Cardiomyopathy and Arrhythmia

Genetic Testing Recommendations

PROVINCIAL GENETICS PROGRAM
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Ontario Health

Table of Contents

Introduction

Ontario Health has been mandated by the Ministry of Health to *"implement genetic testing and develop a comprehensive provincial genetics program for all genetic services."* To fulfill this mandate, the Provincial Genetics Program (PGP) was launched in April 2021. The PGP and Provincial Genetics Advisory Committee (PGAC) identified cardiogenetics as a priority domain for development in Ontario, resulting in the formation of the Cardiogenetics Expert Group in May 2022. The role of the Expert Group is to develop evidence-based guidance for the provision of genetic diagnostics and counselling services.

The recommendations in this report were initially developed by working groups in collaboration with clinicians, laboratory scientists, administrators, and patient and family advisors, and then refined and approved by consensus of the Expert Group.

Please note that data about prevalence, detection rate of molecular testing, penetrance, and age of diagnosis represents the best data available in the literature, which, however, remains limited for some of the conditions presented.

Guidance Document Scope

This document offers recommendations related to genetic assessment and testing for inherited cardiomyopathies and arrhythmias, with a focus on the following:

- Clinical considerations for delivery of genetic testing services
- Eligibility criteria for genetic testing
- Evidence-based multigene panels

The inherited cardiomyopathy and arrhythmia panels (Figure 1) encompass genes for the following clinical diagnoses[a]:

- **Cardiomyopathy panel:** hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic cardiomyopathy, left ventricular noncompaction cardiomyopathy, and select syndromic causes of cardiomyopathy[b].
- **Arrhythmia panel:** long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, short QT syndrome, cardiac conduction disease, ventricular and unspecified arrhythmias, arrhythmogenic cardiomyopathy/other cardiomyopathies, and select syndromic causes of arrhythmogenic conditions[b].

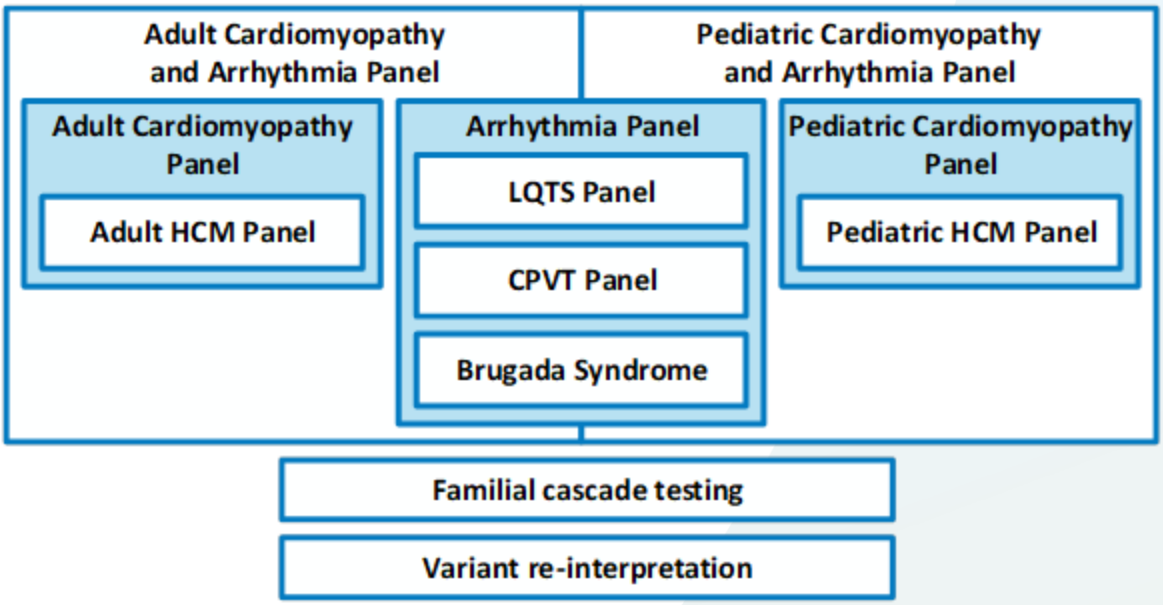
The intended audience for this guidance document includes medical geneticists, genetic counsellors, cardiologists, other cardiac physicians (e.g., cardiac surgeons), and other non-genetics physicians who

[a] Genes associated with most mitochondrial cardiomyopathies are not included, please see Appendix B.
[b] The syndromic causes included were selected because cardiomyopathy or arrhythmia can be the first manifestation of the disease.

provide care to patients and families with known or suspected inherited cardiomyopathies and arrhythmias.

Specific guidance related to ongoing cardiac surveillance is outside the scope of this document, however, management plans should be informed by the presentation of the disease in the family, taking into consideration the observation of significant variability in penetrance and expressivity seen within and among affected families.

Figure 1. Cardiomyopathy and Arrhythmia Genetic Testing Strategy[c]



CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; LQTS, Long QT syndrome.

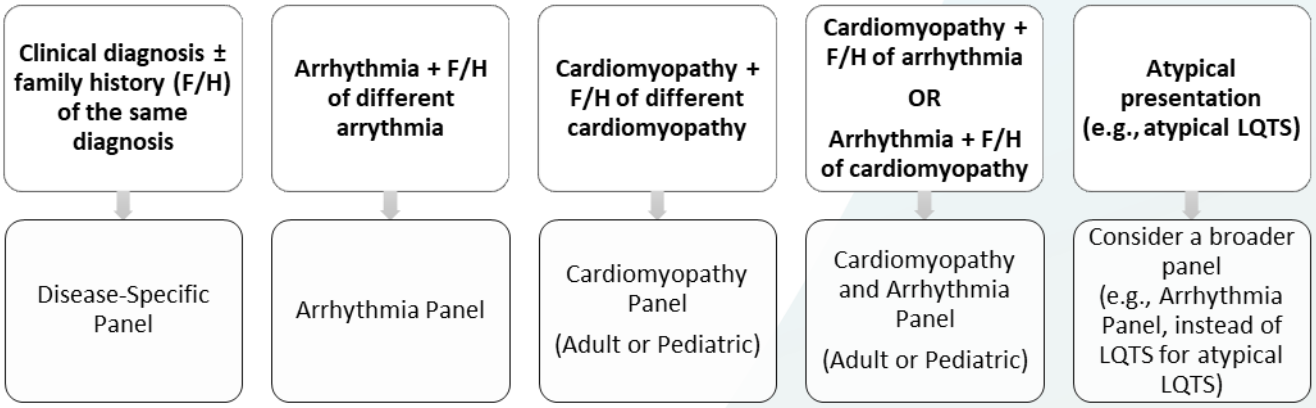
[c] Individuals 18 years old and under should be offered the pediatric panel. Moreover, individuals diagnosed (typically up to age 25 years old) should be eligible for the pediatric panel if the ordering clinician deems it appropriate (Consideration of pediatric genes).

Points to Consider for Genetic Testing

To achieve standardized care and equitable access to cardiogenetic testing in Ontario, the following points to consider were developed to assist physicians and genetic counsellors delivering genetic testing for inherited cardiomyopathies and arrhythmias:

1) **Appropriate utilization of the cardiomyopathy and arrhythmia panels:** A targeted approach to genetic testing is recommended when clearly indicated by the individual and/or family phenotype. However, a broad multigene panel has benefits in conditions with significant genetic heterogeneity and phenotypic overlap (Figure 2). The choice of panels should be driven by clinical judgement, informed by the patient phenotype, family history, and diagnostic certainty.

Figure 2. Genetic Testing Utilization Considerations



F/H, family history; LQTS, long QT syndrome.

a. **Consideration of non-genetic etiologies:** Genetic testing may not be indicated for individuals with phenotypes explained by secondary and/or acquired causes (e.g., coronary disease, hypertension, drug intoxication). However, genetic testing can still be considered for individuals with cardiomyopathies or arrhythmias when a non-genetic cause is identified but a clinical suspicion remains of an underlying genetic predisposition (e.g., peripartum cardiomyopathy, alcoholic cardiomyopathy)[1].
b. **Consideration of cardiomyopathy pediatric genes in young adults:** The pediatric panels were designed to consider metabolic, mitochondrial, and syndromic causes associated with cardiomyopathy in children[2]. Appropriate utilization of adult versus pediatric panels should be guided by the age of onset of symptoms for the individuals living with cardiomyopathy or arrhythmia in the family. Clinicians attending to young adults can consider requesting the analysis of the pediatric genes depending on the age at diagnosis (typically up to 25 years), family history, and pathophysiology of the condition.
c. **Clinical features suggestive of an underlying genetic syndrome:** For some individuals with cardiogenetic conditions, broader testing such as genome-wide sequencing (GWS), will be the

appropriate first line testing (Genome-wide sequencing). While the patient's first presenting symptomatology might be cardiac-related, other clinical features suggestive of an underlying genetic syndrome such as congenital malformations, dysmorphic features and/or neurocognitive impairments might also be present. The later can be particularly difficult to appreciate in individuals under the age of 36 months. Therefore, to select the best testing option, a physical examination by a medical geneticist is recommended for children 36 month of age and under and for patients for whom there are clinical concerns about potential dysmorphic features.

