TIDE BC

Year 1 Evaluation

Treatable Intellectual Disability Endeavor in British Columbia

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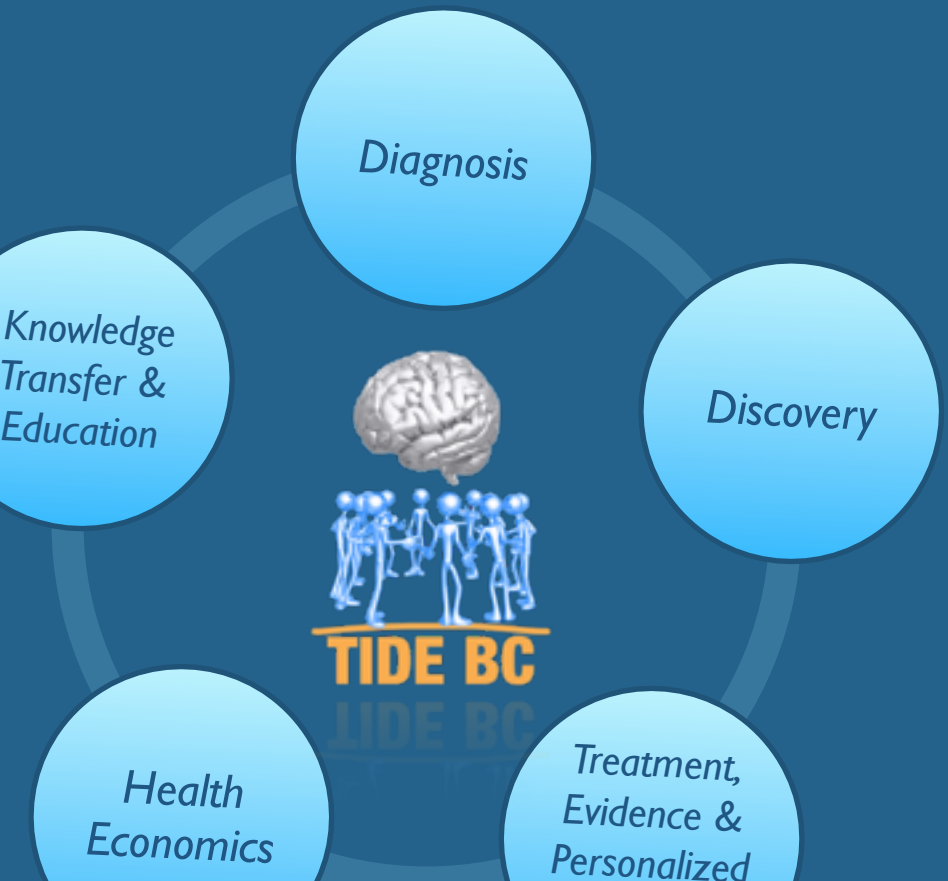


Preamble

TIDE-BC is the first Collaborative Area of Innovation at BC Children's Hospital, funded by the BCCH Foundation. After a 6 month-period required to firmly establish collaborations, operations and project management, the TIDE officially started flowing in September 2011.

This interim evaluation comes at 15 months of full TIDE operations, reporting deliverables and milestones achieved during the first term of our 36-month research and care program. While this is a very short period over which to demonstrate improvement of child health and bridge the ringroad between CFRI/CMMT and the hospital, most outcomes integral to supporting TIDE's vision have been achieved and even exceeded during this time.

The purpose of this report is to provide a first comprehensive look at TIDE-BC's activities and accomplishments. The report begins with an overview of the framework guiding the evaluation of the entire project aimed to provide both a qualitative and quantitative analysis of TIDE. This first evaluation is mainly geared toward scientific and more quantitative outcomes. Patient/family and provider satisfaction has been gleaned for specific aspects of the project; an overall more qualitative account comprising the views of all involved stakeholders' on TIDE accomplishments will follow in next years' evaluations.

The key achievements shown here lay the foundation for TIDE's most sustainable activities into the future. Our team rides this wave of innovation and collaboration with only one mission: to improve the health and wellbeing of children and youth in British Columbia.

December 2012

Sylvia Stöckler, MD PhD (project leader)
Clara van Karnebeek, MD PhD (lead clinician-scientist)

Ten TIDE highlights

1. The TIDE Diagnostic Protocol

- Has been implemented and is currently being used by more than 20 physicians at BCCH.
- In the first year pilot project, treatable ID was identified in 5% and causal diagnosis was achieved in 35% of 210 ID patients, saving 6 months of diagnostic delay and $1200 of costs per patient.
- For each patient, de-identified phenotypic data paired with DNA/urine are stored in TIDE registries, providing a rich resource for future research on genetic ID.
- A collaboration with Child Health BC / BC Pediatrics Society and the American College of Medical Genetics has been established to promote the provincial, national and international dissemination and adoption of the TIDE protocol.

2. The treatable ID WebAPP

- Supporting the protocol has generated multiple reviews and awards on (inter-)national platforms.

3. The TIDE Complex Diagnostic Clinic

- Has been established as new collaborative platform and causal diagnoses have been confirmed in 8 out of 13 most challenging ID cases. The multi-specialist evaluation in this clinic was experienced with a high degree of satisfaction by patients/parents and participating physicians, and analyzed as cost- and time-effective for the family and health-care system.

4. The TIDE Diagnostic Lab

- Has developed a framework and technologies to meet the growing demand for TIDE biochemical tests, and simultaneously reduced inappropriate test requisitions.

5. The TIDEX Gene Discovery Team

- Has developed the TIDEX protocol synergizing cutting edge -omics technologies with the clinical and metabolic phenotyping strategies.
- Applying this protocol, the TIDEX-Team has discovered one novel treatable intellectual disability gene (CA-VA deficiency) and has 5 other novel disease genes are in the pipeline of validation through collaboration with international experts.

6. The TIDE Treatment Team

- Has united physicians and scientists from over 20 countries to form expert consortia and establish disease registries and guidelines for two exemplary rare treatable IDs (PDE and GAMT deficiency).
- Has developed a new treatment approach for Pyridoxine Dependent Epilepsy and published first outcomes.
- Has developed the theoretical framework and implemented first clinical protocols for n=1 studies.

7. The TIDE Care Team

- Has developed novel tools for assessment for patient outcomes, and their application in n-of-1 studies could function as a model for personalized medicine in BC Children's Hospital.
- Has established collaborations to investigate and manage unrecognized adverse drug reactions in children with complex neurodevelopmental conditions.
- Has developed the framework for an online communication platform for patients with metabolic diseases involving the hospital-based team of care-providers.

8. The TIDE Health Economy Team

- Has completed a health economic analysis of the benefits of early recognition of treatable IDs.
- Has completed a cost effectiveness analysis for sapropterin hydrochloride, an expensive drug for a treatable ID.

9. TIDE Communication team

- The digital presentation of TIDE via our website, the treatable ID App, the newsletters as well as the coverage of our project in social media and news channels, makes TIDE a high profile project.

10. The TIDE Education Team

- Has developed the framework for a new undergraduate medical genetics curriculum acknowledging treatable ID as a leading learning objective, and is actively educating clinical and research trainees in all aspects of the TIDE program.

From CAI grant application 2011 to TIDE reality & achievements 2012

Title & Leader	Year 1	Year 2	Year 3
Diagnosis Now! *Development & Implementation of a diagnostic protocol prioritizing treatability* **Team Leader** *Clara van Karnebeek*	Consensus & ethics approval obtained; Protocol implemented in 3 divisions; 200 pts evaluated; patient database established; data entered 200 pts; multispecialty ID clinic established	Protocol adapted according to evaluation; expansion implementation to all physicians in 3 divisions & select physicians in psychiatry & SHHC; expected ~800 pts evaluated & data entered into database; multispecialty clinic pt number expanded	Protocol adapted according to evaluation; continued expansion implementation; expected >800 pts evaluated & data entered into database; multispecialty clinic pt number expanded; involvement of community pediatricians to prepare province-wide implementation
Infrastructure *Facilitating implementation and evaluation of protocol* **Team Leader** Hilary Vallance / Graham Sinclair	Referral system established for community pediatricians; new method plasma amino-acid (PAA) analysis developed; GAMT newborn screening pilot project started	New PAA method introduced as routine method additional new test methods developed GAMT newborn screening pilot project continued	Additional new test methods implemented GAMT newborn screening pilot project continued
Preparing for the future *Innovative Technologies & Tools* **Team Leader** Wyeth Wasserman	Post-doctoral scientist in bio-informatics recruited; 5 patient trio's selected & DNA extracted	Evaluation state-of-art technology completed; supplier identified & contracted; whole exome/genome sequencing in selected trio's performed; bio-informatic analysis initiated; 5 new patient trio's recruited & DNA extracted	Whole exome/genome sequencing in selected trio's performed; 5 new patient trio's recruited & DNA extracted; bio-informatic analysis completed in 15 patient trio's
Treatment is our Premise *Providing access to and best evidence of treatment* **Team Leader** Sylvia Stockler **/** Jean Paul Collet	Therapy initiated for all patients diagnosed with treatable IEM; technical platform for research established; draft of theoretical framework for evaluation completed; international patient registries established; n=1 trial process in place & tested in 2 pts; anthropological & ethics input for clinical research initiated	Patient registry expanded; 2-3 pilot RCT's for new treatments completed; anthropological & ethics input transferred into clinical and research applications	Patient registry expanded; International clinical research network functioning w/ >5 countries; complementary funding received for 1 multicenter RCT; novel specific anthropological & ethics knowledge created
Managing the project and accounting to society *Evaluation and Health Economy* **Team Leaders** CvanKarnebeek, Wynona Giannasi, Carlo Marra, Sylvia Stockler	Questions & Areas of evaluation formulated; Framework & Tools Established; Collection relevant data; Participant satisfaction surveys & interviews initiated	Collection relevant data; Participant satisfaction surveys & Interviews continued; Summative evaluation report(s) completed & communicated	Improvements based on evaluation in all WPs collection relevant data; participant satisfaction surveys & interviews; summative evaluation report(s) completed & communicated; Best Care Practice formulation initiated
Linking to Endusers *Knowledge Translation & Dissemination* **Team Leaders** Roderick Houben & Clara van Karnebeek	Apps & Websites created & accessible; KT evaluation plan established; Dissemination of TIDE-BC information to BCCH stakeholders; Planning of social media & events	Dissemination of TIDE-BC information to BC stakeholders; peer-reviewed manuscripts (WP1-8) submitted; Implementation social media & events	(Inter-)National dissemination to stakeholders; Peer-reviewed publications & new manuscripts (WP1-8) submitted
Fostering careers *Education & Mentoring* **Team Leader** Linlea Armstrong	Undergraduate curriculum developed; TIDE-BC teaching rounds established; Research projects defined for trainees	Undergraduate curriculum implemented at UBC; Elective resident & fellow rotation in the multi-specialty ID clinic; Development Young Investigator projects for TIDE-BC research fellows	Submission of Young Investigator Grant proposals
Growing & Innovating: *Research Opportunities* **Team Leader** Sylvia Stöckler	Infrastructure for research projects established	Integration of projects into the TIDE-BC framework	TIDE-BC research cluster expanded beyond the CAI

The original table with 'deliverables' form the TIDE grant application. The colors indicate the progress made so far:
Green = deliverable met | Blue = deliverable / activity in progress

Section 1: Introduction

ABOUT INTELLECTUAL DISABILITY

Intellectual Disability (ID) [IQ <70], is a debilitating disorder which affects every area of life including cognitive, behavioural and social skills. At the age of less than five years it is called global developmental delay (GDD).

An astounding 2.5% of the general population suffers this debilitating condition, which translates into 1000 newborns per year in BC alone.

The challenges for families are devastating and the impact to society is astronomical. In fact, the medical costs are estimated to exceed those of cardiovascular disease and cancer combined[1,2].

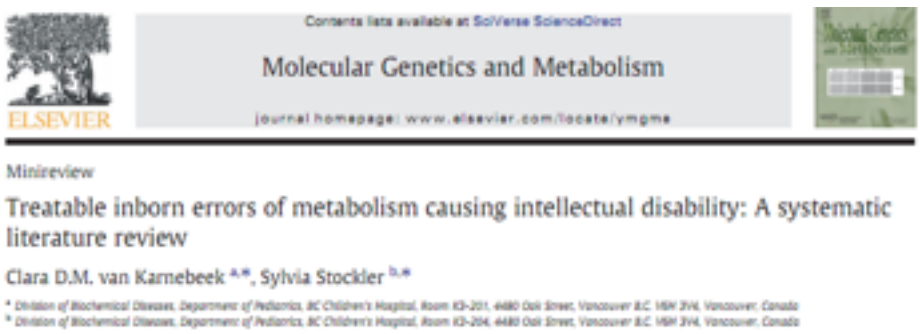
Early recognition of rare but treatable inborn errors of metabolism (IEM) is crucial for minimizing brain damage and reduction of health care costs. ID has traditionally been viewed as a non-treatable condition. Recently, advances in science have allowed the development and application of treatments and effects on cognitive functioning and development. Such new treatments prevent or minimize brain damage, thereby improving the lives of children who otherwise would suffer from serious disease.

It was the systematic review, "*Treatable inborn errors of metabolism causing intellectual disability: A systematic literature review"* which revealed 81 treatable IDs that created the foundation for the Treatable Intellectual Disabilities Endeavour in BC (TIDE BC).

TREATABILITY AND IMPROVED OUTCOMES > KEY ISSUES IN MODERN MEDICINE

In the era of translational and personalized medicine, treatablility and individualized outcomes have become key issues. Our systematic literature review on treatable IDs came at the right time addressing a thus far unmet need: Interventional approach to allow patients to reach their full potential.

This is probably one reason why our article is the most frequently downloaded article from the peer-reviewed journal '*Molecular Genetics and Metabolism*'.


Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

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

Clara D.M. van Karnebeek [a,*], Sylvia Stockler [b,*]

[1] *W.J. Meerding, L. Bonneux, J.J. Polder, M.A. Koopmanschap, P.J. van der Maas, Demographic and epidemiological determinants of healthcare costs in Netherlands: cost of illness study, BMJ 317 (1998) 111–117*

[2] *C. Doran, Seinfeld, R. Madden, M. Otim, S. Horstead, L. Ellis, E. Emerson, How much does intellectual disability really cost? First estimates for Australia, Journal of Intellectual & Developmental Disability 37 (2012) 42-49*

IMPETUS FOR CHANGE

The literature review laid the foundation for TIDE, which went on to translate this knowledge into new practice to enhance patient outcomes. BC Children's Hospital now holds global leadership for the interventional approach to ID, through TIDE's wealth of activities focussed on improving diagnosis and care for treatable inborn errors of metabolism, specifically to:

- Place diagnosis of treatable ID at the forefront of diagnostic evaluation
- Utilize synergistic effect of metabol(om)ics and genomics to discover new treatable IDs
- Improve / create evidence for treatments
- Create culture and develop methods / infrastructure for patient centered care and outcomes
- Understand the health economic impact of diagnosing treatable ID
- Create electronic tools to support clinical decision making
- Translate, transfer, and disseminate knowledge
- Innovate education
- Bridge research and clinical practice

This report outlines the evidence for TIDE successfully meeting and exceeding its vision.

ABOUT TIDE

TIDE is a new care and research initiative with a focus on diagnosis and treatment of ID. A four-year project, TIDE is the first Collaborative Area of Innovation at BC Children's Hospital and Sunny Hill Health Centre for Children led by Dr. Sylvia Stockler, Professor of Pediatrics and Head of the Division of Biochemical Diseases with Dr. Clara van Karnebeek, Clinical Assistant Professor of Pediatrics & Biochemical Genetics.

Capitalizing on its collaborative nature, TIDE is harnessing the skills and expertise of local and international clinicians and researchers. TIDE is demonstrating how trans-disciplinary collaboration and systematic screening for treatable ID can yield earlier diagnosis and treatment for children and is leading the way by creating and using evidence to improve child health. New knowledge through research is continuously translated into better care and outcomes.

