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Development and early evaluation of clinical decision support for long QT syndrome population screening

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Abstract

Aim: Long QT syndrome (LQTS) is an inherited condition that predisposes individuals to prolongation of the QT interval and increased risk for Torsade de Pointes. Pathogenic variants in three genes - *KCNH2*, *KCNQ1* and *SCN5A* - are responsible for most cases of LQTS, and recent advances in genetic testing have improved knowledge of the disease, increased access to follow-up, and reduced adverse cardiovascular outcomes.

Methods: Based around our preemptive genetic screening platform which includes the three long QT genes listed above, we developed and implemented a clinical decision support (CDS) module that alerts prescribers whenever a QT-prolonging medication is ordered for patients with a genetic predisposition to LQTS.

Results: Of the 13,777 individuals screened, twenty-seven tested positive for a pathogenic or likely pathogenic variant of *KCNH2*, *KCNQ1* or *SCN5A*. In a subsequent early evaluation of the CDS and clinical processes, the number of QT-prolonging medications in this cohort decreased by 20% and new QT-prolonging medications were avoided in approximately 1/3 of new prescription orders.

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Conclusions: While long-term evaluation is needed, early data support the benefit of utilizing CDS in expanded roles, such as drug-gene-disease interactions where rare genetic variants intersect with everyday prescribing.

Keywords: Brugada syndrome, clinical decision support (CDS), long QT syndrome (LQTS), pharmacogenomics

INTRODUCTION

One out of 2000 individuals has an inherited risk for prolonged QT interval, known as Long QT syndrome (LQTS)[1]. Three genes - *KCNH2*, *KCNQ1* and *SCN5A* - account for approximately 75% of genetically identifiable cases[2,3]. LQTS is classified into types based on a particular gene: Long QT Type 1 (LQT1; OMIM 192500) is associated with *KCNQ1*, LTQ2 (OMIM 613688) is associated with *KCNH2*, and LQT3 (OMIM 603830) is associated with *SCN5A*. *SCN5A* can also manifest as Brugada syndrome (OMIM 601144), which has a similar but unique clinical presentation and treatment options. Gain-of-function variants in *SCN5A* lead to more sodium influx into cardiomyocytes through aberrant channel gating and cause LQTS, a primary electric disease of the heart. Loss-of-function variants in *SCN5A* lead to lower expression of *SCN5A* or production of defective $Na_v1.5$ proteins and cause Brugada syndrome (BrS), an electrical disease with minor structural changes in the heart[4]. LQTS is characterized by delayed repolarization of the ventricular myocardium, QT prolongation (QTc > 480 ms as the 50th percentile among LQTS cohorts), and increased risk for Torsades de Pointes (TdP)-mediated syncope, seizures, and sudden cardiac death (SCD) in an otherwise healthy young individual with a structurally normal heart[5]. Given the life-threatening nature of these outcomes, the detection of at-risk individuals is of great clinical value.

The manifestations of LQTS are highly variable, even amongst family members with the same pathogenic variant, as a consequence of the low penetrance present in LQTS[6]. Therefore, management is focused on the prevention of syncope, cardiac arrest, and sudden death. Data suggests that medical management of patients with inherited risk for LQTS improves cardiac event outcomes. It is estimated that untreated patients have a mortality rate of about 20% within the first year[7]. However, patients receiving treatment and follow-up have demonstrated fewer breakthrough cardiac events and a lower risk of SCD in LQTS. Among treated LQTS patients, annualized rates of SCD range from 0.05% to 1.3%[8]. While there are many factors influencing these outcomes, early detection, referral to specialty care, and appropriate treatment likely play a major role in improving outcomes.

The key modalities for treatment of LQTS include pharmacotherapy with beta-blockers and procedural intervention via either implantable cardioverter-defibrillator (ICD) or left cardiac sympathetic denervation (LCSD). An expert consensus statement outlining how to diagnose and treat individuals with hereditary LQTS recommends beta-blockers first-line in patients with a diagnosis of LQTS who are asymptomatic with QTc > 470 ms and/or symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF)[9]. Beta-blockers are useful in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤ 470 ms based on American College of Cardiology/American Heart Association Clinical Practice Guidelines. Recommended beta blockers per the ACC/AHA clinical guidelines include propranolol and nadolol[10]. ICD implantation is recommended in patients with a diagnosis of LQTS who are survivors of sudden cardiac arrest. ICD implantation may also be considered in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy[9]. For individuals who are intolerant to or incompletely treated by beta blockers, LCSD has also shown benefits in reducing cardiac events[11-13]. Lifestyle modifications are often encouraged in addition to treatment. Awareness of potential triggers - strenuous exercise, emotional stress, auditory stimuli (for LQT2), and dietary monitoring - can help reduce

the risk for cardiac events, though the overall frequency of routine life events precipitating arrhythmias appears to be relatively low[14]. Individuals with *KCNH2* pathogenic variants should reduce exposure to loud, sudden noises such as alarm clocks.