2) **Clinical genetics service delivery:** Genetic testing is generally provided following genetic counselling by a qualified geneticist, genetic counsellor, and/or physician with specialized training or expertise in genetics. However, genetic testing initiated by non-genetics physicians may help to improve timely and equitable access. In such cases, the ordering physician should be knowledgeable about the gene-based management guidelines. Predictive testing (i.e., in an unaffected individual), testing in pediatric populations, variant interpretation update, and expanded testing are best conducted by individuals with expertise in genetic counselling and/or heritable cardiomyopathies or heritable arrhythmias (Cascade testing for a known variant, testing relatives for variants of uncertain significance, clinical judgement). Interdisciplinary pathways and new models of care should be encouraged such that clinical assessment and testing are timely and equitable, following locally established protocols and processes for results disclosure and risk assessment.
3) **Identification of the proband in the family:** In the absence of a known familial pathogenic/likely pathogenic (P/LP) variant, molecular testing should be initiated on a source of germline DNA from an affected/informative individual. This may include testing post-mortem samples and/or stored DNA of a deceased relative if it is the most informative DNA source available.
4) **Collection of family history:** A detailed 3-generation family history is instrumental in the assessment of individuals with or at risk for cardiomyopathy and/or arrhythmia. It can help clarify the differential diagnosis, identify the most appropriate family member to initiate diagnostic genetic testing, select the most appropriate genetic test, interpret variants, assess risk, and recommend early detection and prevention options to at-risk family members. In circumstances where family history is extremely limited (e.g., adopted individual), molecular testing might be considered at the clinician's discretion, considering relevant clinical information (e.g., age of presentation, paucity of other risk factors, electrophysiologic and imaging phenotype, etc.)
5) **Variant re-interpretation:** In the past few years, the importance of variant re-interpretation in cardiogenetics has increasingly been recognized[3–9]. Variant re-interpretation can have very significant impacts on the care of patients and their at-risk relatives[10]. Variant re-interpretation by the laboratory is indicated when at least one of the following criteria are met:
    a. Evidence from ClinVar, gnomAD, and/or other reputable sources suggest that the variant interpretation might have changed.

b. Guidelines for interpretation of variants in the gene of interest have been updated since the last interpretation by American College of Medical Genetics and Genomics (ACMG)/Association of Molecular Pathology (AMP), ClinGen Variant Curation Expert Panels, ClinGen Sequence Variant Interpretation Working Group, and/or other reputable sources.
c. New familial segregation data has become available.
d. Variant interpretation may impact options for prenatal testing and/or management in an ongoing pregnancy.

6) **Cascade testing for a known variant:** If a P/LP variant in a gene associated with a heritable cardiogenetic condition has been confirmed in an individual following genetic testing, testing should be offered to all first-degree relatives for the known variant(s). Reporting of molecular testing results should include an updated variant interpretation by the testing laboratory.
   a. Testing of more distantly-related biological relatives can be considered depending on clinical circumstances (e.g., intervening relative[s] unavailable or do not consent to testing).
   b. Before offering testing for a known variant, the interpretation of the variant should be reviewed for new evidence (e.g., ClinVar, gnomAD). If there is evidence suggesting that the variant interpretation may have changed, a formal re-interpretation could be requested from the laboratory (when possible, re-interpretation should be requested from the laboratory who initially interpreted the variant).
   c. The timing of when to offer predictive molecular testing to an unaffected at-risk child should take into consideration the clinical actionability of the result[11]. Shared decision making between the patient, family, and health care professional is strongly encouraged. When available, the use of clinical decision aids such as the ones made freely available at the University of Alberta (Should My Child(ren) Have Predictive Genetic Testing?) should be encouraged[11,12].
   d. When offering testing for a known variant, every effort should be made to provide the testing laboratory with a copy of the original test report to aid in variant interpretation and to ensure consistency in interpretation of variants. If a testing lab interprets a familial variant differently than the original testing laboratory, every effort should be made by the testing laboratory to contact the original laboratory and discuss the differences to arrive at a consensus. This may result in additional reports being addended.

7) **Testing relatives for variants of uncertain significance:** If a variant of uncertain significance (VUS) in a gene associated with a heritable cardiogenetic condition has been confirmed in an affected individual following genetic testing, the interpretation of the VUS should be reviewed prior to considering testing in blood relatives. If there is evidence suggesting that the variant interpretation may have changed, a formal re-interpretation could be requested from the laboratory.
   a. In general, testing unaffected at-risk relatives for a VUS is not recommended.

b. Testing other affected relatives to determine if a VUS segregates with disease in the family may be helpful. Testing unaffected individuals can be considered in some cases, but issues of incomplete penetrance and age-related penetrance need to be carefully considered. Familial segregation alone is typically not sufficient evidence to prove pathogenicity of a variant, but it can sometimes contribute to variant re-classification[13]. In most circumstances, a VUS should not be used to alter medical management. Nonetheless, clinical judgement should be used.
c. Testing unaffected parents can be considered to establish that a variant is *de novo* or that 2 variants are in trans when detected in a gene associated with an autosomal recessive condition.

8) **Clinical judgement:** In families and individuals that are suspicious for a hereditary risk, clinicians may use clinical judgment to support genetic testing decisions as detailed below.
   a. **Expanded testing following uninformative cardiomyopathy and/or arrhythmia panel results:** Expanded genetic testing with a broader panel or GWS may be warranted if traditional genetic testing strategies have not identified the underlying cause of disease in a family. This may include, for example, multiple affected siblings where the parents are consanguineous. The decision to expand genetic testing should be associated with a reasonable likelihood of clinical benefit to the patient/family.
   b. **Expanded testing for affected relatives in a family with a known variant:** If there is an unusual phenotype in the patient being assessed, such as an atypical or more severe presentation of disease or significant family history of disease on the other side of the patient's family, a broader multigene panel may be indicated rather than known variant testing. The clinician should consider the known intra-familial variability in expressivity when making such clinical judgements.
   c. **Additional testing strategies:** Clarifying certain genetic test results can be challenging. Potential strategies to support interpretation such as RNA analysis, mosaicism testing, or chromosomal microarray are outside the scope of this document.
   d. **Not offering genetic testing:** Clinicians may decide not to proceed with genetic testing if the clinical benefit and/or diagnostic yield is predicted to be low based on the pattern of disease in the family and affected individuals.
9) **DNA banking and/or storage:** Banking or storage of DNA facilitates future molecular testing following acute cardiac events and/or to support risk assessment for surviving relatives following a cardiac death. DNA banking or storage should therefore be available for patients presenting with sudden cardiac arrest (SCA), in critical condition, and/or medically unstable, even if the patient has received a transfusion.
10) **Testing turnaround time:** Expedited testing with a turnaround time (TAT) of ≤ 2 weeks may be required to support management in an ongoing pregnancy. Moreover, in rare circumstances expedited testing might also be warranted when it will influence decision making about transplant

or goals of care in a critically ill infant. In the majority of cases, TAT of ≤ 8-10 weeks is clinically appropriate.

Note: When a disease-causing variant is not identified, first-degree relatives of affected individuals should benefit from clinical cardiac surveillance/phenotyping as clinically indicated.

Arrhythmia

Inherited cardiac arrhythmias are a group of disorders that involve abnormal heart rhythms. They typically present without structural abnormalities or macroscopic evidence of disease. However, they are often the cause of sudden cardiac death (SCD). The most common inherited cardiac arrhythmias are[15,16]:

- Long QT syndrome (LQTS); prevalence 1 in 10,000 to 1 in 2,500[16]
- Catecholaminergic polymorphic ventricular tachycardia (CPVT); prevalence 1 in 10,000 or less[17]
- Brugada syndrome (BrS); prevalence 1 in 3,000[18] to 1 in 2,000[1]
- Short QT syndrome (SQTS); prevalence 1 in 5,000[19]

Inherited cardiac arrhythmias are primarily inherited in an autosomal dominant manner. A P/LP variant in a gene linked to inherited arrhythmia can provide diagnostic, prognostic, and therapeutic information for probands[20]. The potential impact and predicted clinical utility of genetic testing differs across inherited arrhythmia syndromes. When a P/LP variant is confirmed in a family, it allows for cascade testing of at-risk blood relatives to support early detection and prevention of adverse events.

Arrhythmias are genetically heterogeneous, meaning that the condition can be caused by a pathogenic variant(s) in any one of a number of genes. A pathogenic variant will not be identified for every individual and the absence of a pathogenic variant in a clinically-affected individual does not exclude a clinical diagnosis of a heritable condition.

The electrocardiographic phenotype including, where appropriate, the response to provocation testing (exercise/pharmacological) should be considered to determine the most appropriate test for an individual.

Long QT Syndrome

Long QT syndrome (LQTS) is characterized by QT prolongation and frequently accompanied by T-wave abnormalities. Symptoms of LQTS can include syncope, but many patients are asymptomatic. LQTS can lead to torsade de pointes (TdP) and SCD. LQTS is typically diagnosed by a cardiologist with expertise in electrophysiology. The Schwartz score is a diagnostic scoring system that includes the length of the QTc, other electrocardiogram (ECG) features, clinical history of syncope, and family history. A Schwartz score of 1.5-3.0 indicates intermediate probability of LQTS, while a score >3.5 indicates high probability (detection rate of 70-85%)[21].

The prevalence of LQTS is approximately 1 in 2,500 people. Clinical manifestations tend to occur during childhood or adolescence. Among symptomatic index cases, the untreated 10-year mortality is 50%[1]. The incidence and triggers for cardiac events vary depending on the specific gene involved. Genotype also affects medical management. For example, a sodium channel blocker may be added to the pharmacological treatment of individuals with LQTS type 3 while beta-blockers are the preferred pharmacological agents for other types of LQTS. Therefore, an accurate and prompt diagnosis is critical in this patient population.

At least 12 genes are associated with inherited LQTS, but disease-causing variants in *KCNQ1*, *KCNH2*, and *SCN5A* account for the majority of detectable disease-causing variants. LQTS is typically inherited in an autosomal dominant manner. However, it is possible for multiple disease-causing variants (either bi-allelic variants in the same gene or heterozygous variants in more than one gene) to co-occur in the same individuals, which leads to greater severity. In addition, there are also *bona fide* forms of autosomal recessive QT prolongation. The penetrance of LQTS is approximately 50% and the detection rate by molecular testing in affected individuals is approximately 80%.

In addition to non-syndromic inherited arrhythmias, a number of recognizable genetic syndromes are associated with cardiac arrhythmia and QT prolongation, including:

- Jervell Lange and Nielson: hearing loss (*KCNQ1* and *KCNE1*)
- Timothy: Syndactyly, autism/intellectual disability, seizure, hypotonia, dysmorphism, congenital heart disease (*CACN1AC*)
- Triadin cardiac arrhythmia: negative T waves in precordial leads (*TRDN*)
- Andersen-Tawil syndrome: QTU (not QT) prolongation, periodic paralysis/hyperkalemic episodes, ventricular tachycardia (VT), and bidirectional VT (rare TdP), and dysmorphic features (*KCNJ2*)

Exclusion of secondary causes for QT prolongation is of paramount importance for LQTS.