TIDE's Goals and Objectives

The deliverables for TIDE were originally set forth as work packages:

1. Diagnosis
2. Biochemical testing
3. Genomics
4. Treatment, evidence, care
5. Health Economics
6. Communication and knowledge translation
7. Education

As the project has matured and evolved, the following areas -*each led by clinical, research and/or subject matter experts and supported by a multidisciplinary team*- are now the core areas of focus for TIDE:

Figure 1: *the five core areas of TIDE BC*

TIDE principal collaborators

- Linlea Armstrong, MD
- Jean Paul Collet, MD PhD
- Lori d'Agincourt PhD
- Wynona Giannasi, MPA
- Roderick Houben, MA
- Osman Ipsiroglu, MD PhD
- Bill McKellin, PhD
- Clara van Karnebeek, MD PhD
- Carlo Marra, PhD
- Colin Ross, PhD
- Graham Sinclair, PhD
- Sylvia Stockler, MD PhD
- Hilary Vallance, MD
- Wyeth Wasserman, PhD

About the TIDE Team

The innovative momentum of the TIDE team resides in its diversity ranging from clinicians from the various clinical specialities involved in diagnosis, treatment and care of children with ID, to lab scientists involved in diagnosis of metabolic and genetic causes of ID, to bio-informations, health economists, social scientists, health care professionals, educators and administrators.

Their complementary expertise is synergistic all in achieving TIDEs mandate of collaborative innovation. The different scientific approaches and the diversity of personalities lends our group a lively, colourful touch.

Currently there are 19 paid resources committed to the TIDE project, one clinician scientist, two PhD students, one post-doctoral fellow, two lab technologists, three research assistants, one genetic counsellor, one research manager, one health economist, two psychologists, one administrative support, and four consultants providing project management, communications and evaluation leadership and support.

There are over 60 resources providing governance, leadership and guidance, leading research and providing patient care, ranging from hospital executive, clinicians (metabolic specialists, neurologists, medical geneticists, developmental pediatricians, psychiatrists), (biochemical, cyto- and molecular) genetic researchers, senior lab scientists, and social scientists (medical anthropology, ethics). Please refer to Appendix A for a list of all collaborators.

These valued human resources are the most significant assets to the project – each contributing to the success of TIDE. As TIDE portfolio continues to expand its reaches within BC Children's Hospital, across the province, the country and globally, additional clinical and research resources will be brought onto the project as needed to support TIDE's key deliverables.

Section 2: Evaluation Framework

To systematically evaluate TIDE, a comprehensive evaluation framework was developed. In consultation with TIDE leaders, project goals were mapped to clear outcomes for each area of focus. The evaluation framework outlines how TIDE's activities are expected to lead to intended outcomes *(Figure 2)*.

LOGIC MODEL

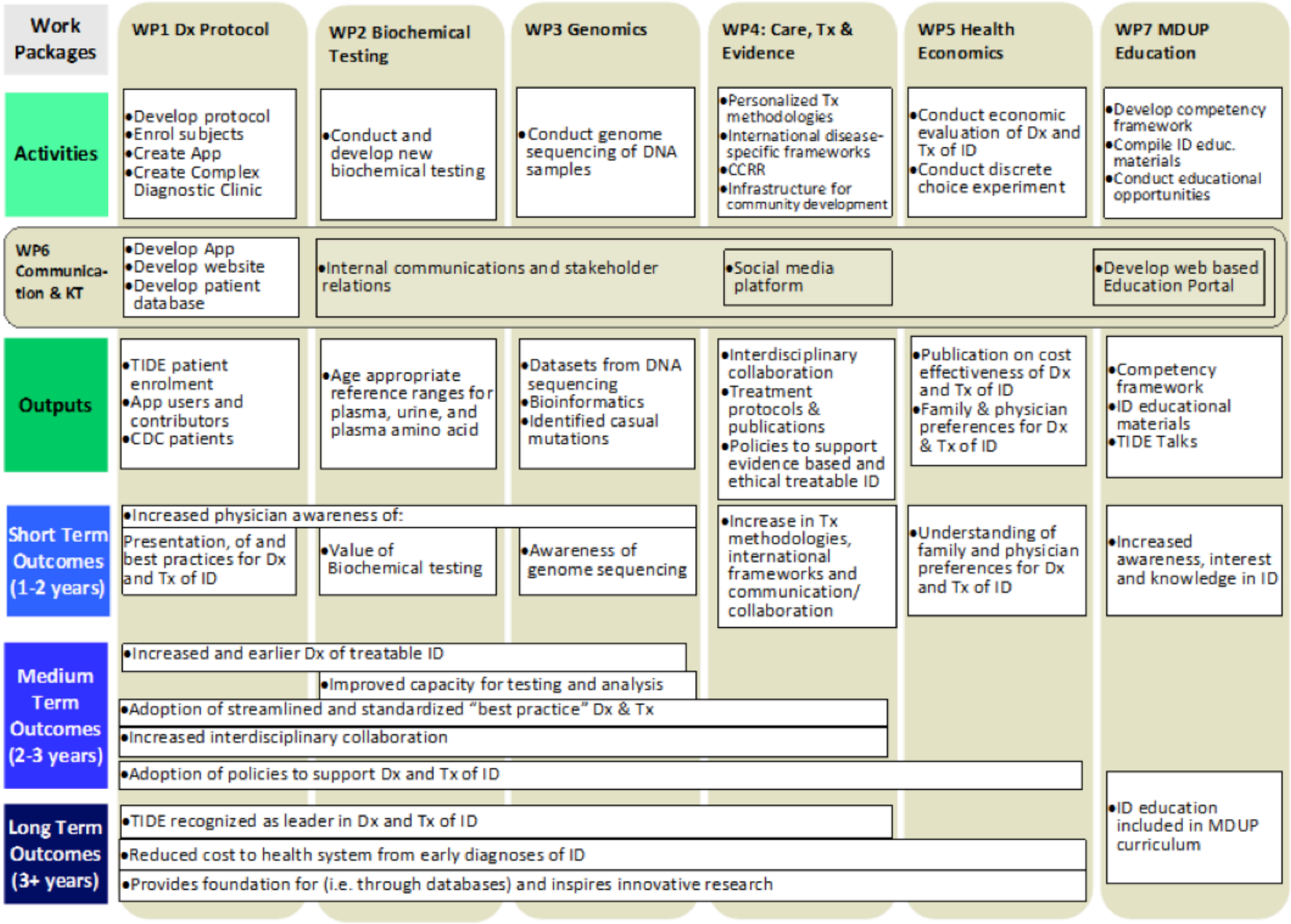
In addition to the master logic model *(Figure 2)* for the entire project, logic models were developed for each original work package and have been used to guide the evaluation process. The logic models illustrate how human and financial resources are utilized to carry out activities that support TIDE's mandate (*inputs*) and demonstrates how inputs are used to develop opportunities for innovative collaboration (*outputs*).

DATA SOURCES

A mixed methodology has been used to conduct this first year evaluation. The focus is on illustrating how TIDE is meeting its intended outcomes using the following existing data sources:

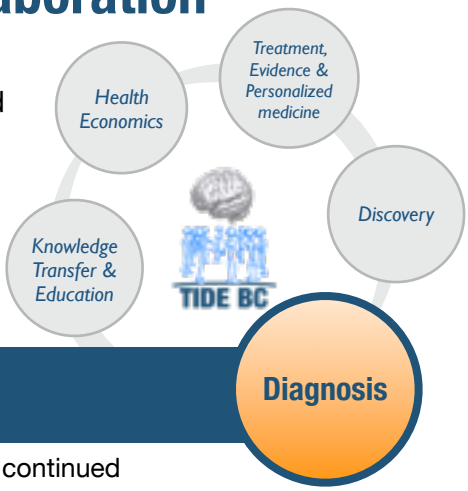
- Document review *(meeting minutes and attendance, CME credits, etc.)*
- Quantitative review of deliverables *(i.e. data and quantifiable outcome analyses)*
- Qualitative data, including patient/family and provider satisfaction with respect to specific project deliverables *(i.e. satisfaction surveys and interviews)*
- PubMed searches

Figure 2: Logic Model



Section 3: Evidence of Innovative Collaboration

This section provides a comprehensive review of TIDE's activities and accomplishments to date.



3.1 TIDE PROTOCOL

With the systematic review laying the groundwork for the TIDE protocol and continued leadership from *S. Stockler and C. van Karnebeek* the TIDE protocol:

- has been developed,
- approved by the TIDE Advisory Board (in March, 2012),
- adopted throughout Biochemical Diseases, Neurology and Medical Genetics within BC Children's,
- and leveraged to form the creation of international guidelines.

A retrospective study *(2000-2010 in BCCH)* showed that systematic application of the TIDE diagnostic protocol **saves more than $1000- of unnecessary diagnostic testing and at least 6 months diagnostic delay per patient suffering a treatable ID.**

We cannot afford to miss any child with a treatable disease: Time is brain, and without therapy, irreversible brain damage occurs.

About the Protocol

The TIDE protocol is a two-tiered screening tool is superimposed to current diagnostic guidelines and parameters. The 1st tier comprises routine metabolic screening tests and should be performed in all individuals with unexplained DD/ID as it has the potential to identify 53% of all treatable diseases. The 2nd tier investigations for the remaining disorders are ordered based on the clinical signs and symptoms of the patient. The protocol is supported by an app *(see www.treatable-id.org)*, which comprises up to date information on all 81 IEMs, diagnostic tests, therapies and a search function based on signs and symptoms.

Figure 3: *The TIDE Protocol superimposing the the identification of treatable disease to existing practice parameters*

1st Tier: Non-Targeted screening to identify 43 (53%) treatable IEMs

Blood:
- ammonia, lactate
- plasma amino acids,
- total homocysteine
- acylcarnitine profile
- copper, ceruloplasmin

Urine:
- organic acids
- purines & pyrimidines
- creatine metabolites

2nd Tier: Targeted metabolic work-up to identify 38 (47%) treatable IEMs requiring 'specific testing'

- **according to patient's symptomatology patient (table 4) & clinician's expertise**
- **utilization of textbooks & digital resources** (App: www.treatable-ID.org)
- **consider the following biochemical / gene tests:**
  - plasma cholestanol
  - plasma 7-dehydroxy-cholesterol:cholesterol ratio
  - plasma pipecolic acid & urine AASA
  - plasma very long chain fatty acids
  - plasma vitamin B12 & folate
  - serum & CSF lactate:pyruvate ratio
  - enzyme activities (leucocytes): arylsulphatase A, biotinidase, glucocerebrosidase, fatty aldehyde dehydrogenase
  - urine deoxypyridonoline
  - urine oligosaccharides & glycosaminoglycans
  - CSF amino acids
  - CSF neurotransmitters
  - CSF:plasma glucose ratio
  - CoQ measurement fibcroblasts
  - molecular analyses: *NPC1, NPC2, SLC19A3, PDHA1, DLAT, PDHX, SPR, TH* genes

Implementation in BC Children's: the TIDE Pilot Study

In the first year of the TIDE study 'pilot phase', 210 patients with global developmental delay / intellectual delay of unknown cause were enrolled into the study, 64% of whom were male. Patients were referred primarily from Biochemical Diseases (n=112) and Neurology (n=75) with a smaller number (n=16) coming from Medical Genetics. Over half of patients had already been thoroughly tested for an underlying cause. The patient enrollment, data entry and DNA collection was performed by a group of motivated research coordinators: Mrs. M. Lafek, Mr. T. Murphy, Mrs. M. Boldut

All patients in the TIDE study were enrolled with parental consent for de-identified data-entry into the TIDE RedCAP database (in collaboration with Neurodevnet) and storage of DNA in the TIDE DNA registry. Collection of data allows for analysis of TIDE protocol effectiveness and the extensive phenotypic data provides the essential piece for future research on treatable ID, especially combined with paired patient DNA samples. In collaboration with Neurodevnet (Mrs. Elodie Portales), the team is currently developing an automated patient clinic letter which can be generated from the TIDE RedCAP database. This will prove a time- and cost-saving initiative for both physicians and secretaries.

Description TIDE cohort year 1

More than half of patients was estimated to suffer a moderate to severe degree of ID *(see Table 1)*. Detailed phenotyping of symptoms for each child was performed with classification into different categories of clinical presentation *(see Table 2)*. More than 85% suffered significant co-morbidity, with autism and epilepsy as most prominent other presenting disease feature.

SEVERITY	NUMBER OF SUBJECTS
Unknown	9
Borderline	4
Mild	73
Moderate	90
Profound - severe	29

Table 1:
Severity of Developmental Delay/Intellectual Disability (ID)

Many of the patients had multiple neurological abnormalities (average of 2, ranging from 0-8) and non-neurological abnormalities (average of 3, ranging from 0-13). The most frequent neurological abnormalities were hypotonia (40%), behavioral/psychiatric disturbance (40%), and epilepsy (30%). The most common non-neurological abnormality was facial dysmorphisms (50%). The TIDE patients were representative of the diverse population affected by DD/ID as co-morbidity classification findings reveal.

ID CLASSIFICATION	
Unspecific ID	30
Familial ID	2
X-linked ID	0
Epileptic encephalopathy	4
ID plus epilepsy	31
ID plus dysmorphic features	39
ID plus multiple congenital anomalies	8
ID plus leukodystrophy / white matter abnormalities	5
Neurodegenerative DD	3
ID plus autism	43
ID plus psychiatric disorders	11
ID plus neurologic deficit	18
ID plus structural brain abnormalities	6
ID plus failure to thrive / poor somatic growth	9
Total ID	**210**

Table 2:
Classification of Intellectual Disability type (most prominent co-morbidity)

Although for majority of patients, testing is still in progress, more than 5% of patients were diagnosed with a treatable ID. This is a higher number than expected and provides solid evidence that the TIDE approach is a fruitful one, with the potential to minimize brain damage and optimize the child's functioning. Of all TIDE 1st tier screening tests, the creatine metabolite analysis has the highest yield. **Other causes of ID were also identified, including chromosomal abnormalities, syndromes, and non-treatable metabolic diseases in about 1 out of every 3 patients.** An etiologic diagnosis is extremely important for each child as it ends the diagnostic odyssey, prevents further testing, improves genetic counseling and management and brings closure for the family.

Our study shows that even in patients who had been previously investigated, the TIDE protocol still can identify a hitherto missed treatable or other condition.

The TIDE Protocol is a key tool in helping to support collaboration between five divisions (primarily Biochemical Diseases, Neurology and Medical Genetics) to achieve TIDE's goal of optimizing outcomes of children through early diagnosis of treatable conditions. The use of the protocol is not only helping to support patient care but is also a signal of adoption of a clinical practice change. **Most BC Children's Hospital physicians are now using the TIDE protocol** and medical students, residents and fellows are also being educated to use the protocol in daily practice though ongoing teaching opportunities from the TIDE team. The protocol has also been the topic of many 'knowledge sharing' opportunities for TIDE *(see Appendix B for a comprehensive list of TIDE knowledge translation activities, including journals, presentations, etc.)*

With the evidence that the pilot study has now generated, identifying a treatable disease in more 1 out of 20 ID patients, our goal is to formally transition the TIDE protocol from research into standard care of care. Already this is happening as the Laboratory records show that more than hundred children with ID (outside of the study) have also been screened in BC Children's Hospital with the TIDE first tier of blood and urine tests.

A Family's journey towards receiving a diagnosis ...

TIDE-BC is demonstrating an impact for families. Five-year old Nathan's life has improved immensely, as has his family's. At the age of three, suffering from developmental delay, autism and seizures but undiagnosed despite having seen 15 specialists, TIDE-BC first tier testing revealed creatine in Nathan's urine. He was referred to TIDE-BC at BCCH where he was diagnosed with Creatine Transporter Deficiency, one of the rare yet treatable disorders causing intellectual disability for which the TIDE program promotes active screening.

Consulting neurologist Dr. Chau points to TIDE-BC as the program that enabled the diagnosis. *'Now that we have the TIDE study with a comprehensive testing protocol we are enhancing our ability to diagnose intellectual disabilities which are causally treatable*'. In response to being informed of the diagnosis, Vanessa, an appreciative mom says, *"Dr. Clara van Karnebeek explained everything so well to us and gave us wonderful information. She made us feel at ease"*. Further testing confirmed the presence of a defect in Nathan's X chromosome preventing the manufacture of normally functioning creatine transporter, important for providing energy to the brain.

Dr. van Karnebeek initiated an innovative therapy for Nathan; while not curable, this intellectual disability has become treatable as demonstrated by Nathan's story with creatine, glycine and arginine supplements three times a day to enhance the brain creatine or energy content. The treatment has resulted in his improvements, as is evident on imaging as well as in his cognitive and behavioural functioning. As Nathan's mom reports, *'Nathan used to smash his head against the wall and could not communicate. The other day he stood at the window singing about the sun. He couldn't talk before'.*

Creation of International Guidelines

TIDE is the first in the world to systematically apply a protocol to the identification of treatable ID. As a result of the protocol TIDE leaders have been invited to write the ID guidelines for the American College of Medical Genetics *(manuscript currently under review)* [3]. These guidelines propose more extensive testing in the 1st tier (urine oligosaccharides and muocpolysaccharides) increasing diagnostic potential to 65% of all diseases. If our Biochemical Genetics Laboratory is able to secure an extra MS machine, BCCH will also be able to perform these tests at high-throughput to benefit ID patients in BC.

