Developments in evidence creation for treatments of inborn errors of metabolism

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Communicating Editor: Georg Hoffmann

Funding information
BC Children’s Hospital Research Foundation; Canadian Institute of Health Research, Grant/Award Number: TR3-119195; Foundation Metakids

Abstract
Inborn errors of metabolism (IEM) represent the first group of genetic disorders, amenable to causal therapies. In addition to traditional medical diet and cofactor treatments, new treatment strategies such as enzyme replacement and small molecule therapies, solid organ transplantation, and cell-and gene-based therapies have become available. Inherent to the rare nature of the single conditions, generating high-quality evidence for these treatments in clinical trials and under real-world conditions has been challenging. Guidelines developed with standardized methodologies have contributed to improve the practice of care and long-term clinical outcomes. Adaptive trial designs allow for changes in sample size, group allocation and trial duration as the trial proceeds. n-of-1 studies may be used in small sample sized when participants are clinically heterogeneous. Multicenter observational and registry-based clinical trials are promoted via international research networks. Core outcome and standard data element sets will enhance comparative analysis of clinical trials and observational studies.

Abbreviations: AGREE, Appraisal of Guidelines for Research and Evaluation; CIMDRN, Canadian Inherited Metabolic Diseases Research Network; COMET, Core Outcome Measures in Effectiveness Trials; CORD, Canadian Organization for Rare Disorders; COS, Core Outcome Measure Set; EURODIS, Rare Diseases Europe; GA1, glutaric aciduria type 1; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HSEM, horizontal saccadic eye movement; IEM, inborn error of metabolism; ISPOR, International Society for Pharmacogenomics and Outcome Research; MCAD, medium chain acyl-CoA dehydrogenase; NIH, National Institutes of Health; NORD, National Organization for Rare Disorders; PCOM, patient-centered outcome measure; PDE-ALDH7A1, pyridoxine-dependent epilepsy-aldehyde dehydrogenase 7A1; PKU, phenylketonuria; PRO, patient-reported outcome; RDCRN, Rare Disease Clinical Research Network; SIGN, Scottish Intercollegiate Guideline Network.

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Patient-centered outcome-research as well as patient-led research initiatives will further accelerate the development of therapies for IEM.

KEYWORDS
evidence-based medicine, orphan drugs, participatory research, personalized medicine, rare diseases

1 | INTRODUCTION

Inborn errors of metabolism (IEM) represent the first group of genetic disorders which have become amenable to causal therapies. The successful treatment of phenylketonuria (PKU) with a phenylalanine-reduced diet in the 1950s was the first proof of principle of an intervention at the metabolic level for a genetic defect. During the following decades, medical diet and cofactor therapies were developed for numerous IEM affecting the intermediary metabolism of aminoacids, fatty acids, and sugars. For lysosomal storage diseases, enzyme replacement therapies, delivered via the intravenous or the intrathecal route have been developed. Solid organ transplantation (liver, kidney), cell-based therapies (stem cell-, hepatocyte transplantation,) and small molecule therapies targeting subcellular molecular pathophysiology also have become available for an increasing number of IEM. In a 2011 systematic literature review, 81 IEM causing intellectual disability were identified, which are amenable to at least one causal treatment modality, and numbers are steadily increasing due to the discovery of novel IEM genes via omics technologies. The pace of these developments is accelerated by drug repurposing strategies aiming to find new indications for already approved pharmacological agents. With this strategy, costly preclinical safety studies can be eliminated once a drug candidate has been identified for a new clinical indication. Read through and antisense oligonucleotide/exon skipping strategies as well as new delivery systems for the replacement and correction of defective genes and gene products will potentially expand the spectrum of treatment options for IEM. Finally, the formation of an International Rare Disease Research Consortium (IRDiRC) back in 2010, uniting European and North American research and development efforts has given an ultimate boost to orphan drug development (www.irdirc.org/goals/).

