

Office of Population Health Genomics

Paper:
ACCE Review Summary:
The Long-QT Syndrome (LQTS)

Purpose: To provide an evaluation of genetic testing for LQTS in Australia using the ACCE framework

12 Dec 2006 (Updated 23rd February 2009)

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Government of **Western Australia**
Department of **Health**

ACCE REVIEW - Long-QT Syndrome (LQTS)

Disorder/Setting

What is the specific clinical disorder?

- Inherited Long-QT Syndrome (LQTS) manifests in two forms:
 - Romano-Ward Syndrome (RWS) is inherited in an autosomal dominant fashion and displays cardiac abnormalities and normal hearing. Its prevalence is unknown, but has been estimated at 1 in 7,000 persons in the US population (Vincent 2000).
 - Jervell and Lange-Nielsen Syndrome (JLNS) is characterised by marked QT prolongation with a higher incidence of sudden death and bilateral sensori-neural deafness. JLNS is fairly rare in the general population (autosomal recessive), with an estimated population frequency of 1.6-6 per million in children in the UK (Tranebjaerg et al. 1999).
- There are at least ten distinct LQTS subtypes (LQT1-10) based on both clinical and genetic findings. Subtypes LQT1-3 are the most common phenotypes and account for more than 90% of mutations identified (Napolitano et al. 2005).

Disease characteristics

What are the clinical findings?

- LQTS is characterized by syncopal (fainting) episodes, ventricular tachycardia and cardiac arrest. A set of diagnostic criteria based on electrocardiographic findings (such as Torsade de Pointes or T-wave anomalies), clinical history and family history has been published to assist in the identification of cases (Schwartz 1985; Schwartz et al. 1993):

1993 LQTS Diagnostic criteria

Schwartz et al. (1993)

ECG Findings¹

Points

A. QT _c ²	
≥ 480 msec	3
460-470 msec	2
450 msec (in males)	1
B Torsade de Pointes ³	2
C T-Wave alternans	1
D Notched T wave in three leads	1
E Low heart rate for age ⁴	0.5

Clinical history

A Syncope³

	With stress	2
	Without stress	1
B	Congenital deafness	0.5
	Family history⁵	
A	Family members with definite LQTS ⁶	1
B	Unexplained sudden cardiac death below age 30 among immediate family members	0.5
1	In the absence of medication or disorders known to affect these electrocardiographic features.	
2	QT calculated by Bazett's formula, where $QTc = QT/\sqrt{RR}$	
3	Mutually exclusive	
4	Resting heart rate below the second percentile for age (Davignon et al. 1980).	
5	The same family member cannot be counted in A and B.	
6	Definite LQTS is defined by a LQTS score ≥ 4 .	
	Scoring: ≤ 1 point: low probability of LQTS; 2-3 points: intermediate probability of LQTS; ≥ 4 points: high probability of LQTS.	
	<ul style="list-style-type: none"> • Patients are screened for the presence of congenital LQTS for a variety of reasons, with more than 60% identified when family members undergo a screening electrocardiogram (ECG) (Moss & Robinson 1992). • The clinical phenotype is highly variable: Thirty percent of those with mutations do not have a prolonged QT interval, but are still at 10% risk for major cardiac events before 40 years of age if untreated (Priori et al. 2003). 	

