


## REVIEW ARTICLE

# Developments in evidence creation for treatments of inborn errors of metabolism

Sylvia Stockler-Ipsiroglu<sup>1</sup>  | Beth K. Potter<sup>2</sup> | Nataliya Yuskiv<sup>1</sup> |  
Kylie Tingley<sup>2</sup> | Marc Patterson<sup>3</sup> | Clara van Karnebeek<sup>4,5,6</sup>

<sup>1</sup>Division of Biochemical Genetics, Department of Pediatrics, and BC Children's Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada

<sup>2</sup>School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

<sup>3</sup>Division of Child and Adolescent Neurology, Departments of Neurology Pediatrics and Medical Genetics, Mayo Clinic Children's Center, Rochester, Minnesota

<sup>4</sup>Departments of Pediatrics and Clinical Genetics, Amsterdam University Medical Centres, Amsterdam, The Netherlands

<sup>5</sup>Department of Pediatrics, Radboud University Medical Centre, Nijmegen, The Netherlands

<sup>6</sup>Department of Pediatrics, BC Children's Hospital Research Institute, Centre for Molecular Medicine and Therapeutics, Vancouver, British Columbia, Canada

## Correspondence

Sylvia Stockler-Ipsiroglu, Division of Biochemical Genetics, Department of Pediatrics, and BC Children's Hospital Research Institute University of British Columbia, K-204-4480 Oak Street, Vancouver, BC V6H 3V4, Canada.  
Email: sstockler@cw.bc.ca

**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; CODR, 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.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. *Journal of Inherited Metabolic Disease* published by John Wiley & Sons Ltd on behalf of SSIEM.

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.<sup>1</sup> The successful treatment of phenylketonuria (PKU) with a phenylalanine-reduced diet in the 1950s<sup>2</sup> 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,<sup>3</sup> 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<sup>4</sup> 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/](http://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

### Synopsis

Analysis and grading of evidence is a quality improvement tool for existing therapies for inborn errors of metabolism. Generation of high-level evidence for new therapies will be accelerated through alternative trial designs, development of standardized core outcome sets, international rare disease registries, and patient-led research initiatives.

(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.<sup>5</sup> 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”.<sup>3</sup> The use of aminoacid supplementation in amino- and organo acidopathies is based on similar nonanalytical evidence.<sup>6</sup> Alfadhel et al<sup>7</sup> 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 L-

carnitine supplementation for multiple acyl-CoA dehydrogenase (MCAD) deficiency is not recommended as per expert opinion,<sup>8</sup> 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.<sup>9,10</sup> 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.<sup>11</sup> 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)<sup>12</sup> and Grading of Recommendations, Assessment, Development and Evaluations (GRADE)<sup>13</sup> 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)<sup>14</sup> 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.<sup>15</sup>

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<sup>36</sup> and on glutaric aciduria type 1 (GA1)<sup>21</sup> which contain stronger recommendations compared to their early versions.<sup>20,35</sup> 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.

**TABLE 1** Treatment guidelines of IEM and methods used for their development

Condition/reference	Methodology
Aromatic amino acid decarboxylase deficiency <sup>16</sup>	SIGN, GRADE
Cobalamin deficiencies <sup>17</sup>	SIGN, GRADE
Cystathionine beta synthase deficiency <sup>18</sup>	SIGN
Galactosemia <sup>19</sup>	GRADE
GA1 <sup>20</sup>	SIGN
GA1 <sup>21</sup>	SIGN, GRADE
Glycogenosis type 1 <sup>22</sup>	Literature review and consensus; no grading of evidence level and recommendation strength
Glycogenosis types 6 and 9 <sup>23</sup>	Literature review and consensus; no grading of evidence level and recommendation strength
Maple syrup urine disease <sup>24</sup>	Evidence-consensus based <sup>25</sup>
Methylmalonic and propionic aciduria <sup>26</sup>	SIGN
Phenylalanine hydroxylase deficiency <sup>27</sup>	SIGN and consensus agreement on recommendation strength
Phenylalanine hydroxylase deficiency <sup>28</sup>	Evidence-consensus based <sup>25</sup>
PKU <sup>29</sup>	SIGN
Phosphomannomutase 2-congenital disorders of glycosylation <sup>30</sup>	SIGN
Propionic academia <sup>31</sup>	Evidence-consensus based <sup>25</sup>
Pyridoxine-dependent epilepsy (ALDH7A1-related) <sup>32</sup>	GRADE
Tetrahydrobiopterin deficiencies <sup>33</sup>	SIGN, GRADE
Tyrosinemia type 1 <sup>34</sup>	AGREE
Urea cycle defects <sup>35</sup>	SIGN
Urea cycle defects <sup>36</sup>	SIGN, GRADE
Very long chain acyl CoA dehydrogenase deficiency <sup>37</sup>	Oxford Centre for evidence-based methods
3-Methylcrotonyl CoA carboxylase deficiency <sup>38</sup>	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.<sup>39</sup>

