ISSN: 2766-967X

Journal of Heart and Cardiovascular Science

Review Open Access

Inherited Arrhythmia Syndromes and the Variant of Uncertain Significance: Cascade Testing When the Result Is Ambiguous

Aileen Strathmore[1*], Bastiaan Roosendaal[2], Zsofia Almasi-Bartha[3]

[1]*Department of Inherited Cardiac Conditions, Severn Institute of Cardiovascular Medicine, Bristol, United Kingdom*
[2]*Department of Clinical Genetics, Randstad Heart Institute, The Hague, Netherlands*
[3]*Department of Genetic Counselling, Danube Bend Institute of Cardiology, Vac, Hungary*

*Correspondence to: Aileen Strathmore, Department of Inherited Cardiac Conditions, Severn Institute of Cardiovascular Medicine, Bristol, United Kingdom
E-mail: a.strathmore@sicm.ac.uk

Received: 16 January 2025; Accepted: 24 May 2025; Published: 28 October 2025

Copyright: © 2025 Strathmore A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

The inherited arrhythmia syndromes -- long QT syndrome (LQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) among them -- cause sudden cardiac death in people whose hearts are structurally normal, and a genetic diagnosis in an affected proband is what makes it possible to test relatives before, rather than after, a life-threatening event [1]. Genetic testing for these conditions has matured from a research tool into routine clinical practice over the last two decades, guided since 2015 by a shared five-tier framework -- pathogenic, likely pathogenic, uncertain significance, likely benign, benign -- from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) [2].

That framework was built to be conservative, and it works as intended most of the time: most results returned to a proband are not ambiguous. But a meaningful minority are, and a variant of uncertain significance (VUS) is a different kind of result to receive and to act on than either a clearly pathogenic or a clearly benign one. A VUS confirms nothing and rules out nothing; it says only that the evidence available today does not clear the bar in either direction. For the proband that is unsatisfying. For a family considering whether to test asymptomatic relatives, it is a genuinely different clinical problem, because the entire logic of cascade testing -- test relatives for the one variant already shown to track with disease in this family -- depends on already knowing that the variant is disease-causing [3].

This review sets out what the published evidence says about that problem: how often a VUS result actually occurs, how often and in which direction it is later reclassified, what the 2022 multi-society consensus statement instructs clinicians to do with it in the meantime, and what is known about the practical and psychological cost of getting the classification wrong in either direction.

Material and Methods

This is a narrative review, not a systematic review with a pre-registered protocol. Sources were identified through targeted literature searches and citation tracking among the ACMG/AMP and multi-society consensus statements governing cardiac genetic testing, ClinGen-framework gene-validity reappraisals for LQTS and Brugada syndrome, cohort studies of variant reclassification frequency in inherited arrhythmia clinics, a study of long QT syndrome overdiagnosis, a study documenting ancestry-related variant misclassification, and a systematic review and meta-analysis together with a qualitative study of the psychological impact of receiving a VUS result. All percentages, counts, and effect estimates reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated.

Results

Three syndromes, three genetic architectures

LQTS, Brugada syndrome, and CPVT differ enough in their genetics that a single statement about "the VUS problem" in inherited arrhythmias risks obscuring real differences between them. LQTS has a minimum prevalence of about 1 in 2,534 apparently healthy live births, likely closer to 1 in 2,000 once borderline, ungenotyped cases are accounted for, and three genes -- KCNQ1, KCNH2, and SCN5A -- account for the great majority of genotype-positive cases [4]. Brugada syndrome is less common, estimated at 2 to 5 per 10,000 people, with SCN5A loss-of-function variants identified in an estimated 15% to 30% of cases and roughly 19 further genes proposed as contributory over the years [5]. CPVT is rarer still, estimated at 1 in 10,000 or less, and its genetics are comparatively concentrated: pathogenic RYR2 variants account for approximately 60% to 70% of cases and CASQ2 for approximately 5%, leaving roughly a quarter of clinically diagnosed patients with no identified pathogenic variant in any known gene at all [6]. Table 1 sets these three profiles out together.

A gene panel for any of these conditions, in other words, is not a single well-validated test but a bundle of genes with very different levels of underlying evidence -- and that heterogeneity in evidence quality is itself a major source of downstream VUS and misclassification risk, as the next section sets out.

