https://doi.org/10.35336/VA-1474

POSSIBILITIES AND DIFFICULTIES OF DIAGNOSTICS OF HEREDITARY ARRHYTHMIC SYNDROMES IN REAL CLINICAL PRACTICE

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The review article discusses current aspects of diagnostics of hereditary arrhythmic syndromes, according to clinical guidelines, and dificulties that have arisen in real clinical practice, as well as possible ways to solve them. A systemic and multidisciplinary approach to solving these problems will contribute to increasing the effectiveness of clinical genetic studies and thereby improving the prevention of malignant arrhythmias and sudden cardiac death.

Key words: sudden cardiac death; channelopathies; hereditary arrhythmias; genetic testing

Conflict of Interest: none.
Funding: none.
Received: 24.02.2025 **Revision received:** 05.05.2025 **Accepted:** 22.05.2025
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For citation: Iskenderov BG, Lokhina TV, Burmistrova LF. Possibilities and difficulties of diagnostics of hereditary arrhythmic syndromes in real clinical practice. *Journal of Arrhythmology*. 2025;32(2): 62-72. https://doi.org/10.35336/VA-1474.

Hereditary arrhythmias account for more than half of all initially unexplained cases of sudden cardiac death (SCD) in young individuals [1-3]. Among these, inherited arrhythmias caused solely by abnormalities in cardiac ion channels - known as channelopathies - are identified in approximately 30% of cases, whereas idiopathic structural heart abnormalities, particularly hypertrophic cardiomyopathy (HCM), are detected in around 70% of cases [1, 4]. Inherited arrhythmic syndromes without structural cardiac changes are responsible for approximately 10% of the 1.1 million annual cases of SCD in Europe and the United States [5-7]. Early diagnosis of hereditary arrhythmias may significantly reduce the risk of SCD, as in roughly 30% of cases, SCD is the initial manifestation of these disorders [4, 8].

Monogenic diseases may underlie SCD, and the most frequently encountered entities include the following major nosological forms, which present with unique but often overlapping clinical phenotypes and genetic associations: Long QT syndrome (LQTS), Short QT syndrome (SQTS), Brugada syndrome (BrS), Catecholaminergic polymorphic ventricular tachycardia (CPVT), Early repolarization syndrome (ERS), and idiopathic ventricular fibrillation (VF) [6, 9].

The detection rate of hereditary arrhythmias and the overall effectiveness of SCD prevention depend, in addition to medico-social factors, on the awareness and practical competencies of general practitioners and non-specialised clinicians [10, 11]. This may partly explain the discrepancy between the reported prevalence of hereditary arrhythmias in the general population and actual clinical practice, which typically involves the documentation of isolated case reports. According to a survey conducted by the European Heart Rhythm Association (EHRA) across 23 European countries, more than 50% of clinical centres do not participate in any form of registry - whether national or European - for hereditary arrhythmias, likely due to the low detection rate of such conditions [1, 6, 10].

In clinical practice, hereditary arrhythmias are most often identified in their syndromic forms - such as Brugada syndrome, Jervell and Lange-Nielsen syndrome, Timothy syndrome, and Andersen-Tawil syndrome - which are characterised by both cardiac and extracardiac phenotypes [12-14]. However, hereditary arrhythmias may also present with non-specific symptoms - such as syncope, palpitations, or seizures - and are frequently overlooked by clinicians. This can be attributed to the presence of functionally risky alleles or low-penetrance genetic variants in the general population, whose phenotypic expression requires the presence of additional risk factors, including drug effects, electrolyte imbalances, fever, and others [7, 10].

In recent years, the accessibility of high-tech medical care for patients with cardiovascular diseases, including those with life-threatening arrhythmias, has significantly improved in the Russian Federation. As a result, the number of implantations of cardioverter-defibrillators and pacemakers, as well as the frequency of ablation procedures, has increased substantially [15]. Consequently, this necessitates the optimisation of specialised medical services to improve access to medical genetic testing for patients with hereditary cardiac arrhythmias, along with the development and implementation of educational programmes aimed at raising awareness and enhancing the competencies of healthcare professionals.

Given the above, it is of particular interest to present a systemic approach to the diagnosis of hereditary arrhythmias and to analyse the potential causes of misdiagnosis or delayed diagnosis of these conditions in real-world clinical practice. It is important to note that a detailed analysis of diagnostic challenges - particularly those related to known limitations or misinterpretation of test results - may enhance the effectiveness of medical genetic care for patients with suspected channelopathies.

The literature review was conducted using international databases such as PubMed, Scopus, Web of Science, and the Cochrane Library, as well as Russian-language sources including eLibrary.

