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Curbside Consults

Management of Inherited Arrhythmia Syndromes: A HiRO Consensus Handbook on Process of Care

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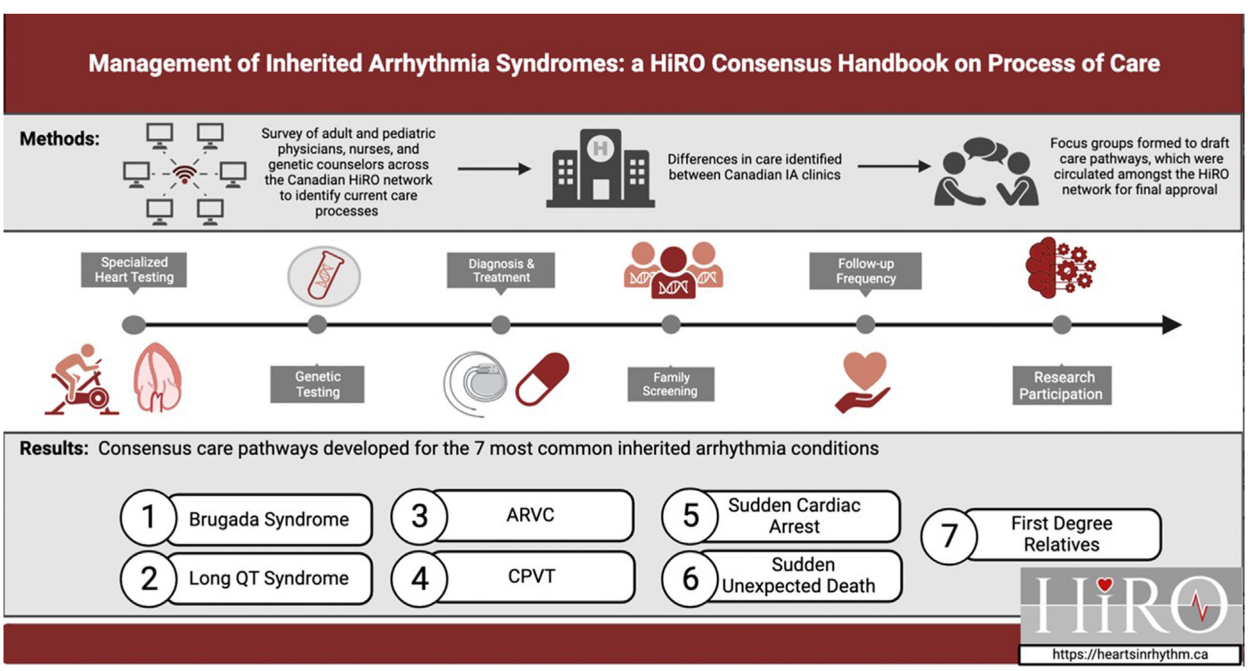

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ABSTRACT

Inherited arrhythmia syndromes are rare genetic conditions that predispose seemingly healthy individuals to sudden cardiac arrest and death. The Hearts in Rhythm Organization is a multidisciplinary Canadian network of clinicians, researchers, patients, and families that aims to improve care for patients and families with inherited cardiac conditions, focused on those that confer predisposition to arrhythmia and sudden cardiac arrest and/or death. The field is rapidly evolving as research discoveries increase. A streamlined, practical guide for providers to diagnose and follow pediatric and adult patients with inherited cardiac conditions represents a useful tool to improve health system utilization, clinical management, and research related to these conditions. This review provides consensus care pathways for 7 conditions, including the 4 most common inherited cardiac conditions that confer predisposition to arrhythmia, with scenarios to guide investigation, diagnosis, risk stratification, and management. These conditions include Brugada syndrome, long QT syndrome, arrhythmogenic right ventricular cardiomyopathy and related arrhythmogenic cardiomyopathies, and catecholaminergic polymorphic ventricular tachycardia. In addition, an approach to investigating and managing sudden cardiac arrest, sudden unexpected death, and first-degree family members of affected individuals is provided. Referral to specialized cardiogenetic clinics should be considered in most cases. The intention of this review is to offer a framework for the process of care that is useful for both experts and nonexperts, and related allied disciplines such as hospital management, diagnostic services, coroners, and pathologists, in order to provide high-quality, multidisciplinary, standardized care.

RÉSUMÉ

Les syndromes d'arythmie héréditaires sont des troubles génétiques rares qui prédisposent des personnes en apparence en bonne santé à un arrêt cardiaque soudain et à la mort. L'organisation Hearts in Rhythm Organization est un réseau multidisciplinaire canadien qui regroupe des cliniciens, des chercheurs ainsi que des patients et leurs proches dans le but d'améliorer les soins prodigués aux patients atteints de maladies cardiaques héréditaires et à leur famille, en particulier dans le cas des maladies qui entraînent une prédisposition à l'arythmie et à un arrêt cardiaque soudain et/ou à la mort. Puisque ce champ de recherche évolue rapidement, la mise au point d'un guide pratique et simple à l'intention des professionnels de la santé pour le diagnostic et le suivi des patients enfants et adultes présentant une maladie cardiaque héréditaire serait donc un outil intéressant pour améliorer l'utilisation du système de santé et la prise en charge clinique de ces maladies tout en orientant la recherche à ce propos. La présente synthèse expose les trajectoires de soins faisant l'objet d'un consensus pour sept maladies, dont les quatre maladies cardiaques héréditaires les plus courantes qui prédisposent à l'arythmie. Elle présente aussi des scénarios pour orienter les examens, le diagnostic, la stratification du risque et la prise en charge des patients. Ces maladies sont le syndrome de Brugada, le syndrome du QT long, la cardiomyopathie arythmogénique du ventricule droit et les cardiomyopathies arythmogènes associées, et la tachycardie ventriculaire polymorphe catécholaminergique. En outre, une approche pour la prise en charge de l'arrêt cardiaque soudain, de mort subite inattendue et des membres de la famille immédiate de la personne touchée est proposée. L'orientation vers des cliniques spécialisées en cardiogénétique doit être envisagée dans la plupart des cas. L'objectif est d'établir un cadre de soins qui soit utile pour les experts et les non-experts ainsi que pour les professionnels des domaines connexes, par exemple le personnel de l'administration hospitalière et des services diagnostiques, les coroners et les pathologistes, en vue d'offrir des soins multidisciplinaires normalisés de grande qualité.

Inherited arrhythmia (IA) syndromes are a rare and complex group of genetic conditions that predispose seemingly healthy individuals to sudden cardiac arrest (SCA) and death (SCD). Brugada syndrome (BrS), long QT syndrome (LQTS), arrhythmogenic right ventricular cardiomyopathy (ARVC), and catecholaminergic polymorphic ventricular tachycardia (CPVT) are 4 of the most common IA syndromes, each with

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unique but overlapping clinical presentations and genetic associations. An additional subset of presumed IA syndromes presents with unexplained cardiac arrest (UCA) or SCD, in which an event in a seemingly healthy individual occurs without a clear underlying etiology.

The Hearts in Rhythm Organization (HiRO) is a Canadian network focused on clinical excellence, research, and patient and family involvement, with an intention to promote guideline-recommended multidisciplinary care for families affected by inherited cardiogenetic syndromes. Members include adult and pediatric physicians, genetic counselors, nurses, administrative and clerical staff, trainees, patients, and family members. The current article presents a summary of the HiRO consensus on the process of care related to the management of the 7 most common referral conditions. This summary is intended to complement the extensive and rapidly changing literature on best practices for specific clinical problems.

The specific Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS) consensus statement regarding IAs has not been updated since 2013.[1] In the decade since publication, significant evolution of practice, particularly regarding genetic testing, has occurred.[2-4] Genetic testing is a key aspect of diagnostic evaluation, and decision aids to guide in that process have been published.[5] Although most IA syndromes are inherited in an autosomal dominant manner, corresponding phenotypes can vary widely.[6] In general, management includes risk mitigation based on lifestyle, and medical, interventional, and device therapies, which all require shared decision-making. Many patients benefit from simple drug avoidance, and from guidance on safe physical activity, depending on the underlying syndrome and personal risk. Conservative management measures are suggested for patients who are asymptomatic or have only provoked electrocardiogram (ECG) changes (eg, during exercise or fever). Invasive interventions, such as implantable cardioverter defibrillator (ICD) implantation, are reserved for those at highest risk.

The HiRO has a key goal of providing access to expert care for patients and families at risk, which includes provision of a clinic toolkit for new or growing clinics. Although guidelines recommend multidisciplinary care, the practical process of care, including the nature and frequency of testing, the timing and oversight of genetic testing, and the related custody of the variants that arise, are frequently queries at mentored new clinics. Community healthcare practitioners are often the first point of contact for many suspected IA cases, and follow-up and family care also often falls on these providers. However, a streamlined practical guide for healthcare providers to use to diagnose and follow patients with suspected IA syndromes does not otherwise exist.