Syndrome	Estimated prevalence	Principal gene(s)	Genetic yield / notes
LQTS	~1:2,000 live births [4]	KCNQ1, KCNH2, SCN5A	3 genes definitive/strong of 17 ever reported [7]
Brugada syndrome	2-5 per 10,000 [5]	SCN5A	SCN5A in 15-30% of cases; only gene with definitive evidence of 21 reported [8]
CPVT	~1:10,000 or less [6]	RYR2, CASQ2	RYR2 ~60-70%, CASQ2 ~5%; ~25% of cases genotype-negative [6]

Table 1: Prevalence, principal genes, and genetic-testing yield across the three inherited arrhythmia syndromes reviewed here [4-6].

How solid is the evidence behind the genes on the panel?

A variant cannot be classified more confidently than the evidence linking its gene to disease allows, and systematic, ClinGen-framework reappraisals of that gene-level evidence have produced results that should give pause to anyone treating a positive result from a large arrhythmia gene panel as uniformly reliable. An international, multicentered reappraisal of the 17 genes ever reported to cause congenital LQTS found that only 3 (KCNQ1, KCNH2, SCN5A) have definitive evidence for typical LQTS and a further 4 (CALM1, CALM2, CALM3, TRDN) strong evidence for atypical presentations, with 1 gene (CACNA1C) reaching only moderate evidence; the remaining 9 genes -- more than half of those ever reported -- were classified as having only limited or disputed evidence [7]. Figure 1 sets this distribution out directly. The authors were explicit that these disputed-evidence genes "should not inform clinical decision-making" without substantial additional support [7].

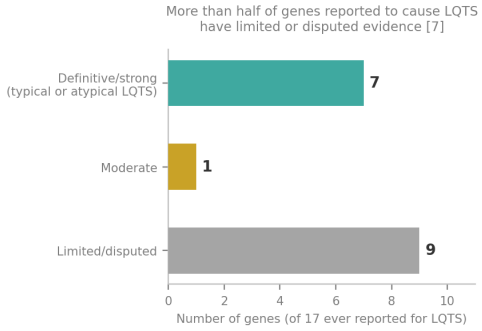

Figure 1: Evidence-based reappraisal of the 17 genes ever reported to cause congenital LQTS, by gene-validity tier [7].

Brugada syndrome's gene panel fared still worse under the same evidence-based framework. Of 21 genes ever reported to cause the syndrome, only SCN5A retained definitive evidence of causality; the other 20 were reclassified as disputed, with the reappraisal's authors concluding that "routine genetic evaluation of genes other than SCN5A is not warranted in the clinical care of BrS patients at this time" [8]. Figure 2 sets this single-gene concentration of evidence out visually. A positive result on a gene other than SCN5A from an older or broader Brugada panel, in this light, is now itself a source of interpretive uncertainty regardless of how it was originally reported.

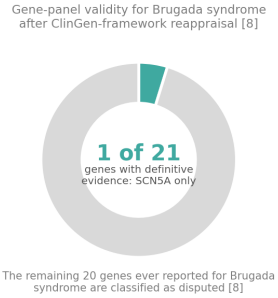

Figure 2: Gene-validity classification for Brugada syndrome after ClinGen-framework reappraisal of the 21 genes ever reported [8].

What happens to a VUS over time?

A single gene panel's evidence base is one axis of uncertainty; the other is that variant classifications themselves are not static. A study following 517 patients from 440 families attending a United Kingdom inherited arrhythmia clinic over 16 years found that 94 patients (18.2%) carried a VUS at some point, comprising 87 unique variants once duplicates across family members were removed [9]. On re-review, 28 of those 87 unique VUSs (32.2%) were eventually reclassified: 11 (12.6%) were upgraded to (likely) pathogenic and 17 (19.5%) were downgraded to (likely) benign, while the remaining 59 (67.8%) remained uncertain [9]. Figure 3 and Table 2 set these three outcomes out together. The same study found that even the supposedly firmer end of the classification spectrum is not immune to revision: of 138 variants originally reported as pathogenic or likely pathogenic, 7 (5.1%) no longer met that threshold under contemporary ACMG/AMP criteria, with 3 downgraded to (likely) benign and 4 to VUS [9].

A separate, frequently cited estimate places the mean time to VUS reclassification at approximately 7 years -- long enough that a family's practical decisions about surveillance and testing of relatives will, in most cases, have to be made and lived with well before the variant's status is finally settled [9].

