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RESEARCH REPORT

Metabolic Clinic Atlas: Organization of Care for Children with Inherited Metabolic Disease in Canada

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Abstract *Introduction*: Nearly all children in Canada with an inherited metabolic disease (IMD) are treated at one of the country's Hereditary Metabolic Disease Treatment Centres. We sought to understand the system of care for paediatric IMD patients in Canada in order to identify sources of variation and inform future research priorities.

Methods: Treatment centres were contacted by email and invited to complete a web-based survey. The questionnaire addressed, for each centre, the population size served and scope of practice, available human resources and clinic services and research capacity. Survey responses were analyzed descriptively.

Results: We received responses from 13 of the 14 treatment centres invited to participate. These centres represent at least 85% of the Canadian population, with over half of the centres located in southern Ontario and Quebec. All centres reported paediatric patients with IMDs as their main patient population. A variety of dedicated staff was identified; every centre reported having at least one physician and one dietician. The most common ancillary services available included telehealth (11/12 respondents) and biochemical genetic laboratory testing (10/12), with a high variability of access to on-site laboratory tests. A majority of centres indicated access to additional off-site services, but barriers to these were reported. All but one centre indicated previous experience with research.

Conclusions: The variation we identified in the organization of care highlights the need to investigate the association between practice differences and health outcomes for paediatric IMD patients to inform policies that establish equitable access to services that are beneficial.

Introduction

Although individually rare, collectively, inherited metabolic diseases (IMDs) represent a substantial population health burden in Canada and internationally. Studies have estimated the Canadian birth prevalence for diagnosed IMDs to be from 1 in 2,500 to 1 in 1,900 (Applegarth et al. 2000; Auray-Blais et al. 2007). The currently observed Canada-wide prevalence of all IMDs is likely somewhat higher than both these estimates, due to a number of factors including improved identification strategies such as expanded newborn screening (Schulze et al. 2003; Wilcken et al. 2003), improved diagnostic services and awareness of less recognized conditions, longer survival for IMD patients due to newly developed therapies and immigration of populations at higher risk of particular IMDs.

The majority of health care in Canada is publically funded to provide care to all based on need rather than ability to pay (Health Canada 2011). Public health insurance programmes in all provinces and territories cover both primary and secondary physician and hospital care, with limited coverage for allied health services outside of hospitals (Health Canada 2011). Coverage for pharmaceuticals and other products relevant to IMD, such as medical foods or supplements, varies amongst provinces and territories (Health Canada 2011). Nearly all children in Canada diagnosed with an IMD receive specialized care at one of 16 Hereditary Metabolic Disease Treatment Centres. At these centres, paediatric IMD patients have access to specialist physicians and services to manage diagnosis, treatment and follow-up care.

The goal of this study was to provide a broad overview of the organization of specialized care for IMD children in Canada, in order to identify areas of practice variation and inform priorities for future research examining how service provision affects outcomes. We invited Canadian Hereditary Metabolic Disease Treatment Centres to complete a survey to:

1. Describe their centre's scope of practice, in terms of the population and types of patients served
2. Identify the human resources available and the specific clinical services offered or to which they have access
3. Describe their research capacity

Methods

Sample Selection and Survey Implementation

The recently established Canadian Inherited Metabolic Diseases Research Network (CIMDRN) is a practice-based research network that aims to inform care and ultimately to improve outcomes for children with IMD in Canada and beyond (Potter et al. 2013). Fourteen of the 16 Canadian Hereditary Metabolic Treatment Centres form the practices in this research network. By email, we invited one metabolic physician at each of these 14 centres to participate in the survey. Physicians were asked to seek assistance from other knowledgeable staff at the centre as needed. The survey was administered online, between January and March 2013 using FluidSurveys (www.fluidsurveys.com), a secure online questionnaire tool. Ethics approval was obtained from The Children's Hospital of Eastern Ontario Research Ethics Board.

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Questionnaire Content and Data Analysis

Survey questions were divided into three categories:

1. Scope of practice (patient populations)
2. Human resources and clinic services
3. Research capacity

The questionnaire required approximately 30 minutes to complete. We used Microsoft Excel (2011) to conduct descriptive analysis, reporting relevant means and proportions.