LQTS genetic testing eligibility criteria

1) Individuals with a strong clinical suspicion or clinical diagnosis of **LQTS** defined as meeting at least one of the following criteria:
   a. LQTS risk score ≥3.5[21].
   b. QTc ≥500 ms on repeated 12-lead ECG.
   c. QTc ≥480 ms on repeated 12-lead ECG AND an unexplained syncopal episode.
   d. QTc ≥480 ms on repeated 12-lead ECG AND a history of sudden unexplained death under the age of 60 in a first or second degree relative.
   e. Pre-pubertal individuals with a QTc >460 ms[d].

Genetic test options include:

- LQTS Panel
- If additional red flags (Figure 2) consider:
  - Arrhythmia Panel
  - CM and Arrhythmia Panel

[d] Consider consultation with a pediatric cardiologist with expertise in electrophysiology.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by episodic adrenergically mediated ventricular arrhythmias in response to acute exertional or emotional stress. The condition occurs in the absence of structural heart disease and resting electrocardiographic abnormalities such that a normal appearance to a resting 12 lead ECG is expected. These can sometimes present as syncope occurring during exercise or acute emotion.

CPVT is rare with an estimated prevalence estimated of 1:10,000 or less[17]. The mean onset of symptoms is between age 7 and 12 years; onset as late as the fourth decade of life has been reported. Approximately 30% of affected individuals experience at least one cardiac arrest and up to 80% have one or more syncopal events. SCD may be the first manifestation of the disease[15].

CPVT is commonly inherited in an autosomal dominant manner[15]. In 65% of CPVT probands, the disorder is associated with pathogenic variants in the *RYR2* gene, however, CPVT is genetically heterogeneous with phenotypic overlap with other inherited cardiac arrhythmias. Approximately 25% of individuals diagnosed with CPVT lack a pathogenic variant in a known CPVT-related gene[17].

CPVT genetic testing eligibility criteria

1) Individuals with a strong clinical suspicion or clinical diagnosis of **CPVT** defined as meeting at least one of the following criteria:
   a. Structurally normal heart, normal resting ECG, and unexplained exercise or catecholamine-induced bidirectional VT, polymorphic ventricular premature beats or VT/ventricular fibrillation (VF) in an individual under 40 years of age.
   b. Structurally normal heart and coronary arteries, normal resting ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT/VF in an individual over 40 years of age.

Genetic test options include:

- CPVT Panel
- If additional red flags (Figure 2) consider:
  - Arrhythmia Panel
  - CM and Arrhythmia Panel

Brugada Syndrome

Brugada syndrome (BrS) is characterized by classical, well-described electrocardiographic abnormalities that carry an increased risk of life-threatening ventricular arrhythmias and SCD. It is estimated that BrS may be involved in between 18-28% of sudden deaths and cardiac arrests with a mean age of SCD of approximately 40 years[1]. Although rare, pediatric cases of SCD are seen, and clinical presentations may therefore include sudden infant death syndrome and sudden unexpected nocturnal death syndrome. While the classical ECG features are well described, these may be transient and manifest during fever or provocation testing.

BrS has a prevalence of 1 in 2,000 to 3-5 in 10,000[18]. The largely sporadic presentation of the disorder and low penetrance in families with rare variants, suggests that BrS has a more complex inheritance pattern than Mendelian/monogenic pattern[22]. The detection rate of molecular testing for BrS is approximately 30%[18], with 1% of affected individuals confirmed to have a *de novo* variant. Sodium channel blocker testing may be appropriate for patients with a P/LP or rare VUS[20].

Please note that features of other sodium channel disorders can coexist with type 1, 2, 3 Brugada patterns.

Brugada Syndrome genetic testing eligibility criteria

1) Individuals with a strong clinical suspicion or clinical diagnosis of **BrS** and/or sodium channel disease defined as meeting at least one of the following criteria:
   a. Spontaneous type 1 ("coved-type") ST-segment elevation (characterized by ST-segment elevation ≥2 mm [0.2 mV] in ≥1 right precordial leads [V1-V3] positioned in the 4th, 3rd, or 2nd intercostal space).
   b. Type 1 ST-segment elevation unmasked using a sodium channel blocker. Relevant features, may also include:
      i. Documented VF or polymorphic VT.
      ii. Syncope of probable arrhythmic cause.
      iii. Family history of SCD <45 years old with negative autopsy.
      iv. Coved-type ECG in family members.
      v. Nocturnal agonal respiration.
      vi. Premature atrial arrhythmias at age <30 years.

Genetic test options include:

- *SCN5A* test
- If additional red flags (Figure 2):
  - Arrhythmia Panel
  - CM and Arrhythmia Panel

Short QT Syndrome

Short QT syndrome (SQTS) is a rare but life-threatening familial disorder characterized by an abnormally short QT interval on the ECG[23]. SQTS increases the risk of a cardiac arrhythmia and SCD.

SQTS was first identified in 2000; since then, only about 250 cases have been reported in the scientific literature. SQTS is associated with incomplete penetrance and variable expressivity. Although SQTS may be diagnosed in children if they show clear cardiac symptoms, or if a positive family history is suspected, it is difficult to establish a specific age of onset. Consequently, the incidence of SQTS in the general population remains unclear.

In cases where the genetic cause is known (20-30%) the disease-causing variant is inherited in an autosomal dominant manner.

SQTS genetic testing eligibility criteria

1) Individuals with a strong clinical suspicion or clinical diagnosis of SQTS defined as meeting at least one of the following criteria:
   a. A QTc ≤330 ms.
   b. A QTc <360 ms, AND one or more of the following:
      i. Family history of SQTS.
      ii. Family history of SCD ≤40.
      iii. Survival of a VT/VF episode in the absence of heart disease.

Genetic test options include:

- Arrhythmia Panel
- If additional red flags (Figure 2):
  - CM and Arrhythmia Panel

Cardiac Conduction Disease

Cardiac conduction disease (CCD)/progressive cardiac conduction disease (PCCD) is a heterogeneous condition. It may present as a primary conduction disease or in association with structural heart disease[24].

CCD/PCCD is rare, and its true prevalence is unknown, however, approximately 50 familial PCCD cases have been described in the literature[25]. Inherited CCD/PCCD is marked by variable expression and incomplete penetrance both within and among affected families. It is commonly inherited in an autosomal dominant fashion. CCD/PCCD may also occur in the context of some neuromuscular disorders (e.g., 90% of individuals with myotonic dystrophy type 1 [DM1][26]). Genetic testing for DM1, a trinucleotide expansion disorder not detected by sequencing and exome sequencing, should be pursued for individuals with signs and symptoms in keeping with the disorder (for more information, visit Myotonic Dystrophy Type 1). Pathogenic variants in arrhythmia-related genes are identified in approximately 50% of index cases.

CCD/PCCD can occur in non-isolated forms, and may precede and overlap with congenital heart disease, cardiomyopathy, or extracardiac manifestations phenotypes[27].

Consideration for non-genetic causes of CCD include fibrotic degeneration, ischemia, infiltrative and infectious processes, valve calcifications, tumours, and thyroid dysfunction[1].

CCD genetic testing eligibility criteria

1) Individuals with a strong clinical suspicion or clinical diagnosis of **CCD** defined as meeting at least one of the following criteria:
   a. Unexplained progressive conduction abnormalities in young (<50 years) individuals with structurally normal hearts in the absence of skeletal myopathies, especially if there is a family history of CCD[27].
   b. Disturbed electrical impulse propagation in the atrioventricular node and His-Purkinje system.
   c. CCD when there is early age of diagnosis or a suspicion of laminopathy, especially if there is a family history of CCD[1].

Genetic test options include:

- Arrhythmia Panel
- If additional red flags (Figure 2):
  - CM and Arrhythmia Panel

Ventricular and Unspecified Arrhythmias

Ventricular arrhythmia (VA) is a broad term encompassing a range of arrhythmias from premature ventricular complexes (PVCs) through to VT to VF. Consequently, the associated clinical presentation can be equally broad from an asymptomatic, incidental findings on PVCs through to SCD.

The most common etiology for VA in adults is ischemic heart disease. While this may occur in isolation, given its high prevalence, it may also coexist with acquired conditions such as myocarditis or structural heart diseases, which in themselves may also result in VA. Where such a secondary etiology is considered unlikely, exploration of the family history, additional clinical testing, and ultimately the identification of genetic variants associated with heritable arrhythmias, and cardiomyopathies are critical steps in the investigation and management of these conditions. Involvement of a cardiologist with expertise in the inherited arrhythmia syndromes to guide further testing, and interpretation of the results is usual in such cases.

The role of molecular testing should be strongly considered if a secondary etiology is deemed unlikely to explain the patient's phenotype. Where electrophysiological investigations and/or imaging are strongly suggestive of a specific underlying diagnosis (e.g., LQTS, cardiomyopathy, etc.), targeted testing for such a condition should be offered. However, if after appropriate clinical evaluations/phenotyping, a specific underlying diagnosis is not uncovered or if features remain atypical for any single condition, a broader molecular testing panel in the form of a comprehensive arrhythmia or arrhythmia and cardiomyopathy panel are appropriate.

Ventricular arrhythmia genetic testing eligibility criteria

1) Individuals without structural heart disease who meet at least one of the following criteria:
   a. Unexplained resuscitated cardiac arrest.
   b. Sustained VT/VF.
   c. Concerning arrhythmia history (e.g., recurrent exertional syncope, unexplained near drowning/agonal breathing).
   d. Family history of unexplained SCA in phenotype negative individuals.

Genetic test options include:

- Arrhythmia panel
- If additional red flags (Figure 2):
  - CM and Arrhythmia Panel

Adult Cardiomyopathies

Cardiomyopathy (CM) is a disease of the heart muscle. It impacts the ability of the heart to pump blood and can present as heart failure, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and SCD.

For the purposes of this document, the Expert Group focused on the five main forms of cardiomyopathy[28]:

- Dilated cardiomyopathy (DCM); prevalence 1 in 2,500, incidence 5-7 per 100,000 per year[29]
- Hypertrophic cardiomyopathy (HCM); prevalence 1 in 500
- Restrictive cardiomyopathy (RCM); prevalence unknown
- Arrhythmogenic cardiomyopathy (ACM); prevalence 1 in 5,000[30,31]
- Left ventricular noncompaction cardiomyopathy (LVNC); incidence 8-12 in 1 million per year[32]

All forms of cardiomyopathy can affect both adults and children and the clinical considerations described above are relevant to all age groups.