While the traditional diet- and supplement-based treatments have been implemented over decades on an empirical basis, with the advent of new therapies, the generation of high-quality evidence has become a new paradigm in the world of IEM. However, the determination whether an intervention works under experimental (clinical trial) and real-world (postmarketing) conditions is restricted for reasons such as small heterogeneous patient populations, incomplete understanding of the natural history, lack of validated outcome measures and limited postmarketing surveillance. Additionally, benefits of these treatments are often below the expectations of affected individuals, as results obtained in the experimental setting of clinical trials, may not always translate into meaningful clinical and patient-oriented outcomes.

Creation of scientific evidence for treatments of rare diseases is a rapidly evolving field. This article provides an overview of existing and innovative strategies for evidence generation in the field IEM and is aimed for clinicians acting in the intersection between patient care, industry collaboration, and payer accountability.

2 | CLINICAL PRACTICE GUIDELINES

An analysis of existing treatment modalities for IEM has shown that 60% have been supported only by nonanalytic studies (case reports and series) and expert opinion, whereas in clinical practice most of these therapies are considered “standard of care”. The use of aminoacid supplementation in amino- and organo acidopathies is based on similar nonanalytical evidence. Alfadhel et al found that for the majority (74%) of medicines used in IEM, the published dosages were based on nonanalytical evidence only.

There is also considerable variation in clinical practice for many of these therapies. For example, oral t-
carnitine supplementation for multiple acyl-CoA dehydrogenase (MCAD) deficiency is not recommended as per expert opinion, whereas survey data indicate that up to one third of metabolic physicians recommend L-carnitine for all or most of their patients with MCAD deficiency. Additionally, concerns have been raised that corrections of biochemical concentrations in certain conditions may lead to overtreatment without improvement of the long-term clinical outcomes. Furthermore, major uncertainties exist when it comes to the therapeutic management of mild variants of IEM, which are now increasingly detected by newborn screening.

Guidelines, based on rigorous evidence rating and transparent grading of recommendations have become an important tool for the standardization of clinical management of IEM. For the majority of these guidelines methodologies established by Scottish Intercollegiate Guideline Network (SIGN) and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) have been used. While in SIGN, the strength of recommendation is directly related to the quality of evidence (high-quality evidence = strong recommendation; low-quality evidence = weak recommendation), in GRADE, the strength of recommendation is additionally determined by the balance between benefits and downsides of an intervention as estimated by multistakeholder expert panels. GRADE also allows upgrading and downgrading of established evidence according to the certainty to which the true effect of an intervention is similar to the effect estimated according to the results of a respective experimental or observational study.

Appraisal of Guidelines for Research and Evaluation (AGREEII) is another instrument that assists guideline developers to provide scientific rigor and transparency in the development and reporting of guidelines. It also helps assessing the quality of existing guidelines. Using AGREEII criteria, an evaluation of 55 clinical practice guidelines for a total of 685 IEM affecting the central nervous system published between 2000 and 2015 showed that the quality of the recommendations was acceptable in most of the guidelines analyzed and that the methodological rigor applied improved over time.

Table 1 shows treatment guidelines for IEM developed during the last decade. The evolution of guidelines in the field of IEM can be followed by means of two recently published guidelines on urea cycle defects and on glutaric aciduria type 1 (GA1) which contain stronger recommendations compared to their early versions. This is not only due to the availability of higher quality evidence studies published in the interim, but also to a switch from SIGN to GRADE methodology as the latter allows the integration of expert votes on clinical relevance of a particular treatment and benefit for the individual.