This review intends to provide a HiRO expert consensus on care pathways to guide investigation, diagnosis, risk stratification, and follow-up of patients and family members with suspected or confirmed IA syndromes, SCD, and UCA. These care pathways are applicable to pediatric and adult patients. Each scenario is supported by a hypothetical patient presentation to demonstrate how to utilize each care pathway to support clinical decision-making.

Methods

To achieve these goals, these care pathways were created to support general management of patients and families with IA syndromes. Expert adult and pediatric physicians, nurses, and genetic counselors across the Canadian HiRO network were surveyed as a means to understand current local care pathways at IA clinics. From those results, focus groups were formed to draft algorithms that were then circulated and presented at the annual HiRO symposium for final approval. A discrete care pathway was developed for consideration of BrS, LQTS, ARVC and related arrhythmogenic cardiomyopathies (ACMs), CPVT, SCD, and UCA. Steps are colour-coded to denote starting points, action/tests, results, diagnoses, and research participation opportunities (Figs. 1-7).

$1 \rightarrow 8$, $2 \rightarrow 1$, $3 \rightarrow 2$, $4 \rightarrow 3$, $5 \rightarrow 4$, $6 \rightarrow 9$, $7 \rightarrow 5$, $8 \rightarrow 6$, $9 \rightarrow 7$

Important to note is that individual cases are more complex than a summative care path, and clinical presentations often are not straightforward, requiring multidisciplinary expertise to navigate the cardiovascular and genetic nuances. The HiRO firmly believes in guideline-recommended multidisciplinary team care of patients and families, and it provides publicly available patient and provider resources, enabling expert care (www.heartsinrhythm.ca).

BrS

Background

BrS classically is seen in young adult men, who are at risk of arrhythmic syncope or cardiac arrest, particularly during sleep or at rest. Patients also may be incidentally diagnosed in the context of an abnormal ECG. BrS is defined as a 12-lead ECG with coved ST elevation and T-wave inversion in the right precordial leads (Fig. 8).[7] A definite diagnosis requires spontaneous type 1 ECG changes in leads V_1-V_2, with a probable diagnosis reached with a provoked type 1 ECG pattern (with either fever or sodium-channel blocker challenge). Loss-of-function variants in the *SCN5A* gene are the most common culprits in BrS; however, although family histories corroborate a genetic component to BrS, a single genetic culprit is often not identified, suggesting that inheritance is polygenic in nature.[8-10] Clinical risk and management is in part determined by the presence of a type 1 pattern, whether spontaneous or provoked, and whether incidental or symptomatic (Fig. 1).

Provocation of a type 1 pattern can be achieved by use of a sodium-channel blocker (eg, procainamide or ajmaline) challenge. Sodium-channel blocker challenge use is somewhat controversial due to the lack of a gold-standard comparison and to the variability in sensitivity and specificity across sodium-channel blockers.[11,12] Ajmaline is not available in Canada, so procainamide is most commonly used. A positive sodium-channel blocker challenge supports the diagnosis of BrS, and risk-management strategies can be implemented to reduce the risk of SCD or syncope. However, sodium-channel blocker challenges should be approached with caution and assessed on a case-by-case basis. These tests generally have a low detection rate, but the balance of risk with a missed provoked type 1 pattern supports pursuing comprehensive

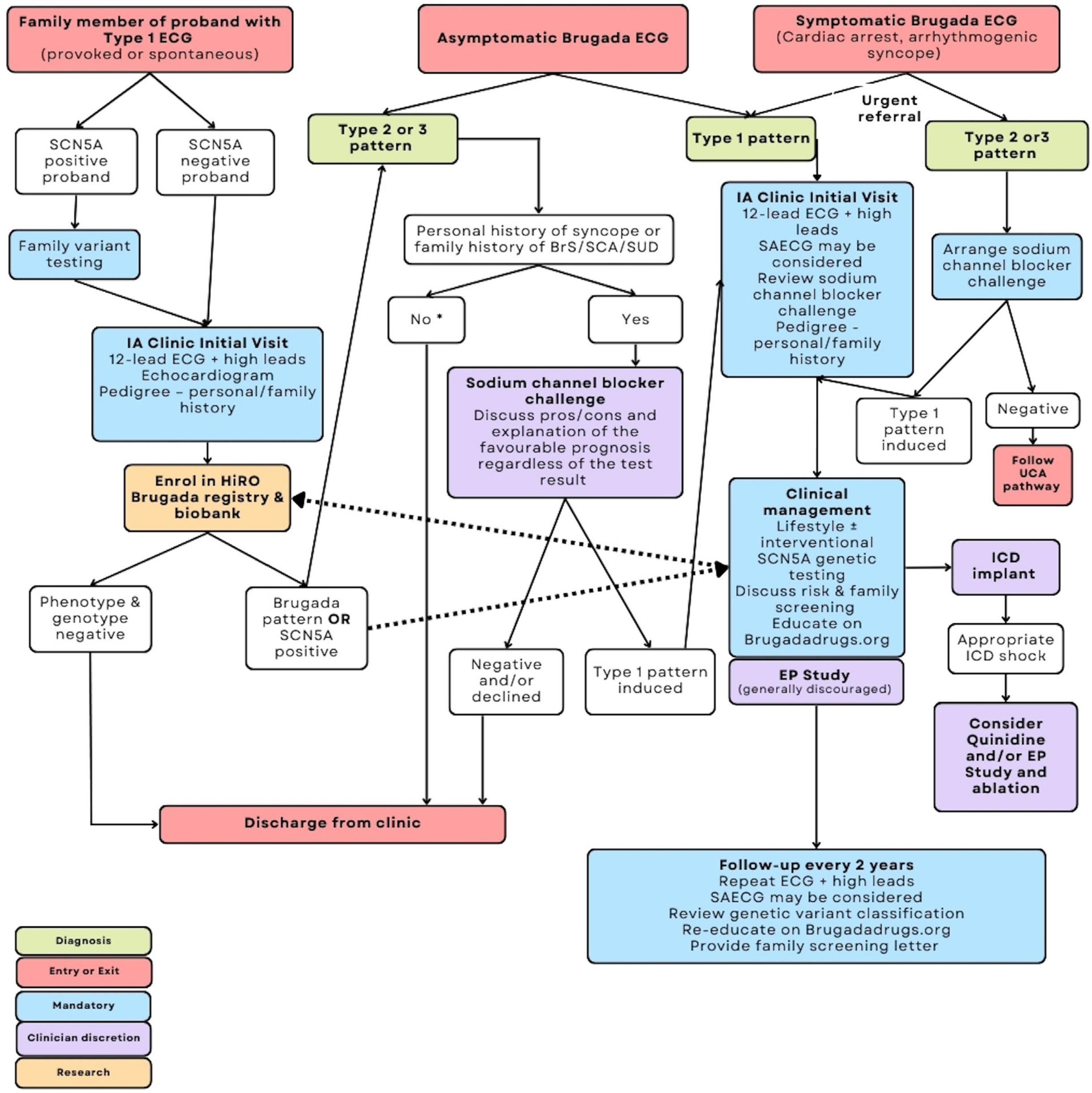

Figure 1. Care pathway for diagnosis and management of Brugada syndrome. BrS, Brugada syndrome; ECG, electrocardiogram; EP, electrophysiology; HiRO, Hearts in Rhythm Organization; IA, inherited arrhythmia; ICD, implantable cardioverter defibrillator; SAECG, signal-averaged ECG; SCA, sudden cardiac arrest; SUD, sudden unexpected death. *Consider sodium-channel blocker challenge in very selected cases (require medication listed on Brugadadrugs.org to avoid). Drug-induced type 1 pattern & no family history ≠ Brugada syndrome (Shanghai criteria).

testing. Further, the specific agent used can impact results, with ajmaline being more likely to provoke a type 1 pattern, with a greater probability of a false positive.[13-15] A 24-hour Holter monitor is not routinely included in the initial IA clinic visit but may be considered in specific cases at clinic staff discretion. Electrophysiology studies are generally discouraged for BrS cases because of their limited discriminative power, but they may be considered in specific cases. Consultation with an IA specialist is recommended. Important to note is that a confirmed BrS diagnosis, although helpful in guiding clinical care, also could have both psychological and practical (eg, insurance) implications; notably, the absolute risk of an inducible type 1 pattern is not well understood, so the absolute benefit of a diagnosis is unclear.[7,16]

Management of BrS includes lifestyle, pharmacologic, and interventional components. The highest-risk patients are those with a spontaneous type 1 ECG pattern and a history of cardiac arrest or arrhythmic syncope; in these patients, ICD implantation should be considered.[16] In patients who receive appropriate ICD shocks, quinidine therapy and/or an electrophysiology study and ablation may be considered. We recommend that an IA specialist be consulted in these cases.