The clinical utility of genetic testing for patients and families with cardiomyopathy is significant. Genetic testing can confirm and/or clarify the diagnosis, inform management recommendations, and enable cascade screening of relatives (Cascade testing). Cascade testing can help to support early detection of diseases including cardiovascular conditions leading to possible reduced morbidity and mortality in relatives of the affected individual(s)[33].

Adult Hypertrophic Cardiomyopathy

HCM is a relatively common condition, affecting 1 in 500 individuals. HCM is primarily a disease of the sarcomere although there are a number of non-sarcomeric pathogenic variants with moderate to strong evidence of pathogenicity. Disease-causing variants are identified in approximately 20-30% of cases with no family history and in 60% of familial cases[1]. There are also several HCM phenocopies, defined as syndromic and infiltrative conditions that can 'mimic' HCM. Notable phenocopies can include lysosomal and glycogen storage diseases, RASopathies and amyloidosis. Recognition of HCM phenocopies is critical as management will differ significantly from that of sarcomeric HCM[34]. Establishing a differential diagnosis can help to guide decisions about genetic testing.

For patients with a phenotype specific for *TTR* amyloidosis, expedited single gene analysis is appropriate given the clinical actionability of this diagnosis.

Adult HCM genetic testing eligibility criteria

1) Individuals with a strong clinical suspicion or clinical diagnosis of **HCM** defined as meeting at least one of the following criteria:
   a. Unexplained left ventricular hypertrophy with a maximum wall thickness ≥15 mm in adults.
   b. More limited hypertrophy (13-15 mm) in the context of family history of HCM.
   c. Suspicion of clinical diagnosis of HCM with borderline dimensions, particularly in patients without a history of hypertension, without concentric hypertrophy, and in young or female patients.

Genetic test options include:

- Adult HCM Panel
- If additional red flags (Figure 2) consider:
  - Adult CM Panel, or
  - Adult CM and Arrhythmia Panel

Adult Dilated Cardiomyopathy

DCM is one of the most common causes of heart failure. Estimates of prevalence are challenging as DCM is a clinically heterogenous set of conditions with genetic, acquired, and secondary causes, reduced and/or incomplete penetrance, and underreporting[29]. Generally, the prevalence of DCM is quoted at 1 in 2500 individuals in the general population, but some reports suggest it could be as high as 1 in 250. Approximately 20-35% of individuals with DCM have a positive family history of the disease and the yield of genetic testing may be as high as 20-50% in familial cases[1].

50-70% of DCM is idiopathic while 30-50% is inherited, primarily in an autosomal dominant manner[2]. DCM is the most genetically heterogenous of the cardiomyopathies, with autosomal recessive, X-linked, and mitochondrial patterns of inheritance also reported. Non-heritable etiologies for dilated cardiomyopathies include infection/sepsis (notably, 10-20% of DCM cases can also be linked to acute myocarditis), diet, endocrinopathy, congenital heart defects resulting in secondary DCM (e.g., coarctation), ischemia, and/or cancer[35].

Establishing a differential diagnosis to determine if the cause of DCM is most likely sarcomeric or syndromic, including neuromuscular conditions (e.g., DM1), laminopathy, or metabolic, can help guide decisions about appropriate genetic testing. Genetic testing for DM1 should be pursued for individuals with signs and symptoms in keeping with the disorder (for more information, visit Myotonic Dystrophy Type 1). Also, additional risk factors for DCM such as exposure to drugs or toxins, nutritional deficiency, myocardial injury caused by infectious agents, autoimmune disorders (i.e., sarcoidosis), or peripartum cardiomyopathy[35,36] should be considered during diagnosis.

Not every dilation is associated with a cardiomyopathy (characterized by systolic dysfunction). For example, athletes with dilation but without systolic dysfunction are not considered to have DCM.

Adult DCM genetic testing eligibility criteria

1) Individuals with a strong clinical suspicion or clinical diagnosis of **DCM** defined as meeting at least one of the following criteria:
   a. Left ventricular or biventricular systolic dysfunction (ejection fraction of less than 50%) and dilatation that are not explained by abnormal loading conditions or coronary artery disease.
   b. Left ventricular or biventricular global systolic dysfunction without dilatation (defined as left ventricular ejection fraction (LVEF) < 45%), not explained by abnormal loading conditions or coronary artery disease[36].
   c. Left ventricular or biventricular dilatation.

Genetic test options include:

- Adult CM Panel
- If additional red flags (Figure 2):
  - Adult CM and Arrhythmia Panel

Adult Restrictive Cardiomyopathy

RCM is a relatively rare cardiomyopathy, and prevalence estimates are not known. RCM may be inherited or acquired. Potential causes include auto-immune conditions, iron overload, parasites, malignancy, toxins. Genetic factors may also play a role in the development of RCM and a genetic diagnosis can aid in clinical management.

Multiple genetic variants, environmental factors and epigenetic modifications may also influence the disease presentation. As a result, there tends to be considerable variability in RCM presentation. The age of disease onset, the severity of the disease, and the disease phenotype can differ, even among patients in the same family[37].

Secondary causes of a restrictive cardiomyopathy (e.g., amyloidosis, sarcoidosis, hemochromatosis) are relevant considerations in the differential diagnosis.

Adult RCM genetic testing eligibility criteria

1) Individuals with a strong clinical suspicion or clinical diagnosis of **RCM** defined as meeting at least one of the following criteria:
   a. Presence of impaired left ventricular (LV) filling.
   b. Diminished diastolic volume with normal/near-normal LV wall thickness and ejection fraction.

Genetic test options include:

- Adult CM Panel
- If additional red flags (Figure 2):
  - Adult CM and Arrhythmia Panel

Adult Arrhythmogenic Cardiomyopathy

ACM is characterized by progressive fibrofatty replacement of the myocardium which may or may not compromise systolic function. There are 3 phenotypic variants of ACM for which genetic testing is part of the diagnostic criteria: arrhythmogenic right ventricular cardiomyopathy (ARVC), biventricular variant, and arrhythmogenic left ventricular cardiomyopathy (ALVC)[2,38,39]. The clinical diagnosis may be made by cardiac MRI, surgical, autopsy, or biopsy tissue. The fibrofatty replacement of the myocardium increases the risk of arrhythmia and SCD.

The prevalence of ACM is about 1 in 1,000 to 1 in 5,000 people ACM usually affects young adults. In the paediatric cases, SCA occurs at approximately 15 years of age and episodes of sustained VT at approximately 16.7 years[40]. Typically, ACM is inherited in an autosomal dominant manner although an autosomal recessive pattern of inheritance has also been reported. Variants linked to ACM tend to have variable penetrance and expressivity that may imply that environmental factors also play a significant role. The reported diagnostic yield in ACM is highly variable across studies, however, is estimated to be in the range of 50-60%.

Clinicians should consider morpho-functional abnormalities, repolarization and depolarization ECG changes, ventricular arrhythmias, and tissue characterization findings as described on the Padua Criteria[41], as well as syndromic presentations (e.g., Naxos disease) for appropriate test selection.

Adult ACM genetic testing eligibility criteria

1) Individuals with a clinical diagnosis of **ACM** as per the 2020 Padua criteria[42].
   a. Individuals who would fulfill diagnostic criteria if a disease-causing variant in a gene associated with ACM was identified are also eligible for testing.

Genetic test options include:

- Adult CM Panel
- If additional red flags (Figure 2):
  - Adult CM and Arrhythmia Panel

Adult Left Ventricular Noncompaction Cardiomyopathy

LVNC is characterized by abnormal development of the cardiac muscle of the ventricle. This leads to prominent trabeculations[43–45]. Patients with LVNC may also have features of DCM or HCM, but not all patients with LVNC will have an impaired ejection fraction[46]. LVNC is associated with progressive left ventricle dysfunction. In some patients, the right ventricle is also involved[43,44]. LVNC may increase the risk of arrhythmia, thromboembolic events, and heart failure[43,44,46].

LVNC is a rare form of cardiomyopathy. Every year, 8-12 per 1 million people are estimated to be affected by the disease[47]. LVNC is typically inherited in an autosomal dominant manner, but cases of autosomal recessive and X-linked recessive patterns of inheritance have also been reported[45,47]. Diagnostic yield for LVNC varies depending on the population, but published studies show a range of up to 38%[48].

Note that genetic testing is not indicated in isolated (incidental) LVNC with normal LV function, no arrhythmia, no associated syndromic features, and no family history.

Adult LVNC genetic testing eligibility criteria

1) Individuals with a strong clinical suspicion or consistent phenotypic features of **LVNC** defined as meeting at least one of the following criteria:
   a. Cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history and electrocardiographic/echocardiographic/MRI phenotype.
   b. Clinical diagnosis of LVNC cardiomyopathy associated with other cardiac or non-cardiac syndromic features.

<u>Genetic test options include:</u>

- Adult CM Panel
- If additional red flags (Figure 2):
  - Adult CM and Arrhythmia Panel

Pediatric Cardiomyopathies

Pediatric cardiomyopathy is a rare, genetically heterogeneous disease that affects approximately 1 in 100,000 infants and children under 20 years of age[49,50]. Pediatric-onset cardiomyopathies are associated with an increased risk of life-threatening arrhythmia, severe heart failure, and cardiac transplant when compared to adult-onset cardiomyopathies. Pediatric cardiomyopathies are also more likely to be syndromic and therefore establishing the diagnosis can have additional impact for the non-cardiac health care management of the child. While very rare in adults, recessive conditions and bi-allelic variants are well described in pediatric-onset cardiomyopathies.

Not all cardiomyopathies have a genetic basis, but many do have a genetic etiology, and there is some molecular overlap amongst the five forms (i.e., HCM, DCM, RCM, ACM, and LVNC). The diagnostic yield of genetic testing for cardiomyopathies ranges between 10-60% depending on the form of cardiomyopathy and it is reported that the yield is higher for individuals with added family history[2]. Routine use of clinical genetic testing in pediatric cardiomyopathy is recommended. For the purposes of this section, analysis of the pediatric genes can be considered for individuals diagnosed up to 25 years of age (Consideration of cardiomyopathy pediatric genes in young adults).