Evaluation of the acceptance of guidelines is a future task to define their practicability and practice-based variance.<sup>40</sup> 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.<sup>41</sup> 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- $\beta$ -cyclodextrin,<sup>42</sup> a lipid chelator; armimoclolomol, a heat shock protein inducer<sup>43</sup>; and vorinostat, a histone deacetylase inhibitor.<sup>44</sup> Additionally, the group of lysosomal storage disorders harbors numerous conditions for which enzyme replacement therapies and small molecule therapies are being developed simultaneously.<sup>45</sup>

Methodological reviews of alternative study designs<sup>46,47</sup> 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).<sup>48,49</sup>

*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.<sup>50,51</sup> 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.<sup>52</sup> 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<sup>48,49</sup> 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.<sup>41</sup> A blind start study design to investigate a

novel enzyme replacement therapy for mucopolysaccharidosis type 7<sup>53</sup> 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.<sup>54</sup> 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.<sup>55</sup> 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,<sup>56</sup> 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.<sup>57</sup> Standardization of individual trial reporting<sup>58</sup> allows meta-analysis of data obtained from single patients, which has the potential to generate the highest level of evidence.<sup>59</sup>

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<sup>2</sup> 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.<sup>60</sup> A randomized double-blind placebo-controlled n-of-1 trial of L-arginine was performed in a female patient with ornithine transcarbamylase deficiency.<sup>61</sup> 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.<sup>62</sup>

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.<sup>63</sup> 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/rdcrn>) 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 Supplement 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](http://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.<sup>64</sup>

## 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<sup>65</sup> 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.<sup>66,67</sup> 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.<sup>68</sup>

*Contact registries* facilitate rapid implementation of studies by expediting recruitment and enrollment.<sup>69,70</sup> 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.<sup>70</sup> 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](http://www.pdeonline.org)). Since the discovery of the underlying genetic defect in the lysine degradation pathway (ALDH7A1 deficiency),<sup>71</sup> nutritional lysine reduction therapies (protein restriction and arginine supplementation) have been considered as add-on therapies to traditional pyridoxine supplementation.<sup>72,73</sup> 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](http://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.<sup>74-76</sup> 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.<sup>77</sup> Registry-based postmarketing surveillance will become particularly relevant with the increased demand for adaptive licensing.<sup>78</sup> 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<sup>79</sup> 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.<sup>80</sup> 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.<sup>81</sup>

As an example, Patterson et al<sup>82</sup> 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<sup>83,84</sup> 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.<sup>85</sup> 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 Effectiveness Trials) have promoted the use of literature reviews and multistakeholder consensus approaches to develop standardized COS for evaluative studies.<sup>86,87</sup> These and similar methods have been adopted in rare disease settings.<sup>88,89</sup> Using these methodologies, our group recently has developed COS have been developed for PKU and MCAD deficiency.<sup>90</sup>

### 7.3 | Standard data element sets

An initiative has been undertaken by the global RD Registry Program (GRDR) (<https://grdr.ncats.nih.gov/>) 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.<sup>91</sup> 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.<sup>92,93</sup> Based on these criteria, van der Lee et al<sup>94</sup> 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<sup>95</sup> 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<sup>90</sup> which were developed in partnership with patients and family members.<sup>96</sup> Similar efforts have been considered for the development of outcome measures for pediatric mitochondrial disorders.<sup>97</sup>