PREVALENCE OF HEREDITARY ARRHYTHMIAS IN THE GENERAL POPULATION

It is important to note that current data on the prevalence of individual cardiac channelopathies in the general population are primarily derived from international multicentre studies. These studies have contributed to the development of electronic databases that account for the ethnic, racial, and geographic characteristics of specific hereditary arrhythmic syndromes [3, 5, 10]. For example, the prevalence of Brugada syndrome (BrS) in European and North American populations ranges from 0.012% to 0.26%, whereas in endemic regions of Southeast Asia, it is significantly higher, reaching 0.7% to 1.0% [12]. The global prevalence of Jervell and Lange-Nielsen syndrome is estimated at 1 to 6 cases per 1 million people, with a rate of approximately 1 per 200,000 in Scandinavian countries [3, 16]. Cardiac channelopathies, together with genetic cardiomyopathies, are among the leading causes of morbidity and mortality in the paediatric population, with an annual incidence of 1.1 to 1.5 per 100,000 children under the age of 18 [7, 17].

The variability in the detection rates of cardiac channelopathies may also be explained by the extensive genetic heterogeneity of specific populations and the influence of environmental factors [18, 19]. For instance, the prevalence of SQTS, defined by a corrected QT interval (QTc) ≤300 ms, was highest among African Americans (5.8 per 100,000), followed by Caucasians (3.2), Latin Americans (1.8), and individuals of Asian or Pacific Islander descent (1.6) [3, 15]. The asymptomatic course of latent hereditary diseases further reduces the apparent population frequency of inherited arrhythmias. For example, in 40% of genotyped cases of LQTS, QT intervals fall within the normal range [20, 21]. Thus, the actual prevalence of LQTS is believed to be higher than currently reported figures [13, 16]. Epidemiological studies estimate that the individual prevalence of LQTS, BrS, and CPVT is approximately 1 in 2,000 [5, 22]. The rarest hereditary arrhythmia is SQTS, with a prevalence ranging from 0.1% to 0.003% in the general population [7, 15], whereas ERS is considerably more common, with a reported prevalence ranging from 1% to 13% [23].

The prevalence estimates of LQTS and SQTS are affected by several methodological limitations, including inaccuracies in QT interval measurement on standard electrocardiograms (ECG), as well as the absence of universally accepted diagnostic threshold values for QT intervals, which serve as ECG markers for LQTS and SQTS [13, 24]. Furthermore, the widespread clinical use of ajmaline challenge testing has significantly increased the reported frequency of BrS, leading to what has been termed drug-induced “Brugada phobia” [25]. In this context, it has been reported that in Europe, 70% of asymptomatic patients diagnosed with BrS received this diagnosis following a positive ajmaline test [6].

CLINICAL APPROACH TO THE DIAGNOSIS OF CARDIAC CHANNELOPATHIES

The clinical diagnosis of hereditary arrhythmias is often challenging due to their non-specific symptoms, the occasional absence of ECG patterns, and the predominance of latent (asymptomatic) presentations. The key components for establishing a diagnosis of channelopathy include a thorough evaluation of presenting symptoms, targeted exploration of the patient’s medical and family history, and a rational approach to diagnostic testing [6, 26, 27]. Given that affected individuals may initially present to physicians of various specialities - such as general practitioners, internists, paediatricians, or neurologists - it is crucial that the ability to recognise signs of hereditary arrhythmias is not limited to cardiologists alone.

Symptomatic presentations of hereditary arrhythmias allow for earlier and more frequent detection compared to asymptomatic forms [1, 28]. The most common and life-threatening manifestations include syncope, seizures, and sudden cardiac death, often triggered by specific stimuli. Syncope, in particular, presents a significant diagnostic dilemma, as it may range from a benign vasovagal episode to a potentially fatal event caused by polymorphic VT or VF [2, 13, 29].

In channelopathies, arrhythmogenesis may present as various types of VT, each carrying differential diagnostic significance. For instance, LQTS is most commonly associated with polymorphic VT of the torsades de pointes type; in Brugada syndrome (BrS), polymorphic VT is also characteristic [27, 30]. CPVT typically manifests as bidirectional VT, characterised by alternating polarity of the dominant QRS complexes [31], whereas arrhythmogenic right ventricular cardiomyopathy (ARVC) is marked by monomorphic VT with a left bundle branch block morphology. These arrhythmias may terminate spontaneously, but they also carry the risk of degenerating into VF, requiring electrical defibrillation. During such arrhythmic episodes, patients frequently report palpitations, dizziness, dyspnoea, chest pain, profound fatigue, and sensations of fear or panic.

It should be noted that in syndromic variants of channelopathies, the cardiac phenotype is often accompanied by extracardiac, multisystemic manifestations, which may aid in diagnosis but can also lead to mismanagement. For example, LQTS combined with congenital bilateral sensorineural deafness is characteristic of Jervell and Lange-Nielsen syndrome [13], while facial dysmorphism and syndactyly are features of Andersen-Tawil syndrome [14].