Children with cardiomyopathy can either present as the proband in their family or with a known family history. The likelihood of a child having a family history is higher for HCM (59%) and LVNC (50%) than in DCM (28%) and RCM (20%)[51].

Consideration for syndromic presentations is relevant in children with dysmorphic features, congenital anomalies and/or other medical co-morbidities. A detailed dysmorphology exam by a medical geneticist is recommended in children under age 36 months with suspicion of syndromic features that may be subtle and/or challenging to diagnose (Syndromic presentations).

Pediatric Hypertrophic Cardiomyopathy

HCM is characterized by hypertrophy of the heart muscle. 42% of childhood cardiomyopathies are classified as HCM. It is the leading cause of SCD in children[49]. HCM has an overall incidence of 0.47 per 100,000 children, with the incidence being 3x higher in children under 1 year of age[52]. Approximately 60% of HCM is inherited in an autosomal dominant manner[53], and the primary genetic cause of HCM involves disease-causing variants in genes that encode sarcomeric proteins[54]. However pediatric HCM is complicated and encompasses a heterogenous group of disorders.

The recommended baseline metabolic investigations include, at a minimum, acylcarnitine profile, carnitines, urine oligosaccharides, and mucopolysaccharides fractionation. If the metabolic testing uncovers a diagnosis, HCM molecular testing should be cancelled.

Approximately 20% of children with Noonan syndrome (NS) present HCM[55] and should be considered when selecting the appropriate testing strategy. Targeted testing for NS may be considered if the clinical presentation is highly suspicious (Noonan syndrome). Also, cardiomyopathy may occur for about two-thirds of individuals with Friedrich ataxia (FA). Since FA is caused by triple expansion repeats, it will not be detected by sequencing, and single gene testing (*FXN*) should be requested if it is a diagnostic consideration. Genetic testing for FA should be pursued for individuals with signs and symptoms in keeping with the disorder (Friedreich Ataxia). Establishing a differential diagnosis that could include sarcomeric etiologies, syndromic conditions (e.g., RASopathies, Friedreich ataxia) and metabolic disorders (mitochondrial, glycogen storage disorder, fatty acid oxidase disorder, lysosomal) can help guide decisions about genetic testing.

Pediatric HCM genetic testing eligibility criteria

1) Children with a strong clinical suspicion or clinical diagnosis of **HCM** who meet the following criteria:
   a. Z score greater than 2.0 standard deviations (as per the Boston calculator) for interventricular septum and/or posterior left ventricular wall.

Genetic test options include:

- Pediatric HCM Panel
- If additional red flags (Figure 2):
  - Pediatric CM Panel
  - Pediatric CM and Arrhythmia Panel

Pediatric Dilated Cardiomyopathy

DCM is the most common form of pediatric cardiomyopathy, accounting for approximately 55-60% of all pediatric cardiomyopathies[56]. It has an incidence of approximately 0.57 cases per 100,000 children[57]. Some major causes for pediatric DCM include infections, inflammation, toxic causes (including chemotherapy), genetics, and inborn errors of metabolism[40]. The prognosis for these children is poor, with 40% requiring a cardiac transplant or dying within 5 years after diagnosis[58]. Genetic DCM is inherited in an autosomal dominant pattern, although autosomal recessive, X-linked recessive, and mitochondrial inheritance can occur[57].

The recommended baseline metabolic investigations include acylcarnitine profile, carnitines, urine organic acids and serum CK. If the metabolic testing uncovers a diagnosis, DCM molecular testing should be cancelled.

Establishing a differential diagnosis to determine if the cause of DCM is most likely sarcomeric or syndromic, including neuromuscular conditions (e.g., DM1), laminopathy, or metabolic, can help guide decisions about appropriate genetic testing. Genetic testing for DM1 should be pursued for individuals with signs and symptoms in keep with the disorder, for more information, visit Myotonic Dystrophy Type 1. Also, alternate probable aetiologies such as infection/sepsis, metabolic, nutrition, endocrine, congenital heart defects resulting in secondary DCM (e.g., coarctation), ischemia, or oncology[35] should be considered during diagnosis.

Pediatric DCM genetic testing eligibility criteria

1) Children with a strong clinical suspicion or clinical diagnosis of **DCM** who meet the following criteria:
   a. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) Z scores greater than two and decreased ejection fraction <55%.

Genetic test options include:

- Pediatric CM Panel
- If additional red flags (Figure 2):
  - Pediatric CM and Arrhythmia Panel

Pediatric Restrictive Cardiomyopathy

RCM is the rarest form of cardiomyopathy. It accounts for about 2.5-4.5% of all pediatric cardiomyopathy cases[37,46]. In children, the annual incidence is 0.03-0.04 per 100,000 patients[46]. However, as per Bagnall et al, the diagnostic yield of molecular testing for RCM was approximately 80%, albeit in a small cohort of twenty patients. The prognosis of RCM tends to be poor. Many patients experience arrhythmias, thromboembolic events, and SCD. Cardiac transplantation is often required[37,43,59].

Multiple genetic variants, environmental factors and epigenetic modifications may also influence the disease presentation. As a result, there tends to be considerable variability in RCM presentation. The age of disease onset, the severity of the disease, and the disease phenotype can differ, even among patients in the same family[37].

Secondary causes of a restrictive cardiomyopathy (e.g., amyloidosis, sarcoidosis, hemochromatosis) are relevant considerations in the differential diagnosis.

Pediatric RCM genetic testing eligibility criteria

1) Children with a strong clinical suspicion or clinical diagnosis of **RCM** who meet the following criteria:
   a. Coexistence of persistent restrictive pathophysiology, commonly with atrial dilatation, and nondilated ventricles, regardless of ventricular wall thickness and systolic function[60].

Genetic test options include:

- Pediatric CM Panel
- If additional red flags (Figure 2):
  - Pediatric CM and Arrhythmia Panel

Pediatric Arrhythmogenic Cardiomyopathy

ACM is characterized by progressive fibrofatty replacement of the myocardium which may or may not compromise systolic function. The clinical diagnosis may be made by cardiac MRI, or tissue biopsy (surgical or autopsy). The fibrofatty replacement of the myocardium increases the risk of arrhythmia and SCD. While ACM most often impacts the right ventricle, it can also impact the left ventricle or be bi-ventricular[2,38,39]. The prevalence of adult ACM is estimated between 1 in 1,000 to 1 in 5,000 people, but pediatric prevalence is not yet known[61]. ACM exhibits primarily an autosomal dominant inheritance pattern, but autosomal recessive cases have been reported[30,31]. ACM usually affects young adults (20-40 years) and accounts for 22% of cases of SCD among athletes[43]. In the rare cases when it affects children, the phenotype tends to be more severe[39].

Pediatric ACM genetic testing eligibility criteria

1) Children with a clinical diagnosis of **ACM** as per the 2020 Padua criteria[41,42].
    a. Individuals who would fulfill diagnostic criteria if a disease-causing variant in a gene associated with ACM was identified are also eligible for testing.

Genetic test options include:

- Pediatric CM Panel
- If additional red flags (Figure 2):
    - Pediatric CM and Arrhythmia Panel

Pediatric Left Ventricular Noncompaction Cardiomyopathy

LVNC is a rare form of cardiomyopathy. Every year, 8-12 per 1 million people are estimated to be affected by the disease[47]. In the pediatric population, the annual incidence is estimated to be 0.12-0.81 per 100,000 patients. LVNC may comprise approximately 5% of all pediatric cardiomyopathy cases[2,43,46]. In the small Bagnall cohort of twelve pediatric patients with LVNC, the detection rate of molecular testing was 25%[51]. LVNC may also be present in patients as part of Barth syndrome, Noonan syndrome, and more[2,46,62].

Note that genetic testing is not indicated in isolated (incidental) LVNC with normal LV function, no arrhythmia, no associated syndromic features, and no family history.

Pediatric LVNC genetic testing eligibility criteria

1) Children with a strong clinical suspicion or consistent phenotypic features of **LVNC** defined as meeting at least one of the following criteria:
   a. Cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history and electrocardiographic/echocardiographic/MRI phenotype.
   b. Clinical diagnosis of LVNC cardiomyopathy associated with other cardiac or non-cardiac syndromic features.

<u>Genetic test options include:</u>

- Pediatric CM Panel
- If additional red flags (Figure 2):
  - Pediatric CM and Arrhythmia Panel

Genome-wide Sequencing

In Ontario, GWS is clinically funded for individuals with complex multisystem disorders. Some patients whose clinical presentation includes a cardiac phenotype may currently be eligible for funded exome sequencing. The Expert Group recommends the eligibility for GWS should be expanded to include patients with complex cardiac disease involving multiple cardiac phenotypes.

GWS may be carried out as either genome sequencing or exome sequencing that includes detection of both large and gene/exon/sub-exon level deletions and duplications (i.e., structural variants). Variant filtering and prioritizing should follow a genotype-driven strategy, supplemented by phenotype-driven analysis to identify the variants relevant to the patient's phenotype[14]. The decision between implementing exome or genome sequencing is beyond the scope of this document. When a patient would be eligible for GWS and for panel testing, the decision between panel testing or GWS, beyond eligibility criteria, should account for the technical differences between approaches. A more detailed comparison of the pros and cons of different testing strategies is outlined in Appendix C.

GWS may be considered for individuals who meet at least 2 of the following criteria:

- Congenital structural heart defect.
- Arrhythmogenic condition and/or cardiomyopathy, not believed to be secondary to a structural heart defect.
- Aortopathy, not believed to be secondary to a structural heart defect.
- Other clinical features suggestive of a genetic syndrome (e.g., major non-cardiac congenital anomaly, dysmorphic features, global developmental delay/intellectual disability) (Clinical features suggestive of an underlying genetic syndrome).

