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Minireview

Treatable inborn errors of metabolism causing intellectual disability: A systematic literature review

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ABSTRACT

Background: Intellectual disability ('developmental delay' at age<5 years) affects 2.5% of population worldwide. Recommendations to investigate genetic causes of intellectual disability are based on frequencies of single conditions and on the yield of diagnostic methods, rather than availability of causal therapy. Inborn errors of metabolism constitute a subgroup of rare genetic conditions for which an increasing number of treatments has become available. To identify all currently treatable inborn errors of metabolism presenting with predominantly intellectual disability, we performed a systematic literature review.

Methods: We applied Cochrane Collaboration guidelines in formulation of PICO and definitions, and searched in Pubmed (1960–2011) and relevant (online) textbooks to identify 'all inborn errors of metabolism presenting with intellectual disability as major feature'. We assessed levels of evidence of treatments and characterised the effect of treatments on IQ/development and related outcomes.

Results: We identified a total of 81 'treatable inborn errors of metabolism' presenting with intellectual disability as a major feature, including disorders of amino acids (n=12), cholesterol and bile acid (n=2), creatine (n=3), fatty aldehydes (n=1); glucose homeostasis and transport (n=2); hyperhomocysteinemia (n=7); lysosomes (n=12), metals (n=3), mitochondria (n=2), neurotransmission (n=7); organic acids (n=19), peroxisomes (n=1), pyrimidines (n=2), urea cycle (n=7), and vitamins/co-factors (n=8). 62% (n=50) of all disorders are identified by metabolic screening tests in blood (plasma amino acids, homocysteine) and urine (creatine metabolites, glycosaminoglycans, oligosaccharides, organic acids, pyrimidines). For the remaining disorders (n=31) a 'single test per single disease' approach including primary molecular analysis is required. Therapeutic modalities include: sick-day management, diet, co-factor/vitamin supplements, substrate inhibition, stemcell transplant, gene therapy. Therapeutic effects include improvement and/or stabilisation of psychomotor/cognitive development, behaviour/psychiatric disturbances, seizures, neurologic and systemic manifestations. The levels of available evidence for the various treatments range from Level 1b,c (n=5); Level 2a,b,c (n=14); Level 4 (n=45), Level 4–5 (n=27). In clinical practice more than 60% of treatments with evidence level 4–5 is internationally accepted as 'standard of care'.

Conclusion: This literature review generated the evidence to prioritise treatability in the diagnostic evaluation of intellectual disability. Our results were translated into digital information tools for the clinician (www.treatable-id.org), which are part of a diagnostic protocol, currently implemented for evaluation of effectiveness in our institution. Treatments for these disorders are relatively accessible, affordable and with acceptable side-effects. Evidence for the majority of the therapies is limited however; international collaborations, patient registries, and novel trial methodologies are key in turning the tide for rare diseases such as these.

Contents

Abbreviations: DD, global developmental delay; ID(s), intellectual disability (-ies); IEM(s), inborn errors of metabolism(s); MPS, Mucopolysaccharidosis.

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1. Introduction

Intellectual disability (ID) is a life-long and debilitating condition with deficits in cognitive functioning (IQ<70) and adaptive skills [1,2]. ID is often associated with behavioural problems (autism, hyperactivity, aggressivity and self-injurious behaviour), epilepsy and other neurological disabilities, all resulting in psychological, social and economic burdens [3,4]. In children <5years of age with deficits in two or more developmental domains (e.g. fine/gross motor skills, speech, interaction, etc.), the term global developmental delay (DD) is applied [5]. Here we will use the term ID collectively for both ID and DD. ID is frequent, affecting 2–3% of children and adults worldwide. ID is the disease category with one of the largest health care costs [6]. The etiology of ID is diverse, including infectious, traumatic and toxic causes. Genetic etiologies constitute the most frequent cause and are demonstrable in more than 50% of individuals with ID [7], ranging from numeric and structural chromosomal abnormalities and submicroscopic Copy Number Variants to methylation abnormalities, and to single gene defects [8].

Current guidelines aimed at structuring the evaluation of genetic causes of ID, are based on frequencies of single conditions and yield of diagnostic methods and procedures [9]. Therefore, karyotyping and array-comparative genomic hybridisation, which yield a causal diagnosis in 20% of cases, is standard practice as part of the first-line investigation [10]. Unfortunately these high diagnostic yields do not translate into therapeutic benefit, as at the present time causal therapy is not available for most conditions identified by these investigations. One category of genetic conditions is amenable to treatment however: inborn errors of metabolism (IEMs). This group of single gene disorders is not systematically screened for [11], despite increasing opportunities to causally treat and profoundly improve prognosis.

The yield of routine metabolic investigations of ID/DD patients varies from 0.8 to 2.5% [7,9,12], but detailed metabolic reassessment yielded a previously unknown causative IEM in up to 14% of cases [13,14]. Based on these studies, concerns have been raised that treatable diagnoses may be missed if we weigh too heavily on current practice parameters [15]. In addition, during the past decades the number of IEM which has become amenable to causal therapy has constantly increased. Although technologies for better recognition have been introduced into clinical practice, this has not translated into practice guidelines for diagnostic evaluation children with ID such as those of the American College of Medical Genetics (1997) [16], the American Academy of Pediatrics (2006) [17], and the American Academy of Neurology (2003) [18]. To strengthen our level of understanding in an evidence-based manner, we performed a systematic literature review to: 1) investigate the number of treatable IEM presenting with ID; and 2) to characterise types of treatments and evidence for effect. In stark contrast to the general notion that only few IEMs are treatable, we identified as many as 81 IEMs with ID as a major clinical feature.

2. Methods and results

For the design of this systematic review we followed Cochrane Collaboration methodology (http://www.cochrane.org/training/cochrane-handbook) as closely as possible. All steps were performed by two independent reviewers (CvK and SS) with regular consensus meetings. The main goal of our review was to identify all treatable IEMs presenting with ID as a major feature. We characterised the clinical and diagnostic recognition patterns as well as treatment modalities pertinent to the identified IEMs, and made an attempt to assess the level of available evidence and effect of the various treatments on clinical outcome measures.

2.1. Identification and characterisation of treatable IEMs causing ID

2.1.1. Literature search

Definitions of terms relevant for the search strategy and key words for terms indicating developmental delay/intellectual disability, inborn error of metabolism, and treatment are shown in Table 1A and B.

We searched Pubmed (http://www.ncbi.nlm.nih.gov/pubmed; 1960–August 2011) using a combination of the keywords identified. We also reviewed all chapters of the textbook '*Metabolic and Molecular Bases of Inherited Disease*' [19] as well as the online version www.ommbid.com [20], with special attention to reports on treatment of IEMs presenting with ID.

2.1.2. Definition of outcomes

The ideal outcome of therapy for an IEM is improvement of IQ and related developmental scores. As improvement of co-morbid features such as epilepsy, neurologic, behavioural or psychiatric problems is often a prerequisite for improved cognitive outcomes these were included as 'secondary outcomes'. An example of such developmental improvement is seen in patients with GLUT-1 deficiency in whom the ketogenic diet is successful in controlling medicine refractory epilepsy [21]. Beneficial changes in neuro-imaging and neurologic deficits were also designated secondary outcomes, as for some disorders this is the most objective parameter of improvement, e.g. stemcell transplant in X-linked Adrenoleukodystophy [22]. Improvements in biochemical markers of disease indicating metabolic control were

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Table 1
Definitions and search terms.

A. Definitions used in systematic literature review.

Global developmental delay (DD): applied to age<5 years; significant delay (=performance two standard deviations or more below the mean on age-appropriate, standardised norm-referenced testing) in two or more of developmental domains including gross/fine motor skills, speech/language, cognition, social/personal, activities of daily living [2].

Intellectual disability (ID): applied to age≥5 years and manifesting before age 18 years, historically referred to as 'mental retardation'; intellectual functioning level (IQ) less than 70 to 75 and significant limitations in two or more adaptive skills [1,5].

Inborn error of metabolism (IEM): genetic disease involving a disorder of metabolism with confirmation based on the internationally accepted diagnostic test(s) for that IEM (gene mutations, enzyme deficiency, or specific biochemical marker). This term excludes endocrine disorders such as hypothyroidism and hyperinsulinism.

