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Retrospective analysis supports algorithm as efficient diagnostic approach to treatable intellectual developmental disabilities

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ABSTRACT

Background: Intellectual developmental disorders (IDD[1]), characterized by a significant impairment in cognitive function and behavior, affect 2.5% of the population and are associated with considerable morbidity and healthcare costs. Inborn errors of metabolism (IEM) currently constitute the largest group of genetic defects presenting with IDD, which are amenable to causal therapy. Recently, we created an evidence-based 2-tiered diagnostic protocol (TIDE protocol); the first tier is a 'screening step' applied in all patients, comprising routinely performed, wide available metabolic tests in blood and urine, while second-tier tests are more specific and based on the patient's phenotype. The protocol is supported by an app (www.treatable-ID.org).
Objective: To retrospectively examine the cost- and time-effectiveness of the TIDE protocol in patients identified with a treatable IEM at the British Columbia Children's Hospital.
Methods: We searched the database for all IDD patients diagnosed with a treatable IEM, during the period 2000–2009 in our academic institution. Data regarding the patient's clinical phenotype, IEM, diagnostic tests and interval were collected. Total costs and time intervals associated with all testing and physician consultations actually performed were calculated and compared to the model of the TIDE protocol.
Results: Thirty-one patients (16 males) were diagnosed with treatable IDD during the period 2000–2009. For those identifiable via the 1st tier ($n = 20$), the average cost savings would have been $311.17 CAD, and for those diagnosed via a second-tier test ($n = 11$) $340.14 CAD. Significant diagnostic delay (mean 9 months; range 1–29 months) could have been avoided in 9 patients with first-tier diagnoses, had the TIDE protocol been used. For those with second-tier treatable IDD, diagnoses could have been more rapidly achieved with the use of the Treatable IDD app allowing for specific searches based on signs and symptoms.
Conclusion: The TIDE protocol for treatable forms of IDD appears effective reducing diagnostic delay and unnecessary costs. Larger prospective studies, currently underway, are needed to prove that standard screening for treatable conditions in patients with IDD is time- and cost-effective, and most importantly will preserve brain function by timely diagnosis enabling initiation of causal therapy.

1. Background

1.1. Treatable inborn errors of metabolism and intellectual developmental disabilities

Intellectual developmental disorders (IDD) are a common and etiologically diverse set of health conditions, recently described as being "meta-syndromic" by the World Health Organization International Classification of Diseases Working Group on the Classification of Intellectual Disabilities [1]. They are lifelong, debilitating conditions affecting between 2% and 3% of children and adults globally [1]. IDD

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[1] **Abbreviations:**
Intellectual developmental disorders (IDD)
Inborn Errors of Metabolism (IEM)
Treatable Intellectual Disability Endeavour (TIDE)
Whole Exome Sequencing (WES).

