Diagnostic accuracy of the 12-lead electrocardiogram in the first 48 hours of life for newborns of a parent with congenital long QT syndrome

Yalile Perez, MD, MS,[*1] Kathryn E. Tobert, BA,[†1] Michaela J. Saunders, XX,[*] Katrina B. Sorensen, XX,[†] J. Martijn Bos, MD, PhD,[*†‡] Michael J. Ackerman, MD, PhD[*†‡]

*From the *Division of Pediatric Cardiology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, [†]Department of Molecular Pharmacology and Experimental Therapeutics, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, Minnesota, and [‡]Division of Heart Rhythm Services, Department of Cardiovascular Medicine, Windland Smith Rice Genetic Heart Rhythm Clinic, Mayo Clinic, Rochester, Minnesota.*

BACKGROUND Long QT syndrome (LQTS) is an autosomal dominant disorder characterized by a prolonged QT interval. Electrocardiographic (ECG) screening in the first 48 hours of life may be misleading, even in newborns with a genotype-positive LQTS parent.

OBJECTIVE The purpose of this study was to determine the ECG's diagnostic accuracy in the first 48 hours of life for neonates born to a parent with LQTS.

METHODS A retrospective review of all neonates born at Mayo Clinic to a parent with ≥1 pathogenic variant in a LQTS-causative gene who had least 1 ECG in the first 48 hours and genetic test results were available. The sensitivity and specificity of the diagnostic ECG were calculated using Bazett's heart rate–corrected QT (QTc) thresholds of 440, 450, 460, and 470 ms.

RESULTS Overall, 74 infants (36 females [49%]) were included (mean QTc interval on the first ECG 489 ± 54 ms; 68% LQTS genotype-positive). The mean QTc interval in the first 48 hours for neonates that ultimately were genotype-positive was greater (506 ± 52 ms) than that for genotype-negative neonates (455 ± 41 ms) ($P = .0004$). When using a recommended threshold QTc interval of ≥440 ms, 6 of 50 genotype-positive neonates (12%) were missed (underdiagnosed) and 17 of 24 genotype-negative neonates (71%) were overdiagnosed (sensitivity 88%; specificity 29%).

CONCLUSION The newborn ECG should not be used in isolation to make the diagnosis of LQTS since it will result in many misclassifications. Genetic testing must be initiated before discharge, and proper anticipatory guidance is vital while awaiting test results.

KEYWORDS Long QT syndrome (LQTS); Bazett's heart rate–corrected QT (QTc) interval; Neonatal electrocardiogram; Genetic testing

(Heart Rhythm 2022;■:1–6)

Introduction

Congenital long QT syndrome (LQTS) is one of the most common cardiac channelopathies affecting ~1 in 2000 persons.[1–3] Currently, >15 genes have been implicated in LQTS. However, the majority of LQTS is caused by pathogenic variants in 3 genes (*KNCQ1*, *KCNH2*, and *SCN5A*) that encode the critical pore-forming α subunits of the ion channels essential to the cardiac action potential.[4,5] LQTS is inherited typically in an autosomal dominant manner whereby a single genetic variant is inherited from one of the parents. In general, de novo pathogenic mutations are rare, and the penetrance and expressivity of the disorder are highly variable.[6]

LQTS is characterized by a prolonged QT interval on the 12-lead surface electrocardiogram (ECG). Although patients can present with arrhythmic syncope or seizures, sudden cardiac arrest, or death, most patients are asymptomatic.[7] β-Blockers, predominantly nadolol and propranolol, are the mainstay treatment of all types of LQTS, reducing the mortality from 50% in symptomatic high-risk untreated patients to <2% in those who are treated.[2] However, symptomatic patients treated with β-blockers still have a 3% annualized risk of LQTS-associated breakthrough cardiac events (eg, arrhythmic syncope, seizures, and aborted cardiac arrest).[7]

