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ORIGINAL ARTICLE

The accessibility and utilization of genetic testing for inherited heart rhythm disorders: a Canadian cross-sectional survey study

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Abstract The genetic basis of many sudden death-related conditions has been elucidated. These include inherited arrhythmias and arrhythmogenic cardiomyopathies, termed inherited heart rhythm disorders (IHRD). Advising on and interpreting genetic testing is challenging for the general cardiologist. This has led to the development of interdisciplinary clinics for IHRD in varying stages of establishment in Canada. We sought the viewpoints and patterns of practice of Canadian IHRD experts, and assessed their ability to access genetic testing for IHRD using a national cross-sectional survey. Of 56 participants, most were physicians (68%) or genetic counselors (19%). Despite working collaboratively, most genetic counselors (59%) were either not satisfied or only somewhat satisfied with their relationships with physicians. Ninety percent of participants were involved in offering genetic evaluation, including 80% who felt that testing was usually/always accessible. Most offered genetic testing to confirm clinical diagnosis and/or direct family screening. Post-mortem genetic analysis was sought by 69% of respondents; however, a lack of retained tissue and/or poor tissue preparation hindered this process. Family screening was usually recommended in the setting of a pathogenic/likely pathogenic variant. The most commonly perceived barrier to genetic testing was cost to the healthcare system. More than a quarter of patients waited ≥ 6 months for funding. An ability to engage at-risk relatives was rated as limited/poor by 34% of participants. Despite the establishment of several interdisciplinary clinics, timely access to affordable testing, supported by strong team communication, continues to be a barrier to genetic testing in Canada.

Keywords Inherited arrhythmia · Cardiovascular genetics · Sudden death · Cardiomyopathy · Channelopathy

Introduction

Sudden death in young, apparently healthy individuals is often caused by inherited heart rhythm disorders (IHRD) including various forms of cardiomyopathy and arrhythmia. While cardiomyopathy can be evident at autopsy, inherited arrhythmias cause sudden arrhythmic death syndrome (SADS) in the absence of overt structural heart disease. IHRDs have several established genetic causes, and molecular evaluation can be informative in living (Krahn et al. 2009) and deceased patients (Gollob et al. 2011). These advancements have improved the diagnosis and treatment of IHRD, and also facilitated potentially life-saving family screening measures. The judicious conduct and interpretation of genetic testing is a challenge, particularly with the advent of larger genetic panels. As such, experts recommend that these conditions be evaluated in interdisciplinary clinics (Ackerman et al. 2011; Gollob et al. 2011; Priori et al. 2013), which report high diagnostic yields (Hofman et al. 2013) at reasonable cost (Janzen et al. 2016).

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There are currently seven interdisciplinary clinics for IHRD in Canada spread across six provinces, with a similar number at various stages of formalization. These typically include physicians, genetic counselors, nurses, and administrators. We sought to determine the viewpoints, practice patterns, access, and barriers to genetic testing for IHRD in the Canadian healthcare system.

Methods

Between April 2015 and May 2016, interdisciplinary clinics and their members were recruited via email to complete a survey through the Hearts in Rhythm Organization (HiRO; https://heartsys.org/5/hiro/). HiRO is a national organization that was conceived and founded during the study period. By connecting Canadian IHRD patients and their providers, the organization seeks to unify clinical care, research, and educational and advocacy initiatives for IHRD across the country. The investigators for the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER), which enrolls Canadian survivors of cardiac arrest and their first-degree relatives, formed the early membership of HiRO (Krahn et al. 2009). CASPER has been an important registry in the field of cardio-genetics. It has led to numerous publications pertaining to IHRD, and now includes an enrollment exceeding 1200 patients (Herman et al. 2016; Mellor et al. 2017; Somani et al. 2014; Steinberg et al. 2016; Vittoria Matassini et al. 2014). In the present study, we recruited participants from the initial HiRO/CASPER membership, and through web-based searches of the 17 Canadian universities with medical schools, and by contacting administrators from the seven established IHRD clinics in Canada. These programs were all affiliated with a major university as follows: (1) University of British Columbia, (2) Western University, (3) University of Ottawa, (4) University of Toronto (Hospital for Sick Children), (5) University of Manitoba, (6) Dalhousie University, and (7) Memorial University. There is no standardization among provinces with respect to the role of cardiologists and medical geneticists in these settings. However, all IHRD clinics have access to a consultant medical geneticist or genetic counselor to assist with variant interpretation as a minimum standard. Given that there was no previous standardization of IHRD care in Canada, and that very few physicians are in private practice in our universal healthcare system, we felt that this systematic approach captured most specialists in the area. Eligible participants included providers affiliated with Canadian interdisciplinary clinics or those with advanced expertise in IHRD. The questionnaire addressed provider viewpoints, experience, practice patterns, and barriers to genetic testing (Supplemental Fig. S1), and was adapted for the different professional roles. Recipients were asked to forward the survey to other members of their clinic if applicable. Providing location of practice was made voluntary to preserve participant anonymity if desired. Chi-square and Wilcoxon Rank Sum testing was used for univariate analysis with $p < 0.05$ defined as statistical significance. Certain questions were not applicable to every respondent (e.g., a question about family counseling may not be applicable to a nurse-administrator). As such, to enhance the clarity of the results, we present the data as a percentage of total responses for each question.