| Condition/referenc | Methodology |
|--------------------|-------------|
| Aromatic aminoacid decarboxylase deficiency | SIGN, GRADE |
| Cobalamin deficiencies | SIGN, GRADE |
| Cystathionine beta synthase deficiency | SIGN |
| Galactosemia | GRADE |
| GA1 | SIGN |
| GA1 | SIGN, GRADE |
| Glycogenosis type 1 | Literature review and consensus; no grading of evidence level and recommendation strength |
| Glycogenosis types 6 and 9 | Literature review and consensus; no grading of evidence level and recommendation strength |
| Maple syrup urine disease | Evidence-consensus based |
| Methylmalonic and propionic aciduria | SIGN |
| Phenylalanine hydroxylase deficiency | SIGN and consensus agreement on recommendation strength |
| Phenylalanine hydroxylase deficiency | Evidence-consensus based |
| PKU | SIGN |
| Phosphomannomutase 2-congenital disorders of glycosylation | SIGN |
| Propionic academia | Evidence-consensus based |
| Pyridoxine-dependent epilepsy (ALDH7A1-related) | GRADE |
| Tetrahydrobiopterin deficiencies | SIGN, GRADE |
| Tyrosinemia type 1 | AGREE |
| Urea cycle defects | SIGN |
| Urea cycle defects | SIGN, GRADE |
| Very long chain acyl CoA dehydrogenase deficiency | Oxford Centre for evidence-based methods |
| 3-Methylcrotonyl CoA carboxylase deficiency | Oxford Centre for evidence-based methods |

Abbreviations: AGREEII, Appraisal of Guidelines for Research and Evaluation; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; IEM, inborn errors of metabolism; PKU, phenylketonuria; SIGN, Scottish Intercollegiate Guideline Network.

Guidelines are important tools for quality assurance of the clinical management of IEM, which, as shown in the case of GA1, leads to an improvement of long-term outcomes.
Evaluation of the acceptance of guidelines is a future task to define their practicability and practice-based variance.\(^4^0\) Updates of guidelines are imperative as evidence-creating literature emerges. Harmonization of methodologies is necessary to be able to compare the quality of guidelines in the future.

3 | ALTERNATIVE TRIAL DESIGNS

With the current trend to simultaneously develop multiple treatment modalities for single IEM, alternative clinical trial designs with the ability to evaluate treatments in small populations within a short time are more than ever needed.\(^4^1\) One of the first IEM for which multiple treatments have been developed at the same time is Niemann-Pick type C disease: In addition to the existing treatment with Miglustat, trials for three new treatments have been performed simultaneously: 2-hydroxypropyl-β-cyclodextrin,\(^4^2\) a lipid chelator; armimocimol, a heat shock protein inducer\(^4^3\); and vorinostat, a histone deacetylase inhibitor.\(^4^4\) Additionally, the group of lysosomal storage disorders harbors numerous conditions for which enzyme replacement therapies and small molecule therapies are being developed simultaneously.\(^4^5\)

Methodological reviews of alternative study designs\(^4^6,4^7\) have created algorithms to facilitate choosing which methodological strategy to use in consideration of factors specific to the disease (eg, disease progression) and intervention (eg, duration of effect).\(^4^8,4^9\)

Adaptive clinical trial designs provide a powerful methodology allowing response-adaptive or sequential randomization as well as changes in sample size, trial duration, or group allocation as a trial proceeds.\(^5^0,5^1\) These designs may decrease the amount of time participants not responding to the treatment spend in a trial making them available for participation in other trials. In group-sequential adaptive designs, an intervention tested in a trial becomes the control treatment in a subsequent trial, which allows several treatment modalities to be trialed at the same time.\(^5^2\) Response-adaptive designs are an option for explorative trials as they have the potential to identify subpopulations of treatment responders. Randomized placebo-phase, randomized-withdrawal, early escape, stepped wedge, and crossover trials\(^4^8,4^9\) may help bolster participant recruitment thus increasing the study sample size and improving explanatory power of the study. These designs are reportedly more attractive to patients and families over conventional trial designs because each participant is guaranteed the active treatment at some point during the study or the amount of time participants will spend on the active treatment is increased.\(^4^1\) A blind start study design to investigate a novel enzyme replacement therapy for mucopolysaccharidosis type 7\(^5^3\) is the first example of the use of an adaptive trial design in IEM.