Results

Scope of Practice

Of the 14 centres invited to participate in the survey, we received completed surveys from 13 (response rate of 93%). These 13 centres care for the majority of IMD children in all ten provinces and three territories in Canada, serving geographic catchments with populations of 500,000 to over six million and representing at least 85% of the Canadian population (Fig. 1). Over half of the participating centres are located in southern Ontario and Quebec (Fig. 1). Five centres were classified as large clinics serving populations of over two million, four centres were considered mid-sized serving >1–2 million people and the remaining four were classified as small serving one million or fewer people.

All centres reported their main patient population as IMD patients; phenylketonuria (PKU) was the most common diagnosis. Some clinics also reported providing services to patients with non-IMD conditions (e.g. neurologic disorders, autism, other genetic diseases). All centres reported at least 20 paediatric IMD patients currently in their care; six centres (46%) reported having over 100 paediatric IMD patients. Eight respondents indicated a second clinic in their catchment area providing some diagnostic or treatment services to IMD patients; these were mainly neurology clinics or adult care facilities and a specific clinic in New Brunswick for PKU patients. Four (31%) centres reported a separate adult clinic in the same catchment area to help manage the transition from paediatric to adult care; 12/13 centres reported having adult (>18 years old) IMD patients under their care, including pregnant women.

Human Resources and Clinic Services

All participating centres reported at least one physician and one registered dietician on staff. Other staff identified included nurses, genetic counsellors, pharmacists, psychologists, social workers, administrative assistants and research coordinators (Fig. 2a). Number of staff varied across centres (Fig. 2b), and as expected, larger centres reported more staffing resources. Roles for staff members included clinical, administrative, teaching and research responsibilities. Physicians, nurses, dieticians and genetic counsellors are most heavily involved in primary patient contact, initial consultations and case coordination, with some contributions from social workers and psychologists. 77% (10/13) of centres reported that they use an inter-professional model of care for their patients. We defined 'inter-professional care' in the questionnaire as an integrated approach to health-care delivery in which the collaboration amongst practitioners of different disciplines or with different skills and knowledge allows for the delivery of patient health care by the most appropriate health-care practitioner.

The most common ancillary services provided by the centres (i.e. in addition to direct patient care) were telehealth (11/12 centres who responded to these questions), biochemical genetic laboratory testing (10/12), a specialized pharmacy (8/12) and a dispensary for medical foods/supplements (8/12). Patient/family workshops (7/12) and patient/family support groups (6/12) were also provided by some centres. Over 80% of the centres reported access to other services for patients and families, either within or outside the clinic. These services included additional prenatal genetic diagnostic care (11/13 centres), genetic counselling (10/12) and social work (11/13). When asked about barriers to patients' access to services, several centres reported challenges associated with access to nutritional services (e.g. feeding devices, parenteral nutrition) and psychological services, mainly due to long wait lists and/or being located off-site. There was high variability amongst the 12 centres that reported on the availability of specific on-site laboratory tests (Table 1). The tests most commonly available were urinalyses for organic acids and plasma/urine amino acid analyses (92% of centres).

Research Capacity

Twelve of the 13 responding centres (92%) indicated previous involvement with research including industry-funded trials (11/12 centres), survey or interview-based studies (9/12), diagnostic studies (8/12), retrospective studies using chart abstraction (7/12) and nonindustry-funded trials (5/12). Staff responsibilities specific to research were highly variable, but involvement included physicians, nurses, dieticians, genetic counsellors, administrative assistants and research coordinators. Important reasons for participating in research included: contributing to the improvement of care for IMD patients (100%), contributing to the scientific understanding of