Results

Fifty-six IHRD experts responded including those affiliated with each of the seven Canadian interdisciplinary clinics. The survey was shared with 70 individuals providing an estimated response rate of 80% (estimated based on forwarding of the survey). The respondents included 36 physicians (68%), 10 genetic counselors (19%), 5 managers/administrators (9%), and 2 nurses/nurse practitioners (4%) who largely practiced in large communities (population > 1,000,000; 63%). Among physicians, most received core training in internal medicine (54%) or pediatrics (26%), and the majority were electrophysiologists (75%). Only one physician (3%) was a medical geneticist and eight cardiologists (22%) had advanced training/expertise in genetics. Sixty-four percent of respondents worked in a dedicated IHRD clinic at least once per month. Physicians and genetic counselors worked together closely: 46% of physicians saw patients with a genetic counselor and 67% of genetic counselors had direct contact with an electrophysiologist in clinic. However, most genetic counselors (56%) were somewhat or not satisfied with their relationship with physicians. Respondents were comfortable managing IHRD, but were less familiar with other sudden death-related conditions (Fig. 1).

Approach to genetic testing

Seventy-four percent of respondents used genetic testing for diagnosis/diagnostic clarification and/or family screening, and 16% indicated that genetic testing was used to guide therapeutic decision-making (Fig. 2a). Post-mortem genetic testing was offered by 69% of respondents for SAD victims. Forty percent offer comprehensive, multi-condition panels (i.e., 47–150 genes), while 16% perform a limited analysis of the major channelopathy genes (e.g., *KCNQ1*, *SCN5A*, and *RYR2*). Twenty percent stated that tissue should be retained but would not advise molecular testing. No one pursued whole exome sequencing. All respondents offered cascade family screening if a known pathogenic variant was identified in a SADS victim. Eighty-eight percent made the same screening recommendation for a possible pathogenic variant (termed "likely pathogenic" henceforth based on consensus terminology