Another benefit of early detection is the ability to prevent medication administration of agents known to further prolong the QT interval. Drugs that cause further prolongation of the QT interval or provoke TdP should be avoided, if possible, for all individuals with LQTS. The website CredibleMeds.org (CredibleMeds®) curates a complete and updated list of medications to avoid in individuals with LQTS, and Brugadadrugs.org maintains a list of medications to avoid in individuals with BrS. In situations where medications known to prolong the QT interval cannot be avoided, such as specific oncologic treatments, knowledge of the genetic predisposition can also be of great value in that additional monitoring could be utilized.

Health care workers in all clinical settings routinely evaluate patients for multiple factors, including drug-drug interactions, drug-gene interactions, allergies, dosing recommendations based on age, organ function, or disease states as part of their routine workflows. This is largely facilitated by electronic medical record (EMR) functionality. As our understanding of an individual's clinical picture expands to include genomic data such as variants which lead to prolonged QT, EMR functionality can be leveraged to facilitate provider use of this critical information in any clinical setting. Multiple medications cause QT prolongation making preemptive genomic screening for LQTS quite significant to clinical practice. The knowledge that a patient is predisposed to QT prolongation provides an opportunity at the time of prescribing to order additional tests or to change to alternate therapies as appropriate. Understanding that physician, advance practice provider, pharmacist, and nurse roles and availabilities vary across patient appointment types and clinical settings, we developed methodology that can be adapted to care across multiple points of patient contact.

METHODS

Implementation processes

In 2018, Sanford Health launched a precision medicine program - Imagenetics - aimed at preemptive identification of genetic variants for medically actionable predispositions (MAP) and pharmacogenomic (PGx) variants with the Sanford Chip. Using a high-throughput single nucleotide polymorphism (SNP) genotyping platform with custom content (Infinium Global Screening Array, Illumina, San Diego, CA), results are reported for pathogenic and likely pathogenic variants detected in selected genes associated with predispositions to a variety of health conditions, including LQTS, BrS, cardiomyopathy, familial hypercholesterolemia, and several familial cancers[15,16]. Sanford Imagenetics also utilized a commercial vendor (Color Health, Burlingame, CA) for roughly 1000 patients in lieu of the screening array as a pilot project for next-generation sequencing for both PGx and disease predisposition testing. Eligible patients for the Sanford Chip or Color Health testing included patients 18 years or older who had a primary care provider within Sanford Health and were active users of our EMR patient portal. The test was offered preemptively as a screening tool within the context of outpatient primary care and not as a diagnostic test. The results are stored as discrete data within the laboratory information section of the EMR allowing for clinical decision support (CDS) to fire for MAP and PGx actionable results at the time of therapeutic choice (prescribing). All patient encounters - including initial genetic testing, primary care follow-up, genetic counselor appointments, and cardiology consults - were conducted in the outpatient setting.

Since our platform captures information about both PGx and genetic predisposition to disease, we identified opportunities to leverage the capabilities of both areas. LQTS, in particular, was identified as an area where CDS could be used as an active alert system with the EMR. Therefore, we implemented a system

of CDS alerts to notify prescribers if a high-risk medication was ordered for individuals with a predisposition to either LQTS or BrS. Our team elected to utilize both crediblemeds.org and brugadadrugs.org as clinical references for CDS. The PGx team reviews these lists at scheduled intervals as well as subscribes to updates to ensure our lists remain up to date. Provider and pharmacy education was provided on instances when CDS would generate, which includes an alert specifically triggered upon a pharmacist opening a chart encounter. Additional pharmacy education was provided on specific inpatient interventions with templated documentation to guide possible interventions to address additional risk factors for QT prolongation, such as electrolyte disturbances.

