

Clinical Practice Updates

Canadian Cardiovascular Society Clinical Practice Update on Cardiogenetic Testing

Melanie Care, MSc, (Co-chair),^{a,b} Laura Arbour, MD,^{c,d} Liam R. Brunham, MD, PhD,^{c,e,f}
Susan Christian, MSc, PhD,^g Johannie Gagnon, MSc,^h Robert A. Hegele, MD,^{i,j}
Rebekah Jobling, MD,^{k,l,m} Gavin Y. Oudit, MD, PhD,^{n,o} Thomas M. Roston, MD, PhD,^{p,q}
Laura Zahavich, MSc,^{b,r,s} and Zachary Laksman, MD, MSc, (Co-chair)^t

^a Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada; ^b Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada; ^c Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada; ^d Division of Medical Sciences, University of Victoria, Victoria, British Columbia, Canada; ^e Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; ^f Centre for Heart Lung Innovation, University of British Columbia and Providence Research, St Paul's Hospital, Vancouver, British Columbia, Canada; ^g Department of Medical Genetics, University of Alberta, Edmonton, Alberta, Canada; ^h Cardiovascular Genetics Centre, Montreal Heart Institute, Montreal, Quebec, Canada; ⁱ Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada; ^j Robarts Research Institute, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada; ^k Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, Ontario, Canada; ^l Genome Diagnostics, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada; ^m Cardiac Genome Clinic, Ted Rogers Centre for Heart Research, Toronto, Ontario, Canada and The Hospital for Sick Children, Toronto, Ontario, Canada; ⁿ Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; ^o Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada; ^p Division of Cardiology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; ^q Centre for Cardiovascular Innovation University of British Columbia Vancouver, British Columbia, Canada; ^r Division of Cardiology, The Hospital for Sick Children, Toronto, Ontario, Canada; ^s Department of Genetic Counselling, The Hospital for Sick Children, Toronto, Ontario, Canada; ^t Center for Heart Lung Innovation, Department of Medicine, Division of Cardiology, School of Biomedical Engineering, University of British Columbia, Vancouver, British Columbia, Canada

ABSTRACT

This Canadian Cardiovascular Society clinical practice update provides essential guidance on integrating genetic testing into clinical care for inherited cardiovascular conditions, including primary arrhythmias, cardiomyopathies, aortopathies, familial hypercholesterolemia, and congenital heart diseases. Genetic testing for these conditions is crucial for early detection, risk stratification, and management, and significantly influences patient and family outcomes, particularly regarding sudden cardiac death risk. Historically managed within specialized genetics or cardiology clinics, growing demand and limited resources necessitate evolving care pathways for broader integration into general practice. This update outlines foundational steps such as establishing regional cardiogenetic expertise networks, enhancing genetics literacy among providers, and clarifying

RÉSUMÉ

Cette mise à jour de pratique clinique de la Société cardiovasculaire du Canada fournit des conseils essentiels pour intégrer les tests génétiques aux soins cliniques des maladies cardiovasculaires héréditaires, notamment les arythmies primaires, les cardiomyopathies, les aortopathies, l'hypercholestérolémie familiale et les maladies cardiaques congénitales. Les tests génétiques sont essentiels en présence de ces affections, pour les dépister précocement, stratifier le risque et les prendre en charge. Ils influent considérablement sur l'issue pour le patient et sa famille, particulièrement en ce qui concerne le risque de mort subite d'origine cardiaque. Ces tests étaient jusqu'à alors offerts dans les cliniques spécialisées en génétique ou en cardiologie, mais la demande croissante et les ressources limitées nécessitent un changement dans le parcours de soins et une

Keywords: cardiogenetics; genetic; inherited; sequencing; arrhythmia; cardiomyopathy

Corresponding author: Dr Zachary Laksman, Department of Medicine and the School of Biomedical Engineering, University of British Columbia, Rm. 220 – 1033 Davie Street, Vancouver, British Columbia V6E 1M7, Canada. Tel.: 604-806-8256.

E-mail: ZLaksman@mail.ubc.ca

 @GOuditResearch, @DrLaksman

The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of interdisciplinary experts on this topic. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources.

Received for publication July 4, 2025. Accepted August 27, 2025.

genetic testing indications and methodologies. It critically examines various clinical care models—traditional medical genetics clinics, multidisciplinary specialty clinics, mainstreaming approaches, and hub-and-spoke models—highlighting their strengths and barriers within the Canadian health care context. Key implementation challenges, including variant interpretation, secondary findings, informed consent complexities, and cascade testing barriers are addressed with practical recommendations for clinicians, genetic counsellors, and health care systems. Furthermore, this document emphasizes strategic planning to effectively manage increasing cardiogenetic testing demands, advocates for increased professional training, equitable resource allocation, national standardization, and policy frameworks. By detailing actionable strategies and promoting collaborative interdisciplinary networks, this update supports clinicians and health care administrators in incorporating cardiogenetic testing into routine cardiovascular care, thereby enhancing clinical outcomes and equity across Canada.

intégration plus large de ces tests dans la pratique générale. La mise à jour souligne les étapes fondamentales de cette intégration, comme la mise en place de réseaux régionaux d'expertise en cardiogénétique, l'amélioration des compétences en génétique des professionnels de la santé et la clarification des indications et des méthodologies pour les tests génétiques. Elle examine de manière critique divers modèles de soins cliniques, notamment les cliniques de génétique médicale traditionnelles, les cliniques spécialisées multidisciplinaires, les stratégies d'intégration et les modèles dits en étoile (« hub-and-spoke ») où des centres secondaires s'organisent autour d'un centre principal, pour souligner leurs avantages et leurs inconvénients dans le contexte des soins de santé canadiens. Les principaux défis de mise en œuvre, notamment l'interprétation des variants, les résultats secondaires, les difficultés liées à l'obtention du consentement éclairé et les obstacles aux tests génétiques familiaux, y sont abordés et des recommandations pratiques sont formulées à l'intention des cliniciens, des conseillers en génétique et des systèmes de soins de santé. Ce document met également l'accent sur la planification stratégique nécessaire à une gestion efficace de la demande croissante en tests cardiogénétiques et plaide en faveur d'une augmentation de la formation professionnelle, d'une distribution équitable des ressources, d'une normalisation à l'échelle nationale et de la mise en place de cadres politiques. En proposant des stratégies concrètes et en promouvant des réseaux interdisciplinaires axés sur la collaboration, cette mise à jour aide les cliniciens et les administrateurs de soins de santé à intégrer les tests cardiogénétiques aux soins cardiovasculaires de routine, en vue d'améliorer les résultats et l'équité cliniques partout au Canada.

This Canadian Cardiovascular Society (CCS) clinical practice update is focused on the implementation of genetic testing for inherited cardiovascular conditions (ICVC), including primary arrhythmia disorders (ie, long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia), cardiomyopathies (ie, hypertrophic, dilated, arrhythmogenic, infiltrative), aortopathies, familial hypercholesterolemia, and congenital heart disease. These conditions place individuals and families at risk of morbidity and mortality, and early detection, appropriate management, and risk stratification can improve outcomes. Of particular concern, many of these conditions are associated with an increased risk for sudden death events, even in asymptomatic individuals.¹

The role of genetic testing in the diagnosis and management of ICVC continues to expand thanks to our evolving understanding of genetically mediated heart conditions, and ongoing changes in technology and bioinformatics.^{2,3} Historically in Canada, genetic testing has been managed through medical genetics clinics or specialized cardiology clinics, both of which involve multidisciplinary teams of health care providers including cardiologists, medical geneticists, genetic counsellors, and nurses. However, with growing demands and limited resources, in many regions across Canada use of these models might result in lengthy wait times and/or limited access to cardiogenetic testing.^{4,5} This problem is compounded by the growing indications and increased demand for cardiogenetic testing.⁶⁻¹¹ Although there are international guidelines for test indications, there is a paucity of

resources to support the implementation of cardiogenetic testing in clinical practice, where there are clear opportunities for implementing best practices and quality improvement initiatives, which are imperative to providing comprehensive and equitable care to patients and families.

In this document we emphasize the expansion of access and underscore the crucial need for integrating cardiogenetic testing across various health care services. We simultaneously highlight the complexities involved, and emphasize that ongoing specialized expertise remains essential.^{1,2,6-11} Our primary aim is not to equip cardiologists comprehensively with the intricacies of ICVC and genetic testing. Instead, we provide practical guidance, key considerations, and essential information for clinicians, allied health providers, administrators, and policymakers interested in implementing cardiogenetic testing within their practices or broader health care systems.

Successful integration of cardiogenetic testing into mainstream health care will necessitate innovative strategies for continuous medical education and resource utilization that effectively balance access and demand with evidence-based standards of care. We recognize that specific sections will hold varying relevance for different readers depending on their background, roles, and current stage of implementation. It might therefore be approached modularly, to allow readers to engage with individual sections in any given order, on the basis of specific needs and priorities. Collectively, however, these sections form a cohesive framework and roadmap for initiating and enhancing cardiogenetic testing services:

- **Section 1. Building a foundation:** focused on developing knowledge and fostering professional networks.
- **Section 2. Developing care pathways:** outlines various approaches tailored to differing resource levels and patient needs.
- **Section 3. Genetic testing:** provides detailed insights into available tests, technological advancements, and considerations for special patient populations.
- **Section 4. Informed consent and family care:** ethical considerations and effective communication strategies with patients and their families are discussed.
- **Section 5. Results and follow-up:** the interpretation of test results, handling secondary findings, and appropriate follow-up actions.
- **Section 6. Future planning and policy-making:** highlights strategies and recommendations for sustainable policy development and long-term planning.

1. Building a Foundation

Key messages for physicians and allied health care providers:

- Before routinely incorporating genetic testing into practice, health care providers should consider updating genetics knowledge and literacy (Table 1, Supplemental Appendix S1).
- Proactively establish relationships with regional experts in genetic counselling, medical genetics, cardiology, and cardiogenetics to ensure timely and appropriate patient access to specialized services (Fig. 1, Table 2)
- Understand the clinical indications, benefits, and limitations associated with available genetic testing options (Table 3).

Successful implementation of cardiogenetic testing requires a thoughtful approach to each step in the patient’s journey, including patient triage, test selection, data management, interpretation of reported findings, medical management, family risk assessment, and potential psychosocial and medicolegal implications.² All care providers will have increased exposure and access to cardiogenetic testing and results, and will need to perform individualized needs assessments on the basis of their role in the care pathways being established and within the frameworks outlined herein. Genetic testing can become accessible in general and specialized cardiology practices. For clinicians who are motivated to provide direct access to genetic testing, updated education might be considered via available continuing medical education (CME) activities and/or genetics learning modules that range from basic genetics review courses to more comprehensive, cardiac-specific courses (Table 1). Alternatively, practitioners might choose to leverage relationships with regional experts through informal discussion and/or multi-disciplinary case reviews or gain experience from ongoing medical referrals to those with content expertise.

1.1. Understanding genetic language and testing modalities

Genetics education in undergraduate medical school curricula is limited and is associated with poor recall,

Table 1. Suggested genetics resources for education about general medical and cardiac genetics

Resource	Description
National Human Genome Research Institute. Genomics Education Resource Center (GenomeEd) https://www.genome.gov/GenomeEd	• For medical professionals new to genetics or needing clinical refreshers • Peer-reviewed modules, slide sets, and case studies on topics like genetic testing, inherited diseases, and family history interpretation
AMA Ed Hub: Precision Medicine and Genetics https://edhub.ama-assn.org	• For physicians seeking AMA-accredited genomics CME • Short modules on personalized medicine, genomic testing, and how to interpret results in clinical settings
The Jackson Laboratory - Cardiac Genetics CME https://www.jax.org/education-and-learning	• For cardiologists and primary care providers planning to integrate genetics into cardiovascular care • Free CME/CNE modules using clinical cases covering inherited arrhythmias, cardiomyopathies, and when to refer for genetic testing
AMA Ed Hub - Genomics for Cardiologists https://edhub.ama-assn.org/	• For cardiologists seeking CME in genomics and precision medicine • Short-form modules on when and how to use genetic testing in patients with cardiovascular disease, such as familial hypercholesterolemia, cardiomyopathy, and sudden cardiac death syndromes
European Society of Cardiology. CardioGenetics eLearning https://www.escardio.org/	• Designed for cardiologists • Continuing education modules and webinars on clinical genetics and its role in cardiology

Resources for cardiologists and other health care providers in planning to access and/or incorporate genetic testing into clinical practice.