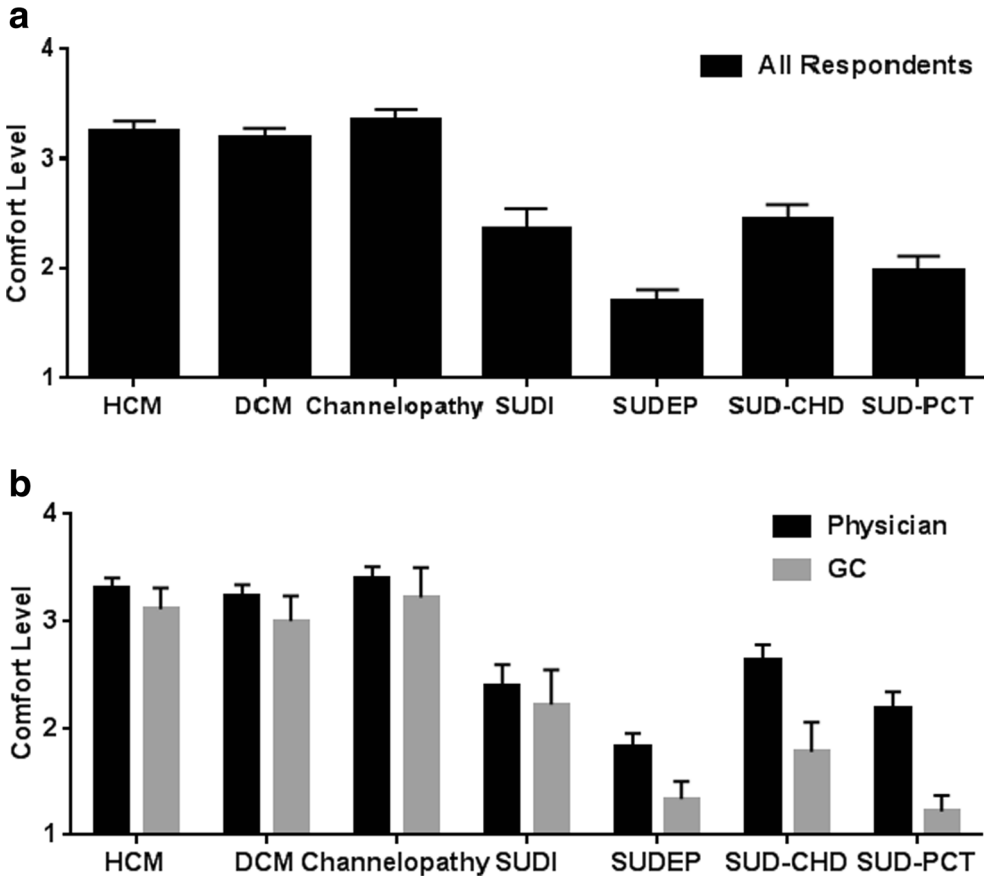

Fig. 1 Comfort level (1–4 scale: 1 = expert comfort, 4 = uncomfortable) in evaluating various SUD conditions among all respondents (**a**), and comfort level compared between physicians and genetic counselors (**b**). Genetic counselors were less comfortable managing SUD with congenital heart disease, and SUD post-cardiac transplant ($p = 0.008$, and $p = 0.003$, respectively). *HCM* hypertrophic cardiomyopathy, *DCM* dilated cardiomyopathy, *SUDI* sudden unexpected death of infancy, *SUDEP* sudden unexpected death of epilepsy, *SUD* sudden unexpected death, *SUD-CHD* sudden unexpected death in congenital heart disease, *SUD-PCT* sudden unexpected death post-cardiac transplant, *IC* interdisciplinary clinic, *GC* genetic counselor

(Richards et al. 2015)). Respondents were more likely to offer cascade family screening on the basis of a pathogenic/likely pathogenic variant compared to a variant of undetermined significance (VUS) (64 vs. 6 respondents; $p < 0.0001$).

Accessibility, barriers, and outcomes

Genetic testing was determined to be usually/always accessible by 80% of providers. The patient/family did not pay for testing in any reported case. However, 27% of patients waited ≥ 6 months to receive public healthcare funded testing. Genetic analysis was performed by a variety of laboratories including commercial (53%), hospital-based (21%), and university research-based (17%). The catchment areas of labs were as follows: international (38%), provincial (23%), local/regional (23%), national (10%), and 6% indicated uncertainty about catchment area. A number of barriers to genetic testing were identified (Fig. 2b). A lack of protocols, tissue availability, and/or proper preservation were barriers to post-mortem molecular testing (38 responses; 75%, Fig. 2c). One-third believed that their ability to engage at-risk relatives was limited or poor with 53% of respondents citing privacy-related issues as the most significant barrier. Making a diagnosis via cascade screening changed management in 56% of cases.

Discussion

This study characterizes the patterns of practice, access, and barriers to genetic testing for IHRD among Canadian interdisciplinary clinic providers and IHRD experts. Interpretation of genetic testing is challenging and cardiologists are increasingly relying on interdisciplinary clinics for the evaluation of inherited arrhythmia and cardiomyopathy in Canada. This study demonstrates that these expert-led interdisciplinary clinics can acquire and capably interpret genetic testing at little or no cost to the patient. Accordingly, contemporary studies indicate that Canada sets a strong example in the care of IHRD patients. Recently, one HiRO-affiliated center described excellent outcomes in 720 IHRD patients evaluated over a 9-year period (0.14% mortality) (Adler et al. 2016) and our own IHRD program reported high diagnostic yields at reasonable cost (Janzen et al. 2016).

