The Canadian Inherited Metabolic Diseases Research Network:

Development of a Pan-Canadian Practice-Based Research Network for Inborn Errors of Metabolism

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on behalf of the Canadian Inherited Metabolic Diseases Research Network (CIMDRN)

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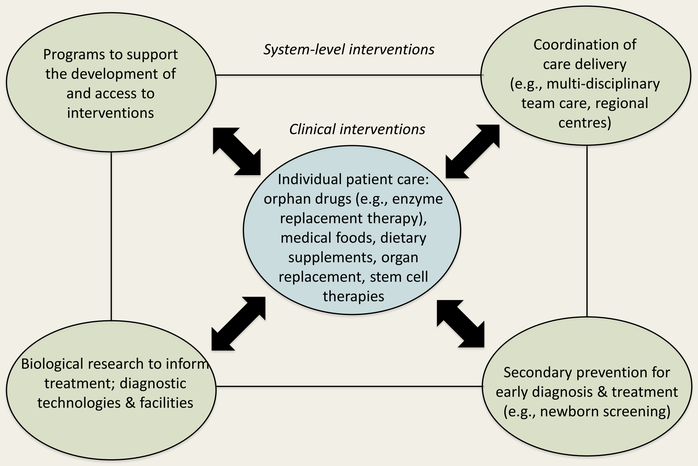
Background

Inborn errors of metabolism (IEM)

- A group of >400 inherited metabolic diseases characterized by defects in one or more biochemical pathways
- Individually rare (birth prevalence 1:10,000 to 1:1,000,000)
- Clinical manifestations range from risk of acute episodic illness to chronic multi-system sequelae
- Treatments typically burdensome and expensive for patients, families, society; and traditionally based on presumed pathophysiology rather than on empirical evidence (challenging to assemble evidence in rare disease context)

Interventions to improve care for IEM

- Inter-dependency of health system-level interventions and clinical interventions at the level of individual patient care:



Need for Evaluative Evidence

Evaluative evidence to support improved care & outcomes for IEM

•Interventions for IEM would ideally be evaluated in a way that:

- Accommodates interaction between clinical care and health system
- Focuses on a range of outcomes

•Relevant outcomes include those described by Berwick et al.'s "triple aim" framework as the goals for effective health care systems (Health Affairs, 2008):

- Improving patient experiences with care
- Improving clinical health outcomes
- Managing health system impacts

•Randomized controlled trials (RCTs) are important for establishing efficacy of clinical interventions but are not always feasible/appropriate:

- Rarity of IEM means number of patients available for study is small
- Traditional RCTs do not account well for clinical heterogenetiy nor complexity of co-interventions embedded in systems of care

•Multiple approaches will be needed to generate the evidence required to inform effective and appropriate care for children with IEM

"Practice-based evidence"

•Clinical evaluative research in a real-world setting: rigorous observational evidence (Westfall et al., 2008, JAMA; Horn & Gassaway, 2010, Med Care)

- "*Practice-based evidence… accommodates multiple concurrent interventions and patient characteristics that reflect actual clinical practice, using data from natural settings to describe the content and timing of treatments that are associated with better outcomes (including patient reported outcomes) for patients with specific characteristics.*" (Horn & Gassaway, 2010, p.S17).

•Identifying the best interventions at the appropriate times for the appropriate patients: personalized care (Feero et al, 2008, J Am Med Inform Assoc)

Objectives & Priority Research Themes

CIMDRN Objectives

•With core funding from a CIHR Emerging Team Grant (2012-2017), we have established a multidisciplinary practice-based research network to develop an evidence-informed approach to health care for paediatric IEM that:

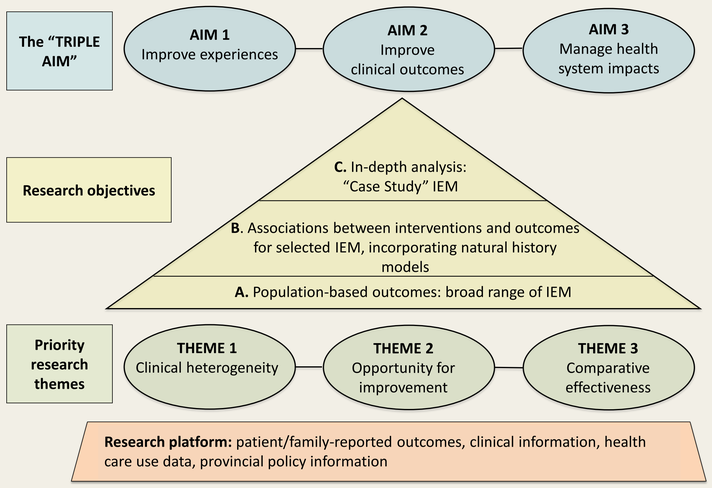
- focuses on outcomes from the triple aim perspective (patient and family experiences, clinical outcomes, health system outcomes);
- considers and integrates a variety of interventions, patient characteristics and other factors that may influence outcomes; and
- emphasizes research themes that capture the highest priority questions across IEM regarding both clinical care and health policy.

Priority research themes

1. *Clinical heterogeneity and personalized care*: Manifestations of many IEM range from mild forms that may require little intervention to severe forms with high risk for morbidity and mortality. There is a need to tailor approaches to health care to account for the needs of individual patients.
2. *Paradigm shift from "urgent care" to "opportunity for improvement":* Traditional treatment goals for many IEM focused on prevention of severe morbidity and mortality. Improvements in available treatments have meant that more patients are surviving with future severe sequelae, leading to a shift in goals toward achievement of optimal outcomes.
3. *Comparative effectiveness:* Treatments for IEM are developing rapidly. We need to critically evaluate the comparative effectiveness of emerging with established therapies, focusing on outcomes across the triple aim.