Bayesian statistics provide a formal mathematical method for combining prior information with current information at the design stage, during the conduct of the trial, and at the analysis stage.\(^5^4\) This is in contrast to traditionally used frequentist statistics in which data analysis is based on information exclusively obtained in the trial itself. Bayesian methods are often applied in adaptive trial designs and can also be applied for post-marketing surveillance purposes and in meta-analysis. Applied for the statistical analysis of trial data obtained from small participant numbers, Bayesian statistics may increase efficiency by formally incorporating prior information into the data analysis.\(^5^5\) The main criticism of using Bayesian methods to improve statistical efficiency is the potential subjectivity in selecting prior information.

4 | N-OF-1 TRIALS

n-of-1 trials are single case experimental design studies,\(^5^6\) in which a single individual is tested with an experimental study protocol such as intra-individual randomization of treatment, and where the individual is their own control. n-of-1 trials typically involve a comparison between two or more experimental time periods, known as phases. They are suitable for chronic conditions anticipated to remain stable during the trial period and for treatments expected to have a rapid onset of effect when started and a short-lived effect when discontinued, allowing multiple cross overs between an active treatment and a placebo and/or a control treatment. They also bear the potential to evaluate personally meaningful outcomes and to make individual treatment decisions in the face of clinical heterogeneity.\(^5^7\) Standardization of individual trial reporting\(^5^8\) allows meta-analysis of data obtained from single patients, which has the potential to generate the highest level of evidence.\(^5^9\)

In contrast to the experimental nature n-of-1 trials, the term n-of-1 study (or single-case-study) should be used for observational uncontrolled studies in single individuals or for studies serving diagnostic or treatment monitoring purpose.

Historically, in the field of IEM, the first example of an individual trial goes back to the 1950s when Bickel et al\(^2\) demonstrated an improvement and deterioration of behaviors and attention on and off a phenylalanine reduced diet in a girl with PKU. Another example is an on and off treatment with pyrimidine nucleoside and nucleotide compounds in four patients with a presumed disorder of increased nucleotide turn-over.\(^6^0\) A randomized double-blind placebo-controlled n-of-1 trial of L-arginine was performed in a female patient with ornithine transcarbamylase deficiency.\(^6^1\) Most recently, an n-of-1 trial was performed to
evaluate a patient-customized oligonucleotide therapy for a patient with type 7 of Batten disease.\textsuperscript{62}

We foresee two main applications for n-of-1 trials: (a) in the context of a large variation in the baseline outcome measures in a small sample size, for example, due to heterogeneous clinical presentation of study participants and (b) in the context of personalized drug development for drugs which are customized to infrequently or privately occurring mutations.

5 | MULTICENTRE RESEARCH NETWORKS

To address the challenge of small, geographically dispersed patient populations, multinational collaborations have emerged to facilitate clinical research for IEM.\textsuperscript{63} Research Networks bear the unique potential to accrue funding for research projects related to the network core areas promising long-term sustainability. Key initiatives include the NIH-based Rare Diseases Clinical Research Networks (RDCRN; https://ncats.nih.gov/rcdrn) such as the North American Mitochondrial Disease Consortium, the Lysosomal Disease Network, the Urea Cycle Disorders Consortium, and the Porphyria Consortium; the Inborn Errors of Metabolism Collaborative (https://www.mphi.org/projects/inborn-errors-og-metabolism-collaborative); and the Nutrition and Dietary Supplementation Interventions for Inborn Errors of Metabolism (https://ods.od.nih.gov/Research/NDSI-IEM.aspx).

European initiatives include The European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) (https://www.e-imd.org); the Unified Registry for Inherited Metabolic Disorders (U-IMD) (https://u-imd.org); the European Reference Network for Rare Hereditary Metabolic Diseases MetabERN (https://metab.ern-net.eu); and United for Metabolic Diseases (https://www.umd.nl).

