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Phenotypes of Overdiagnosed Long QT Syndrome

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ABSTRACT

BACKGROUND Long QT syndrome (LQTS) predisposes individuals to arrhythmic syncope or seizure, sudden cardiac arrest, or sudden cardiac death (SCD). Increased physician and public awareness of LQTS-associated warning signs and an increase in electrocardiographic screening programs may contribute to overdiagnosis of LQTS.

OBJECTIVES This study sought to identify the diagnostic miscues underlying the continued overdiagnosis of LQTS.

METHODS Electronic medical records were reviewed for patients who arrived with an outside diagnosis of LQTS but were dismissed as having normal findings subsequently. Data were abstracted for details on referral, clinical history, and both cardiologic and genetic test results.

RESULTS Overall, 290 of 1,841 (16%) patients with original diagnosis of LQTS (174 [60%] female; mean age at first Mayo Clinic evaluation, 22 ± 14 years; mean QTc interval, 427 ± 25 milliseconds) were dismissed as having normal findings. The main cause of LQTS misdiagnosis or overdiagnosis was a prolonged QTc interval secondary to vasovagal syncope (n = 87; 30%), followed by a seemingly positive genetic test result for a variant in 1 of the main LQTS genes (n = 68; 23%) that was ultimately deemed not to be of clinical significance. Furthermore, patients received misdiagnoses because of a positive family history of SCD that was deemed unrelated to LQTS (n = 46; 16%), isolated/transient QT prolongation (n = 44; 15%), or misinterpretation of the QTc interval as a result of inclusion of the U-wave (n = 40, 14%).

CONCLUSIONS Knowing the 5 main determinants of discordance between a previously rendered diagnosis of LQTS and full diagnostic reversal or removal (vasovagal syncope, "pseudo"-positive genetic test result in LQTS-causative genes, family history of SCD, transient QT prolongation, and misinterpretation of the QTc interval) increases awareness and provides critical guidance to reduce this burden of overdiagnosed LQTS. (J Am Coll Cardiol 2023;81:477-486) © 2023 by the American College of Cardiology Foundation.

Congenital long QT syndrome (LQTS) is a potentially lethal, yet highly treatable, genetic heart disease with an estimated prevalence of 1 in 2,000 persons that is characterized by a prolonged QT interval on a 12-lead electrocardiogram (ECG).[1,2] Patients with LQTS are at an increased risk of arrhythmic syncope or seizure, sudden cardiac arrest, or sudden cardiac death (SCD).[1] Although a prolonged QT interval is the hallmark sign of LQTS, some patients (20%-25%) with LQTS may present with a normal QT interval.[3-5] Despite an increase in physician and public awareness of LQTS over the past 2 decades, the rarity of this condition and the heterogeneity of its clinical presentation add to the difficulty in correctly diagnosing and managing these patients to prevent possible lethal tragedies.

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ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

ICD = implantable cardioverter-defibrillator

LQTS = long QT syndrome

SCD = sudden cardiac death

VUS = variant of uncertain significance

Additionally, although well intended, increased awareness and an increase in ECG screening programs may in fact contribute to an overdiagnosis of this condition.[6]

Historically, the Schwartz score, first described in 1993, provided a diagnostic scorecard for LQTS by relying on ECG findings, clinical history, and family history to estimate the clinical pretest probability of having LQTS.[7] Importantly, the updated Schwartz score includes features of the treadmill exercise stress test as important elements in the overall score tabulation. Over the past decade, clinical genetic testing has become another important avenue for diagnosis whereby the results are used to inform risk stratification, clinical management, and identification of potentially at-risk family members through cascade screening.[8] However, the clinical utility and interpretation of genetic testing are confounded by the high prevalence of variants of uncertain significance (VUSs) identified using variant classification approaches on the basis of the 2015 American College of Medical Genetics and Genomics guidelines.[9] Other ancillary tests that have been used to aid in the diagnosis of LQTS are the epinephrine stress test for concealed (ie, genotype-positive, phenotype-negative) LQTS and the brisk-standing test.[10-12]

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However, despite these various tests, the ECG remains 1 of the most common clinical tests used in the diagnostic process of LQTS. Given the heavy reliance on the ECG, it is imperative that the interpretation of this tool is standardized to avoid overestimation or underestimation of the heart rate-corrected QT interval (QTc interval). As shown previously, a miscalculated QTc interval, a misinterpreted normal distribution of the QTc interval, and misjudged clinical symptoms were some of the main reasons for the misdiagnosis of LQTS in patients.[6]

In light of this work, it is essential that the most common causes of LQTS misdiagnosis are identified to help mitigate the erroneous diagnosis of LQTS and the resultant effects on patients' lifestyles. In our study, we attempted to aid this endeavor by exposing the various reasons that continue to precipitate an overdiagnosis of LQTS.

METHODS

In this Mayo Clinic Institutional Review Board-approved study, we performed a retrospective review of all patients evaluated in the Windland Smith Rice Genetic Heart Rhythm Clinic (Mayo Clinic, Rochester, Minnesota, USA) between July 2000 and October 2021 to identify patients who arrived with a diagnosis of LQTS but who were subsequently dismissed without it. The aim of this study was to identify the main reasons for this discordance and removal of diagnosis. All patients were evaluated clinically and risk stratified by a single genetic cardiologist and LQTS specialist (M.J.A.). Specifically, the data were abstracted for patient demographics, clinical characteristics, cardiologic and genetic test results, ECG records including a manually calculated QTc interval, exercise or epinephrine stress test results, and a family history of SCD or LQTS.

