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Implantable loop recorder monitoring for refining management of children with inherited arrhythmia syndromes

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ORIGINAL RESEARCH

Implantable Loop Recorder Monitoring for Refining Management of Children With Inherited Arrhythmia Syndromes

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***Background*—**Implantable loop recorders (ILRs) are conventionally utilized to elucidate the mechanism of atypical syncope. The objective of this study was to assess the impact of these devices on management of pediatric patients with known or suspected inherited arrhythmia syndromes.

***Methods and Results*—**A retrospective chart review was undertaken of all pediatric patients with known or suspected inherited arrhythmia syndromes in whom an ILR was implanted from 2008 to 2015. Captured data included categorization of diagnosis, treatment, transmitted tracings, and the impact of ILR tracings on management. Transmissions were categorized as symptomatic, autotriggered, or routine. Actionable transmissions were abnormal tracings that directly resulted in a change of medical or device therapy. A total of 20 patients met the stated inclusion criteria (long QT syndrome, n=8, catecholaminergic polymorphic ventricular tachycardia,n=9, Brugada syndrome, n=1, arrhythmogenic right ventricular cardiomyopathy, n=2), with 60% of patients being genotype positive. Primary indication for implantation of ILR included ongoing monitoring +/− symptoms (n=15, 75%), suspicion of noncompliance (n=1, 5%), and liberalization of recommended activity restrictions (n=4, 25%). A total of 172 transmissions were received in patients with inherited arrhythmia syndromes, with 7% yielding actionable data. The majority (52%) of symptom events were documented in the long QT syndrome population, with only 1 tracing (5%) yielding actionable data. Automatic transmissions were mostly seen in the catecholaminergic polymorphic ventricular tachycardia cohort (81%), with 21% yielding actionable data. There was no actionable data in routine transmissions.

***Conclusions*—**ILRs in patients with suspected or confirmed inherited arrhythmia syndromes may be useful for guiding management. Findings escalated therapies in 30% of subjects. As importantly, in this high-risk population, the majority of symptom events represented normal or benign rhythms, reassuring patients and physicians that no further intervention was required. **(*J Am Heart Assoc*. 2016;5:e003632 doi:10.1161/JAHA.116.003632)**

Key Words: channelopathy • implantable loop recorder • inherited arrhythmia syndrome • pediatric

Over the last 2 decades, considerable progress has been made in the understanding of primary electrical disorders leading to sudden cardiac death in children and young adults. Many of these, including long QT syndrome, Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and arrhythmogenic right ventricular cardiomyopathy are autosomal-dominant disorders collectively referred to as the inherited arrhythmia syndromes (IAS). Despite advancements in the diagnosis and understanding of IAS, there remain diagnostic uncertainties and management dilemmas.

Genetic testing can be definitive when a pathologic mutation is identified in a patient with a typical clinical history. However, the interpretation of mutations is not always so clear. Specifically, as genetic testing is being utilized on a wide scale, variants of unknown significance are being increasingly identified. Interpreting a novel mutation, or one not previously linked causally to an IAS, particularly if the clinical history suggests a low probability of having the disease, poses a dilemma for the clinician, so-called "genetic purgatory."[1]

After a genetic diagnosis is made for a potentially lethal inherited arrhythmia, considerable uncertainty remains regarding the management and outcomes for an individual

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/5/6/e003632/DC1/embed/inline-supplementary-material-1.pdf

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patient. There is general agreement that a subpopulation of phenotype-positive IAS patients (specifically long QT syndrome and CPVT patients) should receive β-blocker therapy. However, clinicians must exercise clinical judgment when negotiating activity restrictions while taking into account guidelines for sports participation.[2–5]

The use of implantable loop recorders (ILRs) has been reported in pediatric patients with infrequent syncope or palpitations.[6–8] In 2011, Kubala et al[9] published their experience with the use of ILRs in 11 BrS patients where there was clinical suspicion of ventricular arrhythmias. They identified bradycardia and atrioventricular block during syncopal episodes, but no ventricular arrhythmias.