AMA, American Medical Association; CME, continuing medical education; CNE, continuing nursing education.

representing a barrier to current practicing physicians.¹² Although comprehensive genetics expertise is not a requirement, foundational genetic literacy is strongly encouraged to ensure accurate interpretation and communication of results. (Table 1, Supplemental Appendix S1).

ICVC can range from rare single-gene disorders to multisystemic genetic conditions, and appropriate testing modalities similarly vary from single-gene sequencing to candidate gene panels all the way to whole genome testing. Familiarity with the different platforms, their indications, and the limitations of each is critical to providing cardiac genetics care (Table 3).^{13,14} For an approach to determining the most appropriate genetic test, please refer to section 3.1.

1.2. Establishing cardiovascular genetics networks

As the volume of patients eligible for genetic testing expands and genetic testing becomes more widely available, it is increasingly impractical to have all patients referred to a subspecialty clinic. Therefore, establishing connections to develop a network of cardiogenetics experts with whom to consult will be important (Fig. 1). Resources to help identify regional experts are outlined in Table 2.

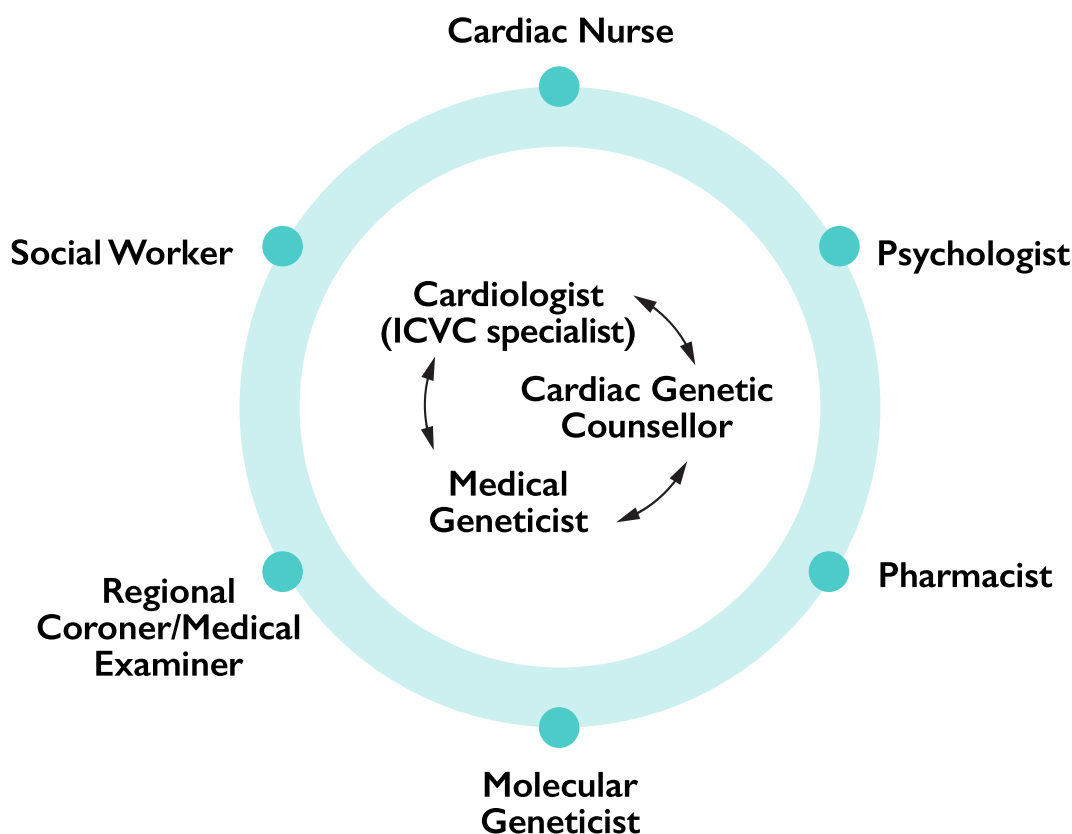


Figure 1. The cardiovascular genetics network. A team of health care providers is important in the care of patients with inherited cardiovascular conditions (ICVC). The core represents clinical specialists with specific expertise and outside, a combination of experts that may be included depending on clinical circumstances. The composition of the core and extended teams should be considered in the context of specific clinical scenarios, clinician expertise, and regional and/or provincial guidance. How clinicians connect with members of their developed networks might vary and could include medical referrals or informal consults and/or discussions.

2. Developing Care Pathways

Key messages for physicians and allied health care providers:

- Optimal patient pathways are informed by test indication and resource availability (Fig. 2).
- Indications for a referral to a regional subspecialist include but are not limited to patients with complex clinical indications or positive or inconclusive genetic testing results (Fig. 3).
- Multiple care models exist (Table 4) and integrating a number of elements from different models might be required to accommodate local resources, geographic constraints, and patient- and disease-specific characteristics of ICVC.

Regional heterogeneity in resource allocation and management is a current barrier to pathway standardization, and thus multiple models of care are outlined in the following sections, along with their strengths and drawbacks. For example, although published guidelines suggest that genetic counselling is required, equitable and timely access to cardiogenetics experts remains a challenge.⁶⁻¹¹ In Canada, despite a single-payer system, current clinic and referral models differ across and within provinces.⁴ In this section,

various considerations and models of cardiovascular genetics care are reviewed, however, elements of multiple models are likely to be required.

2.1. Medical genetics clinics

Historically cardiac genetic testing has been initiated via referral to a medical genetics clinics, with comprehensive genetics assessment, genetic counselling, and testing occurring separately from other medical specialties.¹⁵ The model's primary advantage lies in its ability to provide comprehensive genetics care through dedicated medical genetics assessment, physical exam, and pre- and post-test counselling. For patients with complex medical issues in whom cardiovascular disease might represent 1 element of a multisystem condition or syndrome, this type of extensive assessment is critical. Comprehensive assessment of families can also be integrated into this model.

This model presents several limitations and faces growing challenges. It has the potential to create long wait times due to high demand for genetic services and a shortage of genetic specialists.¹⁶ This leads to delays in genetic testing for index patients and subsequently in the identification of at-risk family members. This model also separates genetic diagnosis from cardiac diagnostics and treatment. Clinical phenotype is

Table 2. Canadian organizations that provide support in identifying regional experts

Organization	Description
Canadian Association of Genetic Counsellors https://www.cagc-accg.ca/?p=find_a_clinic&sub=canadian_clinics	• An organization representing genetic counsellors in Canada • Offers a searchable directory of genetics clinics across Canada that can be filtered according to province and specialty, including “Cardiac Genetics”
HiRO (Hearts in Rhythm Organization) https://hiro.heartsinrhythm.ca/?p=find_a_clinic&sub=canadian_clinics	• Represents a network of individuals dedicated to improving awareness and understanding of inherited cardiac conditions • Provides a list of cardiac genetics centres and experts across Canada
Canadian Sudden Arrhythmia Death Syndromes Foundation Email: info@sads.ca	• Patient advocacy organization dedicated to supporting individuals and families affected by inherited cardiac rhythm disorders • Can provide guidance on regional experts, specialized clinics, and referring patients and genetic counselling services
GADA (Genetic Aortic Disorders Association Canada) https://www.gadacanada.ca/clinics-across-canada-1	• Patient and provider advocacy for genetic aortic conditions like Marfan syndrome, Loeys-Dietz, and familial thoracic aortic aneurysms • Identify regional experts via patient referral and specialist directories

Within these organizations, cardiologists will be able to identify professionals with whom to build relationships and create the individualized networks that suit their unique needs.

a particularly essential element in the interpretation of cardiac genetic testing, and genetic results are increasingly relevant for management. Having cardiac care and genetic testing in separate silos can lead to fragmented care. Therefore, building strong relationships and data-sharing platforms between genetic specialists and cardiac specialists is critical.

There are strategies to help mitigate the limitations of this model. To meet the needs of large referral volumes, various strategies might be developed, such as the implementation of specialty clinic days, or group- or webinar-based models, virtual care, decision aids, chatbots, and educational videos to support the counselling process.¹⁷⁻²¹ Alternatively, some medical genetics services partner with cardiology clinics to provide genetic counselling staff. Medical geneticists are available for complex variant interpretation and atypical case presentations.

2.2. Multidisciplinary specialty clinics

In a multidisciplinary specialty clinic, patients might receive care from a diverse team of health care professionals embedded within the same service. This team might include cardiovascular medicine specialists, genetic counsellors, medical geneticists, nurses, social workers, psychologists, and/or pharmacists. A collaborative approach ensures that genetics assessment, counselling, and testing are combined with cardiac care and integrated into a comprehensive and holistic

care plan.²²⁻²⁴ Integration of genetic information into a multidisciplinary model might be useful for risk prediction and decision-making surrounding therapies.^{1,3,6,7,10,11} Reproductive risks and testing options can also be addressed concurrently including maternal health implications related to pregnancy and risks to offspring.^{25,26}

The multidisciplinary model poses its own challenges because it tends to be resource-intensive, requires significant time, expert personnel, and infrastructure to effectively manage various components of care. Time constraints might also limit the depth of genetic counselling and education provided. In Canada, geography can pose a significant hurdle, because this often requires patients to travel far distances for in-person assessments or specialized testing, although combining in-person and virtual appointments can improve access.¹⁷

2.3. Mainstreaming

Mainstreaming describes a model of care in which nongenetic specialists integrate genetic testing into their practices.²⁷ This involves initial assessment, consent, and pretest education provided by the patient’s primary care provider or cardiologist. Referral to a medical genetics clinic or multidisciplinary specialty clinic is made for complex patients, management questions, patients with unexpected genetic test results, or those who would benefit from dedicated genetic counselling services to discuss communication of the result with family (Fig. 3).

Substantial research has been conducted to evaluate mainstreamed genetic testing in cancer care. Patient satisfaction is high with the introduction of direct cancer genetic testing and has been shown to significantly reduce wait times for genetic results as well as health care costs.^{28,29} Limited research has been done on the effect of mainstreaming in cardiology, although preliminary results from several studies that included cardiogenetics have shown that this model is generally acceptable to patients and providers, and can markedly reduce wait times.^{30,31}

There are notable challenges to this model, particularly the need to upskill providers. Misinterpretation of genetic test results, or incorrect test selection, can lead to inappropriate management decisions, whereas missed opportunities for genetic testing can lead to delays in diagnosis and appropriate care.^{32,33} Some patients might be eligible for more comprehensive testing or evaluation on the basis of their specific clinical presentation or family history, which could be overlooked. Without additional education and resources, providers might be uncomfortable with assuming the primary responsibility for genetic testing.³² To support patients and providers, educational resources, direct and timely referral processes, access to consultant cardiogenetics experts, and considerations of laboratory availability and partnerships will be paramount.

Mainstreaming is likely best suited to common ICVC where there are clear guidelines for genetic testing indications (ie, familial hypercholesterolemia, cardiomyopathies, aortopathies) whereas patients with complex presentations are likely to be better served by upfront referrals to specialty clinics (Fig. 2). The challenges of this model might also be addressed by proactively establishing professional relationships with cardiogenetics experts (Fig. 1) or by

Table 3. Genetic testing modalities, clinical indications, and limitations

Test method	Description	Example of clinical use	Limitations
Gene panel	NGS of a selected set of genes associated with a specific diagnosis	Suspected monogenic disease with a defined genetic differential diagnosis (ie, familial cardiomyopathy, long QT syndrome, aortopathy, familial hypercholesterolemia)	- Identifies variants only in genes included on the requested panel - Decreased detection of some deletions and duplications within genes; providers are advised to contact laboratories to better understand limits of detection - Unlikely to detect large chromosome anomalies (ie aneuploidy, large genomic multi-gene deletions and/duplications, chromosome rearrangements, etc)
Single-variant testing	Targeted sequencing to evaluate the presence or absence of a specific gene variant	Predictive testing of an unaffected individual when a known disease-causing variant is present in a family member (ie first-degree relative of an individual with an identified single-gene finding)	Does not identify additional genetic conditions that might be contributing to disease
Whole-exome sequencing	NGS of protein-coding regions of the genome (exons only)	Broad genetic differential diagnosis with multisystemic or syndromic features (ie congenital heart disease)	- Incomplete coverage of all exons - Unable to detect intronic variants, potentially resulting in missed diagnosis - Decreased detection of deletions and duplications (might need to be combined with other testing, such as chromosomal microarray)
Whole-genome sequencing	NGS of the entire genetic code including nonprotein coding sequence (exons and introns)	Broad genetic differential diagnosis with multisystemic or syndromic features (ie congenital heart disease)	- Currently, minimal understanding of the implications of intronic variation - Decreased detection of specific types of variants (ie, lengthy triplet repeat expansions, balanced structural rearrangements, low-level mosaic and/or heteroplasmic variants)
Karyotype	Microscopic analysis of chromosomes	Confirmation of clinically suspected aneuploidy (ie, Trisomy 21)	Unable to identify etiology of monogenic disease
Chromosomal microarray	Submicroscopic analysis to identify large multigene deletions and duplications	Broad genetic differential diagnosis with multisystemic or syndromic features (ie, complex congenital heart disease with or without multisystem involvement)	- Unable to diagnose monogenic disease - Limited ability to detect deletions or duplications within genes
Fluorescence <i>in situ</i> hybridization	Submicroscopic analysis of specific and/or targeted chromosome regions	Confirmation of defined microdeletion syndrome (ie, clinical suspicion of 22q11.2 deletion syndrome)	Detects specific alterations within the requested chromosomal region only
Polygenic risk score	Combined analysis of multiple genetic variants across the genome to estimate an individual's genetic predisposition to a specific disease or trait	Identify individuals at higher genetic risk for common conditions likely caused by multiple genetic and environmental factors to enable earlier lifestyle interventions or targeted preventive treatments (ie, coronary artery disease)	- Analyzes only specific, previously-identified variants and does not involve comprehensive sequencing - Cannot identify rare monogenic causes of cardiovascular disease - Remains under investigation and clinically utility remains uncertain

NGS, next-generation sequencing.

considering more formal collaborations such as regional multidisciplinary case review meetings or education rounds.

