A Framework for Developing Case Definitions and Clinical Measures to Support Longitudinal Research on Outcomes for Inborn Errors of Metabolism

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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)
- Characterized by clinical heterogeneity
- Important to obtain a timely diagnosis and implement effective disease management

Research on inborn errors of metabolism

- Scientific research has led to earlier detection, improved biological understanding and corresponding development of new therapeutics in the field of rare diseases and IEMs in particular
  - Many diagnosed IEM patients have increased lifespans with fewer severe sequelae, reducing mortality and severe morbidity
- **A current priority is longitudinal follow-up of IEM patients post-diagnosis to evaluate outcomes and inform care**

Value of Robust Clinical Follow-up Data

- IEM are rare and clinically heterogeneous: robust longitudinal clinical data are sparse and can be challenging to gather and interpret
- Collaborative, multi-center research is an important tool for evaluating health care for individuals with rare diseases: permits more robust study designs with larger samples and greater statistical power for understanding clinical effectiveness
- Multi-center collaboration also affords opportunities to take advantage of "natural experiments":
  - Evidence of substantial variation in both treatment practices and outcomes for IEM across centers, in Canada and elsewhere (Potter et al., 2012, GIM; Potter et al., 2012, JIMD)
  - **"Practice-based evidence"**: clinical evaluative research in a real-world setting: rigorous observational evidence (Westfall et al., 2008, JAMA; Horn & Gassaway, 2010, Med Care)
  - Collection of existing clinical information on care and outcomes, to identify patterns of interventions associated with better outcomes in particular groups of patients
- A multi-center practice-based evidence program necessitates agreement among centers on a minimum dataset comprised of rigorous yet parsimonious measures of baseline and time-varying clinical variables and biomarkers
  - Such research also requires consensus case definitions or standardized collection of important diagnostic parameters

Objectives

- **The Canadian Inherited Metabolic Diseases Research Network (CIMDRN)** is a national, multidisciplinary practice-based research network designed to develop the evidence needed to improve outcomes for children with IEM
- **As part of CIMDRN's program of research, our clinical data collection working group aims to identify meaningful longitudinal clinical outcomes and the intermediate indicators of disease management that will help us to predict such outcomes**
  - Toward this goal, here we present a framework we have developed to guide the systematic collection of clinical data useful for longitudinal research within CIMDRN

Methods

Network of centers

- Nearly all children diagnosed with IEM in Canada receive care from one of 16 Hereditary Metabolic Disease Treatment Centres, based at pediatric academic health sciences centres
- CIMDRN's clinical investigators represent metabolic physicians based at nearly all (>14) of these treatment centres, working together with investigators in the clinical evaluative sciences
- With foundational funding from the Canadian Institutes of Health Research (CIHR), we will collect retrospective and prospective clinical data for Canadian children receiving care at treatment centres, with consent

Disease List

TARGET INBORN ERRORS OF METABOLISM
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, Maple syrup urine disease (MSUD), N-acetylglutamate synthetase (NAGS) deficiency, Ornithine transcarbamylase (OTC) deficiency, 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

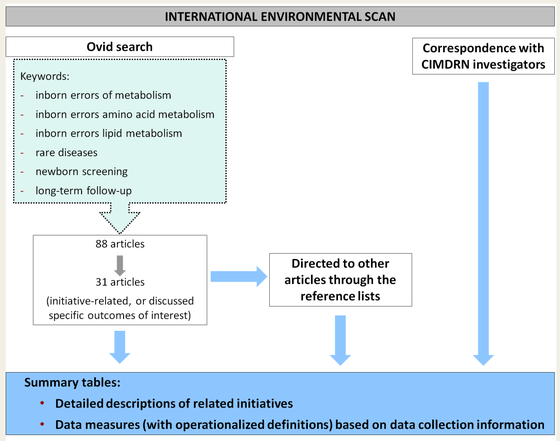
- Priority diseases **(BOLD)** for in-depth longitudinal data collection:
  - Challenges in diagnosis: for example, existence of "non-classic" cases of uncertain prognosis identified by newborn screening
  - Pressing questions regarding care
  - Known variation in interventions and outcomes
  - Policy relevance
- For the remaining diseases, we will collect a "minimum" clinical dataset, to describe prevalence and diagnostic characteristics and to create a consent-based contact registry to support future research