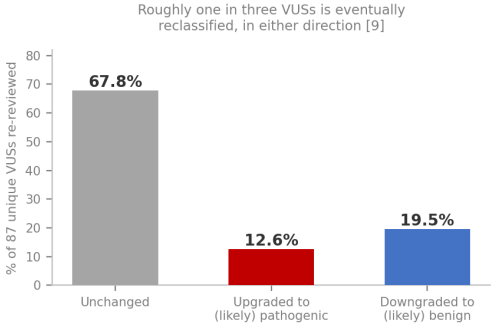

Figure 3: Outcome of re-review for 87 unique VUSs identified in an inherited arrhythmia clinic over 16 years [9].

Reclassification outcome	n (of 87)	% of VUSs
Unchanged (remains VUS)	59	67.8%
Upgraded to (likely) pathogenic	11	12.6%
Downgraded to (likely) benign	17	19.5%

Table 2: Reclassification outcome for the 87 unique variants of uncertain significance identified in a 16-year inherited arrhythmia clinic cohort [9].

When misclassification causes harm

Uncertainty that resolves slowly is one problem; uncertainty that is resolved wrongly, in the confident direction, is a different and arguably more serious one. A study of long QT syndrome overdiagnosis found that 290 of 1,841 patients (16%) referred with an original diagnosis of LQTS were ultimately determined to have normal findings after expert re-evaluation [10]. Genetic variants that had been misclassified as pathogenic -- described by the authors as "pseudo"-positive genetic results -- accounted for 23% of these overdiagnoses, second only to vasovagal-physiology-related QTc prolongation at 30% and ahead of an unrelated family history of sudden death (16%), transient or isolated QT prolongation (15%), and technical measurement error from U-wave inclusion (14%) [10]. Figure 4 sets these five causes out together. The clinical stakes of an overdiagnosis driven by a misclassified genetic result are not abstract: the same body of work has documented unnecessary implantable cardioverter-defibrillator (ICD) implantation, exercise restriction, and medication as downstream consequences of long QT overdiagnosis, imposing real procedural risk and lifestyle burden for a diagnosis that did not, in fact, apply [10].

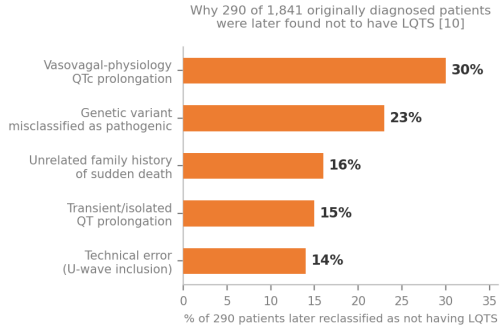

Figure 4: Contributing causes among 290 patients whose original LQTS diagnosis was later overturned on expert re-evaluation [10].

Framed the other way round, roughly 1 in 6 of everyone referred to that overdiagnosis study's centre with an existing LQTS label did not, in fact, have the condition, and a genetic result that had been over-called as pathogenic was the second most common reason why -- nearly as common as the QT-prolonging effect of vasovagal physiology itself [10]. That is a useful corrective to a natural assumption that a genetic result, once reported as positive, is the most secure part of a patient's diagnosis: on this evidence it is not necessarily more secure than the electrocardiographic findings it is often used to confirm, and it can drive exactly the same kind of downstream

overtreatment that overdiagnosed phenotypic LQTS does [10].

Ancestry gaps in the reference data behind a classification

Misclassification does not fall evenly across patient populations. A widely cited analysis found that variants originally classified as pathogenic for hypertrophic cardiomyopathy were significantly more common among Black Americans than among white Americans in reference population cohorts (P<0.001), a frequency inconsistent with a rare, highly penetrant disease allele and one that led to reclassification of those variants as benign once adequately diverse reference data became available [11]. The root cause identified was not a flaw specific to any one variant but underrepresentation of Black Americans in the control cohorts originally used to establish pathogenicity thresholds -- a structural gap in the reference data, not a one-off error, meaning the same mechanism plausibly affects the arrhythmia-syndrome gene panels reviewed here wherever population-matched reference frequency data for a given ancestry group remains sparse [11]. A VUS classification, in other words, is not solely a property of the variant itself: it also reflects how well the population from which the patient comes is represented in the databases a laboratory consults.

The practical implication for cascade testing is direct: a family of predominantly non-European ancestry is, on this evidence, more likely to receive an uncertain or a wrongly confident result in the first place, which means the downstream choice between predictive cascade genetic testing and clinical screening of relatives described in the next section is not evenly distributed across the population either. Closing that reference-data gap is therefore not a separate equity project sitting alongside the clinical problem of the ambiguous result; it is one of the more direct ways of shrinking how often the problem arises at all [11].

