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Challenges and opportunities for integrating genetic testing into a diagnostic workflow: heritable long QT syndrome as a model

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Abstract

Background: An increasing number of diagnostic evaluations incorporate genetic testing to facilitate accurate and timely diagnoses. The increasing number and complexity of genetic tests continue to pose challenges in deciding when to test, selecting the correct test(s), and using results to inform medical diagnoses, especially for medical professionals lacking genetic expertise. Careful consideration of a diagnostic workflow can be helpful in understanding the appropriate uses of genetic testing within a broader diagnostic workup.

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Content: The diagnosis of long QT syndrome (LQTS), a life-threatening cardiac arrhythmia, provides an example for this approach. Electrocardiography is the preferred means for diagnosing LQTS but can be uninformative for some patients due to the variable presentation of the condition. Family history and genetic testing can augment physiological testing to inform a diagnosis and subsequent therapy. Clinical and laboratory professionals informed by peer- reviewed literature and professional recommendations constructed a generalized LQTS diagnostic workflow. This workflow served to explore decisions regarding the use of genetic testing for diagnosing LQTS.

Summary and outlook: Understanding the complexities and approaches to integrating genetic testing into a broader diagnostic evaluation is anticipated to support appropriate test utilization, optimize diagnostic evaluation, and facilitate a multidisciplinary approach essential for achieving accurate and timely diagnoses.

Keywords

arrhythmias; diagnosis; genetic testing; long QT syndrome

Introduction

A 2015 National Academies report, *Improving Diagnosis in Healthcare*, reported that as many as 5% of US adults receiving outpatient healthcare experience a diagnostic error [1, 2]. The report emphasizes the need to improve healthcare provider collaboration, patient engagement, and processes. This is particularly true for molecular genetic testing, where selection of the most appropriate test and interpretation of results requires specialized knowledge. As of 2019, molecular genetic testing is invaluable in diagnosis and management of cancer, cardiomyopathy, intellectual disability, rare diseases of unknown etiology, and other conditions [3–6].

Integrating genetics into the diagnostic workflow can provide valuable insights into the diagnosis and management of the patient. However, the application of genetic principles, knowledge of familial health conditions, and understanding the uses and limitations of laboratory tests introduces complexity to the diagnosis that requires an integrated, coordinated, multidisciplinary approach to achieve an accurate and timely diagnosis. There are lessons for clinicians, laboratory professionals, and others in exploring a representative diagnostic workflow that illustrates challenges and approaches to patient care when genetics, which includes genetic testing, is a component of the diagnostic process. A diagnostic workflow for long QT syndrome (LQTS), a condition predisposing to lethal cardiac arrhythmia, and sudden cardiac death, provides a good model for exploring these issues (Figure 1). The peer-reviewed literature and input from this manuscript's co-authors that included board-certified cardiologists, clinical and laboratory geneticists, and a genetic counselor informed the presentation of this workflow developed to reflect a realistic diagnostic evaluation that accommodates expected variations in practice [7–15].

LQTS is an arrhythmia disorder of cardiac action potential repolarization characterized by the prolongation of the QT interval. LQTS may manifest with polymorphic ventricular tachycardia, ventricular fibrillation, and sudden cardiac death in otherwise young and

healthy children and adults [16]. LQTS provides a good diagnostic model because of the following:

- LQTS is clinically well defined and life threatening.
- LQTS is variable in presentation, making diagnosis and management challenging.
- Physiological testing is sufficient to make a diagnosis of LQTS.
- There are life-saving interventions.
- It is important to distinguish heritable from acquired (e.g. drug-induced) during the diagnostic evaluation.
- DNA testing can inform a diagnosis when physiologic testing is uninformative.
- Physiological and DNA testing are used to determine LQTS subtypes that may influence the choice of therapy.
- Genetic test results can be useful to identify affected relatives.
- Professional guidance is available to inform the clinical evaluation of patients with arrhythmias with specific reference to LQTS and use of genetic testing [13].