Causal of ID/DD: sufficient evidence in literature from bench and/or clinical research to make a pathophysiological relationship between IEM and ID/DD highly likely.

Treatable ID: if a particular therapeutic modality is capable of preventing or improving ID/DD phenotype, or halting/slowing neurocognitive decline (with acceptable adverse effects) in the IEM, ie positively influencing the 'outcome measures' .

Therapeutic modalities: dietary restriction/supplement, co-factor/-enzyme, vitamin, substrate inhibition, (small molecule) substrate reduction, enzyme replacement, bone marrow and hematopoietic stem cell transplant, gene therapy.

Outcome measure/effect: primary = IQ, developmental testing score/performance, survival; secondary = epilepsy, behaviour, psychiatric, neurological deficit (e.g. movement disorder), neuro-imaging, systemic symptoms influencing developmental/cognitive performance (e.g. ichtyosis, liver disease).

Levels of evidence: Level 1a = systematic review of RCT's, 1b = individual RCT, 1c = 'All or None' [=(prolongation of) survival with therapy]; Level 2a = systematic review of cohort studies, 2b = individual cohort study, 2c = 'Outcomes Research' [focussed on end results of therapy for chronic conditions, including functioning and quality of life (http://www.ahrq.gov/clinic.outfact.htm)]; Level 3 = systematic review of case–control studies; Level 4 = individual case–control study or case-series/report; Level 5 = expert opinion without critical appraisal; based on physiology, bench research or first principles.

Standard of care: a formal treatment process a physician will follow for a patient with a specific illness, which experts generally accept as 'best clinical practice'.

Individual patient basis: decision to start specific treatment depends on patient characteristics (ie disease stage), physician's opinion, availability of treatment, potential side-effects.

B. Terms used for search strategy in Pubmed (www.pubmed.org).

Developmental delay/intellectual disability: mental retardation, learning disorder(s), developmental disability/ disabilities, learning disability/disabilities, intellectual disability/disabilities, developmental delay, intelligence/classification, mentally disabled (persons), childhood/juvenile Alzheimer's, childhood/juvenile dementia, neurodegenerative disease].

Inborn error of metabolism: metabolic disease(s), inborn error(s) of metabolism, metabolic disorder(s), metabolic condition(s), inherited metabolic disease(s), inherited metabolic disorder(s), biochemical disease(s)].

Treatment: treatment, therapy, cure, trial, (dietary) supplement, (dietary) restriction, diet, substrate inhibition, small molecule substrate reduction, enzyme replacement, vitamin(s), co-factor(s), bone marrow transplant, hematopoietic stem cell transplant, umbilical cord blood transplant(−ation), gene therapy.

also designated secondary outcomes, but only if these correlated closely with neurodevelopmental outcome; e.g. Kuvan therapy which in addition to dietary phenylalanine restriction can further improve blood phenylalanine levels, thereby prevent brain damage) [23]. Finally, as some therapies make the difference between life and death (e.g. haematopoietic stemcell transplant for Hurler syndrome) [24], 'survival' which obviously allows for development was also included as an outcome measure.

2.1.3. Inclusion/exclusion criteria

In general, we considered only IEMs for which a) a causal relationship with ID is likely; b) articles which have been published in English language and peer-reviewed journals, reporting one or more of the defined treatment outcomes in human(s).

We included conditions irrespective of whether they are captured in Newborn Screening panels.

We included IEMs presenting with severe co-morbid features such as epilepsy (e.g. Pyridoxine Dependent Epilepsy due to *ALDH7A1* deficiency) and or congenital malformations (Smith–Lemli–Opitz Syndrome), because despite early presentation, the aetiology may remain unclear until later in life thus presenting as unclarified complex ID.

IEMs for which treatment has only recently become available and/or reported to be effective, were included if the case report(s) provided a solid and detailed description of outcome: this applied in the following instances: cPMP (Cyclic Pyranopterin Monophosphate/Precursor Z) treatment resulted in seizure contol and improved psychomotor development and head growth in an infant with Molybdenum Co-factor Deficiency [25]; Creatine, glycine, and arginine therapy improved epilepsy and behaviour in a female with creatine transporter deficiency [29]; Arginine therapy has proven effective in preventing metabolic stroke and thus slowing neurodegeneration both clinically and on neuro-imaging in patients with MELAS syndrome (13513G>A mutations) [26].

In case of contradictory literature reports on presence versus absence of therapeutic effect in an IEM, the quality and level of evidence were weighed in combination with the pathophysiologic rationale and/or target of therapy. Effects of cholesterol supplements and statins in Smith–Lemli–Opitz patients are contradictory in the literature, but included because of the qualitative strength of the study designs (including outcome measures) and reporting of the positive reports and the rationale behind the treatment itself. [27,28]. This is true also for creatine, arginine and glycine supplements in Creatine Transporter Deficiency. Mercimek-Mahmutoglu et al. (2010) [29] reported positive effects on behaviour and seizure control for single female patient, whilst Valayannapoulos et al. [30] identified improvements in muscular symptoms but not in cognitive or psychiatric manifestations.

We excluded IEMs for which ID is not a consitent finding and/or for which treatment has not or inconsistently proven effect on intellectual or related outcomes:

- In Galactosemia treatment with a galactose free diet prevents life-threatening liver failure, but despite good diet control a majority of patients develops speech delay, low IQ scores and ataxia [31];
- In Prolidase deficiency oral Ascorbate and Manganese (co-factor of prolidase), consistently improves skin ulcers but neurological outcomes are only infrequently affected [32];
- In Hartnup disease and Tyrosinemia type 3, ID is not a consistent part of the clinical picture [33,34] and treatment has only been shown to be effective for skin lesions.
- Farber disease (a lysosomal storage disorder) causes somatic problems due to the granulomatous inflammation; but for mild cases – the only form amenable to treatment with haematopoietic stem cell transplanation – ID is *not* part of the clinical picture [35].
- In histidinemia, which was previously considered a treatable ID, natural history studies of cases identified through newborn screening suggested that there is likely no causal relationship between the biochemical trait and ID [36].

Finally we excluded IEMs for which reports of therapeutic effect are only available in conference abstract form. For example, Vockley et al. [37] presented two patients with SC4MOL deficiency (OMIM#607545), a defect in cholesterologenesis, with positive response to statins and cholesterol/bile acid supplements, at the American Medical Genetics 2010 meeting but the case has not been published yet. Another example is the presentation at the 'Society for the Study of Inborn Errors of Metabolism' Annual Symposium 2011 by Cario et al. [38] of Dihydrofolate Reductase Deficiency (OMIM#613839); folinic acid reportedly improves the features of this complex hematological and neurological disease accompanied by cerebral folate deficiency. Also, case reports of treatable IDs referred to only as 'unpublished data' in an article were excluded from this review; e.g. S-adenosylmethionine supplementation in

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PRPS1 spectrum diseases (phosphoribosylpyrophosphate synthetase) by de Brouwer et al. [39].

2.1.4. Treatable IDs

The literature search in Pubmed (1960–2011) yielded 2945 articles. Based on the defined inclusion/exclusion criteria we identified 71 treatable IDs. The search in the textbook '*Metabolic and Molecular Bases of Inherited Disease*' [19] and its online version www.ommbid.org [20] yielded another 10 treatable ID. All 81 treatable IDs including MIM number, biochemical deficiency and corresponding gene (s), are listed in Table 2. In this table IEMs are grouped according to the biochemical phenotype as presented in standard textbooks, and alphabetically. This type of classification has proven valuable for didactic purposes and systematic comprehension of IEMs.

2.1.5. Clinical features

The main clinical recognition patterns of each of the 81 treatable IEM with ID as a predominant feature, are shown in Supplements I and II in the online version of this journal. These supplementary tables lists the main clinical presentation of each disease, i.e. *the most characteristic, specific and consistent signs and symptoms*.

We subdivided the clinical features in neurological and non-neurological:

Neurologic features include ataxia, behavioural disturbance, dementia, dystonia, encephalopathic crisis, epilepsy, hearing loss, hypotonia/myopathy, neuro-imaging abnormalities (basal ganglia, cerebellum, cerebrum, cysts/dysgenesis, white matter, mixed), neuropathy, ocular movement abnormality, psychiatric disturbance, sensorineural hearing loss, spasticity, stroke, vision loss. All IEM except one (Tyrosinemia type II) are associated with at least one additional prominent neurologic feature, of which the most frequent are epilepsy and various types and degrees of movement disorders (e.g. spasticity, dyskinesia, ataxia etc.). However, many of these conditions can present with ID as sole feature for a considerable time prior to manifestation of the full phenotype. Examples include disorders of creatine sythesis and transport, female OTC deficiency, unrecognised PKU, and mild Homocystinuria.

