Study Design

The Hearts in Rhythm Organization: A Canadian National Cardiogenetics Network

Brianna Davies, MSc, CGC,a Jason D. Roberts, MD,b Rafik Tadros, MD, PhD,c,d Martin S. Green, MD,e Jeffrey S. Healey, MD,f Christopher S. Simpson, MD,g Shubhayan Sanatani, MD,h Christian Steinberg, MD,i Ciorstí M. MacIntyre, MD,j Paul Angaran, MD,k Henry Duff, MD,l Robert Hamilton, MD,m Laura Arbour, MD,n Richard Leather, MD,o Colette Seifer, MD,p Anne Fournier, MD,q Joseph Atallah, MD,t Shane Kimber, MD,s Bhavanesh Makanjee, MD,t Wael Alqarawi, MD,e Stephanie Clarke, MSc, CGC, CCGC, Zachary W.M. Laksmi, MD, Karen Gibbs, RN, CCRP,a Vuk Vuksanovic, PhD, Martin Gardner, MD, Mario Talajic, MD, and Andrew D. Krahn, MD1

ABSTRACT

Background: The Hearts in Rhythm Organization (HiRO) is a team of Canadian inherited heart rhythm and cardiomyopathy experts, genetic counsellors, nurses, researchers, patients, and families dedicated to the detection of inherited arrhythmias and cardiomyopathies, provision of best therapies, and protection from the tragedy of sudden cardiac arrest.

Methods: Recently, existing disease-specific registries were merged into the expanded National HiRO Registry, creating a single common data set for patients and families with inherited conditions that put cardiomypathies, Brugada syndrome, and long QT syndrome (LQTS).4 Given that in most of these disorders, symptoms occur in a minority of potentially affected

Received for publication April 16, 2020. Accepted May 23, 2020.

Ethics Statement: The National HiRO Registry has been approved by the University of British Columbia-Providence Health Care (UBC-PHC) Research Ethics Board (H19-01358).

Corresponding author: Dr Andrew D. Krahn, Inherited Heart Rhythm Research, St Paul’s Hospital, 1033 Davie St, Vancouver, British Columbia V6E 1M7, Canada. Tel.: +1-604-682-2344 ext 66863. E-mail: akrahn@mail.ubc.ca

See page 661 for disclosure information.

See page 661 for disclosure information.

Inherited heart rhythm and cardiomyopathy conditions are estimated to affect 1/200 Canadians, with the most common conditions being hypertrophic (HCM) and arrhythmogenic
them at risk for sudden death in Canada. Eligible patients are invited to participate in the registry and optional biobank from 20 specialized cardiogenetics clinics across Canada.

**Results:** Currently, there are 4700 participants enrolled in the National HiRO Registry, with an average of 593 participants enrolled annually over the past 5 years. The capacity to enable knowledge translation of research findings is built into HiRO’s organizational infrastructure, with 3 additional working groups (HiRO Clinical Care Committee, HiRO Active Communities Committee, and HiRO Annual Symposium Committee), supporting the organization’s current goals and priorities as set alongside patient partners.

**Conclusion:** The National HiRO Registry aims to be an integrated research platform to which researchers can pose novel research questions leading to a better understanding, detection, and clinical care of those living with inherited heart rhythm and cardiomyopathy conditions and ultimately to prevent sudden cardiac death.

---

individuals (5%-20%), many living with these conditions are unaware of their increased risk of sudden cardiac death (SCD). Ultimately, deaths due to inherited cardiac conditions contribute to a proportion of the approximately 30,000 Canadians who die each year due to sudden cardiac arrest, with deaths due an inherited cause more likely to affect Canadians at a young age. Once detected, treatments for these conditions are often simple, inexpensive, and highly effective at reducing SCD risk. This highlights the importance of detecting at-risk individuals with family screening, and recognition of that risk leading to expert directed prevention strategies.