2.4. Hub-and-spoke model

In collaboration with key providers and systems-level planning, the aforementioned models might be combined and integrated into a hub-and-spoke framework. In this model, the hub represents the health care professionals with disease and domain-specific expertise, and the spokes include primary care, local specialists, and other allied health

professionals in the community who can help facilitate clinical screening, triage, and appropriate follow-up.

For example, local specialists in the spokes identify patients eligible for genetic testing, provide initial genetic assessment and counselling, connect patients with available resources, and order genetic testing for straightforward indications. Complex cases and patients with positive or complicated genetic test results can be referred directly to the hub where specialists can provide expert guidance and recommendations.

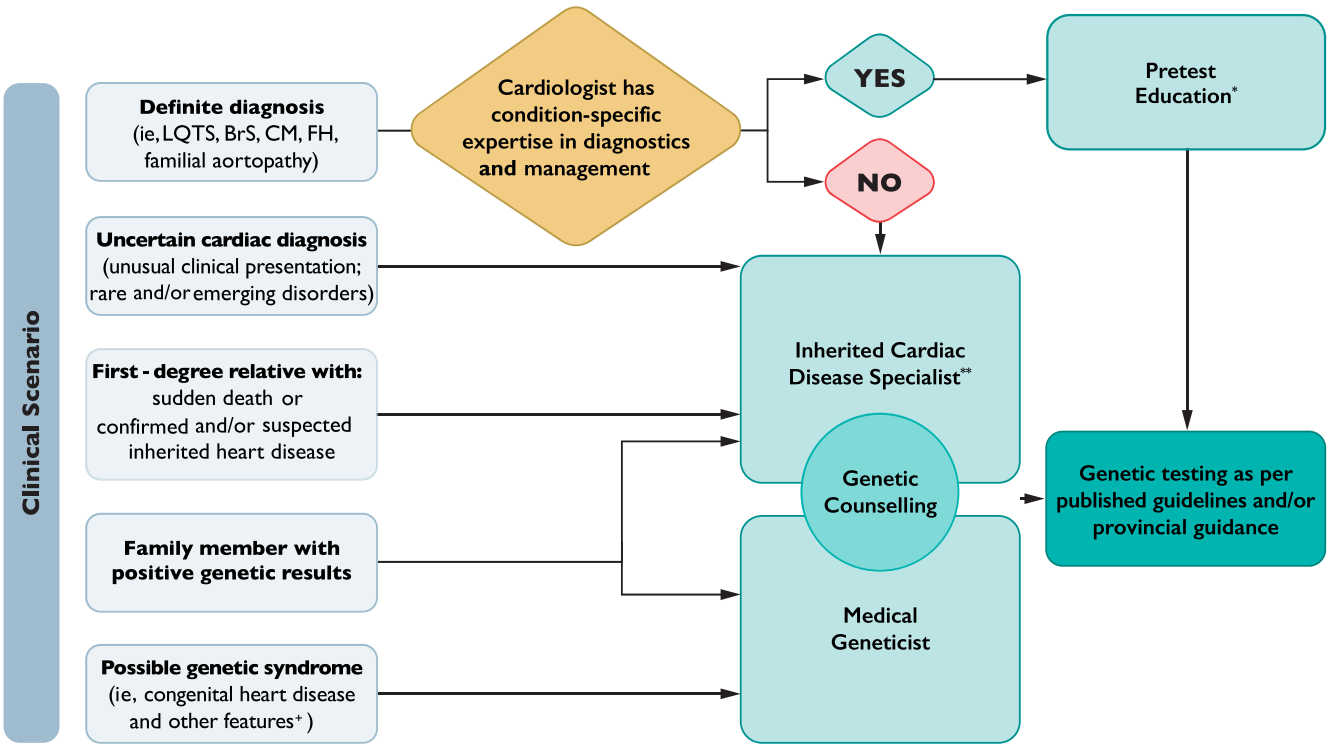


Figure 2. Pathways to genetic testing. This illustration is intended to provide clinicians with a guide to the most appropriate access point to genetic testing for patients, depending on clinical scenario and indication. BrS, Brugada syndrome; CM, cardiomyopathy; FH, familial hypercholesterolemia; LQTS, long QT syndrome. * Published guidelines recommend pretest patient education before genetic testing, which may be provided by any practitioner with knowledge of the associated benefits and limitations and may include in-person discussions, written material, online resources, or a combination of all. ** Specific cardiology subspecialists will depend on the clinical presentation of the patient and could include an inherited arrhythmia clinic or cardiologist with condition-specific expertise (ie, electrophysiologist, heart function specialist, vascular surgeon, endocrinologist, etc). + Might include any combination of dysmorphic features, developmental delay, and multisystem medical issues.

Cardiologists, medical geneticists, genetic counsellors, and other allied health providers in the hub focus on high-risk and complex cases within their areas of expertise. The highly

specialized team within the hub is able to provide clinical assessment, interpret complex genetic results, and create care plans for patients who return to local primary care providers,

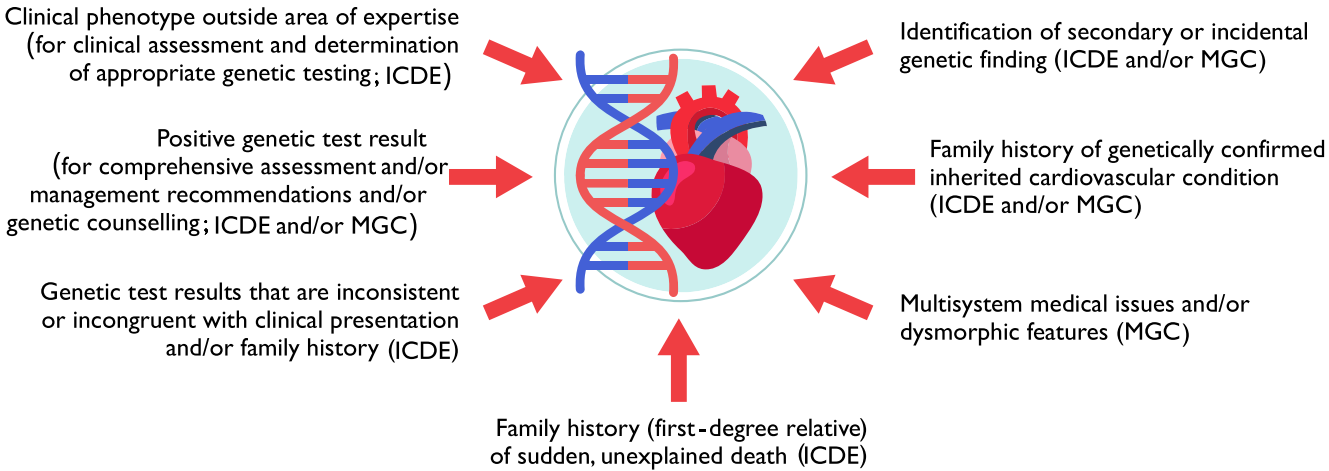


Figure 3. Indications for subspecialist referral. Common scenarios when referral to a subspecialist with expertise in cardiovascular genetics might be considered are illustrated. This is not exhaustive and relies heavily on individual expertise and clinical judgement. ICDE, inherited cardiac disease expert, may include inherited arrhythmia clinic or cardiologist with condition-specific expertise; MGC, medical genetics clinic.

Table 4. Models of cardiogenetics service delivery

Service delivery model	Benefits	Challenges	Example of clinical use	Strategies for implementation
Medical genetics clinic	• Comprehensive medical genetics evaluation, when needed • Coordinated genetics assessment and genetic counselling	• Lengthy wait times • Separation of genetic testing and interpretation from cardiac assessment and/or phenotyping	• Complex congenital heart disease • Multisystem medical issues • Possible syndromic diagnosis (ie, connective tissue disorder) • Preconception and/or family planning • Predictive genetic testing for unaffected family members	• Group or virtual genetic counselling (for straightforward indications) • Focused specialty clinic days • Co-opt genetic counsellors from medical genetics as a bridge between genetics and cardiology clinics
Multidisciplinary inherited heart disease clinic	• Care provided by multiple health care providers with specific expertise in ICVC • Coordinated cardiac diagnosis and/or management and genetic counselling and/or testing • Effective genetic test interpretation in the context of expert cardiac phenotyping	• Requires substantial human health resources • Coordinating schedules, workflows, and responsibilities among numerous specialists • Limited access in geographically remote locations resulting in significant travel	• Assessment for possible ICVC and/or uncertain clinical diagnosis (ie, LQTS, BrS, ARVC, CPVT, etc) • Genetically confirmed ICVC • First-degree relative with clinical and/or genetic ICVC diagnosis • Rare and/or emerging conditions (ie, calcium release deficiency syndrome) • Sudden cardiac death in a first-degree relative	• Identify specialists with relevant expertise across disciplines • Cooperate with all team members to develop scheduling and communication strategies • Work with institution administrators and health ministries to provide appropriate support
Mainstreaming	• Improved access with limited delay • Genetic test interpretation occurs in the context of primary cardiology care	• Limited genetic counselling • Requires some degree of comfort with ICVC and genetics knowledge • Possible misinterpretation of genetic findings • Potential delays for cardiac and/or genetics assessment and genetic counselling with positive or uncertain results	• Clear, nonsyndromic diagnosis (ie, HCM, DCM, FH, non-syndromic aortopathy)	• Consider web- or app-based resources to help with pretest education • Develop relationships with regional ICVC and genetics experts for consultation, as needed • Cooperate with specialty clinics to streamline referral processes for positive or urgent genetic results
Hub-and-spoke	• Ensures best access point depending on indication and complexity • Reduces travel burden by providing local care for routine management and/or surveillance • Avoids duplication of services and/or specialists and expensive infrastructure	• Requires strong infrastructure for communication and data-sharing • Potentially disrupted care because of miscommunication or communication delays	• Could be developed for any and all indications	• Plan and develop regional networks of experts (hubs) and local care providers (spokes) • Work with health authorities to provide global support for infrastructure and network development

ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; FH, familial hypercholesterolemia; HCM, hypertrophic cardiomyopathy; ICVC, inherited cardiovascular conditions; LQTS, long QT syndrome.

specialists, and allied health care providers in the spokes who can provide longitudinal care.

By centralizing specialized cardiology and genetic expertise in a primary hub and connecting them to regional spokes, this model ensures patients benefit from advanced cardiac genetic services, regardless of their geographic location. Because of the necessity of frequent and accurate modes and methods of communication and data sharing, this type of model will require a system-level approach to funding and care planning to ensure integrated health services, and interconnected patient data and management platforms.