The variable presentation of LQTS can result in delayed or missed diagnoses [17]. Proper diagnosis of LQTS and subsequent therapy have been reported to reduce mortality to around 1% over a 10-year period [14]. In one report, 39% of patients with LQTS had delayed diagnosis after presentation; they received initial diagnoses of epilepsy, breath-holding attacks, and vasovagal syncope. Recognition of a family history of LQTS can be lifesaving as sudden cardiac death can occur at a young age in the absence of treatment [17]. Similarly, efficacious use of genetic testing is useful to establish a diagnosis, identify disease subtypes that can influence therapy selection, and to identify other family members at risk for LQTS. In summary, LQTS is a highly variable genetic condition for which there are physiological diagnostic criteria, and for which DNA testing is useful for diagnosis, therapy selection, and identifying risk to other family members.

Clinical and genetic aspects of LQTS

Criteria for diagnosing LQTS are established (Table 1) [13]. LQTS can be heritable or acquired. Medication-induced acquired LQTS is the most common cause of the acquired form. Acquired LQTS is more frequent than the heritable form. In some instances, it may be challenging to differentiate the heritable from acquired forms of LQTS because exposure to a trigger associated with acquired LQTS may uncover previously undiagnosed LQTS [18].

Prevalence of heritable LQTS in the US is approximately 1:2500 [19]. Sequence variants in LQTS genes are present at higher rates in sudden cardiac death cohorts without known heart disease [20]. Pathogenic sequence variants associated with cardiac ion channels or their underlying structural or trafficking apparatus can cause heritable LQTS with three genes (responsible for LQTS subtypes 1–3) responsible for approximately 90% of genotype-positive LQTS and another 12 genes accounting for <5% of the remaining cases [7, 9, 13].

LQTS is typically autosomal dominant, but a rare form, Jervell-Lange Nielsen syndrome, is autosomal-recessive with a prevalence of ~1 in 4 million.

Approximately 50% of patients manifest non-specific symptoms associated with LQTS. Determination of a prolonged QT interval by an electrocardiogram (ECG) provides a definitive result but this test lacks sensitivity. Approximately 25% of patients diagnosed with LQTS have a normal QT interval at the time of testing [19, 21]. Genetic testing in combination with family history can assist in the diagnosis of heritable LQTS [10, 22] and identifying other family members at risk. Genetic testing is also useful to confirm or identify subtypes of LQTS that may inform the type of therapy administered (Table 1). Therapies include modification of exercise, avoidance of triggering stimuli, avoidance of QT prolonging medications, prescription of beta-blockers, placement of implantable cardioverter defibrillators, and surgical left cervicothoracic sympathetic ganglionectomy.

Walking through an LQTS diagnosis

It is instructive to walk through the diagnostic workflow depicted in Figure 1 after which a more in-depth discussion is presented that will explore the complexity of DNA testing as a component of the diagnostic process and insights useful for clinical practitioners. A hypothetical, but realistic, patient illustrates the application of the workflow.

Initial presentation

The clinical scenario begins with a 17-year-old male with loss of consciousness during basketball practice. He regains consciousness quickly and is evaluated in the emergency department (ED) at the local hospital. He says he takes no medication and is not aware of familial heart disease. The parents confirm this. There is no evidence of dehydration. ECG and electrolyte measurements are normal. The ED physician refers the patient to outpatient Cardiology and Neurology.

Outpatient follow-up

For the hypothetical patient, a neurologist found no evidence of neurologic cause. At the cardiology consult, parents are present. The patient has no prior medical history relevant to loss of consciousness. However, the cardiologist discovers the potential for a relevant family history for LQTS in learning about an uncle that died in an unprovoked collision involving a single vehicle who had a son that died in a witnessed pool drowning. Consultation with the physician who treated the uncle did not reveal any indication of an evaluation for a cardiac condition.

