A Framework for Developing Clinical Measures to Support Long-term Follow-up of Patients with Inborn Errors of Metabolism

Newborn screening and inborn errors of metabolism
- Newborn screening programs aim to identify babies with rare, treatable conditions, such as inborn errors of metabolism (IEM)
- Important to obtain a timely diagnosis and implement effective disease management
- Successful in reducing mortality and severe morbidity
- Scientific investigations have led to earlier detection, improved biological understanding and corresponding development of new therapeutics for IEM
- With the advances in newborn screening and discoveries through scientific research, many diagnosed IEM patients have increased lifespans with fewer severe sequelae
- A current priority is longitudinal follow-up of IEM patients post-screening and 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 investigating 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, 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

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 / single enzyme disorders
  - Phenylketonuria (PKU) deficiency
  - Histidinemia (HPD) deficiency
  - Homocystinuria (HCM) deficiency
  - Carnitine deficiency
  - Medium chain acyl CoA dehydrogenase (MCAD) deficiency
  - Long chain acyl CoA dehydrogenase (LCAD) deficiency
  - Classic inborn errors of metabolism
    - Organic acid disorders
      - Methylmalonic acidemia
      - Propionic acidemia
    - Fat-soluble acidosis disorders
      - Carnitine deficiency
      - Medium chain acyl CoA dehydrogenase (MCAD) deficiency
    - Non-fatty acidosis disorders
      - Methylmalonic acidemia
      - Propionic acidemia
  - Other disorders
    - Albinism
    - Phenylketonuria (PKU)
    - Maple syrup urine disease

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 “minimal 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

Example Disease: Phenylketonuria (PKU)

Table: Longitudinal clinical measures (priority diseases)

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<thead>
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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