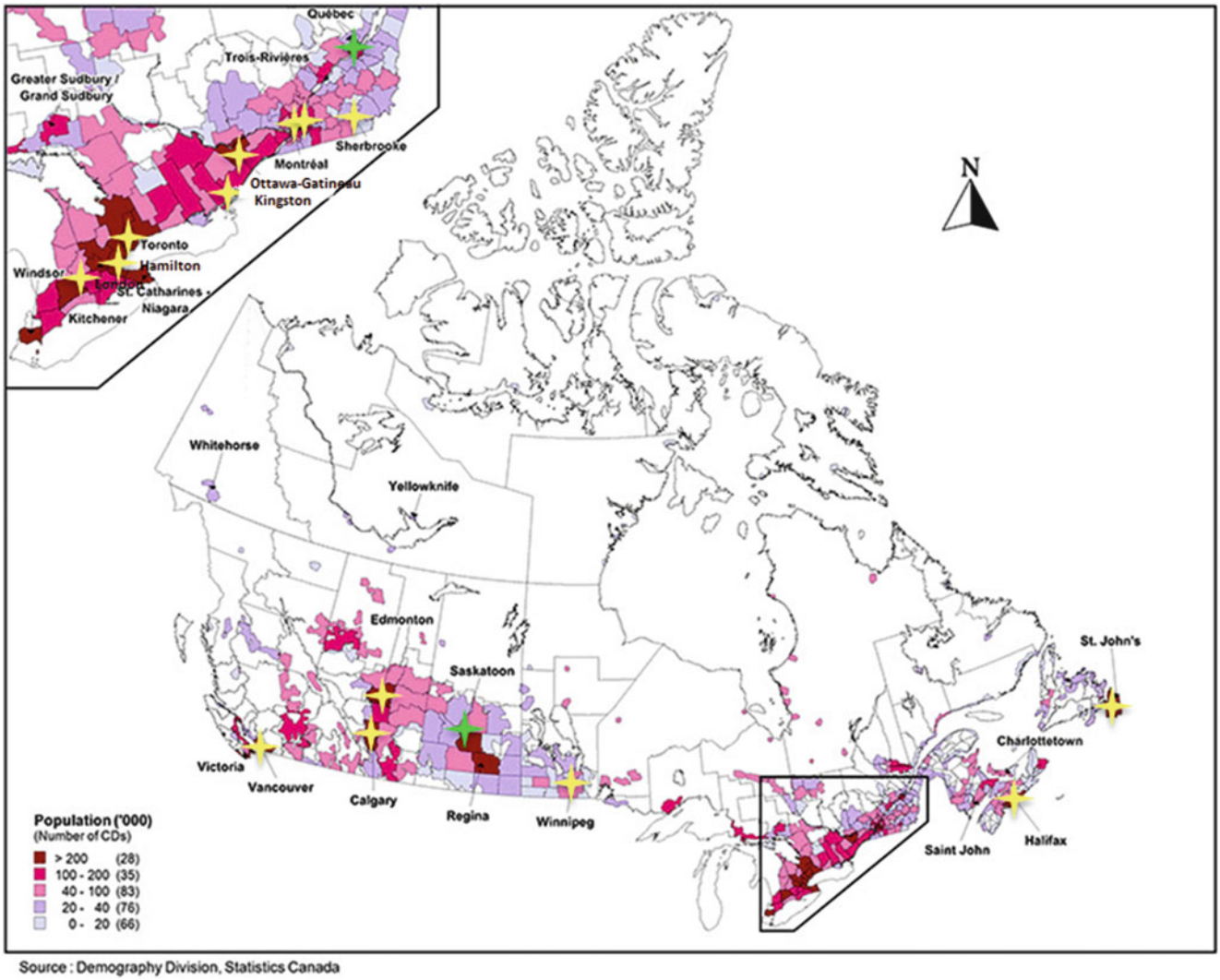


Fig. 1 Population density map of Canada using the most recent census data (Statistics Canada 2011) indicating the location of all 16 Hereditary Metabolic Disease Treatment Centres. Centres participating in CIMDRN are indicated in yellow. Centres highlighted in green were not part of CIMDRN at the time of data collection. Survey data was collected from January–March 2013

IMDs (100%) and building professional and inter-centre relationships (92%). Centres expressed barriers to involvement in research related to workload (100%) and concerns about research sustainability due to limited funds (85%).