The non-neurologic features affect the following anatomic/organ systems: bones and joints, dermatology, endocrinology, eye, facial dysmorphism, growth and stature, heart, gastrointestinal, haematology, immunology, kidney, liver, odour. For 55 out of the 81 (69%) treatable IEM, a non-neurologic feature is a prominent part of the phenotype.

We emphasise that that absence or presence of specific signs and/or symptoms not fitting our list does not rule out the specific disorder in a patient. Also, these lists are subject to change as new diagnostic techniques provide novel insights into the spectrum of phenotypic presentation and natural history of metabolic diseases. For the most recent and updated version of these lists, please visit our website www.treatable-id-org.

2.1.6. Diagnostic tests

To facilitate a practical guide for biochemical and genetic diagnosis, we assessed which tests are necessary to diagnose each of the conditions. Accordingly we grouped the diseases into IEMs diagnosed via 'metabolic screening tests' versus IEMs diagnosed via 'single test per single disease' approach. As screening tests we defined those tests in blood and urine, which are readily available in biochemical laboratories in most developed countries, and with a yield of at least 2 IEMs per test. Fig. 1 depicts the type and the yield of the specific metabolic screening tests, demonstrating that urine organic acid profiling is a powerful screening test with the potential to identify 22 IEMs.

Overall, these screening tests reliably provide clues for diagnosis for 62% (50/81) of all treatable IDs. For the remaining 31 treatable IDs (38%), a specific 'one test per one disease' approach is required. The respective conditions and the nature of the most specific diagnostic tests are shown in Table 3. Treatable IDs, for which biochemical markers are difficult to interpret, and/or conventional diagnostic approach requires an invasive procedure or poorly accessible test (ie only performed in a very few centres worldwide) are shown in Table 4. Primary gene analysis is likely the most effective diagnostic approach for the 20 genes underlying these conditions.

2.2. Identification and characterisation of treatment modalities

2.2.1. Literature search

To ensure comprehensiveness of treatment modalities, we identified all relevant references reporting outcome/effect for each of the selected treatments and IEMs. We searched Pubmed (1960–2011) combining as keywords all known names for each IEM as well as gene and enzyme with the relevant therapeutic modalities. For all IEMs the pages on 'therapy' of each relevant chapter in the textbook '*Metabolic and Molecular Bases of Inherited Disease*' [19] as well as the online version www.ommbid.com [20] were searched as well the textbook '*Inborn Metabolic Diseases: Diagnosis and Treatment*' [40]. The Cochrane Database of Systematic Reviews (www.cochrane.org/cochrane-reviews) and Cochrane Central Register of Controlled Trials (http://www.ovid.com/site/products/ovidguide/cctrdb.htm) were searched using as keywords the names for each IEM.

A total of 91 causal therapies were identified, each with a proven effect on primary and/or secondary outcomes as previously defined. For 10 IEMs two distinct treatments are available. An overview of all therapies for each IEM is provided in Table 5, along with corresponding level (s) of evidence, therapeutic effect(s), current use in clinical practice.

2.2.2. Levels of evidence

We assessed the *quality of evidence* for the beneficial effect of each therapeutic modality, on primary and/or secondary outcome(s) measure for each corresponding IEM by adopting the 'Oxford Centre for Evidence Based Medicine Levels of Evidence 2009' approach in 'best available' fashion to the relevant peer-reviewed literature (http://www.cebm.net). Detailed critical appraisal of each literature report for the outcome of causal treatments in the 81 IEMs was outside of the scope of the study; instead we screened the studies for general quality of study design (incl. outcome measures) and reporting. As the level of evidence of treatment may vary per literature report, the highest available level was awarded based on those studies with qualitatively strong study design and reporting. In summary, for 21% of causal therapies, the level of evidence is high (1 or 2), whilst for the remainder (almost 80%) the evidence ranks at levels 4 to 5.

2.2.3. Effect(s) of treatments on outcome measures

We defined and coded outcome measures as follows: treatment improves psychomotor/cognitive development/IQ (A); treatment improves behaviour (B); treatment prevents acute metabolic decompensation (C); treatment prevents, halts, or slows deterioration (D); treatment improves neurological manifestations (E); treatment improves seizure/epilepsy control (F); treatment improves systemic manifestations (G). Outcome measures of the various treatments are shown in Table 5. Most therapies sorted a positive effect on multiple outcomes, varying from 1 to 5. Interestingly improvement of cognitive/psychomotor development, ie the primary outcome, is only achieved for 20% of IEM whilst for the majority of treatable IDs the secondary outcomes are positively influenced by therapy.

2.2.4. Treatments and clinical practice

For rare diseases, the level of evidence is usually not decisive in treatment protocols; therefore we also defined the clinical significance according to the current clinical practice in treating these IEMs, by specifying whether administration of a specific therapy is considered 'Standard of

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Table 2
Overview of all 81 treatable IDs.
In this table, the IEMs are grouped according to the biochemical phenotype as presented in standard textbooks, and alphabetically. Of note, primary CoQ deficiency was considered as one single IEM even though more though 6 genes have been described; this is true as well for MELAS and Pyruvate Dehydrogenase Complex deficiency.