These guidelines will pave the way for a change in clinical practice around the globe, ie following the TIDE approach to prioritize treatability in the evaluation of ID. TIDE therefore stands to impact the lives of the 2-3% of children suffering ID worldwide.

Collaboration with Child Health BC and the BC Pediatric Society to Spread the Protocol across BC

To ensure that every child in BC has access to our high standard of diagnostic care, TIDE has joined forces with Child Health BC to spread the protocol across the province. On September 28th, 2012 a consensus building session was held with support from Child Health BC to bring together a reference group of pediatricians from across the province, as well as other clinical experts and care providers to ensures the adoption of the TIDE protocol across BC. With input from the group a BC version of the TIDE protocol was created (see Figure 4), and is currently being piloted with a reference group of 10 community pediatricians from across the province. This initiative allows to decentralize care and decrease wait lists for BCCH, as community paediatrician can perform much of the diagnostic work-up themselves.

The next phase will see collaboration with the BC Pediatric Society to further spread the protocol to all community pediatrician offices across BC. TIDE plans to continue the collaboration with Child Health BC to support local capacity building through the delivery of regional clinics. A plan for formal evaluation is being generated.

[3] *van Karnebeek, C., Shevell, M., Zschocke, J., Moeschler, J., and Stockler, S. "ACMG Practice Guideline: The Metabolic Evaluation of the Patient with Developmental Delay & Intellectual Disability for Treatable Inborn Errors of Metabolism (Genetic in Medicine)."*

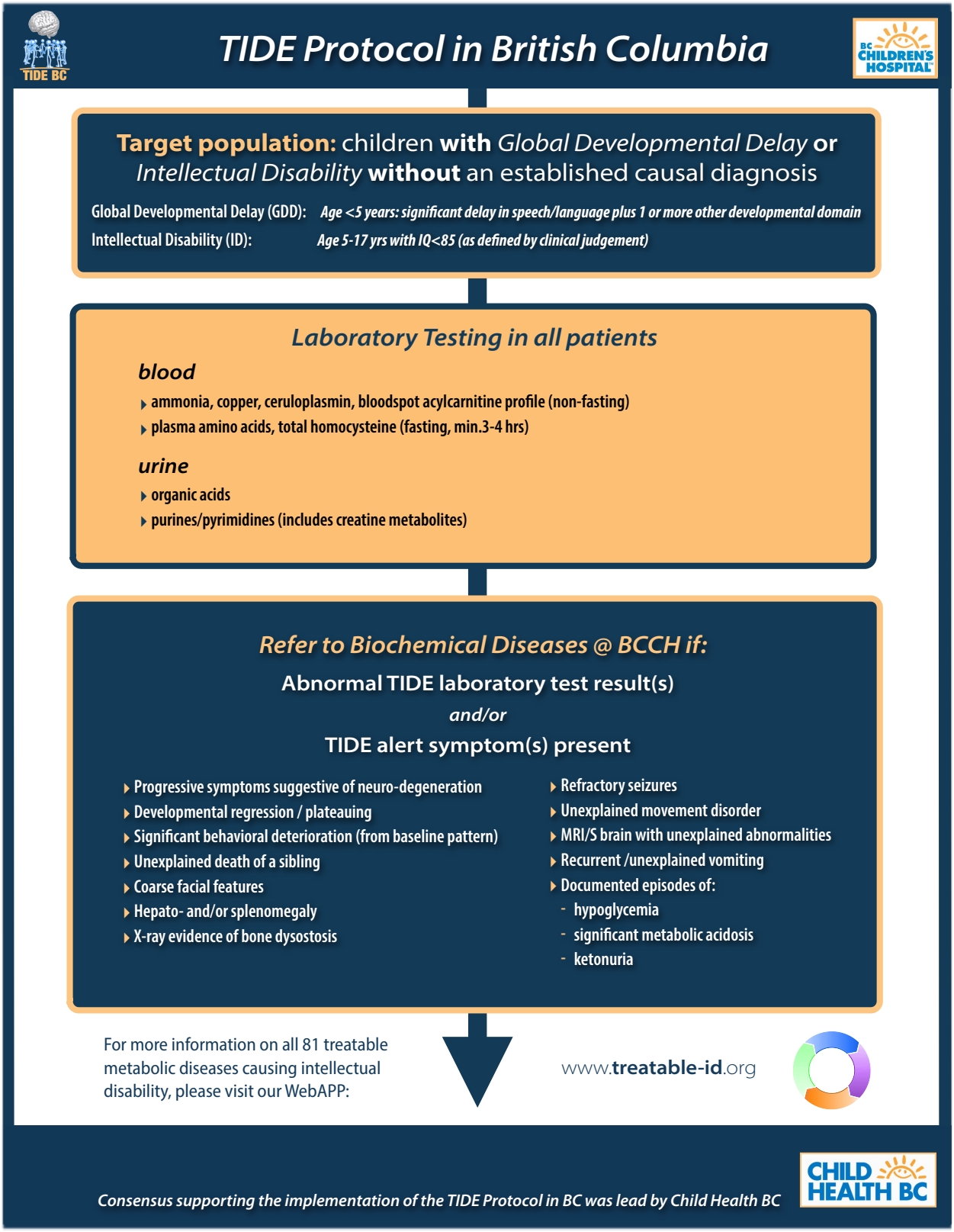


Figure 4: *TIDE protocol for BC Pediatricians*

3.2 COMPLEX DIAGNOSTIC CLINIC

Diagnosis

For many patients who do not receive a diagnosis further diagnostic work-up is required. For the most challenging of cases, the true 'mystery patients with severe, multi-organ involvement, who must have something genetic, but remain without a diagnosis despite the million dollar work-up of endless testing and clinic visits, TIDE has established the Complex Diagnostic Clinic. The CDC addresses the thousands of different causes, diagnostic challenges, the diagnostic odyssey associated with the 'million dollar work-up', physicians not collaborating, endless visits and tests, non-coordinated appointments, non-communicating specialists and desperate parents without a diagnosis for their child. The objectives of the CDC are:

- To streamline non-coordinated specialist appointments and reduce the burden for patients (50% of patients are simultaneously referred to 2 departments and 25% to 3 departments).
- To streamlines tests and enhance the diagnostic yield through a state-of-the-art collaborative evaluation.
- To save families multiple trips to BC Children's.
- To determine how collaborative multidisciplinary clinical assessment impacts physicians' ability to diagnose complex ID patients.

Results

During the first five clinics:

- 13 patients were seen in 8 months: 6 were referred from Biochemical, 6 from Neurology, and 1 from Medical Genetics. These 13 patients were evaluated by 30 specialists *(from Biochemical Diseases, Neurology, Medical Genetics, Psychiatry, Developmental Pediatrics, Hematology, Dermatology, Gastroenterology and Rheumatology)*.
- The average patient was 8 years old and was nearly 3 before being referred BC Children's.
- The average CDC patient was seen at 5+ diagnostic services.
- An etiologic diagnose was identified and confirmed in seven (>50%) patients. These included three monogenic disorders, two copy number variants, one mitochondrial disorder, and one multifactorial (environmental+genetic). In another three 'probable diagnoses' is under consideration, awaiting further testing and whole exome sequencing was successfully completed in 1 patient and underway in 2 siblings.

Family and Provider Satisfaction

Baseline interviews conducted with all families prior to the clinic find that families are eager for specialist collaboration and appreciative of this innovative approach and hopeful for a plan for the future. Post CDC survey findings reveal care and communication/collaboration outcomes are being achieved from both patients and physicians.

All families reported expectations were met, all rated the CDC positively, all would recommend CDC and two thirds reported the experience at the CDC to be an improvement over previous experiences aiming for a diagnosis.

Providers reported the clinic was providing a platform for next generation sequencing, saving time by communicating directly with specialists about individual patients, providing a forum for education and enabling a quicker diagnosis for patients.

Interestingly, the one key area for improvement, noted by both families and providers, is the opportunity for providers to see the patient in the same room together. This may prove to further enhance communication and collaboration and support multidisciplinary care.

> *"Understanding the gene that is responsible for my son's condition because of coming to the Clinic is a huge relief. I can finally stop blaming myself for something I may have done while I was pregnant. After 6 years of guilt, it feels awesome to know what's going on. We still have a huge journey ahead but now I can let go.*

CDC Demonstrating Financial Benefits

While a direct comparison cannot be made between the traditional model of multiple sequential or parallel visits to different clinicians versus one multidisciplinary clinic visit, it is clear that there are financial gains to be made from both the health system and family costs using a coordinated approach to multidisciplinary care. There are substantial opportunities for cost savings to the health care system in the areas of clinical consultation and testing and savings to families, through unnecessary trips to BC Children's.

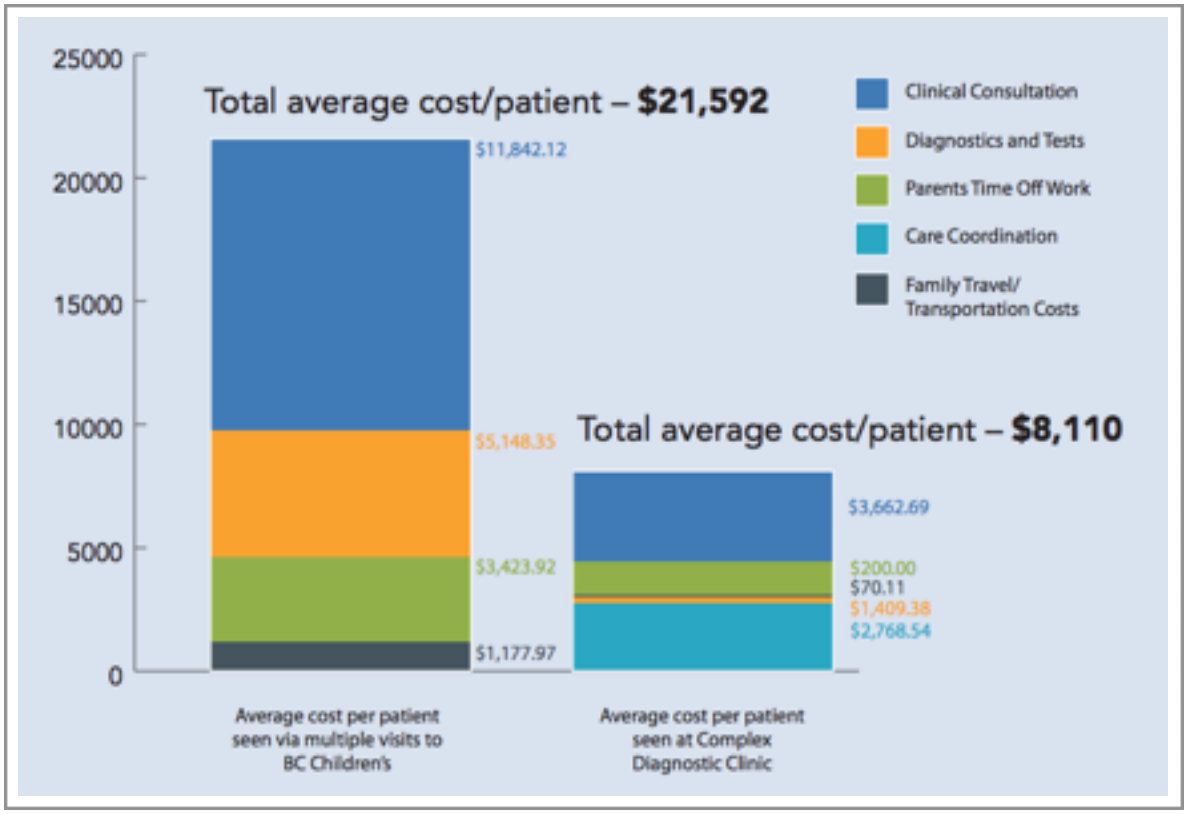


Figure 5: *CDC illustrating financial benefits to the health system and to patients/families*

Key Findings

Through the evaluation it is apparent that the clinic is:

- Producing diagnoses for patients who were previously undiagnosed.
- Ending the diagnostic journey for families with clinician agreement that a non-pathogenic condition is present in the child.
- Yielding fewer necessary tests.
- Providing an education platform, translating research to evidence based practice.
- Demonstrating how multidisciplinary collaboration impacts the quality of patient care.
- Demonstrating financial benefits to families and to the system.
- Providing access to whole exome sequencing.

The future directions of the clinic includes exploring solutions to further streamline the coordination of the Clinic and to transform this integrated approach into clinical practice.

The TIDE Diagnostic Team at BC Children's Hospital

Department of Pediatrics

Division of Biochemical Diseases

- Maria Boldut
- Lori d'Agincourt
- Susan Failanga
- Ruth Giesbrecht
- Gabriella Horvath
- Mir Lafek
- Yolanda Lillquist
- Pam Lukes
- Ramona Salvarinova
- Stefanie Schaumann
- Michelle Sebastiano
- Kathy Withers
- Sylvia Stockler
- Clara van Karnebeek

Division of Pediatric Neurology

- Vann Chau
- Mary Connolly
- Michelle Demos
- Juliette Hukin
- Tyler Murphy
- Vesna Popovska
- Kathryn Selby

Division of Developmental Pediatrics

- Osman Ipsiroglu
- Nancy Lanphear
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- Elizabeth Mickelson

Department of Medical Genetics

- Linlea Armstrong
- Cornelius Boerkoel
- Christele du Souich
- Anna Lehman
- Suzanne Lewis
- Barbara McGillivray
- Tanya Nelson
- Millan Patel
- Marion Thomas
- Margot Van Allen

CMMT/CFRI

- Wyeth Wasserman
- Colin Ross

Department of Pathology and Laboratory Medicine

- Patrice Eydoux
- Tanya Nelson
- Graham Sinclair
- Hilary Vallance

Department of Child and Adolescent Psychiatry

- Susan Baer
- Anthony Bailey
- Robin Friedlander

Evaluation

- Wynona Giannasi

3.3 TIDE DIAGNOSTIC LAB

Diagnosis

The TIDE Diagnostic Lab, a partnership with the Biochemical Genetics Lab at BC Children's (*Drs. Hilary Vallance & Graham Sinclair*), has a lead role in supporting the diagnosis of intellectual disabilities, as demonstrated through the achievements below.

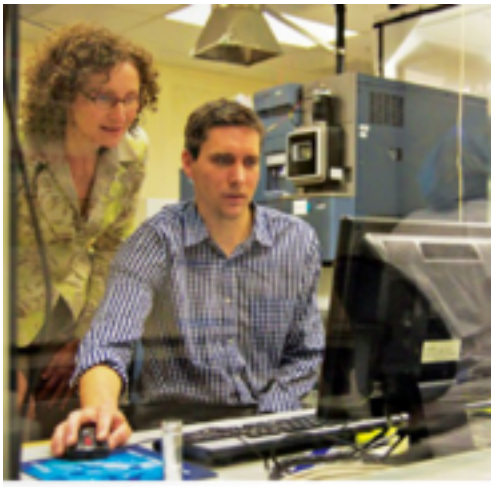
Improving Test Efficiency for Disorders of Amino Acid Metabolism

Seventeen of the 81 treatable causes of ID included in the TIDE protocol can be diagnosed through the analysis of amino acids in plasma. The Biochemical Genetics Laboratory at BC Children's Hospital routinely measures amino acids in >2000 plasma samples per year to investigate children for these, and related metabolic disorders. At an analysis time of almost 4 hours per sample, the current method has reached capacity.

In order to increase capacity, the lab is developing an alternative plasma amino acids method utilizing the high specificity of tandem mass spectrometry to increase the efficiency of this testing. The new MS/MS data acquisition method has been established.

- 15 minute chromatography is now run with separation of all 48 amino acids and 22 internal standards.
- Pre-analytical sample preparation method has been established.
- The limit of detection has established for all species (sensitivity is acceptable for all).
- Compilation of samples across analytical and age ranges for reference intervals is ongoing.

Using this technology the per sample run time is reduced while simultaneously extending the panel of amino acids measured to > 40. This technological innovation will increase capacity for testing while decreasing the overall cost of the testing, greatly improving the efficiency of investigations for these treatable causes of ID.