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.<sup>98</sup> Guidelines for developing and using PROs in studies of rare diseases were published by the International Society for Pharmacoeconomics and Outcomes Research.<sup>99</sup> 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.<sup>100</sup> 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<sup>101</sup> and all NIH-funded RDCRN consortia have patient advocacy groups as research partners.<sup>102</sup>

*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](http://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.<sup>103</sup> 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.<sup>104</sup>

*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.abeontherapeutics.com](http://www.abeontherapeutics.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](http://curegm1.org)) and the Ryan Foundation ([ryanfoundation.org](http://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,<sup>105-107</sup> diversity and inclusiveness of patients participating in research can contribute to bias and inequities in competition for funding.<sup>105,108</sup> Educational initiatives such as [fyeworkstraining.com](http://fyeworkstraining.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.

### ORCID

Sylvia Stockler-Ipsiroglu  <https://orcid.org/0000-0002-6542-423X>

### REFERENCES

1. Scriver CR. Garrod's Croonian lectures (1908) and the charter 'inborn errors of metabolism: albinism, alkaptonuria, cystinuria, and pentosuria at age 100 in 2008. *J Inherit Metab Dis*. 2008;31(5):580-598. <https://doi.org/10.1007/s10545-008-0984-9>.
2. Bickel H, Gerrard J, Hickmans EM. Influence of phenylalanine intake on phenylketonuria. *Lancet*. 1953;265(6790):812-813.
3. van Karnebeek CD, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. *Mol Genet Metab*. 2012;105(3):368-381.
4. Sun W, Zheng W, Simeonov A. Drug discovery and development for rare genetic disorders. *Am J Med Genet A*. 2017;173(9):2307-2322. <https://doi.org/10.1002/ajmg.a.38326>.
5. Potter BK, Khangura SD, Tingley K, Chakraborty P, Little J. Translating rare-disease therapies into improved care for patients and families: what are the right outcomes, designs, and engagement approaches in health-systems research? *Genet Med*. 2016;18:117-123.
6. van Vliet D, Derks TG, van Rijn M, et al. Single amino acid supplementation in aminoacidopathies: a systematic review. *Orphanet J Rare Dis*. 2014;9:7. <https://doi.org/10.1186/1750-1172-9-7>.
7. Alfadhel M, Al-Thihli K, Moubayed H, Eyaïd W, Al-Jeraisy M. Drug treatment of inborn errors of metabolism: a systematic review. *Arch Dis Child*. 2013;98(6):454-461. <https://doi.org/10.1136/archdischild-2012-303131>.
8. Spiekerkoetter U, Bastin J, Gillingham M, Morris A, Wijburg F, Wilcken B. Current issues regarding treatment of mitochondrial fatty acid oxidation disorders. *J Inherit Metab Dis*. 2010;33(5):555-561. <https://doi.org/10.1007/s10545-010-9188-1>.
9. Potter BK, Little J, Chakraborty P, et al. Variability in the clinical management of fatty acid oxidation disorders: results of a survey of Canadian metabolic physicians. *J Inherit Metab Dis*. 2012;35:115-123.
10. Walter JH. L-carnitine in inborn errors of metabolism: what is the evidence? *J Inherit Metab Dis*. 2003;26(2-3):181-188.
11. Leonard JV. Komrower lecture: treatment of inborn errors of metabolism: a review. *J Inherit Metab Dis*. 2006;29(2-3):275-278.
12. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ*. 2001;323(7308):334-336. <https://doi.org/10.1136/bmj.323.7308.334>.
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.
14. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182(18):E839-E842. <https://doi.org/10.1503/cmaj.090449>.
15. Cassis L, Cortès-Saladefont E, Molero-Luis M, et al. Review and evaluation of the methodological quality of the existing guidelines and recommendations for inherited neuro-metabolic disorders. *Orphanet J Rare Dis*. 2015;10:164. <https://doi.org/10.1186/s13023-015-0376-9>.
16. Wassenberg T, Molero-Luis M, Jeltsch K, et al. Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency. *Orphanet J Rare Dis*. 2017;12:12. <https://doi.org/10.1186/s13023-016-0522-z>.
17. Huemer M, Diodato D, Schwahn B, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. *J Inherit Metab Dis*. 2017;40(1):21-48. <https://doi.org/10.1007/s10545-016-9991-4>.
18. Morris AA, Kožich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inherit Metab Dis*. 2017;40(1):49-74. <https://doi.org/10.1007/s10545-016-9979-0>.
19. Welling L, Bernstein LE, Berry GT, et al. International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. *J Inherit Metab Dis*. 2017;40(2):171-176. <https://doi.org/10.1007/s10545-016-9990-5>.