Reasons for misdiagnosis or overdiagnosis were categorized as follows: clinical, defined as errors in assessment of the patient's symptoms and personal history; diagnostic, defined as errors in interpreting the results of instruments or tests used to evaluate for LQTS; genetic, defined as misinterpretation of genetic test results; and family, defined as erroneous labeling of LQTS in the patient on the basis of family history of LQTS or a history of sudden death. Each category had several subcategories for additional detail.

STATISTICAL ANALYSIS. All continuous variables were presented as mean ± SD. All categorical variables were presented as frequencies and percentages. Student's *t*-test was used to compare continuous variables, when appropriate. All analyses were 2-tailed, and statistical significance was set at a value of $P \leq 0.05$.

RESULTS

The clinical characteristics of the misdiagnosed cohort and a comparison of the dismissed patients vs the true LQTS patients are summarized in **Table 1** and Supplemental Table 1, respectively. Overall, there were 290 of 1,841 (16%) patients (average age at their first Mayo Clinic visit was 22 ± 14 years; 174 female [60%]) who arrived at Mayo Clinic with a referral diagnosis of LQTS but who were dismissed subsequently as having normal findings following further evaluation. Interestingly, 20% of the dismissed patients were self-referred, whereas 80% were referred by a physician, although the groups have similar clinical characteristics (**Table 1**). The average referral QTc interval of the misdiagnosed patients was 504 ± 39 milliseconds. Before their Mayo Clinic visit, 232 patients (80%) had been started on β-blockers for their alleged LQTS diagnosis, and 22 patients (8%) had received an implantable cardioverter-defibrillator (ICD). Following evaluation and risk stratification at Mayo Clinic, the average QTc interval for these patients was 427 ± 25 milliseconds, which

was significantly lower than the referral QTc interval ($P < 0.0001$). Of the 290 dismissed patients, over a mean follow-up of 3 ± 5 years thus far, none have reported any events post-Mayo Clinic evaluation and are presumed well. Furthermore, we conducted an Accurint (LexisNexis Risk Solutions) search for vital status, and to date, 2 patients (0.7%) have died of non-LQTS-related causes postevaluation and dismissal.

On review, a single reason for initial diagnosis of LQTS could be identified for 195 of 290 patients (67%), whereas for the remainder of the patients (33%), 2 or more factors contributed to the erroneous overdiagnosis (Table 1). The main reasons for overdiagnosis of LQTS on the basis of the previously described categories are summarized in Table 2: clinical (38%), diagnostic (29%), genetic (17%), and family (16%). In Table 2, "unique reasons" refers to the number of patients who were misdiagnosed solely on the basis of that unique category provided, and "total reasons" refers to the total number of patients who were misdiagnosed with that specific category as 1 of the factors that led to their misdiagnosis. Within the clinical category, 87 patients (30%) were misdiagnosed with LQTS because of temporary QT prolongation following a vasovagal syncopal event, which was overall the most common reason for misdiagnosis. Following vasovagal syncope, the average QTc interval measured in the emergency department was 487 ± 27 milliseconds vs the average QTc interval at Mayo Clinic evaluation of 422 ± 15 milliseconds ($P < 0.0001$). An example ECG is provided in Figures 1A and 1B, which illustrate the initial referral ECG showing transient QT prolongation in the emergency department following vasovagal syncope that prompted an LQTS diagnosis, as well as the later ECG obtained at Mayo Clinic that led to a reversal of this misdiagnosis. Another cause of misdiagnosis in the clinical category was an isolated or transient event of QT prolongation for various reasons in 44 (15%) patients, including panic attack, metabolic disturbances, anorexia, drug-induced QT prolongation, sinus arrhythmias, and pregnancy (Figure 1C).

Delving into the diagnostic reasons for misdiagnosis, these were mainly driven by errors in assessment or calculation of the ECG's true QTc interval. The main reason for QTc interval overestimation was inclusion of the U-wave in the QT interval, which occurred in 40 patients (14%) (Figures 2A and 2B). In Figure 2A, for example, the QTc interval on the referral ECG was estimated to be 580 milliseconds by an outside physician. At Mayo Clinic, after excluding the U-wave from the measurement, the QTc

TABLE 1 Clinical Characteristics and Treatments of the Patients "Dismissed as Having Normal Findings"

	Total Cohort (N = 290)	Self-Referred (n = 58)	Physician Referred (n = 232)
Clinical characteristics			
Female	174 (60)	28 (48)	146 (63)
Age, y, at first Mayo Clinic visit	22 ± 14	19 ± 13	22 ± 15
Average referral QTc interval	504 ± 39	479 ± 17	508 ± 40
Average Mayo Clinic QTc interval	427 ± 25	424 ± 23	427 ± 25
Treatment before Mayo Clinic			
BB	232 (80)	43 (74)	189 (81)
ICD	22 (8)	3 (5)	19 (8)
Treatment after Mayo Clinic			
BB discontinued	194/232 (84)	41/43 (95)	153/189 (81)
BB continued	38/232 (16)	2/43 (5)	36/189 (19)
ICD extraction	10/22 (45)	1/3 (33)	9/19 (47)
Number of reasons for overdiagnosis			
Patients with 1 reason	195 (67)	41 (71)	154 (66)
Patients with 2 reasons	87 (30)	15 (26)	72 (31)
Patients with ≥3 reasons	8 (3)	2 (3)	6 (3)

Values are n (%), mean ± SD, or n/N (%); the percentages provided are out of the column totals unless noted otherwise.