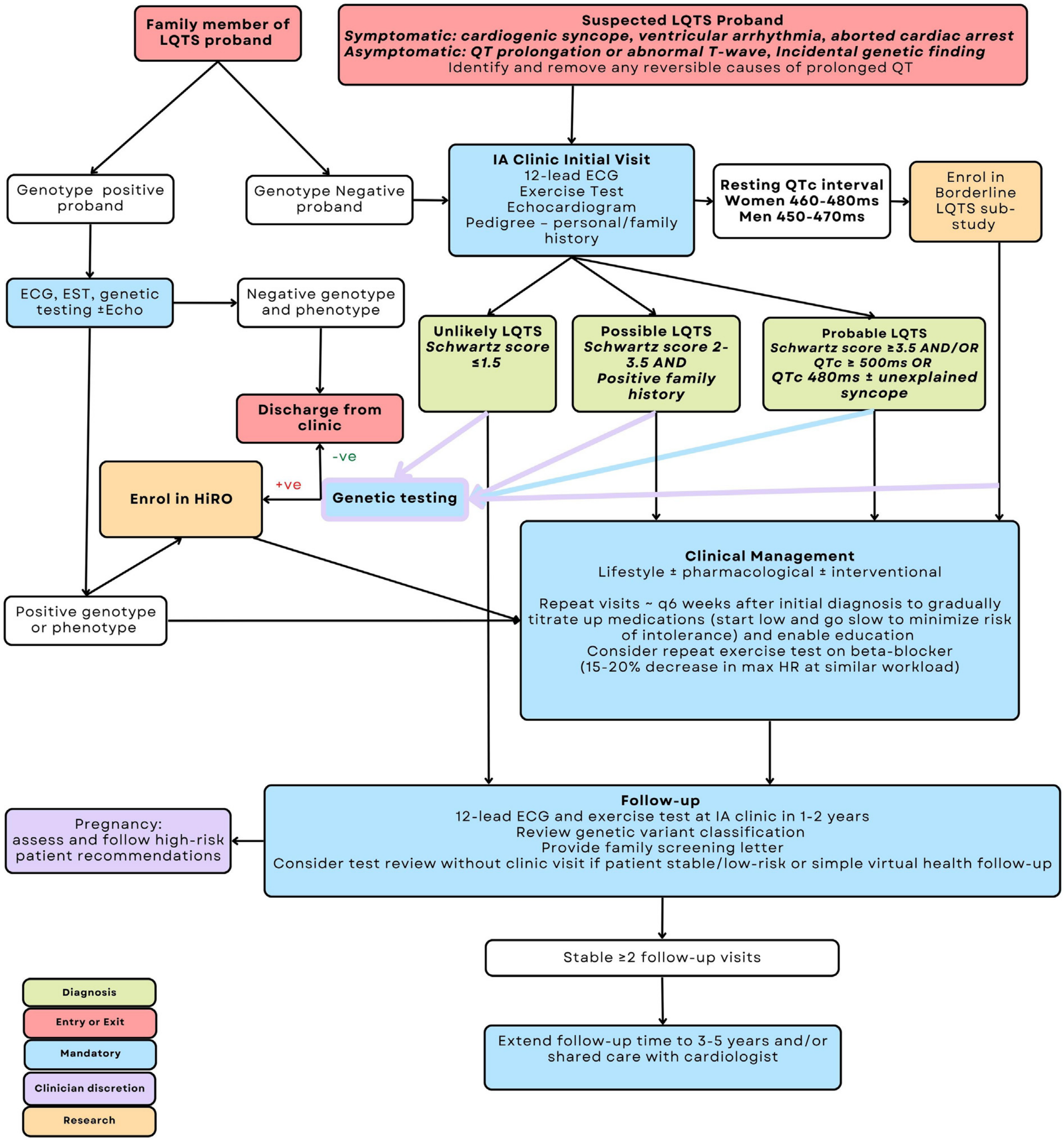

Figure 2. Care pathway for diagnosis and management of long QT syndrome (LQTS). ECG, electrocardiogram; EST, exercise stress test; HiRO, Hearts in Rhythm Organization; HR, heart rate; IA, inherited arrhythmia; max, maximum; QTc, corrected QT interval.

Illustrative case

A 35-year-old man had an ECG performed for routine screening, which incidentally found a type 2 Brugada pattern (Fig. 8). He did not report any personal history of associated symptoms, such as syncope, but his father died suddenly in his sleep at age 50 years, and an autopsy was not performed. In light of the type 2 Brugada ECG pattern and the positive family history, the patient was referred for a sodium-channel blocker challenge. Prior to completing the test, the implications of a positive result were discussed with the patient. In this case, the patient was referred to a specialized IA clinic, where a sodium-channel blocker challenge provoked a type 1 pattern. Risk-management strategies were initiated, including avoidance of certain drugs (www.brugadadrugs.org), aggressive treatment of fever with acetaminophen, and lifestyle management (Table 1). In coordination with a genetic counsellor, *SCN5A* genetic testing also was pursued. However, an actionable variant was not identified, as is common in most BrS cases.[7] The patient was considered to be at low risk, so conservative management focused on risk avoidance was recommended (Table 1). Given that the patient was

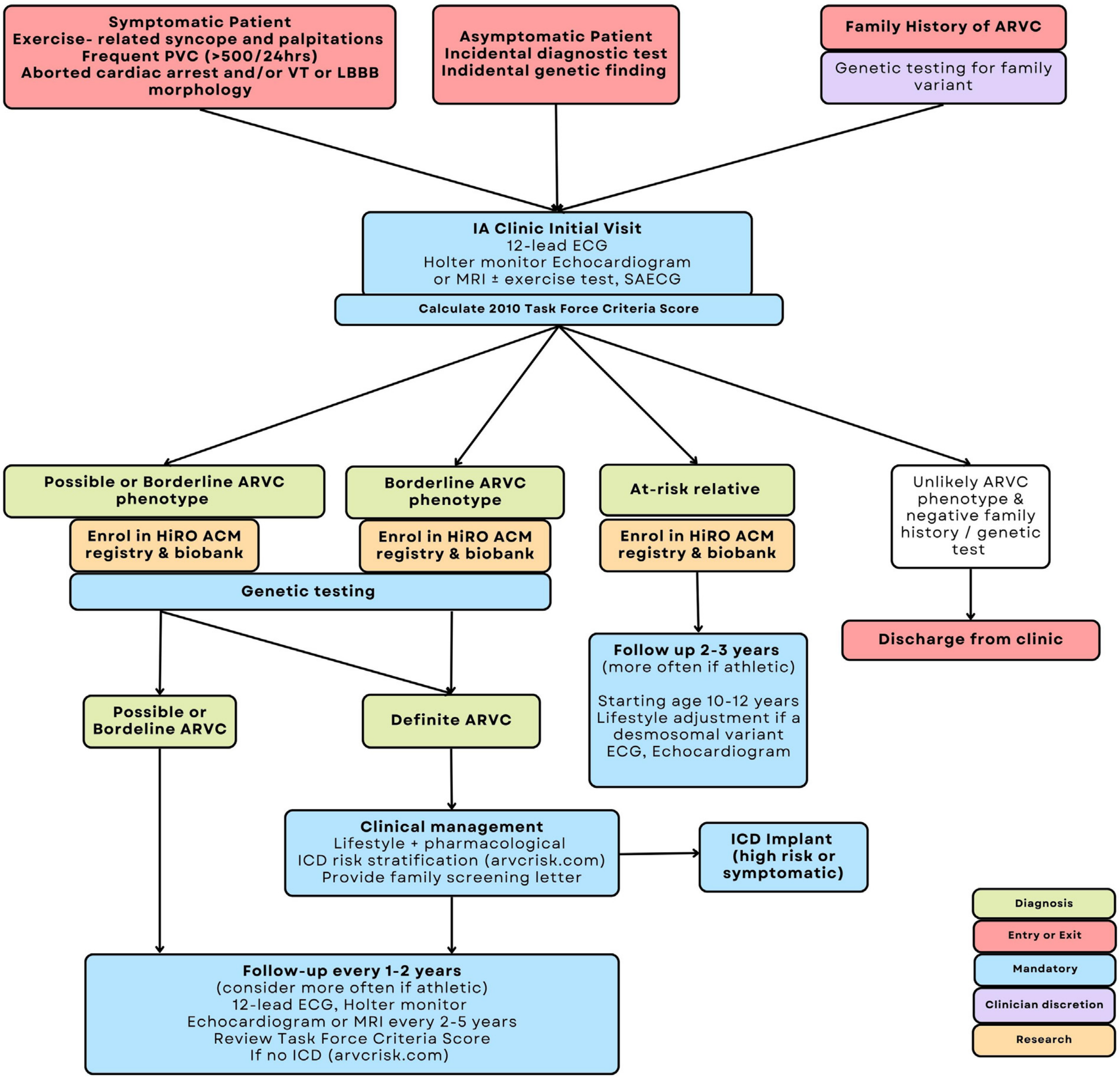

Figure 3. Care pathway for diagnosis and management of arrhythmogenic right ventricular cardiomyopathy. ACM, arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram; HiRO, Hearts in Rhythm Organization; IA, inherited arrhythmia; ICD, implantable cardioverter defibriallator; MRI, magnetic resonance imaging; PVC, premature ventricular contraction; SAECG, signal-averaged ECG; VT, ventricular tachycardia.