20. Kölker S, Christensen E, Leonard JV, et al. Diagnosis and management of glutaric aciduria type I—revised recommendations. *J Inherit Metab Dis*. 2011;34(3):677-694.
21. Boy N, Mühlhausen C, Maier EM, et al. Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type I: second revision. *J Inherit Metab Dis*. 2017;40(1):75-101. <https://doi.org/10.1007/s10545-016-9999-9>.
22. Kishnani PS, Austin SL, Abdenur JE, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med*. 2014;16(11):e1.
23. Kishnani PS, Goldstein J, Austin SL, et al. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2019;21(4):772-789. <https://doi.org/10.1038/s41436-018-0364-2>.
24. Frazier DM, Allgeier C, Homer C, et al. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. *Mol Genet Metab*. 2014;112(3):210-217. <https://doi.org/10.1016/j.ymgme.2014.05.006>.
25. Singh RH, Rohr F, Splett PL. Bridging evidence and consensus methodology for inherited metabolic disorders: creating nutrition guidelines. *J Eval Clin Pract*. 2013;19(4):584-590.
26. Baumgartner MR, Hörster F, Dionisi-Vici S, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic academia. *Orphanet J Rare Dis*. 2014;9:130. <https://doi.org/10.1186/s13023-014-0130-8>.
27. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med*. 2014;16(2):188-200. <https://doi.org/10.1038/gim.2013.157>.
28. Singh RH, Cunningham AC, Mofidi S, et al. Updated, web-based nutrition management guideline for PKU: an evidence and consensus based approach. *Mol Genet Metab*. 2016;118(2):72-83. <https://doi.org/10.1016/j.ymgme.2016.04.008>.
29. van Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis*. 2017;12:162. <https://doi.org/10.1186/s13023-017-0685-2>.
30. Altassan R, Péanne R, Jaeken J, et al. International clinical guidelines for the management of phosphomannomutase 2-congenital disorders of glycosylation: diagnosis, treatment and follow up. *J Inherit Metab Dis*. 2019 Jan;42(1):5-28. <https://doi.org/10.1002/jimd.12024>.
31. Jurecki E, Ueda K, Frazier D, et al. Nutrition management guideline for propionic acidemia: an evidence- and consensus-based approach. *Mol Genet Metab*. 2019;126(4):341-354. <https://doi.org/10.1016/j.ymgme.2019.02.007>.
32. Coughlin CR, Tseng LA, Abdenur JE, et al. Consensus guidelines for the diagnosis and management of pyridoxine-dependent epilepsy due to  $\alpha$ -aminoacidic semialdehyde dehydrogenase deficiency; 2020
33. Opladen T, López-Laso E, Cortès-Saladelafont E, et al. Consensus guideline for the diagnosis and treatment of tetrahydrobiopterin (BH4) deficiencies. *Orphanet J Rare Dis*. 2020;15(1):126. <https://doi.org/10.1186/s13023-020-01379-8>.
34. Chinsky JM, Singh R, Ficicioglu C, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. *Genet Med*. 2017;19(12):1-16. <https://doi.org/10.1038/gim.2017.101>.
35. Häberle J, Boddart N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis*. 2012;7:32. <https://doi.org/10.1186/1750-1172-7-32>.
36. Häberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. *J Inherit Metab Dis*. 2019;42(6):1192-1230. <https://doi.org/10.1002/jimd.12100>.
37. Arnold GL, van Hove J, Freedberg D, et al. A Delphi clinical practice protocol for the management of very long chain acyl-CoA dehydrogenase deficiency. *Mol Genet Metab*. 2009;96(3):85-90. <https://doi.org/10.1016/j.ymgme.2008.09.008>.
38. Arnold GL, Koeberl DD, Matern D, et al. A Delphi-based consensus clinical practice protocol for the diagnosis and management of 3-methylcrotonyl CoA carboxylase deficiency. *Mol Genet Metab*. 2008;93(4):363-370.
39. Heringer J, Boy SPN, Ensenauer R, et al. Use of guidelines improves the neurological outcome in glutaric aciduria type I. *Ann Neurol*. 2010;68:743-752.
40. Yuskiv N, Potter B, Stockler S, et al. Canadian Inherited Metabolic Diseases Research Network (CIMDRN). Nutritional management of phenylalanine hydroxylase (PAH) deficiency in pediatric patients in Canada: a survey of dietitians' current practices. *Orphanet J Rare Dis*. 2019;14(1):7.
41. Tingley K, Coyle D, Graham ID, et al. Canadian inherited metabolic diseases research network. Using a meta-narrative literature review and focus groups with key stakeholders to identify perceived challenges and solutions for generating robust evidence on the effectiveness of treatments for rare diseases. *Orphanet J Rare Dis*. 2018;13(1):104. <https://doi.org/10.1186/s13023-018-0851-1>.
42. Ottinger EA, Kao ML, Carrillo-Carrasco N, et al. Collaborative development of 2-hydroxypropyl- $\beta$ -cyclodextrin for the treatment of Niemann-Pick type C1 disease. *Curr Top Med Chem*. 2014;14(3):330-339.
43. Kirkegaard T, Gray J, Priestman DA, et al. Heat shock protein-based therapy as a potential candidate for treating the sphingolipidoses. *Sci Transl Med*. 2016;8(355):355ra118. <https://doi.org/10.1126/scitranslmed.aad9823>.
44. Helquist P, Maxfield FR, Wiech NL, Wiest O. Treatment of Niemann-Pick type C disease by histone deacetylase inhibitors. *Neurotherapeutics*. 2013;10(4):688-697.
45. Parenti G, Andria G, Ballabio A. Lysosomal storage diseases: from pathophysiology to therapy. *Annu Rev Med*. 2015;66:471-486.
46. Gagne JJ, Thompson L, O'Keefe K, Kesselheim AS. Innovative research methods for studying treatments for rare diseases: methodological review. *BMJ*. 2014;349:g6802.
47. Tudur Smith C, Williamson PR, Beresford MW. Methodology of clinical trials for rare diseases. *Best Pract Res Clin Rheumatol*. 2014;28(2):247-262. <https://doi.org/10.1016/j.berh.2014.03.004>.
48. Cornu C, Kassai B, Fisch R, et al. Experimental designs for small randomised clinical trials: an algorithm for choice. *Orphanet J Rare Dis*. 2013;8(48):1-12.
49. Gupta S, Faughnan ME, Tomlinson GA, Bayoumi AM. A framework for applying unfamiliar trial designs in studies of