Data collection

- Key sources will be from retrospective chart abstraction and prospective data entry during clinical encounters
- Data will be collected on patient characteristics, clinical interventions, and outcomes
- Secure electronic data capture tool: Research Electronic Data Capture (REDCap)

Framework development

- Based in part on an environmental scan to identify related initiatives in Canada and internationally



- Key initiatives/collaborations:
  - Newborn Screening Translational Research Network (NBSTRN) – Longitudinal Pediatric Data Resource (LPDR)
  - Maternal Infant Child & Youth Research Network (MIYCRN)

Framework

- **Longitudinal clinical measures categories:**
  - **Clinical descriptors, Interventions, Confounders**, **Outcomes**
- The framework includes:
  - general/common and disease-specific data elements
  - baseline/constant and longitudinal/time-varying measures
- Through baseline and time-varying collection of clinical descriptors, approach allows analysis of clinical heterogeneity, including outcomes associated with varying diagnostic categories
- Inclusive case definitions designed to ascertain all individuals with a given diagnosis in order to include the full spectrum of clinical heterogeneity

Minimum dataset (all diseases)

Demographics	Diagnosis	Secondary Diagnoses
General patient information	Definition should be broad so as to reflect clinical heterogeneity and be as inclusive as possible of individuals with possible health issues related to this IEM	Diagnoses resulting from complications of their primary diagnosis or treatment thereof, as well as unrelated acute or chronic diagnoses

Longitudinal clinical measures (priority diseases)

CLINICAL DESCRIPTORS	INTERVENTIONS	CONFOUNDERS	OUTCOMES
Variables informing diagnosis, tissue involvement, severity, and pathophysiology related to primary diagnosis and/or other acute/chronic diagnoses	Exposures that are manipulated by care providers to change natural history	Hypothesized factors that might influence the outcome / natural history	Variables reflecting the health and functional status of the patient, including patient/family-centered variables

Example Disease: Phenylketonuria (PKU)

Demographics	Diagnosis	Secondary Diagnoses

- Identifiers
- Family history
  - Affected family members
- Socioeconomic status
- Treatment centre
	- Ascertainment
	- Newborn screening
	- Laboratory studies
	  - Phenylalanine
	  - Tyrosine
	- Imaging studies
	- Other diagnostic testing
		- Other chronic diagnoses
		  - Onset
		  - Severity
		  - Health care visits
		- Acute/intermittent diagnoses

CLINICAL DESCRIPTORS	INTERVENTIONS	CONFOUNDERS	OUTCOMES

- Prenatal history
- Neonatal history
- Measurements
- Health status
- Laboratory studies: monitoring
	(Prescribed vs actual)
	- Care coordination
	- Pharmacotherapy
	- Nutrition
	  - Phenylalanine
	  - Protein
	  - Formulas
	- Counseling
	- Home monitoring
		- Laboratory studies
		- Nutrition
		- Imaging studies
		- Education
		- Health status
		- Risk factors
		- Family structure
		- Socioeconomic status
		- Geography
		- Treatment team
			- Health status
			- Development assessment
			- Education
			  - School placement/function/performance
			- Behavioral issues
			- Pharmacotherapy
			- Treatment
			  - Complications
			  - Compliance
			- Complications of underlying disease
			- Biomarkers

Next Steps

- Develop data elements with operationalized definitions within the framework categories for all CIMDRN IEM targets
- Finalize elements with consensus process including all participating metabolic disease centres
- Translate framework into a database (REDCap) to collect clinical data

Value and Contributions

- **The framework supports practice-based evidence to overcome critical challenges of clinical longitudinal research on outcomes for IEM and other rare diseases**
- Consensus among multidisciplinary representatives from all hereditary metabolic disease centres in Canada
- Tools can be adapted for other rare diseases in other jurisdictions

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