Funding Sources: This work was supported by the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death Program. Disclosures: Dr Ackerman is a consultant for Abbott, ARMGO Pharma, Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Invitae, LQT Therapeutics, Medtronic, and *UpToDate*. Dr Ackerman and Mayo Clinic have a potential equity/royalty relationship with AliveCor, Anumana, and Pfizer. The rest of the authors report no conflicts of interest. [1]Dr Perez and Ms Tobert are coequal first authors. **Address reprint requests and correspondence:** Dr Michael J. Ackerman, Windland Smith Rice Genetic Heart Rhythm Clinic and the Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Guggenheim 501, 200 First St SW, Rochester, MN 55905. E-mail address: ackerman.michael@mayo.edu.

1547-5271/$-see front matter https://doi.org/10.1016/j.hrthm.2022.01.041

The increased awareness by the medical community and availability of effective treatments of this potentially lethal disorder have led to different opinions regarding the optimal timing for routine ECG screening in infants. Some experts advocate not performing an ECG screening before the age of 3 to 4 weeks, while others recommend ECG screening as early as possible in order to identify at-risk infants and before the peak incidence of SIDS.[8,9] However, previous studies have shown that ECG screening in the first week of life may result in a high number of false-positive results, which in turn may cause significant psychological stress for the family and contribute to potentially unnecessary interventions.[9,10] Another challenge of early neonatal ECG screening is that the Bazett's heart rate–corrected QT (QTc) interval varies significantly in the first few days of life.[11,12] Healthy newborns can have a physiological prolongation of the QTc interval throughout the first 2 months of life after which it starts decreasing.[12] Lastly, measurement errors are common when calculating the QTc interval in newborns since T waves can be isoelectric or have a low amplitude, making the measurement of the QT interval difficult.[12]

As such, early diagnosis of congenital LQTS is challenging and raises the question on what should be done for newborns from a parent with LQTS. Thus, the purpose of this study was to determine the diagnostic accuracy of ECGs obtained in the first 48 hours of life (day of life 0 and 1) to identify congenital LQTS in newborns born to a genotype-positive parent where there is already a 50% pretest probability of disease substrate.

Methods

Study population and study design

In this Mayo Clinic Institutional Review Board–approved study, we conducted a retrospective review of the electronic medical records of 74 newborns who were born to a parent with genotype-positive LQTS. This research adhered to the Helsinki Declaration as revised in 2013. The electronic medical records were reviewed for demographic information, family history, genetic testing results, and ECG data. Newborns were included if they met the following criteria: (1) at least 1 LQTS genotype-positive parent, (2) an ECG performed in the first 48 hours of life (day of life 0 or 1), and (3) LQTS genetic test results available for the newborn.

ECG evaluation

A 12-lead ECG was obtained with a commercially available recording device (GE Marquette) and recorded at the standard speed of 25 mm/s. The QTc interval determined by the device was obtained for all newborns. Subsequently, all the QT intervals were verified manually by a genetic cardiologist (M.J.A.) with expertise in genetic arrhythmia syndromes. The QT interval was measured from the onset of the Q wave to the end of the T wave (the point where the descending limb of the T wave intersects the isoelectric line). The QT interval was corrected for time (QTc) using Bazett's formula (QT interval divided by the square root of the preceding R-R interval).

Previously published QTc cutoff values for the diagnosis of congenital LQTS were used in this study. A prolonged QTc interval was defined as a QTc interval of ≥440 ms in the limb lead II or precordial lead V_5. A QTc interval of ≥440 ms corresponds to the 97.5th percentile or 2SDs above the mean QTc interval for newborns (400 ± 20 ms).[10] Additionally, more traditional cutoff QTc values (450, 460, and 470 ms) were used to determine the effect on the diagnostic accuracy of the ECG for the detection of LQTS.

Statistical analysis

Frequency and percentage are reported for categorical variables. Data are presented as median (range) for nonnormally distributed data and mean ± SD for normally distributed data. Differences between groups were tested using the χ^2 test or the Fisher exact test for categorical variables, as appropriate. Sensitivity, specificity, likelihood ratios, and positive predictive value (PPV), and negative predictive value (NPV) were calculated. Probability values of <.05 are considered statistically significant. Statistical analysis was computed using GraphPad Prism software (version 9, GraphPad Software, San Diego, CA).