Biochemical category	Disease name	OMIM#	Biochemical deficiency	Gene(s)
Amino acids	HHH syndrome (hyperornithinemia, hyperammonemia, homocitrullinemia)	238970	Ornithine translocase	*SLC25A15 (AR)*
	l.o. Non-ketotic hyperglycinemia	605899	Aminomethyltransferase/glycine decarboxylase/ glycine cleavage system H protein	*AMT/GLDC/GCSH (AR)*
	Phenylketonuria	261600	Phenylalanine hydroxylase	*PAH (AR)*
	PHGDH deficiency *(Serine deficiency)*	601815	Phosphoglycerate dehydrogenase	*PHGDH (AR)*
	PSAT deficiency *(Serine deficiency)*	610992	Phosphoserine aminotransferase	*PSAT1 (AR)*
	PSPH deficiency *(Serine deficiency)*	614023	Phosphoserine phosphatase	*PSPH (AR)*
	Tyrosinemia type II	276600	Cytosolic tyrosine aminotransferase	*TAT (AR)*
Cholesterol & bile acids	Cerebrotendinous xanthomatosis	213700	Sterol-27-hydroxylase	*CYP27A1 (AR)*
	Smith–Lemli–Opitz Syndrome	270400	7-Dehydroxycholesterol reductase	*DHCR7 (AR)*
Creatine	AGAT deficiency	612718	Arginine: glycine amidinotransferase	*GATM (AR)*
	Creatine transporter Defect	300352	Creatine transporter	*SLC6A8 (X-linked)*
	GAMT deficiency	612736	Guanidino-acetate-N-methyltransferase	*GAMT (AR)*
Fatty aldehydes	Sjögren–Larsson syndrome	270200	Fatty aldehyde dehydrogenase	*ALDH3A2 (AR)*
Glucose transport & regulation	GLUT1 deficiency syndrome	606777	Glucose transporter blood–brain barrier	*SLC2A1 (AR)*
	Hyperinsulinism hyperammonemia syndrome	606762	Glutamate dehydrogenase superactivity	*GLUD1 (AR)*
Hyperhomocysteinemia	Cobalamin C deficiency	277400	Methylmalonyl-CoA mutase and homocysteine : methyltetrahydrofolate methyltransferase	*MMACHC (AR)*
	Cobalamin D deficiency	277410	C2ORF25 protein	*MMADHC (AR)*
	Cobalamin E deficiency	236270	Methionine synthase reductase	*MTRR (AR)*
	Cobalamin F deficiency	277380	Lysosomal cobalamin exporter	*LMBRD1 (AR)*
	Cobalamin G deficiency	250940	5-Methyltetrahydrofolate-homocysteine S-methyltransferase	*MTR (AR)*
	Homocystinuria	236200	Cystathatione β-synthase	*CBS (AR)*
	l.o. MTHFR deficiency	236250	Methylenetetrahydrofolate reductase deficiency	*MTHFR (AR)*
Lysosomes	α-Mannosidosis	248500	α-Mannosidase	*MAN2B1 (AR)*
	Aspartylglucosaminuria	208400	Aspartylglucosaminidase	*AGA (AR)*
	Gaucher disease type III	231000	ß-Glucosidase	*GBA (AR)*
	Hunter syndrome (MPS II)	309900	Iduronate-2-sulfatase	*IDS (X-linked)*
	Hurler syndrome (MPS I)	607014	α-L-iduronidase	*IDUA (AR)*
	l.o. Metachromatic leukodystrophy	250100	Arylsulfatase A	*ARSA (AR)*
	Niemann–Pick disease type C	257220	Intracellular transport cholesterol & sphingosines	*NPC1 NPC2 (AR)*
	Sanfilippo syndrome A (MPS IIIa)	252900	Heparan-N-sulfatase	*SGSH (AR)*
	Sanfilippo syndrome B (MPS IIIb)	252920	N-acetyl-glucosaminidase	*NAGLU (AR)*
	Sanfilippo syndrome C (MPS IIIc)	252930	Acetyl-CoA glucosamine-N-acetyl transferase	*HGSNAT (AR)*
	Sanfilippo syndrome D (MPS IIId)	252940	N-acetyl-glucosamine-6-Sulfatase	*GNS (AR)*
	Sly syndrome (MPS VII)	253220	β-glucuronidase	*GUSB (AR)*
Metals	Aceruloplasminemia	604290	Ceruloplasmin (iron homeostasis)	*CP (AR)*
	Menkes disease/Occipital horn syndrome	304150	Copper transport protein (efflux from cell)	*ATP7A (AR)*
	Wilson disease	277900	Copper transport protein (liver to bile)	*ATP7B (AR)*
Mitochondria	Co enzyme Q10 deficiency	607426	Coenzyme Q2 or mitochondrial parahydroxybenzoate-polyprenyltransferase; aprataxin; prenyl diphosphate synthase subunit 1; prenyl diphosphate synthase subunit 2; coenzyme Q8; coenzyme Q9	*COQ2, APTX, PDSS1, PDSS2, CABC1, COQ9 (most AR)*
	MELAS	540000	Mitochondrial energy deficiency	*MTTL1, MTTQ, MTTH, MTTK, MTTC, MTTS1, MTND1, MTND5, MTND6, MTTS2 (Mt)*
	PDH complex deficiency	OMIM# according to each enzyme subunit deficiency: 312170; 245348; 245349	Pyruvate dehydrogenase complex (E1α, E2, E3)	*PDHA1 (X-linked), DLAT (AR), PDHX (AR)*
Neurotransmission	DHPR deficiency (*biopterin deficiency*)	261630	Dihydropteridine reductase	*QDPR (AR)*
	GTPCH1 deficiency (*biopterin deficiency*)	233910	GTP cyclohydrolase	*GCH1 (AR)*
	PCD deficiency (*biopterin deficiency*)	264070	Pterin-4α-carbinolamine dehydratase	*PCBD1 (AR)*
	PTPS deficiency (*biopterin deficiency*)	261640	6-Pyruvoyltetrahydropterin synthase	*PTS (AR)*
	SPR deficiency (*biopterin deficiency*)	612716	Sepiapterin reductase	*SPR (AR)*
	SSADH deficiency	271980	Succinic semialdehyde dehydrogenase	*ALDH5A1 (AR)*
	Tyrosine Hydroxylase Deficiency	605407	Tyrosine Hydroxylase	*TH (AR)*
Organic acids	3-Methylcrotonyl glycinuria	GENE OMIM # 210200; 210210	3-Methylcrotonyl CoA carboxylase (3-MCC)	*MCC1/MCC2 (AR)*
	3-Methylglutaconic aciduria type I	250950	3-Methylglutaconyl-CoA hydratase	*AUH (AR)*
	β-Ketothiolase deficiency	203750	Mitochondrial acetoacetyl-CoA thiolase	*ACAT1 (AR)*
	Cobalamin A deficiency	251100	MMAA protein	*MMAA (AR)*
	Cobalamin B deficiency	251110	Cob(I)alamin adenosyltransferase	*MMAB (AR)*
	Ethylmalonic encephalopathy	602473	Mitochondrial sulfur dioxygenase	*ETHE1 (AR)*

(continued on next page)

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Table 2 (*continued*)

Biochemical category	Disease name	OMIM#	Biochemical deficiency	Gene(s)
	l.o. Glutaric acidemia I	231670	Glutaryl-CoA dehydrogenase	*GCDH (AR)*
	Glutaric acidemia II	231680	Multiple acyl-CoA dehydrogenase	*ETFA, ETFB, ETFDH (AR)*
	HMG-CoA lyase deficiency	246450	3-Hydroxy-3-methylglutaryl-CoA lyase	*HMGCL (AR)*
	l.o. Isovaleric acidemia	243500	Isovaleryl-CoA dehydrogenase	*IVD (AR)*
	Maple syrup urine disease (variant)	248600	Branched-chain 2-ketoacid complex	*BCKDHA/BCKDHB/ DBT (AR)*
	l.o. Methylmalonic acidemia	251000	Methylmalonyl-CoA mutase	*MUT (AR)*
	MHBD deficiency	300438	2-Methyl-3-hydroxybutyryl-CoA dehydrogenase	*HSD17B10 (X-linked recessive)*
	mHMG-CoA synthase deficiency	605911	Mitochondrial 3-hydroxy-3-Methylglutaryl-CoA synthase	*HMGCS2 (AR)*
	l.o. Propionic acidemia	606054	Propionyl-CoA carboxylase	*PCCA/PCCB (AR)*
	SCOT deficiency	245050	Succinyl-CoA 3-oxoacid CoA transferase	*OXCT1 (AR)*
Peroxisomes	X-linked adrenoleukodystrophy	300100	Peroxisomal transport membrane protein ALDP	*ABCD1 (X-linked)*
Pyrimidines	Pyrimidine 5-nucleotidase superactivity	GENE OMIM # 606224	Pyrimidine-5-nucleotidase Superactivity	*NT5C3 (AR)*
Urea cycle	l.o. Argininemia	207800	Arginase	*ARG1 (AR)*
	l.o. Argininosuccinic aciduria	207900	Argininosuccinate lyase	*ASL (AR)*
	l.o. Citrullinemia	215700	Argininosuccinate Synthetase	*ASS1 (AR)*
	Citrullinemia type II	605814	Citrin (aspartate–glutamate carrier)	*SLC25A13*
	l.o. CPS deficiency	237300	Carbamoyl phosphate synthetase	*CPS1 (AR)*
	l.o. NAGS deficiency	237310	N-acetylglutamate synthetase	*NAGS (AR)*
	l.o. OTC Deficiency	311250	Ornithine transcarbamoylase	*OTC (X-linked)*
Vitamins/co-factors	Biotinidase deficiency	253260	Biotinidase	*BTD (AR)*
	Biotin responsive basal ganglia disease	607483	Biotin transport	*SLC19A3(AR)*
	Cerebral folate receptor-α deficiency	613068	a.o. Cerebral folate transporter	*FOLR1 (AR)*
	Congenital intrinsic factor deficiency	261000	Intrinsic factor deficiency	*GIF (AR)*
	Holocarboxylase synthetase deficiency	253270	Holocarboxylase synthetase	*HLCS (AR)*
	Imerslund Gräsbeck syndrome	261100	IF-Cbl receptor defects (cubulin/amnionless)	*CUBN & AMN (AR)*
	Molybdenum co-factor deficiency type A	252150	Sulfite oxidase & xanthine dehydrogenase & aldehyde oxidase	*MOCS1, MOCS2, (AR)*
	Pyridoxine dependent epilepsy	266100	Pyridoxine phosphate oxidase	*ALDH7A1 (AR),*
	Thiamine responsive encephalopathy	606152	Thiamine transport	*SLC19A3 (AR)*

l.o. = late-onset form.
Mode of inheritance: for each gene is denoted as AD = autosomal dominant, AR = autosomal recessive, Mt = mitochondrial; X-linked = X-linked.
OMIM#: denotes the Online Mendelian Inheritance in Man (www.omim.org) number for the specific disease (versus gene), unless otherwise indicated.