BB = β-blocker; ICD = implantable cardioverter-defibrillator.

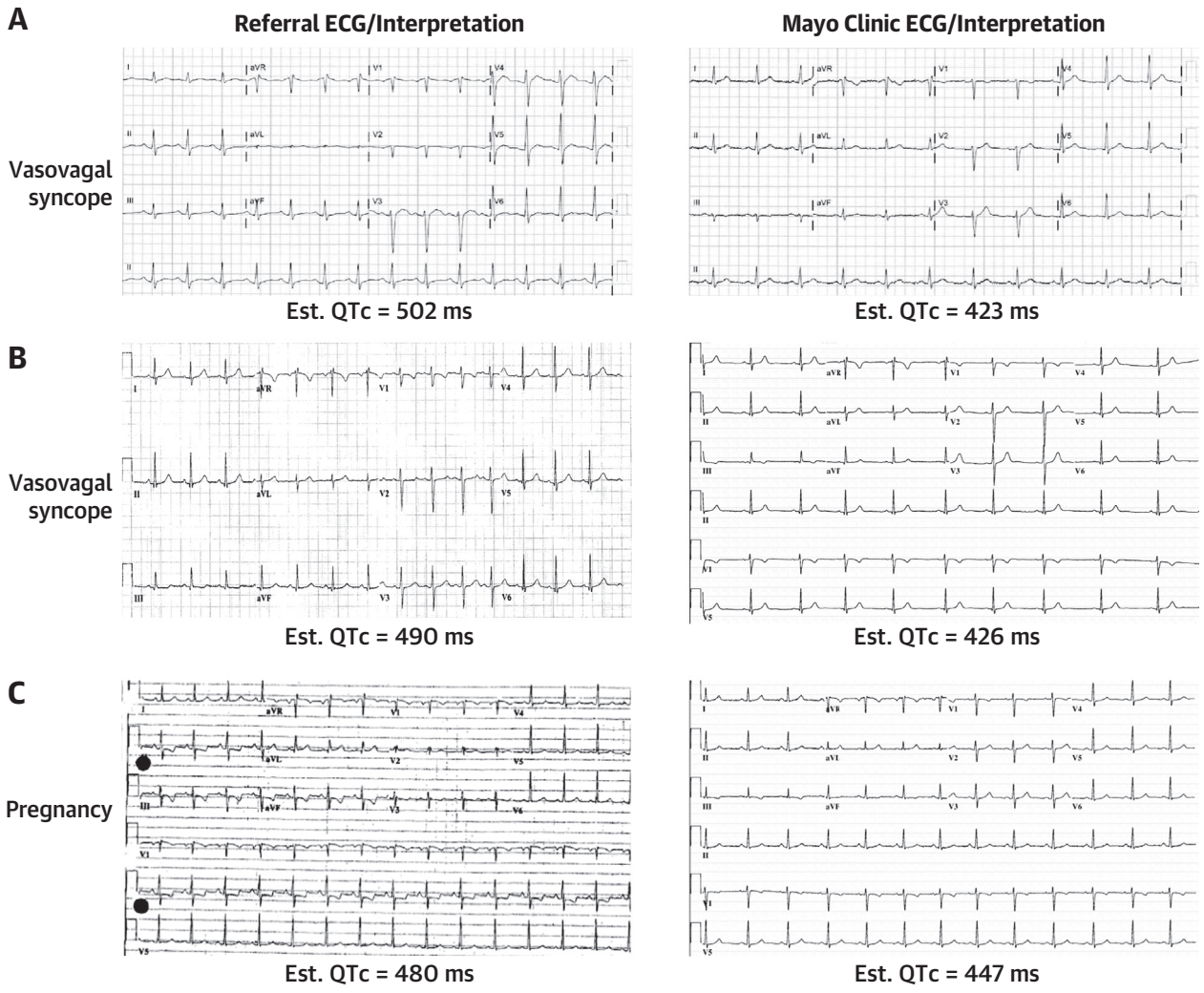
TABLE 2 The 4 Main Categories and Associated Subcategories Leading to Overdiagnosis of LQTS

	Unique Reasons[a] (n = 195)	Total Reasons[b] (N = 394)
Clinical (38%)		
Vasovagal syncope	50	87
Isolated or transient QT interval prolongation (panic attack, chest pain, sepsis, stress, hypoglycemia, hypokalemia, anorexia, drug induced, sinus arrhythmias, pregnancy)	31	44
Exercise related QT interval prolongation (stops post detraining)	5	6
Personal history of seizures	3	5
Personal history of SCA	1	3
Misdiagnosis of JLNS (seizures and deafness)	2	3
Diagnostic (29%)		
Inclusion of U-wave	24	40
Borderline QTc interval	21	36
Overestimation of the QT interval on epinephrine or isoproterenol test	8	24
Overestimation on stress test or tilt test	1	7
Overestimated on screening ECG	0	4
Overestimated on Holter monitor	2	2
Wide QRS	1	2
Genetic (17%)		
Variant positive/phenotype negative	9	68
Family (16%)		
Family history of SCD (myocardial infarction) or SUD or QT interval prolongation	28	46
Family history of false LQTS diagnosis	9	17

[a]Unique reasons refers to the number of patients who were misdiagnosed solely on the basis of the reason provided in the corresponding row. [b]Total reasons refers to the total number of patients who were misdiagnosed, with the associated subcategory being 1 of the reasons that led to their misdiagnosis.