The Canadian Inherited Metabolic Diseases Research Network (CIMDRN, www.cimdrn.ca) has established a research platform involving more than 50 investigators and 14 of 16 Inherited Metabolic Disease Treatment Centres across Canada. Since its inception in 2013, this network has conducted research to evaluate clinical outcomes for new or existing IEM therapies and offers work packages for the assessment of patient-reported and health systems outcomes.\textsuperscript{64}

6 | REGISTRY-BASED EVIDENCE

Many of the multicenter initiatives described above maintain patient registries.

In recent years, there has been a call to standardize the various registry elements such that data can be compared across different registries and shared for integrated data analysis. Adopting common data elements to standardized ontologies, such as the human phenotype ontology,\textsuperscript{65} is now considered best practice in setting up a rare disease patient registry. In addition, several other recommendations have been developed to guide the establishment of rare disease patient registries including suggestions around registry governance, core data sets, information systems, data quality monitoring, and confidentiality.\textsuperscript{66,67} The CIMDRN recently has published lessons for consideration in future research initiatives for rare diseases based on their experience with the establishment of a comprehensive database for IEM.\textsuperscript{68}

Contact registries facilitate rapid implementation of studies by expediting recruitment and enrollment.\textsuperscript{69,70} For example, the NIH-funded RDCRN has established a contact registry in which patients with the conditions studied by each of the participating consortia (several of which include IEM) can enroll.\textsuperscript{70} Patients who are part of the contact registry receive information about the RDCRN’s research activities as well as invitations to participate in specific clinical studies.

6.1 | Registry-based observational studies

In cases where clinical trials cannot be performed, registries with well-defined clinical endpoints can elevate the evidence created by observational studies. An example is the observational registry for pyridoxine-dependent epilepsy (PDE) (www.pdeonline.org). Since the discovery of the underlying genetic defect in the lysine degradation pathway (ALDH7A1 deficiency),\textsuperscript{71} nutritional lysine reduction therapies (protein restriction and arginine supplementation) have been considered as add-on therapies to traditional pyridoxine supplementation.\textsuperscript{72,73} Because nutritional lysine reduction has proven safe in other conditions affecting the lysine degradation pathway (GA1), most patients with PDE were started on this treatment modality without hesitation, despite uncertainties regarding its effectiveness in improving the long-term clinical outcome. At this point, a controlled clinical trial would have been impossible to conduct mainly because of difficulties finding and retaining treatment naïve controls for the entire duration of a trial. A longitudinal observational study of patients enrolled in pdeonline.org will allow for the evaluation of clinical benefits of this new treatment approach.

6.2 | Registry-based trials

The registry-based randomized trial is an innovative methodology, which involves the embedding of
intervention trials within observational cohort studies or patient registries. Strengths include efficiencies in patient recruitment and data collection and access to long-term follow-up data. Recruitment of patients from routine clinical settings also helps to determine whether and to what extent results obtained from clinical trials are valid outside the context of the experimental setting. In SPOR INFORM RARE (lab.research.sickkids.ca), a group of patients/caregivers, health care providers, policymakers, methodologists, and ethicists are currently developing innovative registry-based randomized trials to address priority questions for three treatable rare diseases: PKU, mucopolysaccharidoses, and spinal muscular atrophy.

6.3 | Registries for postmarketing surveillance

Postmarketing registries have been implemented to evaluate longer lasting utilities associated with drug therapies for rare diseases such as real life benefits for the patient and the society and considerations of cost-effectiveness. Registry-based postmarketing surveillance will become particularly relevant with the increased demand for adaptive licensing. The adaptive licensing approach aims to link regulatory approval for a limited indication with iterative postmarketing evidence-generation, guiding further expansion of the indication where appropriate. Schuller et al describe an example of how an adaptive licensing approach centered on iterative evidence development through high-quality registry data could have strengthened the regulation and funding process for enzyme replacement therapy in Fabry disease.

Currently, most postmarketing registries are industry-sponsored. Although these registries have been useful in evaluating certain treatment-related outcomes, they are prone to incomplete data collection (drug vs disease-centered registry) and data fragmentation. Independent disease-centered registries are mostly free of such bias; however, sustainable funding for the maintenance of such registries has been a major roadblock.