Given the significant impact certain medications may have on a patient's QT interval, it is vital that real time decision support is available to both prescribers and pharmacists involved in the care of the patient. Due to the severity of the consequences of a prolonged QT interval, including the risk of death, CDS must be actionable (real-time and highly reliable). Frontline staff would be alerted when prescribing a medication with the potential to prolong the QT interval in patients who tested positive for genetic variants associated with LQTS shown in Figure 1, top panel. Our initial approach consisted of utilizing medications curated at CredibleMeds® to review for QT prolongation potential; however, after working with our genetics team, we later also added medications curated at Brugadadrugs.org for individuals who may also be at risk for BrS shown in Figure 1, center panel. Additionally, an advisory based on the genetic variants regardless of medication ordering was created to facilitate pharmacists to conduct a comprehensive review shown in Figure 1, bottom panel. The comprehensive review is supported through a pharmacist intervention workflow which prompts a review of patient characteristics that may prolong the QT interval, such as medications, electrolyte abnormalities, history of cardiac abnormalities, blood glucose, gastrointestinal distress, and vital signs. In addition, a pharmacist on the PGx team will review all patients with a positive variant and provides medication recommendations to the primary care provider in patients not admitted to the hospital.

CredibleMeds® (Available from: https://www.crediblemeds.org/) and BrugadaDrugs.org (Available from: https://www.brugadadrugs.org) were chosen as primary medication references, given the comprehensive material and well-curated information. Our standard process is to review medications that would trigger these alerts quarterly and as needed with any updates to the lists or additional data available. At the time of writing, we have made twelve revisions since the implementation of these interruptive alerts in July 2019. A recent update included collaboration between the PGx and research pharmacy teams to include investigational medications that have warnings about QT prolongation. The CDS triggers on all medications are listed as medications to be avoided in patients with LQTS.

These alerts were approved by interdisciplinary committees (Clinical Decision Support Committee and Pharmacy Optimization Committee) prior to implementation. Education was provided to frontline staff via newsletters. Additionally, education was provided to inpatient pharmacy staff across the Sanford Health institution regarding the disease state as well as modifiable risk factors and treatment. Staff development was presented by a member of the PGx team, and references were made available via the internal website to be available in real time for pharmacy staff.

Cohort evaluation

Following implementation and clinical utilization, we sought to complete a retrospective periodic evaluation of the LQTS CDS alert system. The study was reviewed and approved by the Sanford Health Institutional Review Board (study #00002071). The primary objective of our review was to describe basic demographics and clinical processes related to LQTS or BrS in a cohort of patients undergoing preemptive genetic