Strengths identified

The interdisciplinary model, supported by genetic counselors, nurses, and physicians, provides the ideal setting to discuss the implications of genetic testing with patients and their families, including insurance, family planning, and psychosocial considerations (Caleshu et al. 2016; Erskine et al. 2013; Grosse

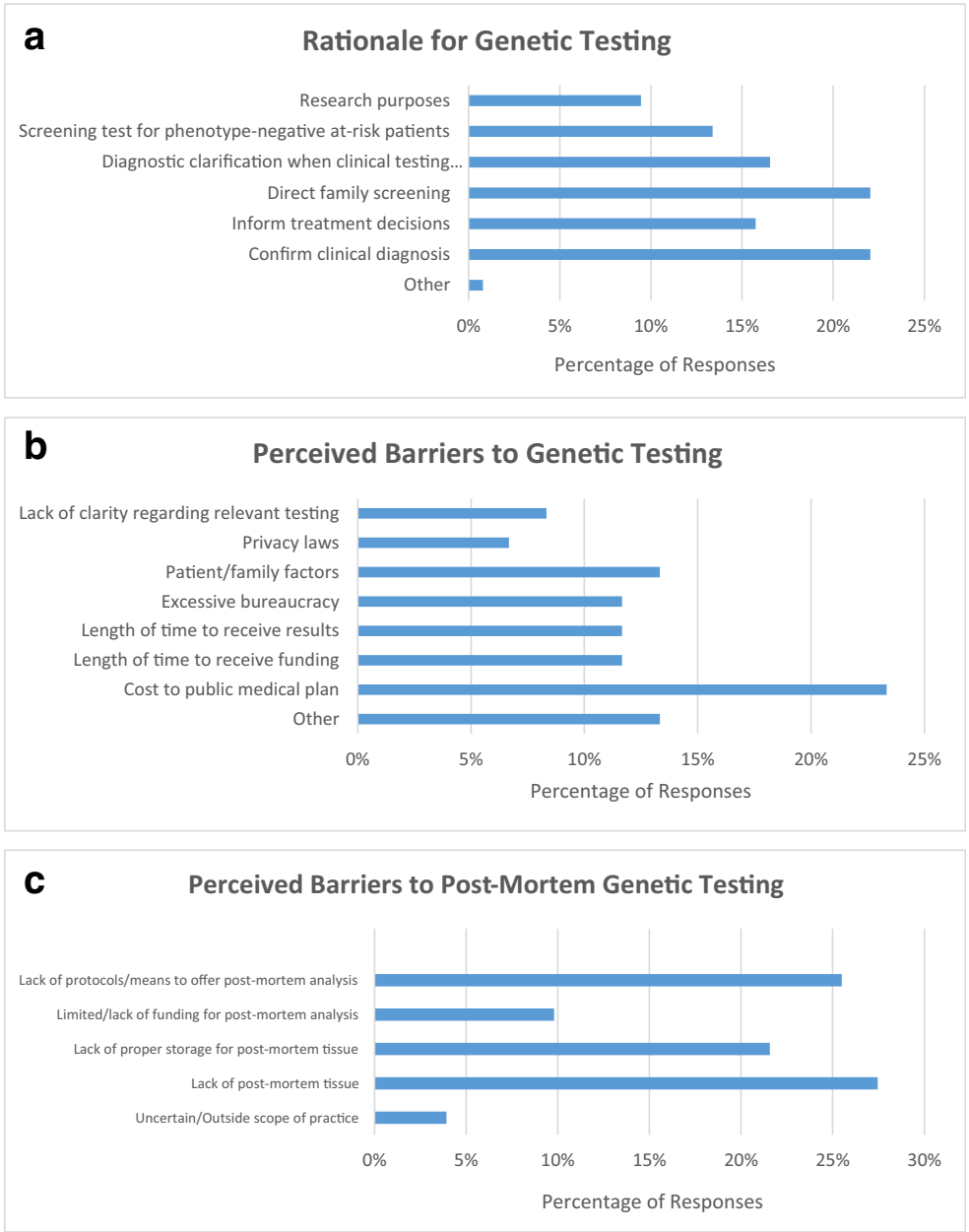

Fig. 2 Rationale for offering genetic testing in patients with IHRD (**a**), perceived barriers to genetic testing (**b**), and perceived barriers to offering post-mortem molecular analysis in SUD conditions without a phenotype (**c**)

et al. 2009). Our findings show that the majority of providers are electrophysiologists without formal genetics training which highlights the vital role that genetic counselors play in this field. For example, genetic counselors are well-equipped to discuss the implications of a VUS, a common occurrence in the IHRD population (Ackerman et al. 2011; Gollob et al. 2011). In our study, providers rarely recommended family screening for a VUS in the absence of an obvious phenotype, reflecting awareness of the adverse consequences of genetic misdiagnosis (Ackerman 2015). Instead, providers appropriately recommended screening on the basis of a pathogenic/likely pathogenic variant. No one pursued whole exome sequencing, which is emerging as a research tool, but has limited clinical utility at present. As these advances are adopted into clinical practice, the role and importance of genetic counselors is likely to grow.