Identifying potential arrhythmic triggers often provides valuable diagnostic clues for channelopathies. For

example, arrhythmic events occurring during physical exertion, particularly swimming, are suggestive of LQT1, while syncope induced by sudden loud auditory stimuli is typical of LQT2 [32]. As both physical and emotional triggers are physiologically associated with increased catecholamine release, syncope in such contexts is a hallmark of CPVT [33]. Arrhythmias that occur during sleep or rest, or in the context of fever, may indicate LQT3 or BrS, which are associated with pathogenic variants in the *SCN5A* gene [12, 22].

It is also important to emphasise that the likelihood of phenotypic expression - and thus the probability of diagnosing a hereditary arrhythmia - is determined by incomplete penetrance and variable expressivity of the disease-causing genes [7, 18]. Nearly all hereditary arrhythmic syndromes exhibit incomplete penetrance (i.e. <100%) [4]. For example, the clinical penetrance of various LQTS genotypes ranges widely from 25% to 100%, with an average of approximately 40% [16]. This implies that a portion of affected individuals will remain asymptomatic. Therefore, a normal corrected QT interval (QTc) on ECG does not exclude LQTS in first-degree relatives of affected individuals. In this regard, the likelihood of a positive genetic test is highest in individuals with the strongest phenotypic expression [18]. Additionally, due to age-related penetrance in several hereditary arrhythmias, repeat evaluation during adolescence or early adulthood is recommended for at-risk children [17, 34].

ALTERNATIVE DIAGNOSES REQUIRING DIFFERENTIAL CONSIDERATION

Given that symptomatic patients with recurrent syncope due to VTor VF may be misdiagnosed and followed for extended periods under the label of “epilepsy,” they may receive ineffective antiepileptic therapy [29]. Therefore, a detailed family history and ECGevaluation are mandatory in all patients with seizure-like episodes that are negative on electroencephalography (EEG), in young children with atypical seizures during febrile episodes, and in families with a history of sudden infant death syndrome (SIDS) [17, 35].

Unlike arrhythmic syncope, epileptic seizures typically have a prodromal phase, including premonitory symptoms (auras). In the case of aborted cardiac arrest, syncope is usually brief and only rarely accompanied by convulsions. In contrast, most epileptic seizures are associated with prolonged, generalised convulsions, followed by profound fatigue, postictal exhaustion, and sometimes tongue biting. Malignant arrhythmias have been shown to occur in a substantial proportion of generalised seizure episodes and are considered a possible pathophysiological link between unexplained sudden death and epilepsy [29]. In one cohort of patients with LQTS, abnormal EEG findings were observed in 71% of cases compared with 13% in the control group ($p < 0.01$) [35]. Detailed evaluation of these patients revealed mutations in the *KCNQ1* gene, which is responsible for LQT1. Notably, *KCNQ1*, which encodes a potassium channel, is expressed not only in the heart but also in the forebrain and brainstem [24, 35]. Thus, some patients with a diagnosis of epilepsy may have coexisting hereditary arrhythmias and face a particularly high risk of fatal arrhythmias [13]. Consequently, any history of sudden death in a family with a member presenting with atypical seizure activity should prompt a thorough cardiological investigation.

Primary periodic paralyses and neuromuscular channelopathies in children also merit attention in the context of cardiac channelopathies. For example, in patients with Andersen-Tawil syndrome (the classic form of LQT7), potassium-sensitive transient periodic paralysis is almost invariably present. These episodes often occur against the background of generalised weakness and typically present without myotonic signs [14]. Such episodes of muscle weakness usually begin before the age of 10 or during adolescence.

ECG PATTERNS OF HEREDITARY ARRHYTHMIAS AND CHALLENGES IN RESTING ECG INTERPRETATION

A common manifestation of the cardiac phenotype in hereditary arrhythmias is ECGabnormalities, including various rhythm and conduction disturbances [4]. ECG patterns specific to individual channelopathies play a critical role in their diagnosis. Therefore, resting 12-lead ECG is an essential component of the initial evaluation in suspected cases of channelopathy. A detailed analysis of all ECG parameters should be conducted, as abnormalities in atrial and ventricular depolarisation and repolarisation may coexist [27, 30].

A corrected QT interval (QTc) ≥500 ms on serial standard ECGs, in the absence of secondary causes of QT prolongation, serves as a strong diagnostic criterion for LQTS according to the LQTS scoring system (Fig. 1) [13, 20]. Conversely, a QTc ≤330 ms is a key criterion for the diagnosis of SQTS [15]. However, these cut-offs represent extreme QTc deviations, potentially resulting in underdiagnosis of LQTS and SQTS in milder cases.