The Hearts in Rhythm Organization (HiRO, pronounced hero, [https://heartsinrhythm.ca](https://heartsinrhythm.ca)) is a team of Canadian inherited heart rhythm and cardiomyopathy experts, genetic counsellors, nurses, researchers, patients, and families dedicated to improving the awareness and detection of inherited heart rhythm disorders and cardiomyopathies. This organization was founded by the Canadian Genetic Heart Rhythm group, an existing collaboration of Canadian clinician-investigators working together on 3 national research registries, including the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER),[9-12] the Canadian Arhythmogenic Right Ventricular Cardiomyopathy (ARVC) Registry,[13] and the National Long QT Syndrome Registry (LQTS).[14-16] In 2016, this group of investigators expanded their annual research meeting to include knowledge users, extending invitations to health care professionals and trainees from Canada’s inherited heart rhythm and cardiomyopathy clinics, as well as patients and families living with these disorders. HiRO has since grown into a comprehensive national team, integrating clinical excellence, research, education, and patient engagement to identify genetic causes of SCD and devise effective screening and prevention systems. The vision for HiRO is to set the standard for excellence in care of inherited heart conditions (Fig. 1).
Investigators requesting stored biobank samples for genetic studies will be solicited to return genetic data for inclusion in the HiRO Registry. Over time, the HiRO Registry aims to generate a genomic sequencing databank for future studies as an alternative to using stored samples.

Novel genetic variants identified as part of a study using HiRO biobank samples will be classified by the study team according to the 2015 American College of Medical Genetics and Association for Molecular Pathology standards and guidelines for the interpretation of sequence variants. Any variant classified as pathogenic or likely pathogenic in a gene associated with an inherited heart rhythm or cardiomyopathy condition will be returned to local investigators to be shared with the study participant. An ethics board approved process for results disclosure is in place. Incidental or secondary genetic findings not related to

| Figure 1. The Hearts in Rhythm Organization (HiRO) vision, mission, and goals. SADS, sudden arrhythmogenic death syndrome; SUDS, sudden unexplained death syndrome. |

| Goals: |
| --- |
| 1. To ensure high-quality, standardized care for inherited heart condition patients and families across Canada, measured by: |
| a. The number of multidisciplinary clinics across Canada (minimum requirement: cardiologist and genetic counsellor) |
| b. The resources and services provided by clinics |
| c. The number of patients and family members seen in those clinics |
| d. The number of clinics with embedded research involvement (currently 20) |
| 2. To facilitate collaborative research, and engage patients and families in the process, measured by: |
| a. The number of patients and family members enrolled in research studies across Canada |
| b. The successful operation of a patient advisory council |
| c. The creation of a single common dataset for all patients and families at risk for sudden death (5-year goal: capture >90% of eligible patients seen in HiRO clinics) |
| d. The proportion of studies that include patient and family input and perspective (target 80% at 5 years) |
| 3. To translate research to the healthcare system and general public, measured by: |
| a. The number of visits per year to the HiRO website and social media sites |
| b. The involvement of HiRO members in policy and guideline development |
| 4. To prevent sudden death from inherited arrhythmias, measured by: |
| a. Development of a national SUDS/SADS detection surveillance system using clinical data sources and public/social media reports |
| b. Link reported deaths to an ethical communication process to ensure family engagement in HiRO |
| c. Link HiRO members with integration of pathology and coroner services for active engagement of families after sudden death to deliver evaluation and prevention measures |
| d. Sudden death event rate change over time: develop accurate incidence measures and compare over time |
| 5. To create a value proposition for volunteers so that they are contributing to a bigger, better impact in solving the health problem of inherited heart conditions. |
cardiac health are not returned to participants. A genetic counsellor is available as part of the HiRO research team to facilitate in conveying results of future studies using HiRO samples.

Data collection

Following the informed consent process, a core baseline dataset is collected for all National HiRO Registry participants, including clinical demographics and health history, family history, clinical genetic testing results, and a list of cardiac testing performed. A baseline electrocardiogram (ECG) is also collected, with a preferred XML file format. If available, the variant call files or binary alignment map files are requested from the clinical genetic testing laboratory for inclusion in the registry. This allows clinical genetic testing results to be reanalyzed over time. Each participant is assigned a working diagnosis and strength according to study specific definitions (Table 2). This core data set was developed with the primary goal of facilitating case finding for future research studies (Supplemental Appendix S2).

A more expansive data set, including results of clinical cardiac investigations, medication history, disease-specific variables, and ongoing follow-up data, is collected for cases that meet active substudy inclusion criteria (Fig. 4). Currently, active substudies include the existing CASPER, National ARVC Registry, National LQTS Registry as well as the newly created National Brugada Registry. Inclusion criteria for each of these substudy registries can be found in Table 3. All CASPER substudy participants with an unexplained cardiac arrest whose underlying etiology remains unexplained after systematic clinical evaluation have case data included in the “Role of Electrophysiology Testing in Survivors of Unexplained Cardiac Arrest” (EPS ARREST) registry (clinicaltrials.gov: NCT03079414), evaluating the role of the invasive electrophysiology study in this patient population. Funding to create a National HCM Registry and Biobank has been recently obtained and will be available as of April 2020. In addition to the current HiRO Registry enrolling sites, the HCM registry and Biobank will also include specialized HCM clinics.