Care' or rather decided on an 'Individual (Patient) Basis'. We defined '*Standard of Care*' as a formal treatment process a physician will follow for a patient with a specific illness, which experts generally accept as 'best clinical practice'. The majority for all treatments (n = 63/69%) are considered Standard of Care. For the remaining 31%, the decision to initiate treatment is made on an '*Individual (Patient) Basis*', i.e. a combination of patient characteristics (disease stage: e.g. Loes Score for X-linked Adrenoleukodystrophy), physician's opinion, availability of treatment, potential side-effects.

For all 91 therapies, Table 6 provides a numeric overview of distribution amongst the various levels of evidence levels, and for each level separately the distinction between types of clinical practice. Not suprisingly, all treatments for these rare metabolic diseases with high evidence levels – ranking at 1 or 2 (n = 19/ 21%) – are internationally accepted as Standard of Care except for the stemcell transplant for X-linked Adrenoleukodystrophy. However, for therapies with low levels of evidence (4–5: case series/reports or expert opinion) which constitute the bulk of 91 treatments, this also true. More than 60% (45/72) is accepted as 'best clinical practice', despite solid evidence for therapeutic effect.

2.2.5. References and information sources

Given the limited space available in printed journals, it was not possible to generate a detailed list of references for each treatable IEM. We aimed to provide relevant overview articles for each addressing general aspects of the disease as well as treatment specifics. For a comprehensive information on each of the treatable IDs, we kindly refer the reader to the 'disease pages' on our website and to the textbooks '*Inborn Metabolic Diseases: Diagnosis and Treatment*' [40] and '*Metabolic and Molecular Bases of Inherited Disease*' [19].

3. Discussion

This systematic review is the first evidence-based approach to demonstrate the significance of inborn errors of metabolism (IEMs) in the diagnostic work up of intellectual disability/developmental delay. Whilst current recommendations for the diagnostic work up of ID prioritise frequency of conditions and yield of diagnostic tests, our approach prioritises treatability over frequency and strategises metabolic/biochemical evaluation in a two-tiered fashion.

Several reviews have been published about metabolic causes of intellectual disability, mostly reflecting expert opinions and individual expertise in the field of IEM [41–43]. The need for multiple tests to exclude a few rare to ultra-rare conditions, and the limited availabilities of laboratories offering comprehensive diagnostic testing, explains why outside highly specialised centres, metabolic work up of patients with ID is tedious, cost consuming and still remains incomplete in many cases. Because of all these limitations, the diagnostic yield of metabolic testing has been reportedly low in patients presenting with ID. Our approach focusses on treatable IEM, because even rare, treatability clearly justifies extensive work-up of otherwise unrecognised conditions.

In this review we identified 81 IEMs with ID as major clinical feature. Arguably, the incidence of the individual 81 conditions is low, ranging from 1:10,000 to less than 1:200,000 [53]. Their recognition is of importance however, because treatability overweights the rare nature of these conditions [15]. Collectively their incidence in the ID

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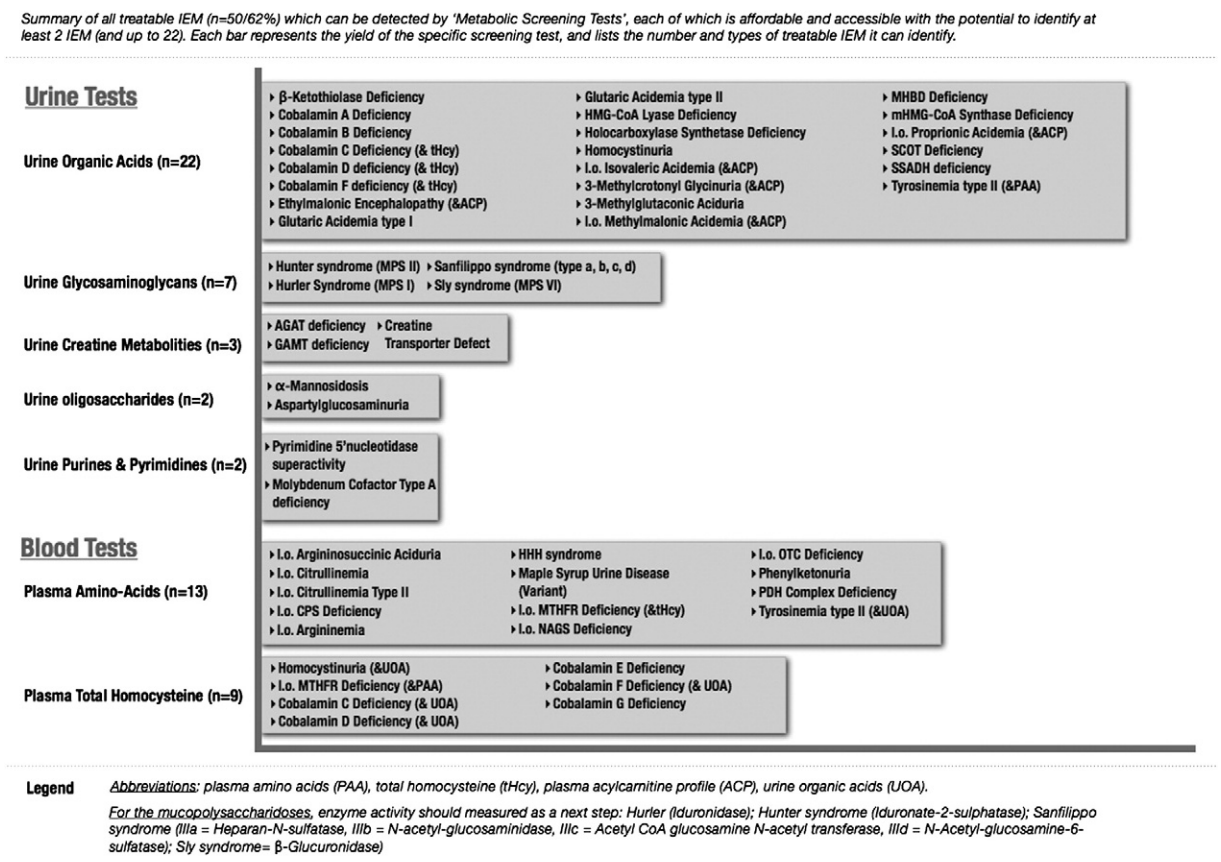

Fig. 1. Bar graph depicting the yield of 'Metabolic Screening Tests'.

population may be much higher than currently estimated, as shown by a study performed in the Sylvia Tòth centre in the Netherlands [13]. Through a multidisciplinary approach and expertise in IEMs, the diagnostic yield in individuals with ID exceeded 10%, standing in sharp contrast to frequently quoted yields of 0.5%.

The majority of conditions identified in this systematic review presents with more multiple co-morbidities including epilepsy, neurologic symptoms and signs, and behavioural and psychiatric disturbances. Systemic manifestations occur in 69% of conditions. However, the clinical spectrum of treatable ID is variable and the absence of co-morbidites does not exclude the presence of a treatable ID. Rather the clinical picture is determined by the state of disease progression and by particular disease variants. For example, progressive neurologic decline is characteristic of advanced stages of X-linked Adrenoleukodystrophy. However, signs of ID and subtle loss of cognitive functions with behavioural disturbances are often the first manifestations. Recognition of the diagnosis at this early disease stage opens a unique window of opportunity for causal treatment with stem cell transplantation, which at a later stage is not effective any more. Thus whilst clinical co-morbidities are traditionally considered characteristic of metabolic causes of ID, the absence of such co-morbidities does not exclude them. This is true also for neurodegeneration, as many of the IEMs on our list present with 'stable ID', i.e. without a history of regression or plateauing.

'Late-onset' or atypical variants of conditions typically presenting as acute metabolic decompensation in the neonatal period deserve special attention. Whilst patients with acute metabolic crisis are diagnosed before they are assessed for developmental delay/intellectual disability, the clinical presentation of the late onset forms of these conditions is unspecific and of chronic nature. For example, OTC deficiency typically manifests with severe neonatal hyperammonemia with extremely poor outcomes in affected males, whereas females with late-onset variants with OTC deficiency often present with ID and/or behavioural problems as only manifestation(s) [44]. Timely recognition of the underlying metabolic defect allowing appropriate treatment to control blood ammonia levels, not only helps to prevent acute hyperammonic crises at a later stage of life, but also improves cognitive functions and behaviour.