3. Genetic Testing

Key messages for physicians and allied health care providers:

- Cardiogenetic test indications are increasingly informed by guidelines and expert consensus documents that are continually updated. Before offering genetic testing, cardiologists should confirm that it is indicated and appropriate on the basis of the clinical scenario and relevant guidelines. Current recommendations are included in [Supplemental Appendix S2](#).
- Cardiogenetic testing should be considered probabilistic, and practitioners can familiarize themselves with test-specific limitations and pitfalls listed in [Tables 3 and 5](#).
- Teams responsible for sudden death investigations should implement a comprehensive and standardized approach that includes consideration of molecular autopsy, and ensure appropriate collection and storage of biological samples whenever possible.

Table 5. Genetic testing strategy according to clinical indication^{2,3,7-11}

Condition	Suggested genetic testing approach*	Rationale
HCM		
Nonsyndromic*	HCM targeted gene panel [†]	Nonsyndromic HCM has a defined phenotype with limited phenotypic overlap and a well defined gene list, which generally includes common phenocopies such as Fabry disease
Syndromic	Consider syndrome-specific panel on the basis of clinical features (ie, Noonan syndrome) vs WES/WGS	HCM in the setting of other multisystem disease can represent various clinical diagnoses and targeted panel testing might result in delayed diagnosis and appropriate management
DCM nonsyndromic	DCM targeted gene panel [†] vs broad cardiomyopathy panel [†]	There is substantial phenotypic and genotypic overlap observed in patients with DCM. Smaller DCM-specific panels might result in missed diagnosis, whereas larger panels might result in increased identification of variants of uncertain significance. Testing strategy should take unique clinical presentation into consideration to ensure coverage of all relevant genes.
ARVC		
Meets task force diagnostic criteria	ARVC targeted gene panel [†] vs broad cardiomyopathy panel	Only a small number of genes are associated with ARVC, as defined by the 2010 Task Force diagnostic criteria. There is increasing evidence for more diverse genetic etiologies of arrhythmogenic cardiomyopathies that affect one or both ventricles.
Arrhythmogenic cardiomyopathy	Broad cardiomyopathy panel	With the exception of a clear ARVC diagnosis that meets 2010 Task Force criteria, broad cardiomyopathy testing should be strongly considered
Other cardiomyopathies; restrictive cardiomyopathy, LVNC	Targeted gene panel (ie, LVNC panel) vs broad cardiomyopathy panel	The genetic contributions to these conditions are not well understood and very few genes have been strongly or definitely associated with disease. In the absence of additional clinical features (ie, left ventricular systolic dysfunction in LVNC), the value of genetic testing should be carefully considered
Brugada syndrome*	Targeted Brugada testing - <i>SCN5A</i> only	<i>SCN5A</i> is the only gene definitely associated with Brugada syndrome, to date.
LQTS		
Unequivocal or borderline diagnosis*	LQTS targeted panel [†]	Targeted genetic testing for clinically confirmed LQTS is relatively high (approximately 75%) and in individuals who are highly suspected to have LQTS, small panel testing is generally suggested
Prolonged QT with other unusual cardiac presentation and/or syndromic features	Broad arrhythmia panel	Rare inherited arrhythmia syndromes might present with prolonged QT, sometimes in addition to other cardiac and noncardiac features. In cases of unusual electrocardiogram findings, broad panel encompassing additional arrhythmia syndrome genes might result in a higher diagnostic yield
		In populations with known high risk of LQTS, targeted testing of known variants that increase risk might be considered first
SQTS*	SQTS targeted panel [†]	SQTS is an extremely rare inherited arrhythmia with a small number of associated genes (Walsh/Adler - SQTS gene curation). Broad panels are likely to identify variants of uncertain significance in genes not relevant to clinical presentation
CPVT*	CPVT targeted panel [†]	CPVT is defined by specific diagnostic criteria and targeted panels now typically include genes that result in phenotypic overlap with relevant inherited arrhythmia syndromes (ie, LQTS). Broad panels are likely to identify variants of uncertain significance in genes not relevant to clinical presentation, but might be considered in cases with atypical features although referral to inherited arrhythmia specialists is suggested in these circumstances

Table 5. Continued.

Condition	Suggested genetic testing approach*	Rationale
Other rare or emerging arrhythmia syndromes (ie, calcium release deficiency syndrome)	Targeted or broad panel testing [†] depending on clinical presentation	Rare and emerging arrhythmia disorders might not be well defined with respect to diagnosis or genetic etiology. Strongly consider referral to subspecialist with expertise in inherited heart disease
Sudden cardiac death		
Survived	Dependent on clinical assessment	In living individuals who experienced an unexplained cardiac arrest, genetic testing should be determined on the basis of clinical assessment and phenotype
Deceased; clear phenotype on autopsy	Phenotype-specific panel [†]	Postmortem genetic testing and interpretation of molecular autopsy is complex. Strongly consider referral to multidisciplinary clinic with expertise in inherited heart disease.
Deceased; unexplained and/or negative autopsy	Broad cardiac (cardiomyopathy and arrhythmia) panel [†]	
FH*	FH targeted panel [†]	Limited causative genes have been identified in FH and negative genetic test results do not exclude a clinical diagnosis. Polygenic factors are also important determinants of cholesterol, but no standardized testing exists to date
Aortopathy*	Thoracic aortic aneurysm and dissection panel [†]	Syndromic causes of aortopathy are easily missed because of variable presentation and reduced penetrance. Therefore, full panel testing including syndromic and nonsyndromic genes should be included for all eligible individuals
CHD	Chromosomal microarray vs CHD gene panel [†] vs WES/WGS	Genetic testing in this population can be diverse and highly phenotype-dependent. Strongly consider consulting with or referring patients to medical genetics clinic Prenatal identification of congenital heart malformation requires medical genetics involvement before decisions about fetal testing
AF	There are currently no recommended genetic tests for AF	For individuals with early-onset AF, especially in the presence of a family history of AF, consider referral to inherited arrhythmia specialist for assessment

In addition to cardiac presentation, clinicians need to consider other potentially relevant medical issues and family history when determining the most appropriate genetic test. In cases of unusual or multisystem presentations, referrals to subspecialists with relevant expertise should be considered.

AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; CHD, congenital heart disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; FH, familial hypercholesterolemia; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; LVNC, left ventricular noncompaction; SQTs, short QT syndrome; WES, whole-exome sequencing; WGS, whole-genome sequencing.

* In instances of clear or unequivocal clinical diagnoses, targeted disease-specific panel testing is the suggested strategy.

[†] Targeted panels should include, at a minimum, all genes assessed to have definitive, strong, or moderate evidence to contribute to stated conditions as evaluated by expert consortia (<https://clinicalgenome.org/>,³⁹ <https://panelapp.genomicsengland.co.uk/>⁴⁰), or in the absence of a related gene curation effort, critical evaluation of available evidence.

For more than 2 decades, the study of genes that contribute to long QT syndrome, aortopathy, cardiomyopathy, hypercholesterolemia, congenital heart disease, and other cardiomyopathy-related conditions has provided clinically relevant information and has become an accepted standard of practice.^{2,34} Although one of the most generalizable indications for genetic testing is to provide the opportunity to facilitate genetic screening in family members of affected individuals, genetic test results are also increasingly important in tailoring medical management. For example, genetic results are recognized to predict the efficacy of β -blocker therapy in patients with long QT syndrome,³⁵ and influence the timing of intervention in patients with arrhythmogenic cardiomyopathies and aortopathies.^{7,11,36} For example, implantable cardioverter-defibrillator placement is recommended sooner in men who carry the *TMEM43* p.Ser358Leu variant because of the presentation of ventricular arrhythmias earlier in the

disease course.³⁶ It is important for clinicians to be aware of specific genetic variants that might be considered higher risk, and potentially require more aggressive management. In circumstances in which relevant therapies are primarily on the basis of clinical phenotype, genetic information can still provide important prognostic information.³⁷

3.1. Genetic test selection

Genetic testing is not always indicated and therefore the first consideration must always be appropriateness of testing on the basis of clinical scenario and relevant guidelines. When eligibility criteria have been met, the specific test selection will then need to be considered. Genetic testing can vary from the sequencing of a single variant or gene in cases of a highly specific clinical diagnosis, to the analysis of the entire genome. Depending on the test method, different types of

	Associated risks	Expert Opinion
Ordering the wrong genetic test	• Delayed diagnosis of hereditary disease due to incorrect test request • False reassurance about genetic risk	• Select testing by following published guidelines and provincial guidance • If unsure, consider consulting with or referring to subspecialist for determination of most appropriate testing
Genetic testing in the absence of associated/relevant phenotype	• Inability to accurately interpret genetic test results, particularly VUS • Misattributed risks associated with VUS (clinicians and patients) • Incidental findings	• Determine appropriate genetic testing in the context of clinical presentation • Avoid shotgun genetic testing strategy • Consider referral to subject matter expert in the setting of equivocal diagnosis or unusual clinical presentations
Testing unaffected family members for a VUS	• Inaccurate risk assessment • False reassurance with negative results • Prematurely discharging at-risk individuals from clinical screening	• Do not offer VUS testing for cardiac risk assessment purposes • Base surveillance recommendations for family members on family history and clinical assessment, not genetic results
Predictive genetic testing without genetic counselling	• Increased patient anxiety • Decisional regret • Maladaptive behaviour post-testing	• Ensure all at-risk family members are referred for genetic counselling prior to predictive genetic testing

Figure 4. Genetic testing pitfalls. Knowing the correct testing strategy is important when incorporating genetic testing into practice. Outlined are some common mistakes and how to avoid them. VUS, variant of uncertain significance.

genomic variation will or will not be detected. To find variation within single genes, DNA sequencing using next-generation sequencing technologies is typically most effective. To identify larger chromosomal anomalies or rearrangements, cytogenetic analyses are required. It is important to appreciate the uses, capabilities, and limitations of each modality (Table 3). In addition to test selection, outlined below in Sections 3.1 and 3.2, practitioners should be aware of other common pitfalls in genetic testing, outlined in Figure 4.

Gene panels are currently first-line tests for most ICVC including cardiomyopathies, arrhythmia syndromes, thoracic aortic aneurysms, and familial hypercholesterolemia,^{2,9-11} whereas genome-wide sequencing (GWS), including whole-exome and whole-genome sequencing, is quickly becoming the standard for patients with multisystem or syndromic conditions. Disease-specific guidelines and province-specific guidance (if available) must be considered to ensure the most appropriate genetic test selection in any given clinical scenario. In some instances, small targeted gene panel testing is most appropriate whereas at other times a broader approach

might be warranted. Diagnosis-specific genetic testing strategies are outlined in Table 5.

When ordering gene panels, physicians should consider the gene content of panels (genes that are included), which vary across laboratories. Panels that include more genes will not necessarily lead to a better diagnostic rate if a panel includes genes that are not relevant to the phenotype or have only limited association with a given disease. Larger panels also have a greater chance of returning variants of uncertain significance, which might lead to unnecessary downstream testing and anxiety for patients.³⁸ Genetic test selection is further complicated by the variable presentation of ICVC and overlapping phenotypes, which might not be entirely covered by a single panel.