Areas for improvement

Several limitations exist in the current IHRD care model. It is concerning that genetic counselors often lacked satisfaction in their relationships with physicians. The small sample of genetic counselors makes it challenging to characterize this finding. There was also an apparent lack of mental health providers involved in the interdisciplinary model. These professionals should play a role in IHRD patient care, given that anxiety and grief are common after the sudden death of a relative (Ingles et al. 2016). Several respondents also indicated

that they would initiate genetic testing for research purposes, which is not justifiable without additional rationale. In contradiction to current guidelines (Gollob et al. 2011; Priori 2013), a minority recommended genetic screening in the absence of a phenotype. Interestingly, many of the survey participants authored the Canadian guidelines on IHRD (Gollob et al. 2011), yet appeared not to fully adhere to these recommendations, highlighting that exceptional and nuanced circumstances often exist in this field. The lengthy delay in funding approval for genetic testing is also worrisome. A delay of ≥ 6 months in more than a quarter of patients may be exacerbated by additional factors in clinical practice, including specimen access and shipping, local funding approval processes, and inadequate tissue preservation. It is possible that some families wait nearly a year for genetic results, with attendant risk to undiagnosed family members.

Study limitations

This study examines the use of genetic testing in Canadian IHRD clinics which may not be representative of the international experience. It is important to note that this study was conducted in a publicly funded single payer healthcare system, which almost certainly affects the availability of genetic testing. We allowed respondents to opt out from providing location of practice to help ensure anonymity. As such, it was not possible to undertake further in depth comparisons between clinics and location. The potentially fragmented nature of IHRD care in Canada also creates inherent limitations. No universal process for referral or assessment of this population exists among Canadian provinces or clinics. It is possible that some eligible participants were missed during our recruitment process because they practice outside the major Canadian cardio-genetics centers. We sought to minimize this possibility by asking for the survey to be forwarded to individuals who may have been missed, and by reviewing the CASPER/HiRO membership. The study design also may have introduced recall bias, and the design of the survey tool, which was intended to be completed in a timely manner (< 10 min), may have not adequately addressed nuanced circumstances. Thus, we did not include exhaustive lists of clinical scenarios that would have been necessary to determine appropriateness of pursuing genetic testing. Sampling bias may have been introduced by asking participants to forward the survey to other members of their clinic.

Recommendations

IHRD leaders need to address several challenges based on the findings of this study. Firstly, policies that expedite funding for genetic testing are needed, given that undiagnosed IHRD can be life-threatening. Clinicians also find it difficult to identify and properly counsel relatives of IHRD patients who are potentially at-risk of sudden death. To address this issue, we recommend that clinicians provide their patients with a letter that can be voluntarily shared among relatives to assure that appropriate referral and screening are arranged. Despite studies supporting the use of molecular autopsy following a SAD (Bagnall et al. 2016; Torkamani et al. 2016), proper and consistent retention of post mortem tissue is variable in Canada. We suggest that coroners/medical examiners and clinicians devise policies to ensure that post-mortem tissue is retained in an organized and appropriate manner. Lastly, it was alarming to find that many genetic counselors were not fully satisfied about their relationships with IHRD physicians. Given the vital role that genetic counselors play in an interdisciplinary model, further studies are needed to characterize and address this problem.

Conclusions

This study demonstrates a substantial improvement in our ability to care for IHRD families in Canada. Data from 2010 indicates that not a single SADS victim in the province of British Columbia underwent post-mortem molecular testing (Lim et al. 2010). Patients are now able to access genetic testing at no personal cost, and an increased proportion of SAD victims receive post-mortem molecular evaluation. Our findings should encourage non-experts to consider guideline-directed referral to interdisciplinary clinics (Adler et al. 2016; Gollob et al. 2011; Priori 2013). The newly established Hearts in Rhythm Organization (https://heartsys.org/5/hiro) provides a forum for patient engagement, inter-professional collaboration, and refinement of the interdisciplinary model. We believe that the international community can learn from the Canadian IHRD experience to build toward the common goal of improving the care and ensuring the safety of our patients and their families.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest to declare, and all had full access to the data, contributed to the study, and take responsibility for its integrity.

Human studies and informed consent All procedures followed were in accordance with the ethical standards of the Helsinki Declaration of

1975, as revised in 2000 (5). Consent for participation was presumed based on a willingness to complete the survey, and respondents could remain anonymous at their own discretion.

Animal studies No animal studies were carried out by the authors for this article.

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