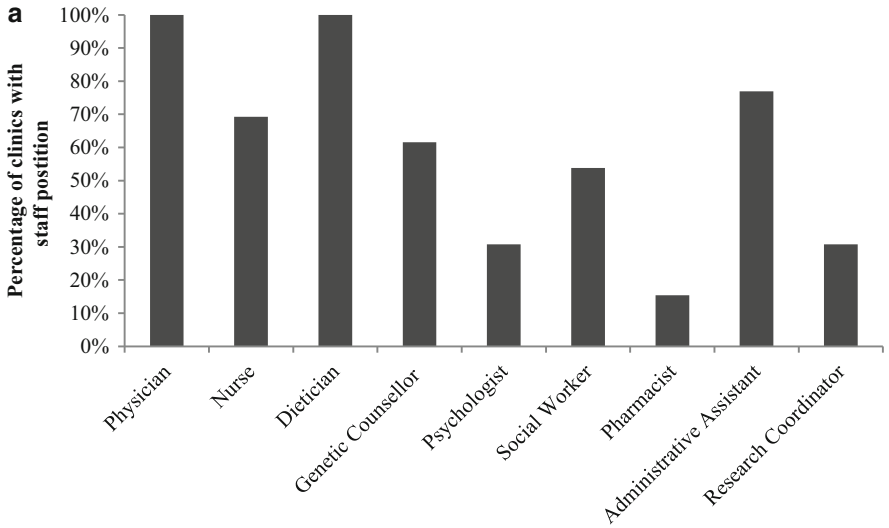
Discussion

Summary and Interpretation

We found important variation in the organization of care in Canada for paediatric IMD patients. Variation in IMD management has been noted in other jurisdictions (Leonard 2006), and although the results of our survey are from Canadian clinics, there is much that could be pertinent to health care for IMDs internationally. Specifically, the variation we identified highlights the need for evaluative evidence to better understand whether these differences in care are associated with differences in patient outcomes and provides an opportunity to generate that evidence using observational study designs that capitalize on practice variation as 'natural experiments' (Horn and Gassaway 2007).

Our survey results demonstrate variation in human resources and services available at Canadian IMD treatment centres. This variation in clinical infrastructure may reflect clinical heterogeneity in the complex needs of patients with different types of IMDs, including the needs of specific high-risk populations at some of the centres (e.g. First Nations or founder populations, immigrant communities). Further research is needed to determine a more specific

a



b

Staff Position	Full-time Equivalent (FTE) Staff		
	Median	Minimum	Maximum
Physician	1	0.3	4.5
Nurse	0.5	0	3
Dietician	1	0.2	2.8
Genetic Counsellor	0.1	0	2
Psychologist	0	0	0.5
Social Worker	0.1	0	1
Pharmacist	0	0	0.2
Administrative Assistant	0.6	0	3
Research Coordinator	0	0	3

Fig. 2 (**a**) Proportion of IMD centres ($n = 13$) reporting staff position at their centre and (**b**) median number of full-time equivalent staff for participating IMD centres ($n = 13$), indicating minimum and maximum values

profile of IMD patients across centres; precise patient numbers for these rare diagnoses are challenging to estimate accurately, as is the distribution of patients by age, ethnic background, disease severity and presence of co-morbidities. Alternatively, differences may reflect differences in provincial/territorial health service organization and prioritization.

Similar to trends in both the United States and the United Kingdom, we also found that many adult IMD patients in Canada are being treated in paediatric centres (Burton et al. 2006; Berry et al. 2013). Consideration of the transition from paediatric to adult health care is a current priority as new therapies make it possible for greater numbers of IMD patients to survive into adulthood (Dionisi-Vici et al. 2002; Lee 2002; Mütze et al. 2011). There is growing evidence that suggests it is beneficial for centres to establish transition protocols and, depending on the volume of patients in a centre, separate clinics for adult patients (Lee 2002; Mütze et al. 2011; Sirrs et al. 2014).

Not surprisingly, centres that serve a larger population have more resources. However, what is not known is the ratio of resources to patients at the centres, whether the organization of resources at the centres is effective or not and how these factors are linked to clinical and patient-centred outcomes. There is also limited evidence regarding the value of allied health services for particular IMD populations, such as psychology and occupational therapy. Similar to our study findings, barriers to these services have been reported elsewhere (Camfield et al. 2004; Berry et al. 2013). Research to answer these questions is necessary to determine what resources and services should be offered at each centre to optimize health outcomes.

Table 1 Summary of laboratory tests available on-site at participating IMD centres ($n = 12$)

Test provided	% 'Yes'
Organic acid analysis	92
Plasma/urine amino acids	92
Total and free carnitine	67
Bloodspot phenylalanine	67
Bloodspot acylcarnitine profile	58
Plasma acylcarnitine profile	50
Lysosomal enzymology	50
Urine MPS fractionation	42
Urine oligosaccharide fractionation	42
Respiratory chain enzymology	33
mtDNA point mutation analysis	33
mtDNA quantification and deletion/duplication analysis	25
Other analytes (e.g. purines, succinylacetone, VLCFA, etc.)	67
Other enzymology (e.g. VLCAD, Gal-1-PUT, etc.)	42
Other molecular analyses for IMD	33
Other bloodspot tests	33

