address this for better insights.

Understanding treatment effects requires detailed knowledge of disease natural history at different ages.[35] Rare diseases face challenges like limited patient numbers, geographical dispersion, and a lack of specialized researchers, impeding systematic data collection. Collaborative clinical research can improve our understanding and help determine treatment effects.

4.2.3 | What to tell patients about the effect of treatments?

Based on the findings of this study, no definitive conclusion can be drawn about the expected treatment effect. When analyzing the HPO terms that most frequently show a treatment effect, *abnormality of the nervous system* and *abnormality of metabolism/homeostasis* are the most reported. However, these are also the organ systems most frequently affected by IEMs.[36] As such, it is not possible to provide an expectation regarding the anticipated treatment effect for all IEMs. Within each ICIMD category, and even within a single IEM, the prognosis for treatment course varies. Therefore, we advise consulting the provided references for treatment(s) in IEMbase, and using this information to communicate treatment expectations to the patient. To make a well-informed decision, it would be necessary to evaluate what percentage of treated patients respond to a treatment and to what extent. However, this is beyond the scope of this study.

Also, within a single IEM, patients can respond differently; those severely affected may not show a benefit from treatment, while patients with milder phenotypes may (e.g., L-serine in GRIN2B-neurodevelopmental disorder,[37] avoidance of fasting and carbohydrate-rich diet in carnitine palmitoyltransferase 2 deficiency[38]).

Some treatments may not be able to prevent disease progression, but may slow progression (e.g., enzyme replacement therapy in mucopolysaccharidosis type VI[35]). Additionally, there may be a specific subgroup/genetic variant in which a treatment is effective. For example, enzyme replacement therapy is only effective for Gaucher type 1 but not for the neurological symptoms in Gaucher types 2 and 3.[39,40]

4.2.4 | How should treatment effects be monitored?

First and foremost, physicians should adhere to established guidelines and protocols as much as possible when monitoring response to treatment. These guidelines provide structured frameworks for selecting appropriate monitoring parameters to assess treatment response and adjust therapy as needed. In the absence of guidelines, treatment references from IEMbase can be consulted to determine which symptoms are expected to show a treatment effect and within what timeframe. In such cases, more personalized monitoring is necessary.[39]

4.2.5 | When are metabolites useful for monitoring the effect of therapies?

In more than half of the treatable IEMs, an association with a metabolite was identified. These metabolites may sometimes serve as biomarkers, but not always (e.g., glucose is not considered a biomarker as it is not disease-specific). The availability of a disease-related metabolite is enabling for prognosis, diagnosis, and treatment monitoring.[41] One of the criteria for a metabolite's utility in treatment monitoring is its requirement to be disease-specific and responsive to the treatment.[42] For example, in Fabry disease, the metabolite Lyso-Gb3 (globotriaosylsphingosine) is used to monitor the effectiveness of treatment[43]: enzyme replacement therapy reduces plasma Gb3 and improves pain-related quality of life,[44] gastrointestinal symptoms,[45,46] as well as energy and activity levels.[47] Also, the use of a metabolite offers a potential avenue for personalized therapies and precise monitoring, enabling a more targeted approach to managing IEMs. In a significant portion of disorders, however, no specific metabolite exists. The absence of disease-specific metabolites is a problem, often making it difficult to evaluate drug effectiveness.[42] This underscores the ongoing need for research into novel disease-related metabolites to improve treatment evaluation.

4.3 | Evidence levels in treatment decision-making

Most treatment strategies had limited evidence levels of 4 or 5, based mainly on case series and case reports. Remarkably, enzyme replacement therapies achieved level 1b in 35% of cases, likely due to more robust trials, clear mechanisms of action, and significant improvements in disease severity.[48] The levels of evidence for the other treatment strategies were limited.

Conducting an RCT for IEMs and other rare diseases is often unfeasible due to their rarity.[49] Definitions of "rare disease" vary globally: in Europe, it affects fewer than 1 in 2000 people, while in the United States, fewer than 200 000 people,[50,51] corresponding to 1 in 1666 based on a population of approximately 333 million. In rare diseases, alternative study designs like n-of-1 trials are often used, despite being viewed as lower evidence than RCTs. However, according to The Oxford Levels of Evidence, n-of-1 studies also provide level 1 evidence.[52] The results of n-of-1 trials may be more relevant for the treatment of a specific rare disease or individual patient.[53] n-of-1 and other alternative trial designs generate real-world evidence crucial for optimizing treatments.[54] This underscores a potential incongruence between the level of evidence and the relevance of a specific treatment for a specific patient or disease. For example, creatine has a significant and highly relevant effect in arginine amidinotransferase deficiency, yet the level of evidence is low.[55] Overall, in rare diseases, the relevance of treatment effects often outweighs the formal level of evidence in clinical decision-making.