The National HiRO Registry uses a custom research data gathering, management, and reporting system known as Pedigree Pro (PDG) to facilitate electronic data capture, generate reports, and track biobank samples for all enrolled participants. PDG is entirely web-based and accessed online through a virtual private cloud server hosted on Canada’s installation of Amazon Web Service. No personal identifying information is included in the data system, with all documents deidentified by the site research coordinator before being uploaded into the data system. Cases entered in the HiRO Registry are assigned a unique study identifier that is recorded alongside the participant’s name on a master list decoder sheet (.ods file), with all family cases enrolled across Canada linked via an assigned family identifier. PDG offers investigator sites the ability to display and search identified data contained on the master decoder sheet by loading the master decoder sheet into the PDG interface. The data system can read information contained on the file and allow an investigator site user to search the system by patient name without the personal information.

Table 1. National Hearts in Rhythm Organization (HiRO) Registry inclusion and exclusion criteria

| **HiRO Registry inclusion criteria** | **HiRO Registry exclusion criteria** |
|-------------------------------------|-------------------------------------|
| **Inherited arrhythmias (IA):**  
  long QT syndrome (LQT), short QT syndrome (SQ),  
  catecholaminergic polymorphic ventricular tachycardia (CPVT),  
  Brugada (BrS),  
  arrhythmogenic right ventricular cardiomyopathy (ARVC), familial cardiac conduction disease (FCCD) | Known sarcoidosis  
  Mitral valve prolapse unless unexplained cardiac arrest or syncope with documented PMVT  
  Heart failure/nonfamilial dilated cardiomyopathy without a positive family history of affected FDRs or SDRs  
  Aortopathies including Marfan syndrome, Ehlers Danlos, familial thoracic aortic aneurysm, and dissection  
  Neuromuscular disease  
  Familial hypercholesterolemia |
| **Inherited cardiomyopathies (ICM):**  
  hypertrophic cardiomyopathy (HCM), Mendelian dilated cardiomyopathy (DCM) including lamin and phospholambin (LMNA and PLN), and left ventricular noncompaction (LVNC) |  |
| **Unexplained cardiac arrest syndromes:** including early repolarization (ER), idiopathic ventricular fibrillation (IVF), short coupled IVF (SCIF), polymorphic ventricular tachycardia not otherwise diagnosed (PMVT, NYD), sudden arrhythmic death syndromes (SADS), and malignant mitral valve prolapse (MVP) |  |
| **Deceased cases of sudden cardiac death:** suspicious for an inherited arrhythmia cardiomyopathy |  |
| **Carriers of a pathogenic or likely-pathogenic variant in an IA- or ICM-related gene not otherwise meeting criteria** |  |
| **Unaffected first- and second-degree relatives of anyone meeting the above criteria** |  |

FDR, first-degree relative; SDR, second-degree relative.
identifiers of the participants being compromised. However, this information is not included in the data system and does not leave the investigator’s research office. Each biobank sample is also coded with a unique barcode, which is scanned directly into the system, linking the sample to the case data in addition to tracking the sample’s location. Participating research investigator centres can access data and generate reports for their local participants. Access to the entire HiRO data system is restricted to the HiRO coordinating centre and the HiRO steering committee.

In addition to online data entry, PDG supports the upload of clinical documents in multiple file formats, allowing for diagnostic tests to be uploaded directly into the system. This enables a core lab approach to test interpretation, with cardiac test results being entered in the data system by study team members not involved in the clinical care of the participant. Custom tools for online test reading, such as electronic calipers for ECG reading, are built-in directly to PDG. Furthermore, the data system allows the upload of file formats that contain certain variables stored as metadata, including ECGs as XML files and echocardiogram or magnetic resonance imaging files as DICOM images. When these files are uploaded to PDG, any data variables collected in the National HiRO Registry are extracted from metadata and automatically populated, eliminating the need for manual data entry. Furthermore, ECGs as XML files have the advantage of automated, client-side deidentification, removing the need for manual deidentification before data system upload.