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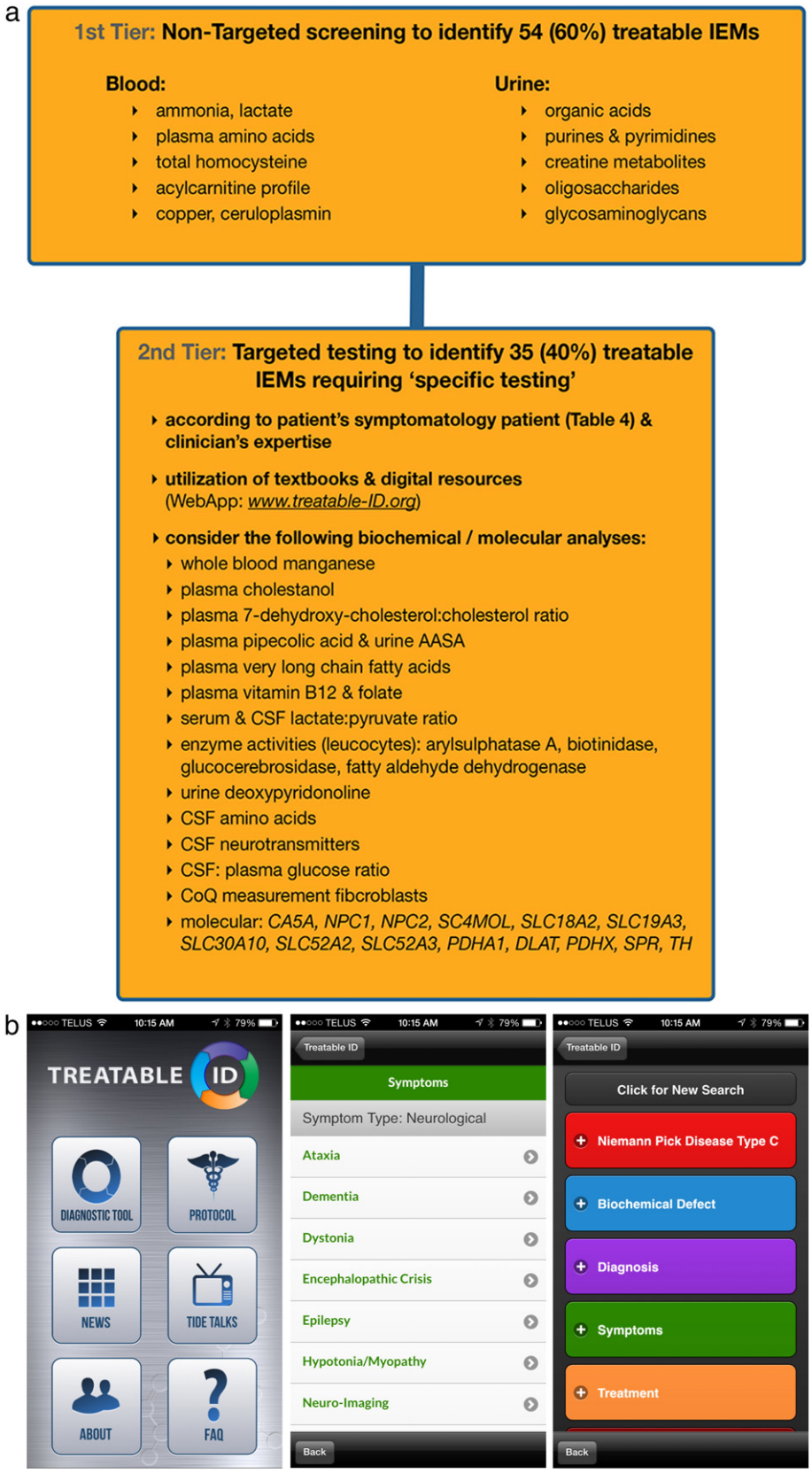

Fig. 1. (a) Two-tiered algorithm for the identification of treatable IDDs [15]. (b) TIDE Web-app as knowledge translation tool to enhance diagnosis and treatment of IEMs in patients presenting with IDD. The interactive menus include: biochemical group, signs and symptoms, diagnostic tests, treatment and evidence. These screenshots are taken from the mobile app available in the app Store or at www.treatable-id.org.

Table 1
Costs of the 1st-tier tests ($CAD).

Blood	
Bloodspot acylcarnitines	$41.28
Plasma amino acids	$78.42
Plasma total homocysteine	$22.97
Serum ceruloplasmin	$10.15
Serum copper	$49.19
Urine	
Urine creatine metabolites	$65.01
Urine glycosaminoglycans	$59.55
Urine oligosaccharides	$32.65
Urine organic acids	$105.41
Urine purines and pyrimidines	$63.34
Total	**$527.97**

encompass both intellectual disability (IQ of < 70, at ≥5 years of age) and Global Developmental Delay, which describes deficits in ≥2 of 5 domains of normal development (e.g., fine and gross motor, speech, and social skills) [2–4]. IDD is associated with the highest healthcare costs of any disease– almost equivalent to the economic impact of stroke, heart disease and cancer combined [5,6]. While the etiologies of IDD vary and include infectious, traumatic and toxic origins, genetic anomalies represent the most frequent causes, demonstrable in over 50% of patients [7], and range from numeric and structural chromosomal abnormalities and submicroscopic rearrangements, to methylation abnormalities and single gene defects [8,9]. De Ligt et al. [10] published a diagnostic yield of 16% (with the majority *de novo* mutations) for a whole exome sequencing study in 100 severe IDD trios.

Current recommendations for the evaluation of genetic causes of IDD are based on the frequencies of single conditions and yield of diagnostic methods and procedures [11]. First-line, widely available clinical investigations include karyotyping and array-comparative genomic hybridization which yield a causal diagnosis in up to 20% of cases [12,13]. However, medical intervention targeting the underlying defect and/or pathogenesis is currently unavailable for most of the conditions identified. By contrast, inborn errors of metabolism (IEM), which represent the largest group of genetic defects associated with IDD, are uniquely amenable to beneficial causal treatment, defined as a medical intervention targeting the underlying defect and/or pathogenesis.