Results

A total of 74 newborns (36 females [49%]) met the inclusion criteria. Table 1 summarizes the demographic characteristics of the cohort. Following genetic testing, disease-causing variants were found in 50 infants (68%), of whom 23 (46%) had type 1 LQTS (LQT1) (*KCNQ1*), 15 (30%) had LQT2 (*KCNH2*), 8 (16%) had LQT3 (*SCN5A*), and 4 (8%) had multiple LQTS-associated pathogenic variants for LQT1 and LQT2. The remaining 24 newborns (32%) had a negative genetic test result for their parent's LQTS-causative variant and are designated throughout as genotype-negative. Online Supplemental Tables 1 and 2 summarize the parental and newborn genetic variants.

ECG analysis

Overall, the mean QTc interval for all newborns on their first ECG was 489 ± 54 ms. The mean QTc interval was expectantly greater in genotype-positive infants than in genotype-negative infants (506 ± 52 ms vs 455 ± 41 ms, respectively; $P = .0004$). Figure 1 shows the QTc distribution among the genotype-positive and genotype-negative newborns, illustrating the large overlap in QTc values in the first 48 hours of life, which can make diagnosing LQTS in this cohort challenging.

Using a QTc threshold of ≥440 ms, the ECG obtained in the first 48 hours of life correlated with the genotype-positive status in 44 infants (88%) (Table 2A). In other words, there was an 88% probability (true-positive) that newborns with a QTc interval of ≥440 ms would have their variant-specific cascade genetic test come back positive. Additionally, 7 of 24 patients with a QTc interval of ≤439 ms

Table 1 Cohort Demographic Characteristics

Characteristic	All newborns	Genotype-positive	Genotype-negative
n	74 (100)	50 (68)	24 (32)
Sex			
Male	38 (51)	29 (58)	9 (38)
Female	36 (49)	21 (42)	15 (62)
QTc interval (ms)		506 (370–667)	448 (374–567)
LQTS genotype			
LQT1 (*KCNQ1*)		23 (46)	
LQT2 (*KCNH2*)		15 (30)	
LQT3 (*SCN5A*)		8 (16)	
LQTM		4 (8)	

Values are presented as median (range) or n (%).

LQT1, 2, 3 = type 1, 2, 3 long QT syndrome; LQTM = long QT–associated mutation; LQTS = long QT syndrome; QTc = Bazett's heart rate–corrected QT.

(29%) were later found to be genotype-negative (true-negative). Conversely, 6 genotype-positive newborns (12%) were missed (underdiagnosed; false-negative) since they had a QTc interval of ≤440 ms and 17 newborns (71%), later found to have a negative genetic test result, would have been diagnosed wrongly with LQTS (overdiagnosed; false-positive). Overall, the sensitivity of the ECG to diagnose LQTS was 88% and specificity 29% with a PPV of 72% and an NPV of 54%.

In the subgroup of newborns that would have been wrongfully diagnosed with LQTS on the basis of their initial ECG (QTc cutoff of 440 ms), 9 of them (38%) had a QTc interval between 441 and 469 ms, 5 (21%) between 470 and 499 ms, and 3 (6%) had a significantly prolonged QTc interval of ≥500 ms (QTc interval 504, 567, and 572 ms; Table 3). All genotype-negative infants with an initial QTc interval of ≥500 ms had a LQT2 genotype-positive parent (Online Supplemental Table 1). None of them were initiated on β-blocker therapy in the newborn period. There were 5 genotype-negative newborns who had a QTc interval between 470 and 499 ms (4 from a LQT2 genotype-positive mother and 1 from a LQT1 genotype-positive mother). One infant received β-blocker therapy, which was discontinued once the genetic testing resulted negative for LQTS.