In an effort to identify occult arrhythmias, as well as to accurately assess cardiac rhythms during symptomatic events, we have implanted ILRs in selected patients with a documented or suspicious history for IAS. The intent of this study is to categorize the findings of continuous ILR monitoring and the impact it had on tailoring the management of potentially life-threatening arrhythmias to individual patients.

Methods

After obtaining approval from the Institutional Review Board at Washington University School of Medicine, a retrospective chart review was undertaken. Informed consent was waived per Institutional Review Board approved protocol. Patients who underwent ILR implantation with a known or suspected diagnosis of an IAS from 2008 to 2015 were identified. IAS diagnoses in this analysis included long QT syndrome, CPVT, BrS, and arrhythmogenic right ventricular cardiomyopathy. Patients who were not known or suspected IAS patients were not included in the analysis. Data collected included categorization of diagnosis, treatment, transmitted tracings, and the impact of the ILR on patient management. Transmissions were categorized as symptomatic (patient triggered), autotriggered (device triggered), or routine, though transmission could fall into >1 category. Transmission data were categorized as "actionable" if the arrhythmia detected led directly to a change of medical or device therapy. Patient-specific programming of tachycardia and bradycardia zones was performed at time of implant, taking into account patient age, medications, and previous documented arrhythmia data (when available).

Statistical Analysis

Results are predominantly descriptive findings and expressed as percentages, with mean values (and SD) for continuous variables.

Results

Clinical Patient Data

A total of 20 patients (11 males, 9 females) were implanted with an ILR for confirmed (n=11, 55%) or suspected (n=9, 45%) IAS: 10 with a Reveal ILR (2008–2013), and 10 with a LINQ ILR (2014–2015). The average age at time of implant was 12.5±3.6 years. Primary indication for implantation of ILR included ongoing monitoring +/− symptoms (n=15, 75%) suspicion of noncompliance (n=1, 5%), and liberalization of guideline-recommended activity restrictions (n=4, 25%).

IAS diagnoses included long QT syndrome (n=8, 40%; average QTc 466 ms), CPVT (n=9, 45%), arrhythmogenic right ventricular cardiomyopathy (n=2, 10%), and BrS (n=1, 5%). Genetic testing yielded 60% (n=9/15) genotype-positive and 40% (n=6/15) genotype-negative patients with no genetic testing performed in 5 patients. Specifically, 6 patients had an identified pathologic mutation (with 3 of the 6 patients having compound mutations) and 3 patients with identified variants of unknown significance (Table 1).

Transmission Data

A total of 172 total transmissions were received, with an average of 8.6±7 ILR downloads/patient. There were 12 transmissions (7%) yielding actionable data in 6 patients. (Table 2).

In the LQT group, there were 58 total transmissions (actionable data n=1, or 2%), in the CPVT group there were 100 transmissions (actionable data n=10, or 10%), in the arrhythmogenic right ventricular cardiomyopathy group there were 8 transmissions (actionable data n=1, or 13%) and lastly, in the BrS group there were 6 transmissions (actionable data n=0) (Table 2). The majority of actionable events, 10/12 (83%), occurred in patients with a diagnosis of CPVT.

A total of 33 transmissions were labeled by patients as symptom episodes, including chest pain, syncope, dizziness, palpitations, nausea, and seizure. Of the 33 symptom events, 3 (10%) had an actionable tracing resulting in change of medication or device with the remaining 30 transmissions (90%) demonstrating sinus rhythm/sinus tachycardia +/− premature ventricular contractions. Additionally, 42 automatic transmissions were received with 8 (19%) transmissions demonstrating actionable data, predominantly in the CPVT population. The remaining 34 automatic transmissions (81%) demonstrated sinus rhythm/sinus tachycardia and occasionally isolated premature ventricular contractions. Nine transmissions were identified as both symptom and automatic transmissions, with 1 of these transmissions (11%) yielding actionable data. Eighty-eight routine transmissions were downloaded with no actionable data in those transmissions (Figure; Table S1).