4.4 | Limitations and strengths

Limitations encountered during this study include the scarcity of robust clinical data for rare IEMs, which posed challenges in determining treatment efficacy. Second, the evolving landscape of IEM therapies requires regular updates and continuous monitoring of new treatments. And third, most therapies exhibited evidence levels 4 or 5, reflecting the inherent difficulty in conducting RCTs for rare diseases. Finally, our criteria for identifying metabolites specific to IEMs may have unintentionally excluded some relevant ones.

Strengths of this study include its comprehensive approach, encompassing the identification of treatable IEMs, an extensive literature review, and systematic extraction of treatment efficacy data. Furthermore, the clear documentation of treatment strategies, evidence levels, and effects on clinical outcome measures, including biomarkers, provides valuable insights into available treatments. Third, this study offers a user-friendly,

accessible resource for healthcare professionals centralizing treatment data online. Lastly, this study may help to streamline reimbursement procedures and enhance accessibility to therapies.

4.5 | Future perspectives

The Metabolic Treatabolome is a dynamic resource that evolves with ongoing research and therapeutic advancements. As new therapies are developed and evidence on their effectiveness is updated, future versions will reflect these advancements compared to the 2024 edition. Consequently, regular updates to the IEMbase treatment module will be essential, requiring several strategies. First, we will establish an efficient mechanism for data aggregation and validation to integrate new treatments and assess their efficacy and safety. Second, fostering a real-time information exchange among stakeholders will ensure that the latest advancements in IEM treatments are included in IEMBase. Third, continuous surveillance of emerging therapies will be maintained through collaboration among healthcare professionals, geneticists, researchers, and patient community representatives. IEMbase already has an infrastructure in place for updates, with input from a panel of 70 international specialists in the field of IEMs, the editorial board, and the broader metabolic community. New submissions are reviewed by two board members, with expert input sought when necessary. Since the publication of the ICIMD, 111 new disorders have been added over 3 years. A similar system will be applied to the Metabolic Treatabolome.

Additionally, the link between this study's finding and newborn screening will be essential. Identifying treatable IEMs and assessing treatment options support the goals of newborn screening, which enable early intervention and prevent severe complications.[56] The results of this study can help expand and optimize screening programs. Engaging patients and families is also key, as their insights can shape therapy development. However, maintaining data integrity in IEMbase requires avoiding anecdotal or incorrect information.

Lastly, we encourage physicians, researchers, patients, and others involved to provide feedback and input for IEMbase; together we strive for continuous improvements and updates.

4.6 | Conclusion: the Metabolic Treatabolome for better management of IEMs and other rare diseases

This study presents the Metabolic Treatabolome, offering a comprehensive overview of treatable IEMs, the largest group among treatable monogenic disorders. We aim to keep this resource up to date so it continues to have a meaningful impact for patients and families as well as healthcare professionals, researchers, and stakeholders involved in managing IEM patients. The project's significance extends beyond IEMs, setting an example for other rare diseases, showcasing the potential benefits of systematically aggregating treatment-related data for more insights, better management, and improved health outcomes for rare diseases patients, families, and professionals alike.

AUTHOR CONTRIBUTIONS

EMMHvK: Data curation; investigation; methodology; project administration; writing—review and editing. **BdH**: Formal analysis; investigation; methodology; project administration; writing—original draft. **BH**: Data curation; formal analysis; methodology; software; writing—review and editing. **JCvdM**: Investigation; methodology; writing—review and editing. **BMB**: Investigation; methodology; writing—review and editing. **BW**: Software; writing—review and editing. **ARM**: Formal analysis; writing—review and editing. **WWW**: Conceptualization; methodology; writing—review and editing. **CRF**: Conceptualization; investigation; methodology; validation; writing—review and editing. **CDvK**: Conceptualization; funding acquisition; investigation; methodology; supervision; validation; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare no other conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Clara D. van Karnebeek, upon reasonable request.

ETHICS STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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