asymptomatic, an ICD was not recommended. An echocardiogram or cardiac magnetic resonance imaging (MRI) typically would be offered to assess for any structural heart disease. Follow-up visits should be with the IA clinic every 1-2 years, including an ECG with high leads, review of genetic classification and family screening, and re-education regarding drug avoidance and fever management.

With no identified pathogenic or likely pathogenic genetic variant in the proband, cascade genetic testing for family members is not available. Most cases of gene-negative BrS are sporadic, but cardiac screening in first-degree family members is still recommended. The proband's mother, siblings, and children were referred to an IA clinic and underwent a 12-lead ECG, with standard and high lead placement, along with a review of personal and family history. All the relatives had normal cardiac evaluations, with no Brugada pattern identified on ECG, and they were discharged from the clinic. In this scenario, negative genetic testing in the proband, and the absence of a phenotype in other relatives, reduces the level of suspicion that the father's death was related to BrS, although this possibility cannot be ruled out. However, important to note is that, given that the father died at an age over 40 years, if BrS was the culprit, the subsequent risk to family members is not increased definitively.[17]

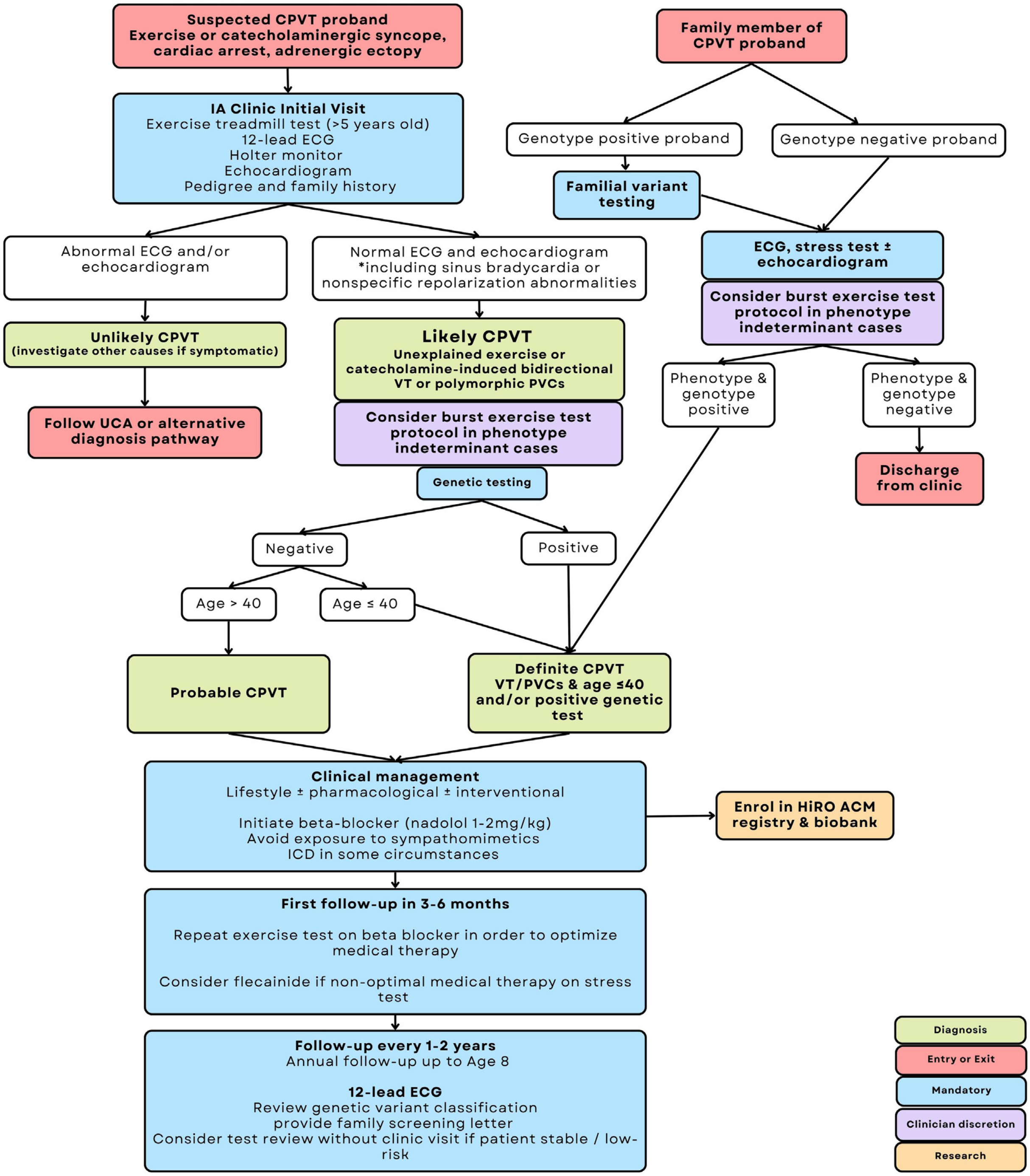

Figure 4. Care pathway for diagnosis and management of catecholaminergic polymorphic ventricular tachycardia (CPVT). ACM, arrhythmogenic cardiomyopathy; ECG, electrocardiogram; HiRO, Hearts in Rhythm Organization; IA, inherited arrhythmia; ICD, implantable cardioverter defibriallator; PVC, premature ventricular contraction; UCA, unexplained cardiac arrest; VT, ventricular tachycardia.

LQTS

Background

Congenital LQTS is characterized by prolonged repolarization, with the greatest risk of arrhythmia generally occurring at elevated heart rates. The Schwartz score is used to stratify patients into unlikely ($\leq$ 1.5 points), possible (2-3 points), or probable ($\geq$ 3.5 points) LQTS groups based on history and ECG findings (Fig. 2; Supplemental Table S1).[18,19]

A systematic approach to measuring the QT interval can improve reliability and detection of prolonged QT intervals. The tangent method is widely used by IA specialists as a reliable method at a wide range of heart rates.[20] In this method, the end of the QT interval is defined as the intercept