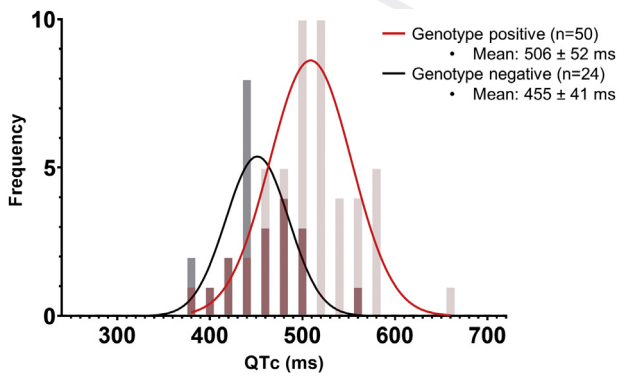

Figure 1 Distribution of corrected QT (QTc) values for genotype-positive and genotype-negative neonates in the first 48 hours of life.

Since the sensitivity and specificity of a test vary depending on the threshold value selected, we performed the same analysis using different QTc thresholds. Using a cutoff QTc value of 450 or 460 ms, there was no change in the sensitivity of the ECG (88% and 86%, respectively; Tables 2B and 2C) but 1 more infant would have been missed by the test at the 460 ms cutoff (false-negative rate 14%; Table 2C). Additionally, 6 or 7 fewer infants would have been classified erroneously as having LQTS (true-negative rate increased from 7 to 13 and 14 newborns, respectively), resulting in a higher specificity (54% and 58%) and lower false-positive rate (46% and 42%) at the 450 ms and 460 ms cutoffs. In total, 17 neonates (23%) would have been misclassified (over- or underdiagnosed) at these thresholds.

Increasing the threshold QTc interval to ≥470 ms resulted in 4 additional newborns being underdiagnosed with the true-positive rate decreasing to 78%. Ultimately, 19 patients (26%) would have been over- or underdiagnosed (Table 2D). At this cutoff, the sensitivity was 78%, specificity 67%, PPV 83%, and NPV 59%.

Discussion

Our results show that the prediction of LQTS genotype status based on ECG interpretation alone is challenging, especially in the newborn period. It is well known that the QTc interval varies significantly in the first week of life.[12] Previous large studies have shown that the mean QTc interval measured on the fourth day of life is 400 ± 20 ms with a 97.5th percentile value of 440 ms. Unlike adults, no gender differences are observed.[10,13] Additionally, healthy newborns can have a physiological prolongation of the QTc interval throughout the first 2 months of life before the QTc interval fully normalizes.[14]

The exact mechanism responsible for this QTc variability has not been elucidated, but the autonomic nervous system may play an important role.[15] At birth, the sympathetic innervation of the heart is not fully developed and does not become functionally complete until ~6 months of life. One of the hypotheses is that there might be an imbalance of the right and left cardiac sympathetic nerves, which could contribute to the prolongation of the QT interval.[16,17] Other possible explanations are that a newborn's variable cardiac repolarization reserve has some molecular underpinnings. For instance, the level and expression profile of the *KCNH2* gene, the second most common gene associated with LQTS, can vary depending on the developmental age and how the messenger RNA transcript is spliced.[18] This physiological phenomenon—mimicking loss-of-function mutations in *KCNH2*-mediated LQT2—could potentially contribute to some of the observed QT variability. Lastly, QT prolongation in newborns may be caused by electrolyte abnormalities such as hypocalcemia, hypokalemia, and hypomagnesemia as well as prenatal and postnatal exposure to drugs that can block the I_{Kr} channel involved in ventricular repolarization, such as macrolide antibiotics and prokinetic agents.[11] Central nervous system abnormalities such as interventricular