Organizations including ClinGen and Genomics England provide frameworks for evaluating gene-disease associations, updated by groups of international experts and made publicly available.^{39,40} The intent is to delineate the quality of evidence that link genes to specific diseases and thereby provide clinicians with the information they need to determine appropriate gene panel content for any indication. Genes are categorized as

Table 6. Selected genetic cardiac and cardiometabolic conditions in Canadian founder subpopulations*

Subpopulation	Disorder name (OMIM number)	Inheritance and clinical features	Gene/founder variant(s)	Comments
Newfoundland and Labrador ⁴⁴	Arrhythmogenic right ventricular cardiomyopathy (604400)	AD; highly penetrant ventricular arrhythmias and sudden death, progressive RV dilation and dysfunction, uniquely extremely high-risk phenotype	<i>TMEM43</i> /p.Ser358Leu	Recommendations for early ICD placement in post pubertal men, and women older than 30 years
Quebec, Saguenay-Lac-Saint-Jean ⁴⁵	Familial hypercholesterolemia (143890)	ASD; early atherosclerosis, elevated low-density lipoprotein cholesterol, skin and tendon lipid deposits	<i>LDLR</i> /p.Trp87Gly <i>LDLR</i> /promoter_exon1 deletion (> 15 kb)	1:90 in Quebec vs 1:300 in ROC
Quebec, Saguenay-Lac-Saint-Jean ⁴⁵	Familial chylomicronemia (238600)	AR; severe dyslipidemia and pancreatitis risk	<i>LPL</i> /p.Gly215Glu <i>LPL</i> /p.Pro234Leu <i>LPL</i> /p.Asp277Asn	1:60,000 in Quebec vs 1:300,000 in ROC
Quebec, Eastern region ^{46,47}	Chronic atrial and intestinal dysrhythmia (616201)	AR; atrial dysrhythmias, sick sinus syndrome, valve anomalies, chronic intestinal pseudo-obstruction, cerebral small vessel disease	<i>SGOL1</i> /p.Lys23Glu	Very rare; prevalence unknown
Oji-Cree, Northern Ontario-Manitoba ⁴⁸	Type 2 diabetes (142410)	ASD; susceptibility to early onset of diabetes with increased risk of myocardial infarction, stroke, and PAD	<i>HNF1A</i> /p.Gly319Ser	Heterozygotes and homozygotes have two- and fourfold higher diabetes risk, respectively
Alberta Hutterite Brethren ⁴⁹	Nonischemic cardiomyopathy with ataxia syndrome (also called 3-methylglutaconic aciduria type V) (610198)	AR; early-onset nonischemic cardiomyopathy, growth failure, cerebellar ataxia	<i>DNAJC19</i> /c.130-1G>C	Mainly in Dariusleut sect
Alberta Hutterite Brethren ⁵⁰	Arrhythmogenic right ventricular cardiomyopathy 11 (610476)	AR: severe arrhythmogenic right ventricular cardiomyopathy; there might be biventricular cardiac aneurysms, arrhythmias. AD: milder phenotype	<i>DSC2</i> /p.Gln554X	Found in Dariusleut and Lehrerleut sects
Gitksan First Nation, Northern British Columbia ⁵¹⁻⁵³	Long QT syndrome 1 (607542)	AD; increased susceptibility to long QT syndrome, decreased slow delayed rectifier K ⁺ currents	<i>KCNQ1</i> /p.Val205Met <i>KCNQ1</i> /p.Leu353Leu [†] <i>ANK2</i> /p.Ser646Ser [†]	1:125 in Gitksan vs 1:2000 in ROC; successful model of community-based research and clinical care delivery

AD, autosomal dominant; AR, autosomal recessive; ASD, autosomal semidominant; ICD, implantable cardioverter-defibrillator; MIM, Online Mendelian Inheritance in Man; PAD, peripheral artery disease; ROC, rest of Canada; RV, right ventricular.

* Other founder variants are enriched in certain geographic regions in Canada, which are encountered in clinical practice but have not yet been widely publicized or reported.

[†] Considered to be modifier variants.

having definitive, strong, moderate, or limited evidence to support clinical relevance. It is, however, important to recognize that reviews and consensus recommendations are completed at discrete time points and might not be updated despite the availability of new research or guidelines.

GWS for clinical use is increasingly available in Canada and is quickly becoming first-line testing for multisystem or syndromic disorders.⁴¹ In nonsyndromic ICVC, GWS has been shown to inform clinical diagnoses in some panel-negative cases.^{42,43} The relative diagnostic yield of GWS vs panel testing in most nonsyndromic ICVC has not been well established.

When there is a choice, clinicians need to ensure that only laboratories that are accredited by recognized bodies should be used for clinical testing. These include Accreditation Canada Diagnostics, Clinical Laboratory Improvement

Amendments, and the College of American Pathologists. In Canada, there is marked interprovincial variability with respect to genetic testing availability. Certain provinces provide local institutional (in-house) clinically accredited testing, whereas in other provinces, international commercial labs are being used. The names and content of diagnostic panels are not standardized, and available options might be determined according to jurisdiction. Clinicians will need to familiarize themselves with regional guidance around accessing and ordering genetic testing.

3.2. Cardiogenetic testing and specific populations

Canada has many ancestrally diverse populations resulting in important considerations regarding the genetic etiology of several ICVC (Table 6).⁴⁴⁻⁵³ Clinicians working with these

populations might wish to take this into consideration, while recognizing the benefits and limitations associated with targeted genetic testing.

3.3. Molecular autopsy in individuals with sudden cardiac death

Sudden cardiac death (SCD), defined as sudden natural death of presumed cardiac cause, is a catastrophic event that can serve as the first clinical manifestation of heart disease. Although ischemic heart disease is the predominant cause of SCD in older adults, genetic cardiomyopathies, channelopathies, and aortopathies are more frequently observed among younger individuals.⁵⁴⁻⁵⁷ Sudden death is not, in and of itself, a specific diagnosis or phenotype, however, because of the significant potential for an underlying genetic etiology, it is essential that autopsy evaluations are conducted for initially unexplained SCD. Not only is this important for identifying the cause of death but also to ensure that when appropriate, family members receive appropriate screening and counselling.^{58,59} Although most SCD in young persons (younger than 35 years) is caused by inherited cardiac disease, it also accounts for a significant percentage in individuals aged 36-49 years. The prevalence in cases in older adults (older than 50 years) remains poorly understood.⁶⁰

A notable percentage of SCD cases remain unexplained, and molecular autopsy has been shown to increase diagnostic yield when combined with a comprehensive autopsy.^{57,61} Molecular autopsy, defined as genetic testing performed on DNA extracted from retained tissue or blood samples from the deceased, is valuable when autopsy findings suggest a possible genetic condition, when autopsies yield no definitive cause, or in select cases when an autopsy is not available. In cases in which cardiomyopathy or aortopathy is identified, genetic testing can clarify the underlying etiology and facilitate genetic testing of first-degree relatives.⁶²⁻⁶⁶ Because of the increasing recognition of concealed cardiomyopathies, current guidelines advocate for combined arrhythmia and cardiomyopathy panels in cases of unexplained SCD.⁶¹ When genetic testing yields no pathogenic findings, first-degree relatives are still recommended to undergo clinical screening in line with best practices, because detailed investigations of first-degree relatives can result in a diagnosis of inherited cardiac disease in 20%-50% of families.^{60,61} Other conditions such as coronary artery disease might have a hereditary component and could be candidates for postmortem testing in the future to enable screening of family members.

Molecular autopsy programs are complex and require a system-wide multidisciplinary approach to case acquisition, biobanking, consent, testing, family screening, and management. There are a number of molecular autopsy programs established in Canada that range from local practice to provincial protocols. Establishing robust molecular autopsy programs in Canada requires significant investment in infrastructure and the establishment of tightly integrated multidisciplinary networks. The creation of centralized biobanks are critical for storing and accessing DNA samples for genetic testing in SCD cases and are recommended in the American College of Medical Genetics and Genomics recent guidelines.⁶¹ Ideally, comprehensive and standardized

processes will be developed with regional coroners and medical examiners to enable access to and consent for post-mortem testing and the timely return of results in an equitable and compassionate manner.

3.4. Polygenic risk scores

Polygenic risk scores (PRS) quantify an individual's genetic risk for a trait or disease on the basis of the cumulative effect of multiple genetic variants. PRS can be generated using microarray or next-generation sequencing data and require extensive postprocessing, including adjustments for population stratification and ancestry (Table 3). PRS for cardiovascular conditions show great promise for clinical application, and some North American commercial laboratories are reporting these for coronary artery disease risk and cardiomyopathy, and the American Heart Association has advocated for its future implementation.⁶⁷ However, PRS for most cardiovascular disorders should currently be considered as research tools that are not ready for routine clinical use.⁶⁸

4. Informed Consent and Family Care

Key messages for physicians and allied health care providers:

- Ordering cardiogenetic testing must be accompanied by a thorough discussion with patients regarding the potential implications, benefits, and limitations of genetic testing before initiating the process. General guidance is outlined in Figure 5 but can be tailored to test indication and clinical circumstance. Clinicians are advised to reflect on their current genetics knowledge and clinical expertise as well as the capacity to have these conversations with respect to time commitment, before deciding whether genetic testing should be arranged directly or via referral to a cardiogenetics expert.
- In Canada, the primary responsibility for communicating genetic risk to family members falls directly to patients. When ordering genetic testing, a clear strategy should be developed to assist patients in communicating genetic risk information to at-risk relatives, and ensure that appropriate clinical screening and genetic testing is accessible.
- Predictive genetic testing in unaffected relatives of an individual who carries a pathogenic or likely pathogenic variant, often referred to as cascade genetic testing, should be facilitated by referral to expert cardiogenetics teams, which include qualified genetic counsellors (see section 5.1).
- Patients with ICVC who are considering family planning should be referred to specialized centres for reproductive risk counselling, inheritance education, and exploration of available reproductive options.

Providing patients with a comprehensive understanding of the potential outcomes and implications of genetic test results is essential for the successful integration of genetic testing into clinical practice. The nature of these discussions varies depending on indication for testing and clinical scenario,

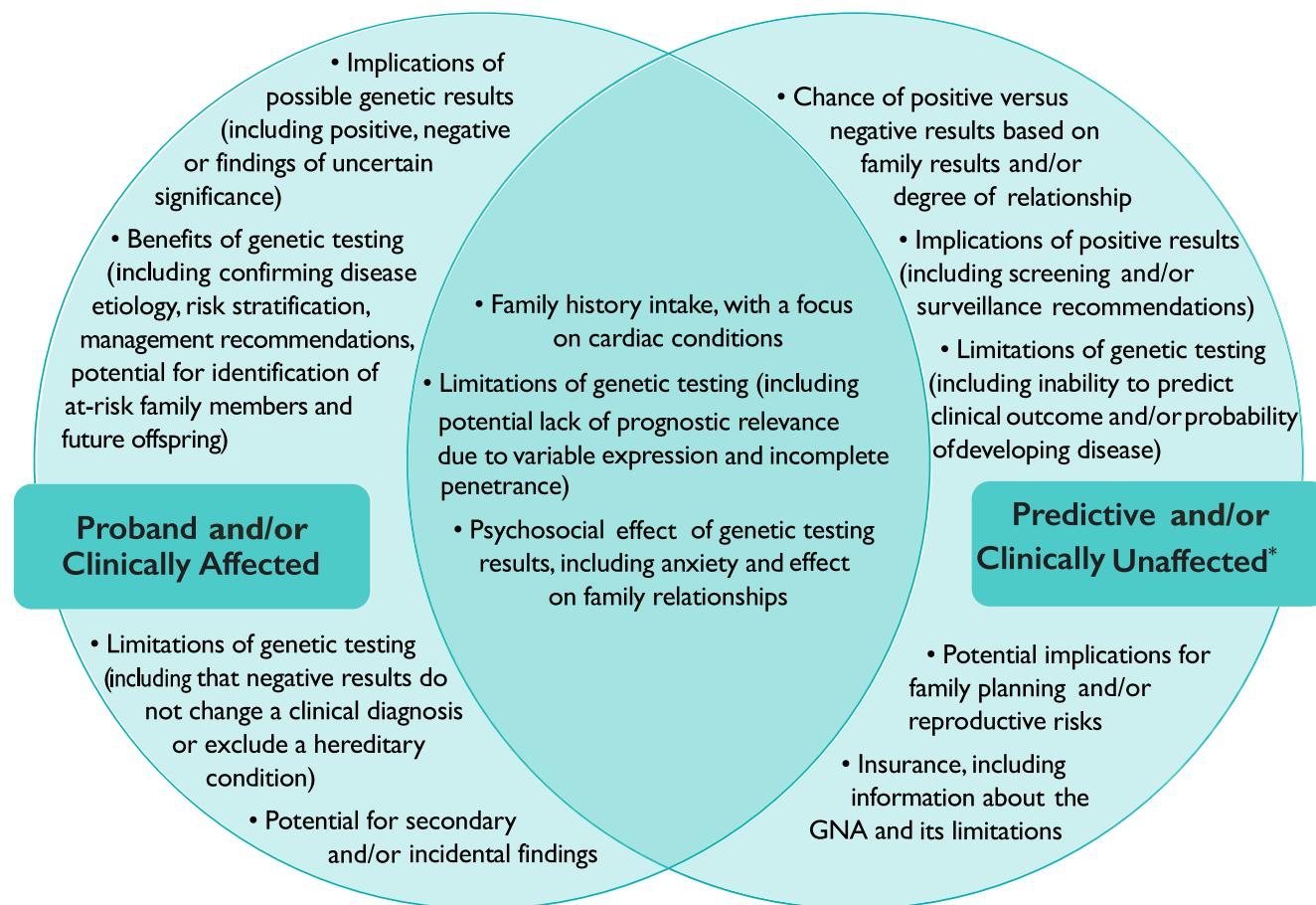


Figure 5. Pretest education and genetic counselling considerations. Generally recommended information to be included in pretest education and/or genetic counselling are shown.^{2,16} GNA, genetic non-discrimination act. * For predictive testing in unaffected individuals, consider referral for formal genetic counselling via medical genetics or inherited heart conditions specialty clinic.

however, key elements have been identified to maximize patient adaptation and improve outcomes. These include discussions about the utility and limitations of genetic testing, certainty of results, and communication of potential risks to family members (Fig. 5).⁶⁹

4.1. Pretest genetic counselling and informed consent

In addition to helping patients understand the risks, benefits, and limitations of a given test, pretest counselling also prepares patients for potential test results, and addresses associated psychosocial factors. Access to qualified genetic counsellors in Canada is currently limited. Clinicians who offer routine genetic testing for straightforward indications can become familiar with the important considerations to provide pretest education and consider referral to centres with dedicated genetic counsellors in more complex scenarios. These considerations vary depending on whether the patient is the index case (the first affected family member to undergo genetic testing) or an unaffected family member undergoing predictive genetic testing (Fig. 5).