The patient’s ECG and echocardiogram test results are normal. The echocardiogram rules out structural heart disease and cardiomyopathy leaving arrhythmias, secondary to channelopathies that include LQTS, higher on the differential diagnosis. With the available clinical and family history data, a risk (Schwartz) score is calculated to estimate the likelihood of LQTS that for this case is low to intermediate [23]. Follow-up exercise testing (non-resting ECG) of the patient is equivocal. Because LQTS and several other arrhythmias are heritable, ECG testing of the parents may provide evidence for familial disease. Parental results are equivocal. The next step in the diagnostic workflow is Holter monitoring that

collects ECG data continuously for a period of 12–24 h [11]. In this hypothetical scenario, Holter monitoring does not resolve the diagnostic odyssey. These negative results reduce, but do not eliminate, clinical suspicion for LQTS.

Genetic testing with counseling is the final step in the workflow. Genetic testing can identify disease-associated sequence variants within genes associated with various arrhythmias that include LQTS. Discovering a pathogenic LQTS sequence variant supports a diagnosis for LQTS. On the other hand, the absence of a pathogenic finding does not exclude a diagnosis for LQTS.

Discussion

The emergency department encounter

Diagnosis, triage, and treatment of health conditions requiring immediate treatment is the primary focus of ED physicians. Diagnosing LQTS in the absence of physiological indications is challenging. ED clinicians do not generally have the time to collect a detailed family history because of competing priorities and multiple patients requiring the attention of ED clinicians [24, 25]. Molecular genetic tests for cardiac conditions are not typically ordered in ED settings because they do not inform management decisions in a timely manner and other, immediately useful, testing modalities are available (e.g. ECG). The ED physician refers the hypothetical patient to specialists for follow-up because clinical suspicion remains for a potentially serious health condition related to the patient's presentation.

The outpatient encounter with a cardiologist

The cardiologist collects a detailed family history at the beginning of the encounter. Cardiologists and many specialists receive training to recognize such clues as in our scenario where the single car collision and witnessed drowning raise suspicion for a familial cardiac condition. A family history may also be useful to identify relatives potentially affected with an arrhythmia from information provided by the patient. Acquiring a relative's medical information contained within their medical record to learn more is possible but can be challenging because policies at the patient's and relative's medical practice may restrict access until informed consent from the relative(s) is obtained and administrative processes completed. From a US federal regulatory perspective, the Health Insurance Portability and Accountability Act of 1996 (45 C.FR § 164.506) allows but does not require healthcare providers to voluntarily choose to obtain an individual's consent for it to use and disclose information about him or her for treatment, payment, and healthcare operations. Consulting with a genetic counselor can serve to expedite these processes. These professionals have specialized training to serve as a bridge between institutions, clinicians, patients, relatives, and administrators to facilitate informed consent processes and gain access to clinical data. For clinicians not having ready access to these professionals, the National Society of Genetic Counselors (http://www.nsgc.org, accessed May 22, 2019) links healthcare providers to genetic counselors as one of its services.

ECG results from the patient's parents can be useful toward identifying a familial condition. A parent diagnosed with LQTS raises the prospect and increases the pretest probability for the patient having this condition but in itself is not diagnostic for the patient [26]. Such testing may not be readily available for the parents. For example, access to testing can vary because insurers may not reimburse for this service. On the other hand, asymptomatic parents who are tested and diagnosed with a potentially serious cardiac condition may find access and cost to life insurance affected. Therefore, it is important to inform the parents about these issues related to the benefits and risks of potential findings.

Holter monitoring assesses the risk for an arrhythmia typically over a period of one or more days when other means have failed to identify the problem. While this seems ideal for a dynamic condition like LQTS, studies are lacking that describe the utility of Holter monitoring in terms of the diagnostic yield [8, 11].

The efficacy of available therapies for LQTS vary by disease subtype. ECG, including T-wave morphology and QT responses to exercise, can identify certain LQTS subtypes. Genetic test findings are also useful for assigning disease subtypes, which for LQTS may also direct genotype-specific medical therapy in some cases.