We found that a considerable proportion of treatable IDs (62%) can be reliably detected through a panel of metabolic screening tests on blood (total homocysteine, plasma aminoacids) and urine (organic acids, purines and pyrimidines, creatine and guanidinoacetate, glycosaminoglycans, oligosaccharides). In general these tests are offered by most biochemical genetics laboratories around the world at affordable prices and with considerable yield per test. Careful interpretation of results – in particular for mild and atypical disease variants – seems to be crucial in this respect. Foremost interpretation of results below the normal range is challenging. For example, a subtle decrease of both plasma and CSF serine levels was initially not considered significant in a 2-year old girl with developmental delay and seizures sufficiently controlled with antiepileptic mono-therapy; however, thorough diagnostic work-up revealed two potentially disease-causing mutations on the *PGDH* gene along with decreased serine synthesis in cultivated skin fibroblasts. Diagnosis of a serine biosynthesis defect in this patient not only extends the phenotypic spectrum of the disease, but more importantly provides the opportunity to start serine supplements with the aim of improving neurologic status and development as well as prevention of any future deterioration (*personal communication CvK and SS*). A systematic approach including screening of all patients with ID under standardised pre-analytical conditions and with careful analysis of apparently unspecific results will show the true diagnostic value of these metabolic screening tests, in particular in the recognition of mild and atypical variants of treatable amino-acidopathies and organic acidurias.

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Table 3
All IEMs (n = 31/38%) requiring a 'specific test' for diagnosis.
The IEMs are listed per biochemical category, and for each the specific biochemical/genetic diagnostic test. Abbreviations include: CSF = cerebrospinal fluid, l.o. = late-onset form, PAA = plasma amino acids, Phe = phenylalanine.

Biochemical category	Disease	Specific diagnostic test
Amino acids	l.o. Non-ketotic hyperglycinemia	CSF amino acids (& PAA)
	PHGDH deficiency (*serine deficiency*)	CSF amino acids (& PAA)
	PSAT deficiency (*serine deficiency*)	CSF amino acids (& PAA)
	PSPH deficiency (*serine deficiency*)	CSF amino acids (& PAA)
Cholesterol/bile acids	Cerebrotendinous Xanthomatosis	Plasma cholestanol
	Smith–Lemli–Opitz Syndrome	Plasma 7-dehydrocholesterol:cholesterol ratio
Fatty aldehydes	Sjögren–Larsson syndrome	Fatty aldehyde dehydrogenase enzyme activity
Glucose transport & regulation	GLUT1 deficiency syndrome	CSF glucose:plasma glucose ratio
	Hyperinsulinism hyperammonemia syndrome	*GDH* gene analysis (& ammonia, glucose, insulin)
Lysosomal	Gaucher disease type III	Glucocerebrosidase enzyme activity (lymphocytes)
	l.o. Metachromatic leukodystrophy	Arylsulfatase-A enzyme activity
	Niemann–Pick disease type C	Filipin staining test (fibroblasts) & *NPC1*/*NPC2* gene analyses
Metals	Aceruloplasminemia	Serum ceruloplasmin, copper, iron, ferritin
	Menkes disease-occipital horn syndrome	Serum copper & ceruloplasmin; urine deoxypyridinoline
	Wilson disease	Serum copper & ceruloplasmin, urine copper
Mitochondrial	Co enzyme Q10 deficiency	Coenzyme Q10 (fibroblasts) & gene(s) analysis (see Table 2)
	MELAS	Mitochondrial DNA mutation testing (see Table 2)
	PDH complex deficiency	Blood & CSF lactate:pyruvate ratio (enzyme activity, gene(s) analysis)
Neurotransmitters	DHPR deficiency (*biopterin deficiency*)	CSF neurotransmitters & biopterin loading test
	GTPCH deficiency (*biopterin deficiency*)	CSF neurotransmitters & biopterin loading test
	PCD deficiency (*biopterin deficiency*)	CSF neurotransmitters & biopterin loading test
	PTPS deficiency (*biopterin deficiency*)	CSF neurotransmitters & biopterin loading test
	SPR deficiency	CSF neurotransmitters & biopterin/Phe loading test
	Tyrosine hydroxylase deficiency	CSF neurotransmitters & *TH* gene analysis
Peroxisomal	X-linked Adrenoleukodystrophy	Plasma Very Long Chain Fatty Acids
Vitamins/co-factors	Biotinidase deficiency	Biotinidase enzyme activity
	Biotin responsive basal ganglia disease	*SLC19A3* gene analysis
	Cerebral folate receptor deficiency	CSF tetrahydrofolate
	Congenital intrinsic factor deficiency	Plasma Vit B12, folate
	Imerslund Gräsbeck syndrome	Plasma Vit B12, folate
	Pyridoxine dependent epilepsy	Urine α-aminoadipic semialdehyde & plasma pipecolic acid
	Thiamine-responsive encephalopathy	*SLC19A3* gene analysis

The clinical signs and symptoms may be clue to diagnosis for those conditions, which are not detectable by any of the aforementioned screening tests. In this review we indentified 31 conditions which require a 'single test per single disease' approach. As many of these tests are invasive (e.g. requiring skin biopsies), and expensive (because laborious and offered only by a few laboratories worldwide), a careful clinical differential diagnosis is mandatory for a time- and cost-effective diagnostic evaluation.

Primary gene analysis is a way to enhance the diagnostic yield in conditions with unspecific clinical and biochemical presentation. For example, low urinary excretion of guanidinoacetate is characteristic of AGAT deficiency, a treatable disorder of creatine synthesis, but the detection of low levels continues to pose an analytical challenge, as currently available methods mainly detect extreme elevations of accumulating metabolites. The current diagnostic approach to Niemann–Pick Disease Type C requires demonstration of free cholesterol via filipin staining in cultivated skin fibroblasts. This test is invasive, time- and cost-consuming, available only in a limited number of labs worldwide and not always sensitive. In the future, high-throughput sequencing technologies will likely lower the diagnostic threshold for such disorders, through facilitation of analysis of multiple genes in one sample for afforfable prices. Advances in sequencing coverage, bio-informatics and insight into the significance of detected mutations is prerequisite.

Table 4
IEMs (n = 13) for which molecular analysis might serve as the primary 'specific test'.

Direct molecular or gene(s) analysis was deemed the most appropriate diagnostic approach for an IEM if: the biochemical marker is unavailable or unreliable *and*/*or* the test requires an invasive procedure *and*/*or* the test is difficult to access. This table lists a total of 13 such IEMs with 30 encoding genes.

IEM	Gene(s)
AGAT deficiency	*AGAT*
Biotin responsive basal ganglia disease	*SLC19A3*
Cerebral glucose transporter deficiency	*SLC6A19*
Co enzyme Q10 deficiency	*COQ2, APTX, PDSS1, PDSS2, CABC1, COQ9*
l.o. CPS deficiency	*CPS*
Creatine transporter deficiency	*SLC6A8*
Hyperinsulinism–hyperammonia syndrome	*GDH*
MELAS	*MTTL1, MTTQ, MTTH, MTTK, MTTC, MTTS1, MTND1, MTND5, MTND6, MTTS2*
l.o. NAGS deficiency	*NAGS*
Niemann-Pick disease type C	*NPC1* & *NPC2*
Serine biosynthesis defects	*PHGDH, PSAT, PSPH*
Sjögren–Larssen disease	*FALDH*
Thiamine-responsive encephalopathy	*SLC19A3*

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Table 5
Overview of all causal therapies (n = 91).
This Table provides an overview of the specific therapy/-ies available for each IEM with relevant level(s) of evidence, therapeutic effect(s) on primary and/or secondary outcomes and use in clinical practice. For 10 IEMs, two therapies are available; these are listed separately (in brackets).