In 2012, van Karnebeek and Stockler published a systematic literature review [14] that (1) investigated the number of treatable IEM presenting with IDD and (2) characterized the types of treatments and evidence for their effect. They identified 81 treatable IEM with IDD as a major clinical feature for which treatment was available (91 total) that improved/stabilized the IDD phenotype, cognitive ability or related neurological features [14].

1.2. The TIDE diagnostic algorithm and App

Based on the data generated by the systematic review, we created a two-tiered protocol (TIDE protocol) to enhance early diagnosis of treatable ID and started a 3-year pilot project, Treatable Intellectual Disability Endeavour (TIDE) in 2011, evaluating patients with undiagnosed ID via this protocol [15].

The first-tier is a screening step, involving biochemical group tests that potentially indicate 60% of the currently known treatable IDD (Fig. 1a). These blood and urine tests are provided by most biochemical genetics laboratories, at relatively affordable prices. It is the intent that this first-tier testing be applied by community pediatricians and specialists to *all* patients (irrespective of age, phenotype, family background, previous diagnostic work-up) who present with idiopathic or unexplained IDD, in order to effectively exclude a majority of the treatable IEM without need for referral to a specialized center.

The second tier comprises specific tests, which should be performed based on the patient's clinical phenotype, according to the clinician's expertise and differential diagnosis; these tests in general are more expensive and sometimes invasive [15,16].A freely accessible digital resource app was also developed to support the TIDE algorithm, (www.treatable-id.org as well as a native app via the app store, see Fig. 1b), and is endorsed by the rare disease community [17] The app allows for the creation of a list of differential diagnosis according to symptoms and signs of the single treatable IDD and thus facilitates, particularly the second tier of the protocol which is based on an astute clinical differential diagnosis.

While awaiting the final results of this larger prospective 3-year TIDE study with systematic protocol implementation in 3 divisions in our pediatric academic center, we set out to generate proof-of-concept for the usefulness of the TIDE protocol via the current analysis.

This article reports a retrospective analysis of IDD patients diagnosed between 2000 and 2009 with one of the 81 treatable IEM. We aimed to describe the type of diagnoses, clinical symptoms, and revealing tests as well as the diagnostic costs and timelines for those patients, in order to support the clinical utility and cost-effectiveness of the protocol. Additionally, these data provide a useful 'baseline' for evaluation of the forthcoming prospective TIDE implementation study (2011–2014) [15].

1.3. Hypothesis and objectives

Here we hypothesize that for patients presenting with unexplained IDD in British Columbia's Children's Hospital (BCCH) between 2000 and 2009 (the period that preceded the TIDE protocol or acute awareness and focus on treatability in our institution), and in whom a treatable IEM was diagnosed the time to diagnosis, costs, and burden

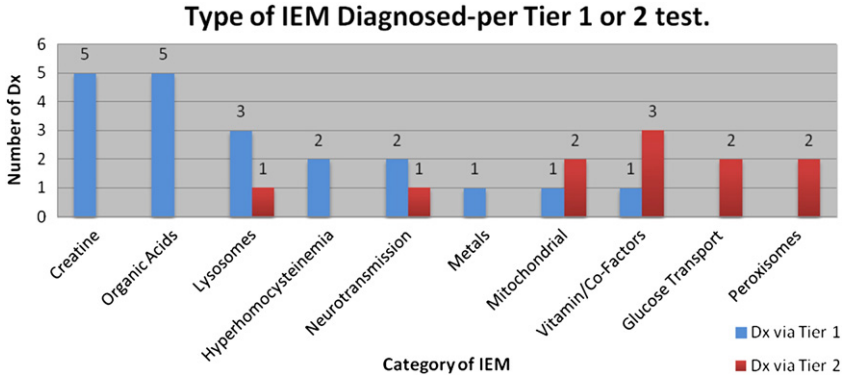

Fig. 2. Creatine incl. creatine transporter deficiency (CTD), GAMT deficiency, and CTD with GAMT deficiency; Organic acids incl. BKT, MSUD, 3-methylglutaconic aciduria, and glutaric aciduri type 1; lysosomes incl. Gaucher's disease type IA, Sanfilippo syndrome (MPS III A), Hunter syndrome (MPS II), and Hurler syndrome (MPS I); hyperhomocysteinemia incl. cobalamin C and D deficiencies; neurotransmission incl. 6-PTPS deficiency and SSADH deficiency; mitochondrial incl. MELAS and pyruvate dehydrogenase complex deficiency; Vitamin/Co-Factors incl. holocarboxylase synthetase deficiency and pyridoxine-dependent epilepsy (PDE); glucose transport incl. GLUT-1 deficiency; metals incl. Menke's disease; and peroxisomes incl. X-linked adrenoleukodystrophy (X-ALD).