ECG = electrocardiogram; JLNS = Jervell and Lange-Nielsen syndrome; LQTS = long QT syndrome; SCA = sudden cardiac arrest; SCD = sudden cardiac death; SUD = sudden unexplained death.

FIGURE 1 Example ECGs Leading to Overdiagnosis of Long QT Syndrome

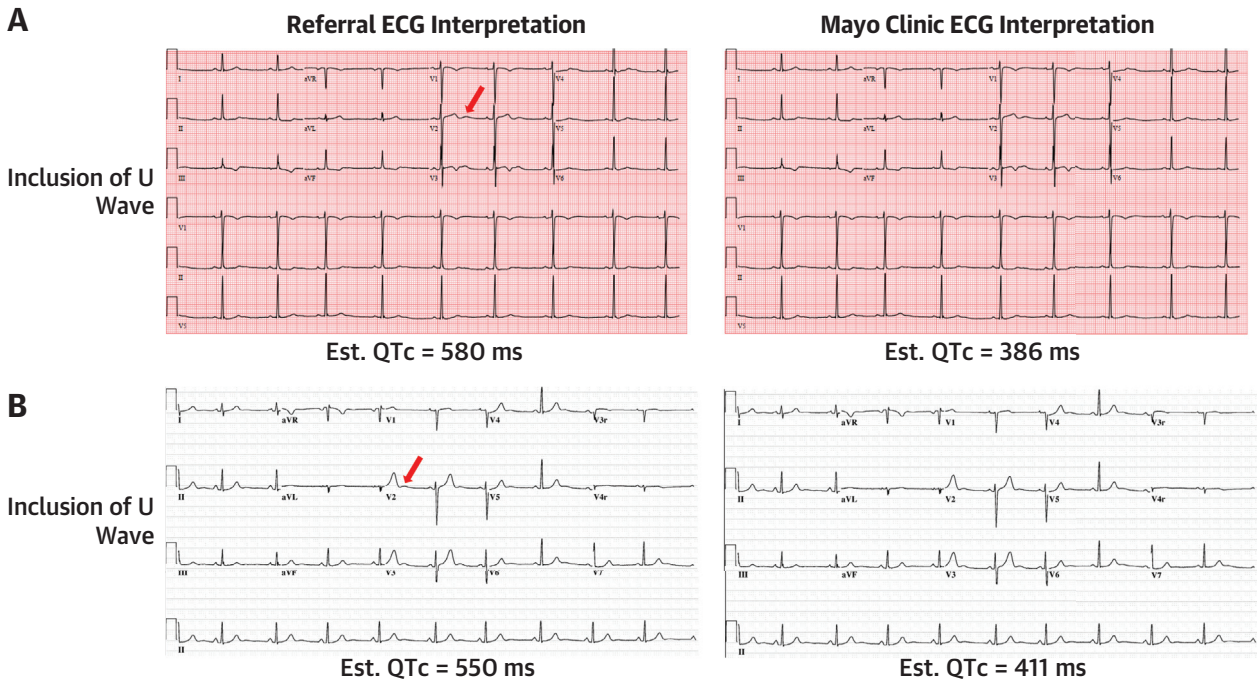


(A and B) Left, An instance of transient QT prolongation secondary to vasovagal syncope that led to a misdiagnosis of long QT syndrome. **Right,** A new electrocardiogram (ECG) of the same patient obtained at Mayo Clinic during evaluation showing a normal QTc interval, which aided in reversal of the long QT syndrome misdiagnosis. **(C) Left,** A prolonged QTc interval during pregnancy. **Right,** QTc shortening post-pregnancy. Est. = Estimated.

interval on the same ECG was determined to be 386 milliseconds. QTc interval overestimation by U-wave inclusion was followed by adjudication of a "borderline" QTc interval in 36 patients (12%), which at the time of these patients' evaluation was based on the older guideline cutoffs of QTc interval values of ≥450 milliseconds in men and ≥460 milliseconds in women.[13] The third most common cause of misdiagnosis in the diagnostic category was overestimation of the QT interval on epinephrine or isoproterenol testing in 24 (8%).