Certain pathological ECG findings at rest, when unexplained by other conditions, may raise suspicion for cardiac channelopathies:

- Prolonged or shortened QT/QTc intervals;
- Ventricular extrasystoles triggered by exercise stress testing;
- Downsloping (coved-type) or saddle-back ST-segment elevation in leads V1-V3 (Fig. 2);
- T-wave alternans (inverted or abnormal T waves);
- Conduction delays (sinoatrial, atrioventricular, or intraventricular blocks);
- Epsilon waves in leads V1-V3;
- Prominent U waves in precordial leads, extending the QT-U interval;
- Prominent J waves, with or without ST-segment elevation, particularly in posterior or posterolateral leads;
- PQ (PR) segment depression in inferior leads.

Despite the diagnostic value of resting ECG, it presents limitations across nearly all types of channelopathies. Accurately determining the QT interval can be difficult, adversely affecting the timely and accurate diagnosis of LQTS and SQTS. This is particularly the case in the presence of ST-T wave morphological abnormalities (e.g. biphasic, low-amplitude, or inverted T waves), which may result from bundle branch block, electrolyte

imbalances, ventricular hypertrophy, digoxin effect, and other causes [8, 24].

The most precise method for determining the end of the T wave is the tangential method, in which a tangent is drawn from the steepest slope of the T wave to intersect the isoelectric line. To correct for heart rate (HR) variability, the QT interval is converted to QTc using mathematical formulae, most commonly Bazett's formula. Even among experts, QT measurement errors in LQTS may range from 10 to 70 ms [16]. A prevalence study of SQTS based on more than 6.3 million ECG recordings from 1.7 million individuals using automated ECG analysis identified 1,086 cases with QTc ≤300 ms; however, only 45 of these were confirmed upon manual QT measurement [5].

It is also known that prominent U waves in precordial leads - commonly seen in Andersen-Tawil syndrome and ankyrin-B syndrome - may mimic QT-U interval prolongation. When U waves are excluded from the QT calculation, the resulting QT intervals are typically normal or borderline (Fig. 3) [8, 18]. Accordingly, ongoing debates persist as to whether ankyrin-B syndrome and Andersen-Tawil syndrome should be classified as "typical" forms of LQTS [13].

EXPANDED EVALUATION OF PATIENTS WITH SUSPECTED HEREDITARY ARRHYTHMIA

When clinical assessment raises a strong suspicion of a specific cardiac channelopathy, additional investigations - including genetic testing - are warranted. Situations such as sudden death in young family members, unexplained syncope, documented VT or VF, or atypical epilepsy in the presence of specific triggers should prompt further diagnostic work-up.

Exercise Stress Testing

In patients presenting with symptoms suggestive of channelopathy and a seemingly normal resting ECG, an exercise stress test may be performed. According to the EHRA, exercise testing was used in 36-82% of patients with syndromic inherited arrhythmias [6]. Given that approximately 40% of LQTS cases show a normal QT interval at rest, assessing the QT/QTc response during exercise is recommended [32]. QTc shortening is expected in LQT2 and LQT3, while paradoxical QTc prolongation during exercise is characteristic of LQT1. The appearance of polymorphic or bidirectional VT during the active phase of the test, which subsides during recovery, is a hallmark of CPVT [22, 33]. However, only 63% of CPVT patients exhibit a positive exercise test, and a negative result does not exclude the diagnosis [31]. When the standard stress test fails to induce arrhythmias despite strong clinical suspicion, a "burst" exercise protocol - designed to provoke a rapid heart rate increase - can improve the likelihood of VT induction [34].

High Precordial Lead ECG Placement

It has been shown that recording leads V1-V3 at one to two intercostal spaces higher than standard positions can unmask a concealed type 1 BrS ECG pattern, particularly in cases with saddle-back ST elevation [12]. Echocardiographically guided lead placement at the anatomical location of the right ventricular outflow tract increases the detection rate of type 1 BrS ECG pattern compared to standard lead positioning: 100% vs. 43% ($p < 0.001$) [25]. Additional diagnostic criteria include the Corrado index for type 1 ECG and β-angle measurement for type 2 [8].

Holter ECG Monitoring

Holter monitoring is used to detect latent rhythm and conduction abnormalities in patients with suspected hereditary arrhythmias. It also helps in identifying the presence of arrhythmic triggers. In Europe, Holter ECG was used in 63-83% of cases involving suspected inherited arrhythmias [6].

The BrS ECG pattern is often intermittent, with a reproducibility rate of only 25% in repeat ECGs [26]. In such cases, Holter monitoring may help reveal a dynamic type 1 BrS pattern, avoiding the need for drug provocation. Holter is also useful for children who cannot perform exercise testing and for patients whose symptoms are emotionally, rather than physically, triggered [32]. When arrhythmic syncope is suspected, implantable cardiac monitors capable of recording ECG continuously for 6 to 24 months may assist in diagnosing arrhythmias [36].