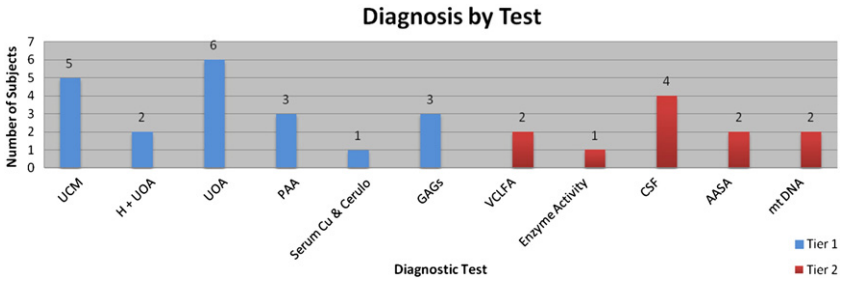

Fig. 3. UCM = urine creatine metabolites, H + UOA = homocysteine and urine organic acids; PAA = plasma amino acids, Cu & Cerulo = serum copper and ceruloplasmin, GAGs = urine glycosaminoglycans, VCLFA = plasma very long chain fatty acids, AASA = urine α-aminoadipic semialdehyde.

of unnecessary testing exceed that which would have been achieved with application of 2012 TIDE protocol for each patient at their initial evaluation.

2. Methods

2.1. Ethics

This study was approved by the Regional Ethics Board at BCCH, University of British Columbia.

2.2. Patient identification

The biochemical diseases and biochemical genetics laboratory databases and paper files were searched for any patient (age 2 months to < 18 years) diagnosed at BCCH between 2000 and 2009 with 1 of the 81 treatable IEM potentially identifiable by the TIDE protocol [14]. Patient exclusion criteria were as follows: IDD was not the main presenting feature; IEM were diagnosed via newborn screening [18], diagnosis was established outside of British Columbia; and medical records were incomplete to an extent, which precluded accurate collection of predetermined data elements. A diagnosed IEM that does not belong to the 81 treatable IDDs was identified in the systematic review by van Karnebeek and Stockler (2012) [14].

2.3. Data collection

Individual patient data were collected from an electronic health records database and conventional hardcopy medical records. Demographic data including date of birth, gender, first consultation with a specialist at BCCH, and age at diagnosis were recorded along with information regarding diagnostic investigations and specialist consultations (those directly involved for work-up on cause of IDD including geneticists, metabolic specialists, neurologists, ophthalmologists, endocrinologists, etc.). The data were stored under coded subject identification numbers in a secure Excel spreadsheet.

Phenotypic features were categorized according to the presence of a number of neurologic and non-neurologic abnormalities. Neurologic abnormalities included dementia/neurologic degeneration, epilepsy, hypotonia/muscle weakness, movement disorder, neuropathy, stroke, psychiatric abnormality or autism, behavioral disorder, or neuroimaging abnormalities. Non-neurologic abnormalities included clinical features not affecting the CNS. Further categorization of patients based on the 'revealing test' dichotomized patients as follows: Group 1 = patients diagnosed via the first-tier tests (Fig. 1a) often followed by molecular analysis or other specific investigations for final confirmation, or Group 2 = the remaining patients diagnosed by specific metabolic tests as indicated by phenotypic features (e.g., cerebrospinal fluid investigations, enzymatic assay, or single gene or mt.DNA tests).

2.4. Cost analysis

Costs of biochemical tests were gathered from the Provincial (British Columbia) Medical Service Plan index [19]. According to our TIDE protocol, each patient would undergo first-tier screening and thus these costs apply to each child identified with one of 81 treatable IEM between 2000 and 2009. Second-tier tests were patient specific and thus calculated on a per case basis. The majority of these second-tier tests was not available in BC but rather performed on a commercial basis by clinical laboratories in Canada and/or the USA. The costs are presented in Canadian currency contemporary to 2013 for all tests analyzed.

2.5. Definition of diagnostic interval

For a realistic diagnostic trajectory, we defined 'time to diagnosis' as the interval between the patient's first diagnostic consultation with a specialist in pediatric neurology, biochemical or metabolic diseases or medical genetics in BCCH and the date at which a diagnosis was confirmed. For the theoretical TIDE protocol trajectory, we calculated a 1-month minimum interval, as this is the average time required to return first-tier test results at BCCH (range: 3 days—8 weeks).