The next category considered was genetic testing. Overall, 196 patients (68%) underwent genetic testing, with 34 patients (17%) having their genetic test after their Mayo Clinic evaluation. Of the 196 patients, 68 patients (35%) seemingly tested positive for a variant in 1 of the LQTS-associated genes, with 46 (68%) patients having a company-graded VUS, 19 (28%) with a variant graded as pathogenic or likely pathogenic, and 3 (4%) with a single-nucleotide variant (formerly known as a single-nucleotide polymorphism). After evaluation at Mayo Clinic, all these

FIGURE 2 **Inclusion of U-Wave Leading to Overdiagnosis of Long QT Syndrome**



(A and B) The same electrocardiogram (ECG) obtained elsewhere with a difference in **(left)** referral QT measurement or QTc calculation vs **(right)** Mayo Clinic measurement after excluding the U-wave. Est. = Estimated.

variants were deemed clinically of no significance on the basis of variant grade as well as a lack of clinical evidence of LQTS (Table 3). Details of these 68 cases, including the reason for genetic testing and expert variant adjudication postevaluation on the basis of clinical history, family history, and diagnostic tools, are provided in Supplemental Table 2.

TABLE 3 **Variant Adjudication Before and After Mayo Clinic Evaluation**

Company genetic testing	
Received genetic testing	196 (68)
Did not receive genetic testing	94 (32)
Company genetic test results	
Negative LQTS genetic test	128 (65)
Variant "positive"	68 (35)
VUS	46 (68)
P/LP	19 (28)
Sequence variant	3 (4)
Mayo clinic variant adjudication	
Total variants adjudicated	68 (100)
VUS	47 (69)
B/LB	9 (13)
Irrelevant to LQTS	8 (12)
Sequence variant	4 (6)

Values are n (%).
B/LB = benign/likely benign variant; LQTS = long QT syndrome; P/LP = pathogenic/likely pathogenic variant; VUS = variant of uncertain significance.

Finally, we evaluated the impact of the misdiagnosis on the lifestyle of the patients. Of the 290 patients, 130 patients (45%) had been restricted from competitive sports before their Mayo Clinic evaluation because of a presumed diagnosis of LQTS. These restrictions were lifted postevaluation at Mayo Clinic, thus allowing these patients to go back to their athletic activities without any adverse effects during follow-up.

Among these 290 overdiagnosed patients, 232 (80%) had been started on β-blockers. Following comprehensive evaluation and removal of the LQTS diagnosis, β-blockers were discontinued in 194 of 232 patients (84%), whereas 38 patients (16%) opted to continue the medication because of their perception of protection and lessened anxiety despite the dismissal of their LQTS diagnosis. Nonetheless, the average duration of β-blocker use was 2.3 ± 4 years, translating into 451 patient-years of unnecessary medical therapy. Furthermore, 10 of the 22 patients (45%) who received an ICD underwent ICD extraction without complications. Of the remaining 12 patients

who chose to continue with ICD therapy, 7 patients (58%) were recommended to have an ICD extraction, but these patients reported anxiety related to device extraction complications as the primary reason for continuing with the ICD. The other 5 patients continued with ICD therapy given their history of neurocardiogenic syncope (n = 3), first-degree atrioventricular block (n = 1), or bileaflet mitral valve prolapse (n = 1). Notably, 23 additional patients (8%) had received an outside recommendation for an ICD, but instead they sought a second opinion at Mayo Clinic before proceeding with ICD placement. Post-Mayo Clinic evaluation, ICD use was not recommended for any of these patients.

DISCUSSION

Unfortunately, with an increased awareness of LQTS comes the risk of overdiagnosis. Of note, within our clinical practice, more than 1 of every 6 patients who arrive with a diagnosis of LQTS leave Mayo Clinic's dedicated LQTS specialty clinic without that diagnosis. In fact, most of these patients leave without any diagnosis of any important SCD-predisposing cardiovascular condition. With nearly 500 unnecessary years of drug therapy, years of competitive sports disqualifications, and with one-half of the overdiagnosed patients who had ICDs leaving without their ICDs, the implications of this continued high frequency of overdiagnosed LQTS are profound. It is surprising and sobering to observe that the issues we presented surrounding diagnostic miscues in LQTS in 2007 are just as prevalent today.[6] Importantly, compared with our 2007 publication, our current overall cohort is 10 times larger, including a misdiagnosed cohort that is 4 times larger. Here we report our experience with reversal of an outside misdiagnosis of LQTS and highlight 4 main categories and the top 5 reasons within those categories that perpetuate this issue (**Central Illustration**).