Table 2 Contingency tables at various cutoff QTc values

(A)			
	Genotype-positive (n = 50 [68%])	Genotype-negative (n = 24 [32%])	Sensitivity: 88%
QTc ≥ 440 ms	44 (88)	17 (71)	Specificity: 29% PPV: 72% NPV: 54%
QTc ≤ 439 ms	6 (12)	7 (29)	Accuracy: 69%
			Positive LR: 1.2
			Negative LR: 0.4
(B)			
	Genotype-positive (n = 50 [68%])	Genotype-negative (n = 24 [32%])	Sensitivity: 88%
QTc ≥ 450 ms	44 (88)	11 (46)	Specificity: 54% PPV: 80% NPV: 68%
QTc ≤ 449 ms	6 (12)	13 (54)	Accuracy: 77%
			Positive LR: 1.9
			Negative LR: 0.2
(C)			
	Genotype-positive (n = 50 [68%])	Genotype-negative (n = 24 [32%])	Sensitivity: 86%
QTc ≥ 460 ms	43 (86)	10 (42)	Specificity: 58% PPV: 81% NPV: 67%
QTc ≤ 459 ms	7 (14)	14 (58)	Accuracy: 77%
			Positive LR: 2.0
			Negative LR: 0.2
(D)			
	Genotype-positive (n = 50 [68%])	Genotype-negative (n = 24 [32%])	Sensitivity: 78%
QTc ≥ 470 ms	39 (78)	8 (33)	Specificity: 67% PPV: 83% NPV: 59%
QTc ≤ 469 ms	11 (22)	16 (67)	Accuracy: 74%
			Positive LR: 2.4
			Negative LR: 0.3

Values are presented as n (%).
LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; QTc = corrected QT.

hemorrhage or increased intracranial pressure can manifest as a transiently prolonged QT interval.[19] Other identifiable causes for acquired QT prolongation include exposure to maternal antiarrhythmic agents, factors related to the delivery, and measurement errors that are common when calculating the QTc interval in newborns.[20] While rare causes, especially in the specific subset of patients studied in this article, all these factors should be taken into consideration when interpreting a neonatal ECG.

This study demonstrates that even in a cohort of newborns having a 50% pretest probability for having a disease-causative variant for LQTS, reliance on their clinically indicated ECG, using the recommended threshold in the first 48 hours of life, would have resulted in many erroneous classifications.

The ideal screening test for LQTS would have the highest sensitivity (the ability to correctly identify individuals with the disease; low false-negative rate) and specificity (correctly identifying those without the disease; low false-positive results) possible.[21] The newborn ECG had a relatively high sensitivity around 86%–88% using the various QTc thresholds, which is a favorable characteristic for a screening test since it will not miss as many subjects with the disease, but it was not specific, resulting in a high number of false-positive results, again emphasizing the importance of confirmatory genetic testing in this cohort in order to make a definitive diagnosis. It is difficult for a screening test to have a high sensitivity and specificity, so the physician may need to trade off one for the other or, in this case, adjust the QTc cutoffs to achieve the highest sensitivity and specificity. As demonstrated in our analysis, a QTc cutoff of 440 ms would have captured most newborns with LQTS, but some newborns without LQTS screened positive. A QTc cutoff of 450 ms provides the highest sensitivity and a QTc cutoff of 460 ms gives the highest specificity as compared with a QTc interval of 440 or 470 ms. However, there is inconsistency in providers on what QTc threshold is considered abnormal and ultimately depends on the ECG interpreter. It is also important to define the population who would benefit the most from newborn ECG screening, such as neonates with parental LQTS, since they will have the highest pretest probability of having the disease that will affect the PPV and NPV of the ECG as a screening test. Universal ECG screening to identify infants with possible LQTS, in a population with a low prevalence of the disease, would only lead

Table 3 Breakdown of QTc values among genotype-positive and -negative newborns who had a prolonged QTc interval, using a threshold of 440 ms

QTc interval (ms)	Genotype-positive	Genotype-negative
≥440	44 (88)	17 (71)
441–469	5 (10)	9 (38)
470–499	8 (16)	5 (21)
≥500	31 (62)	3 (12)

Values are presented as n (%).
QTc = corrected QT.