Practically, this argues for laboratories and multidisciplinary teams to record and, where possible, report the ancestry composition of the reference cohorts behind a given classification alongside the classification itself, so that a clinician reviewing an ambiguous result for a patient from an underrepresented population can weigh that context explicitly rather than treat every VUS as equally uncertain for equally understood reasons [11].

None of this is a criticism of any individual laboratory's original classification decisions, made in good faith against the reference data available at the time. It is, instead, a reminder that the reference data itself is a moving target, and that a result issued years ago against a thinner, less diverse reference set deserves the same periodic scrutiny that this review has already argued a VUS deserves on its own terms [7,8,11].

Cascade testing when the proband's result is ambiguous

The 2022 EHRA/HRS/APHRS/LAHRS expert consensus statement addresses this exact scenario directly: "a VUS that has not been upgraded to [likely pathogenic] should not be used to facilitate cascade screening; rather, clinical screening is required" [3]. Figure 5 sets out the resulting decision pathway. When a proband's result is pathogenic or likely pathogenic, cascade genetic testing of relatives for that specific variant is informative: a relative who tests negative for a confirmed familial variant can, in general, be released from further surveillance [1,3]. When the result is a VUS, that shortcut is not available, and relatives instead require standard clinical screening -- resting and exercise electrocardiography, echocardiography, and other phenotype-based assessment appropriate to the suspected syndrome -- regardless of whether they carry the variant [1,3]. Segregation data gathered from that clinical screening, in turn, is one of the forms of evidence that can eventually feed back into reclassifying the variant itself, closing the loop between family-level clinical evaluation and laboratory-level variant curation over the years it typically takes [1,9].

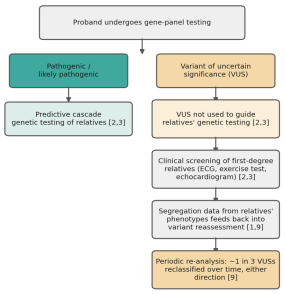

Figure 5: Recommended pathway for testing relatives of a proband whose inherited-arrhythmia genetic result is a VUS, versus one that is pathogenic or likely pathogenic [1,3,9].

This guidance is unambiguous in principle, but it does not remove the practical difficulty a family faces: clinical screening of every first-degree relative is more resource-intensive, less definitive per relative, and typically needs to be repeated periodically for years rather than resolved by a single genetic test, precisely because the shortcut a confirmed pathogenic variant would have provided is not available.

In practice this makes the genetic counsellor, rather than the laboratory report alone, the hinge of the whole process: someone has to explain to a family why a result that sounds inconclusive still changes nothing about which relatives need an electrocardiogram, coordinate the clinical screening pathway with cardiology colleagues, and revisit the case when the laboratory eventually issues an amended report [1,3].

None of the three syndromes reviewed here are exempt from this coordination burden, but it falls differently across them: a Brugada syndrome family in whom the only

informative gene is SCN5A has a comparatively narrow, if still imperfect, target for reclassification effort, whereas an LQTS family whose proband's variant sits on one of the nine genes with only limited or disputed evidence is, by construction, working with a result that may never resolve to full confidence no matter how long clinical screening continues [7,8].

The psychological weight of an ambiguous result

A VUS result is not only a clinical-management problem; it is also, for the person who receives it, a different psychological experience than either a clear negative or a clear positive. A systematic review and meta-analysis of 15 studies on VUS outcomes found that, measured on the Multidimensional Impact of Cancer Risk Assessment (MICRA) scale, patients receiving a VUS reported significantly higher genetic-test-specific distress than those receiving a negative result (mean difference 3.73, 95% CI 0.80-6.66, P=0.0126), but significantly lower distress than those receiving a clearly positive result (mean difference -7.01, 95% CI -11.31 to -2.71, P=0.0014) [12]. Figure 6 sets this intermediate position out as a forest plot. The same review found that behavioral and clinical management changes after a VUS result were statistically similar to those after a negative result (OR 1.41, 95% CI 0.90-2.21, P=0.182) but far less frequent than after a positive one (OR 0.09, 95% CI 0.05-0.19, P<0.0001), broadly consistent with guidance that a VUS should not, by itself, drive major clinical decisions [12].