<p>Genetic mutations <i>What DNA test(s) are associated with this disorder?</i></p>	<ul style="list-style-type: none"> LQTS is caused by mutations in ten genes, of which eight encode for protein subunits of cardiac ion channels (Roberts 2006). The genes involved and their relative proportions are (Domingo et al. 2006; Modell & Lehmann 2006; Roberts 2006; Vatta et al. 2006): <table border="1" data-bbox="676 305 1827 711"> <thead> <tr> <th>Subtype</th> <th>Gene</th> <th>Proportion</th> </tr> </thead> <tbody> <tr> <td>LQT1</td> <td>KCNQ1/KvLQT1</td> <td>45.9%</td> </tr> <tr> <td>LQT2</td> <td>hERG/KCNH2</td> <td>41.7%</td> </tr> <tr> <td>LQT3</td> <td>SCN5A</td> <td>9.3%</td> </tr> <tr> <td>LQT4</td> <td>ANKB/ANK2</td> <td>rare</td> </tr> <tr> <td>LQT5</td> <td>MinK/IsK/KCNE1</td> <td>2.0%</td> </tr> <tr> <td>LQT6</td> <td>MiRP1/KCNE2</td> <td>1.1%</td> </tr> <tr> <td>LQT7</td> <td>Kir2.1/KCNJ2</td> <td>rare</td> </tr> <tr> <td>LQT8</td> <td>CACNA1C</td> <td>unknown prevalence</td> </tr> <tr> <td>LQT9</td> <td>CAV3</td> <td>unknown prevalence</td> </tr> <tr> <td>LQT10</td> <td>SCN4B</td> <td>rare</td> </tr> </tbody> </table>	Subtype	Gene	Proportion	LQT1	KCNQ1/KvLQT1	45.9%	LQT2	hERG/KCNH2	41.7%	LQT3	SCN5A	9.3%	LQT4	ANKB/ANK2	rare	LQT5	MinK/IsK/KCNE1	2.0%	LQT6	MiRP1/KCNE2	1.1%	LQT7	Kir2.1/KCNJ2	rare	LQT8	CACNA1C	unknown prevalence	LQT9	CAV3	unknown prevalence	LQT10	SCN4B	rare
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<p>Screening process <i>What is the clinical setting in which the test is to be performed?</i></p> <p><i>Are screening questions used?</i></p> <p><i>Is it a stand-alone test or is it one of a series of tests?</i></p> <p><i>Are all tests performed in all instances (parallel) or are only some tests performed on the basis of other results (series)?</i></p>	<ul style="list-style-type: none"> Genetic testing is likely to be offered to symptomatic patients presenting to paediatric and adult cardiology clinics. Clinical data, as opposed to screening questions, will be used to ascertain the target population for LQTS genetic testing. Importantly, those patients who have the highest clinical probability for LQTS (Schwartz Score ≥ 4) are those in whom a LQTS gene mutation is most likely to be detected (72%) (Tester et al. 2006). This mandates the need to ensure that careful consideration is given to the selection of patients for genetic testing. Careful consideration of the phenotypic information available for an individual patient (e.g. ECG patterns, known triggers etc.) can guide genetic testing to the most likely mutations. 																																	

Analytic Validity	
<p>Analytic Sensitivity/ Analytic Specificity</p>	<ul style="list-style-type: none"> • External proficiency testing remains the only major reliable source available for computing analytic sensitivity and specificity, however this does not yet exist for LQTS genetic testing. • DNA sequencing is recognized as the “gold standard” in mutation detection. cDNA sequencing of mRNA extracted from PHA-stimulated lymphocytes is likely to be the method utilised in this setting. • Screening techniques such as single-strand conformation polymorphism (SSCP) or denaturing high performance liquid chromatography (dHPLC) allow an initial, less expensive and more rapid screen to be performed. Abnormal results can then be analyzed by DNA sequencing. • A study of 192 LQTS patients determined that the analytic sensitivity of SSCP is 75% and dHPLC is 100% when compared to DNA sequencing (Ning et al. 2003). • A study of 192 LQTS patients determined that the analytic specificity of SSCP and dHPLC to be 100% (Ning et al. 2003). • The distribution of mutations may not be distributed evenly across the genome. In a study of 310 probands with a known LQTS mutation, 58% of mutations were restricted to one of 64 codons in the genes for LQT1, LQT2 and LQT3 (Napolitano et al. 2005).
<p>Quality Control <i>Is an internal QC program defined and externally monitored?</i></p> <p><i>If appropriate, how is confirmatory testing performed to resolve false positive results in a timely manner?</i></p> <p><i>Have repeated measurements been made on specimens?</i></p>	<ul style="list-style-type: none"> • In Australia, the technical competency of genetic testing is monitored by the accreditation scheme operated by the National Association of Testing Authorities, Australia (NATA). • Accredited laboratories are required, among other things, to employ quality management systems, comply with laboratory design and fitting standards, properly document test requests and specimens, and to be enrolled and participate in external proficiency testing programs. • Confirmatory testing is additional testing to verify the finding of a mutation(s). It is likely to be useful because of occasional false positive test results. • Guidelines and measurements to ensure that false positives are minimized should be developed prior to the implementation of genetic testing for LQTS. This could include the use of a duplicate sample from the patient or repeating the test again on the original sample.