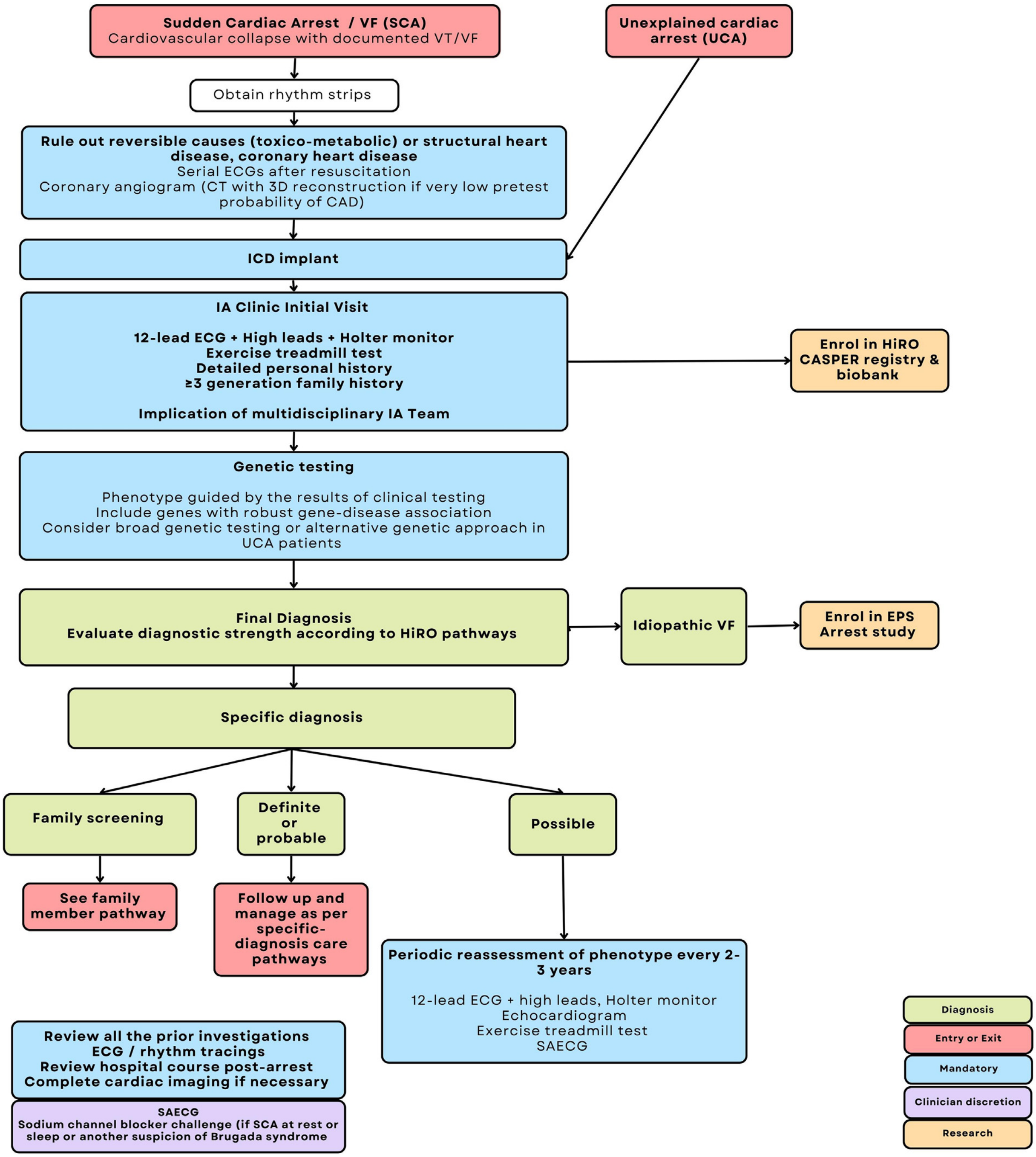

Figure 5. Care pathway for diagnosis and management of sudden cardiac arrest (SCA). CAD, coronary artery disease; CASPER, Cardiac Arrest Survivors With Preserved Ejection Fraction Registry; CT, computed tomography; ECG, electrocardiogram; EPS, electrophysiology study; HiRO, Hearts in Rhythm Organization; IA, inherited arrhythmia; ICD, implantable cardioverter defibrillator; SAECG, signal-averaged ECG; UCA, unexplained cardiac arrest; VF, ventricular fibrillation; VT, ventricular tachycardia.

of the tangent line from the steepest slope of the T-wave and the isoelectric line. Correction of the QT interval for heart rate most often is done using Bazett's formula, but its performance characteristics may be suboptimal, particularly at extremes of heart rates, but no broadly accepted alternative is used in practice.[21-23] Notably, an important overlap is present in the QT interval distributions in those with genetic LQTS and the general population. This overlap underlies the difficulty in establishing a diagnosis of LQTS using the baseline ECG. The probability of LQTS, as determined using the corrected QT (QTc) interval measured using the tangent or the threshold methods, as well as age and sex, can be estimated using a recent case-control study (https://www.qtcalculator.org/).[24] Important to note is that the diagnosis of LQTS is

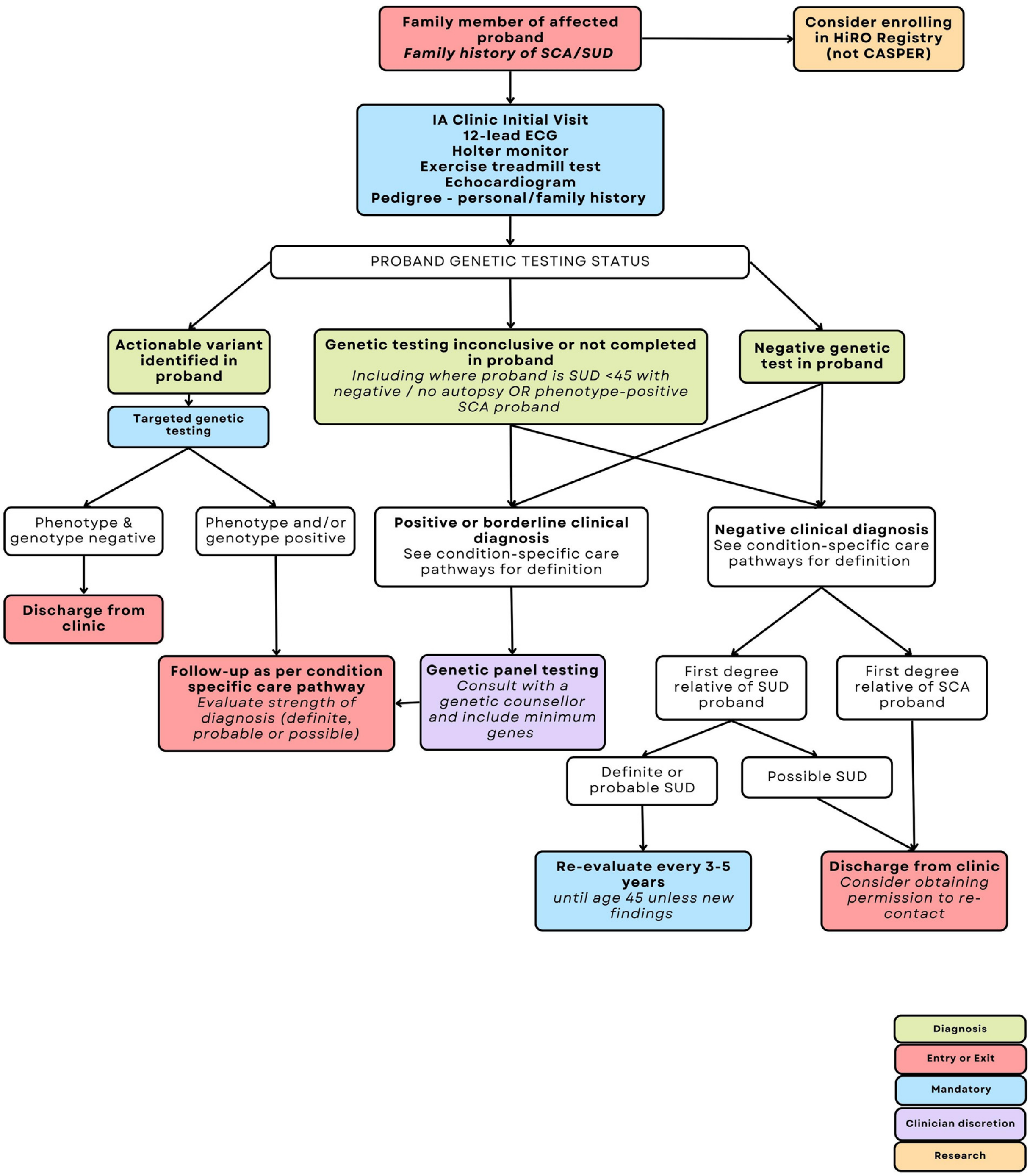

Figure 6. Care pathway for diagnosis and management of first-degree family members. CASPER, Cardiac Arrest Survivors With Preserved Ejection Fraction Registry; ECG, electrocardiogram; HiRO, Hearts in Rhythm Organization; IA, inherited arrhythmia; SCA, sudden cardiac arrent; SUD, sudden unexpected death.

based on persistent QTc interval prolongation, highlighting the importance of performing repeated ECGs in patients in whom LQTS is suspected.