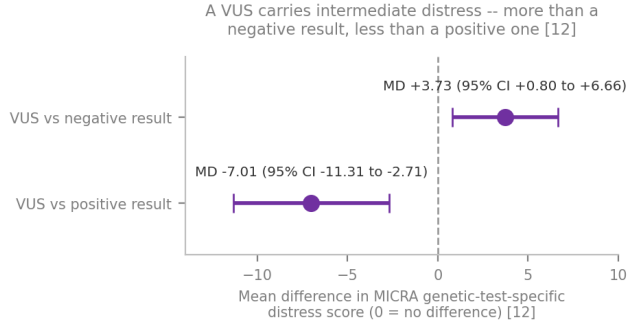

Figure 6: Mean difference in MICRA genetic-test-specific distress score for patients receiving a VUS versus a negative or a positive genetic test result, systematic review and meta-analysis of 15 studies [12].

A smaller qualitative study of seven hypertrophic cardiomyopathy patients who had received a VUS result found that, contrary to what the quantitative distress literature might suggest in isolation, receiving a VUS "did not seem to have a serious psychosocial impact" for most participants, who managed the uncertainty through acceptance, compartmentalization, and hope for eventual reclassification, with concern for family members emerging as an overarching theme across interviews [13]. Together, these findings suggest that an ambiguous result is psychologically real but, for many patients, manageable -- provided the counselling that accompanies it explains clearly what the result does and does not mean, particularly for the relatives a patient will inevitably worry about next.

Discussion

Taken together, these findings describe a genuine tension rather than a problem awaiting a single fix. Genetic testing for the inherited arrhythmia syndromes is mature enough to guide real clinical decisions, and the 2022 multi-society consensus statement gives clinicians clear, evidence-based instructions for what to do when a result is ambiguous: do not use an unresolved VUS to justify cascade genetic testing, and fall back on clinical screening of relatives instead [3]. That instruction is sound and should be followed. But following it correctly does not make the underlying uncertainty disappear -- it relocates the burden from a single genetic test onto years of repeated clinical surveillance for every untested relative, at real cost in appointments, anxiety, and, per the overdiagnosis literature reviewed here, occasional unnecessary intervention when a VUS is wrongly treated as settled in practice despite the guidance [10].

The psychological evidence reviewed here complicates any simple assumption about which way clinicians should err. A VUS produces less distress than a positive result and prompts fewer unwarranted management changes than one, which argues against inflating its apparent certainty [12]. But the same literature shows that patients living with a VUS are not indifferent to it either, and the overarching concern for family members that surfaces in qualitative accounts of the experience is precisely the concern that cascade-testing guidance has to answer for, not merely acknowledge [12,13].

The gene-validity reappraisals reviewed here point toward part of the underlying fix: much of today's classification uncertainty traces back not to any single ambiguous variant but to genes that should never have carried definitive-level clinical weight in the first place [7,8]. Systematic, ClinGen-style gene curation-followed by variant-level re-analysis on that firmer footing-is the mechanism by which a meaningful fraction of today's VUSs and even some of today's confidently reported pathogenic calls will eventually resolve [7-9]. The ancestry disparity documented here adds a further, distinct obligation: broadening population reference databases is not a matter of general equity alone, it is a direct route to fewer VUS and false-pathogenic calls for patients whose ancestry group remains underrepresented in the data a laboratory consults today [11].

None of this argues for treating a VUS as if it were more informative than it is; it argues for treating the systems that generate and revisit a classification -- gene curation panels, reference databases, and periodic clinic re-review -- as being just as much a part of a family's ongoing care as the initial test result itself, since it is those systems, more than any single laboratory report, that will ultimately determine whether an ambiguous result today resolves clearly tomorrow [7-9,11].

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and it draws statistics from cohorts, guideline panels, and reappraisals that differ in setting, country, and time period; the 18.2% VUS rate and 32.2% reclassification rate reported from one 16-year United Kingdom clinic cohort should not be read as a universal figure applicable to every laboratory or population [9]. The gene-validity reappraisals for LQTS and Brugada syndrome are themselves snapshots that will be revisited as further evidence accumulates, and no equivalent systematic reappraisal for CPVT's full historical gene list was identified for this review [7,8]. The qualitative VUS-experience study cited here is a preprint that has not completed peer review, is based on only seven participants with hypertrophic cardiomyopathy rather than an inherited arrhythmia syndrome specifically, and its reassuring finding should not be generalized to every patient or every condition without corroborating data [13]. Finally, this review did not identify CPVT- or Brugada-specific quantitative psychological-outcome data comparable to the LQTS- and cancer-adjacent literature summarized here, so the distress findings reported in Figure 6 are best read as evidence about VUS results from multigene panel testing broadly rather than about these three syndromes individually [12].