<p>Assay <i>Is testing qualitative or quantitative?</i></p> <p><i>What range of patient specimens have been tested?</i></p> <p><i>How often does a test fail to give a useable result?</i></p> <p><i>What is the within- and between laboratory precision?</i></p> <p><i>How similar are results obtained in multiple laboratories, using the same or different technology?</i></p>	<ul style="list-style-type: none"> • The test is qualitative: the presence of a mutation indicates that the patient has definite LQTS and given the 10% likelihood of death in the next 10 years, should be treated if not already. • Given that only 60-75% of affected persons have detectable mutations (Modell & Lehmann 2006), a person who tests negative for the mutation cannot be excluded from risk. • Genomic DNA in LQTS mutational studies has typically been derived from peripheral blood lymphocytes and more rarely from buccal cells (Modell & Lehmann 2006). • Failure of the genetic test can be due to pre-analytic factors (e.g. poor sample), analytic errors (e.g. operator error, equipment malfunction) or post-analytic errors (incorrect interpretation of results). Information regarding the source of errors could be obtained via external proficiency testing schemes. • Data derived from external proficiency testing schemes can be used to compare intra- and inter-laboratory variation in LQTS testing. Such a program could be readily implemented by utilising existing agencies such as NATA (see quality control section below).
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Clinical Validity

Clinical Sensitivity

Are there methods to resolve clinical false positive results in a timely manner?

- About 65-70% of LQTS patients have an identifiable LQTS mutation (Schwartz et al. 2006). Importantly, those patients who have the highest clinical probability for LQTS (Schwartz Score ≥ 4), are those in whom a mutation is most likely to be detected in one of the LQTS genes (Tester et al. 2006). Targeted genetic testing, by analyzing the most likely gene(s) based on phenotype improves the detection rate to 78%, with 90% of mutations detected in the first gene examined (van Langen et al. 2003).
- Since there is considerable overlap in QT duration between known mutation carriers and non-mutation carriers, it is likely that some of the latter group may harbour mutations in as yet unidentified LQTS genes (false negatives) (Napolitano et al. 2005).
- Clinical false positives include those who have a genetic mutation for LQTS but are asymptomatic and remain so for life. Further research is needed to evaluate lifetime risks of LQTS for patients who are asymptomatic and receive a positive genetic test result.

Clinical Specificity

- Specificity of genetic testing is 56% when compared to LQTS diagnosis by Schwartz Score ≥ 4 (Tester et al. 2006).
- A proportion of those who are found to have a mutation will also be asymptomatic and hence not currently undergoing treatment (Napolitano et al. 2005). The proportion of asymptomatic carriers varies with subtype (LQT1 = 36%; LQT2 = 19%; LQT3 = 10%) (Priori et al. 2003).
- Excluding two common polymorphisms, 25% of healthy, black subjects and 14% of healthy, white subjects have at least one non-synonymous mutation in the genes responsible for LQT1, LQT2, LQT5 and LQT6 (Ackerman et al. 2003).
- Several mutations which have been attributed to LQTS, may also be present in a healthy population (false-positives), although these individuals may have sub-clinical LQTS or develop overt symptoms in the future (Ackerman et al. 2004).

<p>Prevalence <i>What is the prevalence of the disorder in this setting?</i></p> <p><i>Has the test been adequately validated on all populations to which it may be offered?</i></p>	<ul style="list-style-type: none">• In the general population, LQTS has an estimated prevalence of 1 in 5,000-7,000, however this number may be underestimated due to the existence of asymptomatic individuals.• In a family-focused, cascade screening approach, 3.5 mutation-carrying relatives are identified for each index case (van Langen et al. 2003).• The genetic testing in Western Australia is still undergoing development and thus has not been widely tested.
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<p>Predictive Values <i>What are the positive and negative predictive values?</i></p> <p><i>What are the genotype and phenotype relationships?</i></p>	<ul style="list-style-type: none"> • The positive and negative predictive values have not been determined in this setting. • The inherited form is now known to be due to 10 different genes, with three genetic loci responsible for the majority of cases (subtypes LQT1, LQT2 and LQT3). • Genetic loci can predict disease outcome, with LQT1 having less events than LQT2 or LQT3 (Priori et al. 2003). • Triggers also vary between subtypes, with cardiac events in LQT1 often being precipitated by exercise, in LQT3 by sleep or rest, and in LQT2 by exercise or rest, and also by sharp auditory stimuli or emotional stresses (Schwartz et al. 2001). • Typical ECG patterns have been identified for subtypes LQT1-3, although 12% of LQT1 and LQT2 carriers and 35% of LQT3 have an atypical pattern (Zhang et al. 2000). • The consideration of phenotypic information can provide a useful starting point when undertaking genetic testing.
<p>Penetrance <i>What are the genetic, environmental or other modifiers?</i></p>	<ul style="list-style-type: none"> • Given that the severity and manifestation of the inherited form of the disease varies greatly even within families sharing the same mutation, the presence of modifying genes and other factors seems likely. • An additional genetic mutation which can modulate the phenotype of patients with mutations in one of the common LQTS genes has already been described (Crotti et al. 2005). • Gender may also modulate the phenotype, with the risk for each gender varying with age (Priori et al. 2003). Males tend to be at a greater risk of cardiac events during childhood, although a gender risk reversal occurs in mid- to late- adolescence placing females at greater risk after this time (Locati et al. 1998). There is also a significant increase in the incidence of cardiac events in the 9-month post-partum period, mainly among women who are identified as LQT2 genotype carriers (Seth et al. 2007). • An acquired form of LQTS is precipitated mainly by exposure to drugs. This form may also have a genetic aetiology, with 10 to 15% of individuals with drug induced LQTS having mutations in the ion channel genes (Roberts 2006).