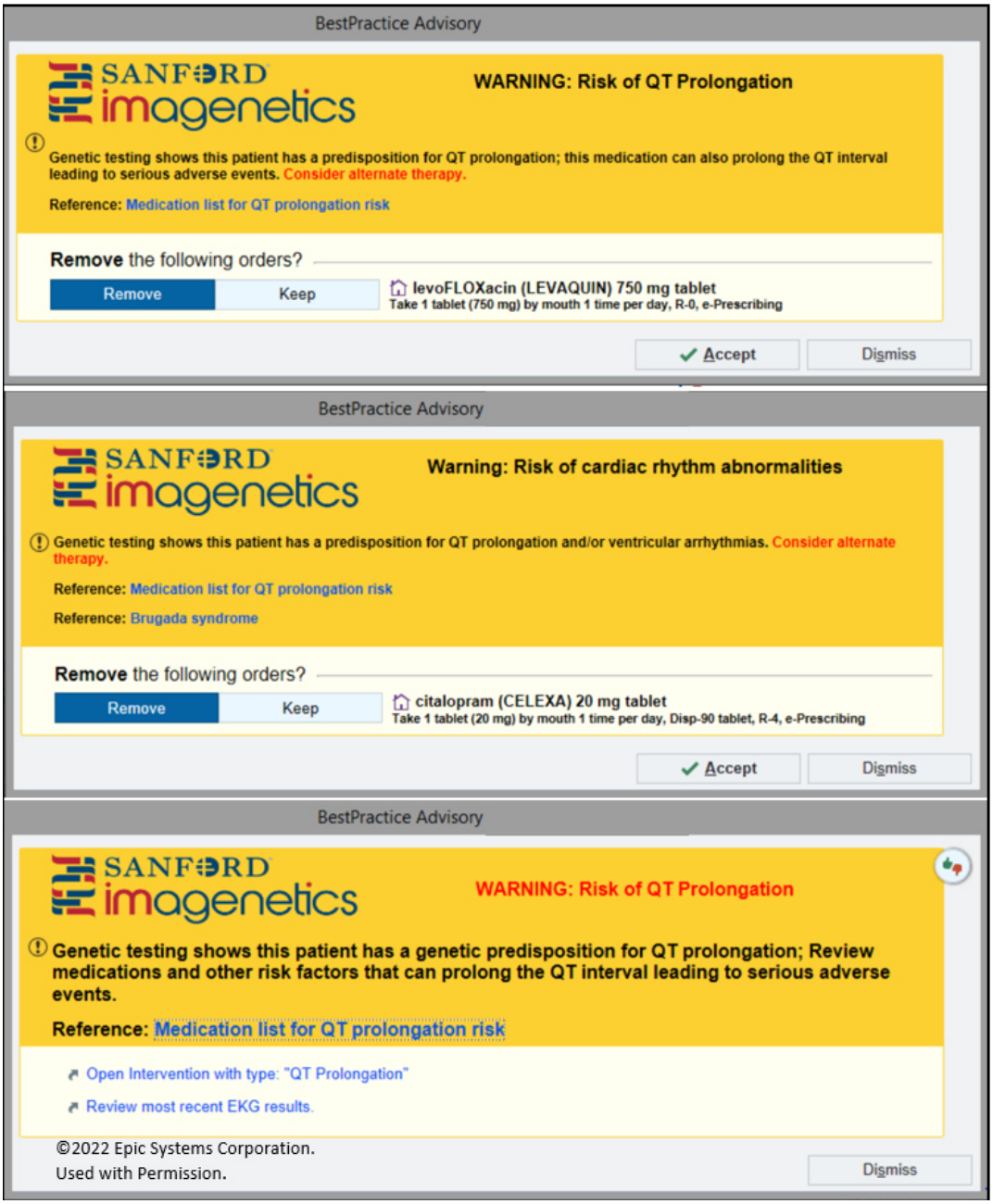

Figure 1. CDS Alerts developed for Long QT (LQTS)and Brugada Syndrome (BrS). Top panel: Alert encountered by frontline staff when placing an order for a medication which may prolong QT interval. Center panel: Alert encountered by frontline staff when a potential medication could precipitate a cardiac rhythm abnormality. Bottom panel: Alert generated upon pharmacist entry into a patient's chart in which a patient has a genetic variant for LQTS or BrS

screening. Secondary objectives were (1) To determine whether receipt of genetic results impacted the number of QT-prolonging medications in individuals with pathogenic or likely pathogenic variants for LQTS or BrS; and (2) to assess whether CDS impacted medication adjustment and future selection of medications. Data was collected from existing records in our EMR from the earliest available electronic records (approximately 2010) through October 31, 2021. All individuals with a pathogenic or likely pathogenic variant of *KCNH2, KCNQ1* or *SCN5A* were included in the evaluation cohort. Due to the low

prevalence of positive genetic variants in our population, the demographics reported were constrained to age and sex.

We used a combination of automated data query and manual chart review to collect data. Demographics and genetic testing results were assessed descriptively. In order to assess medication changes pre- and post-genetic testing, we reviewed the active medication list immediately prior to genetic testing results (i.e., pre-genetic testing) and compared those against the medication list following the first consult visit. Any medications determined to be QT-prolonging (per Brugadameds.org or CredibleMeds) at both time points were counted. A t-test was used to compare the average number of QT-prolonging medications pre- and post-testing. Consult visits, procedural records, and electrocardiogram (ECG) data were collected and analyzed using descriptive statistics.

To evaluate the impact of CDS on prescribing practices, we compiled a list of all Long QT alerts that were triggered from the time of implementation; this list contained the alert type, patient identifier, provider name, and action taken. Using this list, we reviewed all patient encounters - clinic or hospital visit -- during which a Long QT alert was triggered. If by the close of the encounter, no new QT-prolonging medications were ordered, it was inferred the alert was *accepted* by the provider. If a QT-prolonging medication was newly ordered or reordered (i.e., refilled), the alert was deemed *rejected* by the provider. Some orders were particularly difficult to quantify. For instance, the EMR does not record the medication name on the CDS alert report, and an additional manual chart review was needed to exactly determine which medications caused the alert to fire. Additionally, given the routine use of order sets (which could include multiple QT-prolonging medications) in the inpatient encounters, there were some instances in which multiple concurrent medications could trigger a CDS alert. In the event that a CDS alert could not be associated with a specific medication, it was classified as unknown. Descriptive statistics were used to assess this data.