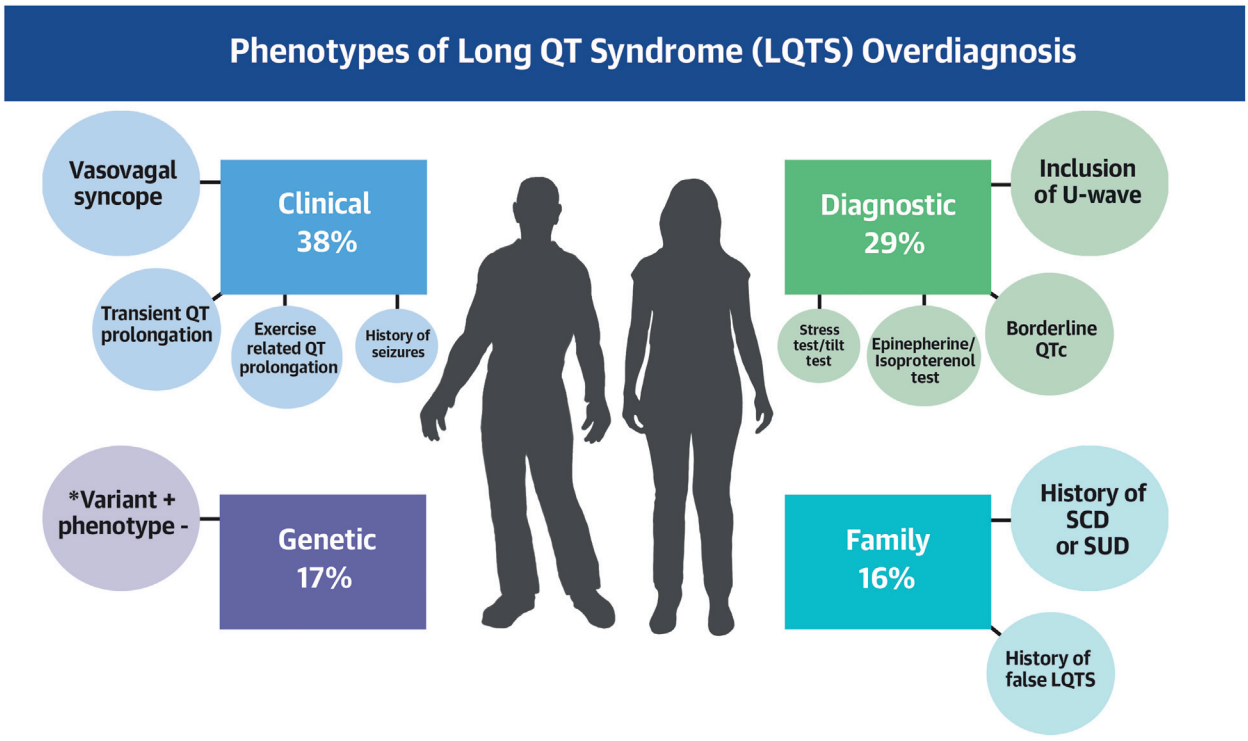
The most common cause of LQTS misdiagnosis was QT prolongation following vasovagal syncope, which was misinterpreted as an LQTS-attributed syncope. It is important to recognize that syncope in LQTS is caused by a pathologic ventricular arrhythmia (torsades de pointes), which causes nearly instantaneous cerebral hypoperfusion and nearly instant, with negligible forewarning, fainting or syncope. Vasovagal syncope does not result from an underlying electrical abnormality but is instead caused by a sudden abrupt drop in heart rate and/or blood pressure in response to triggers such as stress, heat exposure, and prolonged standing. The prodrome for vasovagal syncope typically includes features such as lightheadedness, nausea, diaphoresis, and/or pallor, whereas an arrhythmogenic syncope typically occurs abruptly and without a warning sign. Therefore, it is important to recognize that QT prolongation caused by LQTS can lead to arrhythmogenic syncope, whereas vasovagal syncope can lead to transient QT prolongation. Although the pathogenesis of non-arrhythmogenic syncope and the resultant changes observed on the ECG are incompletely understood, it has been hypothesized that dynamic changes in the autonomic tone may contribute to this phenomenon.[14]

The autonomic imbalances, namely, decreased sympathetic and increased vagal tone that underlie vasovagal syncope and other dysautonomias, affect cardiac repolarization and thus the QT interval and QT dispersion. Although large-scale data exhibiting QT prolongation postvasovagal syncope are not available, in our cohort of dismissed patients with normal findings, the average QTc interval measured in the emergency department following vasovagal syncope was 487 ± 27 milliseconds vs the average QTc interval at Mayo Clinic evaluation of 422 ± 15 milliseconds ($P < 0.0001$). Furthermore, we previously showed, albeit in a smaller study, QTc prolongation in patients presenting with vasovagal syncope to the emergency department and subsequent QTc normalization on a follow-up ECG.[15] As such, an ECG immediately following (vasovagal) syncope can be misleading.

Finally, an analysis of syncope triggers between unaffected family members and LQTS patients showed that family members experienced benign, vasovagal syncope resulting from factors such as heat, dehydration, and menses, unlike LQTS patients, whose arrhythmogenic syncope was precipitated by exercise or auditory triggers.[16] Thus, proper assessment of the syncope, including the events surrounding the syncopal episode and family history, must be taken into account to avoid mislabeling vasovagal syncope as LQTS-triggered syncope.

The second most common cause of LQTS misdiagnosis was an apparently positive genetic test for 1 of the LQTS-causative genes, a finding that brings to light the occasional overuse of genetic testing in the clinical setting. According to the latest guidelines, genetic testing for LQTS should be recommended for patients with a high index of clinical suspicion for LQTS.[17] Genetic testing, when used correctly, can be a powerful tool to confirm the diagnosis of LQTS. However, it is just as important to remember that when this testing is used incorrectly (ie, in the setting

