Building a pan-Canadian practice-based research network for inherited metabolic diseases: the first two years of the Canadian Inherited Metabolic Diseases Research Network (CIMDRN)


CIMDRN: Overview of network and research priorities

A practice-based research network

• Nearly all children in Canada who are diagnosed with an inborn error of metabolism (IEM) receive care at one of 16 Hereditary Metabolic Disease Treatment Centres
• Survey results identify differences across these Centres in individual treatment practices and in the organization of care ([Chakraborty et al., under review; Potter et al., JAMs, 2012])
• Opportunity for “practice-based research”: rigorous observational evidence to evaluate existing care across clinical settings (Wathen et al., 2008; JAM, Horn & Davies, 2010, Med Care)

Funded through a CIHR Emerging Team Grant (2012-2017), CIMDRN is both a network of 14 Hereditary Metabolic Disease Treatment Centres, and a growing network of 40+ investigators, including clinical researchers and evaluative scientists (Potter, Chakraborty et al, Genet Med, 2013):

Goals

• CIMDRN aims to develop an evidence-informed approach to care for pediatric IEM that:
  • integrates the evaluation of policy-level and clinical interventions while considering patient characteristics and other factors that may influence outcomes;
  • addresses high priority research themes that can provide generalizable insights; and
  • focuses on outcomes that capture patient and family experiences with care, clinical endpoints, and health system impacts: the “triple aim” ([Bareis et al., Health Affairs, 2008])

Priority research themes

1. Clinical heterogeneity and personalized care: Manifestations of many IEM range from mild to severe; there is need to tailor care to account for individual needs
2. Paradigm shift from “urgent care” to “opportunity for improvement”: Improvements in available treatments have meant that more patients with IEM are surviving with fewer severe sequelae, with a shift in treatment goals toward optimizing outcomes
3. Comparative effectiveness: Treatments for IEM are developing rapidly. We need to critically evaluate the comparative effectiveness of emerging with established therapies

Research stream 1: Clinical interventions and outcomes

Eligible IEM (N=29 total; those in bold type are prioritized for in-depth study)

Amino acid disorders

Phenylpyruvate hydroxylase (PAH) deficiency, phenylpyruvic aciduria (PAH and PPA) deficiency, Jervell-Lange-Nielsen syndrome (JLNS), congenital bilateral cataracts (CBC), hyperphenylalaninemia (HPA) deficiency, 4-hydroxyphenylpyruvate (4HPP) hydroxylase deficiency, organic aciduria (phenylpyruvic aciduria, pyruvate), non-congenital methylmalonic acidemia (NCCMA)

Organic acid disorders

3-1-Methylalcohol deficiency, tricarboxylacidemia (TCA) deficiency, propionic acidemia (PA)

Fatty acid oxidation disorders

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency, long chain acyl-CoA dehydrogenase (LCAD) deficiency, free carnitine uptake defect (FDU), long-chain 3-hydroxyacyl-CoA dehydrogenase [LCHAD] deficiency, trifunctional protein (TFP) deficiency, carnitine palmitoyltransferase (CPT) deficiency

Other disorders

Inherited hypophosphatasia (IH), phosphatidyl inositol glycosides (PIG) deficiency, congenital muscular dystrophy (CMD), Epidermolysis bullosa (EB), X-linked ichthyosis (XLI), cutis laxa (CLE), 3-hydroxyglutaryl-CoA dehydrogenase deficiency (HGD), zellweger syndrome, cerebrohepatorenal syndrome (ZRS)

Development of an enrollment protocol and clinical research database

• Working groups (subgroups of CIMDRN investigators) developed standard sets of clinical data elements, including common variables to collect across all eligible IEM (table above), and disease-specific variables for the IEM that we selected as priorities for in-depth study
• Variables had to encompass key patient characteristics, interventions, and outcomes; and be feasible to abstract in a standard way using chart reviews at 14 centres
• Variables were operationalized in a REDCap system for secure web-based remote data entry; data stored centrally in a database at Children’s Hospital of Eastern Ontario Research Institute
• A consent-based patient/family enrollment protocol was developed: eligible children have an IEM listed above, receive care at a participating Centre, and are born between 2006 and 2015
• Phased rollout of clinical data collection: 5 Centres volunteered to be first to submit the enrollment and clinical protocol for Research Ethics Board (REB) approval
• As of May, 2014: REB approval at 4 Centres, >20 participants enrolled

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Research stream 2: Patient/family-reported outcomes

Scoping review to identify relevant outcomes and self-administered measures

• To inform the development of a questionnaire for families enrolled in CIMDRN, we conducted a scoping review of the literature on patient and family-reported outcomes relevant to complex chronic pediatric diseases ([Khangura et al., under review])
• Among 304 reviewed articles, we identified 43 unique outcomes and 405 measurement tools suitable for self-administered questionnaires, e.g.

Qualitative studies with patient support organizations and CIMDRN families

• To gain further insight into key issues and outcomes important to families that we will prioritize for our CIMDRN parent questionnaire, 2 qualitative studies are underway/planned:
  • With funding from the Rare Disease Foundation, a telephone interview study to ascertain views of patient support and advocacy organizations is near completion
  • A telephone interview study with CIMDRN families is planned for fall, 2014

Survey of CIMDRN treatment centres

• To inform the development of the practice-based research network and describe the organization of care for pediatric patients with IEM in Canada, we conducted a web survey with the treatment centres participating in CIMDRN (n=14) ([Chakraborty et al., under review])
• Results highlighted variation in human resources and access to services, e.g.

Health services impact of newborn screening for IEM in Ontario

• Beginning with MCAD deficiency, we used screening and diagnostic confirmation data from Newborn Screening Ontario linked with health care administrative datasets at the Institute for Clinical Evaluative Sciences to document health services use and costs for children affected with an IEM and those with false positive newborn screening results ([Karaceper et al, in preparation])
• Analysis will be completed for other IEM in Ontario and findings compared across diseases; this approach will also be adapted for other provinces

Lessons learned in building a practice-based research network

Key challenges

• Balance between comprehensiveness and feasibility: the science of practice-based research requires comprehensive data collection to evaluate care while accounting for confounding factors, but this is time-intensive and costly; compromises are necessary for feasibility
• Engagement: Our network is large and geographically dispersed – engaging members has been critical to our early successes but meeting in person is a challenge
• Administration versus science: While a large time investment is needed to establish and coordinate a national database and network, early productivity is essential for sustainability

Future priorities

• More extensive engagement with both our external advisory board and our participating patients/Families is a priority for CIMDRN’s next three years and beyond
• We have begun to establish international collaborations in the fields of IEM and newborn screening research; this is essential for improving care, particularly for the rarest IEM

Value

• We expect CIMDRN’s research to lead to specific recommendations for delivering care to children with IEM and that our methods will yield insights generalizable to other rare diseases
• We have established a research network in pediatric IEM with high potential for sustainability

Note: several posters and platform presentations include further details about research projects mentioned above More information: Genet Med 2013;15(6):415-422, www.cimdrn.ca, contact: bpotter@uottawa.ca