**HiRO organizational structure**

Overseen by the HiRO Executive Committee, HiRO’s organizational structure is currently composed of 4 multidisciplinary working groups, which align with the organizations current goals and priorities as set alongside HiRO patient partners (Fig. 5). These working groups are supported by the HiRO Coordinating Centre, providing infrastructure support by organizing meetings, facilitating communication between groups, and overseeing the HiRO website and social media accounts (https://heartsinrhythm.ca, @HeartsInRhythm).

**HiRO Research Committee: The National HiRO Registry.** The HiRO Research Committee’s primary mandate is to oversee design, recruitment, data collection, and study proposal review for the National HiRO Registry. The recent combination of the existing CASPER, ARVC, LQTS national registries and novel Brugada registry into 1 umbrella registry will allow for improved resource utilization, more efficient knowledge translation efforts, and a better capacity to answer novel research questions, particularly for genetic conditions in which phenotypes may vary. Overall, the National HiRO Registry aims to involve a majority of Canadian inherited heart rhythm and cardiomyopathy patients in clinical research, to develop a large case registry of participants at risk of SCD due to genetic conditions, as well as their unaffected first-degree relatives. The primary study objectives of the National HiRO Registry are to:

(a) Better characterize the natural history and disease progression of inherited heart rhythm and cardiomyopathy patients by identifying cardiovascular and genetic risk factors for life-threatening arrhythmia.

(b) Establish genotype-phenotype correlations to compare cases with known disease-causing genetic variants, evaluate novel gene modifiers, and discover genetic mechanisms of disease by harnessing stored biobank samples.

(c) Develop risk model outputs and surveillance systems to prevent SCD from inherited heart rhythm and cardiomyopathy conditions.

(d) Develop new care pathways, including improved guidance for prevention and treatment of inherited heart rhythm and cardiomyopathy conditions in addition to facilitating knowledge translation.