A presumptive diagnosis of LQTS is sufficient to prescribe therapy. Elements of the clinical presentation, family history, and physiologic test results can inform the making of a presumptive diagnosis in the absence of a definitive ECG result. A definitive diagnosis is sufficient to begin identifying other family members at risk for LQTS. Genetic testing results can confirm, but not preclude, a diagnosis for LQTS in the presenting patient [15, 19, 27]. Sequence analysis may also identify variants of unknown significance. As our understanding about the genetics of arrhythmias builds over time, the number of variants of unknown significance will likely decrease. This raises the question regarding whether a patient lacking a definitive genetic diagnosis requires periodic reevaluation to account for new knowledge. The American College of Medical Genetics and Genomics released a Points-to-Consider statement that addresses reevaluation and reanalysis of genomic test results. One perspective shared is the need for clinical laboratories to respond to external requests for reevaluation or reanalysis in a timely manner and having policies that reflect this (https://www.nature.com/articles/s41436-019-0478-1.pdf, accessed May 22, 2019).

Selection and ordering of the molecular genetic test for LQTS

Selection of the appropriate genetic test for LQTS can be challenging because of the multiple tests available, many differing by the number of LQTS-relevant and other arrhythmia/cardiac genes interrogated (Figure 2). For LQTS, approximately 90% of disease-associated variants occur in the three canonical LQTS-causative genes. These are included in the majority of gene panels listed within the Genetic Testing Registry (https://www.ncbi.nlm.nih. gov/gtr, accessed May 22, 2019), a database to which clinical laboratories can submit information about the tests they offer [28]. As of 2019, gene panel testing is the most common type of test offered according to the Genetic Testing Registry. As of 2019, there were 24 laboratories listed within the United States offering molecular genetic testing for LQTS. Data entry is voluntary, raising the likelihood that there are additional laboratories offering LQTS testing in the US.

Choosing the best test for a given patient requires consideration of the clinical presentation, family history, potential differential diagnoses, and knowledge of the genes included within the test panels under consideration. Laboratory expertise and resources (e.g. information on website) can be helpful to gain an understanding of the tests available, their uses, and limitations, prior to test ordering. Costs and turn-around times vary and are additional considerations for the clinician ordering genetic tests. On the other hand, test selection often requires knowledge beyond the limits of the patient's physician and a consultation with a laboratory professional, medical geneticist, or genetic counselor is useful. The extent to which clinicians know about or take advantage of this consultative role is not clear [29].

Clinical laboratories may review test orders for appropriateness but this can be challenging because the laboratory may not receive or otherwise have access to important clinical information about the patient and family. The absence of this information does not preclude performing the test. Without this information, the laboratory provides a generic interpretation that may not be optimal for informing clinical decisions [27]. For example, a laboratory may classify a variant as one of unknown significance in the absence of data to support a pathologic or benign classification. If in fact, there is evidence only available to the clinician that the finding is a pathogenic familial variant, a re-classification of the variant to pathogenic is in order.

Another factor in test selection is that physicians may be constrained to the tests they order because of limitations imposed by institutional contractual agreements and health insurance coverage. Testing outside contractual agreements, if permitted, often requires a justification that undergoes review. Studies are lacking that investigate the influence of these policies for making accurate and timely diagnoses. Costs and turn-around times vary and are additional considerations for the clinician ordering genetic tests.

Assigning clinical relevance to a sequence variant

For heritable conditions, such as LQTS, professional guidance is available for classifying sequence variants using a variety of criteria that categorize findings as pathogenic, likely pathogenic, benign, likely benign, or of unknown significance [30]. However, variation exists in the application of these criteria for classifying variants [31]. To reduce this variability, electronic variant classification tools are available that apply criteria in a uniform manner [32]. This reduces but does not eliminate variability. These processes use data from a number of databases. However, many of these databases primarily support research and are not curated to support clinical applications. One study reported misclassification of 27% of literature-annotated disease-associated mutations within a number of frequently accessed databases [33]. Consequently, professional judgment prevails in the assessment of the quality of data derived from these databases for clinical applications and may still require manual curation [34]. This is primarily an issue for the rarer sequence variants where published studies are limited or absent in the peer-reviewed literature. Nonetheless, experience and expertise in performing and reporting clinical sequence analyses can be an important factor in choosing the testing laboratory.