RESULTS

Our initial EMR query yielded a total of 13,777 patients who had received preemptive genetic screening that included medically actionable predispositions. Of these, a cohort of 27 individuals (1 in 510) were found to have a pathogenic or likely pathogenic variant of *KCNH2*, *KCNQ1* or *SCN5A*. The cohort was predominantly female (81.5%) with an average age of 54. The median duration of observation for this study was 19 months (range 2.9-38.6 months). Basic demographic data and a list of the genes for the entire cohort can be found in Table 1. Of the 27 individuals included in this review, 51% (n = 14) were found to have a variant in *KCNQ1*; all but two *KCNQ1* variants were deemed pathogenic. *SCN5A* and *KCNH2* accounted for 37% (n = 10) and 11.1% (n = 3) of the discovered variants, respectively. Due to the relatively high frequency of pathogenic variants in this population, an additional review was performed to determine whether individuals with positive variants were related. We found one pair of second-degree relatives within the *KCNQ1* variant group and another pair of first-degree relatives within the *SCN5A* variant group. To the best of our knowledge, no other individuals in the study were related.

Within the study cohort, 24 individuals received ECG monitoring secondary to the genetic testing result. On ECG, the median QTc was 460 ms (range: 400-512 ms), with sixteen individuals at or above 450 ms. Two individuals were noted to have QTc above 500 ms. Post-testing ECG was compared against baseline ECG; no statistical difference was noted (data not shown). Six patients were subsequently diagnosed with clinical LQTS: three were started on beta-blocker therapy at the time of cardiology consult, two have received no beta-blockers to date, and one had a previous intolerance to beta-blocker therapy. After developing significant QT prolongation on the stress test, this individual was subsequently started on a beta-blocker.

Table 1. Pathogenicity and Frequency of LQTS and BrS variants encountered in preemptive screening population

Gene	Positional change	Protein change	Pathogenicity[†]	*N* (%)
KCNH2	c.98A>C	N33T	Likely pathogenic (LQT2)	2 (7.4)
	c.2145G>A	A715=	Likely pathogenic (LQT2)	1 (3.7)
KCNQ1	c.477+5G>A	Intron variant	Pathogenic (LQT1)	3 (11.1)
	c.535G>A	G179R	Pathogenic (LQT1)	1 (3.7)
	c.1552C>T	R391*	Pathogenic (LTQ1)	4 (14.8)
	c.1588C>T	Q403*	Pathogenic (LQT1)	3 (11.1)
	c.1792_1793del	K598fs	Likely pathogenic (LQT1)	2 (7.4)
	c.1893dup	R632fs	Pathogenic (LQT1)	1 (3.7)
SCN5A	c.673C>T	R225W	Pathogenic (BrS or LQT3)	1 (3.7)
	c.2582_2583delTT	F861fs	Pathogenic (BrS)	1 (3.7)
	c.3911C>T	T1304M	Likely pathogenic (LQT3)	7 (25.9)
	c.3926G>A	R1309H	Likely pathogenic (BrS)	1 (3.7)

[†]Associated clinical subtype is denoted. Certain variants in SCN5A can manifest clinically as either Brugada or Long QT Syndrome. The "=" means a silent or synonymous change in the amino acid. The "*" denotes missense variant, a change to a stop codon which truncates the protein.

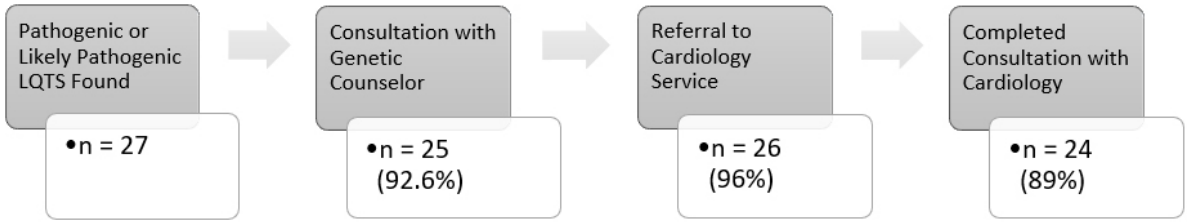

Figure 2. Patient referrals and consults following receipt of pathogenic or likely pathogenic results.

Following the identification of the study cohort, we completed a review of new consults, procedures, and medications specifically ordered in response to pathogenic/likely pathogenic results. A consult flow diagram is displayed in Figure 2. Nearly all patients (25 of 27, 92.6%) received a follow-up consultation visit with a genetic counselor to review the results and address questions. Patients were further referred to cardiology, and as of the time of data collection, 24 (89%) patients had either been seen by a cardiologist or had an appointment pending. Only one patient had previously established care with a cardiologist, and prior to testing, there was no documented history of LTQS or BrS. The median time from discovery of a pathogenic variant to cardiologist follow-up was 38 days (range: 14-109 days). There have been no subsequent referrals to medical genetics for follow-up.