7 | OUTCOME RESEARCH

7.1 | Surrogate vs clinically meaningful outcome measures

Choosing sensitive and specific outcomes for the evaluation of an intervention is essential for the design of clinical trials. Surrogate outcome measures indicating quantifiable changes in response to therapy within a short time period are particularly relevant in chronic neurologic/neurodegenerative conditions for which meaningful clinical outcomes would not be detected during the time period of a typical trial. However, while surrogate outcomes may be useful for proof-of-principle studies and for hypothesis generation, a surrogate endpoint is not necessarily a valid predictor of the net effect of a treatment.

As an example, Patterson et al published results of a randomized controlled trial for Miglustat in Niemann-Pick type C disease. After 12 months, a treatment subgroup showed a significant improvement in horizontal saccadic eye movement (HSEM) velocity, which had been chosen as the primary outcome. At that time, the clinical significance of these findings was questioned, as the correlation of HSEM velocity with clinically meaningful outcomes such as neurologic and cognitive functions was unclear. Only years later, two subsequent natural history studies confirmed a correlation of HSEM velocity with disease duration, severity, and ataxia.

7.2 | Core outcome sets

A core outcome measure set (COS) is an agreed minimum set of outcomes that should be measured and reported in any clinical trial performed in a specific disease. COSs are of particular importance for IEM as their use not only permits meta-analysis of treatment effectiveness from single trials including small patient numbers, but also supports comparative analysis of observational cohorts across different metabolic centers. Initiatives such as COMET (Core Outcome Measures in Effective ness Trials) have promoted the use of literature reviews and multistakeholder consensus approaches to develop standardized COS for evaluative studies. These and similar methods have been adopted in rare disease settings. Using these methodologies, our group recently has developed COS have been developed for PKU and MCAD deficiency.

7.3 | Standard data element sets

An initiative has been undertaken by the global RD Registry Program (GRDR) to standardize the collection of natural history data in observational registries for rare diseases. Specifically, 75 core data elements have been recommended for future disease registries, facilitating their integration into a global data repository. In individuals with cognitive, motor, communication, and sensory impairments, their visual and verbal abilities, discrepancies between their chronological and their developmental age, as well as
their attention span need to be considered in the choice of the most appropriate test instrument. Based on these criteria, van der Lee et al defined standardized outcome measures for the assessment of cognitive and adaptive functions in patients with neuronopathic mucopolysaccharidoses.

7.4 Patient-centered and patient-reported outcomes

As patients may prioritize different outcomes relative to physicians, it is critical to consider patients’ daily experience of the rare disease, their preferences, core concepts, and values in initiatives that seek to establish core outcome sets. For the development of patient-centered outcome measures (PCOM) specific to rare diseases, Morel and Cano propose a combination of qualitative and quantitative research methodologies allowing efficient utilization of data from small patient samples.

Integrating patient-centered care in IEM, PCOM have been included in the recently published COS for PKU and MCAD deficiency which were developed in partnership with patients and family members. Similar efforts have been considered for the development of outcome measures for pediatric mitochondrial disorders.

A subset of PCOM are patient-reported outcomes (PROs); PROs reflect constructs that are best reported by patients themselves and have increasingly been recognized as important in intervention studies related to rare diseases. Guidelines for developing and using PROs in studies of rare diseases were published by the International Society for Pharmacoeconomics and Outcomes Research. This report addresses key points in identifying, selecting, and implementing PROs specific to the field of rare diseases and presents recommendations such as partnering with patient organizations, using a range of tools, and adapting existing outcome measurement instruments that are generic or can be modified from similar conditions.