Genetic testing of unaffected relatives for known familial variants is often referred to as cascade genetic testing. Pretest genetic counselling with a qualified genetic counsellor is

generally suggested for patients who undergo cascade genetic testing. Of particular importance in this group is a discussion about the potential for genetic discrimination. Canada has a genetic nondiscrimination act, to prevent employers and insurers from accessing genetic testing results, however, there are certain limitations such as the possibility of collecting nongenetic data about family history, and current health status, which might lead to discrimination nonetheless.⁷⁰ There might also be different psychological and emotional considerations for individuals with positive genetic findings in the absence of a clinical diagnosis, and these should be considered as important components of informed consent for predictive genetic testing.²

Genetic testing for children is approached in a different manner than testing adults and depending on age and capacity, children might be unable to consent for themselves. In children, the benefit of knowing the genetic status is weighed against their right to privacy and autonomy.⁷¹ Knowledge about local legislation is important, because age at the time of consent for genetic testing varies, and might precede age at majority.

Predictive testing of unaffected children is usually recommended for children at risk of conditions that are actionable in childhood, for whom detection and

subsequent treatment could improve prognosis. This is relevant for many cardiac genetic conditions that carry a risk of morbidity and mortality at young ages. Implications of predictive genetic testing should be covered and tailored to the level of comprehension of the child, if present. Shared decision-making is recommended to determine the most appropriate timing for testing.⁷¹⁻⁷⁴ Because of these unique considerations, referrals to a pediatric cardiogenetic specialist might be most appropriate for facilitating genetic testing in children.

4.2. Caring for families

When an individual is diagnosed with any of the ICVC, communication to family members regarding recommendations for cardiac screening and the availability of genetic testing is paramount. If a likely pathogenic or pathogenic (LP/P) gene variant is identified (see section 5.1), cascade genetic testing is available to at-risk family members. In the absence of a significant genetic finding, clinical screening for relatives is disease-dependent and should be managed on the basis of published guidelines.⁶⁻¹¹

Every province in Canada has laws that prohibit the disclosure of health information without informed consent.⁷⁵ Consequently, the primary responsibility for communication about genetic risk falls directly to patients. Documented factors that facilitate family communication and cascade testing include pre- and post-test genetic counselling, education of at-risk family members in specialized clinics, and provision of written material in the form of a family letter that can be shared with at-risk relatives ([Supplemental Appendix S3](#)).⁷⁶⁻⁷⁸ Conversely, low perceived personal risk has been identified as a barrier to coming forward for testing and/or screening, and thus education about risk is critical in disseminating accurate information to family members.⁷⁹

Cascade testing in Canada has particular and unique challenges. In many jurisdictions, a medical referral is required to initiate care, potentially resulting in lengthy delays. When possible, self-referrals from at-risk family members should be considered to alleviate barriers to access, particularly because of a shortage of primary care providers in some regions. Canada's large geographical area and provincial differences in accessibility of clinical screening and/or genetic testing can result in additional barriers to access. This includes not only proximity or physical access to a specialized centre, but also discrepancies between provincial health ministries with respect to accessing genetic testing.

To reduce some of these barriers, clinicians are encouraged to request that patients sign a release of information form at the time of results disclosure to aid in sharing information across centres for at-risk family members. Providing patients with a copy of their own genetic test results can also reduce barriers to access because individuals can share these directly with family members.

4.3. Family planning options

Discussions about reproductive risks can be emotionally charged, and the implications of decreased penetrance and variable expression are complex. Although the presence of a LP/P variant indicates an increased risk for a specific condition, it often provides limited prognostic information. In

addition, before pursuing genetic testing in this context, it is critical that there is sufficient evidence that the variant is causative for the cardiac condition in question.

Historically, invasive prenatal testing including amniocentesis or chorionic villus sampling has been the most accessible option to investigate the possibility of genetic causes when fetal anomalies (including congenital heart defects) are present or can be used for single-gene testing of a fetus who is at risk for a known familial pathogenic variant. Both are widely available but are performed at different stages of pregnancy, and are associated with small risks of procedure-related pregnancy loss.⁸⁰ Prenatal testing is available across Canada and should include an informed discussion and support.⁸¹

Preimplantation genetic testing (PGT) involves genetic testing on embryos for the purpose of identifying embryos with a monogenic disorder or aneuploidy.⁸² PGT for ICVC offers an opportunity for families to greatly reduce the risk of conceiving a child with the familial condition. However, provincial funding for *in vitro* fertilization and/or PGT varies and personal costs for patients can be substantial.

Referral to centres that specialize in reproductive risk counselling and testing is generally encouraged for families interested in prenatal diagnosis or PGT so they can be provided with the most accurate information. In addition, it is recommended that individuals diagnosed in childhood be referred for genetic counselling when transitioning to adult care to review inheritance and family planning options.

5. Results and Follow-up

Key messages for physicians and allied health care providers:

- Not all genetic variants are disease-causing. Variants of uncertain significance or those that lack robust evidence to link them to a clinical phenotype should generally not be incorporated into clinical decision-making or family management ([Fig. 6](#)).
- Determinations of the pathogenicity of a genetic variant, or variant interpretations are probabilistic and can change over time; periodic reassessment by cardiogenetics experts or testing laboratories is recommended.
- When ordering cardiogenetic testing, one must be knowledgeable about secondary (incidental) findings and have strategies in place to ensure patient access to appropriate specialists and genetic counselling when such findings arise.^{83,84}

5.1. Interpreting genetic testing

The American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines are the global standard for classification of genetic variants in Mendelian (single-gene) disorders.^{85,86} The interpretation and classification of genetic test results are considered probabilistic and can change over time. There are 5 classification categories (pathogenic, likely pathogenic, variant of uncertain significance [VUS], likely benign, and benign), which are on the basis of the probability of pathogenicity as determined according to numerous pieces of evidence. For a variant to reach

	Pathogenic and/or Likely Pathogenic Variant	Variant of Uncertain Significance	Negative
Interpretation	• > 90% probability of pathogenicity⁸¹ • Generally diagnostic of genetic condition	• 10%-90% probability of pathogenicity⁸¹ • Does not confirm or eliminate genetic diagnosis	• No variants reported • Genetic diagnosis cannot be excluded
Suggested Action	• Assess for concordance with clinical presentation (confirm the result makes sense in the context of your patient) • Management decisions to be made on the basis of published guidelines • Consider referral to a subspecialist* • Refer for genetic counselling • Recommend clinical screening and genetic counselling for family members	• Consider referral to subspecialist* for further assessment and genetic test interpretation • Management decisions to be made on the basis of clinical presentation and family history • Consider referral for genetic counselling	• Management decisions to be made on the basis of clinical presentation and family history • Recommend family screening on the basis of strength of clinical diagnosis and family history • If suspicion of genetic condition remains high, consider referral to subspecialist* for further assessment
Pitfalls to Avoid	• Interpret result with caution if it is not consistent with clinical presentation	• Avoid managing as confirmation of diagnosis • Avoid making management decisions based on genetic result • Genetic testing for family members cannot be used to assess risk and is not indicated	• Avoid the assumption that there is no genetic cause, particularly in the setting of strong clinical phenotypes and/or positive family history • Do not assume reduced risk to family members solely on the basis of genetic test result

Figure 6. General principles in genetic test interpretation. * Subject matter expert could include a cardiologist with expertise in inherited heart disease, medical genetics, endocrinology, *et cetera*. Referrals should be initiated as soon as genetic results are communicated with patients, to allow specialty clinics to triage according to urgency.

a classification of likely pathogenic, there must be sufficient evidence that the probability of pathogenicity is at least 90%. Similarly, there must be < 10% probability of pathogenicity for a variant to reach a classification of likely benign.⁸⁵ Likely benign variants are generally considered to be of little or no clinical significance and are often not reported. Any variant that has a 10%-90% probability of pathogenicity is considered to be of uncertain significance and must be interpreted with caution in the context of each patient's unique clinical picture. Depending on the testing lab, not all VUS are reported.

Despite the availability of published guidelines, clinicians should be aware of bias, and the subjective nature of genetic interpretation, which can result in discrepant reporting across sites.⁸⁷⁻⁸⁹ Although publicly available resources including

ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) exist to help navigate these challenges, it is imperative that genetic test results be reviewed critically, repeatedly over time, and always in the context of the clinical condition. In some circumstances, interpretation of genetic results can be complicated, and might benefit from a multidisciplinary approach involving cardiologists and genetics professionals to ensure accurate and meaningful conclusions.⁹⁰

Although genetic test interpretation can present challenges, providers should be reassured that results are typically reported in ways that are accessible and meaningful for nongenetics experts. However, there are some general principles that should be applied to genetic test result interpretation and their use in clinical decision-making across the spectrum of ICVC that can be shown in Figure 6.

5.2. Ongoing reevaluation of genetic findings

Because of the ongoing evolution of available evidence, the interpretation of genetic test results might change over time, potentially requiring repeated contact with patients and families to provide and explain updated results.⁸³ Various studies on the frequency of variant reclassifications in cardiomyopathy and arrhythmia genes have shown significant pathogenicity reassignments over time.^{91,92} When downgraded from LP/P variants to VUS, clinicians might need to contact patients and family members previously discharged from clinical care on the basis of what were believed to be informative negative genetic test results. For variants upgraded to LP/P, contact with family members needs to be established to initiate cascade genetic testing.^{93,94} Clinical reassessment is a critical component of cardiogenetic follow-up, because the progression or evolution of clinical findings can alter the pre- or post-test probability of a genetic diagnosis, and might require additional or expanded testing.⁹⁵

The reevaluation process poses several challenges including a lack of clarity regarding responsibility, suggested frequency for variant reassessment, and the need for additional resources. Molecular diagnostic laboratories might on occasion provide updated reports on the basis of new evidence, however, this is not universal. Nonetheless, labs remain a valuable resource and are generally willing to reassess reported variants when contacted by clinicians.

5.3. Managing secondary findings

A secondary finding refers to a result obtained from genetic testing that is unrelated to the indication for testing, but believed to be of medical value for patient care.^{83,84} Current guidelines include recommendations for reporting of secondary findings in 81 disease-related genes, including 38 genes associated with cardiovascular disease, as well as other genes related to hereditary cancer syndromes and inborn errors of metabolism.⁸⁴

Because of the increasing clinical implementation of whole-exome and whole-genome sequencing, secondary findings are becoming more prevalent, and clinicians who incorporate genetic testing into their practices are encouraged to familiarize themselves with related guidelines. When ordering genetic testing, providers will need to recognize that secondary findings might be reported in genes associated with conditions that are unfamiliar or outside of their expertise. Appropriate follow-up will involve referring patients to a medical genetics team or an appropriate specialist to ensure appropriate risk assessment, follow-up, and cascade screening (Fig. 2). In addition, there are important considerations with respect to pretest education, informed consent, and the right to opt out of having secondary findings reported.^{84,96}

5.4. Proactive genetic screening and/or direct-to-consumer genetic testing

Proactive genetic screening refers to genetic testing in healthy individuals with the intention of identifying genetic variants associated with hereditary disorders. Theoretically, a significant advantage of this approach is its ability to detect at-risk individuals before clinical symptoms emerge, to facilitate early interventions that can prevent disease progression

and/or manage associated risk. In Canada, this is not covered by provincial health services, however, is increasingly available for a fee to individuals who are willing to pay privately. In some instances, patients can access testing directly from commercial genetics labs, without primary physician involvement (also known as direct-to-consumer [DTC] testing). Some studies have shown that up to 6% of individuals who participate in proactive genetic screening have a clinically significant finding in a gene associated with one or more ICVC.⁹⁷

Upon receiving a positive result, patients are likely to be reintegrated into the public health system for risk assessment and ongoing surveillance. This poses several challenges because the predictive value of genetic testing in this context remains limited because of our lack of knowledge around the true penetrance of many of these disorders. The interpretation of gene variants in the absence of any relevant phenotype or family history can also be difficult, particularly when there are discrepancies in the classification of an identified variant.