During follow-up evaluation, additional testing was ordered on most patients [Table 2]. The most common were echocardiogram, stress tests, and Holter monitoring, accounting for 52%, 22%, and 22% of patients, respectively. No deaths, ventricular arrhythmias, or significant cardiovascular events have been reported in any patients in the study cohort since receiving genetic testing results. Notably, upon a detailed review of consult notes, ECG results, and diagnostic codes, none of the patients carrying an *SCN5A* pathogenic/likely pathogenic variant were found to have BrS. However, three individuals in the study carry an *SCN5A* variant associated with BrS. Two variants (c.2582_2583delTT and c.3926G>A; 2 patients) are associated solely with BrS, and one variant (c.673C>T; 1 patient) has evidence linking it to either BrS or LQTS.

Table 2. Description of additional care received following receipt of genetic results

Modality of care	Events *n* (%)
Provider consultations	
Genetic counselor	25 (92.6%)
Cardiology	24 (89%)
Medical genetics	0 (0%)
Additional testing	
Echocardiogram	14 (52%)
Stress test	6 (22%)
Zio patch/holter monitor	6 (22%)
Tilt table procedure	1 (4%)
Calcium score	2 (7%)
Medications changes	
Discontinued 1+ QT-prolonging medication	6 (22%)
Addition of beta-blocker	2 (7%)

Medication changes were relatively uncommon following receipt and evaluation (through cardiology consultation) of genetic testing results. The key modality of LQTS treatment - beta-blockers - were added for two patients. Considering that two other patients were previously prescribed a beta-blocker, a total of 4 (15%) patients for whom beta-blockers were clinically indicated were taking a beta-blocker by the end of the present evaluation period. However, there have been several QT-prolonging medications (per CredibleMeds.org criteria) that were discontinued following genetic testing; a total of eight medications (tizanidine, sertraline x2, fluconazole, amiodarone, esomeprazole, omeprazole, hydroxychloroquine) were discontinued from six patients. The mean number of QT-prolonging medications decreased from 1.48 to 1.19 [$P = 0.0352$, Figure 3].

CDS acceptance

Long QT CDS alerts were implemented in July 2019; since then, 264 unique alerts have been triggered for 22 patients. Ninety-eight patient encounters were identified, during which at least one CDS alert was fired. Alerts were accepted in 30% (29 of 98) of encounters, and 91% ($n = 89$) of alerts occurred in the outpatient setting (typically primary care). Among all encounters, there was a total of 138 medications that fired a Long QT alert. The median number of alerts per encounter was 2 (range: 1-14); however, among inpatient-only encounters, the median increased to 5 (range 2-14). The rationale for acceptance or rejection of the alert was not possible in most cases due to the scope of this preliminary review. However, anecdotally there were multiple instances in which "new" QT-prolonging medications led to increased monitoring (e.g., ECG) or discussion with the cardiology team.

Medications linked to LQTS alerts were categorized by class and this data is summarized in Table 3. Amongst all medication orders associated with a LQTS alert ($n = 138$), 29% of medications were ultimately not ordered, which was classified as an "Accepted" alert. Conversely, medications that were ordered despite a LQTS alert (i.e., "Rejected") accounted for 71% of all alerts. Numerically, there appeared to be no difference between prescriber acceptance rates in the outpatient versus inpatient procedural setting. In the outpatient setting, refill medication orders tended to be rejected at a higher frequency (43%) than new medication orders (27%). There were a few notable outliers in prescriber actions, namely a high rejection rate for mental health medication refills in the outpatient setting and a high rejection rate for antiemetics in the inpatient procedural setting. Alert acceptance rates were highest among acid suppression and weight loss medications in the outpatient setting - both ≥ 40%.