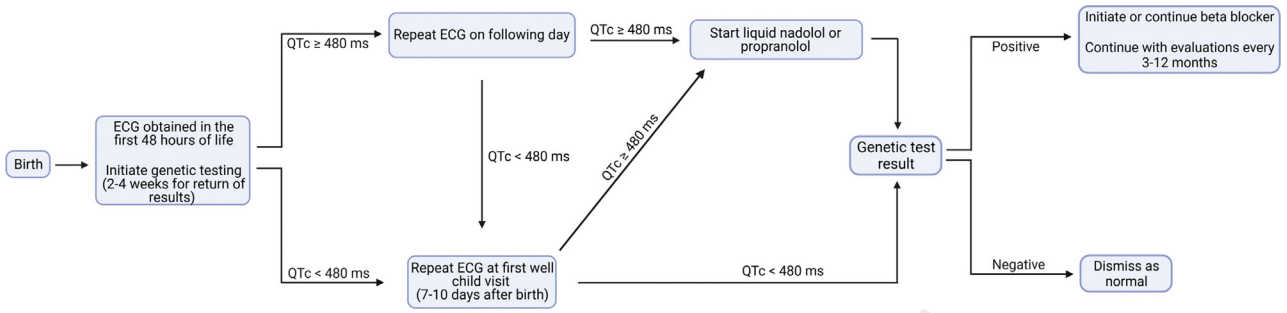

Figure 2 Recommendations for electrocardiographic (ECG) evaluation in newborns suspected of long QT syndrome (LQTS). QTc = corrected QT.

to a higher number of misdiagnoses and is not recommended by the authors.

The consequences of misclassifications need to be considered when analyzing the newborn ECG since a premature overdiagnosis of LQTS might lead to unnecessary interventions, such as additional ECGs and 24-hour Holter monitors, or prescription of β-blockers that can come with unpleasant side effects. Additionally, the emotional ramifications of being misdiagnosed should not be underestimated. While there are no studies on the psychological effects on parents of a misdiagnosed newborn, parents of children newly diagnosed with LQTS have higher distress scores and higher levels of disease-related anxiety and depression, which persisted even after 18 months of the diagnosis. These parents reported being hypervigilant of their children's symptoms and had significant preoccupation for the children's future, highlighting the role of psychological support during this period.

In our Mayo Clinic Windland Smith Rice Genetic Heart Rhythm Clinic, based on our >20 years' experience in caring for >1400 patients with LQTS, our current standard of care is summarized in Figure 2 and begins with obtaining a 12-lead ECG sometime during the first 24 hours of life for all babies born to a LQTS-positive parent. This should be done nonurgently. We do not transfer the neonate immediately after delivery to a monitored unit for observation and allow the newborn to bond with the mother if there are no other obstetrical or medical contraindications to do so.

Even without doing the ECG, the baby has a 50% chance of inheriting the LQTS-causative variant, and the ECG might provide pregenetic test anticipation as to whether the newborn is LQTS positive. A first 24-hour QTc interval of ≥500 ms likely indicates the presence of LQTS, but QTc normalization and negative genetic test results are still possible. The newborn's blood is sent out for variant-specific confirmatory testing with a result returned in 2–4 weeks. We repeat the ECG again on the next day. If both ECGs show persistent and marked QT prolongation (QTc interval ≥ 480 ms), we then initiate either liquid nadolol or liquid propranolol and keep the baby in the hospital for an additional 2–3 days, typically.

If in contrast the QTc value is <480 ms, we simply watch and wait for the genetic test result, outlining QTc preventive measures in the meantime and repeating the ECG at the baby's first well-child visit in 7–14 days whenever possible. If the genetic test result is positive but the QTc interval has remained <480 ms, we review and implement the overarching LQTS-relevant preventive measures and then deliberate whether to initiate prophylactic β-blocker or simply continue to monitor with every 3- to 6-month ECGs and 24-hour ambulatory monitoring. With this approach, we have never had a newborn presentation of a LQTS-triggered cardiac event among those infants with a QTc interval of <480 ms who were dismissed untreated while waiting and subsequently were positive for their parent's LQTS-causative variant.