**HiRO Clinical Care Committee.** The HiRO Clinical Care Committee is composed of cardiac genetic counsellors, nurses, physicians, and patient/family partners working together to standardize and improve delivery of care across provinces for those living with inherited heart rhythm and cardiomyopathy conditions. A primary goal of the clinical care committee is to
| Condition | Strength = Definite | Strength = Probable | Strength = Possible |
|-----------|---------------------|---------------------|---------------------|
| LQTS | QTc ≤ 360 ms and one or more of: 1. pathogenic variant 2. family history of SQTS 3. family history of sudden death < 40 y 4. Survival of VT/VF in the absence of heart disease | QTc ≤ 360 ms and one or more of: 1. pathogenic variant 2. family history of SQTS 3. family history of sudden death < 40 y 4. Survival of VT/VF in the absence of heart disease | Unequivocal pathogenic variant carrier with a QTc ≥ 360 ms |
| Acquired LQTS (aLQTS) | QTc ≤ 360 ms and one or more of: 1. pathogenic variant 2. family history of SQTS 3. family history of sudden death < 40 y 4. Survival of VT/VF in the absence of heart disease | QTc ≤ 360 ms and one or more of: 1. pathogenic variant 2. family history of SQTS 3. family history of sudden death < 40 y 4. Survival of VT/VF in the absence of heart disease | Unequivocal pathogenic variant carrier with a QTc ≥ 360 ms |
| BrS7 | J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a 12-lead ECG | SCD victim with a negative autopsy and medical chart review, with a previous ECG demonstrating J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a 12-lead ECG | No |
| CPVT7 | Short-coupled PVCs (RR < 350 ms) triggering polymorphic VT/VF, where other known electrical and myocardial diseases have been excluded | Resuscitated ventricular fibrillation and documented recurrent short-coupled PVCs (< 350 ms) without demonstration of PVC-triggered VT/VF, where other known electrical and myocardial diseases have been excluded | No |
| SQTS | QTc < 330 ms | QTc < 360 ms and one or more of: 1. pathogenic variant 2. family history of SQTS 3. family history of sudden death < 40 y 4. Survival of VT/VF in the absence of heart disease | Unequivocal pathogenic variant carrier with a QTc ≥ 360 ms |
| ERS7 | J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a 12-lead ECG | SCD victim with a negative autopsy and medical chart review, with a previous ECG demonstrating J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a 12-lead ECG | No |
| SCVF (Steinberg) | Short-coupled PVCs (RR < 350 ms) triggering polymorphic VT/VF, where other known electrical and myocardial diseases have been excluded | Resuscitated ventricular fibrillation and documented recurrent short-coupled PVCs (< 350 ms) without demonstration of PVC-triggered VT/VF, where other known electrical and myocardial diseases have been excluded | No |
| UCA/IVF7,20,21 | Resuscitated cardiac arrest from a shockable rhythm, where known etiologies have been excluded, including cardiac imaging, stress/epinephrine, and procainamide testing | Resuscitated cardiac arrest from a shockable rhythm, where known etiologies have been partially excluded | No |
| SADS | Sudden cardiac death with negative etiology and normal autopsy including cardiac pathology expertise, not otherwise fulfilling diagnostic criteria of specific syndromes | Sudden cardiac death with negative etiology and normal autopsy including cardiac pathology expertise, not otherwise fulfilling diagnostic criteria of specific syndromes | Sudden cardiac death below age 40 in an otherwise healthy individual with incomplete postmortem assessment (autopsy and toxicology) |
| Polymorphic VT | Syncope with documented polymorphic VT without cardiac arrest, where known etiologies have been excluded | Syncope with documented polymorphic VT without cardiac arrest, where known etiologies have been excluded | No |
| Strength = Definite                                                                 | Strength = Probable                                                                 | Strength = Possible                                                                 |
|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| **HCM**<sup>22</sup> Wall thickness ≥ 15 mm (z-score ≥ 2 in children) in 1 or more LV myocardial segments that is not explained solely by loading conditions (eg, SBP > 160), excluding isolated basal septal hypertrophy in the elderly and/or Wall thickness ≥ 13 mm in first-degree relatives of patients with definite HCM or with a pathogenic variant | Wall thickness ≥ 15 mm (z-score ≥ 2 in children) in 1 or more LV myocardial segments that is not explained solely by loading conditions (eg, SBP > 160), excluding isolated basal septal hypertrophy in the elderly and/or Wall thickness ≥ 13 mm in first-degree relatives of patients with definite HCM or with a pathogenic variant |
| Wall thickness ≥ 13 mm in one or more LV myocardial segments that is not explained solely by loading conditions, coronary artery disease, or a recent cardiac arrest | NA                                                                                | NA                                                                                |
| **DCM**                                                                            | LV systolic dysfunction (LVEF < 50%) AND enlargement, that is not explained by abnormal loading conditions, coronary artery disease, or a recent cardiac arrest | NA                                                                                | NA                                                                                |
| **ARVC**<sup>23</sup> Task Force criteria: 2 major or 1 major and 2 minor criteria or 4 minor from different categories | Task Force criteria: 1 major and 1 minor or 3 minor criteria from different categories | Task Force criteria: 1 major or 2 minor criteria from different categories |
| **LYNC**                                                                           | LYNC diagnosed by TTE or CMR                                                      | NA                                                                                | NA                                                                                |
| **UCM**                                                                            | Unclassified cardiomyopathy: presence of cardiomyopathy not fulfilling diagnostic criteria for the 4 other entities, eg, presence of significant fibrosis on magnetic resonance. Describe clinical findings in comments | UCA/SCD with a pathogenic or likely pathogenic variant in a cardiomyopathy gene but no cardiomyopathy phenotype | NA                                                                                |
| **Myocarditis**<sup>24,25</sup> Endomyocardial biopsy-confirmed myocarditis (Dallas criteria) | Clinically suspected myocarditis according to published criteria including CMR evidence, in the absence of an endomyocardial biopsy | Clinically suspected myocarditis according to published criteria in the absence of cardiac magnetic resonance imaging and endomyocardial biopsy |
| **Coronary spasm**<sup>26</sup> Evidence of angina in the absence of fixed coronary artery stenosis ≥ 50% AND Transient ischemic ECG changes during the spontaneous episodes and/or a positive acetylcholine/ergonovine test showing evidence of > 90% coronary vasoconstriction | Polymorphic VT/VF in the absence of fixed coronary artery stenosis ≥ 50% or another etiology AND a positive acetylcholine/ergonovine test showing evidence of > 90% coronary vasoconstriction | Evidence of nitrate-responsive angina in the absence of transient ischaemic ECG changes and coronary artery spasm |
| **Malignant mitral valve prolapse syndrome**<sup>6</sup> Presence of bileaflet mitral valve prolapse in a patient with otherwise unexplained polymorphic VT/VF with frequent complex PVCs thought to originate from the papillary muscle | Presence of bileaflet mitral valve prolapse in a patient with otherwise unexplained polymorphic VT/VF in the absence of frequent PVCs originating from the papillary muscle | Presence of single leaflet mitral valve prolapse in a patient with otherwise unexplained polymorphic VT/VF, without myocardial fibrosis or without assessment for myocardial fibrosis |
| **Pause-dependent VT/VF**                                                           | Polymorphic VT/VF in the context of severe bradycardia with recurrent documented PVCs/VT after pauses | NA                                                                                | NA                                                                                |
| **Unaffected/normal**                                                              | Family member negative for known familial mutation with normal cardiac investigations | Family member with normal cardiac investigations where genetic testing is negative in proband or unavailable OR Family member negative for known familial mutation with borderline cardiac investigations not otherwise fulfilling diagnostic criteria | NA                                                                                |
| **Unclassified genetic variant carrier**                                          | Phenotypically unaffected carrier of a pathogenic or likely pathogenic variant not otherwise fitting other diagnostic criteria | Phenotypically unaffected carrier of a variant(s) of unknown significance not otherwise fitting other diagnostic criteria | NA                                                                                |

ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CMR, cardiovascular magnetic resonance imaging; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; ERS, early repolarization syndrome; HCM, hypertrophic cardiomyopathy; IV, intravenous; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; LVNC, left ventricular noncompaction; PVC, premature ventricular contraction; SADS, sudden arrhythmogenic death syndrome; SBP, systemic blood pressure; SCD, sudden cardiac death; SCVF, short coupled ventricular fibrillation; SQTS, short QT syndrome; TTE, transthoracic echocardiogram; UCA, unexplained cardiac arrest; UCM, unclassified cardiomyopathy; VF, ventricular fibrillation; VT, ventricular tachycardia.
practices and structure of different Canadian clinics, as well as the committee publishes a quarterly newsletter sharing the future diagnostic and care guidelines. The HiRO clinic care network is responsible for the planning and facilitation of the annual HiRO Symposium, a 2-day meeting. These symposia focus on group discussions to identify differences in care delivery models between provinces, share recent research findings, and identify patient priorities for future awareness goals and research studies.

Alongside the HiRO Symposium, a public forum is held annually to engage the local community, with patients, health care providers, students, and community media invited to attend. Past public forums have also included partnership with Heart and Stroke to facilitate community cardiopulmonary resuscitation and automated external defibrillator training opportunities.

Discussion

The National HiRO Registry aims to be an integrated research platform to which Canadian researchers can pose novel research questions leading to a better understanding, detection, and clinical care of those living with inherited heart rhythm and cardiomyopathy conditions and ultimately to prevent SCD in unsuspecting healthy individuals. Although there are many international registries collecting data on the similar patient populations, the majority focus only on participants and family members of those who have experienced a cardiac arrest or sudden death (eg, Danish Cardiac Arrest registry), or focus on patients with a single disease seen at large tertiary referral centres (eg, International LQTS Registry). Alongside the HiRO Registry, other international registries collect data on specific disease entities, with national registries focusing on patients with a single disease seen at large tertiary referral centres (eg, International LQTS Registry). Both of these registry designs may represent a more severely affected cohort than the general population. By broadening the inclusion criteria of the National HiRO Registry to include multiple phenotypes, this registry will be better equipped to take a genotype-first approach when designing studies, providing researchers the opportunity to identify the different phenotypes present in patients with similar genetic changes, which is a current limitation in disease-specific registries. This national platform also aims to enable identification of participants for future clinical trials and establish itself as a valuable data source in the international inherited heart rhythm and cardiomyopathy research community. Furthermore, creation of the HiRO working groups brings stakeholders in each province together, allowing for a national concerted effort on awareness initiatives, community advocacy, improved clinical care, and prevention of sudden cardiac arrest.

Knowledge Translation

In addition to primary research objectives, knowledge translation initiatives are a critical component of HiRO to both improve awareness and ensure that research findings are appropriately incorporated into clinical care, benefiting participants and other patients. The capacity to enable knowledge translation of research findings is built into HiRO’s organizational infrastructure (Fig. 5), with the 3 additional HiRO working groups supporting ongoing efforts. An established e-mail network between study investigators...
and clinicians allows complex case discussion, and rapid dissemination of study results from the National HiRO Registry directly to clinical care teams across Canada. Furthermore, HiRO has a strong online presence, with the HiRO website (https://heartsinrhythm.ca), Twitter (@HeartsInRhythm), and Facebook accounts becoming an international resource for staying current on the latest cardiogenetic research. Finally, the annual HiRO Symposium has created an ongoing venue to discuss practice changes based on emerging data.