Table 3. Prescriber action taken on medications following LQTS BPA

Medication class	Accepted	Rejected - new	Rejected - refill
Outpatient (*n* = 98)	29 (30%)	27 (27%)	42 (43%)
Acid suppression/GI	8	6	6
Antiemetic	3	1	6
Antimicrobial	2	5	1
Chemotherapy	0	0	4
Hypertension	0	2	2
Mental health	5	4	12
Nasal/allergy	5	7	4
Opioid	2	1	4
Weight loss	3	1	3
Unknown/other	1	0	0
Inpatient procedural orders (*n* = 40)	11 (28%)	29 (73%)	-
Acid suppression/GI	1	2	-
Antiemetic	2	10	-
Antihistamine	3	1	-
Antimicrobial	0	6	-
Sedative	0	5	-
Vasopressor	2	5	-
Unknown/other	3		-
All orders (*n* = 138)	40 (29%)	98 (71%)	

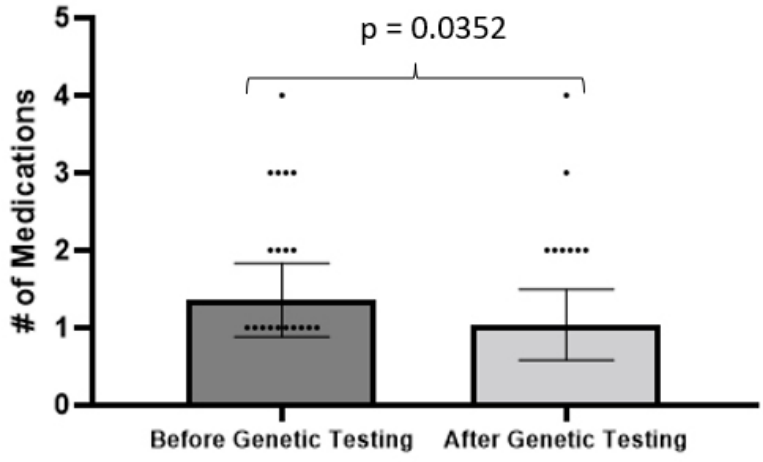

Figure 3. Average number of QT-prolonging medications pre- and post- LQTS genetic testing.

DISCUSSION

In the present manuscript, we describe the implementation process and early evaluation of CDS for three genes predisposing patients to LQTS. This system is designed to notify physicians and advanced practice providers in the event they attempt to prescribe a medication likely to prolong the QT interval. Since implementing our preemptive genetic screening platform in 2016 and the CDS process in 2019, we have identified 27 patients with pathogenic or likely pathogenic variants of *KCNH2*, *KCNQ1* or *SCN5A*. Notably, the overall prevalence of a pathogenic or likely pathogenic variant within our genetic screening population was 1:510, which is substantially more common than previous reports. The majority of patients with a

genetic variant have received additional monitoring and follow-up by a genetic counselor and a cardiologist, and a diagnosis of clinical LQTS has been made for six of the patients. To date, no significant cardiovascular events or deaths have been reported.

Pharmacotherapy plays a vital role in both treatment and avoidance events in patients with LQTS or BrS. Beta-blockers, which are considered the mainstay of preventative therapy, were prescribed for 4 of 6 patients diagnosed with *clinical* LQTS. Avoidance of events is a far more difficult metric to quantify, though our early evaluation has shown that CDS alerts prevent some new QT-prolonging medications and decrease the overall number of active QT-prolonging medications. The CDS was triggered during 98 unique patient care visits (among 22 of the 27 patients) and at least one QT-prolonging medication (new or continuing) was avoided in nearly one third of those visits. Twenty-nine percent of all medications which received a CDS alert were accepted, with the highest acceptance rate in acid suppressing and weight loss medications. In addition, the total number of QT-prolonging medications among all members of the LQTS cohort decreased from 1.48 to 1.19, which was statistically significant. We infer from these data that the interventions - genetic screening, consultative follow-up, and CDS - have a positive short-term impact on medications implicated in LQTS prevention.

There are several limitations that should be addressed with both our implementation and assessment processes. First, the small population and relatively short length of follow-up for this cohort limit the ability to assess major clinical outcomes. Furthermore, the lack of a true comparator group and the retrospective nature of our evaluation permit only associative findings. While we have demonstrated a trend toward avoidance of QT-prolonging medications, the clinical relevance of these numbers is difficult to assess. Our findings should, therefore, be considered hypothesis generating. A more formal evaluation is anticipated as the number of patients in this cohort increases over time. Second, CDS processes are inherently difficult to evaluate unless designed specifically for research evaluation. Since our CDS was designed with the clinical user (i.e., prescriber) in mind, the alerts do not directly associate with some important data fields used in research. For instance, we could not identify some medications flagged by the alerts if the prescriber did not sign the order, which would be the preferred outcome of medication avoidance. It was also difficult to associate alerts with medications when multiple medications were ordered at the same time, such as on order sets or inpatient medication protocols. We were able to manually associate most alerts with medications due to strong clinical documentation, but the scope of future assessment may make this untenable. Finally, the consultative processes and the CDS, while part of an overarching preemptive genetic screening platform, are separate functions and can independently impact medication use and clinical outcomes. Generally, medications used for treatment (e.g., the addition of beta-blockers) came about through consultation and specialist assessment and medication avoidance (e.g., withholding medications after an alert is triggered) resulted from the CDS. However, parsing out the clinical impact of these different functions will involve a more nuanced evaluation. The authors acknowledge the confounding factors in the present assessment, though the overall implementation of preemptive genetic screening for LQTS genes with CDS support does appear to identify and decrease the use of potential interacting medications.