Recognizing the need for a credible and curated database, The National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/clinvar/, accessed May 22, 2019)

developed a resource, Clinvar, which provides information about variants and their disease association [35]. As of April 2019, Clinvar contains approximately 408,000 entries having clinical assertions associated with many medical conditions.

Using genetic test results to inform patient management and identifying family members at risk

A genetic test for LQTS may find pathogenic or likely pathogenic sequence variants or variants of unknown significance. Laboratories typically do not report sequence variants that are benign or likely benign [34]. It is important for clinicians to review the laboratory's test interpretation to determine consistency with the patient's clinical presentation and family history. A discordance can lead to a change of a clinical classification of the variant, such as the example provided earlier where a variant classified to be of unknown significance was reclassified as pathogenic when previously determined to be a disease-associated familial sequence variant. As of 2019, guidance that covers clinician review of genetic test results is lacking. This emphasizes the need for clinicians less knowledgeable about genetics and genetic testing to collaborate with other experts such as laboratory professionals, genetic counselors, or medical geneticists who have the specialized knowledge needed to inform patient management decisions.

Role of health information technology

Health information technology is evolving to facilitate quality patient care and improve the clinical workflow. Perhaps of greatest interest is decision support systems developed to assist clinicians to order appropriate testing and aid in understanding and applying test results. Criteria evaluated in deciding to implement these tools include a clear understanding of benefits to the patient, ease of use, the influence on the clinical workflow, and the cost for implementation and maintenance. A model piloted at the Veterans Administration, Los Angeles as of 2019, is the delegation of electronically placed genetic test orders for review of clinical appropriateness by a clinical geneticist. When a test order was not relevant to the indication for testing or otherwise duplicative, a genetics consult was offered to discuss the appropriate testing regimen. This process led to a reduction in inappropriate test orders [36]. For result reporting, examples of decision support tools are emerging. Rasmussen et al. reported the use of a system to aid clinical decision making that receives and analyzes test results to generate a descriptive phenotype that is deposited into the patient's electronic medical record [37]. Until such systems, or other solutions, gain broader use in the clinical realm, there will continue to be the need to access testing expertise when uncertainty exists about the uses and limitations of genetic tests and results.

Conclusions

The development and use of a diagnostic workflow provides the opportunity to assess the challenges, and approaches to consider when integrating genetic testing into a broader diagnostic evaluation. This exercise provides illustrative examples of challenges and consideration useful to clinicians, laboratory professionals, and others important to deriving an accurate and timely diagnosis for LQTS with relevance to other heritable conditions. The resources noted in Table 2 are intended to assist healthcare professionals in designing

setting-specific solutions to the challenges indicated, based upon the stated considerations. Access to current knowledge and practices relevant to the use of genetics within a diagnostic evaluation is a key element, considering the complexities and dynamic nature of genetics and genetic testing. The National Academies report, *Improving Diagnosis in Health care*, emphasizes the importance of patient engagement and informed decision-making [2]. For genetic conditions, this often brings issues relevant to the patient's family into the diagnostic process. The increasing number and complexity of tests challenges clinicians to maintain current knowledge regarding the uses and limitations of testing. Engaging professionals with genetic testing expertise (e.g. genetic counselor, laboratory professional, physicians having specialized genetic knowledge) relevant to a particular medical discipline (e.g. cardiology) can be helpful to ensure appropriate test selections and application of the test results to patient care decisions.

The LQTS diagnostic workflow illustrates the importance for leveraging knowledge of cardiology, genetics, and laboratory medicine to support a timely and accurate diagnosis. The evolution and use of health information technology and clinical decision support tools will continue to have an important role for those who develop, implement, and use guidance. Equally or more important is effective consultation and collaboration among healthcare professionals and the patient in making accurate and timely diagnoses, particularly for clinical presentations that require expert input of clinical and laboratory professionals, as is the case for LQTS. The National Academies report recommends the use of a diagnostic management team to achieve this [2]. Such a team brings clinicians, lab scientists, and the patient together to determine the optimal diagnostic strategy for the patient. This contrasts to the typical care delivery model for patient referral, with minimal communication among treating physicians and laboratory professionals. Studies suggest that the use of diagnostic management teams can improve coordination of care among healthcare providers, decrease referral times, promote informed decision-making, and achieve higher-quality health outcomes [2, 38].