- rare diseases. *J Clin Epidemiol*. 2011;64(10):1085-1094. <https://doi.org/10.1016/j.jclinepi.2010.12.019>.
50. Chow SC, Chang M. Adaptive design methods in clinical trials—a review. *Orphanet J Rare Dis*. 2008;3:11.
  51. Chow SC, Corey R. Benefits, challenges and obstacles of adaptive clinical trial design. *Orphanet J Rare Dis*. 2011;6:79.
  52. Bayar MA, le Teuff G, Koenig F, le Deley MC, Michiels S. Group sequential adaptive designs in series of time-to-event randomised trials in rare diseases: a simulation study. *Stat Methods Med Res*. 2019;29:962280219862313-962280219861498. <https://doi.org/10.1177/0962280219862313>.
  53. Harmatz P, Whitley CB, Wang RY, et al. A novel blind start study design to investigate vestronidase alfa for mucopolysaccharidosis VII, an ultra-rare genetic disease. *Mol Genet Metab*. 2018;123(4):488-494. <https://doi.org/10.1016/j.ymgme.2018.02.006>.
  54. Gupta SK. Use of Bayesian statistics in drug development: advantages and challenges. *Int J Appl Basic Med Res*. 2012;2(1):3-6.
  55. Hampson LV, Whitehead J, Eleftheriou D, Brogan P. Bayesian methods for the design and interpretation of clinical trials in very rare diseases. *Stat Med*. 2014;33(24):4186-4201.
  56. Smith JD. Single-case experimental designs: a systematic review of published research and current standards. *Psychol Methods*. 2012;17(4):1-61. <https://doi.org/10.1037/a0029312>.
  57. Shamseer L, Sampson M, Bukutu C, et al. CENT group. CONSORT extension for reporting N-of-1 trials (CENT) 2015: explanation and elaboration. *J Clin Epidemiol*. 2016;76:18e46.
  58. Vohra S, Shamseer L, Sampson M, et al. CONSORT extension for reporting N-of-1 trials (CENT) 2015 statement. *J Clin Epidemiol*. 2015:1-7. <https://doi.org/10.1016/j.jclinepi.2015.05.004>.
  59. Zucker DR, Ruthazer R, Schmid CH. Individual (N-of-1) trials can be combined to give population comparative treatment effect estimates: methodologic considerations. *J Clin Epidemiol*. 2010;63:1312-1323.
  60. Page T, Yu A, Fontanesi J, Nyhan WL. Developmental disorder associated with increased cellular nucleotidase activity. *Proc Natl Acad Sci U S A*. 1997;94(21):11601-11606.
  61. Hackett A, Gillard J, Wilcken B. *n* of 1 trial for an ornithine transcarbamylase deficiency carrier. *Mol Genet Metab*. 2008;94:157-161.
  62. Kim J, Hu C, Moufawad El Achkar C, et al. Patient-customized oligonucleotide therapy for a rare genetic disease. *N Engl J Med*. 2019;381(17):1644-1652. <https://doi.org/10.1056/NEJMoa1813279>.
  63. Summar ML, Endo F, Kölker S. On the creation, utility and sustaining of rare diseases research networks: lessons learned from the urea cycle disorders consortium, the Japanese urea cycle disorders consortium and the European registry and network for intoxication type metabolic diseases. *Mol Genet Metab*. 2014;113(1-2):105-108. <https://doi.org/10.1016/j.ymgme.2014.09.002>.
  64. Potter BK, Chakraborty P, Kronick JB, et al. Achieving the “triple aim” for inborn errors of metabolism: a review of challenges to outcomes research and presentation of a new practice-based evidence framework. *Genet Med*. 2013;15(6):415-422. <https://doi.org/10.1038/gim.2012.153>.