3. Results

3.1. Study group

Analyses via Cerner, the hospital database system, showed that on average, 1200–1500 patients (age < 18 years) per year are seen by

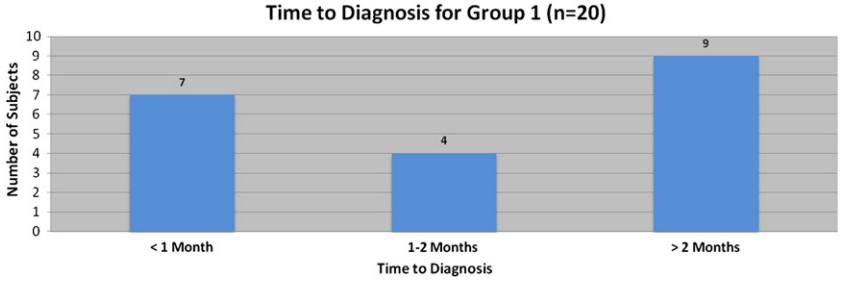

Fig. 4. Group 1: diagnostic interval.

specialists in BCCH for the diagnostic evaluation to define the etiology of their IDD. The search for patients identified 34 IDD individuals diagnosed with 1 of the 81 treatable IDDs; of these, 3 were excluded as the diagnoses were suspected based on family history and prenatal testing and confirmed during the neonatal period via targeted testing. Of the 31 included for this analysis, 16 were females (52%) and 15 were males (−48%) (age range: 2 months–18 years). Table 1 lists the individual patient characteristics, diagnoses, time, and costs of the trajectory (tests and specialist consultation).

3.2. Diagnoses

Fig. 2 depicts the category and number of diagnoses for the entire cohort ($n = 31$), grouped according to biochemical categories. Disorders of organic acids and creatine synthesis and transport comprised the largest proportions (16% each) of diagnosed IEM.

3.3. Yield by test

Fig. 3 depicts the number of diagnoses identified by the first and second-tier tests. First-tier tests identified treatable IEM in 20 (62.4%) patients and second tier in 11 (34.5 %) patients.

3.4. Costs

The total cost for first-tier tests equals $527.97 CAD [14,18]. Table 1 provides the costs of individual tests. For patients diagnosed via the first tier, the mean diagnostic cost of all tests performed was $879.14 CAD: the median cost was $768.12 CAD (range: $478.01–$1997.55 CAD). If the TIDE protocol had been applied, the mean cost would have been reduced to $527.97.

For patients diagnosed via second-tier testing, the mean diagnostic cost of all tests performed was $908.11 CAD, and the median cost was $779.45 CAD (range: $478.01 to $1997.55 CAD). The application of the TIDE protocol in conjunction with TIDE app [14,15,17] would have lowered the total cost for each of these patients to a base of $527.97 CAD, plus the expense of individual second-tier tests on a case-by-case basis.

3.5. Diagnostic Interval for patients with 1st-tier IEM

The diagnostic interval of patients diagnosed via a TIDE first-tier test (i.e., Group 1) is displayed in Fig. 4. In 11 of these patients (55%), the diagnostic interval in reality was ≤1 month (the revealing tests were plasma amino acids or urine organic acids with a turnaround of a few days or weeks). For those patients who were not diagnosed within a month ($n = 9$), the average diagnostic interval was 10 months (range: 2–30 months, median 3 months).

The time to diagnosis is reflected in the total costs; for the 9 patients with a diagnostic trajectory of > 1 month, the mean expenditure on services and tests was $1620.25 CAD, with a median value of $1414.64 CAD (Table 2). While the minimum value of tests and services for this group was $98.22 CAD, the maximum value was $4430.12 CAD. This wide range reflects the phenotypic heterogeneity of IEM (some of which present with specific, easily recognizable symptoms, while the majority is more diffuse and thus challenging) as well as the expertise and experience of the evaluating specialist.

3.6. Diagnostic interval for patients with 2nd-tier IEM

It was not possible to analyze the avoidable time or costs for patients diagnosed with IEM identifiable by the 2nd-tier tests. However, it seems safe to assume that access to the Treatable ID app likely would have reduced both, as it increases awareness of which IEM to look for and facilitates targeted testing based on differential diagnosis, via the function 'Search for IEM based on signs and symptoms' [15,17].

3.7. Neurologic and non-neurologic symptoms

For the whole group ($n = 31$) of patients with IEM identified both by the 1st- and 2nd-tier tests, the relation between the number of neurologic and non-neurologic abnormalities is depicted in Supplementary Fig. 1A and B.