The exercise test is a mainstay of LQTS diagnosis, with a Bruce or modified Bruce protocol recommended for evaluation. As heart rate increases, prolongation of the cQT interval can be exacerbated, and underlying repolarization abnormalities may be revealed. The QT interval at 4-minutes in recovery is the single most useful measure in LQTS on exercise testing.[19,25] A 24-hour Holter monitor is not included routinely in the initial IA clinic visit, but its use may be considered in specific cases at clinic staff discretion. Of all IA syndromes, the genetic basis of LQTS is best understood, and as a result, it plays a large role in confirming or ruling out a diagnosis, especially in cases with low-intermediate probability. Around 80% of gene-positive LQTS cases result from a

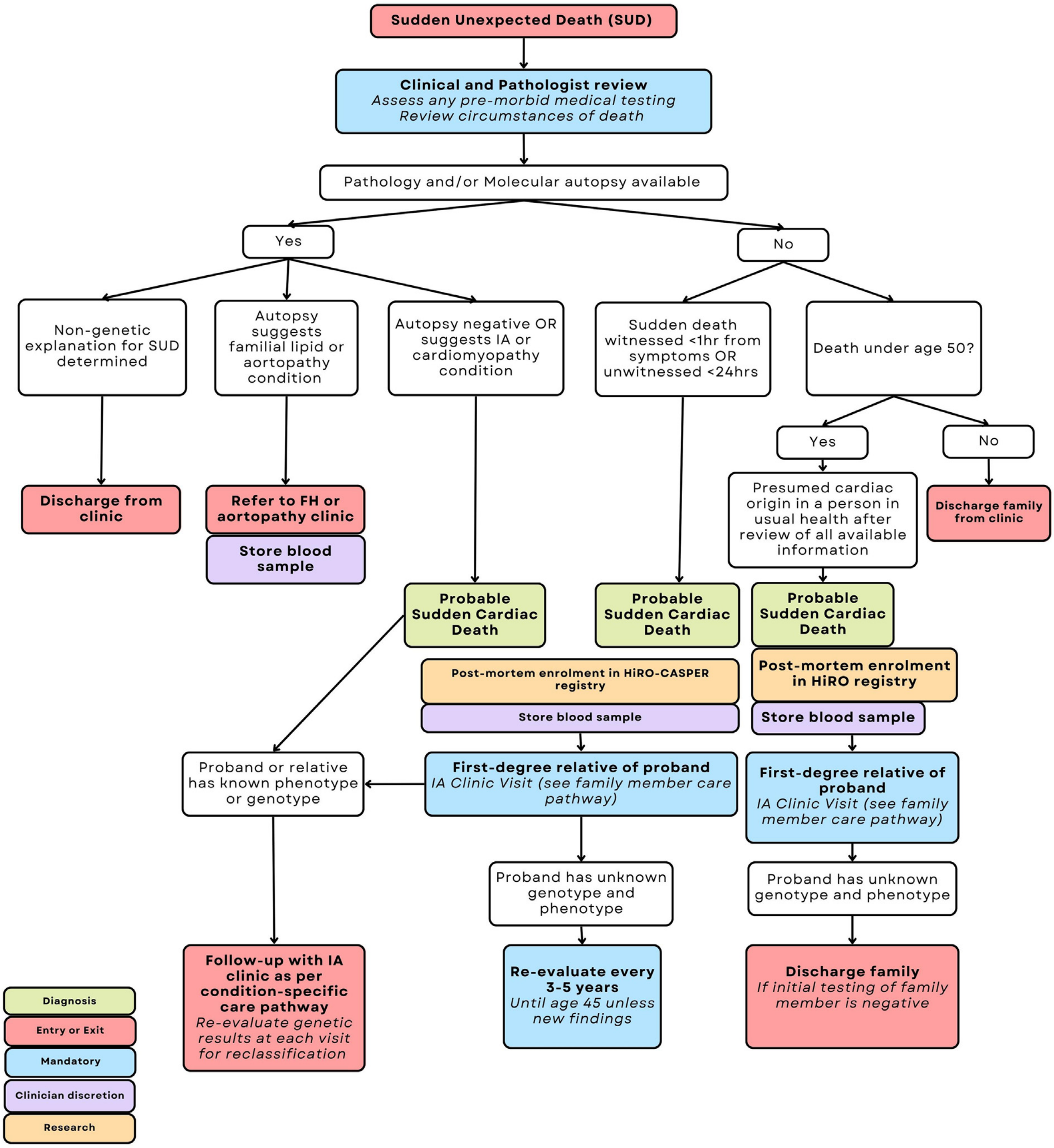

Figure 7. Care pathway for diagnosis and management of sudden unexpected death (SUD). CASPER, Cardiac Arrest Survivors With Preserved Ejection Fraction Registry; FH, familial hypercholesterolemia; HiRO, Hearts in Rhythm Organization; IA, inherited arrhythmia.

mutation in the *KCNQ1* and *KCNH2* genes, which encode voltage-gated potassium channels, or the *SCN5A* gene, which encodes a voltage-gated sodium channel.[26] As a result, genetic testing is also recommended in patients with possible LQTS, following genetic counselling.

Pharmacologic management of LQTS includes avoidance of QT-prolonging medications and initiation of beta-blocker therapy; these 2 factors together drastically reduce the risk of SCA and SCD.[27] A wide variety of medications can prolong the QT interval and predispose the patient to life-threatening ventricular arrhythmia such as torsade de pointes; they should be avoided when possible. A full list can be found at www.crediblemeds.org and the related smartphone app. Beta-blocker therapy in LQTS provides exceptional risk reduction. Adequate blockade and dosage should be assessed by means of an exercise test 4-6 weeks after initiation and/or dose titration. A 15%-20% reduction of maximum heart rate at similar workload is considered adequate beta-blockade; however, small and gradual dose titration is recommended to limit adverse effects and support compliance. Mexiletine can be considered in LQTS type 2 or type 3 (Table 1). A primary-prevention ICD plays a limited role in

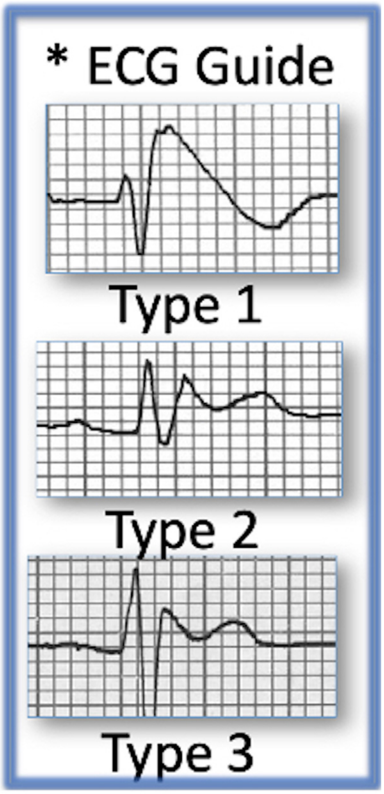

Figure 8. Electrocardiogram (ECG) guide to various Brugada patterns.

LQTS, but it may be considered for those on adequate beta-blocker therapy with breakthrough syncope or prolonged QTc interval on ECG. In those with unlikely or possible LQTS, expert judgment may inform the decision to follow and reassess in select cases based on the clinical and family context.

Illustrative case

A 45-year-old man underwent an ECG as part of employment screening and was incidentally found to have a QTc interval of 475 milliseconds. He was not taking any medications known to prolong the QT interval. He reported no history of syncope, but his brother died suddenly at age 27 years, and a structural cause of death was not identified on autopsy. Given this QTc interval of 475 milliseconds and an unexplained sudden death in a first-degree relative under the age of 30 years, this patient's Schwartz score was 2.5, suggesting possible LQTS.

He was referred to a local inherited arrhythmia clinic, where a repeat resting ECG showed a QTc interval of 470 milliseconds, and exercise stress testing showed QTc prolongation of 490 milliseconds extending into the recovery period. The shared decision to pursue genetic testing was made by the clinic electrophysiologist, a genetic counselor, and the patient.

In this case, a Long QT gene panel was performed, and a pathogenic *KCNQ1* variant was identified, confirming the patient's diagnosis of LQTS. Following the positive genetic test result, beta-blocker therapy was initiated, with nadolol as the preferred agent, and bisoprolol or propranolol alternatives. A treadmill test was performed while the patient was on a beta-blocker, to target a 15%—20% reduction in peak heart rate. Recommended follow-up includes a 12-lead ECG and an exercise test every 1-2 years; if the patient is stable and/or low-risk, test review without an in-person clinic visit, or a virtual clinic visit, can be considered. With regard to first-degree family member screening, some inherited arrhythmia clinics lead with genetic testing when a known pathogenic variant has been identified in the family, and they only perform phenotypic testing (ECG, exercise stress test) in carriers of the variant. Other clinics choose to concurrently complete phenotypic testing in all first-degree family members. Regardless of which approach is used, all first-degree family members of an affected proband should be referred for evaluation, especially in the setting of an identified pathogenic variant. Published decision aids on cascade screening can help with family counseling and decision-making.[5]

ARVC

Background

ARVC is characterized by fibrofatty infiltration of the ventricular myocardium, which results in an increased arrhythmogenic risk. The desmosomes connecting myocardial cells are often abnormal, reducing the strength and integrity of cell-to-cell connections and thus increasing the likelihood of ventricular arrhythmias. Given this, unlike with other inherited arrhythmia syndromes, imaging (echocardiogram or contrast-enhanced cardiac magnetic resonance) plays a role in the diagnosis and risk stratification of ARVC (Fig. 3).