See the Summer 2012 edition of the BC Children's Hospital Foundation's *"Speaking of Children"* magazine for an article showcasing the importance of newborn screening for another treatable ID.

Reduction in Test Duplication

A test utilization study was conducted by lab leaders to evaluate ordering practice for four TIDE first tier assays performed in the Biochemical Genetics Lab:

- Bloodspot acylcarnitines (ACYDOT)
- Plasma amino acids (PAM)
- Urine purines and pyrimidines (PPGC)
- Urine organic acids (ORGS)

The analysis was conducted for a 9 month period prior to the implementation of the TIDE protocol (December 1, 2010-August 31, 2011) as compared to a equal period following protocol implementation (January 1, 2012-September 30, 2012). Changes in overall test order numbers, duplicate test orders, and the rate of rejection of unnecessary duplicates were evaluated for 19 physicians from 3 specialist services participating in the TIDE protocol, as compared to all non-participating physicians. For the duplicate testing comparisons, repeat samples for monitoring of previously diagnosed patients were excluded from the analysis. The following results are highlighted:

- Overall there has been a 3.6% increase in testing for non-participating physicians consistent across all 4 assays. This is the underlying rate of increased testing.
- There has been an absolute reduction in test ordering for PAM and ORGS by TIDE physicians, year-over-year (0.8% and 6% respectively). This decrease is due to both a reduction in duplicate test requests and an increase in the rate of rejection of duplicate request by the lab.
- There has been an increase in TIDE ordering of PPGC and ACYDOT, likely reflecting more patients receiving the full set of first tier tests (previously underutilized).
- There has been a reduction in PAM and ORGS testing somewhat compensates for the increase in PPGC and ACYDOT testing but overall there has been a 6% increase in total testing (1/2 of that is the result of the TIDE protocol, about 140 samples in 9 months).

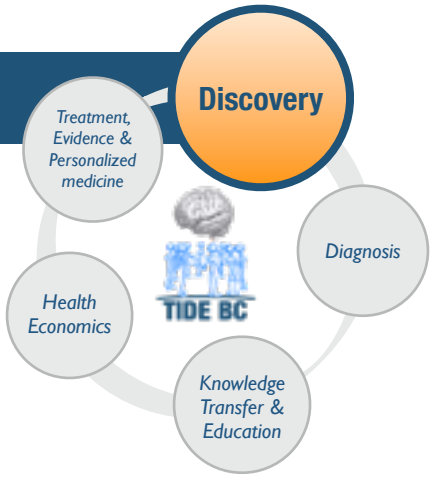
Initiation of GAMT Newborn Screening Pilot

Under TIDE's umbrella, BC Children's Hospital has initiated the first-ever newborn screening for GAMT deficiency. A diagnosis during the newborn period is crucial for preventing brain damage with early treatment allowing normal development. A pilot study to determine the feasibility of implementing a two-tier approach was initiated in September 2012. This is a novel analytical first and second tier measurements for guanidinoacetate integrated into existing tests designed to establish the feasibility of performing this test on a population basis, with the hopes of then proceeding to routine screening for GAMT deficiency in all BC Newborns. Molecular confirmatory testing from bloodspot is currently under development in-house with the Biochemical Genetics Lab at BC Children's.

TIDE Requisition

Due to considerations far beyond the realm of Biochemical Genetics Lab and BC Children's Hospital a TIDE requisition is not possible at this point. Instead a work-around involving stickers for the first tier TIDE tests have been developed and are being distributed to pediatricians, starting with the Child Health BC reference group (see Protocol, figure 4) and then eventually spread via the BC Pediatrics Society to all pediatricians.

3.4 TIDE GENE DISCOVERY



TIDEX was launched as part of the TIDE BC initiative. The aim of TIDEX is to identify new genes and/or mutations causing unexplained cases of DD/ID using the latest cutting edge genomic technologies and analytical methods.

TIDEX was designed by a collaborative group of bio-informaticians and geneticists (led and represented by W. Wasserman and C. Ross) in collaboration with clinicians (led and represented by *C. van Karnebeek and S. Stockler*), to take advantage of new technologies to help crack the code for those families who have undergone the million dollar workup and are still unable to receive a diagnosis for their child's debilitating condition. Figure 6 provides an overview of the key gene discovery processes/steps:

Family Selection

- Clinician / Scientist proposes a complex ID patient with biochemical phenotype (in complex diagnostic clinic or other setting)
- Patient / Family Selection according to TIDEX criteria & scoring system in Complex Clinic (see Figure 7)
- Clear explanation of the goals, timelines, challenges of Next Generation sequencing are discussed with the family as part of informed consent
- Ideally, the family should also be enrolled in the TIDE data & tissue registry as well
- Family members allotted study numbers by research coordinator

Exome sequencing

- EDTA blood (and urine etc as appropriate) on all family members collected via TIDEX requisitions > extraction by Colin Ross' Lab > storage TIDE tissue registry
- Data on clinical history and investigations collected (TIDE dataform filled out by physician) and entered into TIDE Redcap research database
- Dr. Ross's lab will send sample(s) to an outside sequencing centre. Decision will be made case by case as to how many of the family will have exome sequencing or SNP array.
- The time until data return will be variable.

Data analysis

- Dr. Wasserman's lab will align, identify, and annotate variants within a two week period, approx. The following variant types will be called: coding non-synonymous single nucleotide changes, possible splice site changes & indels.
- The annotation of the variants will include the following information:
  - whether or not the variant has been listed in various
  - databases previously, and at what frequency;
  - the predicted effect of the variants;
  - a confidence score indicating how likely the finding is to be real.
- Only variants seeming to segregate appropriately in the family based on exome / SNP array will be reported.
- The clinician will evaluate the variant list to see if an obvious candidate is present. If the clinician would like assistance in this process,is step of analysis.

Validation and Future Directions

- Strong candidate variants in the proband and family will be confirmed by Sanger sequencing
- Opportunities for functional studies, model organisms, and treatment opportunities can then be explored
- Applications for further funding may be needed
- Once validated, genetic counseling and appropriate management for patient and family can be provided

Figure 6: *TIDEX key workflow processes*

Creation of Selection Criteria

Important to the aim of TIDEX is the selection of the 'right' patients and families to undergo this level of sequencing. Selection criteria has been designed (Figure 8) and is used to guide the patient/family selection process.

Results

7 families (up to 25 individuals) have been selected according to TIDEX criteria (ID plus metabolic phenotype of unknown etiology after deep phenotyping and extensive investigations) by the TIDEX collaboration. DNA whole exome sequencing, bio-informatics platform created and used for data interpretation.

- For one family a new gene CA5A has been discovered as novel treatable ID and validated by the Sly Lab in St Louis; this manuscript has been submitted for publication. The finding has a major impact for the family, with treatment being an option, provides a significant understanding of human physiology and metabolic disease and provides numerous research opportunities.
- In four other families, new genes have been discovered as well and are currently in various phases of validation in collaborators with labs in Montreal, Harvard, Maine, Zurich. This success rate is remarkable and only possible through the close collaboration between scientists and clinicians (see table).
- Using the metabolic phenotype as a key criterion has several advantages: it facilitates candidate gene hypotheses, facilitates validation process and offers targets for causal treatment. This approach makes TIDEX unique and fits the interventional approach to ID and the TIDE emphasis on knowledge translation.
- A novel process for selection, pre-sequencing tests, sequencing, bio-informatics and clinical user interface for TIDEX optimal performance and translation from bench to bedside has been developed. The ringroad has been bridged and TIDEX stands as model to similar endeavours in other fields of medicine. As well, TIDE is contributing to bringing whole exome sequencing closer to use in clinical practice as an MSP funded test.
- Education is central and there are many doctoral and postdoctoral students involved, who contribute profoundly to these exciting TIDE gene disoveries: Casper Shyr (PhD student, CIHR awardee), Ekaterina Nosova (post-doctoral fellow), Cynthia Ye (PhD student). International collaborations have been established and are putting TIDEX on the map as experts in metabolic gene discoveries.

Gene discovered	Gene function	Clinical & Metabolic phenotype	Relevance	Validation status / Collaboration
CA5A	Mitochondrial Carbonic Anhydrase VA	Coma, Hyperammonemia, Lactic acidemia, Hypoglycemia, Unspecific organic aciduria	First human defect Treatment available, (carglumic acid, zinc supplements, sick day formula, query sulphonamides)	Validated, submitted for publication / W. Sly (St. Louis)
RMND1	Assembly of mitochondrial respiratory enzyme complexes	Developmental delay, renal insufficiency, sensorineural hearing loss lactic acidosis	Third family with mildest phenotype identified worldwide	In progress E. Shoubridge (Montreal)
ZFYVE20	Rab4/5 endosomal recycling	Intractable epilepsy, microcephaly Intracellular cobalamin processing	First human endosomal recycling defect	In progress S. Coreira (Boston)
ACABC	Acetyl Co-A carboxylase	Biotin responsive metabolic encephalopathy Ketoacidosis	First human defect Treatment available (Biotin)	In progress M. Baumgartner (Zurich)
DSCAML1	Down syndrome cell adhesion molecule like-1	Severe developmental delay, congenital microcephaly, brain atrophy, seizures, vision loss	First human defect; important role in neuron process arborization & symaptic formation	In progress R. Burgess (Maine)
GABRP	gamma-aminobutyric acid (GABA) A receptor	Familial progressive neurodegeneration with dystonia, microcephaly, neurotransmitter abnormalities	First human defect; important role in neurotransmission; potential for treatment	In progress C. Ross (Vancouver)

Figure 7:

Utilizing the Metabolic Phenotype in the identification of candidate genes identified via WES. Out of 7 families investigated, 6 candidate genes were identified which are currently under different stages of validation.

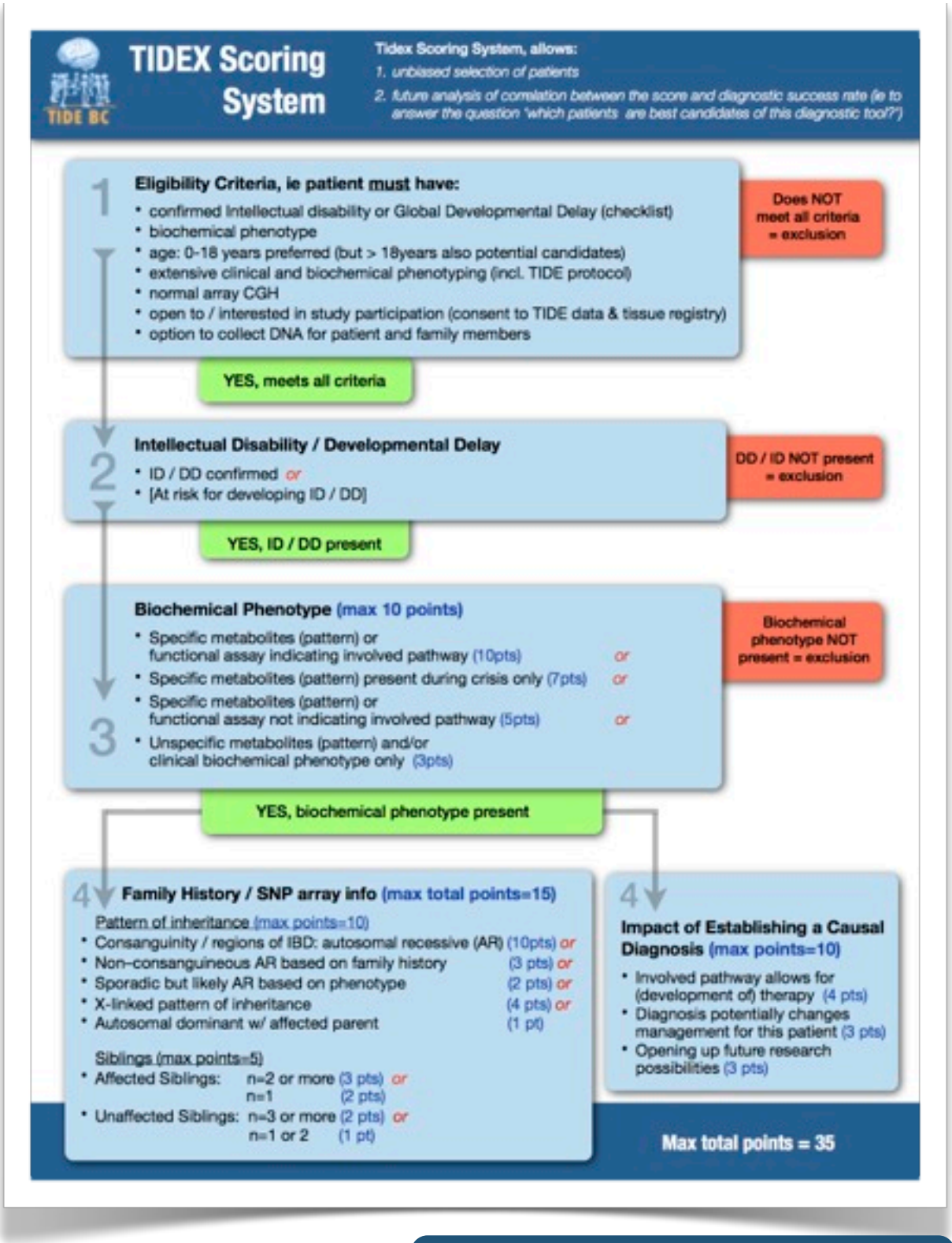
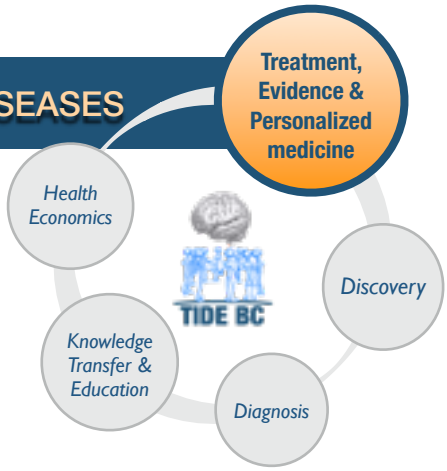


Figure 8: *TIDEX Scoring System*

> *I have been waiting for your email for more than 5 years. The TIDEX discovery gives clinical relevance to my work in the lab.*
>
> - (US scientist and collaborator)

3.5 TIDE EVIDENCE FOR TREATMENTS OF RARE DISEASES

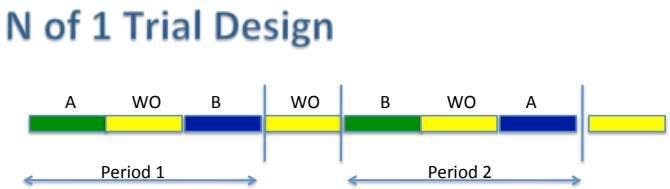


The majority of treatments for rare metabolic diseases, which are accepted as 'standard of care', rank at evidence level 4 or lower. Randomized Clinical trials however, cannot be performed in these conditions due to inherent small sample size. Limited information on natural history along with clinical heterogeneity represents other limitations. N=1 protocols including cross-over trials and cohort designs, can overcome some limitations as they are applied to a single participant. The objectives of this work are to determine whether a novel treatment has a positive effect on relevant outcome(s) for specific patients and to increase the evidence for treatments in patients with rare metabolic disease.

N=1 protocols have been designed for each specific indication with approval from ethics and regulatory authority. Relevant outcomes, follow-up, and patient specific end-points are being evaluated for change from base-line (central parameter and standard deviation) along with patient's personal perception of utility.

In just one year, with the collaboration and input of many experts such as Dr. Rolin Brandt (statistician UBC) and DR. JP Collet (methodologist), TIDE has already made strides in demonstrating evidence for treatments of rare diseases, from the development of small sample size methodology to the application of such practices through various studies of rare diseases (i.e. Phenylketonuria, Pyridoxine Dependent Epilepsy).

> *"When Mason started on the lysine restricted diet it was a dramatic change. At 5 years old he walked like a toddler and within a week he was walking normally. I thought who is this kid?! I felt that there was so much judgment on me as a mom, so it felt good to see the improvement.*
>
> *- parent*



- Used in a single patient
- Randomization, cross over possible
- Meta analyses is used to estimate the overall population effects
- Examples: Creatine transporter deficiency, Glut1 deficiency

Figure 9: *Diagram of an n=1 study showing the cycles on and off therapy. Study design can be (double) blinded, or open label, cross over depending on feasibility and ethical premise*

Pyridoxine Dependent Epilepsy Consortium, Registry and Observational Study

TIDE team has led a new collaboration of clinicians and scientists from across Canada, the USA and Europe investigating dietary lysine restriction as a novel treatment in addition to standard pyridoxine therapy for PDE. Dietary lysine restriction in addition to pyridoxine is showing improvements and has resulted in significant reduction of all damaging biomarkers, with good tolerance and compliance. No adverse events were reported and improvements in age-appropriate skills in 4 out of 5 children were noted and seizure control was maintained or improved in 6 out of 7 children.