Table 1. Clinical Patient Data, Including Genetics, Indications for ILR, and Medical Therapy

Patient	Clinical Diagnosis	Age at Implant (y)	Genetic Test Results	Medical Therapy
1	LQTS	15.9	Negative	None
2	LQTS	4.8	n/a	None
3	LQTS	16.1	Negative	Betaxolol
4	LQTS	11.7	Pathogenic mutation: KCNQ1—Ser566Phe VUS: SNTA1—Arg336Trp	Nadolol
5	LQTS	10.7	Pathogenic mutation: KCNQ1—Arg366Trp	Nadolol
6	LQTS	7.9	Negative	None
7	LQTS	12	Negative	Nadolol
8	LQTS	13	VUS: KCNH2—Ala913Val	None
9	CPVT	18.3	n/a	Noncompliant
10	CPVT	10.6	n/a	Noncompliant
11	CPVT	13.2	VUS: RYR2—c.1465+4C>T, IVS15+4C>T	Nadolol
12	CPVT	17.3	Negative	Atenolol
13	CPVT	7.8	Pathogenic mutation: RYR2—Glu3987Lys	Nadolol
14	CPVT	13.6	Pathogenic mutation: RYR2—Arg4959Gln	Atenolol
15	CPVT	13.1	VUS: CACNA1C—Ile1323Ile VUS: CACNA1C—Ala68Thr VUS: HCN4—Val451Met	Nadolol
16	CPVT	13.2	Pathogenic mutation: KNCJ2—p.R218Q Pathogenic mutation: SCN5A—p.T1304M Benign mutation: AKAP9	Nadolol+flecainide
17	CPVT	10.5	n/a	Nadolol
18	ARVC	14.7	VUS: RYR2—Arg1013Gln	Atenolol
19	ARVC	17.9	n/a	None
20	BrS	7.6	Negative	None

Patient data, including demographic data, clinical data, genetic diagnoses, indications for implant, and medical therapy are presented. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ILR, implantable loop recorders; LQTS, long QT syndrome; n/a, not applicable; VUS, variant of unknown significance.

Outcomes/Current Status

There were no deaths in the patient cohort. At last follow-up, ILRs were explanted in 6/20 (30%) of patients for device end of life. A single patient with CPVT had the ILR upgraded to an implantable cardioverter defibrillator for symptomatic polymorphic ventricular tachycardia. There were no adverse events associated with the device, including infection or erosion.

Discussion

This study represents the only study to date investigating the utility of ILRs in pediatric patients across all inherited arrhythmia syndromes. There are several novel findings from this study. First, symptoms in this patient population do not correlate well with arrhythmic events. Additionally, automatic transmissions were important in detecting subclinical arrhythmias. These data influenced clinical decision making regarding medication titration, addition of medication, medication compliance, and titrating activity levels. Lastly, variants of unknown significance need to be interpreted carefully in the context of the clinical picture and clinician index of suspicion, which are important in guiding decision making.

Important implications arise from these findings. The long QT syndrome patient cohort had the largest number of symptoms transmissions (19 symptoms +/− automatic transmissions/34 total transmissions, 56%) with only 1 symptom tracing (5%) leading to titration in medication regimen. The remaining 95% of symptom events in the long QT population were not associated with arrhythmia. Through the entire cohort of patients, 90% of symptomatic transmissions demonstrated normal sinus rhythm/sinus tachycardia (74%) or minimal rhythm abnormalities such as isolated premature ventricular contractions (16%). Given that the