The 2010 Task Force Criteria constitute the gold standard for diagnosis of ARVC (Supplemental Table S2).[28] Scores should be recalculated in patients with follow-up testing, especially in previously borderline patients, as ARVC can be progressive, and severity may change over time. The nomenclature has recently evolved, with ARVC now being termed ACM, expanding the diagnosis to include diverse phenotypes such as biventricular and left ventricular dominant arrhythmogenic cardiomyopathies, and other genetic forms of cardiomyopathy whose clinical phenotypes can overlap with ARVC.[29,30] In 2020, the Padua Diagnostic Criteria were published to include the broader spectrum of ACM, but the 2010 Task Force Criteria remain most widely accepted and utilized by specialists.[31] Both criteria sets separate clinical findings into major and minor criteria and focus on 12-lead ECG, 24-hour Holter monitor, cardiac imaging (echocardiogram and/or contrast-enhanced cardiac magnetic resonance), and family history. Signal-averaged ECG (SAECG) is becoming less important in the diagnosis of ACM, as understanding of the disease evolves and use of genetic testing expands.[32]

The majority of experimental and clinical evidence indicates that a reduction in high-intensity endurance exercise reduces both ventricular arrhythmia and heart failure risk.[29,33-36] Even after diagnosis, exercise restriction can reduce future ventricular arrhythmia risk.[37] A conservative safe level is usually 30 minutes of brisk walking daily; however, limiting intensity may provide more protection from ventricular arrhythmia, compared to limiting duration of exercise.[38] Evidence suggests that phenotype-negative, genotype-positive patients also benefit from exercise limitation in terms of long-term outcomes.[30] Close follow-up is warranted for patients who continue to exercise.

Table 1. Clinical management of inherited arrhythmia syndromes

	Lifestyle	Pharmacologic	Intervention
ARVC*	Avoid competitive or frequent high-intensity endurance exercise	Beta-blocker: definite phenotype positive ARVC; consider if inappropriate ICD shocks Amiodarone/sotalol: consider with symptomatic arrhythmias ± ICD Flecainide: combination with beta-blockade in patients with refractory arrhythmias	Consider ICD: use risk calculator at https://arvcrisk.com/ Catheter ablation: symptomatic arrhythmias refractory to treatment
BrS	Treat fever with Tylenol Drug avoidance (www.brugadadrugs.org & illicit substances) Carry Brugada ECG	Consider quinidine if ICD shocks	ICD recommended: all symptomatic type 1 (provoked or unprovoked) Catheter ablation: consider with EP study if appropriate ICD shocks
CPVT	Avoid triggers Physical activity safety plan	First-line: Beta-blocker Second-line: flecainide	LCSD or ICD recommended: symptomatic probands despite optimal medical therapy
LQTS	Avoid QT-prolonging medications (www.qtdrugs.org), illicit substances, and triggers (eg. sudden noises) Physical activity safety plan Emphasize importance of beta-blocker adherence	Beta-blocker: prefer nonselective agents, evaluate efficacy with exercise test Mexiletine: consider in LQT2 and LQT3	ICD recommended: breakthrough syncope/LQT on beta-blocker Consider LCSD: high-risk patients, breakthrough cardiac events or medical/device treatment intolerance/refusal

ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ECG, electrocardiogram; EP, electrophysiology; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; LQT, long QT; LQTS, LQT syndrome.

*Non-ARVC arrhythmogenic cardiomyopathy is covered briefly in the text.

Medical and interventional management strategies in ACM include use of beta-blockers and primary ICD implantation, respectively. Beta-blocker therapy is recommended for patients with definite phenotype-positive ACM. Primary-prevention ICD implantation can be considered in high-risk patients. A validated prediction model to assess the risk of ventricular arrhythmias is available at www.arvcrisk.com, which can be useful to inform shared decision-making surrounding ICD use.[39-41] Ablation therapy may be considered in symptomatic arrhythmias refractory to treatment where primary-prevention ICD implantation is not indicated.

In terms of follow-up, re-evaluation of the prediction model at each clinic visit is imperative for accurate ongoing risk stratification. ACM is usually progressive, so maintaining an accurate clinical picture of the severity of disease is important, to support both prognosis and risk-management strategies. Further, reclassification of genetic variants may impact diagnosis strength and arrhythmia risk.

Illustrative case

A 24-year-old male college athlete presented with a SCA while playing hockey and received a secondary-prevention ICD. An echocardiogram showed a left ventricular ejection fraction of 50% and regional right ventricular (RV) akinesia with reduced RV ejection fraction at 39%, which was confirmed by cardiac MRI. His 12-lead ECG showed T-wave inversion in V_1-V_4, and a 24-Holter monitor reported 712 premature ventricular contractions (PVCs). Given these findings, this patient would meet the 2010 task force criteria for definite ARVC, meeting one major criterion for ARVC (T-wave inversion) and 2 minor criteria (RV morphologic features and > 500 PVC/24 hours). The patient was then started on beta-blocker therapy and counselled to stop playing high-level hockey and reduce his exercise intensity. Psychological support was offered in light of the significant lifestyle alteration associated with the diagnosis. The patient met with a genetic counsellor and proceeded with genetic testing, which was negative. First-degree relatives were referred to the clinic for cardiac evaluation. With no identified pathogenic or likely pathogenic genetic variant in the proband, cascade genetic testing for family members was not possible, but surveillance cardiac evaluation was recommended.

The proband was seen for annual evaluation and remained clinically stable over the next 3 years. Eventually, repeat genetic testing was offered, which identified a pathogenic *FLNC* variant, a gene more recently associated with ACM, which had not been included on the original gene panel. Following this finding, first-degree relatives were offered genetic testing for this variant. Relatives who tested negative for the familial variant were discharged from ongoing evaluation. Family members who tested positive for the *FLNC* variant continued to be followed by the specialty IA clinic every 1-2 years to monitor for early signs of disease.

CPVT

Background

CPVT is characterized by rapid polymorphic and bidirectional ventricular tachycardia in the setting of sudden

Figure 9. An example of bidirectional ventricular tachycardia seen on an exercise stress test in a patient with catecholaminergic polymorphic ventricular tachycardia, best depicted in lead III.

adrenergic stimuli and is one of the least-prevalent IA syndromes.[42-44] The resting ECG most often does not show any abnormalities, so a detailed history and provocative testing must be completed to reach a diagnosis (Fig. 4). Symptoms usually present first in children and young adults, although they may be subtle or nonspecific, such as presyncope or palpitations. Further, the context of adrenergic stimuli may vary—from physical exercise, such as swimming, to a rollercoaster ride or emotional stress.[45] A delayed diagnosis or overlooked warning signs are not uncommon and may have catastrophic consequences, especially as a missed opportunity for very effective interventions that can prevent SCA and SCD.[46]

Exercise testing is the mainstay of CPVT diagnosis, mimicking adrenergic stimulation in a clinical setting. However, the sensitivity of standard Bruce protocols, wherein effort is gradually increased, is low. Depending on the specific genetic variant, over 70% of gene-positive patients may have a nondiagnostic exercise test.[47] A new "burst" exercise testing protocol, more closely mimicking the sudden onset of adrenergically triggered arrhythmias, may improve the sensitivity of exercise testing, although further analysis is needed to support its diagnostic role.[48]

The underlying etiology of CPVT is characterized by abnormal Ca^{2+} handling at the sarcoplasmic reticulum. Given this, the most common genetic variants are within the *RyR2* gene encoding the ryanodine receptor, and up to 60% of patients with CPVT present with pathogenic variants.[42] Interestingly, de novo mutations are commonly seen in CPVT probands, but a thorough family screening should still be undertaken, as siblings of a de novo proband carry a 1%-2% risk of harbouring the same mutation as a result of parental germline mutation.[49] Further, false paternity is an uncommon occurrence, but it should be carefully considered in all genetic conditions.

Management of CPVT focuses on avoiding potential triggers when possible and ensuring that safety plans are in place when patients are engaging in stimulating activities. When a diagnosis is confirmed, nonselective beta-blockers (nadolol or propranolol) are the first-line pharmacologic treatment, and flecainide is an effective adjunct. Left cardiac sympathectomy is also effective. ICD use is more limited with CPVT, compared with other IA conditions, as the adrenergic response to an ICD shock may exacerbate the trigger of CPVT. However, ICD use may be considered in probands who remain symptomatic despite optimal medical therapy.