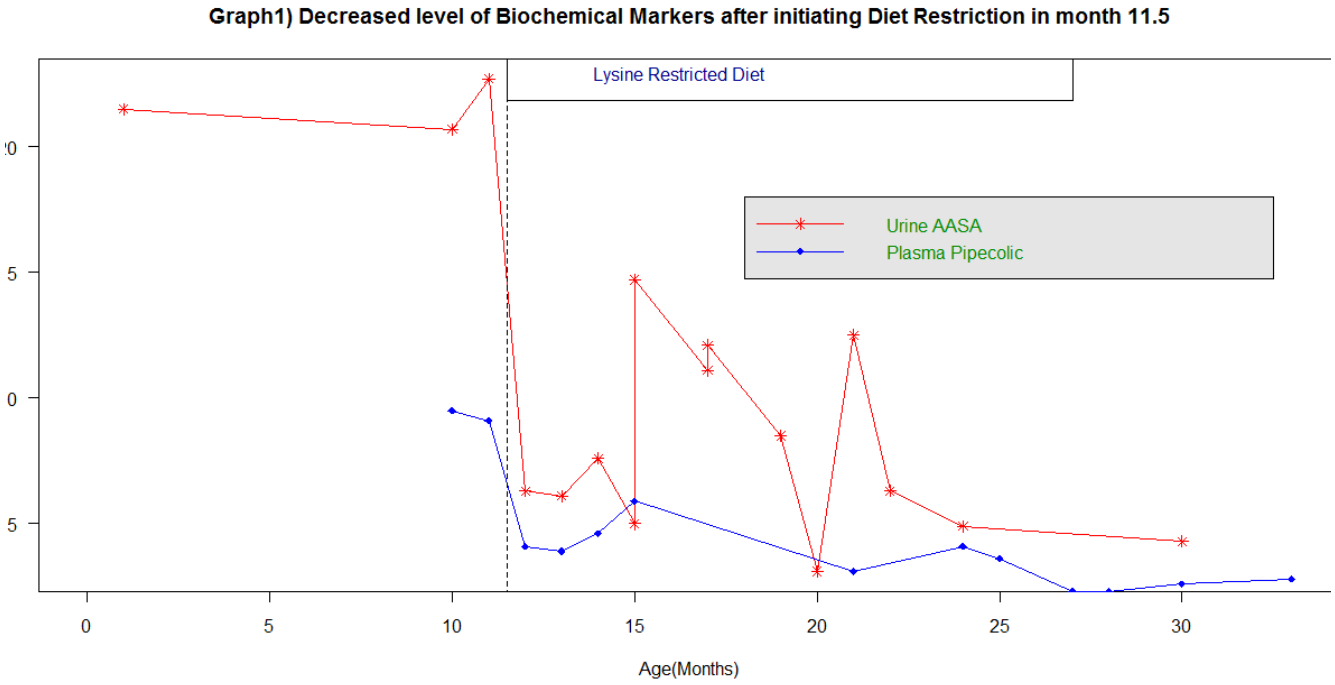


Figure 10: *Effect of Lysine restricted diet on biomarkers (AASA and Pipecolic acid) in a patient with Pyridoxine dependent epilepsy due to Antiquitin (ATQ) deficiency*

Lysine restricted diet for pyridoxine-dependent epilepsy: First evidence and future trials

Clara D.M. van Karnebeek [a,b,1], Hans Hartmann [c,1], Sravan Jaggumantri [b], Levinus A. Bok [d], Barb Cheng [a], Mary Connolly [b,e], Curtis R. Coughlin II [l], Anibh M. Das [c], Sidney M. Gospe Jr. [f,g], Cornelis Jakobs [h], Johanna H. van der Lee [i], Saadet Mercimek-Mahmutoglu [j], Uta Meyer [c], Eduard Struys [h], Graham Sinclair [b,k], Johan Van Hove [l], Jean-Paul Collet [b], Barbara R. Plecko [m], Sylvia Stockler [a,b,*]

A larger study is taking place to generate a stronger level of evidence for the positive effect on neurodevelopmental outcomes and safety of this novel intervention (the 'Developmental Outcome of Early Dietary Lysine Restriction in Pyridoxine Dependent Epilepsy patients', known as the NOEL study). To this end Dr. C. van Karnebeek, Dr. S. Stockler, Dr. JP Collet and Mr. S Jaggumantri have established the international PDE consortium www.pdeonline.org. The mission of this group of more than 30 researchers and physicians worldwide from more than 12 sites, is to conduct future studies using novel trial designs for small patient numbers and digital tools such online registries, research databases, diet Apps, website and social media. This work is a united effort to treat and care for those with rare diseases.

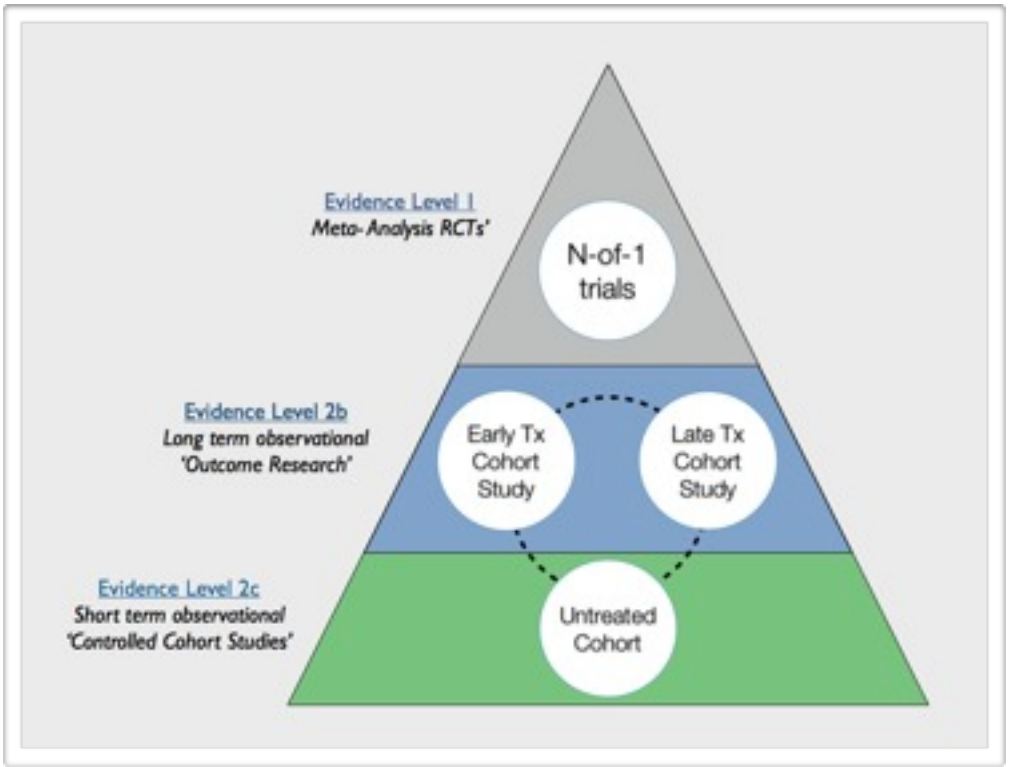


Figure 11:
Evidence Pyramid: In rare diseases we cannot afford to loose any patient to study the evidence of treatments. Therefore every single patient should be included in one of the instruments geared to show evidence, from a disease registry/database to meta analysis of N=1 trials.

Creatine Transporter Deficiency N=1 Trials

Mr. S. Jaggumantri, PhD student supervised by Drs. van Karnebeek, Collet and Stockler have established an innovative protocol for N=1 trials to evaluate the safety and clinical effects of S-Adenosyl Methionine in patients with X-Linked Creatine Transporter Deficiency (SAM-CTD Study). Personalized signs and symptoms are being documented and evaluated for each patient, and brain creatine content is followed through MRIspectroscopy. The goal is to develop a standard personalized protocol for treatment. In the near future the group will also evaluate speech / language through the new functional 3T MRI at BCCH / CFRI.

Phenylketonuria Study

TIDE investigators (led by S Stockler) together with CoPis / collaborators from across Canada received a catalyst grant from CIHR to identify clinically meaningful outcomes in children with PKU treated with sapropterin (Kuvan®), a new drug to improve blood Phe control in patients with PKU.

TIDE experience with N=1 trials is being applied to assess individual outcomes and identify clinically and individually meaningful benefits of this new drug. Psychologists Theresa Newlove, Cynthia Davis and Karen Mackenzie are crucial for the objective measurement of cognitive and behavioural functioning in PKU and other rare diseases patients treated in TIDE. Study coordinator Mrs. Natliya Yuskiv along with dieticians and clinicians in biochemical diseases are contributing fully this study.

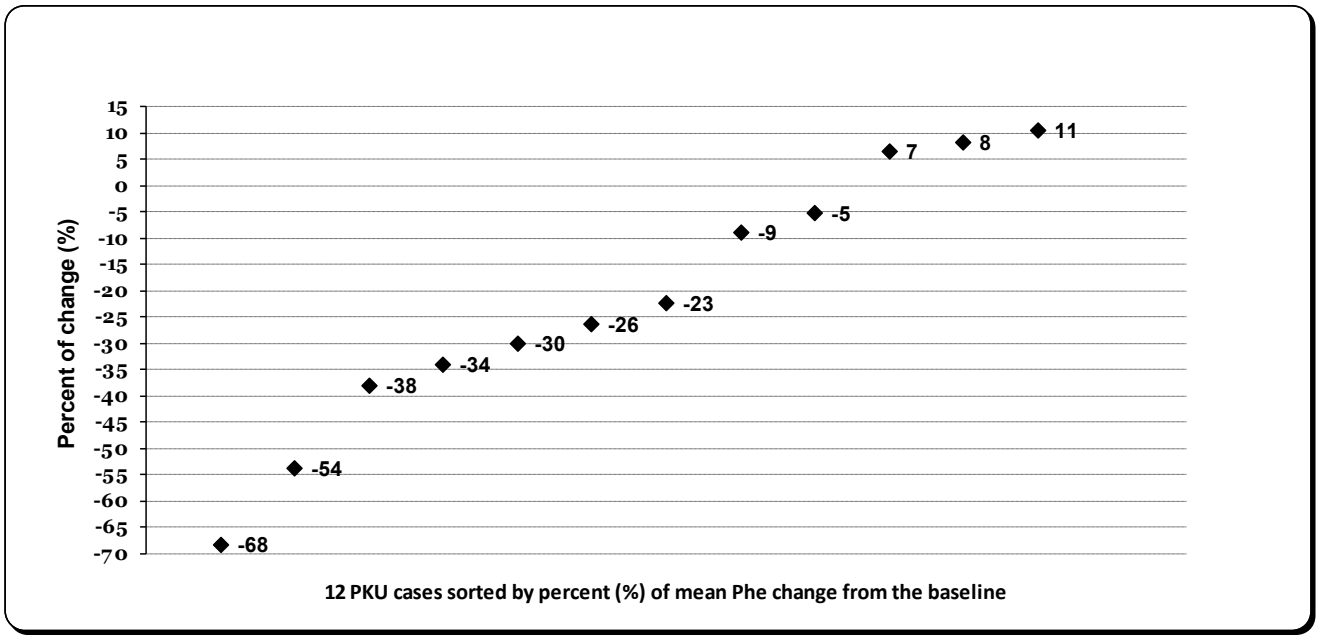


Figure 12: *reduction in blood Phe levels in a random cohort of PKU patients*

Dr Rajavel Elango, a CFRI based nutritional scientist is a collaborator, determining the metabolic fate of nutritional Phenylalanine intake via stable isotope breath test studies which is one of the secondary / surrogate outcomes in this study. The study also includes a cost effectiveness study (done by C Cameron, Ottawa, see section health economics).

3.6 TIDE Personalized Medicine

Treatment, Evidence & Personalized medicine

To support evidence for rare disease treatments, several tools have been developed and used by the TIDE team. Examples include: an online communication platform, therapeutic emplotment, goal attainment scaling and home based video monitoring.

Online Health Communication Platform to Support the Care of Complex Children

Children with medical complexity are often defined as having multiple chronic diseases, high rates of health care utilization and functional limitation. Their care is fragmented across specialties and geographic areas. In this context, communication can be challenging and inadequate and families feel responsible for, and yet ill equipped to coordinate their child's care and ensure continuity of information. The impetus for TIDE to develop an online platform to enhance communication and collaboration was clear. Systemic changes must occur to provide these families with greater support and enhanced communication, both between families and health care providers and between the various members of a child's health care team.

- The objective of this feasibility study led by Dr. Tammie Dewan, is to implement and evaluate the use of a comprehensive online health communication platform in the care of children with medical complexity. At this stage, the main purposes are:
- To establish the use, feasibility and acceptability of this type of intervention
- To establish safety, privacy and confidentiality standards and policies
- To propose a broad evaluation framework for use in larger future studies

The target population is 10-15 children followed by the Biochemical Diseases Clinic at BC Children's Hospital who fulfill the following criteria: DD/ID, multisystem disease requiring care by multiple subspecialists and identified need for care coordination. Each child's health care providers will also be consented for study participation. The online platform consists of private messaging, an electronic library, a symptom tracker, a health vault (storage of medical information) and a community of practice, designed to enhance information sharing between members of the child's healthcare team.

To evaluate the project, participants will undergo semi-structured interview at baseline and every 6 months during the 2-year follow-up period. The content will focus on their opinions regarding the intervention itself, communication and health care delivery. They will also complete surveys addressing usage, acceptability, empowerment and quality of life.

The research team is currently engaged in recruitment of participants so results are not yet available. The intention is to modify and improve upon this intervention based on feedback from study participants, both families and health care providers. Depending on the results of this feasibility study, larger trials may be pursued to provide further evaluation of the intervention.

Tangible achievements thus far include the following:

- Ethics approval has been obtained.
- The creation of a Scientific Advisory Committee comprised of administrators, leaders, impartial clinicians and family representatives has been established to address any quality and safety issues that arise during conduct of the study.
- Individual health care providers have been consented as study participants.
- Standard operating procedures have been developed to enhance the quality of the intervention.

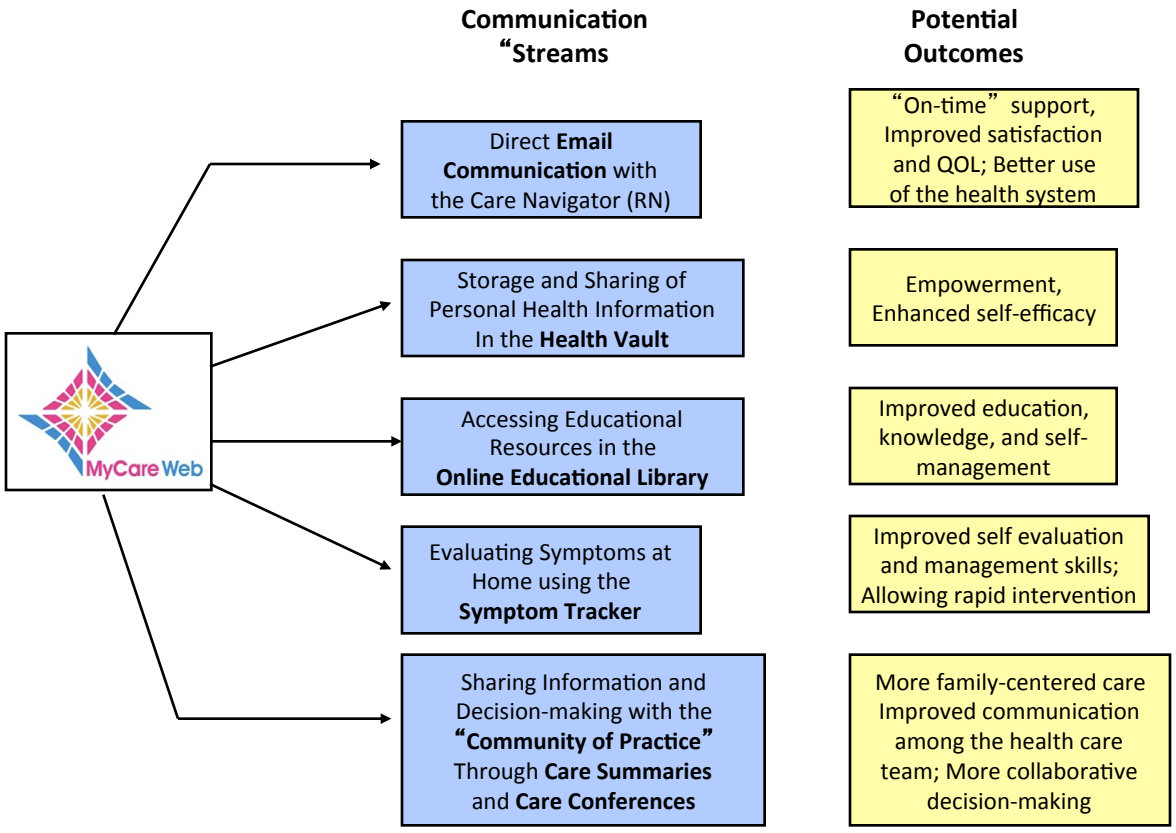


Figure 13: *Communication Stream and potential outcomes for improvements in patient care*

Home Video Monitoring

Led by O Ipsiroglu, a home video monitoring tool has been developed with allow observation of day and night time behaviors in the patients natural environment. The night-time module allows observation of sleep related behaviours. An interface has been developed which enables a quantitative evaluation of movements. This is an important tool to monitor treatments of sleep related disorders such as periodic limb movement, restless legs syndrome. The equipment is sent to the patients homes. The installation is simple and can be done by every parent without major instructions.