CENTRAL ILLUSTRATION **Main Reasons for Long QT Syndrome Overdiagnosis**



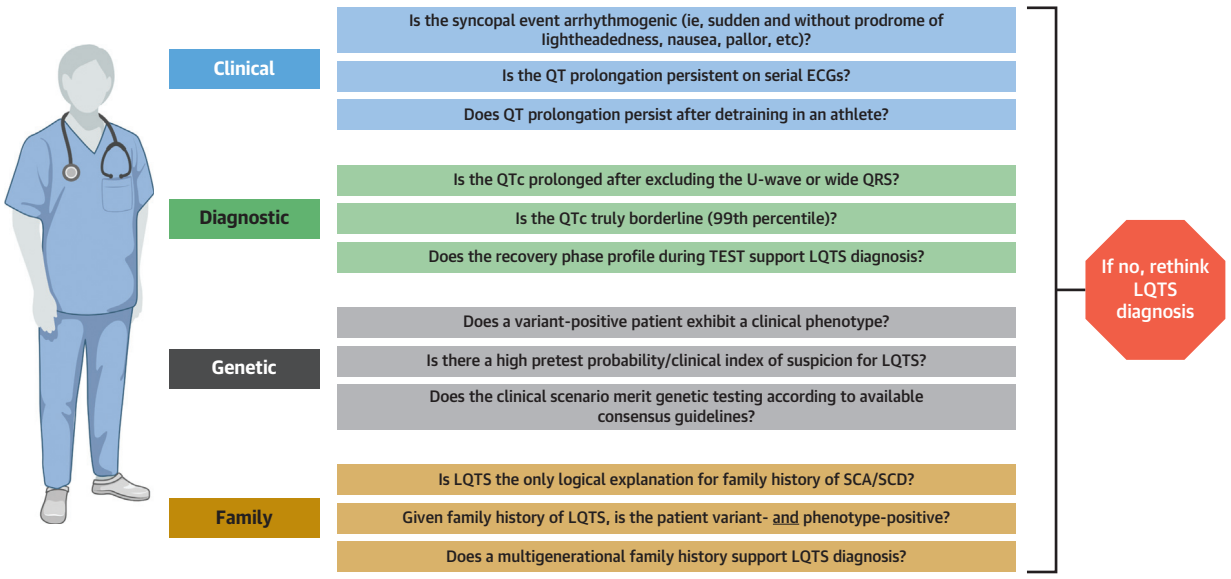
Bains S, et al. J Am Coll Cardiol. 2023;81(5):477–486.

The 4 categories (clinical, diagnostic, genetic, and family) **(in boxes)** that led to a misdiagnosis of long QT syndrome (LQTS) in patients. The corresponding **circles** show the top subcategories that aided in this overdiagnosis phenomenon. *Variant+ refers to a variant of uncertain significance or benign/likely benign variants identified in long QT syndrome-associated genes that were subsequently disregarded after clinical evaluation. Figure created using BioRender. SCD = sudden cardiac death; SUD = sudden unexplained death.

of a weak or absent phenotype), it has the potential to unleash a detrimental cascade that subjects the patient and/or family members to unnecessarily expensive testing, labeling with an erroneous "LQTS/possible LQTS" diagnosis that is extremely difficult to recant, and inappropriate treatment with ICDs and/or pharmacologic therapy.[18] Thus, in the era of genetic testing and cascade screening, it is crucial that the yield of genetic testing and the background rate of so-called genetic noise associated with it are used correctly to aid in the clinician's diagnostic precision. Conversely, there may be cases where genetic testing in combination with clinical assessment and risk stratification is used to dissuade the rendering of an LQTS diagnosis by ruling out ~75% to 80% of LQTS.[19] This is highlighted in the current report, where 34 of 196 patients (17%) received a genetic test at Mayo Clinic to buttress the evidence further to support the removal of their LQTS diagnosis. Interestingly, only 3 of 34 patients (9%) had a genetic test with a positive result for a VUS in 1 of the LQTS-causative genes. After clinical assessment, these variants were found to be of no clinical significance.

The third most common cause of LQTS overdiagnosis was a family history of sudden unexplained death (n = 26), QT prolongation (n = 11), or sudden cardiac arrest or SCD (n = 9). For every patient being evaluated for suspicion of LQTS, a multigenerational family history must be obtained. However, obtaining the family history and using that as the sole basis for diagnosis of LQTS comprises a flawed approach. In our cohort, 28 patients were referred to Mayo Clinic with a diagnosis of LQTS solely on the basis of the presence of the aforementioned factors in their family history. In the event of sudden death, a detailed history of the events pertaining to the death of the deceased must be obtained. Furthermore, if possible, genetic testing on a DNA sample of the deceased

FIGURE 3 Important Questions in the Consideration of LQTS Diagnosis



The 4 main categories that led to misdiagnosis of long QT syndrome (LQTS). Within each category are important questions to ask when evaluating a patient for possible long QT syndrome. If the answer to these questions is negative, one should rethink the diagnosis of long QT syndrome. Figure created using BioRender.
ECG = electrocardiogram; SCA = sudden cardiac arrest; SCD = sudden cardiac death; TEST = treadmill exercise stress test.

should be pursued to understand better the cause of death, rather than using living relatives as surrogates. Most importantly, however, the pretest probability for LQTS in patients in the context of their personal and family history should be used as 1 of the strongest factors for determination of disease susceptibility.