Clinical Utility

Natural History

What is the natural history of the disorder?

- Clinically, LQTS is characterized by syncopal episodes, ventricular tachycardia, and fibrillation. In rare cases, deafness may also be present.
- Many patients with LQTS are asymptomatic and are discovered incidentally based on ECG, family history or having survived an episode of syncope or severe ventricular arrhythmia (Roberts 2006).
- The first cardiac or syncopal event usually occurs in childhood or adolescence (Modell & Lehmann 2006, Dr. Luigi D'Orsogna, *personal comm.*)

Are diagnostic tests available?

- LQTS is diagnosed based on the Schwartz scoring system (see disease characteristics).
- The use of phenotypic information has been suggested as a way to improve genotyping efficiency (see clinical sensitivity).
- Subtle differences in ECG parameters exist between LQTS subtypes 1-3, with 10 distinct patterns observed (Zhang et al. 2000).
 - In individuals with a known LQTS genotype, the sensitivity and specificity of genotype prediction based on ECG trace results is 61%/71% (LQT1), 62%/87% (LQT2) and 33%/98% (LQT3). The sensitivity and specificity improved to 77%/81% (LQT1), 79%/88% (LQT2) and 54%/100% (LQT3) when family data was considered together.
 - Typical ECG patterns were identified in 88% of known LQT1 genotypes, 88% of known LQT2 genotypes and 65% of known LQT3 genotypes.

Costs and Benefits

Is there an effective remedy, acceptable action, or other measurable benefit?

- The prognosis of untreated patients is quite poor with ~20% of patients presenting with syncope dying within one year and 50% within 10 years (Roberts 2006).
- The Guidelines for the Diagnosis and Management of Familial Long QT Syndrome (The Cardiac Society of Australia and New Zealand (CSANZ), 2005) recommend a multifaceted approach to the treatment of LQTS involving removal of triggers and use of beta blocking agents, both of which have variable efficacy depending on genotype.
- A large study from the International LQTS Registry of 869 LQTS patients and family members on beta-blockers (69% symptomatic), demonstrated a mortality rate of 2%, with reductions in any cardiac events from 63% to 28% (Moss et al. 2000). However, symptomatic patients still have a high risk (32%) of recurrent cardiac events within 5 years despite being on beta-blockers. In these patients the use of implantable cardioverter-defibrillators (ICDs) may be warranted (Monnig et al. 2005).

- A follow-up of left cardiac sympathetic denervation (LCSD), found that this procedure reduced the 5 year mortality rate to 5% in symptomatic patients (Schwartz et al. 2004).
- Shimizu (2005) has reviewed the efficacy of genotype specific therapies, which may be summarized as follows:

Genotype-specific therapy based on clinical and experimental data on Long QT syndrome

(Shimizu et al. 2005)

	LQT1 (LQT5)	LQT2 (LQT6)	LQT3
Sensitivity to sympathetic stimulation	+++++ (Sustained ↑ in TDR)	+++ (Transient ↑ in TDR)	- (↓ in TDR)
Torsade de Pointes	Exercise-related	Startle	Sleep/rest
Specific trigger	Swimming	Telephones, alarm clock, postpartum periods	
Exercise restriction	+++++	+++	-
β-Blockers	+++++	+++	-
Potassium supply	++?	++++	++?
Class 1B sodium channel blockers	+++	++++	+++++
Calcium channel blockers ¹	+++	+++	++?
Potassium channel blockers ¹	++	++	-
Pacemaker	++	++	+++++
ICD	++++	++++	+++++
ICD, implantable cardiovascular defibrillator; TDR, transmural dispersion of repolarization; +++++ means most effective			
¹ Based only on experimental data			