Conclusion

A variant of uncertain significance in an inherited arrhythmia gene is common enough, and consequential enough, that managing it is now a routine part of cardiogenetic practice rather than an edge case. The evidence reviewed here supports a clear, if not fully satisfying, position: a VUS should not be used to justify cascade genetic testing of relatives, clinical screening should substitute for it until the variant is resolved, roughly one in three VUSs will eventually be reclassified in either direction over a period that can span several years, and both the gene panels used to generate these results and the reference populations against which variants are judged still have real, documented gaps left to close.

For the practising clinician and genetic counsellor, three practical points from this evidence deserve to be stated plainly rather than left implicit. First, a VUS result should be communicated to the family as a genuinely open question, not as a soft version of a positive result: the guideline-mandated response to it -- clinical screening of relatives rather than single-variant cascade genetic testing -- is a different care pathway, not a watered-down one [1,3]. Second, that pathway is not a one-time decision: because roughly one in three VUSs is eventually reclassified and the mean time to that reclassification runs to years, a family's variant status is worth revisiting periodically rather than filed away after the initial report [9]. Third, when a positive genetic result is used clinically -- to justify an ICD, to release a relative from surveillance, or to end a diagnostic odyssey -- it is worth asking which gene it sits on and how recently that gene's own evidence base was reappraised, since the gene-validity data reviewed here show that this is not a question with a uniform answer across the arrhythmia gene panels in current use [7,8].

1. Priori SG, Wilde AA, Horie M, et al. "HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes". Heart Rhythm 10(2013):1932-1963.

2. Richards S, Aziz N, Bale S, et al. "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology". Genet Med 17(2015):405-424.

3. Wilde AAM, Semsarian C, Márquez MF, et al. "European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases". Europace 24(2022):1307-1367.

4. Schwartz PJ, Stramba-Badiale M, Crotti L, et al. "Prevalence of the congenital long-QT syndrome". Circulation 120(2009):1761-1767.

5. Shukla A, Mohta S, et al. "Brugada Syndrome". In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing (2025).

6. Napolitano C, Mazzanti A, Bloise R, Priori SG. "Catecholaminergic Polymorphic Ventricular Tachycardia". In: Adam MP, et al, eds. GeneReviews [Internet]. Seattle: University of Washington, Seattle (updated 2022).

7. Adler A, Novelli V, Amin AS, et al. "An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome". Circulation 141(2020):418-428.

8. Hosseini SM, Kim R, Udupa S, et al. "Reappraisal of Reported Genes for Sudden Arrhythmic Death: Evidence-Based Evaluation of Gene Validity for Brugada Syndrome". Circulation 138(2018):1195-1205.

9. Young WJ, Maung S, Ahmet S, Kirkby C, Ives C, Schilling RJ, Lowe M, Lambiase PD. "The frequency of gene variant reclassification and its impact on clinical management in the inherited arrhythmia clinic". Heart Rhythm (2024).

10. Bains S, Neves R, Bos JM, Giudicessi JR, MacIntyre C, Ackerman MJ. "Phenotypes of Overdiagnosed Long QT Syndrome". J Am Coll Cardiol 81(2023):477-486.

11. Manrai AK, Funke BH, Rehm HL, et al. "Genetic Misdiagnoses and the Potential for Health Disparities". N Engl J Med 375(2016):655-665.

12. Mighton C, Shickh S, Uleryk E, Pechlivanoglou P, Bombard Y. "Clinical and psychological outcomes of receiving a variant of uncertain significance from multigene panel testing or genomic sequencing: a systematic review and meta-analysis". Genet Med 23(2021):22-33.

13. Thomas PEB, Roberts J. "Psychosocial impacts on patients with Hypertrophic Cardiomyopathy (HCM) who received a Variant of Uncertain Significance". Research Square [preprint] (2024).

Cite this article: Strathmore A, Roosendaal B, Almasi-Bartha Z. Inherited Arrhythmia Syndromes and the Variant of Uncertain Significance: Cascade Testing When the Result Is Ambiguous. J Heart Cardiovasc Sci. 2025; 6: 013-018.