It becomes clear that neurologic symptoms are more common than non-neurologic or systemic signs and symptoms in patients diagnosed with treatable IEM. However, there is no clear relationship between the number of abnormalities and diagnostic delay. Using a Mann–Whitney *U* test, we did not find a statistical difference in time to diagnosis for patients with fewer than 5 versus those with 5 or neurologic abnormalities. The same was true for patients non-neurologic abnormalities.

4. Discussion

4.1. Limitations

The limitations of this study are those inherent to a retrospective review including incomplete records, incomplete capture of subjects, contemporary versus real-time cost estimates in substitution for actual costs at the time of testing and changes in the number of known treatable IEM. There is the potential that IEM, which were discovered after 2001, may have gone undiagnosed, which would coincide with extensive diagnostic testing in other patients who would not have been captured in our cohort. Also, the TIDE model as described in this review is a hypothetical one, and cost differences could change in real-world application. For example, in factoring the projected costs for patients diagnosed via the protocol's second-tier testing, results of the first-tier testing may have informed further testing, and therefore lowered the overall cost of testing per patient.

The costs cited in this review are specific to the province of British Columbia, and the standard diagnostic practice may not be universally representative. Finally, the costs of screening all IDD patients is considerable, especially when diagnostic yield might be relatively small; however, other publications on the TIDE study reveal that ~ 5% are attributable to treatable IEM. As a proportion of these tests are currently done in all patients, it may be more efficacious to test systematically, especially as the phenotype may not always be suggestive of an IEM.

4.2. Considerations

Individuals with IDD can face challenges in daily living ranging from mild functional impairment to complete dependency [20]. As such, the impact on the individual and their caregivers and families varies accordingly, as do the required medical resources and thus costs for families and society [21]. This retrospective analysis reveals that time to diagnosis may be reduced and costs decreased with the implementation of the TIDE protocol. With the exception of stem cell transplant for lysosomal diseases and X-ALD, as well as the drug Miglustat for Niemann-Pick C and Gaucher Type 1 Disease [22,23], the majority of treatments (dietary supplements etc.) are relatively affordable [24,25,15,16]. Further, the costs of treatment to avoid brain damage and improve developmental and functional outcomes are lower when compared to the total accrued cost of lifelong care for a person with IDD [3,6].

As was expected, the yield of the first-tier diagnostic tests was 64%, which coincides with previous analysis and predictions [14,16]. Of the first-tier tests, the urine organic acid assay had the highest diagnostic yield ($n = 6$, see Fig. 2). This finding is not surprising due to the many IEM it can identify [14] and to the frequency with which this test is ordered. Further, some tests have recently been made standard, for example, creatine metabolites in urine, which showed the second highest diagnostic yield. This finding is important validation for the TIDE protocol as creatine transport deficiencies present variably but certainly benefit from treatment, highlighting the need for systematic screening [26–28].

Table 2
Overview of the 31 patients diagnosed with treatable IDDs during the period preceding the TIDE protocol (2000–09).