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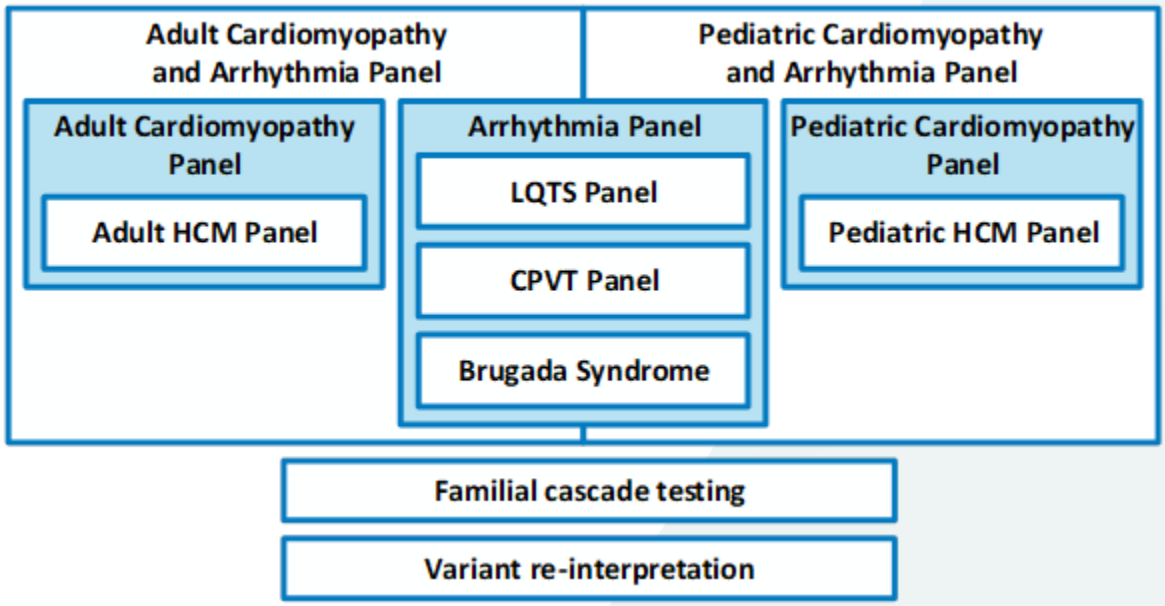
Appendices

Appendix A: Cardiomyopathy and Arrhythmia Panels Eligibility Quick Reference

The Cardiomyopathy and Arrhythmia Panels Eligibility Quick Reference may be helpful to quickly determine eligibility for genetic testing (Figure A1). Please refer to full document for further details, explanatory notes, and references.

Figure A1. Cardiomyopathy and Arrhythmia Genetic Testing Strategy

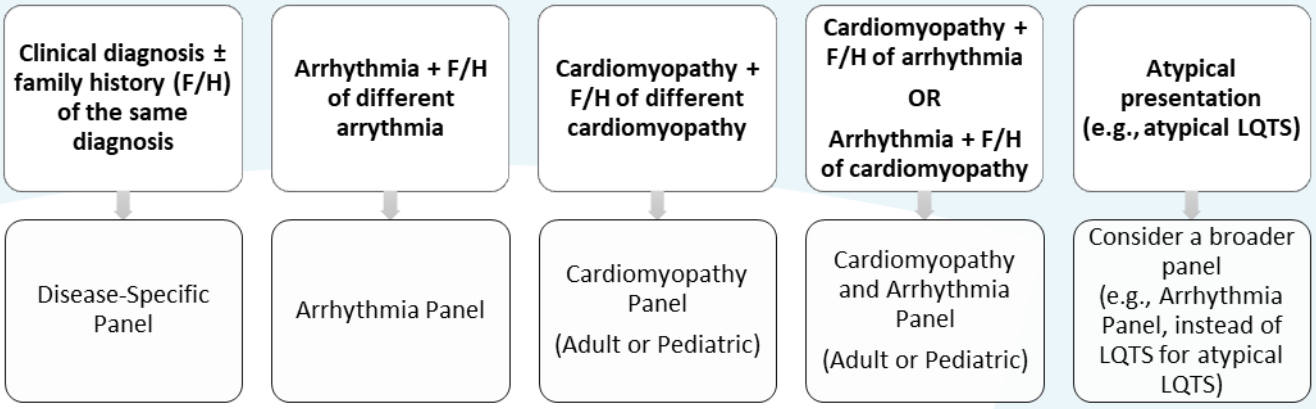


CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; LQTS, Long QT syndrome

A targeted approach to genetic testing is recommended when clearly indicated by the individual and/or family phenotype. However, a broad multigene panel has benefits in conditions with significant genetic heterogeneity and phenotypic overlap (Figure A2). The choice of panels should be driven by clinical judgement, informed by the patient phenotype, family history, and diagnostic certainty.

Decisions regarding genetic testing that rely on clinical judgment, as opposed to strict application of criteria, should be made following consensus of a specialized cardio-genetics team, and/or multidisciplinary case conference. For some cases, discussion with genetics experts and/or electrophysiologists may be sufficient.

Figure A2. Genetic Testing Utilization Considerations



F/H, family history; LQTS, long QT syndrome.

Genetic Testing Eligibility Criteria	Genetic Test Options
General Criteria (All Panels)	
1) Asymptomatic individuals at any age with a first degree relative with a known P/LP variant in a disease-related gene (Cascade testing).	☐ Familial variant
2) Individuals with a clinical diagnosis of cardiomyopathy or arrhythmia who have a close relative with a known P/LP variant in a disease-related gene of the same diagnosis (Clinical judgement).	☐ Familial variant ☐ Targeted panel
3) Individuals with suspected syndromic presentation and meet the GWS criteria (Genome-wide sequencing).	☐ GWS
4) Variant re-interpretation may be considered for when at least one of the following criteria are met (Variant re-interpretation): a. Evidence from ClinVar, gnomAD, and/or other reputable sources suggest that the variant interpretation might have changed. b. Rules for interpretation of variants in the gene of interest have been updated since the last interpretation by ACMG/AMP, ClinGen, and/or other reputable sources. c. New familial segregation data has become available. d. Variant interpretation may impact options for prenatal testing and/or management in an ongoing pregnancy.	☐ Variant re-interpretation
Arrhythmia Panels	
1) Individuals with a strong clinical suspicion or clinical diagnosis of **LQTS** defined as meeting at least one of the following criteria: a. LQTS risk score ≥3.5[21]. b. QTc ≥500 ms on repeated 12-lead ECG. c. QTc ≥480 ms on repeated 12-lead ECG AND an unexplained syncopal episode. d. QTc ≥480 ms on repeated 12-lead ECG AND a history of sudden unexplained death under the age of 60 in a first or second degree relative. e. Pre-pubertal individuals with a QTc >460 ms[d].	☐ LQTS Panel

Genetic Testing Eligibility Criteria	Genetic Test Options
2) Individuals with a strong clinical suspicion or clinical diagnosis of **CPVT** defined as meeting at least one of the following criteria: a. Structurally normal heart, normal resting ECG, and unexplained exercise or catecholamine-induced bidirectional VT, polymorphic ventricular premature beats or VT/ventricular fibrillation (VF) in an individual under 40 years of age. b. Structurally normal heart and coronary arteries, normal resting ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT/VF in an individual over 40 years of age.	☐ CPVT Panel
3) Individuals with a strong clinical suspicion or clinical diagnosis of **BrS** and/or sodium channel disease defined as meeting at least one of the following criteria: a. Spontaneous type 1 ("coved-type") ST-segment elevation (characterized by ST-segment elevation ≥2 mm [0.2 mV] in ≥1 right precordial leads [V1-V3] positioned in the 4th, 3rd, or 2nd intercostal space). b. Type 1 ST-segment elevation unmasked using a sodium channel blocker. Relevant features, may also include: i. Documented VF or polymorphic VT. ii. Syncope of probable arrhythmic cause. iii. Family history of SCD <45 years old with negative autopsy. iv. Coved-type ECG in family members. v. Nocturnal agonal respiration. vi. Premature atrial arrhythmias at age <30 years.	☐ *SCN5A* test
4) Individuals with a strong clinical suspicion or clinical diagnosis of **SQTS** defined as meeting at least one of the following criteria: a. A QTc ≤330 ms. b. A QTc <360 ms, AND one or more of the following: i. Family history of SQTS. ii. Family history of SCD ≤40. iii. Survival of a VT/VF episode in the absence of heart disease. 5) Individuals with a strong clinical suspicion or clinical diagnosis of **CCD** defined as meeting at least one of the following criteria: a. Unexplained progressive conduction abnormalities in young (<50 years) individuals with structurally normal hearts in the absence of skeletal myopathies, especially if there is a family history of CCD[27]. b. Disturbed electrical impulse propagation in the atrioventricular node and His-Purkinje system. c. CCD when there is early age of diagnosis or a suspicion of laminopathy, especially if there is a family history of CCD[1]. 6) Individuals without structural heart disease who meet at least one of the following criteria: a. Unexplained resuscitated cardiac arrest. b. Sustained VT/VF. c. Concerning arrhythmia history (e.g., recurrent exertional syncope, unexplained near drowning/agonal breathing). d. Family history of unexplained SCA in phenotype negative individuals.	☐ Arrhythmia Panel

Genetic Testing Eligibility Criteria	Genetic Test Options
Adult Cardiomyopathy Panels	
1) Individuals with a strong clinical suspicion or clinical diagnosis of **HCM** defined as meeting at least one of the following criteria: a. Unexplained left ventricular hypertrophy with a maximum wall thickness ≥15 mm in adults. b. More limited hypertrophy (13-15 mm) in the context of family history of HCM. c. Suspicion of clinical diagnosis of HCM with borderline dimensions, particularly in patients without a history of hypertension, without concentric hypertrophy, and in young or female patients.	☐ Adult HCM Panel
2) Individuals with a strong clinical suspicion or clinical diagnosis of **DCM** defined as meeting at least one of the following criteria: a. Left ventricular or biventricular systolic dysfunction (ejection fraction of less than 50%) and dilatation that are not explained by abnormal loading conditions or coronary artery disease. b. Left ventricular or biventricular global systolic dysfunction without dilatation (defined as LVEF < 45%), not explained by abnormal loading conditions or coronary artery disease[36]. c. Left ventricular or biventricular dilatation. 3) Individuals with a strong clinical suspicion or clinical diagnosis of **RCM** defined as meeting at least one of the following criteria: a. Presence of impaired LV filling. b. Diminished diastolic volume with normal/near-normal LV wall thickness and ejection fraction. 4) Individuals with a clinical diagnosis of **ACM** as per the 2020 Padua criteria[42]. a. Individuals who would fulfill diagnostic criteria if a disease-causing variant in a gene associated with ACM was identified are also eligible for testing. 5) Individuals with a strong clinical suspicion or consistent phenotypic features of **LVNC** defined as meeting at least one of the following criteria: a. Cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history and electrocardiographic/echocardiographic/MRI phenotype. b. Clinical diagnosis of LVNC cardiomyopathy associated with other cardiac or non-cardiac syndromic features.	☐ Adult CM Panel