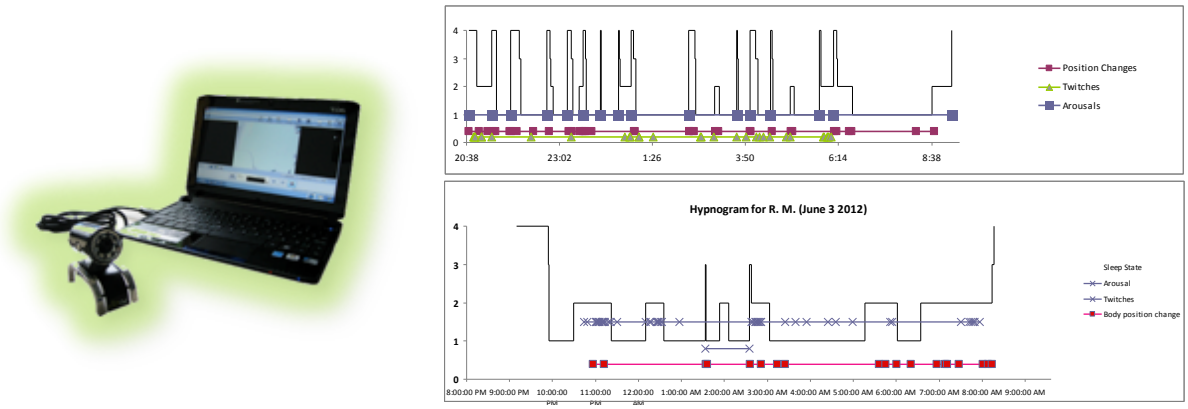


Figure 14: *Home Video Monitoring Equipment (left) and example of overnight tracings of recorded movement patterns and sleep-wake phases in a child with developmental delay and periodic limb movements prior (top) and after a therapeutic intervention (bottom).*

Semistructured Interviewing Technique using the concept of Therapeutic Emplotment

Drs O. Ipsiroglu and B. McKellin are applying therapeutic emplotment and family ecology as a tool to define meaningful outcomes adjusted to the individual patient's needs and abilities to cope. In this way the provider and patient/family work together to define outcomes and measure progress. Both investigators used emplotment as a method to assess reasons why sleep problems in children with FASD are frequently not reported by caregivers and / or not recognised by physicians and health care professionals[4].

Goal Attainment Scaling

Goal attainment scaling methodology facilitates the use of individualized goals, engages patients/families about their individualized goals and facilitates dialogue between patients/families, providers and researchers. Together with emplotment, GAS can be used to define individualized, patient centered outcomes. After a validation phase it can be adopted as a common methodology for n=1 studies across TIDE projects. This tool is not only being used for TIDE (i.e. PKU study), but under the leadership of JP Collet is in the process of being utilized across patient centric and quality improvement initiatives within BC Children's and eventually across the Provincial Health Services Authority.

[4] *Ipsiroglu O, Mckellin B, Carey N, Loock C. They silently live in terror. Why sleep problems and night-time-related quality of life are missed in children with fetal alcohol spectrum disorder. Journal of Social Science and Medicine. Available online December 8, 2012*

Goals	Level of Importance	Assessment
Social –Emotional		
Continued development of friendship development and maintenance skills (i.e. problem solving, adopting others perspective) particularly girl friendships	10	-2 -1 0 +1 +2
Increased self of self-confidence (i.e. decreased need for adult approval and reassurance)	10	-2 -1 0 +1 +2
Decreased anxiety and worry	10	-2 -1 0 +1 +2
Decreased number of crying and frustration meltdowns per week		-2 -1 0 +1 +2
Sleep Goals		
Increased ability to go to sleep by herself (without a parent's direct physical contact)	8	-2 -1 0 +1 +2
Increased ability to stay asleep throughout night	8	-2 -1 0 +1 +2
Increased ability to soothe self back to sleep after night time awakening	8	-2 -1 0 +1 +2
Increased ability to sleep in past 6:00 am	8	-2 -1 0 +1 +2
Education		
Increased ability to remain attentive	8	-2 -1 0 +1 +2
Increased ability to keep body calm and still	7	-2 -1 0 +1 +2
Development of fine motor skills for printing and scissor manipulation; development of gross motor skills for participation in physical education	7	-2 -1 0 +1 +2
Increased confidence in academic ability	10	-2 -1 0 +1 +2
Physical		
Increased body awareness (i.e. sleepiness, hunger)	6	-2 -1 0 +1 +2
Concern	**Level of Concern**	**Assessment**
Concern that Emily will acclimate to the medication so that it is no longer effective (noticed decreased effectiveness in suppressing night time legs twitching)		-2 -1 0 +1 +2
Emily's perception that taking medication means that there is something "wrong with her." She is sometimes reluctant to take medication and is embarrassed		-2 -1 0 +1 +2
Frequent complaints of headache and stomach aches		-2 -1 0 +1 +2
Plateau on continued improvement		-2 -1 0 +1 +2
Long term concern—experimentation with self medicating		-2 -1 0 +1 +2

Figure 15: *Example of a goal attainment scale developed and currently used in the Developmental Pediatrics Sleep Clinic (top) and of a visual aid to facilitate estimation of natural variability of outcomes and changes associated with therapeutic interventions (bottom right).*

3.6 TIDE CARE

Treatment, Evidence & Personalized medicine

This area of TIDE is focused on supporting patient centric care through transdisciplinary communication. Examples of key accomplishments include the following:

Complex Case Review Rounds

Three rounds were held in July, August and September 2011 with a goal of increasing collaboration between clinicians and researchers to determine best treatment options. Evaluation findings from an online survey (n=7) to understand current perceptions and to inform the structure of future Rounds reveal the following:

- Value was reported as high (mean score of 8.5/10) due to multi-specialty assessment (i.e. using evidence from interdisciplinary perspectives) and sub-specialists having the opportunity to discuss a plan for patients rather than writing clinic letters.
- Most significant benefits reported were: collaborating with experts, sharing knowledge from different disciplines, learning from colleagues, creating discussions and better communication and stimulating ideas for improvement and solutions.
- Motivation to participate was due to: an opportunity to collaborate with colleagues, an opportunity to learn from colleagues and the open space provided. CME credits did not have an impact on attending.
- Feedback to support the improvement of/evolution of the Rounds included more structure (i.e. having a moderator, defining the objectives of the Rounds), having a rotating lead from various departments to support the discussion of functional issues, possibly extending the timeframe as cases often go over time and including patients/families (as appropriate).

Most patients discussed in these rounds were on multiple drug therapy exhibiting various adverse drug reactions (ADR) which often remained unrecognized and deteriorated their existing neurodevelopmental problems. Dr Bruce Carleton's (Pharmacosurveillance / Pharmacogenomics) and Dr Eddi Kwan (BCCH Pharmacy), participated in these rounds as experts.
The need for ADR surveillance and potentials for pharmacogenomics research were stressed at the Peter Wall Advanced Study Workshop ("*Phenotyping Sleep Behaviours. Lessons from the Past, Directions for the Future*").

TIDE4Care

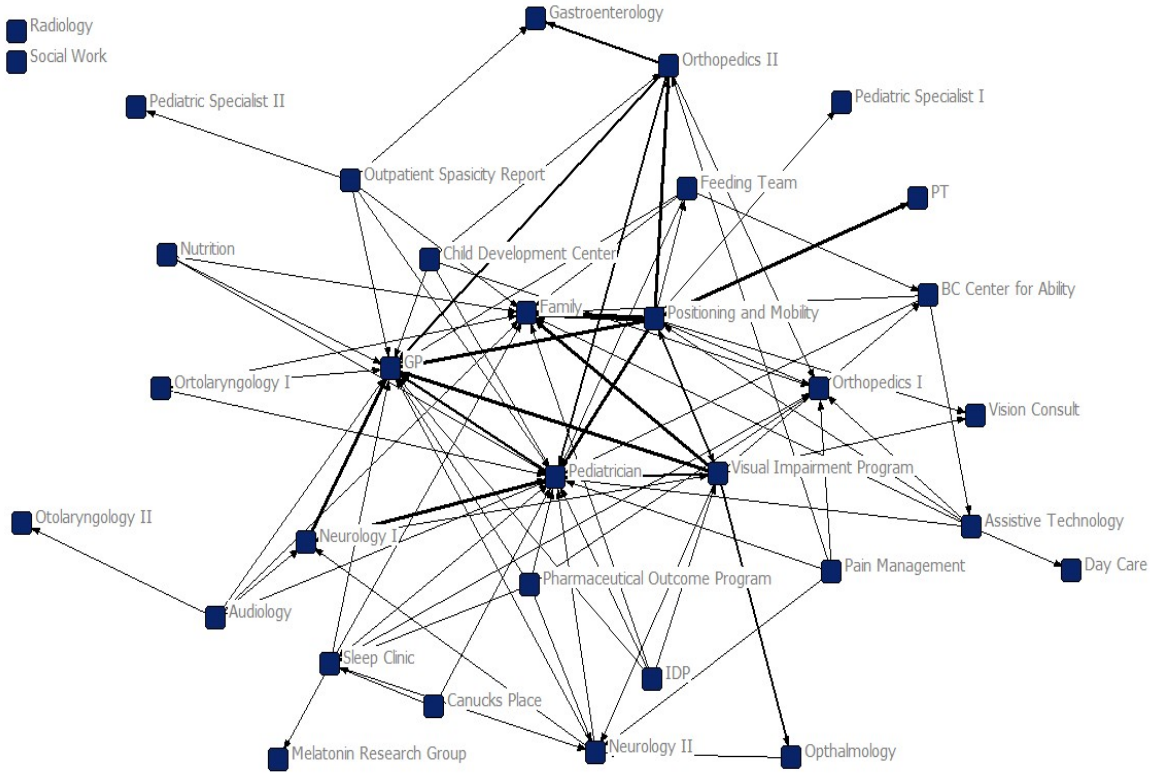
A collaborative retreat, led by S Stockler, was held in July 2012 to build momentum on existing achievements and expertise in methodology, ethics, medical anthropology, and non-categorical care management of children with complex neurodevelopment disorders and rare diseases.

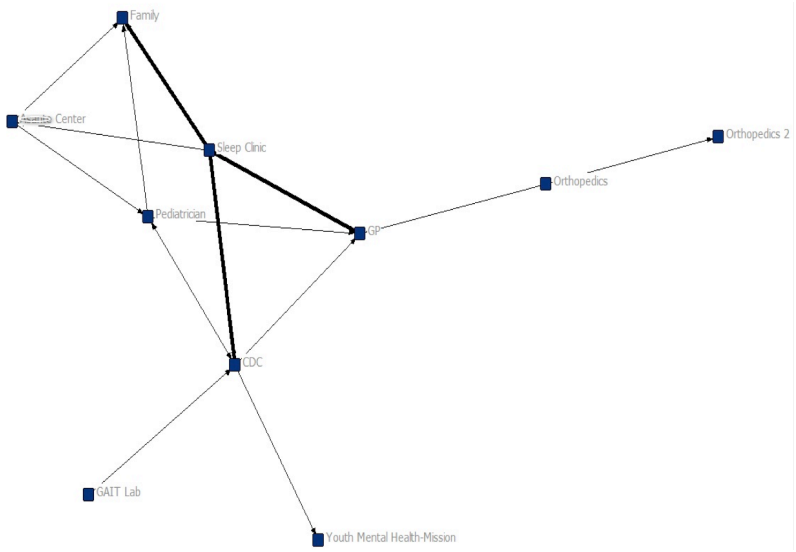
The impetus was two-fold:

- Integration of family ecology and goal attainment scale to improve and measure outcomes
- the desire for enhanced alignment between TIDE projects with personalized care components. The overall goal is to improve care of children with complex needs.

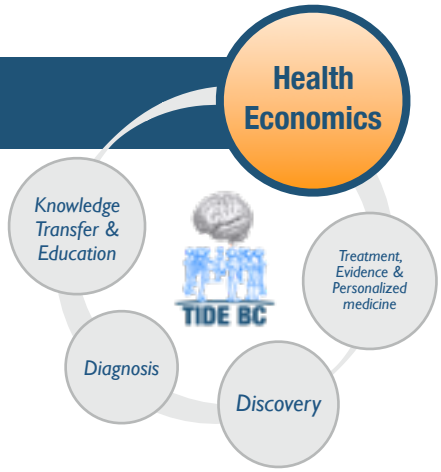
Actions items focused on evaluating existing coordinated care clinics, integrating personalized care tools such as emplotment and GAS into clinic practice, integrating quality improvement language in ethics applications and aligning with PHSA's lean management practice, imPROVE.

Figure 16: *Network Diagram of a patient with complex neurodevelopmental condition and fragmented care, involving numerous specialists and services. The Pediatrician has a central role for some care providers but there are many activities circumventing the central case manager (top); and in a child whose central case management occurs through one speciality clinic according to the predominant diagnosis and care needs (bottom). (S. Mayer, B. McKellin, O.Ipsiroglu 2012)*





3.7 TIDE HEALTH ECONOMICS



Currently there are two cost effectiveness studies underway: one examining the use of Miglustat for Niemann Pick C and another looking at Kuvan for PKU.

Economic Impact and Health Benefits of Early Diagnosis & Treatment of Niemann Pick C

C Marra, T Mohammdi and Clara van Karnebeek are assessing economic and health benefits of early diagnosis and treatment of Niemann Pick C (NPC). The scope of the study is on evaluating the health economic impact of early diagnosis and treatment of NPC using decision-analytic methods. In collaboration with Dr. Sandra Sirrs, the head of the Adult Metabolic Clinic at VGH, the following achievements have been met:

- A literature review has been conducted of NPC, its diagnosis and treatment and relation to ID.
- Cost and efficiency data has been collected for diagnosing and treating NPC, including the following elements:
  - Prevalence of NPC in ID patients
  - Distribution of NPC severity between ID patients (composite disability score)
  - Sensitivity and specificity of metabolic screening test
  - Cost of metabolic screening test
  - Sensitivity and specificity of Clinical Evaluation
  - Cost of Clinical evaluation
  - Cost of NPC related to disability score (Disease Severity)
  - Probability of severe ID if NPC is not detected
- A discrete event simulation model has been designed to estimate the cost effectiveness of early diagnosis and treatment of NPC, comparing the TIDE protocol and current practice adjusted to the NPC Suspicion Index tool.
- Statistical analysis of the simulation model's results.

Methodologically, using discreet event simulation to measure cost effectiveness in this study is an innovative method which enables us to model each individual patient' history and adjust probabilities and outcomes of each stage conditional on patient's characteristics.

The next phase of this work will see the completion of a sensitivity analysis in December 2012 and then final interpretation and discussion of the results to inform publication on this topic.