Disease name	Therapeutic modality (−ies)	Level of evidence	Clinical practice	Treatment effect	Literature references
Aceruloplasminemia	Iron chelation	4	Standard of care	D,E	[45–47]
(X-linked)adrenoleukodystrophy	Stemcell transplantation (Gene therapy)	1c (5)	Individual basis (Individual basis)	D,E (D,E)	[48–50]
AGAT deficiency	Creatine supplements	4	Standard of care	A,D	[51–53]
α-Mannosidosis	Haematopoietic stem cell transplantation	4-5	Individual basis	D	[54]
l.o. Argininemia	Dietary protein restriction, arginine supplement, sodium benzoate, phenylbutyrate (Liver transplantation)	2b (4)	Standard of care (Individual basis)	B,C,D,E,F,G (C)	[55–61]
l.o. Argininosuccinic aciduria	Dietary protein restriction, arginine supplement, sodium benzoate, phenylbutyrate (liver transplantation)	2b (4)	Standard of care (individual basis)	B,C,D,E,F,G (C)	[55–58,60,61]
Aspartylglucosaminuria	Haematopoietic stem cell transplantation	4-5	Individual basis	D	[62]
β-Ketothiolase deficiency	Avoid fasting, sickday management, protein restriction	5	Standard of care	C	[63–65]
Biotin responsive basal ganglia disease	Biotin supplement	4	Standard of care	A,E	[66]
Biotinidase deficiency	Biotin supplement	2c	Standard of care	A,E,G	[67]
Cerebral folate receptor-α deficiency	Folinic acid	4	Standard of care	A,D,E,F	[68,69]
Cerebrotendinous xanthomatosis	Chenodesoxycholic acid, HMG reductase inhibitor	4	Standard of care	B,D,E,G	[70–72]
l.o. Citrullinemia	Dietary protein restriction, arginine supplement, sodium benzoate, phenylbutyrate (Liver transplantation)	2b (4)	Standard of care (Individual basis)	B,C,D,E,F,G (C)	[55–57,60,61]
Citrullinemia type II	Dietary protein restriction, arginine supplement, sodium benzoate, phenylbutyrate (Liver transplantation)	2b (4)	Standard of care (Individual basis)	B,C,D,E,F,G (C)	[50–52,73,55,56]
Co enzyme Q10 deficiency	CoQ supplements	4	Standard of care	E,F	[74,75]
Cobalamin A deficiency	Hydroxycobalamin, protein restriction	4	Standard of care	C,G	[76–79]
Cobalamin B deficiency	Hydroxycobalamin, protein restriction	4	Standard of care	C,G	[76–79]
Cobalamin C deficiency	Hydroxycobalamin	4	Standard of care	C,D,G	[76–79]
Cobalamin D deficiency	Hydroxy-/cyanocobalamin	4	Standard of care	C,D,G	[76–79]
Cobalamin E deficiency	Hydroxy-/methylcobalamin, betaine	4	Standard of care	C,D,G	[76–79]
Cobalamin F deficiency	Hydroxycobalamin	4	Standard of care	C,D,G	[76–79]
Cobalamin G deficiency	Hydroxy-/methylcobalamin, betaine	4	Standard of care	C,D,G	[76,78,79]
Congenital intrinsic factor deficiency	Hydroxycobalamin	4	Standard of care	A,E,G	[80]
l.o. CPS deficiency	Dietary protein restriction, arginine supplement, sodium benzoate, phenylbutyrate (Liver transplantation)	2b & 4	Standard of care (Individual basis)	B,C,D,E,F,G (C)	[55–57,60,61]
Creatine transporter defect	Creatine, glycine, arginine supplements	4-5	Individual basis	F	[29]
DHPR deficiency	BH4,diet, amine replacement, folinic acid	4	Standard of care	A,E	[52]
Ethylmalonic encephalopathy	N-acetylcysteine, oral metronidazol	4	Standard of care	E,G	[81]
GAMT deficiency	Arginine restriction, creatine & ornithine supplements	4	Standard of care	B,D,E,F	[48,52,82,83]
Gaucher disease type III	Haematopoietic stem cell transplantation	4–5	Individual basis	D,G	[84,85]
GLUT1 deficiency syndrome	Ketogenic diet	4	Standard of Care	F	[19,86]
l.o. Glutaric acidemia I	Lysine restriction, carnitine supplements	2c	Standard of care	C,D,E,G	[87,88]
Glutaric acidemia II	Carnitine, riboflavin, β-hydroxybutyrate supplements; sick day management	5	Standard of care	C,G	[89,90]
GTPCH1 deficiency	BH4, amine replacement	4	Standard of care	A,E	[91]
HHH syndrome	Dietary protein restriction, ornithine supplement, sodium benzoate, phenylacetate	4	Standard of care	B,C,D,E,F,G	[92]
HMG-CoA lyase deficiency	Protein restriction, avoid fasting, sick day management,	5	Standard of care	C	[58–60,93]
Holocarboxylase synthetase deficiency	Biotin supplement	4	Standard of care	A,E,G	[94,95]
Homocystinuria	Methionine restriction, +/−pyridoxine, +/−betaine	2c	Standard of care	C,D,G	[96,76]
Hunter syndrome (MPS II)	Haematopoietic stem cell transplantation	4–5	Individual basis	D,G	[24,85,97]
Hurler syndrome (MPS I)	Haematopoietic stem cell transplantation	1c	Standard of care	D,G	[24,85,97]
Hyperammonemia–Hyperinsulinism syndrome	Diazoxide	4–5	Standard of care	D	[98,99]
Imerslund Gräsbeck syndrome	Hydroxycobalamin	4	Standard of Care	A,E,G	[100]
l.o. Isovaleric acidemia	Dietary protein restriction, carnitine supplements, avoid fasting, sick day management	2c	Standard of care	C,G	[101–104,93]
l.o. NAGS deficiency	Dietary protein restriction, arginine supplement, sodium benzoate, phenylbutyrate (Liver transplantation)	2b & 4	Standard of care (Individual basis)	B,C,D,E,F,G (C)	[55–57,105,60,61]
l.o. Non-ketotic hyperglycinemia	Glycine restriction; +/−sodium benzoate, NMDA receptor antagonists, other neuromodulating agents	4-5	Standard of Care	B,D,E,F	[106]
Maple syrup urine disease (variant)	Dietary restriction branched amino-acids, avoid fasting, (Liver transplantation)	4 & 4	Standard of care (Individual basis)	B,C,D (A,C)	[107–110]
MELAS	Arginine supplements	4–5	Standard of Care	C,D,E,F	[26]
Menkes disease occipital horn syndrome	Copper histidine	4	Individual basis	D	[111–113]
l.o. Metachromatic leukodystrophy	Haematopoietic stem cell transplantation	4-5	Individual basis	D	[114,85]
3-Methylcrotonyl glycinuria	Dietary protein restriction; carnitine, glycine, biotin supplements; avoid fasting; sick day management	5	Standard of care	C	[115,116]
3-Methylglutaconic aciduria type I	Carnitine Supplements, Avoid Fasting, Sick Day Management	5	Standard of care	C	[117]
l.o. Methylmalonic acidemia		2c	Standard of care	C,G	[101–104,93]

(continued on next page)

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Table 5 (*continued*)