Genetic Testing Eligibility Criteria	Genetic Test Options
Pediatric Cardiomyopathy Panels*	
1) Children with a strong clinical suspicion or clinical diagnosis of **HCM** who meet the following criteria: a. Z score greater than 2.0 standard deviations (as per the Boston calculator) for interventricular septum and/or posterior left ventricular wall.	☐ Pediatric HCM Panel
2) Children with a strong clinical suspicion or clinical diagnosis of **DCM** who meet the following criteria: a. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) Z scores greater than two and decreased ejection fraction <55%. 3) Children with a strong clinical suspicion or clinical diagnosis of **RCM** who meet the following criteria: a. Coexistence of persistent restrictive pathophysiology, commonly with atrial dilatation, and nondilated ventricles, regardless of ventricular wall thickness and systolic function[60]. 4) Children with a clinical diagnosis of **ACM** as per the 2020 Padua criteria[41,42]. a. Individuals who would fulfill diagnostic criteria if a disease-causing variant in a gene associated with ACM was identified are also eligible for testing. 5) Children with a strong clinical suspicion or consistent phenotypic features of **LVNC** defined as meeting at least one of the following criteria: a. Cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history and electrocardiographic/echocardiographic/MRI phenotype. b. Clinical diagnosis of LVNC cardiomyopathy associated with other cardiac or non-cardiac syndromic features.	☐ Pediatric CM Panel

* Analysis of the pediatric genes can be considered for individuals diagnosed up to 25 years of age.

Appendix B: Cardiomyopathy and Arrhythmia Genetic Testing Panels Summary

The cardiomyopathy and arrhythmia panels are designed to encompass genes associated with the likely differential diagnoses and be sufficiently comprehensive to include cardiogenetic conditions with important clinical overlap. The panels' structure and design should allow flexibility to the ordering clinician to select a targeted or broad panel depending on the diagnostic certainty. The choice of panels should be driven by clinical judgement, informed by the patient phenotype, and dictated by disease certainty.

The panels should capture the coding regions and flanking intron/exon boundaries and identify relevant copy number variants (CNVs) of all genes. Select relevant intronic variants should be included for the genes listed in the panel.

The Expert Group followed an evidence-based framework for each panel to achieve consensus on which genes to include on the cardiogenetics panels. A review of the technical specifications should be completed prior to the implementation of the panels in Ontario. ClinGen and/or Genomic England PanelApp curations were not available for all the disease entities included in the molecular panels.

Evidence Framework for Gene Inclusion

The following constitutes the list of resources and evidence thresholds for inclusion:

Clinical Genome Resource (ClinGen): Genes curated as Moderate, Strong, or Definitive for gene-disease validity in ClinGen.
Genomics England PanelApp: Genes identified as Green using the Genomics England PanelApp and nominated by the Expert Group member(s).
Literature review of consensus papers[e]: Genes listed on review/consensus papers and vetted by the Expert Group members.
Expert consensus: Genes for which there is supportive evidence in the literature and vetted by the Expert Group members.

[e] References:

- Engwerda, Aafke et al. "*TAB2* deletions and variants cause a highly recognisable syndrome with mitral valve disease, cardiomyopathy, short stature and hypermobility." *European journal of human genetics*: EJHG vol. 29,11 (2021): 1669-1676. doi:10.1038/s41431-021-00948-0
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- Rojanasopondist, Pakdee et al. "Genetic Basis of Left Ventricular Noncompaction." Circulation. *Genomic and precision medicine* vol. 15,3 (2022): e003517. doi:10.1161/CIRCGEN.121.003517
- Wilde, Arthur A M 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." *Journal of arrhythmia* vol. 38,4 491-553. 31 May. 2022, doi:10.1002/joa3.12717

Table B1. Gene Contents for the Cardiomyopathy and Arrhythmia Genetic Testing Panels

Genetic Test	Genes
Familial cascade testing	Available for any gene included in the panels below.
Variant re-interpretation	Available for any gene included in the panels below.
Brugada syndrome (1 gene)	*SCN5A*
CPVT panel (8 genes)	*CALM1*, *CALM2*, *CALM3*, *CASQ2*, *KCNJ2*, *RYR2*, *TECRL*, *TRDN*
LQTS panel (12 genes)	*CACNA1C*, *CALM1*, *CALM2*, *CALM3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1*, *SCN5A*, *TECRL*, *TRDN*
Arrhythmia panel (40 genes)	*CACNA1C*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, *CTNNA3*, *DES*, *DSC2*, *DSG2*, *DSP*, *EMD*, *FLNC*, *GLA*, *HCN4*, *JUP*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1*, *LAMP2*, *LMNA*, *NKX2-5*, *PKP2*, *PLN*, *PPA2*, *PRKAG2*, *RBM20*, *RYR2*, *SCN5A*, *SLC22A5*, *SLC4A3*, *TBX5*, *TECRL*, *TMEM43*, *TNNI3K*, *TRDN*, *TRPM4*, *TTN*, *TTR* Non-sequencing tests (not included in panel): *DMPK*[f]
Adult HCM panel (45 genes)	*ABCC9*, *ACTC1*, *ACTN2*, *ALPK3*, *BRAF*, *CACNA1C*, *CSRP3*, *DES*, *FHL1*, *FHOD3*, *FLNC*, *GLA*, *HRAS*, *JPH2*, *KLHL24*, *KRAS*, *LAMP2*, *LZTR1*, *MAP2K1*, *MAP2K2*, *MRAS*, *MT-TI*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *MYO6*, *NRAS*, *PLN*, *PPP1CB*, *PRKAG2*, *PTPN11*, *RAF1*, *RIT1*, *RRAS2*, *SHOC2*, *SOS1*, *SOS2*, *TNNC1*, *TNNI3*, *TNNT2*, *TPM1*, *TRIM63*, *TTR*, *VCL*
Adult cardiomyopathy panel (81 genes)	*ABCC9*, *ACADVL*, *ACTC1*, *ACTN2*, *ALPK3*, *BAG3*, *BRAF*, *CACNA1C*, *CAV3*, *CSRP3*, *CTNNA3*, *DES*, *DMD*, *DSC2*, *DSG2*, *DSP*, *DYSF*, *EMD*, *FHL1*, *FHOD3*, *FKRP*, *FKTN*, *FLNC*, *GAA*, *GATA4*, *GLA*, *HCN4*, *HRAS*, *JPH2*, *JUP*, *KLHL24*, *KRAS*, *LAMP2*, *LDB3*, *LMNA*, *LZTR1*, *MAP2K1*, *MAP2K2*, *MIB1*, *MRAS*, *MT-TI*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *MYO6*, *NEXN*, *NKX2-5*, *NRAP*, *NRAS*, *OBSCN*, *PKP2*, *PLEKHM2*, *PLN*, *PPP1CB*, *PRDM16*, *PRKAG2*, *PTPN11*, *RAF1*, *RBM20*, *RIT1*, *RRAGD*, *RRAS2*, *RYR2*, *SCN5A*, *SHOC2*, *SOS1*, *SOS2*, *TAFAZZIN*, *TBX5*, *TMEM43*, *TMEM70*, *TNNC1*, *TNNI3*, *TNNI3K*, *TNNT2*, *TPM1*, *TRIM63*, *TTN*, *TTR*, *VCL* Non-sequencing tests (not included in panel): *DMPK*[f]
Adult cardiomyopathy and arrhythmia panel (96 genes)	*ABCC9*, *ACADVL*, *ACTC1*, *ACTN2*, *ALPK3*, *BAG3*, *BRAF*, *CACNA1C*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, *CAV3*, *CSRP3*, *CTNNA3*, *DES*, *DMD*, *DSC2*, *DSG2*, *DSP*, *DYSF*, *EMD*, *FHL1*, *FHOD3*, *FKRP*, *FKTN*, *FLNC*, *GAA*, *GATA4*, *GLA*, *HCN4*, *HRAS*, *JPH2*, *JUP*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1*, *KLHL24*, *KRAS*, *LAMP2*, *LDB3*, *LMNA*, *LZTR1*, *MAP2K1*, *MAP2K2*, *MIB1*, *MRAS*, *MT-TI*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *MYO6*, *NEXN*, *NKX2-5*, *NRAP*, *NRAS*, *OBSCN*, *PKP2*, *PLEKHM2*, *PLN*, *PPA2*, *PPP1CB*, *PRDM16*, *PRKAG2*, *PTPN11*, *RAF1*, *RBM20*, *RIT1*, *RRAGD*, *RRAS2*, *RYR2*, *SCN5A*, *SHOC2*, *SLC22A5*, *SLC4A3*, *SOS1*, *SOS2*, *TAFAZZIN*, *TBX5*, *TECRL*, *TMEM43*, *TMEM70*, *TNNC1*, *TNNI3*, *TNNI3K*, *TNNT2*, *TPM1*, *TRDN*, *TRIM63*, *TRPM4*, *TTN*, *TTR*, *VCL* Non-sequencing tests (not included in panel): *DMPK*[f]

[f] Short tandem repeat expansion testing.