| National ARVC Registry² | Inclusion criteria | Exclusion criteria |
|-------------------------|--------------------|--------------------|
| 1. 2010 Revised Task Force Criteria positive or borderline patients | 1. Known condition that mimics ARVC (ie, sarcoidosis) |
| 2. Disease causing ARVC pathogenic mutation carriers meeting no additional TFC | 2. Dilated or hypertrophic cardiomyopathy not compatible with an ARVC genetic variant |
| 3. Variants of uncertain significance carriers with at least 1 minor TFC | 3. Brugada syndrome not compatible with an ARVC variant |
| 4. Age ≥ 2 y | 4. Diagnosis of other known inherited condition that predisposes to sudden death |
| 5. First-degree relatives of 2010 revised TFC-positive or TFC-borderline patients | 5. Life expectancy < 1 y |

| National LQTS Registry | Inclusion criteria | Exclusion criteria |
|------------------------|--------------------|--------------------|
| 1. Gene-positive LQTS patients | 1. Genotype- and phenotype-negative LQTS patients without an affected family member |
| 2. Gene-negative LQTS patients with confirmed phenotypic diagnosis (Schwartz score ≥ 4) | |
| 3. Genotype- or phenotype-negative first-degree family members of genotype- and/or phenotype-positive LQTS patients | |

| National Brugada Registry | Inclusion criteria | Exclusion criteria |
|---------------------------|--------------------|--------------------|
| 1. Patients with a definite diagnosis of Brugada syndrome, defined as ST elevation with type 1 morphology ≥ 2 mm in > 1 of the right precordial leads V1-V2 positioned in the 4th, 3rd, or 2nd intercostal spaces, either spontaneously or after provocation drug test with IV class 1 drugs or during fever | 1. Patients with a type 2 Brugada pattern that does not convert to a type 1 morphology after a provocation drug challenge or in whom a provocation challenge is not performed |
| 2. First-degree family members of those with a definite diagnosis of Brugada syndrome | |
| 3. Sudden death victims with a pathogenic variant in SCN5A leading to decreased Na₃.1.5 function identified on molecular autopsy | |
MacEwing, Darrell and Margaret Porubanec, Robin Thay, and Vickie Pynn for their guidance, support, and partnership.

**Funding Sources**

The study is supported by the Canadian Institutes of Health Research (Hearts in Rhythm Organization, A.D.K., Principal Investigator, RN380020-406814; HCM registry and biobank, R.T., Principal Investigator, RN402587-428321). A.D.K. receives support from the Sauder Family and Heart and Stroke Foundation Chair in Cardiology (Vancouver, BC), the Paul Brunes Chair in Heart Rhythm Disorders (Vancouver, BC), the Paul Albrechtsen Foundation (Winnipeg, MB), the Thay Long QT Syndrome Fund (Edmonton, AB), and Darrell and Margaret Porubanec (Kelowna, BC). J.C.-T., R.T., and M.T. receive support from the Philippa and Marvin Carsley Chair (Montreal, QC). R.T. is a Clinical Research Scholar of the Fonds de la Recherche du Québec — Santé.

**Disclosures**

The authors have no conflicts of interest to disclose.

**References**

1. Maron BJ, Gardin JM, Flack JM, et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4111 subjects in the CARDIA study. Circulation 1995;92:785-9.
2. Schwartz PJ, Stramba-Badiale M, Crotti L, et al. Prevalence of the congenital long QT syndrome. Circulation 2009;120:1761.
3. Peters S, Trümmel M, Meyners W. Prevalence of right ventricular dysplasia-cardiomyopathy in a non-referral hospital. Int J Cardiol 2004;97:499-501.
4. Vutthikraivit W, Rattanawong P, Puthapiban P, et al. Worldwide prevalence of Brugada syndrome: a systematic review and meta-analysis. Acta Cardiol Sin 2018;34:267.
5. Fishman GI, Chugh SS, DiMarco JP, et al. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation 2010;122:2335-48.
6. Pümpel CM, Porter B, Kirsh JA, et al. Scope and nature of sudden cardiac death before age 40 in Ontario: a report from the cardiac death advisory committee of the office of the chief coroner. Heart Rhythm 2013;10:517-23.
7. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932-63.
8. Janzen ML, Cheung C, Sanatani S, et al. Cost analysis of patients referred for inherited heart rhythm disorder evaluation. Can J Cardiol 2017;33:814-21.
9. Kranz AD, Healey JS, Chauhan V, et al. Systematic assessment of patient with unexplained cardiac arrest: Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER). Circulation 2009;120:278-85.
10. Steinberg C, Padfield GJ, Champagne J, et al. Cardiac abnormalities in first-degree relatives of unexplained cardiac arrest victims: a report from...
the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry. Circ Arrhythm Electrophysiol 2016;9:e004274.