Electrophysiological Study (EPS)

In most channelopathies, EPS to induce VT has limited diagnostic value and is not a standard test [8]. The positive predictive value of EPS in channelopathies ranges from 37-50%, and the negative predictive value from 46-97% [22]. Induction of VT using less aggressive pacing protocols (one or two extrastimuli) improves the test's prognostic accuracy. EPS is primarily recommended for risk stratification, determining indications for implantable cardioverter-defibrillator (ICD) implantation in asymptomatic patients, and assessing the efficacy of drug or ablation therapy [8]. However, failure to induce VT does not necessarily indicate low arrhythmic risk, especially in patients with high-risk clinical features.

According to EHRA, EPS is not routinely used to provoke ventricular arrhythmias in 82-98% of European centres, except in BrS, where 39% report its use [6]. VT or VF, the primary endpoints of EPS, are inducible in 60-70% of cases [22].

Drug Provocation Testing

If no other diagnosis is established and the circumstances of sudden cardiac death suggest BrS, provocation testing with class I antiarrhythmic drugs (e.g. ajmaline, flecainide, procainamide) is recommended in first-degree relatives with structurally normal hearts [30]. After intravenous administration, ECG should be recorded using 12-lead Holter or standard ECG with high precordial lead placement (V1-V3). Ajmaline has demonstrated a higher rate of positive results than procainamide or flecainide [12]. However, despite its high sensitivity, the ajmaline test lacks specificity: a type 1 BrS ECG pattern may be induced in patients with LQT3, ARVC, or r'-ST complexes in V1-V3 [30]. Therefore, a positive ajmaline test does not provide useful prognostic information in asymptomatic individuals with type 2 or 3 BrS ECG patterns [8].

Low-dose adrenaline infusion is an alternative diagnostic method in LQTS patients unable to perform stress testing. The adrenaline test has low sensitivity (28%) but high specificity (98%) compared to exercise testing [13].

EHRA data show that pharmacological provocation is used inconsistently across Europe: 90% of centres used

sodium channel blocker tests to diagnose BrS; 36% used isoproterenol testing for CPVT. However, drug provocation is avoided in 80-92% of centres when diagnosing LQTS, SQTS, or early repolarization syndrome (ERS), and in 67% of centres for idiopathic VF [6, 33].

Cardiac Imaging

In cases where arrhythmia is associated with structural heart disease - such as HCM, dilated cardiomyopathy (DCM), or ARVC - modern imaging techniques, including echocardiography and cardiac magnetic resonance imaging (MRI), may provide additional diagnostic insights [1, 7]. Repeat MRIs are recommended to monitor potential phenotypic evolution. According to EHRA, echocardiography is the most frequently used imaging modality, performed in 72-84% of arrhythmology centres in Europe [6].

MRI is more commonly used in patients with BrS, ERS, and idiopathic VF than in those with LQTS, SQTS, or CPVT (27-54% vs. 11-17%). Some centres also include coronary angiography in the evaluation of suspected idiopathic VF (62%) and CPVT (27%) [33]. Myocardial biopsy and signal-averaged ECG are included in diagnostic protocols for idiopathic VF and BrS, although they are rarely recommended as alternatives.

DIAGNOSTIC SCORING SYSTEMS FOR HEREDITARY ARRHYTHMIAS

In clinical practice, diagnostic scoring systems are widely employed to confirm hereditary arrhythmic syndromes. These systems integrate multiple criteria, including ECG patterns, symptom characteristics, family history, and results of genetic testing [13, 15, 33]. This approach is justified by the absence of absolute QTc interval thresholds for diagnosing LQTS or SQTS, as well as the difficulties in distinguishing BrS ECG patterns from QRS-T configurations seen in J-wave syndromes [6, 23, 31].

For example, the QTc threshold for suspecting or diagnosing SQTS varies broadly - from 220 to 360 ms - creating a “grey zone” between 330 and 370 ms [15]. This uncertainty is addressed in the SQTS diagnostic score, which assigns different point values based on the degree of QTc shortening and the strength of diagnostic suspicion. A QTc <370 ms scores 1 point, <350 ms scores 2 points, and <330 ms scores 3 points.

Moreover, diagnostic scores allow for stratification of the likelihood of a specific hereditary arrhythmic syndrome. In the initial evaluation of patients with suspected LQTS using the scoring system proposed by P. J. Schwartz et al. (2020), a total score of ≤1 indicates a low probability of LQTS, 1.5-3 points suggests an intermediate probability, and ≥3.5 points denotes a high likelihood of LQTS [13]. Despite their structured framework, diagnostic scores may have limited sensitivity when applied to relatives of a proband due to the incomplete penetrance of these syndromes [8, 28].