Table 2. Symptom and Actionable Transmission Data by Patient

Patient	Clinical Diagnosis	Actionable Data (No. Transmissions)	If Actionable Data, What Was Rhythm and Resultant Action?	Symptom Events (No. Transmissions)	If Symptom Event, What Was the Rhythm?
1	LQTS	None	n/a	Yes (3)	NSR×2; ST
2	LQTS	None	n/a	Yes (1)	ST
3	LQTS	None	n/a	Yes (6)	ST×6
4	LQTS	None	n/a	Yes (2)	ST×2
5	LQTS	None	n/a	Yes (5)	NSR×5
6	LQTS	None	n/a	None	n/a
7	LQTS	None	n/a	None	n/a
8	LQTS	Yes (1)	Tightly coupled ventricular couplet→Activity Restrictions	Yes (2)	ST; Tightly coupled ventricular couplet
9	CPVT	None	n/a	Yes (6)	ST×3; NSR w/ventricular bigeminy; ST w/isolated PVCs×2
10	CPVT	None	n/a	Yes (2)	ST×2
11	CPVT	None	n/a	Yes (1)	ST
12	CPVT	None	n/a	Yes (1)	ST
13	CPVT	Yes (2)	Polymorphic VT→Initiate of β-blocker AT→Uptitrate of β-blocker	None	n/a
14	CPVT	Yes (4)	Sinus pauses, bidirectional ventricular coupletsàInitiate atenolol Nonsustained VT→Encourage medication compliance Significant sinus pauses→Wean β-blockers Polymorphic VT→Explant ILR; Implant ICD	Yes (1)	TdP
15	CPVT	Yes (1)	Multifocal PVCs→Initiate nadolol	Yes (2)	ST; NSR w/ventricular trigeminy
16	CPVT	Yes (3)	Multifocal PVCs→Uptitrate nadolol Bidirectional VT→Initiate Flecainide Bidirectional Ventricular CoupletsàUptitrate flecainide	Yes (4)	Bidirectional VT; NSR w/ventricular bigeminy×2; NSR w/isolated PVCs
17	CPVT	None	n/a	None	n/a
18	ARVC	Yes (1)	Sinus pause→Wean β-blocker	Yes (1)	ST
19	ARVC	None	n/a	Yes (1)	ST
20	BrS	None	n/a	Yes (4)	ST×3; NSR

Both symptom and actionable data by patent are presented. Details about transmission data are provided. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; AT, atrial tachycardia; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ICD, implantable cardioverter defibrillator; ILR, ; LQTS, long QT syndrome; n/a, not applicable; NSR, normal sinus rhythm; PVCs, premature ventricular contractions; ST, sinus tachycardia; TdP, Torsades de Pointes; VT, ventricular tachycardia.

majority of symptom-driven transmissions were not actionable or lethal arrhythmias, symptoms are not reliable markers for escalation of therapy or guidance around activity. Current practices when caring for these children often includes incorporating symptoms into risk stratification algorithms. ILR data demonstrate that symptoms in this population may not be reliable surrogates for arrhythmia.

Identification of occult arrhythmias is crucial to optimal management of patients with known or suspected IAS. In fact, 19% of automatically recorded transmission contained data that altered the patients' medical course. Prior to the growing use of ILRs in this population, the incidence of subclinical arrhythmias in the IAS population was unknown. Perhaps most concerning was the data collected from the CPVT cohort, where 21% of automatic transmissions yielded actionable data, implying significant subclinical arrhythmia prevalence in this population. Intelligent programming of the ILR in this subpopulation is important in identifying these occult arrhythmic events.

Patients with genetic mutations classified as variants of unknown significance are a growing clinical conundrum. In the cohort presented, 5 patients had genetic variants of unknown significance with 3/5 patients (60%) having actionable tracings. For patients with a documented variant of unknown significance, demonstration of polymorphic ventricular tachycardia would swing the pendulum in the direction of