The quality of the testing laboratory and the nature of the testing performed also needs to be taken into consideration. Not all DTC tests are performed in accredited labs with high levels of quality control, nor do they all use the same methodologies. Additionally, software exists that allows individuals to input their raw genetic data to be reanalyzed outside the setting of the testing laboratory. These analyses must always be interpreted with caution because they are recognized to provide inaccurate results.⁹⁸

Some labs offering DTC genetic testing include additional clinical services such as genetic counselling and patient education resources. However, there is a residual risk that follow-up care and genetic counselling are not comprehensive or integrated within the individual's routine medical care. This has the potential to result in psychosocial strain and poor health outcomes.

As these testing options become more widely available, cardiologists will need to be increasingly aware of how to interpret and manage these types of results. Consulting with or referring to a subspecialist with expertise in ICVC might be helpful, however, some thought will need to be given to this issue to determine appropriate resource allocation.

6. Future Planning and Policy-making

As genetic testing becomes increasingly standard across the spectrum of cardiac care, there are important considerations for health systems and policy planning. Ongoing discussion with health policy organizations will be critical to ensure accessible and equitable care for patients affected by ICVC across all regions of Canada and should take the following issues into consideration.

- Build a robust cardiovascular genetics workforce: integration of genetic testing into health care requires specific knowledge and expertise, and the risks associated with misuse of this information can be significant. To provide patients with the appropriate care, health organizations should consider how to train and retrain physicians (cardiologists, medical geneticists), genetic counsellors, other allied health professionals, and laboratory staff with expertise in

cardiovascular genetics, to meet the growing demand for cardiogenetic testing and management.

- Integrate genetic testing into cardiovascular care pathways: embed cardiogenetic testing into clinical workflows for patients with inherited or suspected ICVC to facilitate early diagnosis and targeted treatment.
- Specialty training and ongoing CME: medical training in clinical genetics is recognized to be lacking in undergraduate medical school curricula across North America, leaving physicians underprepared and uncomfortable with incorporating genetics into routine clinical practice.⁹⁹⁻¹⁰¹ Medical training programs should be encouraged to revisit current standards to increase awareness within the community of inherited disease and genetic testing. Professional societies are also encouraged to consider offering new CME-accredited programs focused on cardiogenetics to increase genetics literacy across the spectrum of cardiac disease.
- Electronic medical records (EMRs): EMRs can revolutionize cardiogenetic testing by integrating genetic results directly into patient profiles, and enabling automated risk stratification, tailored treatment plans, and early disease detection. Pharmacogenomic data can be embedded to optimize medication choices, such as adjusting drug selection and dosing. EMRs can also facilitate cascade screening by linking affected individuals with family members, generating automated alerts for genetic counselling and follow-up testing. Furthermore, integrated pedigree charts can visually track inheritance patterns, improve family risk assessments, and streamline referrals.
- Interdisciplinary collaboration: in Canada's current health system there are many barriers to providing the requisite multidisciplinary and collaborative care required for families with ICVC. There might be no clearer example of this than the varied protocols around sudden death events. National committees or task forces to bring together experts across disciplines to develop national best practices, strategies, and quality assessment and improvement initiatives will be essential in ensuring at-risk family members receive the required care.
- Establish national cardiogenetic registries and quality assurance programs: create a centralized registry for genetic and clinical data to monitor outcomes, facilitate research, and guide policy decisions while ensuring patient privacy and data security. Introduce standards for genetic laboratories and regular audits to ensure accuracy, reliability, and uniformity of test results across the country.
- Enhance access and equity: address disparities in access to genetic testing for underserved populations, including rural, Indigenous, and low-income groups, by subsidizing costs and leveraging telemedicine.
- Focus on cost-effectiveness and resource allocation: conduct health economic evaluations to prioritize testing for high-risk populations and conditions for which early intervention can lead to significant cost savings and improved outcomes. Sustainable funding will be crucial to support the integration of

cardiogenetic testing into routine clinical care and molecular autopsy into SCD investigations across Canada.

- Promote public and professional awareness: launch educational campaigns for the public and health care providers to increase awareness of ICVC and the benefits of genetic testing.
- Support research and innovation: invest in research to identify new genetic variants, develop advanced testing technologies, study implementation policies and practices, and evaluate the long-term effects of cardiogenetic testing on patient outcomes and population health.

Closing Remarks

Genetic testing for ICVC is no longer confined to a small percentage of patients but rather is increasingly indicated across the spectrum of cardiac disease. Although genetic testing has historically been accessed through highly specialized cardiology and genetics clinics, this traditional model is unsustainable, necessitating an evolution of service delivery and health systems planning. Differentiating patients for whom genetic testing in their primary cardiac care setting is appropriate from those who might require referrals to subspecialists will be key to best practices. Practitioners who are motivated to incorporate genetic testing more routinely into their practices are encouraged to reflect on their clinical expertise and genetics knowledge, consider additional educational, and to thoughtfully plan how to manage the nuances of genetic test selection, interpretation, and management. For health systems, ongoing discussions and planning for increased cardiovascular genetic testing demand is paramount.

Acknowledgements

The authors thank Dr Krishnan Ramanathan, Canadian Cardiovascular Society (CCS) Guidelines Committee member, who provided support, guidance, and advice through the duration of development of this guideline as Guidelines Committee Liaison; Ms Christiana Fashola, Ms Carolyn Gall Casey and Ms Stephanie Hong for contributions and support to the co-chairs, primary panel, and the document preparation process.

The authors acknowledge and recognize the ongoing volunteer contributions of all writing panel members, the CCS Guidelines Committee, CCS members, and CCS staff involved in the development, publication, and dissemination of CCS guidelines.

Ethics Statement

All research reported in the current article adheres to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article because this is a clinical practice update

document, no patients were involved in the development of this clinical practice update.

Funding Sources

The CCS gratefully acknowledges the annual contribution of \$10,000 from the Canadian Cardiovascular Society Academy to support in part, the development of high-quality guidelines and clinical practice updates. Please read about the important work of the Canadian Cardiovascular Society Academy at <https://ccs.ca/canadian-cardiovascular-society-academy/>.

Editorial Disclaimer

Given their role as Associate Editors, Robert Hegele and Gavin Oudit had no involvement in the peer review of this article and have no access to information regarding its peer review.

References

- Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;43:3997-4126.
- Musunuru K, Hershberger RE, Day SM, et al. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. *Circ Genom Precis Med* 2020;13:e000067.
- Yogasundaram H, Alhumaid W, Dzwiniel T, Christian S, Oudit GY. Cardiomyopathies and genetic testing in heart failure: role in defining phenotype-targeted approaches and management. *Can J Cardiol* 2021;37:547-59.
- Roston TM, Dewar L, Franciosi S, et al. The accessibility and utilization of genetic testing for inherited heart rhythm disorders: a Canadian cross-sectional survey study. *J Community Genet* 2018;9:257-62.
- Dragojlovic N, Borle K, Kopac N, et al. The composition and capacity of the clinical genetics workforce in high-income countries: a scoping review. *Genet Med* 2020;22:1437-49.
- 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.
- Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;44:3503-626.
- Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy—a Heart Failure Society of America practice guideline. *J Card Fail* 2018;24:281-302.
- Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia. *J Am Coll Cardiol* 2018;72:662-80.
- Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2020;76:3022-55.
- Boodhwani M, Andelfinger G, Leipsic J, et al. Canadian Cardiovascular Society position statement on the management of thoracic aortic disease. *Can J Cardiol* 2014;30:577-89.
- Kapur S, Lichten L, Ali N, Garber KB. Poor recall of genetics curriculum by medical students highlights barriers to use in clinical practice. *J Genet Couns* 2024;33:179-88.
- Kernohan KD, Boycott KM. The expanding diagnostic toolbox for rare genetic diseases. *Nat Rev Genet* 2024;25:401-15.
- Schunkert H, Di Angelantonio E, Inouye M, et al. Clinical utility and implementation of polygenic risk scores for predicting cardiovascular disease: a clinical consensus statement of the ESC Council on Cardiovascular Genomics, the ESC Cardiovascular Risk Collaboration, and the European Association of Preventive Cardiology. *Eur Heart J* 2025;46:1372-83.
- Cohen SA, Gustafson SL, Marvin ML, et al. Report from the National Society of Genetic Counselors service delivery model task force: a proposal to define models, components, and modes of referral. *J Genet Couns* 2012;21:645-51.
- Hoskovec JM, Bennett RL, Carey ME, et al. Projecting the supply and demand for certified genetic counselors: a workforce study. *J Genet Couns* 2018;27:16-20.
- Farnè M, Fortunato F, Neri M, et al. TeleNEwCARE: an Italian case-control TELEgenetics study in patients with Hereditary NEuromuscular and CARDiac diseases. *Eur J Med Genet* 2023;66:104749.
- Schmidlen T, Jones CL, Campbell-Salome G, et al. Use of a chatbot to increase uptake of cascade genetic testing. *J Genet Couns* 2022;31:1219-30.
- Morgan KM, Campbell-Salome G, Walters NL, et al. Innovative implementation strategies for familial hypercholesterolemia cascade testing: the impact of genetic counseling. *J Pers Med* 2024;14:841.
- Christian S, Welsh A, Yetman J, et al. Development and evaluation of decision aids to guide families' predictive testing choices for children at risk for arrhythmia or cardiomyopathy. *Can J Cardiol* 2021;37:1586-92.
- Christian S, Tagoe J, Delday L, et al. IMPACT webinars: Improving Patient Access to genetic Counselling and Testing using webinars—the Alberta experience with hypertrophic cardiomyopathy. *J Community Genet* 2022;13:81-9.
- Zentner D, Thompson TN, James PA, et al. The cardiac genetics clinic: a model for multidisciplinary genomic medicine. *Med J Aust* 2015;203:261.e1-6.
- Ahmad F, McNally EM, Ackerman MJ, et al. Establishment of specialized clinical cardiovascular genetics programs: recognizing the need and meeting standards: a scientific statement from the American Heart Association. *Circ Genom Precis Med* 2019;12:e000054.
- Sadasivan C, Gagnon LR, Hazra D, et al. Early genetic screening and cardiac intervention in patients with cardiomyopathies in a multidisciplinary clinic. *ESC Heart Fail* 2025;12:1942-55.
- Caleshu C, Kasparian NA, Edwards KS, et al. Interdisciplinary psychosocial care for families with inherited cardiovascular diseases. *Trends Cardiovasc Med* 2016;26:647-53.
- Murray B, Tichnell C, Burch AE, Calkins H, James CA. Strength of the genetic counselor: patient relationship is associated with extent of increased empowerment in patients with arrhythmogenic cardiomyopathy. *J Genet Couns* 2022;31:388-97.