For Brugada syndrome, the standard diagnostic framework relies on the expert consensus from the Heart Rhythm Society (HRS), EHRA, and Asia Pacific Heart Rhythm Society (APHRS). In cases of drug-induced BrS ECG patterns, the Shanghai scoring system is recommended [12]. In this model, the diagnosis requires not only a type 1 BrS ECG pattern but also the presence of at least one of the following criteria: documented VF or polymorphic VT, unexplained syncope, sudden cardiac death (SCD) in a family member under 45 years of age with negative autopsy, type 1 BrS ECG pattern in a first-degree relative, or nocturnal agonal respiration [8, 25].

To objectively assess the pre-test probability of CPVT, a dedicated diagnostic score was developed that incorporates modern CPVT phenotype features [31]. The score includes factors that increase (age <40 years, genotype-positive status, family history) or decrease (presence of ventricular ectopy, ischaemic heart disease, prolonged QT interval) the likelihood of CPVT. According to this scale, a score of 3.5 to 12 points corresponds to a high pre-test probability, i.e., a definitive or >90% likelihood of CPVT. Notably, stress-induced polymorphic VT occurring at a heart rate >100 bpm is assigned 4 points - equivalent to a positive genetic test for a pathogenic variant [31].

Given the central diagnostic role of stress-induced polymorphic VT in CPVT, a broad spectrum of patients may fall into the “possible CPVT” category. Future guidelines are likely to refine the criteria for a “high probability” diagnosis of CPVT, especially in light of the substantial proportion of patients who remain genetically inconclusive or genotype-negative.

DIAGNOSTIC GENETIC TESTING

According to the EHRA, approximately 40% of patients and their relatives do not undergo genetic testing [6, 19]. Understanding the genetic and molecular basis of cardiac channelopathies can improve the prevention of SCD. Modern next-generation sequencing (NGS) technologies enable comprehensive assessment of arrhythmia gene panels, typically covering up to 40 genes and their mutations associated with channelopathies [19]. A key element of genetic testing is establishing the clinical relevance of identified variants, as the likelihood of a positive test is highest in individuals with high phenotypic penetrance [18].

For all suspected diagnoses involving channelopathies, the indication for genetic testing should be carefully justified. Genetic testing plays a critical role in identifying “presymptomatic” or “mildly symptomatic” individuals with genotypes associated with increased SCD risk, enabling early implementation of preventive strategies [19, 37].

It is important to note that Russian clinical guidelines on Ventricular Arrhythmias, Ventricular Tachycardia and Sudden Cardiac Death are based on European Society of Cardiology (ESC) recommendations, adapted to the national context, including diagnostic, therapeutic, and accessibility considerations [38, 39]. The level of recommendation (LoR) and level of evidence (LoE) supporting diagnostic genetic testing are closely linked to the likelihood of a positive result, depending on the specific hereditary arrhythmic syndrome.

According to these guidelines [38, 39], comprehensive genetic testing for mutations in *KCNQ1*, *KCNH2*, and *SCN5A*(associated with LQT1-LQT3, the most common subtypes) is recommended for all patients with clinical manifestations of LQTS, a positive family history, and QTc prolongation on resting or provoked ECG (ESC

class I, level A; LoR C, LoE 5). It is also recommended for asymptomatic individuals with no clear clinical signs of LQTS but with a QTc >500 ms on ECG, provided secondary causes of QT prolongation have been excluded (ESC class I, level A; LoR C, LoE 5).

When pathogenic mutations are identified in patients with LQTS or Brugada syndrome, cascade screening of first-degree relatives is recommended - even in the absence of clinical symptoms or ECG abnormalities - to aid in individual risk stratification (ESC class IIa, level B; LoR C, LoE 5) [38, 39]. Conversely, genetic testing is not recommended for individuals with type 2 or type 3 BrS ECG patterns in the absence of symptoms or a family history of SCD (ESC class III, level C; LoR C, LoE 5) [38, 39].

Genetic testing for mutations in *RyR2* and *CASQ2* is recommended for all patients with CPVT and for those with clinical features strongly suggestive of the condition, especially when a family history is present, to guide risk stratification (ESC class I, level C; LoR C, LoE 5) [38, 39]. For patients with SQTS, comprehensive molecular screening for mutations in *KCNH2*, *KCNQ1*, and *KCNJ2* is recommended to identify individual risk (ESC class I, level C; LoR C, LoE 5), although the sensitivity of available tests remains low.

Genetic variants are classified based on the strength of evidence as: benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, or pathogenic [18]. A pathogenic variant supports the clinical diagnosis and may inform both prognosis and treatment, as well as serve as the basis for family screening. With few exceptions, a VUS should not guide clinical management or risk assessment in asymptomatic relatives [40].