Subject number	Gender	Treatable ID/DD diagnosis	Diagnosis via tier:	Age at diagnosis (months)	Avoidable costs[†] ($CAD)	Neurologic abnormalities	Non-neurologic abnormalities
Subject 1[a]	M	Creatine transporter deficiency	1	38	1561.58	• Hypotonia • Movement behavioral • Neuro-imaging	• Dysmorphisms
Subject 8[a]	F	Creatine transporter deficiency	1	80	3012.86	• Dementia • Epilepsy • Hypotonia • Movement • Neuro-imaging	• Stature • Eyes • Skin • Gastrointestinal
Subject 6	M	X-linked creatine transporter deficiency	1	54	1805.61	• Hypotonia • Neuro-imaging	• Dysmorphisms • Stature • Hemato-/immunologic • Gastrointestinal
Subject 7	F	GAMT (creatine) deficiency	1	27	91.18	• Epilepsy • Hypotonia • Movement • Neuro-imaging	• Dysmorphisms • Bones/joints • Skin • Vision loss • Hearing loss
Subject 33[a]	F	GAMT deficiency	1	26	1304.85	• Dementia/neurodegeneration • Hypotonia • Psychiatric/autism behavioral • Neuro-imaging	• Bones/joints • Gastrointestinal • Failure to thrive
Subject 4	F	Beta ketothiolase deficiency (**BKT**)	1	38	104.24	• None	•Lungs • Gastrointestinal • Renal
Subject 14	F	Maple syrup urine disease	1	5	0.00	• Epilepsy • Hypotonia • Neuro-imaging	• Lungs
Subject 20	M	(Intermittent) Maple syrup urine disease	1	73	0.00	• Dementia/neurodegeneration • Hypotonia • Neuro-imaging	Gastrointestinal
Subject 23	F	Glutaric aciduria type I	1	5	0.00	• Hypotonia • Neuropathy • Neuro-imaging	• Stature • Eyes • Bones/joints • Hemato-/immunologic liver/spleen • Failure to thrive • Endocrine • Vision loss
Subject 18[a]	F	3-Methylglutaconic aciduria	1	130	209.24	• Psychiatric/autism • Neuro-imaging	• None
Subject 34	M	Hurler syndrome (MPS I)	1	12	307.46	• Neuro-imaging	• Dysmorphisms • Stature • Bones/joints • Skin • Hemato-/immunological, liver/spleen • Failure to thrive • Vision loss
Subject 26[a]	M	Hunter syndrome (MPS II)	1	23	202.46	• Movement • Neuro-imaging	• Dysmorphisms • Stature • Bones/joints • Lungs • Liver/spleen • Gastrointestinal • Cardiac • Hearing loss
Subject 25[a]	F	Sanfilippo syndrome (MPS III A)	1	48	6.02	• Hypotonia	• Dysmorphisms • Bones/joints • Lungs • Hemato-/immunologic liver/spleen • Gastrointestinal • Vision loss • Hearing loss
Subject 19[a]	M	Menke's disease	1	6	4337.92	• Epilepsy • Hypotonia • Neuro-imaging	• Dysmorphisms • Stature • Eyes • Skin • Lungs • Failure to thrive

Table 2 (*continued*)

Subject number	Gender	Treatable ID/DD diagnosis	Diagnosis via tier:	Age at diagnosis (months)	Avoidable costs† ($CAD)	Neurologic abnormalities	Non-neurologic abnormalities
Subject 2	F	Cobalamin C defect	1	79	6.02	• Epilepsy • Neuropathy • Neuro-imaging	• Hemato-/immunologic • Failure to thrive • Gastrointestinal • Cardiac renal
Subject 5	M	Cobalamin C/D deficiency	1	0	6.02	• Hypotonia • Neuro-imaging	• Skin, lungs • Hemato-/immunologic • Gastrointestinal • Failure to thrive
Subject 24	M	SSADH deficiency	1	43	96.51	• Hypotonia • Neuro-imaging	• Eyes • Bones/joints • Hearing loss
Subject 31[a]	F	SSADH deficiency	1	35	1322.41	• Hypotonia • Movement • Neuro-imaging	• None
Subject 13	M	Holocarboxylase synthetase deficiency	1	0	277.06	• Stroke	• Skin • Lungs • Hemato-/immunologic • Failure to thrive
Subject 10	F	Gaucher's disease type IA	2	78	209.24	• None	• Bones/joints • Lungs • Hemato-/immunologic • Liver and spleen
Subject 21	F	6-PTPS deficiency	2	103	0.00	• Dementia/neurodegeneration • Epilepsy • Hypotonia	• Bones/joints • Skin
Subject 16	M	MELAS	2	173	411.77	• Dementia/neurodegeneration • Epilepsy psychiatric/autism behavior • Neuro-imaging	• Skin • Gastrointestinal • Failure to thrive • Endocrine • Hearing loss
Subject 17	F	MELAS	2	122	110.33	• Dementia/neurodegeneration • Epilepsy • Neuropathy • Stroke • Neuro-imaging	• Eye • Gastrointestinal • Vision loss • Hearing loss
Subject 28	F	Pyridoxine-dependent epilepsy	2	16	611.77	• Epilepsy • Movement	• None
Subject 29	M	Pyridoxine-dependent epilepsy	2	5	828.01	• Epilepsy • Hypotonia • Movement	• Eyes • Skin
Subject 30	F	Pyruvate dehydrogenase complex deficiency	2	3	543.26	• Hypotonia Neuro-imaging	• Hemato-/immunologic
Subject 11	M	GLUT-1 deficiency	2	103	2130.57	• Epilepsy • Hypotonia • Movement • Neuropathy psychiatric/autism neuro-imaging	• Stature • Eyes • Skin • Failure to thrive • Endocrine
Subject 12	M	GLUT-1 deficiency	2	5	6.02	• Epilepsy	• Lungs
Subject 3	M	X-linked adrenoleukodystrophy	2	127	305.62	• Dementia/neurodegeneration • Hypotonia • Movement • Neuropathy • Stroke • Psychiatric/autism behavioral • Neuro-imaging	• Skin • Lung • Renal
Subject 32	M	X-linked adrenoleukodystrophy	2	130	186.57	• Dementia/neurodegeneration • Hypotonia • Neuropathy psychiatric/autism behavioral • Neuro-imaging	• Lungs • Vision loss • Hearing loss

[a]Patients in Group 2 (diagnostic delay of >9 months).
† Priced in CAD. Cost factors in $527.97 for TIDE Tier 1 investigations.