While some institutions have implemented systems designed to alert providers when patients have documented a history of QT prolongation, to our knowledge, no other published literature describes CDS for QT prolongation that directly includes genetic variants of *KCNH2*, *KCNQ1* or *SCN5A*[17,18]. Previously published studies examining prescribers' responses to QT prolongation included QTc > 500 ms and QT-prolonging medications. An antiemetic decision tool alert for postoperative nausea and vomiting described by Hymel and Davies advised prescribers to "Avoid in Congenital Long QT Syndrome" but did not trigger based on genes that put a patient at increased risk for congenital LTQS (cLQTS)[19]. In 2016, Schwartz and

Woosley suggested that future CDS for LQTS should consider including genetic and clinical predictors of LQTS[20]. A 12-year-old child with cLQTS was prescribed azithromycin and died as a result of TdP leading to AV-block associated with QT prolongation[21].

In addition to genetics and medications, hypokalemia, hypomagnesemia, hypocalcemia, hypothyroidism, hypothermia, and extreme bradycardia are factors for LQTS potentially leading to TdP. An ideal alert would include multiple clinical factors including the most recent ECG data. Balancing the complexity of building an alert with succinct but informative CDS, our alerts inform prescribers of the risk for prolonged QT due to genetic and medication factors, and they allow pharmacists reviewing the medication to select to review most recent ECG results and/or open a QT prolongation intervention to address additional modifiable risk factors. This approach allows for pharmacists to further investigate other factors that could contribute to prolonged QT and make recommendations accordingly.

This manuscript provides a roadmap for the implementation of genetic screening CDS to address complex drug-gene-disease interactions. Our preemptive genetic screening platform tests for both an 11-gene PGx panel as well as a MAP portion including 57 genes curated from the American College of Medical Genetics (ACMG) list of secondary findings. Some of the recommendations for positive MAP variants have significant overlap with pharmacy. *CACNA1S* and *RYR1* are included in the ACMG list of secondary findings[22]. Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidelines for *CACNA1S* and *RYR1* variants associated with Malignant Hyperthermia Syndrome, stating certain anesthetics are contraindicated in such patients. Sanford Imagenetics deploys alerts based on these findings; a description of this process has been published elsewhere[23]. Pharmacists can help with therapeutic recommendations for patients with familial hypercholesterolemia genes of *APOB* and *LDLR*. *KCNH2*, *KCNQ1*, or *SCN5A* are also included in the ACMG list, though no current associated CPIC guidelines exist to date. Identifying risk factors for QT prolongation is important given the potential severity of adverse events.

Finally, it should be noted that our approach utilizes clinical pharmacists with specialty training in pharmacogenomics to review PGx results, make medication recommendations, and assist prescribers when questions arise. Many health systems do not employ PGx pharmacists, and while we strongly endorse the use of pharmacists for PGx and drug-gene-disease interactions, medical geneticists and genetic counselors can be used in this capacity. Pharmacists and providers should be aware of the risk of QT-prolonging medications in general, but a heightened awareness should be employed for a patient with a genetic predisposition to QT prolongation. Having CDS alerts in place are a patient safety measure to help alert providers and pharmacists to the potential for additive risk.

DECLARATIONS

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Authors' contributions

Designed study: Baye J, Massmann A, Petry N, Van Heukelom J, Schultz A, Hajek C
Completed data collection: Baye J, Massmann A, Petry N, Schultz A, Van Heukelom J
Analyzed and interpreted data: Baye J, Massmann A, Petry N, Van Heukelom J
Wrote manuscript: Baye J, Massmann A, Petry N, Van Heukelom J, De Berg K, Schultz A, Hajek C

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
These alerts were approved by interdisciplinary committees (Clinical Decision Support Committee and Pharmacy Optimization Committee) prior to implementation. The study of cohort evaluation was reviewed and approved by the Sanford Health Institutional Review Board (study #00002071). Waiver of consent was granted for this study.

Consent for publication
Not applicable.

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