11. Herman AR, Cheung C, Gerull B, et al. Outcome of apparently unexplained cardiac arrest: results from investigation and follow-up of the prospective cardiac arrest survivors with preserved ejection fraction registry. Circ Arrhythm Electrophysiol 2016;9:e003619.

12. Mellor G, Laksman ZW, Tadros R, et al. Genetic testing in the evaluation of unexplained cardiac arrest: from the CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry). Circ Cardiovasc Genet 2017;10:e001686.

13. Krahn AD, Healey JS, Gerull B, et al. The Canadian arrhythmogenic right ventricular cardiomyopathy registry: rationale, design, and preliminary recruitment. Can J Cardiol 2016;32:1396-401.

14. Roberts JD, Krahn AD, Ackerman MJ, et al. Loss-of-function KCNE2 variants: true monogenic culprits of long-QT syndrome or proarrhythmic variants requiring secondary provocation? Circ Arrhythm Electrophysiol 2017;10:e005282.

15. Mellor GJ, Panwar P, Lee AK, et al. Type 8 long QT syndrome: pathogenic variants in CACNA1C-encoded Cav1.2 cluster in STAC protein binding site. Europace 2019;21:1725-32.

16. Roberts JD, Asaki SY, Mazzanti A, et al. An international multi-center evaluation of type 5 long QT syndrome: a low penetrant primary arrhythmic condition. Circulation 2020;141:429-39.

17. The Hearts in Rhythm Organization Website. "Research Team." Available at: https://hiro.heartsinrhythm.ca/research_team. Accessed January 30, 2020.

18. Roberts JD, Gollob MH, Young C, et al. Bundle branch re-entrant ventricular tachycardia: novel genetic mechanisms in a life-threatening arrhythmia. JACC Clin Electrophysiol 2017;3:276-88.

19. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-23.

20. Somani R, Krahn AD, Healey JS, et al. Procarcinamide infusion in the evaluation of unexplained cardiac arrest: from the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER). Heart Rhythm 2014;11:1047-54.

21. Krahn AD, Healey JS, Chauhan VS, et al. Epinephrine infusion in the evaluation of unexplained cardiac arrest and familial sudden death: from the cardiac arrest survivors with preserved ejection fraction registry. Circ Arrhythm Electrophysiol 2012;5:933-40.

22. Authors/Task Force Members, Elliott PM, Anastasakos A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.

23. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533-41.

24. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636-48.

25. Friedrich MG, Sechtem U, Schul-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. J Am Coll Cardiol 2009;53:1475-87.

26. Beltrame JF, Crea F, Kaski JC, et al. Coronary Vasomotion Disorders International Study Group (COVADIS); international standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2017;38:2565-8.

27. Sriram CS, Syed FF, Ferguson ME, et al. Malignant bilealet mitral valve prolapse syndrome in patients with otherwise idiopathic out-of-hospital cardiac arrest. J Am Coll Cardiol 2013;62:222-30.

28. The Hearts in Rhythm Organization Website. "Find a Clinic." Available at: https://hiro.heartsinrhythm.ca/find_a_clinic. Accessed January 30, 2020.

29. Cranston L. Improving Access to Inherited Heart Rhythm Disorder Experts Through eConsult: Innovation New Programs in Canada. EP Lab Digest. Available at: https://www.eplabdigest.com/improving-access-inherited-heart-rhythm-disorder-experts-through-consult-innovative-new-programs-canada. Accessed January 30, 2020.

30. The Hearts in Rhythm Organization Website. “Toolkit.” Available at: https://hiro.heartsinrhythm.ca/toolkit. Accessed January 30, 2020.

31. Paratz ED, Rowsell L, Zentner D, et al. Cardiac arrest and sudden cardiac death registries: a systematic review of global coverage. Open Heart 2020;7:e001195.

Supplementary Material

To access the supplementary material accompanying this article, visit CJC Open at https://www.cjcoopen.ca and at https://doi.org/10.1016/j.cjco.2020.05.006.