The EHRA/HRS/APHRS/LAHRS 2022 consensus introduced the concept of “key genes” (as per the ClinGen resource), which should be prioritised in genetic testing panels to improve clinical yield [18]. The average sensitivity of routine genetic testing is ~65% for LQTS, ~60% for CPVT, ~40% for SQTS, and only 25-30% for BrS [18].

Segregation analysis - the co-segregation of genotype with phenotype in multiple family members - remains the most robust support for pathogenicity [8, 28]. A positive genetic result in a proband enables cascade testing of first-degree relatives for the pathogenic variant. In general, cascade screening is recommended when the outcome will impact clinical decision-making. If no pathogenic or likely pathogenic variant is found in relatives, regular clinical monitoring is advised, as phenotypic expression may vary widely within the same family and may emerge later in life [25, 34].

In 30-40% of unexplained sudden deaths, autopsy fails to identify the cause of death despite comprehensive toxicological and histopathological assessment [41]. In such cases, the presumed cause is often sudden arrhythmic death due to a concealed hereditary arrhythmia [8]. Therefore, in accordance with guidelines, post-mortem genetic testing (molecular autopsy) is recommended in all cases of unexplained SCD, and if a pathogenic or likely pathogenic variant is found, cascade screening should be offered to surviving relatives (ESC class I, level C; LoR C, LoE 5) [38, 39].

The advent of high-throughput sequencing technologies has enabled large-scale sequencing using pan-cardiac panels (typically 50-100 heart-related genes), exome sequencing, or even whole-genome sequencing in cohorts with previously unexplained SCD [41]. One major finding has been the high frequency of pathogenic variants in genes associated with hereditary cardiomyopathies, which account for up to 70% of actionable variants in cases of unexplained SCD [41-43].

The combination of molecular autopsy and clinical-genetic evaluation of surviving family members significantly increases the likelihood of identifying a pathogenic or likely pathogenic variant. In fact, molecular autopsy alone yields unique findings in 15-30% of cases [44]. Nevertheless, only about 70% of clinicians report considering molecular autopsy in suspected hereditary cases of sudden death [2, 10].

CHALLENGES IN INTERPRETING GENETIC TEST RESULTS

Genetic and phenotypic heterogeneity continues to expand, and increasing evidence suggests that some hereditary arrhythmias are oligogenic in nature - that is, caused by interactions between multiple genetic variants [18, 45]. This adds substantial complexity to genetic identification and diagnosis. As a result, selecting the appropriate genetic testing panel and interpreting genotyping results requires specialised expertise and a multidisciplinary approach. The identification of a pathogenic variant indicates an increased risk of phenotype expression, but it is not equivalent to a clinical diagnosis. Conversely, a negative genetic test result does not exclude a clinically justified diagnosis. When a variant is identified, its relevance must be critically evaluated, as it may not represent the primary or sole cause of the condition [18].

Due to phenotype overlap and genetic heterogeneity, choosing the appropriate genotyping strategy can be challenging. The same phenotype may be caused by mutations in different genes - a phenomenon known as “genetic overlap” [11, 17]. Conversely, the same mutation can lead to distinct phenotypes even within a single family (variable expressivity). For example, family members with the same *SCN5A* mutation may present with BrS, LQTS, or conduction system disease [19].

Therefore, in the absence of a specific suspected diagnosis, there is little rationale for broad screening of all known genes associated with SCD. Such testing often reveals variants or mutations that are not causally related to the individual’s disease. Even when a working diagnosis is available, interpretation may still be impossible without both genetic and clinical evaluation of family members - especially when the identified variant has not been previously described. Additionally, the detection of numerous low-impact genes associated with a range of potential effects increases the uncertainty surrounding test interpretation [18].

It is important to note that many genetic variants associated with sudden death in young individuals remain classified as VUS for years, which complicates clinical decision-making [38]. These families should be managed as though they carry a negative genotype, and VUS find-

ings should not inform treatment decisions. However, some of these variants may later be reclassified as likely pathogenic following re-evaluation, in which case targeted lifestyle modifications or avoidance of known arrhythmic triggers in asymptomatic individuals may offer clinical benefit.

Genetic research has predominantly focused on mutations in the primary DNA sequence that affect gene transcription and translation [18]. However, a considerable number of cases involving hereditary ventricular arrhythmias with structurally normal hearts do not reveal a causative gene mutation. Among the potential contributors to such genetically elusive cases are epigenetic mechanisms that alter the expression of arrhythmia-susceptibility genes [46]. In BrS, for instance, although approximately 20 pathogenic genes have been identified, monogenic and polygenic mechanisms together still account for only 20-40% of known cases, leaving 60-80% genetically unexplained [12, 45].