Note: Data were missing on this survey question for one of the participating centres

In addition to availability, access is another concern. Although the location of the treatment centres is proportionate to the geographic distribution of the Canadian population, as well as the birth prevalence of IMDs, patients living in more northern or remote areas have to travel a considerable distance for specialized metabolic care. Further research is needed to determine ascertainment of IMD patients in remote areas and how clinical and patient-centred outcomes are affected by having limited geographic access to services. There were several centres with only one dedicated IMD physician. This may pose problems with access to care for IMD patients outside regular hours. Although our survey was not able to delve into this issue in detail, it is an important consideration for further study. Services such as laboratory testing can be accessed elsewhere; however, turnaround time, costs and quality assurance are important to consider. All centres must send out samples for some metabolic and/or genetic testing as not even the largest centres are able to perform all relevant testing, thus adding another source of variation amongst centres which could potentially impact on care delivery. This issue also raises the question of whether some services can be effectively delivered in patients' home communities rather than at a distant metabolic clinic.

Although Canada has established centres to provide care for IMD patients, the variation in clinical infrastructures we identified reflects the lack of a central mechanism to guide minimum care standards. This is further exemplified with the lack of a national strategy for newborn screening. In Canada, newborn screening programmes are unique to each province and territory, differing in the panel of disorders screened, technologies used, follow-up processes, legal structures and governance (Therrel and Adams 2007; Wilson et al. 2010; Morrison and Dowler 2011). Canada also lacks a national metabolic laboratory network that could set standards and provide coordination for biochemical genetic laboratory tests, on which IMD patients rely for diagnosis, monitoring and informing treatment (Burton et al. 2006; Leonard 2006; Leonard and Morris 2006). Reimbursement decisions for drug funding also differ across the provinces and territories. Health Canada recently announced the development of a Canadian orphan drug framework intended to provide Canadians with better, timelier access to orphan drugs and to encourage and facilitate clinical research in the area of rare diseases (Lee and Wong 2014). Once practice-based research studies have determined what aspects of the system of care have the greatest impact on health outcomes for IMD patients, a mechanism to implement research findings nationally will be critical.

In conclusion, although the majority of Canadian paediatric IMD patients are receiving care from one of the Hereditary Metabolic Disease Treatment Centres, the specific resources and services available vary greatly across the country. This variation in the organization of care for IMDs across Canada presents a unique opportunity for observational practice-based research to determine whether patterns of care are associated with clinically significant differences in patient outcomes.

Limitations

Despite a high response rate (93%), our study was limited by the small number of responding centres ($n = 13$), because of the small number of IMD treatment centres in Canada. Nevertheless, the geographic catchments served by the responding centres support the representativeness of our sample. The three 'missing' centres would likely add further variation to that found amongst the surveyed centres. Survey questions were broad to account for variability amongst clinics; however, some important details may have been missed that could help explain some of the observed variation in services.

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Concise 1 Sentence Take-Home Message (Synopsis) of the Article, Outlining What the Reader Learns from the Article

Variation in the organization of care for paediatric IMD patients in Canada identifies a need to investigate the association between practice differences and health outcomes to enable policy development that will ensure access to services that are effective, equitable and affordable.

Compliance with Ethics Guidelines

Conflict of Interest

Monica F Lamoureux, Kylie Tingley, Jonathan B Kronick, Beth K Potter, Alicia KJ Chan, Doug Coyle, Linda Dodds, Jane Gillis, Grant Mitchell, Anne-Marie Laberge, Julian Little, Kathy N Speechley, Sylvia Stockler, Yannis Trakadis, Lesley Turner, Kumanan Wilson and Pranesh Chakraborty declare that they have no conflict of interests.

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Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Completion and submission of the survey constituted consent to participate in this study. This article does not contain any studies with animal subjects performed by any of the authors.

Contributions

MFL, BKP. Concept and design, analysis and interpretation of data, drafting article and critical revisions of article

KT. Analysis and interpretation of data, drafting article and critical revisions of article

PC, JBK. Concept and design, analysis and interpretation of data and critical revisions of article

AKJC, DC, LD, SD, AF, MG, JG, CRG, AK, JL, BM, JM, AM, JJM, GM, AML, MP, CP, KS, KNS, SS, YT, LT, CVK, KW. Concept and design, and critical revisions of article

PC. Guarantor

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