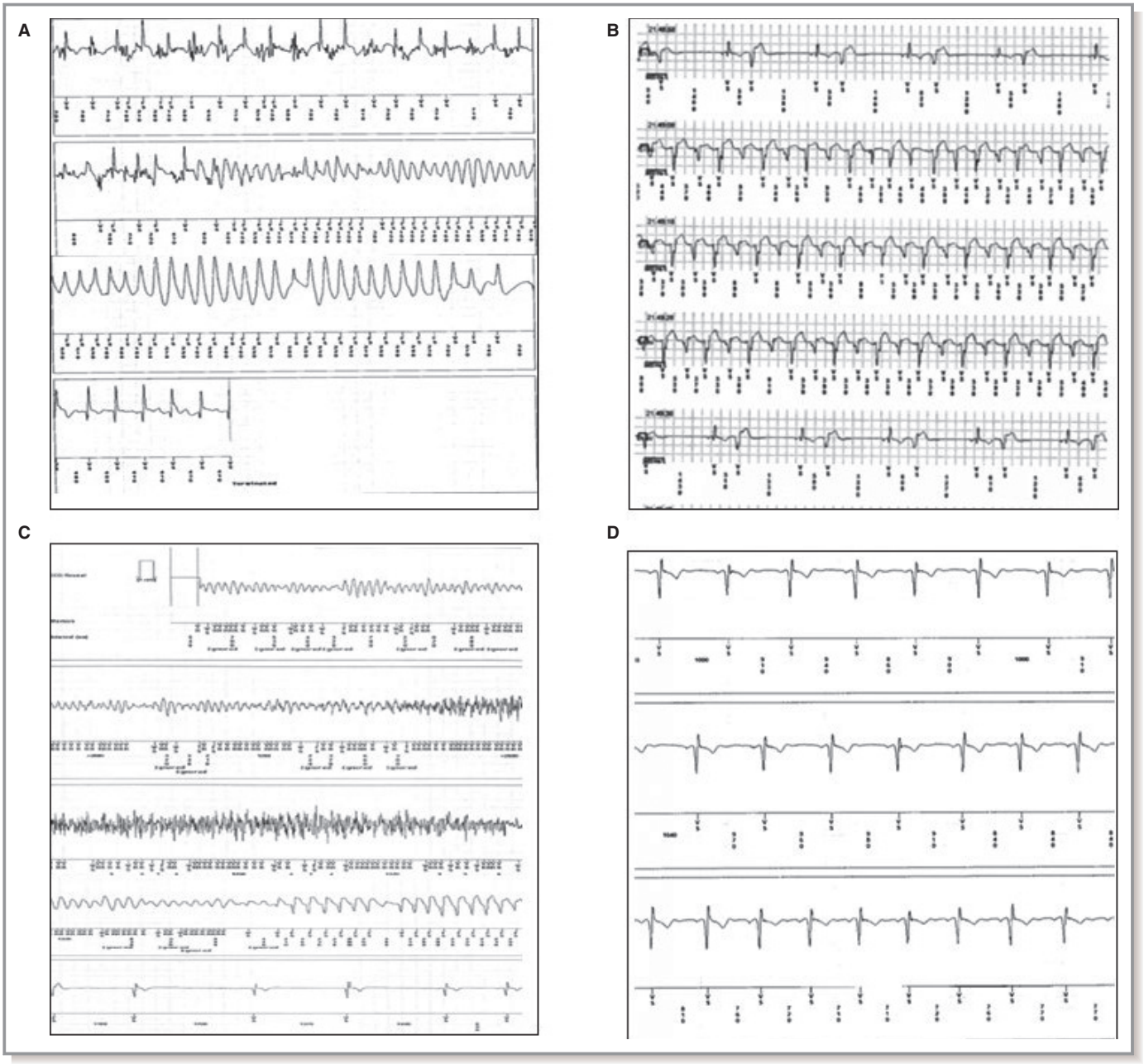

Figure. The tracings shown were obtained from 4 different patients in the cohort. The tracing in (A) represents an ILR download from a patient with genotype-positive catecholaminergic polymorphic ventricular tachycardia (CPVT). This event of polymorphic ventricular tachycardia occurred with activity (running), but the patient was asymptomatic with this event. In response to this event, the patient was started on nadolol. B, Represents a symptom event (chest pain) from a patient being treated with nadolol with genotype-positive CPVT. The tracing demonstrates ventricular bigeminy followed by a bidirectional ventricular tachycardia, which then spontaneously terminates and returns to sinus rhythm with ventricular bigeminy. In response to this event, the patient was admitted for initiation of flecainide in addition to nadolol. C, Represents a patient with genotype-positive CPVT who had a symptom event and a history of noncompliance with medication. This event of polymorphic ventricular tachycardia occurred during a time of emotional stress. Following this download, the patient underwent implantation of an automatic intracardiac defibrillator. The patient tracing in (D) is from a symptom event (chest pain, near syncope) in a patient with long QT syndrome who had just been jogging. He was being treated with betaxolol and was compliant with this medication. The tracing demonstrating sinus rhythm was reassuring that there was not an arrhythmic component to his symptoms. ILR indicates implantable loop recorder.

heightened individual treatment as well as cascade screening of at-risk family members. These data give credence to clinical index of suspicion weighing heavily in clinical decision making.

Guidance around activity is an important part of the ongoing management for these patients. In this cohort, ILRs provided important data to guide in titration of activity level with an acceptable level of risk. After shared decision making

between clinician, patient, and family, and frank conversations about risk, certain patients had liberalized activity guidance with close monitoring by ILR with no documented arrhythmic events. ILRs may be useful in allowing select patients to reenter sports with intensive arrhythmia monitoring.