Conclusion

LQTS positivity, based on the ECG obtained in the first 24–48 hours of life, is uncertain because of the marked QTc variability present in the first week of life. Even in a cohort of newborns with the highest pretest probability for LQTS (50% chance), their newborn ECG should not be used in isolation to make the diagnosis of congenital LQTS but rather it should be combined with the clinically indicated, class I recommended variant-specific, cascade genetic test to ensure the most accurate diagnosis and enable guideline-directed therapies to be instituted properly.

References

1. Simma A, Potapow A, Brandstetter S, et al. Electrocardiographic screening in the first days of life for diagnosing long QT syndrome: findings from a birth cohort study in Germany. Neonatology 2020;117:756–763.
2. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. Circulation 2000;101:616–623.
3. Schwartz PJ, Stramba-Badiale M, Crotti L, et al. Prevalence of the congenital long-QT syndrome. Circulation 2009;120:1761–1767.
4. Ackerman MJ. Cardiac channelopathies: it's in the genes. Nat Med 2004; 10:463–464.
5. Adler A, Novelli V, Amin AS, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. Circulation 2020;141:418–428.
6. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. Circulation 1999;99:529–533.
7. Rohatgi RK, Sugrue A, Bos JM, et al. Contemporary outcomes in patients with long QT syndrome. J Am Coll Cardiol 2017;70:453–462.
8. Schwartz PJ. Pro: newborn ECG screening to prevent sudden cardiac death. Heart Rhythm 2006;3:1353–1355.
9. Saul JP, Schwartz PJ, Ackerman MJ, Triedman JK. Rationale and objectives for ECG screening in infancy. Heart Rhythm 2014;11:2316–2321.
10. Schwartz PJ, Stramba-Badiale M, Segantini A, et al. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998;338:1709–1714.

11. Schwartz PJ, Garson A Jr, Paul T, Stramba-Badiale M, Vetter VL, Wren C. Guidelines for the interpretation of the neonatal electrocardiogram: a Task Force of the European Society of Cardiology. Eur Heart J 2002;23:1329–1344.
12. Walsh SZ. Electrocardiographic intervals during the first week of life. Am Heart J 1963;66:36–41.
13. Stramba-Badiale M, Spagnolo D, Bosi G, Schwartz PJ; MISNES Investigators. Are gender differences in QTc present at birth? Multicenter Italian study on neonatal electrocardiography and sudden infant death syndrome. Am J Cardiol 1995;75:1277–1278.
14. Schwartz PJ, Montemerlo M, Facchini M, et al. The QT interval throughout the first 6 months of life: a prospective study. Circulation 1982;66:496–501.
15. Coumel P. Cardiac arrhythmias and the autonomic nervous system. J Cardiovasc Electrophysiol 1993;4:338–355.
16. Schwartz PJ. Cardiac sympathetic innervation and the sudden infant death syndrome: a possible pathogenetic link. Am J Med 1976;60:167–172.
17. Stramba-Badiale M, Lazzarotti M, Schwartz PJ. Development of cardiac innervation, ventricular fibrillation, and sudden infant death syndrome. Am J Physiol 1992;263:H1514–H1522.
18. Crotti L, Tester DJ, White WM, et al. Long QT syndrome-associated mutations in intrauterine fetal death. JAMA 2013;309:1473–1482.
19. Delogu AB, Iannotta R, Saracino A, Barone G, Romagnoli C. Long QT interval in the newborn. Early Hum Dev 2013;89:S39–S40.
20. Schwartz PJ, Stramba-Badiale M. Repolarization abnormalities in the newborn. J Cardiovasc Pharmacol 2010;55:539–543.
21. Maxim LD, Niebo R, Utell MJ. Screening tests: a review with examples. Inhal Toxicol 2014;26:811–828.