Admittedly, the yield of second-tier tests depends on the expertise of the physician and familiarity with certain IEM. This is illustrated by pyridoxine-dependent epilepsy for which our center has an interest and therefore lower threshold screening [29]. Consequently, we created an app to increase awareness and access to knowledge of IEM (Fig. 1b) [17]. This important tool can direct investigative action through a search engine which presents information about IEM based on clinical features or biochemical deficiency. By providing information about the pathogenesis and confirmatory diagnostic test for each treatable IEM causing IDD clinicians can use the app to select specific tests, thereby reducing time to and cost of diagnoses and improving patient outcomes [15,17]. This app serves as a knowledge translation tool to enhance the diagnoses and treatment of intellectual disabilities. Our estimation of cost of specific metabolic tests otherwise captured by Tier 2 is mediated by

the use of this particular tool. Therefore, we assume the use of the TIDE app could have lowered the testing costs and delay of diagnosis in patients with IEM identifiable by the second-tier diagnoses.

Our analysis of neurologic and non-neurologic features in this cohort revealed that by the time diagnoses were established, many subjects had already developed quite significant abnormalities, further highlighting the importance of the TIDE protocol. However, we did not find a significant relationship of these categories of symptoms with the diagnostic interval, both for first- and second-tier diagnoses. As noted above, the Treatable ID app might well have helped reduce delay as the clinician could have come up with a diagnosis earlier when entering specific phenotypic features (e.g., hepatosplenomegaly for Gaucher disease). Most importantly, some of the first-tier diagnoses (e.g., Hunter syndrome) might well have been picked up via routine metabolic first-tier screening, before the phenotype evolved to show neurologic and systemic symptoms, and thus during a phase when brain damage could have been prevented and the disease course is more amenable to treatment.

It must be stated that our estimations of cost and diagnostic delay are modest. In regards to diagnostic delay, our estimate does not include the time from the first noted symptoms of IDD, i.e., the interval between examination by a general practitioner and first consultation with a specialist from the neurology, biochemical diseases, or medical genetics divisions at our facility. Furthermore, we are only discussing diagnostic cost savings while, in truth, earlier diagnosis can prevent brain damage and progression of IDD and subsequent loss in quality of life, incurred care costs, loss in productivity, and immeasurable qualitative suffering [14,20].

Finally, with the advent of whole exome/genome sequencing the number of IEM is rapidly expanding, for example carbonic anhydrase VA deficiency due to *CA5A* alterations as described by van Karnebeek et al. [30]. Such discoveries imply that the list of treatable IDDs is a moving target and that the protocol should be adjusted to accommodate novel disease and treatments. This indeed has been done and the TIDE app is a perfect tool to adjust to change [15,17].

The increasing use of WES/WGS in clinical practice [31] likely will result in the diagnosis of IEM via genomics requiring subsequent confirmatory biochemical testing. For the time being, the rate of turnaround of biochemical tests is far less than that of WES analysis, and the cost of the TIDE first tier is still less than that of WES on singleton and considerably less than on a trio. Further, biochemical tests carry a much smaller risk of incidental genetic findings [32]. Finally, biochemical tests have proven sensitive and reliable whereas WES may suffer from inconsistent coverage of certain regions [33].

5. Conclusion

The future will see an integration of high throughput genomics and metabolomics into a holistic, advanced approach to the diagnosis of treatable IEM. For now, we still depend largely on routine testing and expertise. The TIDE protocol provides an efficient way of combining the latter, while simultaneously raising awareness among clinicians of the importance of screening for these rare conditions to improve outcomes for IDD patients. This paper lays the foundation for the forthcoming more robust prospective study in a larger number of IDD patients, which will generate more evidence for the utility and efficacy of the protocol. We acknowledge however, that in the near future, we may well see a reversal, i.e., first genomic screening, then metabolic confirmatory testing.

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Disclosures

The authors declare that they have no conflict(s) of interest.

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