8 Patient-led research initiatives

During the past decade, the patients’ role in orphan drug development has evolved from end-users to active participants in research, drug development, advocacy, and societal decision-making. Nongovernmental, patient-driven alliances (eg, CORD, NORD, EURORDIS, Rare Voices Australia) have become strong advocates to promote the development of and access to rare disease therapies. In the United States, the Patient-Centered Outcomes Research Institute has funded patient-powered research networks, several of which involve rare diseases and all NIH-funded RDCRN consortia have patient advocacy groups as research partners.

Patient-partnered registries are becoming increasingly important as they ensure rapid collection of natural history and epidemiological data. As an example, a patient empowered Morquio B disease registry was launched in May 2016 by our team and disseminated through patient-hosted social media (www.morquiob.com). Despite the extreme rarity of this condition, we were able to collect cross sectional natural history data of 25 patients worldwide within a 6-month-time frame. As a caveat, selection bias due to computer skills, literacy, and motivation of patients should be considered in the interpretation of results obtained from studies using patient recruitment from social media.

Patient-partnered leadership. Patient organizations taking leadership in innovative collaborations with pharmaceutical industry is a fascinating development that accelerates the development and testing of new treatments. As an example, 16 national San Filippo Foundations invested into a NASDAQ quoted Biotech Company (www.abeonatherapeutics.com) to develop a gene therapy for MPS3. Similarly, innumerable patient driven fundraising activities for a myriad of IEM have emerged globally during the last decades. CUREGM1 (curegm1.org) and the Ryan Foundation (ryanfoundation.org) are impressive examples of successful patient-initiated fundraising endeavors.

A number of scientific, practical, and ethical challenges are related to patient engagement and co-production of research. Apart from patient engagement in some cases being symbolic or tokenistic rather than truly impactful, diversity and inclusiveness of patients participating in research can contribute to bias and inequities in competition for funding. Educational initiatives such as fyreworkstraining.com providing partnership-based research training will increase the value of patient-partnered research in the future.

9 Conclusion and outlook

Innovative methodological approaches in evaluating medical evidence and utility of therapies for IEM and strong partnerships with end-users and stakeholders involved in their development, application, and evaluation are needed to ensure access to the many new therapies for rare diseases in the near future.

Acknowledgments

The project has been endorsed by: TIDE-BC (Treatable Intellectual Disability Endeavor in British Columbia)
funded by the BC Children’s Hospital Research Foundation; CIMDRN (Canadian Inherited Metabolic Research Network) funded by the Canadian Institutes of Health Research (CIHR); The Priest Family Fund for Morquio B Research, a UBC-based Stewardship Grant, and United for Metabolic diseases funded by Foundation Metakids. The authors thank the patients and families who teach us every day about the importance of increasing knowledge and evidence for rare diseases.

CONFLICTS OF INTEREST
S. S.-I. received educational grants from Biomarin, Shire, Recordati, and serves/served as PI in clinical trials and postmarketing registries sponsored by Actelion, Biomarin, Shire, Ultragenyx. M. P. has consulted for Actelion, Amicus, IntraBio, Novartis, Orphazyme, Shire, and Vtesse, and has received research funding from Actelion and Orphazyme. He owns stock in IntraBio. C. van K. serves as PI for clinical trials sponsored by Vitaflo. B. K. P., N. Y., K. T., and C. van K. have no conflicts to declare.

AUTHOR CONTRIBUTIONS
Sylvia Stockler-Ipsiroglu: Designed the study, conducted the review, wrote and revised the manuscript.
Beth K. Potter: Contributed to section “Evidence creation for established and new therapies” and manuscript writing.
Nataliya Yuskiv: Contributed to aspects in sections “Developments in Treatments for IEM” and “Evidence creation for established and new therapies.”
Kylie Tingley: Contributed to aspects in section “Evidence creation for established and new therapies.”
Marc Patterson: Contributed to aspects in sections “Developments in Treatments for IEM” and “Evidence creation for established and new therapies.”
Clara van Karnebeek: Contributed to the original concept of this article and aspects in sections “Evidence creation for established and new therapies.” All authors reviewed, edited, and approved the manuscript for submission.

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