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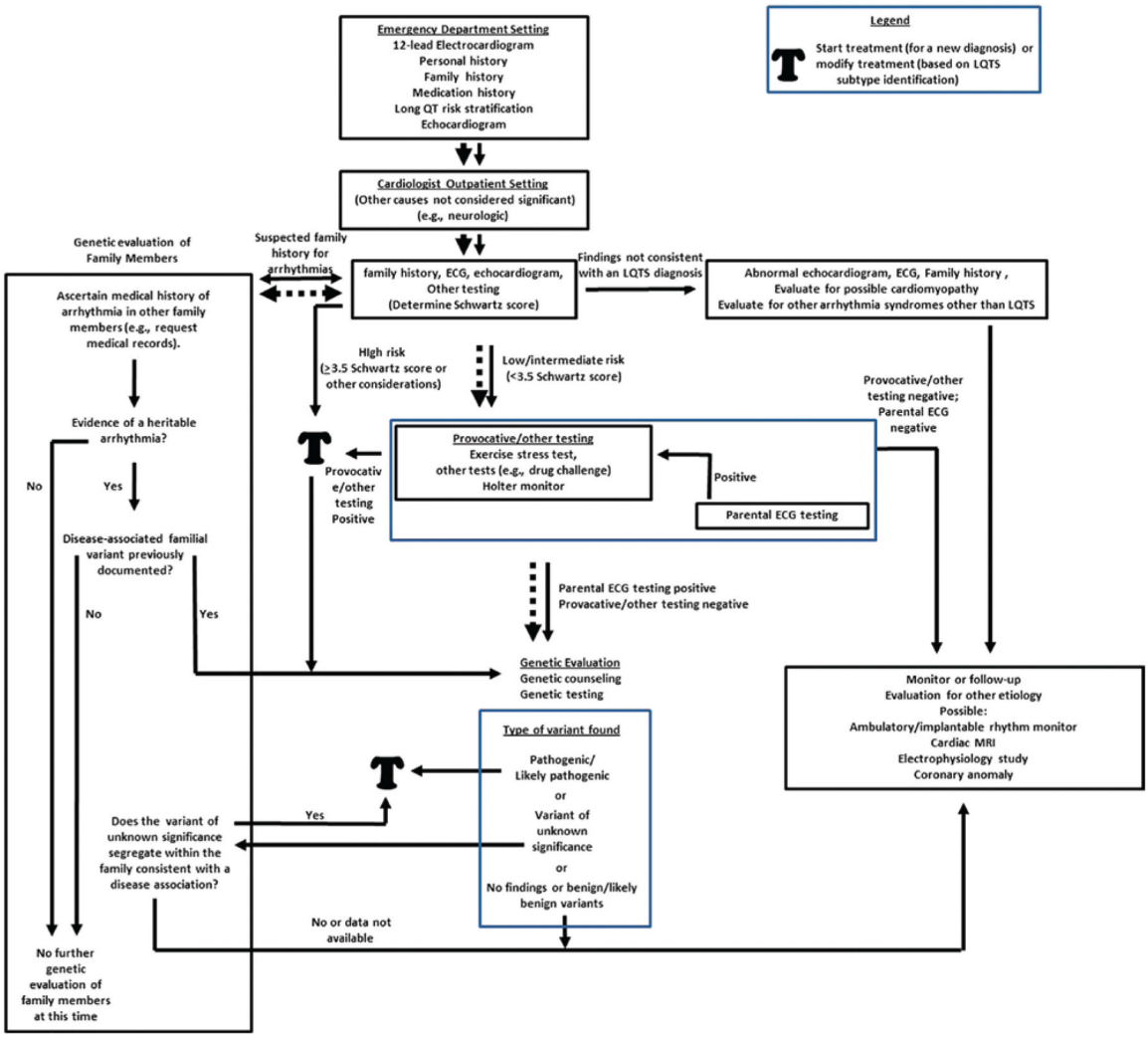

Figure 1: The LQTS diagnostic workflow.