The fourth most common cause of LQTS misdiagnosis was an isolated event of QT prolongation observed in 44 patients. This transient QT prolongation was observed under various conditions, including systemic disease, panic attack, electrolyte disturbances, drug-induced QT prolongation, and pregnancy. In pregnancy, for example, this may be explained in part by anatomical and physiologic changes, including remodeling of ion channels, that occur to support the increased metabolic demands and their resultant effect on cardiac repolarization.[20,21] Moreover, electrolyte imbalances such as hypokalemia secondary to a dilutional effect from increased blood volume or hyperemesis gravidarum may also lead to the observance of temporary QT prolongation during pregnancy. Surprisingly, 31 patients received a diagnosis of LQTS solely on the basis of transient QT prolongation. It is important to remember that a diagnosis of LQTS should seldom be rendered on the basis of ECG findings alone, and almost never after a single ECG. Moreover, as previously mentioned, the Schwartz score is an important diagnostic score that helps quantitatively measure the index of suspicion for LQTS by considering various elements, including ECG QTc values. However, clinicians must respect the dynamic nature of this score and thus allow room for revision and refinement of the diagnosis. One such way to accomplish this is to perform serial ECG evaluations in the patient.

The fifth most common cause of LQTS misdiagnosis was inclusion of the U-wave in the calculation of the QTc interval (n = 40). In 2005, Viskin et al[22] reported a study in which 902 physicians were presented with 2 ECGs of healthy adults and 2 ECGs of patients with LQTS. These investigators found that <50% of the cardiologists accurately measured the QT interval.[22] In fact, correct classification of the QTc interval as "long" or "normal" was determined by <25% of cardiologists and noncardiologists. This study called into question the accuracy of diagnosis in an individual with LQTS whose QT interval was underestimated or vice versa. Remarkably, now almost 2 decades later, the results of that study are once again corroborated by our own experience with outside referral of diagnosis of LQTS on the basis of an inaccurate interpretation of the ECG as 2 of the 5 most common pathways to overdiagnosed LQTS. Moreover, as highlighted in a study by Vink et al,[5] the QTc interval may vary depending on the method (ie,

tangent vs threshold) used for QTc calculation. Thus, the calculated QTc values must be adjusted, instead of using the guideline-provided 99th percentile QTc values as blind cutoffs. Such modifications can aid in decreasing the burden of LQTS overdiagnosis because in our cohort, in addition to the inclusion of the U-wave, another common cause of LQTS overdiagnosis or misdiagnosis was physician adjudication of the QTc interval as "borderline" in 36 patients.

Finally, we would like to highlight another unique avenue that can contribute to the burden of overdiagnosed LQTS. As recently detailed in a study by Dagradi et al,[23] exercise training–induced changes in repolarization of the QT interval can masquerade as LQTS. In the cohort presented here, we corroborate this finding in 6 patients who presented with a referral diagnosis of LQTS that was attributed subsequently to this training-associated QT prolongation that normalized post-detraining.

Overall, while examining a patient for the possibility of LQTS, it is imperative that the clinical symptoms, diagnostic criteria, genetic testing, and family history of each patient are carefully evaluated. As such, we have provided some important questions in the consideration for LQTS diagnosis (**Figure 3**). Some tips to consider include the following: 1) QT prolongation does not necessarily equal LQTS; 2) a computer- or physician-measured QTc interval must be vetted carefully to ensure that the U-wave or wide QRS complex is not included in the calculation; 3) a variant positive genetic test result does not mean definitive disease (ie, the phenotype is crucial); and 4) family history should be evaluated for LQT-specific factors.

STUDY LIMITATIONS. There are several potential limitations related to the retrospective design of this study. First, the quality of the data reviewed varied from source to source. We minimized any potential confounders by including only patients who had a detailed record of a referral diagnosis of LQTS with a clear reason prompting that diagnosis. Furthermore, approximately 20% of the patients were self-referred to Mayo Clinic, whereas the remaining 80% were referred by a physician, although no striking clinical differences were found between the 2 groups (**Table 1**). This can lead to an overrepresentation of the apparent frequency of overdiagnosed LQTS because the referring physicians may not have been confident in their clinical assessments and thus sought a second opinion. However, all patients who were included in this cohort received a diagnosis, were risk stratified, and were treated locally as if they had LQTS whether they were self-referred or physician referred. Finally, although significant numbers of patients (16%) evaluated for LQTS were subsequently dismissed as having normal findings, it is important to remember the bias that may be represented here because Mayo Clinic is a tertiary or quaternary referral center for LQTS. Thus, caution must be taken to avoid misdiagnosing LQTS, as well as missing a diagnosis of LQTS.

CONCLUSIONS

Overall, we have identified and illuminated the various reasons that can lead to an erroneous overdiagnosis of LQTS. Some of the main determinants of discordance between a previously rendered diagnosis of LQTS and full diagnostic reversal or removal were vasovagal syncope, a variant positive genetic test result in 1 of the LQTS-causative genes, a family history of sudden death, isolated QT prolongation, and misinterpretation of the QTc interval. Awareness of these causes, as well as an understanding of screening strategies that can be fine-tuned to reduce this ongoing burden of overdiagnosed LQTS, will be crucial in the clinical setting. Finally, although missing a patient who truly has LQTS can lead to a tragic outcome, the implications of overdiagnosed LQTS are not trivial and are potentially tragic as well.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Evaluation of the phenotype is at least as important as genetic testing to avoid diagnosis of LQTS in patients at little or no risk of disease-associated events.

TRANSLATIONAL OUTLOOK: Research is needed to identify novel biomarkers that predict risk of adverse clinical events associated with LQTS.

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APPENDIX For supplemental tables, please see the online version of this paper.