Moreover, many primary cardiomyopathies (CMPs) initially present with arrhythmias prior to the development of overt cardiomyopathic changes, and may therefore be misinterpreted as primary electrical diseases [44]. Thus, in patients with suspected cardiomyopathy or hereditary arrhythmia, comprehensive genetic testing holds high diagnostic value and may outweigh the burden of ambiguous findings.

AWARENESS AND COMPETENCIES OF PHYSICIANS REGARDING HEREDITARY ARRHYTHMIAS

Given the rarity of hereditary arrhythmias in the general population, their phenotypic variability, and the predominance of asymptomatic carriers among probands' relatives, physician awareness plays a critical role in identifying affected individuals in clinical practice [5, 28]. Moreover, these patients frequently consult physicians across a range of specialties, which may lead to delayed or incorrect diagnoses and result in missed opportunities for effective intervention - despite a high risk of SCD [2, 6, 35].

In recent years, increasing attention has been directed towards evaluating physicians' awareness of hereditary arrhythmias and their attitudes towards implementing appropriate diagnostic procedures, including referrals to specialised centres [6]. A multicentre study conducted under the auspices of the EHRA assessed current management practices for young patients who had survived an SCD episode [1]. The results of this online survey revealed inconsistencies in the application of exercise stress testing, pharmacological provocation, and genetic testing. Notably, two-thirds of physicians did not consult with a geneticist when interpreting genetic test results. Autopsies were performed in only 43% of cases of sudden death, and post-mortem genetic testing in just 37%.

General practitioners can play a significant role in identifying individuals at risk for hereditary arrhythmias by referring them for genetic counselling. A survey of 106 general practitioners found that only 40% had encountered young patients with a family history of SCD in their practice [28]. Despite the importance of family history in the identification and appropriate management of genetic diseases, only 21% of general practitioners and 46% of cardiologists reported having diagnosed hereditary arrhythmias through family screening. Furthermore, approximately 40% of general practitioners and 30% of cardiologists indicated that they would not pursue further investigations even in the presence of a family history of early-onset SCD.

In another study involving 154 surgeons (including general surgeons, obstetricians, and anaesthesiologists), the majority (80%) lacked sufficient knowledge about SCD or hereditary arrhythmias [47]. When asked about the relevance of such knowledge to their professional practice, 35% considered it "not at all important," 32% rated it as "moderately important," and 28.5% believed it to be "very important." Following the survey, 95% of respondents expressed interest in receiving further education on hereditary arrhythmias via online sessions or in-person seminars.

Patient education on managing arrhythmia-related triggers is also crucial. According to EHRA data, nearly all clinics (86-93%) provided patients diagnosed with hereditary arrhythmias with counselling on the importance of avoiding specific arrhythmic triggers [6]. Furthermore, patients were informed about their condition through dedicated websites (77%) and informational brochures (56%). After initiating therapy, 68% of patients were followed by cardiologists in university hospitals, 14% by electrophysiologists, 13% by hospital-based cardiologists, and only 5% by general practitioners.

Collectively, these findings reflect suboptimal adherence to established guidelines in real-world clinical settings. Eliminating the causes of delayed or missed diagnoses - particularly through the implementation of educational programmes targeting physicians on topics such as SCD and hereditary arrhythmias - can enhance the effectiveness of medical and genetic care for patients with suspected channelopathies and their family members.

CONCLUSION

The analysis of real-world clinical practices in the diagnosis and management of patients with hereditary arrhythmias suggests that, despite the life-threatening consequences of cardiac rhythm and conduction disorders for patients and their families, there remains no optimal, comprehensive solution to the complex challenges posed by cardiac channelopathies. Although clinical guidelines for the identification and management of patients at high risk of sudden arrhythmic death - including those with inherited arrhythmic syndromes - are continuously being developed and refined, their implementation in clinical settings remains fraught with difficulties, which may sometimes result in catastrophic outcomes.

In addition to unresolved issues related to the genetic identification of inherited arrhythmic syndromes, the strict adherence to up-to-date clinical guidelines by healthcare providers is of paramount importance. Equally critical is the adoption of a multidisciplinary approach to patient management and the promotion of educational programmes aimed at improving the competencies of relevant medical specialists. Furthermore, there is an urgent need to consolidate efforts across healthcare institutions to develop a unified patient registry and to establish additional dedicated cardiogenetic centres or departments responsible for

coordinating medical and genetic care for affected individuals and their families.

When determining the diagnostic strategy for patients with suspected hereditary arrhythmias, it should also be taken into account that LQTS and BrS together account for more than two-thirds of all cases. Syncope and sudden cardiac death occur in approximately 40% of individuals with hereditary arrhythmias, while the majority of patients are diagnosed during asymptomatic stages.

In conclusion, addressing these challenges in a systematic and integrated manner may contribute to a more accurate understanding of the epidemiology of hereditary arrhythmias and enhance the effectiveness of preventive strategies aimed at reducing sudden arrhythmic death.

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