This diagram illustrates a diagnostic workflow for LQTS. This includes alternate pathways that depend on findings from a particular step in the process. The dotted lines indicate the diagnostic evaluation applicable to the hypothetical patient described in the manuscript.

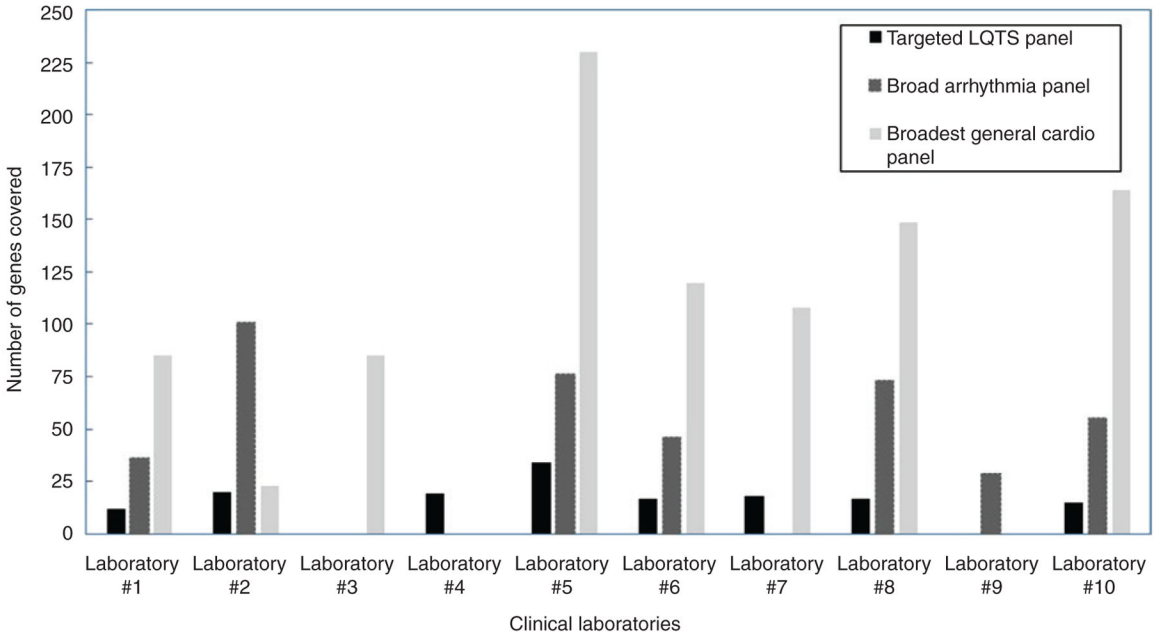

Figure 2:

Variation in molecular genetic tests among clinical laboratories. The Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/, accessed May 22, 2019) provided data for this analysis. Gene panels target only LQTS or a broader set of arrhythmias and other non-arrhythmogenic heritable cardiac disorders.

Table 1:

Clinical Features, laboratory testing, and risk scoring for LQTS.

Clinial features

- Cardiac arrhythmias disorder of repolarization characterized by prolongation of the QT interval that can lead to:
  - Polymorphic ventricular tachycardia
  - Ventricular defibrillation
  - Sudden cardiac death
- Unexplained syncope with
  - Prolonged corrected QT interval (480–500 ms)
  - Without reversible explanation
  - Absence of a known pathogenic mutation
- Can be heritable or acquired (e.g. drug-induced)
- Heritable form is autosomal dominant
- Prevalence of heritable LQTS: ~1:2500