Lastly, 6/20 monitored patients (30%) had arrhythmias identified that prompted interventions including activity restriction, titration of medication, and implantable cardioverter defibrillator implant. These data, which are critically important in guiding patients regarding medical/device therapy and activity restrictions, are increasingly available due to the increased use of ILRs, likely due to lower threshold for implantation. In fact, the newer generation LINQ ILR has the advantage of being markedly (87%) smaller than the previous generation as well as being quickly inserted subcutaneously, thereby lowering the clinician's threshold to recommend the device.[10] Our data support this trend as equal numbers of devices (n=10) were implanted in the 5 years of the Reveal device versus 2 years of the LINQ.

Study Limitations

This study, despite spanning 7 years, is limited by a small sample size and therefore it is difficult to draw statistically significant conclusions. Additionally, this is a retrospective study design and is therefore has the associated biases of retrospective studies. There are inherent limitations in data collection, given programming limitations. Our practice has been to tailor these parameters to be patient specific, taking into account age, activity level, medications, and prior arrhythmic data (when available). However, it is possible that patients may experience ectopy that is slower or shorter than the programmed tachycardia zone, which would therefore not be recorded.

Conclusions

ILRs in patients with suspected or confirmed IAS may be useful for guiding management. Findings escalated therapies in 30% of subjects. As importantly, in this high-risk population, the majority of symptom events represented normal or benign rhythms, reassuring patients and physicians that no further intervention was required. Given the wealth of data ILRs provide in these patients, perhaps ILRs should be considered in all IAS patients who do not meet criteria for implantable cardioverter defibrillators, particularly the CPVT subgroup.

Disclosures

None.

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Supplemental Material

Substrate	# of transmissions	Symptom transmissions	Automatic transmissions	Routine transmissions
LQTS	Total, n=58	12	5	34
	Actionable transmissions, n=1	1	0	0
CPVT	Total, n=100	17	34	49
	Actionable transmissions, n=10	3	7	0
ARVD	Total, n=8	2	3	3
	Actionable transmissions, n=1	0	1	0
BrS	Total, n=6	4	0	2
	Actionable transmissions, n=0	0	0	0
Total	Total transmissions	42	42	88
	Actionable transmissions, n=12	4	8	0

Table S1:

Number of symptom, automatic and routine standard of care transmissions by disease substrate. CPVT = Catecholaminergic polymorphic ventricular tachycardia, LQTS = Long QT syndrome, BrS = Brugada syndrome, and ARVC = Arrhythmogenic right ventricular cardiomyopathy.

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