Cost-effectiveness of Kuvan in Subpopulations of Patients with PKU

This project is funded by a CIHR catalyst grant (Sapropterin (Kuan) for Tratment of Patients with PKU: Identification of subpopulations with substantial clinical benefit. (S Stockler, JP Collet, B Carleton, S Sirrs, J Mitchell). C Cameron, together with Bruce Carleton, Clara van Karnebeek and Sylvia Stockler, has compiled the first Canadian cost-utility analysis that has assessed the value of saproterin ('Kuvan') for patients with non-PKU mild hyperphenylalaninemia, the PKU patient population most responsive to Kuvan. The annual cost of Kuvan is estimated to be as high as $200,000 depending on the age/weight of the child. With costs unlikely to be covered across the wider population, the main objective of the study was to assess the cost effectiveness of Kuvan plus/minus phenylalanine restricted diet compared with phenylalanine restricted diet alone in sub-populations of patients with non-PKU mild hyperphenylalaninemia, the patient population where higher response rates have been observed (manuscript in preparation).

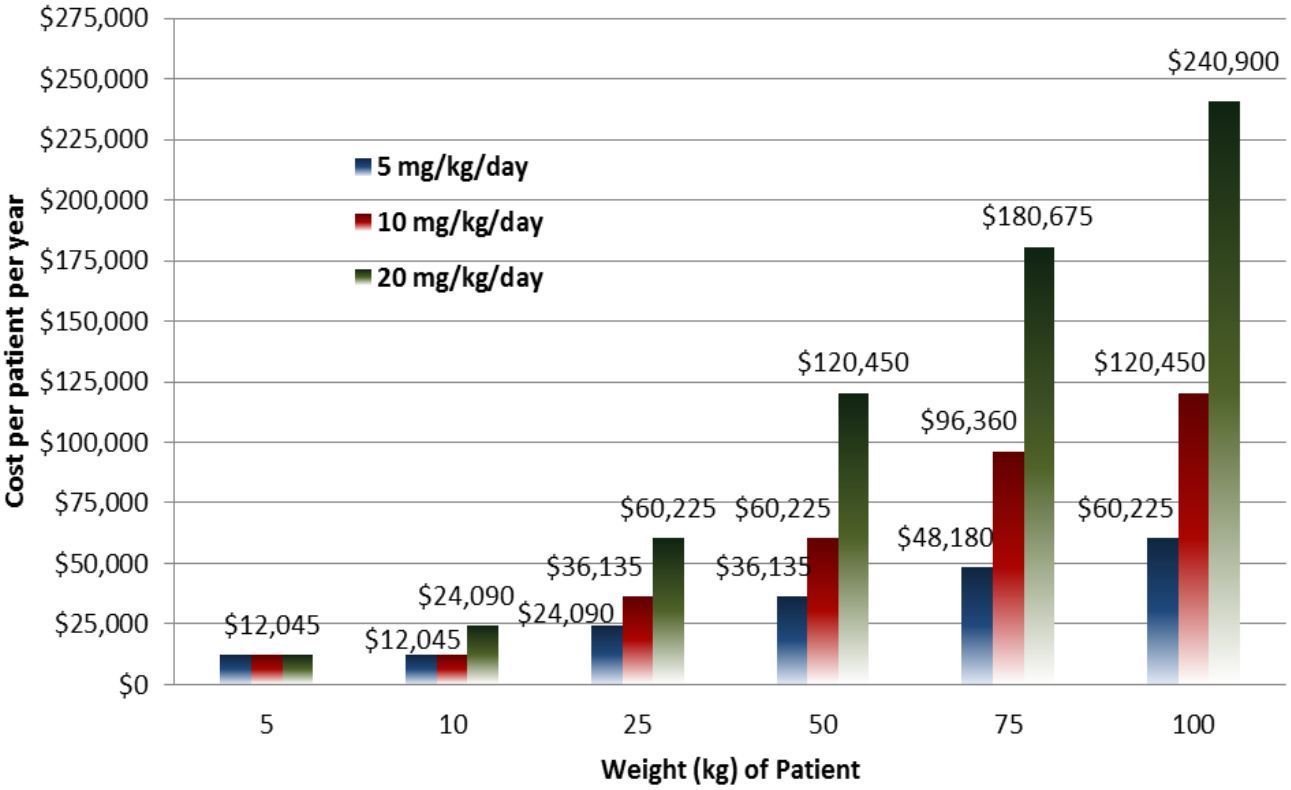
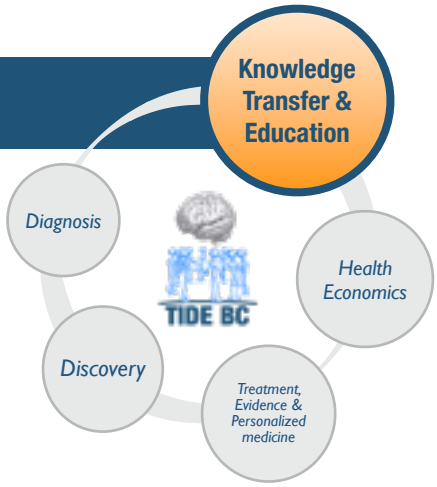


Figure 17: *Incremental costs of sapropterin (Kuvan®) with increasing age (body weight). With current pricing treating the subpopulation of very young children might be most cost effective*

3.8 TIDE APP: *TREATABLE-ID.ORG*



Leveraging the systematic review and supporting the protocol, the TIDE App was created by HealtH2Media in close collaboration with the TIDE leaders and formally launched one year ago in November 2011. This November saw the soft launch of the mobile App. This innovative diagnostic tool and information portal for 81 treatable metabolic diseases causing ID is demonstrating the power of medical technology in advancing diagnosis and supporting earlier/more effective treatment.

Information on the 81 diseases is presented in different ways with search functions: 15 biochemical categories, neurologic and non-neurologic signs and symptoms, diagnostic investigations, therapies and effects on primary and secondary outcomes, and available evidence. For each rare condition a 'disease page' serves as an information portal with online access to specific genetics, biochemistry, phenotype, diagnostic tests and therapeutic options. As new knowledge and evidence is gained from expert input and PubMed searches this tool will be continually updated. The app is an integral part of the protocol.

The TIDE app, completely database driven, recently won an award at the Digital Innovation Summit in October 2012 in Vancouver. It has been accepted by the international community as knowledge translation tool and was published as an article in the Orphanet Journal of Rare Diseases[5].

There have been over 14,000 visits to www.treatable-id.org since the launch of the app. Over 10,000 of those visits are from unique visitors.

- Users (n=120) grade the usefulness of the App at 76%
- 98% of users are willingness to recommend the App to colleagues

[5] *van Karnebeek C, Houben R, Lafek M, Giannasi W, Stockler S. The treatable intellectual disability APP www.treatable-id.org: a digital tool to enhance diagnosis and care for rare diseases. Orphanet Journal of Rare Diseases. 2012, 7:47*

3.9 COMMUNICATION & KNOWLEDGE TRANSFER

Knowledge transfer & Education

TIDE communicates via a variety of different channels, a few of them which are listed below

TIDE Website: *www.tidebc.org*

The TIDE website has matured into an extensive and comprehensive website, updated continuously, featuring project highlights and conveying a wealth of information to stakeholders, from patients/families, providers, and funders/sponsors alike.

Not only used as a communication tool, the website is emerging into a knowledge sharing portal for ID. For example, the "Physicians" page provides clinicians with information on how to apply the protocol and refer their patients to TIDE.

There have been over 3,500 visits to www.tidebc.org since last year. Over 2,000 of those visits are from unique visitors.

Newsletter

To further promote communication and knowledge about TIDE, and to align and draw readers to the website, the TIDE newsletter was created. Two editions have been sent out electronically to the TIDE team, those who have signed up to receive the newsletter on the TIDE website, clinicians, patients (including TIDE patients), families, patient interest groups, researchers, communications leaders, media, etc. as well as distributed via hard copy to various departments within PHSA (Patient and Family Education, Medical Genetics, Neurology, Biochemical Diseases, the Biochemical Diseases Clinic, CFRI, C&W Communications, the Foundation, etc.). Each themed newsletter provides an overview of key accomplishments in each quarter.

To date two newsletters have been developed and distributed:

- The first newsletter was sent out on May 31, 2012 to 195 readers.
- The second newsletter was sent out from November 2-5, 2012 to 378 readers. The increase of the distribution list is mostly due to the fact that people have signed up on the website.

TIDE Patient Stories

A series of patient videos, which are featured on the TIDE website and the online TIDE video channel, allows for a wider spread of knowledge to a varied stakeholder audience. Each video is accompanied by a comprehensive story of the patient and the family's journey.

In conjunction with communicating the patient stories the TIDE team has offered families the opportunity to have professional photos taken of their family as a thank you for their time. As families are interviewed by the project evaluator and/or other communications consultant a professional photographer, Melissa Gidney, has graciously volunteered her services. This provides a lasting and meaningful gift to families.

Presentations, publications & awards

An extensive list of presentations and publications can be found in appendices A & B.
A few highlights are worth mentioning:

- Clara van Karnebeek presented TIDE at Sam Sullivan's Public Salon on May 4th 2011 in the Vancouver Playhouse Theatre.
- Sylvia Stockler and Clara van Karnebeek were recently featured on the front page of the Medical Post (November 2012 edition), with a story written on the impact TIDE is having on patients and families, with the use of the protocol for standardized and state of the art diagnosis of the core of the messaging.
- Awards for TIDE members include the 'Mentoring Award for Early Career Faculty' (Sylvia Stockler), Bluma Tischler Award for Research in Mental Retardation (C. van Karnebeek), the BC Children's Hospital Distinction Award for Patient and Family Centred Care (R. Salvarinova & A. Giezen), Laura McRae Award for Excellence in Pediatric Medicine (C. van Karnebeek), CIHR Doctoral Scholarship Award (C. Shyr), Sanotron Award for Digital Health Innovation (R. Houben).

RALLY

Innovative mental health initiative calls on donors to 'Ride the TIDE'

A revolutionary new research and treatment program at BC Children's Hospital (BCCH) in Vancouver is improving the future of children with intellectual disability (ID) by changing the way physicians diagnose and treat underlying genetic conditions. A debilitating lifelong disorder, ID affects two to three per cent of people worldwide.

Launched in October 2011, and funded by the BC Children's Hospital Foundation, the Treatable Intellectual Disability Endeavour in British Columbia (TIDE-BC, www.tidebc.org) has developed landmark approaches to improve outcomes for children with ID. TIDE-BC has already yielded several world-first achievements, including a state-of-the-art evaluation of each ID patient for treatable metabolic conditions and the discovery of a new treatable ID gene.

"Early identification of ID's rare, yet treatable, underlying diseases allows the initiation of therapy that can prevent or minimize brain damage, and drastically reduce the disease burden and costs associated with ID," says Dr. Clara van Karnebeek, a neurometabolic disorder specialist who co-leads TIDE-BC with BCCH Biochemical Diseases Division head Dr. Sylvia Stockler.

The novel "Ride the TIDE Car Rally" will be held in Vancouver in September 2013 to help raise funds for TIDE-BC's life-changing work. www.ridethetide.ca

Building the Brand

In collaboration with project leaders, TIDE is building its brand, ensuring a consistent look and feel to presentations and paving the way for high profile interest in the TIDE program.

Case in point is the upcoming 'Ride the Tide' car rally (www.ridethetide.ca), a unique fundraising opportunity organized by Mr. M. van Keken, Mr. R. Mang and Mrs. M. Menten with the TIDE leaders, that will allow attendees to showcase their impeccable cars while raising awareness for and sponsoring TIDE. A short article on this topic appeared in the November 15, 2012 edition of the Globe and Mail.

3.10 EDUCATION

Knowledge transfer & Education

All areas of focus have an education and knowledge sharing component built into them through the various affiliations leaders and collaborators have within the BC Children's Hospital, UBC, Department of Pediatrics, etc. Please refer to Appendix B for a comprehensive list of TIDE knowledge translation activities, including journals, presentations, etc.

The focus of this area of focus is on translating current research and clinical practice education surrounding intellectual disabilities into the medical degree undergraduate program. Under the leadership of Dr. Linlea Armstrong & Mrs. Jennifer Thompson, a forum for knowledge sharing and curriculum development model has been developed:

Community of Practice

Through the Education Subcommittee members a community of practice for medical education related to genetics and ID has been developed. A terms of Reference was developed for the Education Subcommittee and to date there have been nine Subcommittee meetings. There has been fair attendance and representation at these meetings (average attendance is 9 per meeting, ranging from 5-8).

The Community of Practice began with the development of an inventory of subcommittee members (54 individuals), including their area of expertise, current teaching activities including public, clinical and research education, and their potential areas of interest and contribution to the Education subcommittee. Through two facilitated sessions this inventory was populated and used to guide the direction of the subcommittee members' involvement.

The next phase saw the discussion of how members could contribute existing knowledge materials to support case based learning.

Findings from an Education Subcommittee satisfaction survey (n=13) reveal:

- 67% report communication is effective.
- 58% report meetings are well prepared and that their attendance at meetings is a valuable use of my time.
- Half feel they are contributing to the meetings.
- 42% report meetings are effectively run.
- 25% feel that collaborative education planning, in general, is an effective use of their time.

What's working well that I'd like to see more of ...

"It's definitely a good idea to have this committee, and to bring together different specialists for synergistic effect."

"The group leaders have been able to maintain progress even with an evolving membership."

What I'd like to see improved...

"Increased speed, concrete material development and use of digital media."

"Greater focus on an efficient use of time, having a clear agenda and meetings to have tangible outcomes."

Medical Degree Undergraduate Competency Framework

Based on the CANMEDS roles framework, the MDUP Competency Framework was developed. Subcommittee members worked together to determine the knowledge, attitudes and skills required for undergraduates in the topic area which would then fall under one or more roles, including communicator, collaborator, manager, health advocate, scholar, professional and/or medical expert:

- Knowledge: describe the biological basis of genetic disease
- Attitudes: demonstrate respect for ethical, legal, and social issues relevant to genetic disease
- Skills: identify potential genetic risk

Virtual Repository

An online repository has been developed to house knowledge materials, i.e. presentations, assessment tools, etc. The intent was originally for Subcommittee members to log in and post their own documents. For efficiency and ease it was determined that only the education area of focus resources would have access to posting resources. Committee members have been encouraged to start to collect and submit materials but none have been received to date.

A recent collaboration endeavour to support the development of an interactive teaching module (with Dr. Vicki Leung) is underway. This would enable the use of technology to support paediatrics education in the more challenging areas according to problem-based learning, including topics of metabolic diseases, medical genetics and developmental paediatrics, all closely related to TIDE.

Section 4: Sustaining and Enhancing the Wave of TIDE

Based on this 1st year evaluation, a retreat with the TIDE principal collaborators was held on Nov 29th, 2012. The main theme of this TIDEnergy meeting was '*Power through Diversity and through Digital Innovations*'.

The discussion centered not only on what TIDE would look like over the next two years but how the benefits of TIDE can be sustained and outcomes translated into research and clinical practice throughout BC Children's, the country and across the globe.

The following key activities can be expected in the coming years:

- **TIDE Protocol**
  - Leverage the adoption of the protocol within Biochemical Diseases, Neurology and Medical Genetics to expand further into Developmental Pediatrics and Psychiatry.
  - Leverage the adoption across BC Children's and the international guidelines to spread the protocol throughout the entire BC paediatrics community.
  - Adoption of the TIDE Protocol in international Practice Guidelines
- **TIDE Diagnostic Clinic**
  - Build on the diagnostic yield and cost effectiveness of the clinic to demonstrate the benefits of a coordinated care model. Use this information to further the interest and adoption of coordinated care for complex children across BC Children's. This will serve to support patient centered care and personalized medicine.
- **TIDE Diagnostic Lab**
  - Build on the decreased duplication in testing and decreased turn-around time due to increase capacity for biochemical testing across the province to support the provincial dissemination of the protocol and accommodate additional testing.
- **TIDE Gene Discovery**
  - Further determine the cost comparisons of single gene testing with exome sequencing to demonstrate the need for provincial funding for sequencing.
  - Continue cutting edge discovery through synergetic application of metabolomics and genomics
- **TIDE Creating Evidence for Treatments of Rare Diseases**
  - Leverage findings from small sample size studies to demonstrate the power of this methodology for creating evidence on par with clinical trials.
  - Apply trial methodologies for small sample sizes in exemplary biochemical diseases / treatable IDs: PDE, GAMT deficiency, GLUT1 deficiency
- **TIDE Care**
  - leverage existing experience and expertise to create infrastructure to monitor and treat ADRs in children with complex neurodevelopmental disorders
  - TIDE E Care leverage results from TIDE E Care pilot project and from existing patient database and ongoing efforts to create tools for home and medical monitoring, using social media.

