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

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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, SGM; 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 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

Background

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
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