27. Quinn E. The future is mainstream: genetic counselling should be embedded in mainstream medicine. *Eur J Hum Genet* 2023;31:1097-8.
28. George A, Riddell D, Seal S, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. *Sci Rep* 2016;6:29506.
29. McCuaig JM, Thain E, Malcolmson J, et al. A comparison of patient-reported outcomes following consent for genetic testing using an oncologist- or genetic counselor-mediated model of care. *Curr Oncol* 2021;28:1459-71.
30. Guerin A, Dinchong R, Guy M, Evans S, Nanji J. P518: The impact of mainstreaming general genetic testing on patient wait-times (abstract). Available from: [https://www.gimopen.org/article/S2949-7744\(24\)00563-6/fulltext](https://www.gimopen.org/article/S2949-7744(24)00563-6/fulltext). Accessed August 18, 2025.
31. Birkenhead K, Sullivan D, Hemmet C, et al. Mainstreaming clinical cardiovascular genetics into primary care. *Heart Lung Circ* 2024;33:S313-4.
32. Scherr CL, Kalke K, Ramesh S, et al. Integrating clinical genetics in cardiology: current practices and recommendations for education. *Genet Med* 2022;24:1054-61.
33. Ackerman JP, Bartos DC, Kapplinger JD, et al. The promise and peril of precision medicine: phenotyping still matters most. *Mayo Clin Proc* 2016;91:1606-16.
34. Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus statement on the state of genetic testing for cardiac diseases. *Europace* 2022;24:1307-67.
35. Schwartz PJ, Crotti L, Insolia R. Long QT syndrome: from genetics to management. *Circ Arrhythm Electrophysiol* 2012;5:868-77.
36. Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm* 2019;16:e301-72.
37. Monda E, Lioncino M, Verrillo F, et al. The role of genetic testing in patients with heritable thoracic aortic diseases. *Diagnostics (Basel)* 2023;13:772.
38. Chen E, Facio FM, Aradhya KW, et al. Rates and classification of variants of uncertain significance in hereditary disease genetic testing. *JAMA Netw Open* 2023;6:e2339571.
39. Rehm HL, Berg JS, Brooks LD, et al. ClinGen—the clinical genome resource. *N Engl J Med* 2015;372:2235-42.
40. Figshare: National Genomic Research Library. Genomics England. Available from: https://figshare.com/articles/dataset/GenomicEnglandProtocol_pdf/4530893. Accessed August 18, 2025.
41. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2021;23:2029-37.
42. Bagnall RD, Ingles J, Dinger ME, et al. Whole genome sequencing improves outcomes of genetic testing in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2018;72:419-29.
43. Lesurf R, Said A, Akinrinade O, et al. Whole genome sequencing delineates regulatory, copy number, and cryptic splice variants in early onset cardiomyopathy. *NPJ Genom Med* 2022;7:18.
44. Hodgkinson KA, Howes AJ, Boland P, et al. Long-term clinical outcome of arrhythmogenic right ventricular cardiomyopathy in individuals with a p.S358L mutation in TMEM43 following implantable cardioverter defibrillator therapy. *Circ Arrhythm Electrophysiol* 2016;9:e003589.
45. Bchetnia M, Bouchard L, Mathieu J, et al. Genetic burden linked to founder effects in Saguenay-Lac-Saint-Jean illustrates the importance of genetic screening test availability. *J Med Genet* 2021;58:653-65.
46. Chetaille P, Preuss C, Burkhad S, et al. Mutations in SGOL1 cause a novel cohesinopathy affecting heart and gut rhythm. *Nat Genet* 2014;46:1245-9.
47. Nehme A, Gioia LC, Jacquin G, et al. Chronic atrial dysrhythmia syndrome is associated with cerebral small vessel disease and predominantly cerebella microbleeds. *Can J Neurol Sci* 2020;47:566-8.
48. Harries LW, Sloman MJ, Sellers EAC, Hattersley AT, Ellard S. Diabetes susceptibility in the Canadian Oji-Cree population is moderated by abnormal mRNA processing of HNF1A G319S transcripts. *Diabetes* 2008;57:1978-82.
49. Ojala T, Polinati P, Manninen T, et al. New mutation of mitochondrial DNAJC19 causing dilated and noncompaction cardiomyopathy, anemia, ataxia, and male genital anomalies. *Pediatr Res* 2012;72:432-7.
50. Gerull B, Kirchner F, Chong JX, et al. Homozygous founder mutation in desmocollin-2 (DSC2) causes arrhythmogenic cardiomyopathy in the Hutterite population. *Circ Cardiovasc Genet* 2013;6:327-36.
51. Arbour L, Rezazadeh S, Eldstrom J, et al. A KCNQ1 V205M missense mutation causes a high rate of long QT syndrome in a First Nations community of northern British Columbia: a community-based approach to understanding the impact. *Genet Med* 2008;10:545-50.
52. Kapplinger JD, Erickson A, Asuri S, et al. KCNQ1 p.L353L affects splicing and modifies the phenotype in a founder population with long QT syndrome type 1. *J Med Genet* 2017;54:390-8.
53. Swayne LA, Murphy NP, Asuri S, et al. Novel variant in the ANK2 membrane-binding domain is associated with ankyrin-B syndrome and structural heart disease in a First Nations population with a high rate of long QT syndrome. *Circ Cardiovasc Genet* 2017;10:e001537.
54. Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. *Nat Rev Cardiol* 2010;7:216-25.
55. Tseng ZH, Olgin JE, Vittinghoff E, et al. Prospective countywide surveillance and autopsy characterization of sudden cardiac death. *Circulation* 2018;137:2689-700.
56. Winkel BG, Holst AG, Theilade J, et al. Nationwide study of sudden cardiac death in persons aged 1-35 years. *Eur Heart J* 2011;32:983-90.
57. Bagnall RD, Weintraub RG, Ingles J, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med* 2016;374:2441-52.
58. Behr E, Wood DA, Wright M, et al. Cardiologic assessment of first-degree relatives in sudden arrhythmic death syndrome. *Lancet* 2003;362:1457-9.
59. Semsarian C, Ingles J, Wilde AAM. Sudden cardiac death in the young: the molecular autopsy and a practical approach to surviving relatives. *Eur Heart J* 2015;36:1290-6.
60. Lynge TH, Albert CM, Basso C, et al. Autopsy of all young sudden death cases is important to increase survival in family members left behind. *Europace* 2024;26:euae128.
61. Stiles MK, Wilde AAM, Abrams DJ, et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden

- unexplained death and patients with sudden cardiac arrest, and of their families. *J Arrhythm* 2021;37:481-534.
62. Webster G, Puckelwartz MJ, Pesce LL, et al. Genomic autopsy of sudden deaths in young individuals. *JAMA Cardiol* 2021;6:1-10.
 63. Grondin S, Davies B, Cadrin-Tourigny J, et al. Importance of genetic testing in unexplained cardiac arrest. *Eur Heart J* 2022;43:3071-81.
 64. Isbister JC, Nowak N, Yeates L, et al. Concealed cardiomyopathy in autopsy-inconclusive cases of sudden cardiac death and implications for families. *J Am Coll Cardiol* 2022;80:2057-68.
 65. Neves R, Tester DJ, Simpson MA, et al. Exome sequencing highlights a potential role for concealed cardiomyopathies in youthful sudden cardiac death. *Circ Genom Precis Med* 2022;15:e003497.
 66. Lahrouchi N, Raju H, Lodder EM, et al. The yield of postmortem genetic testing in sudden death cases with structural findings at autopsy. *Eur J Hum Genet* 2020;28:17-22.
 67. O'Sullivan JW, Raghavan S, Marquez-Luna C, et al. Polygenic risk scores for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2022;146:e93-118.
 68. Klarin D, Natarajan P. Clinical utility of polygenic risk scores for coronary artery disease. *Nat Rev Cardiol* 2022;19:291-301.
 69. Christian S, Dzwiniel T, Baker A, et al. Evaluation of face validity and core concepts of a novel knowledge scale for inherited heart disease: a pilot study. *J Genet Couns* 2025;34:e1995.
 70. CanLII Connects: Reference re genetic non-discrimination act. 2020 SCC 17. Available from: <https://canliiconnects.org/en/summaries/71872>. Accessed August 18, 2025.
 71. Committee on Bioethics, Committee on Genetics, and, American College of Medical Genetics and, Genomics Social, Ethical, Legal Issues Committee: Ethical and policy issues in genetic testing and screening of children. *Pediatrics* 2013;131:620-2.
 72. Landstrom AP, Kim JJ, Gelb BD, et al. Genetic testing for heritable cardiovascular diseases in pediatric patients: a Scientific Statement from the American Heart Association. *Circ Genom Precis Med* 2021;14:e000086.
 73. Hundal K, Scherr CL, Fakhari H, et al. Mapping the use of cardiovascular genetic services in pediatric clinical care: challenges and opportunities for improvement. *Front Genet* 2025;15:1476466.
 74. Moore AM, Richer J. Genetic testing and screening in children. *Pediatr Child Health* 2022;27:243-53.
 75. Ontario e-Laws: Health information protection act, 2004, S.O. 2004, c. 3 - Bill 31. Available from: <https://www.ontario.ca/laws/statute/s04003>. Accessed August 18, 2025.
 76. Dickson MA, Zahavich L, Rush J, et al. Exploring barriers and facilitators to indirect cascade screening for familial hypercholesterolemia in a paediatric/parent population. *CJC Pediatr Congenit Heart Dis* 2023;2:211-8.
 77. Wurtmann E, Steinberger J, Veach PM, Khan M, Zierhut H. Risk communication in families of children with familial hypercholesterolemia: identifying motivators and barriers to cascade screening to improve diagnosis at a single medical center. *J Genet Couns* 2019;28:50-8.
 78. van der Roest WP, Pennings JM, Bakker M, van den Berg MP, van Tintelen JP. Family letters are an effective way to inform relatives about inherited cardiac disease. *Am J Med Genet A* 2009;149A:357-63.
 79. Ormondroyd E, Oates S, Parker M, Blair E, Watkins H. Pre-symptomatic genetic testing for inherited cardiac conditions: a qualitative exploration of psychosocial and ethical implications. *Eur J Hum Genet* 2014;22:88-93.
 80. Salomon LJ, Sotiriadis A, Wulff CB, Odibo A, Akolekar R. Risk of miscarriage following amniocentesis or chorionic villus sampling: systematic review of literature and updated meta-analysis. *Ultrasound Obstet Gynecol* 2019;54:442-51.
 81. Audibert F, De Bie I, Johnson JA, et al. No. 348-joint SOGC-CCMG guideline: update on prenatal screening for fetal aneuploidy, fetal anomalies, and adverse pregnancy outcomes. *J Obstet Gynaecol Can* 2017;39:805-17.
 82. ESHRE PGT-M Working Group, Carvalho F, Moutou C, et al. ESHRE PGT Consortium good practice recommendations for the detection of monogenic disorders. *Hum Reprod Open* 2020;2020:hoaa018.
 83. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013;15:565-74.
 84. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2023;25:100866.
 85. 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.
 86. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genet Med* 2020;22:245-57.
 87. Pepin MG, Murray ML, Bailey S, et al. The challenge of comprehensive and consistent sequence variant interpretation between clinical laboratories. *Genet Med* 2016;18:20-4.
 88. Balmaña J, Digiovanni L, Gaddam P, et al. Conflicting interpretation of genetic variants and cancer risk by commercial laboratories as assessed by the prospective registry of multiplex testing. *J Clin Oncol* 2016;34:4071-8.
 89. Van Dreist SL, Wells QS, Stallings S, et al. Association of arrhythmia-related genetic variants with phenotypes documented in electronic medical records. *JAMA* 2016;315:47-57.
 90. Berberich AJ, Hegele RA. The advantages and pitfalls of genetic analysis in the diagnosis and management of lipid disorders. *Best Pract Res Clin Endocrinol Metab* 2023;37:101719.
 91. Rosamilia MB, Markunas AM, Kishnani PS, Landstrom AP. Underrepresentation of diverse ancestries drives uncertainty in genetic variants found in cardiomyopathy-associated genes. *JACC Adv* 2024;3:100767.
 92. Davies B, Bartels K, Hathaway J, et al. Variant reinterpretation in survivors of cardiac arrest with preserved ejection fraction (the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry) by clinicians and clinical commercial laboratories. *Circ Genom Precis Med* 2021;14:e003235.

93. Das KJ, Ingles J, Bagnall RD, Semsarian C. Determining pathogenicity of genetic variants in hypertrophic cardiomyopathy: importance of periodic reassessment. *Genet Med* 2014;16:286-93.
94. Manrai AK, Funke BH, Rehm HL, et al. Genetic misdiagnoses and the potential for health disparities. *N Engl J Med* 2016;375:655-65.
95. Laksman Z, Dulay D, Gollob MH, Skanes AC, Krahn AD. Evolution of a genetic diagnosis. *Clin Genet* 2014;86:580-4.
96. Katz AE, Nussbaum RL, Solomon BD, et al. Management of secondary genomic findings. *Am J Hum Genet* 2020;107:3-14.
97. Haverfield EV, Esplin ED, Aguilar SJ, et al. Physician-directed genetic screening to evaluate personal risk for medically actionable disorders: a large multi-center cohort study. *BMC Med* 2021;19:199.
98. Tandy-Connor S, Guiltinan J, Krempely K, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. *Genet Med* 2018;20:1515-21.
99. Mital S, Musunuru K, Garg V, et al. Enhancing literacy in cardiovascular genetics: a scientific statement from the American Heart Association. *Circ Cardiovasc Genet* 2016;9:448-67.
100. Haspel RL, Genzen JR, Wagner J, et al. Call for improvement in medical school training in genetics: results of a national survey. *Genet Med* 2021;23:1151-7.
101. White S, Jacobs C, Phillips J. Mainstreaming genetics and genomics: a systematic review of the barriers and facilitators for nurses and physicians in secondary and tertiary care. *Genet Med* 2020;22:1149-55.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at <https://doi.org/10.1016/j.cjca.2025.08.364>.