TIDE Personalized Medicine

- Validate and apply Interview-GAS in TIDE n=1 as well as other n=1 scenarios as they occur in BCCH. Explore the use of tools to pave the way for embedding into the patient safety and quality framework across BC Children's and PHSA.

TIDE Health Economy

- Build on findings from cost analyses for other diagnostic tests and therapies to translate the same methodology to other diseases.
- Work with the Pharmaceutical Services Division of the Ministry of Health to begin discussions on drug funding where appropriate.

TIDE App

- Leverage the power of this App to create other Apps designed to support clinicians in TIDE and expand to related fields of medicine (e.g. genetic epilepsies, metabolic diseases)
- Create app for TIDE project which includes protocol, general information on TIDE etc. (scheduled to hit the app store january 2013)

TIDE Communication and Knowledge Translation

- Leverage the successes of TIDE to build/develop partnerships and entice even more funding groups.
- Increase use of communication platforms such as Podio as team building tool

TIDE Education

- Leverage the knowledge of the multidisciplinary community of practice members to build a repository of learning materials to further support and encourage students into the field of ID.

TIDE Strategic planning

- Leverage TIDE's innovation potentials to seek funding for innovative translational research
- Leverage TIDE's ready to clinical practice potentials to integrate into clinical routine
- Cultivate and Leverage TIDE member's energy, to create a tide culture which will reach out and contribute to fundamental improvements of outcomes of children with developmental and intellectual disabilities

Section 5: Summary and Outlook

This evaluation and the enthusiasm of the TIDE team demonstrates that TIDE is and will be successfully achieving its goals. The majority of short-term (year 1) outcomes are complete - geared toward general uptake and awareness of TIDE initiatives. Several medium-term outcomes (behavioural change) have already been met as detailed in the previous section. A handful of longer-term cultural change outcomes have already been exceeded, most notably the impact TIDE has already had on bridging the ring road between research to clinical practice with exciting new discoveries translating into improved patient care .

Although TIDE is surpassing its mission to generate cutting edge knowledge to facilitate systematic diagnostic assessment, evidence based treatment and individualized care of children with treatable ID, we are only at the beginning of our mission.

The first wave of TIDE is still rising, but many more are needed to pay back to families' and society's commitments to these children and their caregivers.

The diversity within our collaborative group is synergetic, giving TIDE the potential to become a model for personalized medicine in paediatrics and to become an important partner in national and international research networks. TIDE, the first Collaborative Area of Innovation, has planted the fruitful seed for the larger endeavour; our balloons must continue to rise, expanding TIDE's reach to impact the lives of children in BC and beyond.

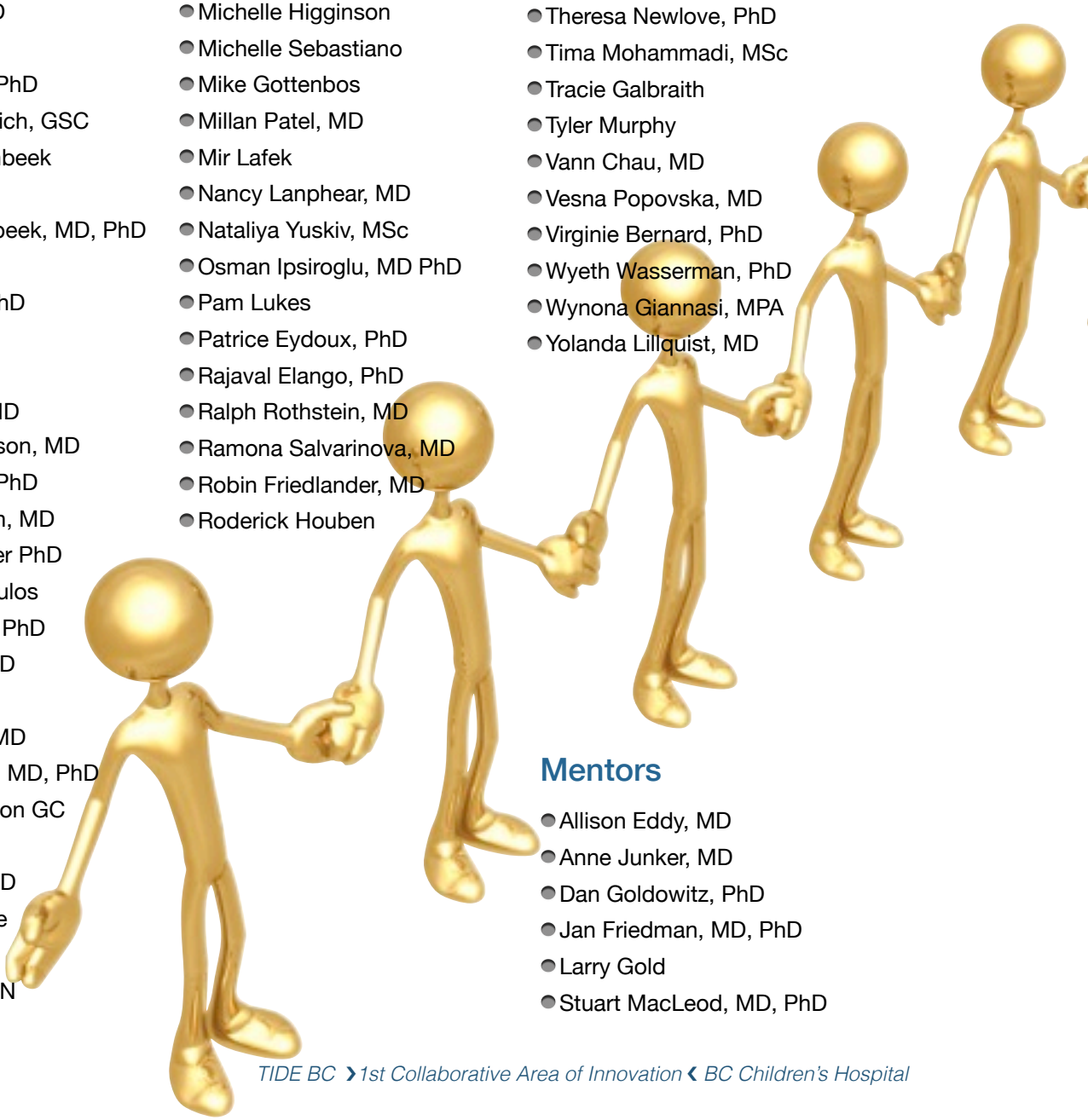
> *Firstly I want to say from the bottom of my heart thank you, thank you, thank you!!*
> *I am over the top excited to learn about this gene discovery as I am sure everyone is! The mystery that is my son is starting to unravel and that is, as his mother, the greatest gift I could ask for.*
>
> *Knowledge is power and even if nothing beneficial to my son stems from this discovery I am more at peace for knowing.*
>
> - mother of a TIDEX patient

> *I am a medical student and aspiring pediatrician at the Northern Ontario School of Medicine on my Peds rotation, preparing a journal club on your absolutely wonderful review study (how much work you must have put into this!!!) on "Treatable inborn errors of metabolism causing intellectual disability."*
>
> *It's so wonderful for the field for you to have undertaken such a task, and the website you've created is incredibly helpful even at my trainee level.*
>
> *I've had an interest in developmental peds and intellectual disabilities for some time now, and you've done something wonderful for the field while at the same time getting me interested in IEMs (the notion of learning about IEMs used to scare me!) Thank you so much!!*
>
> *- Email received via treatable-id.org*

Appendix A: TIDE Leaders, Collaborators & Partners

TIDE TEAM & COLLABORATORS AND RESEARCH & ADMINISTRATIVE SUPPORT

- Alette Giezen, RD
- Allison Rintoul
- Andre Mattmann, MD
- Anita Chiu
- Anna Lehman, MD
- Anthony Bailey, MD PhD
- Barbara Cheng, RD
- Barbara McGillivray MD
- Bill McKellin, PhD
- Bruce Carleton, MD, PhD
- Carlo Marra, PhD
- Casper Shyr
- Chris Cameron, PhD
- Christele du Souich, GSC
- Christine Vandenbeek
- Claire Sowerbutt
- Clara van Karnebeek, MD, PhD
- Colin Ross, PhD
- Cynthia Davis, PhD
- Cynthia Ye
- David Arnold
- Delia Apatean, MD
- Elizabeth Mickelson, MD
- Elodie Portales, PhD
- Gabriella Horvath, MD
- George Alexander PhD
- Georgia Petropoulos
- Graham Sinclair, PhD
- Greg Baldwin, MD
- Harjit Gil
- Hilary Vallance, MD
- Jean Paul Collet, MD, PhD
- Jennifer Thompson GC
- Jennifer Kohm
- Juliette Hukin, MD
- Karen MacKenzie
- Kathy Selby, MD
- Kathy Withers, RN
- Katya Nosova
- Keiko Ueda, MSc
- Linlea Armstrong, MD
- Lori d'Agincourt, PhD
- Lorne Clarke, MD
- Maria Boldut MD, MSc
- Marion Coulter Mackie
- Marion Thomas, PhD
- Mary Connolly, MD
- Maryam Saeri
- Michelle Demos, MD
- Michelle Higginson
- Michelle Sebastiano
- Mike Gottenbos
- Millan Patel, MD
- Mir Lafek
- Nancy Lanphear, MD
- Nataliya Yuskiv, MSc
- Osman Ipsiroglu, MD PhD
- Pam Lukes
- Patrice Eydoux, PhD
- Rajaval Elango, PhD
- Ralph Rothstein, MD
- Ramona Salvarinova, MD
- Robin Friedlander, MD
- Roderick Houben
- Ruth Giesbrecht
- Samara Mayer
- Sandra Sirrs, MD
- Sravan Jaggumantri BSc
- Stefanie Schaumann
- Susan Baer, MD
- Susan Failanga, RN
- Suzanne Creighton, GC
- Sylvia Stockler, MD
- Tammie Dewan, MD
- Theresa Newlove, PhD
- Tima Mohammadi, MSc
- Tracie Galbraith
- Tyler Murphy
- Vann Chau, MD
- Vesna Popovska, MD
- Virginie Bernard, PhD
- Wyeth Wasserman, PhD
- Wynona Giannasi, MPA
- Yolanda Lillquist, MD



Mentors

- Allison Eddy, MD
- Anne Junker, MD
- Dan Goldowitz, PhD
- Jan Friedman, MD, PhD
- Larry Gold
- Stuart MacLeod, MD, PhD

INTERNATIONAL ADVISORY BOARD & COLLABORATORS

- Barbara Plecko, MD *(Zurich, CH)*
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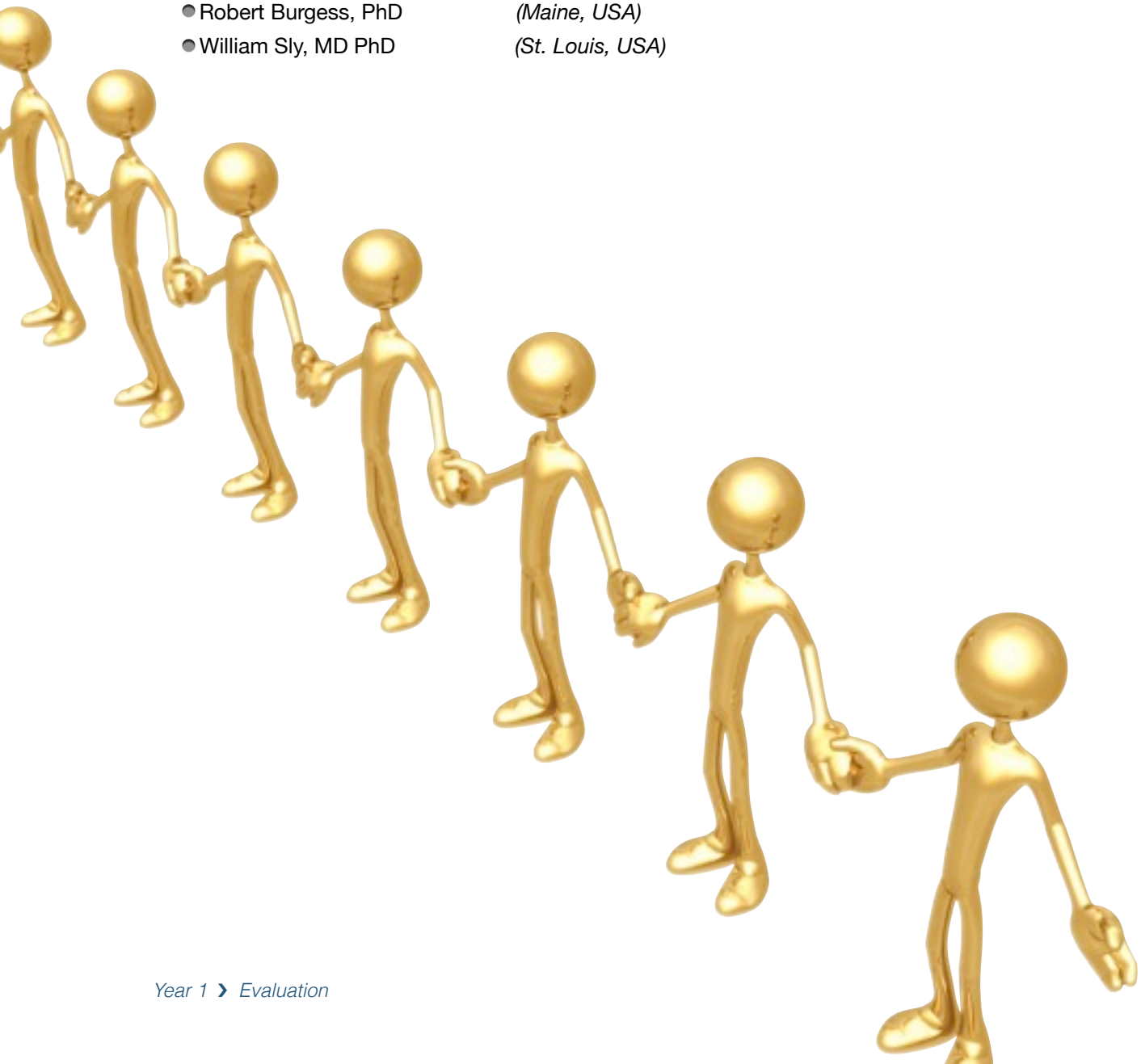

Appendix B: Spreading the Word about TIDE / Key Knowledge Translation Activities

The following provides a list of published journal articles, works submitted and presentations to spread the word of TIDE:

JOURNALS

- van Karnebeek CD, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. Mol Genet Metab 2012 Mar;105(3):368-81. (Epub ahead of print).
- van Karnebeek C, Hartmann H, Jaggumantri S, Bok L, Cheng B, Connolly M, Coughlin C, Das A, Gospe S, Jakobs C, van der Lee H, Mercimek-Mahmutoglu S, Meyer U, Struyst E, Sinclair G, Van Hove J, Collet JP, Plecko B Stockler S. Lysine restricted diet for pyridoxine-dependent epilepsy: first evidence & future trials. Mol Genet Metab 2012: 107 (3): 335-44.
- van Karnebeek C, Houben R, Lafek M, Giannasi W, Stockler S. The treatable intellectual disability APP www.treatable-id.org: a digital tool to enhance diagnosis and care for rare diseases. Orphanet Journal of Rare Diseases. 2012, 7:47.
- Clapham KR, Tu TW, Ganesh VS, Barry B, Chan Y, Mei D, Parrrini E, Funalot B, Dupuis L, Nezarati MM, du Souich C, van Karnebeek C, Guerrini R, Walsh CA. FLNA genomic rearrangements cause periventricular nodular heterotopia. Neurology 2012 Jan 24; 78(4):269-78. Epub 2012 Jan 11.
- Stockler-Ipsiroglu, Clayton P, Connolly M, Coulter-Mackie M, Gospe S, Mahmutoglu S, van Karnebeek C, et al. Mini Review: Pyridoxine dependant epilepsy and antiqutin Deficiency. Mol Genet Metab 2011;104:48-60.
- Stockler S, Moeslinger D, Herle M, Wimmer B, Ipsiroglu OS.Cultural aspects in the management of inborn errors of metabolism. J Inherit Metab Dis. 2012 Nov;35(6):1147-52. doi: 10.1007/s10545-012-9455-4. Epub 2012 Feb 23.
- Hartnett C, Salvarinova R, Yap Todos E, Stockler S. Long term outcomes of blood phenylalanine levels in children with classical PKU. Mol Genet Metab accepted
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