Genetic Test	Genes
Pediatric HCM panel (56 genes)	*ABCC9*, *ACTC1*, *ACTN2*, *AGL*, *ALPK3*, *BRAF*, *CACNA1C*, *CBL*, *CSRP3*, *DES*, *FHL1*, *FHOD3*, *FLNC*, *GAA*, *GLA*, *HRAS*, *JPH2*, *KLHL24, KRAS*, *LAMP2*, *LZTR1*, *MAP2K1*, *MAP2K2*, *MAP3K8*, *MRAS*, *MT-TI, MTO1*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *MYO6*, *NF1*, *NRAS*, *PLN*, *PPP1CB*, *PRKAG2*, *PTPN11*, *RAF1*, *RIT1*, *RRAS*, *RRAS2*, *SHOC2*, *SLC22A5*, *SLC25A4*, *SOS1*, *SOS2*, *SPRED2*, *TAB2*, *TNNC1*, *TNNI3*, *TNNT2*, *TPM1*, *TRIM63*, *TTR*, *VCL* Non-sequencing tests (not included in panel): *FXN*[f]
Pediatric cardiomyopathy panel (100 genes)	*ABCC9*, *ACADVL*, *ACTC1*, *ACTN2*, *AGL*, *ALMS1*, *ALPK3*, *BAG3*, *BRAF*, *CACNA1C*, *CAV3*, *CBL*, *CPT2*, *CSRP3*, *CTNNA3*, *DES*, *DMD*, *DSC2*, *DSG2*, *DSP*, *DYSF*, *EMD*, *FHL1*, *FHOD3*, *FKRP*, *FKTN*, *FLNC*, *GAA*, *GATA4*, *GLA*, *HADHA*, *HADHB*, *HCN4*, *HRAS*, *JPH2*, *JUP*, *KLHL24, KRAS*, *LAMP2*, *LDB3*, *LMNA*, *LZTR1*, *MAP2K1*, *MAP2K2*, *MAP3K8*, *MIB1*, *MRAS*, *MT-TI, MTO1*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *MYO6*, *NEXN*, *NF1*, *NKX2-5*, *NRAP*, *NRAS*, *OBSCN*, *PKP2*, *PLEKHM2*, *PLN*, *PPA2*, *PPP1CB*, *PRDM16*, *PRKAG2*, *PTPN11*, *RAF1*, *RBM20*, *RIT1*, *RRAGD*, *RRAS*, *RRAS2*, *RYR2*, *SCN5A*, *SGCD*, *SHOC2*, *SLC22A5*, *SLC25A20*, *SLC25A4*, *SOS1*, *SOS2*, *SPRED2*, *TAB2*, *TAFAZZIN*, *TBX20*, *TBX5*, *TCAP*, *TMEM43*, *TMEM70*, *TNNC1*, *TNNI3*, *TNNI3K*, *TNNT2*, *TPM1*, *TRIM63*, *TTN*, *TTR*, *VCL* Non-sequencing tests (not included in panel): *DMPK, FXN*[f]
Pediatric cardiomyopathy and arrhythmia panel (113 genes)	*ABCC9*, *ACADVL*, *ACTC1*, *ACTN2*, *AGL*, *ALMS1*, *ALPK3*, *BAG3*, *BRAF*, *CACNA1C*, *CALM1*, *CALM2*, *CALM3*, *CASQ2*, *CAV3*, *CBL*, *CPT2*, *CSRP3*, *CTNNA3*, *DES*, *DMD*, *DSC2*, *DSG2*, *DSP*, *DYSF*, *EMD*, *FHL1*, *FHOD3*, *FKRP*, *FKTN*, *FLNC*, *GAA*, *GATA4*, *GLA*, *HADHA*, *HADHB*, *HCN4*, *HRAS*, *JPH2*, *JUP*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1*, *KLHL24, KRAS*, *LAMP2*, *LDB3*, *LMNA*, *LZTR1*, *MAP2K1*, *MAP2K2*, *MAP3K8*, *MIB1*, *MRAS*, *MT-TI, MTO1*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *MYO6*, *NEXN*, *NF1*, *NKX2-5*, *NRAP*, *NRAS*, *OBSCN*, *PKP2*, *PLEKHM2*, *PLN*, *PPA2*, *PPP1CB*, *PRDM16*, *PRKAG2*, *PTPN11*, *RAF1*, *RBM20*, *RIT1*, *RRAGD*, *RRAS*, *RRAS2*, *RYR2*, *SCN5A*, *SGCD*, *SHOC2*, *SLC22A5*, *SLC25A20*, *SLC25A4*, *SLC4A3*, *SOS1*, *SOS2*, *SPRED2*, *TAB2*, *TAFAZZIN*, *TBX20*, *TBX5*, *TCAP*, *TECRL*, *TMEM43*, *TMEM70*, *TNNC1*, *TNNI3*, *TNNI3K*, *TNNT2*, *TPM1*, *TRDN*, *TRIM63*, *TRPM4*, *TTN*, *TTR*, *VCL* Non-sequencing tests (not included in panel): *DMPK, FXN*[f]

CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; LQTS, Long QT syndrome.

Appendix C: Comparison of Laboratory Genetic Testing Strategies[g]

Testing Strategy	Definition	Pros	Cons
Familial cascade testing	Testing family members for a previously identified P/LP variant. Starts with individuals closely related to the proband and expands to others as additional family members are found to share the P/LP variant.	Clear answer to the presence or absence of P/LP familial variant in the patient undergoing testing. Dismal chance of identifying a VUS. Lower cost per test.	P/LP variants must have previously identified in a relative of the patient. It will not detect previously unidentified etiologies in the family.
Single gene test	Testing and reporting on a single gene which is associated with a condition that is not genetically heterogeneous.	Less capital investment. Simpler informatics. Easier to interpret and report than a genome-wide test. No secondary findings and lower chance of incidental findings. Most laboratories have existing infrastructure.	Del/dup testing must be ordered separately. Cannot 'reflex' to broader testing if using targeted kits. Current practice often tests only the proband requiring familial follow-up when a variant is reported. Typically, only indicated for a very limited number of conditions. Typically, does not cover noncoding regions beyond 10-20 nucleotides from the exon-intron borders.
Multigene panel test	Testing and reporting on a defined set of genes that are clinically valid for a set of indications. Can vary from a small number of genes to >4,000 genes known to be involved in human disease.	Less capital investment than GWS. Simpler informatics than GWS. Easier to interpret and report than a genome-wide test. No secondary findings and lower chance of incidental findings.	Lengthy laboratory development time. Need to continually update the panel when new discoveries are made (inflexible). Requires batching that can be difficult to work into laboratory flow.

[g] Prepared by C. Marshall and A. Vaags in September 2022. Updated by H. Feilotter and L. Bronicki in March 2024.

Testing Strategy	Definition	Pros	Cons
	Can be proband only or trio sequencing for large panels.	Most laboratories have existing infrastructure. Lower cost per test. Possible to report out on del/dup if sequenced to high depth of coverage. Possible to report out on a panel where exome or genome is sequenced (informatics *in silico* panel or genomic 'slice').	Cannot 'reflex' to broader testing if using targeted kits. Current practice often tests only the proband requiring familial follow-up when a variant is reported. Lower overall clinical sensitivity. More likely to report VUS for large panels compared to exome and genome. Typically, does not cover noncoding regions beyond 10-20 nucleotides from the exon-intron borders.
Exome sequencing	Sequencing of the coding portion of all known genes with reporting and interpretation of variants based on provided phenotype. Still a 'targeted' test since only looks at the coding portion of the genome but a broader approach to testing where multiple panels would otherwise be needed.	Requires fewer computation resources than genomes and is easier to analyze. Less costly compared to genomes. Reporting only on variants related to phenotype. Can detect copy number variation but at a lower resolution, compared to panels or genomes (typically 1-2 exons). Possible to report out on a panel where exome or genome is sequenced (informatics *in silico* panel or genomic 'slice').	High capital and infrastructure costs. Complex and expensive informatics compared to panels. Higher cost per test (trios) compared to panels. Potential for secondary and incidental findings, so more genetic literacy is needed for ordering and return of results. Does not detect (most) deep intronic variants. Not designed to detect copy number changes unless coverage is increased to 200x-500x. Requires detailed phenotypic information for variant analysis and interpretation. Less likely to report VUS.

Testing Strategy	Definition	Pros	Cons
Genome sequencing	Sequencing of the entire genome (3 billion base pairs) with reporting and interpretation of variants based on provided phenotype.	Highest clinical sensitivity and diagnostic yield. Analytically sensitive to almost all classes of variation (CNVs, SVs, STRs, MT variants, etc.) so a more 'complete' single test. Can detect causative non-coding changes. Possible to report out on a panel where exome or genome is sequenced (informatics *in silico* panel or genomic 'slice').	Highest capital and infrastructure cost. Complex and expensive informatics. Higher cost per test (trios) and currently higher cost compared to exomes. Requires solution for storage of large amounts of data. Inability to interpret much of the genomes (e.g., non-coding regions). Potential for secondary findings so more genetic literacy is needed for the return of results. Requires detailed phenotypic information for variant analysis and interpretation. Less likely to report VUS.

CNVs, copy number variants; SVs, structural variants; STRs, short tandem repeats; MT, mitochondrial; VUS, variant of uncertain significance.

Appendix D: Acronyms

ACM	Arrhythmogenic cardiomyopathy
ACMG	American College of Medical Genetics and Genomics
AMP	Association of Molecular Pathology
ALVC	Arrhythmogenic left ventricular cardiomyopathy
ARVC	Arrhythmogenic right ventricular cardiomyopathy
BrS	Brugada syndrome
ClinGen	Clinical Genome Resource
CM	Cardiomyopathy
CCD	Cardiac conduction disease
CIQP	Clinical Institutes and Quality Programs
CNV	Copy number variant
CPVT	Catecholaminergic polymorphic ventricular tachycardia
DCM	Dilated cardiomyopathy
DM1	Myotonic dystrophy type 1
ECG	Electrocardiogram
FA	Friedrich ataxia
F/H	Family history
gnomAD	Genome Aggregation Database
GWS	Genome-wide sequencing
HCM	Hypertrophic cardiomyopathy
LQTS	Long QT syndrome
LV	Left ventricular
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
LVNC	Left ventricular noncompaction cardiomyopathy
MT	Mitochondrial
NS	Noonan syndrome
PCCD	Progressive cardiac conduction disease
P/LP	Pathogenic/likely pathogenic
PLMP	Pathology and Laboratory Medicine Program
PGP	Provincial Genetics Program
PGAC	Provincial Genetics Advisory Committee
PVC	Premature ventricular complex
RCM	Restrictive cardiomyopathy
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death

SQTS	Short QT syndrome
STR	Short tandem repeat
SV	Structural variant
VA	Ventricular arrhythmias
VF	Ventricular fibrillation
TAT	Turnaround time
TdP	Torsade de pointes
VT	Ventricular tachycardia
VUS	Variant of uncertain significance