Illustrative case

A 12-year-old girl presented after a near-drowning experience. She jumped off a high diving board and immediately was found unresponsive. After the lifeguard removed her from the pool, she spontaneously regained consciousness. She reported no prodrome to the event, other than feeling quite frightened upon jumping. However, she had experienced intermittent palpitations over the past 3 years, but as they were always associated with stressful situations, she dismissed them. She had no family history of sudden death or cardiac arrest.

Her 12-lead resting ECG was normal, but a standard exercise test showed infrequent polymorphic PVCs at peak exercise. She was retested with the burst exercise protocol, showing frequent bidirectional PVCs and a short run of nonsustained polymorphic ventricular tachycardia at peak exercise (Fig. 9). Given these findings, she had a likely diagnosis of CPVT. She underwent genetic testing, which revealed a pathogenic variant in the *RyR2* gene, supporting this diagnosis. She was started on nadolol (nonselective beta-blocker), and repeat exercise testing a few days later showed only PVCs but no couplets or ventricular tachycardia. Repeat exercise testing 6months later revealed a 25% reduction in peak heart rate and only rare PVCs—the desired therapeutic result. A follow-up 12-lead ECG and exercise test annually were recommended.

Upon first-degree relative screening, neither parent was found to carry the same pathogenic variant, suggesting a de novo mutation. Although this finding effectively rules out

CPVT in her parents, it brings forward a question regarding screening of her 2 siblings. Her siblings carry a 1% risk of inheriting the *RyR2* variant due to the potential of germline mosaicism.[49,50] Given this risk, in this case, her siblings should be evaluated with a 12-lead ECG and an exercise test (standard or burst), and targeted genetic testing may be considered. Given the potentially catastrophic consequences of a missed diagnosis, erring on the side of caution is advised in these scenarios.

Sudden Unexpected Death (SUD) and SCA

Background

SCA and SUD are the 2 most-feared manifestations of IA syndromes. In general, SCA and SUD are defined as cardiac arrest or death within an hour of symptom onset, or with no identifiable prodrome, such as during sleep. Automated external defibrillators (AEDs) are important in resuscitating those who experience SCA, in order to avoid SUD. Advocacy for public availability of AEDs, especially in potentially risky settings, such as swimming pools or sports facilities, helps save lives. Only a very small subset of SCA and SUD are related to IA syndrome, so thorough evaluation is important given the wide differential diagnosis. However, IA syndromes remain an important differential, given the familial nature and prognostic implications, especially when events occur in young individuals.

Ischemic, structural, toxic, or metabolic causes of SCA are more common than IA syndromes and should be ruled out first (Fig. 5). Once excluded, a thorough history should be obtained, including a 3-generation family history. Any potential warning signs (such as syncope without prodrome) and suspicious deaths or deaths at a young age in other family members should be defined as well as possible. Comprehensive phenotypic testing should be completed and used to guide genetic testing. Broad-panel genetic testing can be offered if no phenotype is found, and it should be led by a genetic counsellor in conjunction with a specialized IA clinic.[51] In a subset of patients, a clear etiology may not be found initially; phenotypic testing should be repeated every 2-3 years, as diagnostic findings may be intermittent, and clinical knowledge evolves. For example, short-coupled ventricular fibrillation (SCVF) was recently identified in 6% of previously unexplained SCA.[52] SCVF is initiated by short-coupled premature ventricular contractions, although whether it is a distinct entity or a subphenotype of ventricular fibrillation is currently unclear. This discovery also has treatment implications, as quinidine was identified to be an effective type of pharmacologic management, one not usually prescribed in other etiologies of SCA. A thorough evaluation of SCA probands also has implications regarding the utility of family screening (Fig. 6). If no cause can be found, the yield of family screening is low (3%).[53]

In the case of SUD, a diagnosis requires a different path of investigation, as the proband cannot be prospectively evaluated (Fig. 7). Any available cardiac testing performed prior to the SUD should be tracked and reviewed by an expert. An autopsy should be performed, especially if the deceased was under the age of 35 years. Once these other causes are ruled out, SUD is sometimes referred to as sudden arrhythmic death syndrome (SADS). In these cases, 40% of people will have a negative autopsy, and IA syndromes are the top differential in the absence of structural pathology.[54] As most young, seemingly healthy individuals do not have extensive cardiac testing performed prior to a fatal event, postmortem broad-panel genetic testing often plays a very important role in diagnosis after SUD. Through advocacy and education, saving autopsy tissue for genetic testing has become common practice in many jurisdictions, but efforts remain necessary to ensure that this remains common practice.

After either SCA or SUD, broad-panel genetic testing should be considered in consultation with cardiogenetic experts.[55] A pathogenic variant is more likely to be found if the precipitating event occurred during exercise or a period of extreme emotion.[51] Nevertheless, an identified variant in any family greatly streamlines evaluation and assists in preventing further tragedies for affected families. When possible, either premortem or prospective clinical testing should guide the choice of which genetic panel is tested. Management of those with a positive diagnosis, whether phenotypic and/or genotypic, depends on the syndrome found, as outlined above.

Illustrative case (SCA)

A 31-year-old man experienced SCA during a local marathon. He was successfully resuscitated by a bystander, with an AED available on the racecourse, and was subsequently transferred to the hospital. Unfortunately, no ECG tracings were available for review, but a presumptive diagnosis of SCA was made. His initial in-hospital ECG, echocardiogram, and cardiac MRI showed no abnormalities, and coronary angiogram ruled out coronary artery disease and anomalous coronary artery anatomy. An ICD was implanted, given his SCA.

After discharge, he was assessed at the local IA clinic for a full workup. His family history was notable, as his paternal cousin was found unresponsive after a single motor vehicle accident, and his paternal grandfather died suddenly at age 45 years. Aside from the SCA, the patient did not report any history of arrhythmia symptoms. Further, his 12-lead ECG, Holter monitor, and exercise testing did not reveal any abnormalities. A procainamide challenge was negative for a type 1 Brugada pattern, although suspicion was low because of the adrenergic context. Broad-panel genetic testing was completed, which revealed a variant of uncertain significance in the *KCNQ1* gene, which is often associated with LQTS. First-degree family members were referred for screening but were not offered genetic testing given that the variant of uncertain significance identified in the proband was not considered a diagnostic genetic result.

Two years later, he was seen again for scheduled follow-up with repeated clinical testing and review of genetic variant classification. New data identified the *KCNQ1* variant to be relatively common within the general population, and the variant was downgraded to likely-benign. The patient subsequently had an appropriate ICD shock while out for a brisk walk. Rhythm strip analysis revealed ventricular fibrillation triggered by a PVC, with a coupling interval of 300 milliseconds, which was successfully terminated by ICD shock. Given this context, the patient received a diagnosis of SCVF, and quinidine therapy was initiated. As SCVF is a newly described diagnosis, the implications of this diagnosis on family screening are not yet well understood. SCVF is not typically familial, and no culprit gene has been identified, with the exception of a founder haplotype near the gene *DPP6* in patients of Dutch ancestry. First-degree family members with an abnormal phenotype should continue to be followed, and those with normal phenotypes can be discharged.

Illustrative case (SUD)

A 14-year-old boy was referred after his 42-year-old mother was tragically found dead in her bedroom, presumed to have died in her sleep. An autopsy did not identify a structural or toxic cause of death. Upon review, the family history was positive for sudden death in a distant maternal cousin, but only limited details surrounding this event were available. Broad-panel genetic testing of the saved blood sample was performed, but a pathogenic variant was not identified. The family provided consent for the remaining sample to be stored for research purposes, with permission to contact them if new information arose. Given the undetermined but potentially inherited cause of SUD in his mother, the boy, along with his 2 younger maternal half-siblings, underwent a comprehensive phenotypic evaluation, including a 12-lead ECG, high-lead ECG, signal-averaged ECG, Holter monitoring, exercise stress test, and echocardiogram, all of which were reassuring. He was counselled to return for a follow-up visit in 3-5 years to re-evaluate his own phenotype testing and for potential further genetic testing, depending on new information at the time.

If a pathogenic variant had been identified in the post-mortem sample, this would have greatly streamlined family-member screening, and those who did not carry the variant would not need to be followed. Those who do carry the variant would undergo phenotypic testing and be followed per the specific pathway relating to the likely diagnosis.

Conclusion

A systematic and comprehensive approach to the evaluation of patients and families at risk for IA syndromes is central to diagnostic clarity and precision therapy. Missed diagnoses can have catastrophic consequences, and overdiagnosis is also a concern. Each syndrome has characteristic findings and clinical pathways that will help better understand and diagnose these conditions. Important to note is that not all cases are straightforward; the phenotype and genotype diagnostic effort can take time, and multidisciplinary expert consultation is key to care for patients and families.

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Supplementary Material

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