Diagnostic criteria and risk scoring

- Electrocardiogram to measure QT interval [A diagnosis can be made by a finding corrected for heart rate; >500 ms without reversible cause (e.g. external trigger such as drug or other environmental factor like hypothermia)]
- Genetic testing (to identify a pathogenic variant)
- Risk (Schwartz) scoring (combines several criteria, including ECG findings, clinical, and family history) that is used to determine the likelihood of a diagnosis of LQTS

Features of major LQTS subtypes

General

- LQTS subtypes 1–3 are responsible for approximately 90% of genotype-positive LQTS
- 12 genes responsible for <5% of remaining LQTS cases

LQT1

- The *KCNQ1* gene on chromosome 11
- Associated with loss of function variant
- >50% attributed to pathogenic variants in this gene
- Exercise and emotional stress can precipitate an arrhythmic event
- Clinical response to beta blockers

LQT2

- *KCNH2/hERG* gene on chromosome 7
- Associated with loss of function variant
- 35–40% attributed to pathogenic variants in this gene
- Arrhythmic events precipitated primarily by auditory stimuli
- Clinical response to beta blockers but less than for LQT1

LQT3

- *SCN5A* gene on chromosome 3
- Associated with gain of function variant
- 10–15% attributed to pathogenic variants in this gene

- Often exhibit arrhythmic events during sleep; definitive data lacking regarding effectiveness of beta blockers but thought less than LQT1 or LQT2

Table 2:

Challenges and considerations for the integration of genetics into the diagnostic workflow.

Challenges	Applicability	Considerations in crafting approaches in clinical practice	Examples of relevant guidance and other resources
Making informed decisions about genetic testing	• Clinician(s) (includes physician(s), genetic counselor, and other clinicians, as applicable) • Patient	Explore and implement strategies to advance understanding among clinicians, laboratory professionals, and the patient about the uses and limitations of genetic testing	The American College of Genetics and Genomics (https://www.nature.com/articles/gim201394, accessed May 22, 2019) The National Society for Genetic Counseling (https://www.nsgc.org/page/practiceguidelines, accessed May 22, 2019)
Applying family history to inform, review test selection, and result interpretation.	• Clinician(s) (includes physician(s), genetic counselor, and other clinicians, as applicable) • Laboratory professional	Identify and address obstacles to the collection, interpretation, and sharing of family history among medical professionals	2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death Collecting a Family History (https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000549, accessed May 22, 2019)
Obtaining clinical data of relatives who receive care outside the patient's medical care setting.	• Clinician(s) (includes physician(s), genetic counselor, and other clinicians, as applicable) • Patient • Patient's relatives • Laboratory professional	Identify and address obstacles to information sharing when the relative's data exists outside the patient's medical care setting Review and streamline local policies to expedite the sharing of clinical and family history with healthcare provider external to the local setting	Health Insurance Portability and Accountability Act of 1996 (https://www.hhs.gov/hipaa/for-professionals/index.html, accessed May 22, 2019)
ECG testing for first-degree relatives	• Clinician(s) (includes physician(s), genetic counselor, and other clinicians, as applicable) • Patient's relatives	Explore and address administrative challenges to securing ECG for the patient's first-degree relatives	None identified
Choosing and reviewing the best test of those currently available	• Clinician(s) (includes physician(s), genetic counselor, and other clinicians, as applicable) • Laboratory professional	Clinicians can Increase familiarity with laboratory websites, other resources (e.g. the Genetic Testing Registry), and consultations available with laboratory professionals Laboratory professionals review and explore effective means to share important information about testing with clinicians	Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/, accessed May 22, 2019)
Use of algorithms and data obtained from databases for informing the assignment and review of sequence variant clinical assertions.	• Clinician(s) (includes physician(s), genetic counselor, and other clinicians, as applicable) • Laboratory professional	Understand the level of data curation and the need for additional efforts to assure the accuracy of data brought in from an external data source	Standards and Guidelines for the Interpretation of Sequence Variants (https://www.ncbi.nlm.nih.gov/pubmed/25741868/, accessed May 22, 2019) Clinvar database (curated) (https://www.ncbi.nlm.nih.gov/clinvar/, accessed May 22, 2019)