CIMDRN Practice-Based Research Framework

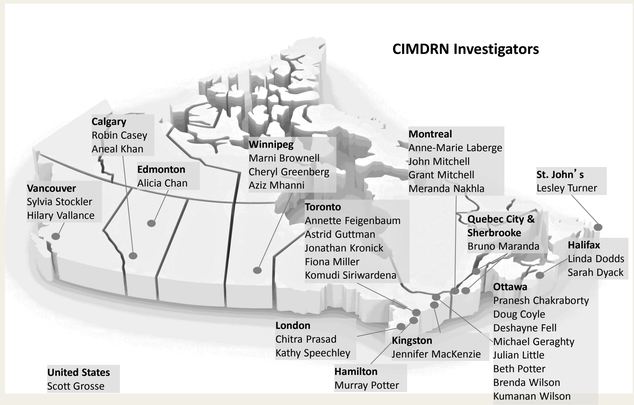
- Integrating our research themes with the need to consider complex, multi-level interventions in a multidisciplinary practice-based context, this framework guides our program of research:



Research Program

- Guided by our practice-based research framework, our initial program focuses on three key objectives:
  - A. To describe the distribution of clinical, patient-centred, and health system outcomes for Canadian children with a broad range of IEM;
  - B. To investigate the association between patterns of clinical and health system interventions and these outcomes for a smaller set of IEM. We will account for differences in patient characteristics and disease severity and use natural history models to generate robust estimates;
  - C. To investigate each priority research theme through a series of "Case Studies". These in-depth analyses will focus on key questions about particular IEM and provide insight into the theme as a whole.
- Our research platform, framework, and network are sustainable tools that can accommodate new research questions, themes, and IEM in the future.

Our Network: Participating Centres &Team Members



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Research Platform

- Our platform has some commonalities with traditional disease registries: observational data, multi-centre, flexible, population-based, longitudinal
- But it is explicitly research driven, to create generalizable knowledge; all data collected will be guided by our research framework
- Participants: We aim to enroll nearly all Canadian children (~1,000) born from 2006-2015 and receiving care at one of Canada's 16 Hereditary Metabolic Disease Treatment Centres for one of the following IEM (bold text = diseases selected for more in-depth study):

Amino acid / urea cycle disorders
Phenylalanine hydroxylase (PAH) deficiency: phenylketonuria (PKU) and non-PKU hyperphenylalaninemia (non-PKU HPA), Arginase (AG) deficiency, Argininosuccinic acidemia (argininosuccinate lyase deficiency, ASA), Carbamyl phosphate synthetase (CPS1) deficiency, Citrin deficiency, Citrullinemia (argininosuccinic acid synthetase deficiency), Homocystinuria: CBS deficiency, Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH) syndrome, N-acetylglutamate synthetase (NAGS) deficiency, Ornithine transcarbamylase (OTC) deficiency, Maple syrup urine disease (MSUD), Tyrosinemia (Type I)

Organic acid disorders
ß-Ketothiolase (BKT) deficiency, Glutaric acidemia type I (GAI), HMG-CoA lyase Deficiency, Isovaleric acidemia (IVA), 3-Methylcrotonyl-CoA carboxylase (3MCC) deficiency, Methylmalonic acidemias (methylmalonyl-CoA mutase deficiency; cobalamin defects), Propionic acidemia (PA)

Fatty acid oxidation disorders
Medium chain acyl-CoA dehydrogenase (MCAD) deficiency, Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, Carnitine uptake defect (CUD), Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency,, Trifunctional protein (TFP) deficiency

Other disorders
Hurler disease (MPS 1), Pyridoxine-dependent epilepsy, Galactosemia (GALT), excluding epimerase and kinase deficiency, Glycogen storage disease type 1 (GSD1, types A and B), Multiple carboxylase deficiency (MCD)/Biotinidase deficiency

Data Collection and Analysis

- For participating children and families, with consent, we will assemble, link and analyze existing observational data from multiple sources:

Data source	Type of information	Method of collection
Health care administrative data	Health services (physician, emergency, hospital care)	Existing datasets linked at individual level
Patient charts: participating treatment centres	Clinical interventions and outcomes	Abstracted by a study research coordinator with families' permission
Clinic-level data from participating centres	Organization of care	Reported by clinical investigators
Patient and family-reported information	Quality of life, experiences with care, psychosocial outcomes	Patient/family surveys, qualitative data
Provincial policy information	Newborn screening, access to therapies	Interviews with decision-makers

CIMDRN's Value and Contributions

- CIMDRN's research will:
  - lead to specific recommendations for delivering care to children with IEM;
  - provide an empirical foundation to support personalized health care decisions and improve understanding of system impacts;
  - yield insights generalizable across IEM, to other rare diseases, and to personalized and patient-centred care;
  - establish a sustainable research network in paediatric IEM that will continue to produce high-quality policy- and clinically-relevant research.
- Potter BK, Chakraborty P et al., Achieving the "triple aim" for inborn errors of metabolism: a review of challenges to outcomes research and presentation of a new practice-based evidence framework, Genetics in Medicine, advance online publication 6 December, 2012.
- www.cimdrn.ca

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CIMDRN RCRMMH

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