Disease name	Therapeutic modality (−ies)	Level of evidence	Clinical practice	Treatment effect	Literature references
	Dietary protein restriction, carnitine supplements, avoid fasting, sick day management				
MHBD deficiency	Avoid fasting, sick day management, isoleucine restricted diet	5	Standard of care	C	[63–65,93]
mHMG-CoA synthase deficiency	Avoid fasting,sick day management, +/−dietary precursor restriction	5	Standard of care	C	[63–65,93]
Molybdenum co-factor deficiency type A	Precursor Z/cPMP	4	Individual basis	A,F	[25]
l.o. MTHFR deficiency	Betaine supplements, +/−folate, carnitine, methionine supplements	4	Standard of care	C,D,G	[76,79]
Niemann–Pick disease type C	Miglustat	1b	Standard of care	D,E	[118–121]
l.o. OTC deficiency	Dietary protein restriction, citrulline supplements, Sodium benzoate/phenylbutyrate (Liver transplantation)	2b & 4	Standard of care (Individual basis)	B,C,D,E,F,G (C)	[55–57,60,61]
PCD deficiency	BH4	4	Standard of care	A,E	[91]
PDH complex deficiency	Ketogenic diet & thiamine	4	Individual basis	D,E,F	[122]
Phenylketonuria	Dietary phenylalanine restriction +/−amino-acid supplements (BH(4) supplement)	2a (4)	Standard of care (Individual basis)	B, D, E (C)	[123,23,124,143]
PHGDH deficiency	L-serine & +/−glycine supplements	4	Standard of care	D,F	[125,126]
PSAT deficiency	L-serine & +/−glycine supplements	4	Standard of care	D,F	[125,126]
l.o. Propionic acidemia	Dietary protein restriction, carnitine supplements, avoid fasting, sick day management	2c	Standard of care	C,G	[101–104,93]
PSPH deficiency	L-serine & +/−glycine supplements	4	Standard of care	D,F	[125,126]
PTPS deficiency	BH4, diet, amine replacement	4	Standard of care	A,E	[91]
Pyridoxine dependent epilepsy	Pyridoxine	4	Standard of care	A,F	[127,128]
Pyrimidine 5-nucleotidase superactivity	Uridine supplements	1b	Standard of care	A,B,F,G	[129]
Sanfilippo syndrome A (MPS IIIa)	Haematopoietic stem cell transplantation	4–5	Individual basis	D	[24,85,97]
Sanfilippo syndrome B (MPS IIIb)	Haematopoietic stem cell transplantation	4–5	Individual basis	D	[24,85,97]
Sanfilippo syndrome C (MPS IIIc)	Haematopoietic Stemcell Transplantation	4–5	Individual Basis	D	[24,85,97]
Sanfilippo syndrome D (MPS IIId)	Haematopoietic stem cell transplantation	4–5	Individual basis	D	[24,85,97]
SCOT deficiency	Avoid fasting, protein restriction, sick day management	5	Standard of care	C	[65]
Sjögren–Larsson syndrome	Diet: low fat, medium chain & essential fatty acid supplements & Zileuton	5	Individual basis	D,G	[130,131]
Sly syndrome (MPS VII)	Haematopoietic stem cell transplantation	4-5	Individual basis	D	[24,85,97]
Smith–Lemli–Opitz syndrome	Cholesterol & simvastatin	4–5	Individual basis	B,D	[27,132,133]
SPR deficiency	Amine replacement	4	Standard of care	A,E	[134]
SSADH deficiency	Vigabatrin	4	Individual basis	B,F	[135]
Thiamine-responsive encephalopathy	Thiamin supplement	4-5	Standard of care	E	[136,137]
Tyrosine hydroxylase deficiency	L-dopa substitution	4	Standard of care	A,E	[138]
Tyrosinemia type II	Dietary phenylalanine & tyrosine restriction	4-5	Standard of care	D,G	[34,139,140]
Wilson disease	Zinc & tetrathiomolybdate	1b	Standard of care	E,G	[113,141,142]

Individual basis: the decision to initiate a specific treatment depends on a careful evaluation of the specific patient characteristics , physician's opinion, availability of treatment, and potential side-effects.
Levels of evidence (source: www.cebm.net): Level 1a = systematic review of randomized controlled trials (RCT), 1b = individual RCT, 1c = 'All or None' (=(prolongation of) survival with therapy); Level 2a = systematic review of cohort studies, 2b = individual cohort study, 2c = 'outcomes research' (focussed on end results of therapy for chronic conditions, including functioning and quality of life (http://www.ahrq.gov/clinic.outfact.htm)); Level 3 = systematic review of case–control studies; Level 4 = individual case–control study or case-series/report; Level 4–5 = single case report; Level 5 = expert opinion without critical appraisal.
Sick day management: intervention(s) to guarantee sufficient fluid and caloric intake to maintain anabolic state, plus continuation/modification of disease specific therapy
Standard of care: initiation of the specific treatment upon diagnostic confirmation is generally accepted by experts world-wide as 'best clinical practice'.
Therapeutic effect(s): A = improves psychomotor/cognitive development/IQ; B = improves behavioural/psychiatric disturbance(s); C = prevents acute metabolic decompensation; D = prevents, halts, or slows clinical deterioration; E = improves neurological manifestations (incl. neuro-imaging); F = improves seizure/epilepsy control; G = improves systemic manifestations.

Normal newborn screening results in a patient with ID of unknown origin should not reassure the clinician that treatable metabolic disorders have been ruled out, because the patient might not have been screened for a particular disease or at all. A "universal" newborn screening, does not exist, as panels still vary from mere 3 to more than 30. In a global society, children may have been born in countries without any newborn screening at all. Even for those IEMs included in most newborn screening programs such as classic organic acidurias and urea cycle defects, 'late-onset' forms consituting treatable IDs can be missed as newborn screening may not be sensitive and specific enough to safely detect such disease-variants.

Treatments include diets (e.g. modified in protein intake); sick day management ensuring sufficient calorie intake during illnesses; supplementation of vitamins, co-factors or nutritional supplements; pharmacological substrate inhibition; organ/stem cell transplantation; and gene therapy. Except for gene therapy and organ/stem cell transplantation, these treatments are relatively safe, non-invasive and affordable. The only expensive treatment included in this review is substrate inhibition therapy for Niemann–Pick Disease Type C. Compliance is an important factor determining the treatment outcomes. This is particularly true for dietary treatments with unphysiological and culturally incompatible composition of the nutritional intake.

Although most treatments have long been established and many are considered 'standard of care', the evidence level for their effect is low. Only one-fifth of the treatments identified in our review has evidence level 1b, c and 2a, b, c whereas the majority of treatments (n = 72) ranks at evidence level of 4 or lower. Paradoxically, 62% of evidence level 4 and 5 treatments are initiated as 'standard of care' by clinicians. This highlights the fact that, due to the rare nature of single conditions, most treatments have only been evaluated on a case for case basis. Thus the low evidence level of treatments for IEM and ID may be due rather to methodological shortcomings than effect-size *per se*.

To enable instant use of the results of this literature review in clinical practice, we have developed *digital tools* by designing an interactive website www.treatable-id.org with downloadable 'App' using

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Table 6
Levels of evidence & clinical practice for all 91 therapies.

Level of evidence	Definition	No. of therapies (% of total therapies; n = 91)	Standard of care (% of therapies with specific evidence level)	Individual basis (% of therapies with specific evidence level)
1a	Systematic review of RCTs	0 (0%)	0 (0%)	0 (0%)
1b	Individual RCT	3 (3%)	3 (100%)	0 (0%)
1c	'All or None'	2 (2%)	1 (50%)	1 (50%)
2a	Systematic review of cohort studies	1 (1%)	1 (100%)	0 (0%)
2b	Individual cohort study	7 (8%)	7 (100%)	0 (0%)
2c	'Outcomes research'	6 (7%)	6 (100%)	0 (0%)
3	Systematic review of case–control studies	0 (0%)	0 (0%)	0 (0%)
4	Case–control study & case series	45 (50%)	32 (71%)	13 (29%)
4–5	Single case report(s)	17(19%)	5 (29%)	12 (71%)
5	Expert opinion	10 (11%)	8 (80%)	2 (20%)
All (1–5)		91 (100%)	63 (69%)	28 (31%)

RapidWeaver software for most types of handheld devices (e.g. BlackBerry, iPad). These digital tools comprise modes to review all treatable IDs according to biochemical defects and categories, diagnostic tests, clinical features, treatment modalities with levels of evidence and effect. In addition, for each of the 81 IEMs a 'Disease Page' has been designed as information portal with links to relevant pages/chapters on online resources (Gene Reviews, Orphanet, OMIM, patient organisations, clinical trials, Pubmed, online 'Metabolic and Molecular Bases of Inherited Disease' etc.). The target audience includes clinicians and scientists active in the diagnostic evaluation of ID (pediatricians, neurologists, biochemical/clinical geneticists, metabolic specialists). Our aim is to enhance awareness and diagnostic recognition of treatable forms of ID. Input from experts around the world is welcomed and will be incorporated in the site. Finally the site will be updated every 3 months according to the continuously expanding list of treatable IDs, treatments, literature evidence, etc.

Finally, based on our literature review we have designed an *evidence-based protocol for the diagnostic evaluation of genetic causes of ID* in children with the premise to consider treatable IEMs at the outset. In the first tier, metabolic screening tests in blood and urine will be performed in all patients, followed by clinical algorithms facilitated by our digital tools for those treatable IDs which require a specific test in the 2nd tier. These metabolic layers will be superimposed and interposed to existing standard genetic and (pediatric) neurologic parameters [17,18]. As part of a funded study on treatable ID, we will implement this protocol in our tertiary care hospital and evaluate the (cost-)effectiveness, efficiency, diagnostic yields and patient and physician satisfaction as prerequisite to expand it to other centres, with the ultimate aim to adopt active identification of treatable IDs as best care practice to improve health outcomes.

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Appendix A. Suplementary data

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