  65. Köhler S, Vasilevsky NA, Engelstad M, et al. The human phenotype ontology in 2017. *Nucleic Acids Res*. 2017;45(D1):D865-D876. <https://doi.org/10.1093/nar/gkw1039>.
  66. Gliklich R, Dreyer N, Leavy M, eds. *Registries for Evaluating Patient Outcomes: A User's Guide*. Vol 2. 3rd ed. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
  67. Kodra Y, Weinbach J, Posada-De-La-Paz M, et al. Recommendations for improving the quality of rare disease registries. *Int J Environ Res Public Health*. 2018;15(8):1-22. <https://doi.org/10.3390/ijerph15081644>.
  68. Tingley K, Lamoureux M, Pugliese M, et al. Canadian inherited metabolic diseases research network. Evaluation of the quality of clinical data collection for a pan-Canadian cohort of children affected by inherited metabolic diseases: lessons learned from the Canadian inherited metabolic diseases research network. *Orphanet J Rare Dis*. 2020;15(1):89.
  69. Krischer JP, Gopal-Srivastava R, Groft SC, Eckstein DJ. The rare diseases clinical research network's organization and approach to observational research and health outcomes research. *J Gen Intern Med*. 2014;29(suppl 3):S739-S744. <https://doi.org/10.1007/s11606-014-2894-x>.
  70. Richesson RL, Sutphen R, Shereff D, Krischer JP. The rare diseases clinical research network contact registry update: features and functionality. *Contemp Clin Trials*. 2012;33:647-656.
  71. Mills PB, Struys E, Jakobs C, et al. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. *Nat Med*. 2006;12(3):307-309.
  72. Coughlin CR II, van Karnebeek CD, Al-Hertani W, et al. Triple therapy with pyridoxine, arginine supplementation and dietary lysine restriction in pyridoxine-dependent epilepsy: Neurodevelopmental outcome. *Mol Genet Metab*. 2015;116(1-2):35-43. <https://doi.org/10.1016/j.ymgme.2015.05.011>.
  73. van Karnebeek CD, Hartmann H, Jaggamantri S, et al. Lysine restricted diet for pyridoxine-dependent epilepsy: first evidence and future trials. *Mol Genet Metab*. 2012;107(3):335-344. <https://doi.org/10.1016/j.ymgme.2012.09.006>.
  74. Lauer MS, D'Agostino RB. The randomized registry trial—the next disruptive technology in clinical research? *N Engl J Med*. 2013;369(17):1579-1581.
  75. Li G, Sajobi TT, Menon BK, et al. Registry-based randomized controlled trials: advantages, challenges and areas for future research. *J Clin Epidemiol*. 2016;80:16-24.
  76. Newman AB, Avilés-Santa ML, Anderson G, et al. Embedding clinical interventions into observational studies. *Contemp Clin Trials*. 2016;46:100-105.
  77. Kesselheim A, Gagne J. Strategies for postmarketing surveillance of drugs for rare diseases. *Clin Pharmacol Ther*. 2014;95(3):265-268.
  78. Eichler HG, Baird LG, Barker R, et al. From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients. *Clin Pharmacol Ther*. 2015;97(3):234-246.
  79. Schuller Y, Arends M, Körver S, Langeveld M, Hollak CEM. Adaptive pathway development for Fabry disease: a clinical approach. *Drug Discov Today*. 2018;125-1257. <https://doi.org/10.1016/j.drudis.2018.02.004>.
  80. Hollak CEM, Aerts JMFG, Ayme S, Manuel J. Limitations of drug registries to evaluate orphan medicinal products for the treatment of lysosomal storage disorders. *Orphanet J Rare Dis*. 2011;6:16.
  81. Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. *Stat Med*. 2012;31:2973-2984.

82. Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol.* 2007;6(9):765-772.
83. Abel LA, Bowman EA, Velakoulis D, et al. Saccadic eye movement characteristics in adult Niemann-Pick type C disease: relationships with disease severity and brain structural measures. *PLoS One.* 2012;7(11):e50947. <https://doi.org/10.1371/journal.pone.0050947>.
84. Walterfang M, Abel LA, Desmond P, Fahey MC, Bowman EA, Velakoulis D. Cerebellar volume correlates with saccadic gain and ataxia in adult Niemann-Pick type C. *Mol Genet Metab.* 2013;108(1):85-89. <https://doi.org/10.1016/j.ymgme.2012.11.009>.
85. Prinsen CA, Vohra S, Rose MR, et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. *Trials.* 2014;15:247. <https://doi.org/10.1186/1745-6215-15-247>.
86. Gargon E, Gurung B, Medley N, et al. Choosing important health outcomes for comparative effectiveness research: a systematic review. *PLoS One.* 2014;9(6):e99111.
87. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials.* 2012;13:132.
88. Choquet R, Maaroufi M, de Carrara A, Vandebussche PY, Dhombres F, Landais P. A methodology for a minimum data set for rare diseases to support national centers of excellence for healthcare and research. *J Am Med Inform Assoc.* 2015;22(1):76-85.
89. Taruscio D, Mollo E, Gainotti S, Posada de la Paz M, Bianchi F, Vittozzi L. The EPIRARE proposal of a set of indicators and common data elements for the European platform for rare disease registration. *Arch Public Health.* 2014;72(1):35.
90. Pugliese M, Tingley K, Chow A, et al. Outcomes in pediatric studies of medium-chain acyl-coA dehydrogenase (MCAD) deficiency and phenylketonuria (PKU): a review. *Orphanet J Rare Dis.* 2020;15:12. <https://doi.org/10.1186/s13023-019-1276-1>.
91. Rubinstein YR, McInnes P. NIH/NCATS/GRDR<sup>®</sup> common data elements: a leading force for standardized data collection. *Contemp Clin Trials.* 2015;42:78-80. <https://doi.org/10.1016/j.cct.2015.03.003>.
92. Engle J. Beyond the WISC: Psychological assessment of cognitive functioning in special populations. <https://pressbooks.bccampus.ca/jengle/>; 2019.
93. Shapiro E, Bernstein J, Adams HR, et al. Neurocognitive clinical outcome assessments for inborn errors of metabolism and other rare conditions. *Mol Genet Metab.* 2016;118(2):65-69.
94. van der Lee JH, Morton J, Adams HR, et al. Cognitive endpoints for therapy development for neuronopathic mucopolysaccharidoses: Results of a consensus procedure. *Mol Genet Metab.* 2017;121(2):70-79. <https://doi.org/10.1016/j.ymgme.2017.05.004>.
95. Morel T, Cano SJ. Measuring what matters to rare disease patients—reflections on the work by the IRDiRC taskforce on patient-centered outcome measures. *Orphanet J Rare Dis.* 2017;12:171.
96. Potter BK, Hutton B, Clifford TJ, et al. Establishing core outcome sets for phenylketonuria (PKU) and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency in children: study protocol for systematic reviews and Delphi surveys. *Trials.* 2017;18(1):603.
97. Koene S, Wortmann SB, de Vries MC, et al. Developing outcome measures for pediatric mitochondrial disorders: which complaints and limitations are most burdensome to patients and their parents? *Mitochondrion.* 2013;13(1):15-24.
98. Basch E, Bennett AV. Patient-reported outcomes in clinical trials of rare diseases. *J Gen Intern Med.* 2014;29(suppl 3):13-15.
99. Benjamin K, Vernon MK, Patrick DL, Perfetto E, Nestler-Parr S, Burke L. Patient-reported outcome and observer-reported outcome assessment in rare disease clinical trials: an ISPOR COA emerging good practices task force report. *Value Health.* 2017;20(7):838-855.
100. Young A, Menon D, Street J, Al-Hertani W, Stafinski T. Exploring patient and family involvement in the lifecycle of an orphan drug: a scoping review. *Orphanet J Rare Dis.* 2017;12(1):188.
101. Fleurence RL, Beal AC, Sheridan SE, Johnson LB, Selby JV. Patient-powered research networks aim to improve patient care and health research. *Health Aff.* 2014;33(7):1212-1219.
102. Merkel PA, Manion M, Gopal-Srivastava R, et al. The partnership of patient advocacy groups and clinical investigators in the rare diseases clinical research network. *Orphanet J Rare Dis.* 2016;11(1):66.
103. Bleier M, Yuskiv N, Priest T, Popurs MAM, Stockler-Ipsiroglu S, Morquio B patient/caregiver survey: first insight into the natural course of a rare GLB1 related condition. *Mol Genet Metab Rep.* 2018;16:57-63. <https://doi.org/10.1016/j.ymgmr.2018.06.006.eCollection>.
104. Golder S, Ahmed S, Norman G, Booth A. Attitudes toward the ethics of research using social media: a systematic review. *J Med Internet Res.* 2017;19(6):e195. <https://doi.org/10.2196/jmir.7082>.
105. Bélisle-Pipon JC, Rouleau G, Birko S. Early-career researchers' views on ethical dimensions of patient engagement in research. *BMC Med Ethics.* 2018;19(1):21.
106. Madden M, Speed E. Beware zombies and unicorns: toward critical patient and public involvement in health research in a neoliberal context. *Front Sociol.* 2017;2(7):1-6.
107. Wicks P, Richards T, Denegri S, Godlee F. Patients' roles and rights in research. *BMJ.* 2018;362:k3193.
108. Carroll SL, Embuldeniya G, Abelson J, McGillion M, Berkesse A, Healey JS. Questioning patient engagement: research scientists' perceptions of the challenges of patient engagement in a cardiovascular research network. *Patient Prefer Adherence.* 2017;11:1573-1583.

**How to cite this article:** Stockler-Ipsiroglu S, Potter BK, Yuskiv N, Tingley K, Patterson M, van Karnebeek C. Developments in evidence creation for treatments of inborn errors of metabolism. *J Inherit Metab Dis.* 2021;44:88–98. <https://doi.org/10.1002/jimd.12315>