- Asymptomatic family members: If LQTS cannot be excluded, the individual should avoid medications contraindicated in LQTS. Those with a long QT interval, especially young people, need to be treated much as someone who has already presented with syncope. Beta blockers should be proposed and sensible limitations placed on sporting activities, particularly swimming (CSANZ 2005).
- The value in screening for LQTS lies in the identification and treatment of asymptomatic family members prior to coronary event. In many patients this can be the first and only indicator of disease.
- Where the patient is already known to have symptoms of LQTS (diagnosis based on clinical findings), confirmatory genetic diagnosis can alter the treatment in a genotype specific way (Dr. Luigi D’Orsogna, *personal comm.*) When the specific familial mutation is known, genetic testing of other family members can then proceed.
- Where the genetic diagnosis is negative and a specific mutation is not being tested for, the diagnosis of LQTS cannot be excluded. Those individuals in whom a diagnosis cannot be excluded should be followed up every 1-5 years with ECG testing. Where the clinical

What is the impact of a positive (or negative) test on patient care?

<p><i>Is there general access to that remedy or action?</i></p> <p><i>Is the test being offered to a socially vulnerable group?</i></p> <p><i>What are the financial costs associated with testing?</i></p> <p><i>What are the economic benefits associated with actions resulting from testing?</i></p>	<p>features indicate possible LQTS, treatment should be implemented as soon as possible, as untreated patients have ~5% risk of mortality per year (Moss et al. 2000).</p> <ul style="list-style-type: none"> • Uptake of the treatments listed is likely to be linked closely to the cost of the procedure. • Consideration must also be given to ensure that regional patients are also able access specialised medical procedures, such as surgery or ICD implantation, which may be located in the metropolitan area. • No, this test will not be limited to a specific population group. • The cost of genetic testing procedures can vary greatly, from less than \$100 to more than \$1000, depending on a number of factors including (ALRC 2003): <ul style="list-style-type: none"> - Test methodology - Laboratory testing strategy - Number of individuals tested - Contractual agreements - Specimen handling - Additional services - Intellectual property • The primary benefits resulting from genetic testing involve identification and treatment of asymptomatic individuals and improved targeting of treatments towards definite LQTS patients. Additional benefits arise for patients who have borderline or inconclusive clinical scores and negative genetic tests, who will not require expensive treatments such as ICDs. • A study by Phillips and co-workers (2005) demonstrated the cost-benefit of combining a clinical diagnosis (such as the Schwartz score) with genetic testing compared with clinical diagnosis alone, was US\$2500 per life year gained. • Additional studies have demonstrated that genetic testing, performed after careful consideration of the patient phenotype, allows eligible genes to be targeted immediately and is more cost-effective than screening for the five major genes or in accordance with gene frequency (van Langen et al. 2003).
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<p>Quality Assurance <i>What quality assurance measures are in place?</i></p>	<ul style="list-style-type: none"> • National Association of Testing Authorities (NATA) <ul style="list-style-type: none"> - Laboratory accreditation • National Health and Medical Research Council (NHMRC) <ul style="list-style-type: none"> - Clinical practice guidelines • Human Genetics Society of Australasia (HGSA) <ul style="list-style-type: none"> - General laboratory practices and professional guidelines
<p>Pilot trials <i>What are the results of pilot trials?</i></p>	<ul style="list-style-type: none"> • Pilot trials have not yet been undertaken in this setting.
<p>Health Risks <i>What health risks can be identified for follow-up testing and/or intervention?</i></p>	<ul style="list-style-type: none"> • The major health risks relating to a person who tested positive for an LQTS mutation are likely to relate to the treatment regime undertaken (e.g. surgery). • Psychosocial problems and concerns for family members may also develop, especially if there is uncertainty in the genetic or clinical diagnosis (Hendriks et al. 2005).
<p>Evaluation <i>What guidelines have been developed for evaluating program performance?</i></p>	<ul style="list-style-type: none"> • If implemented, the Office of Population Health Genomics (Department of Health, WA), will be responsible for drawing up these guidelines.
<p>Facilities <i>What facilities/personnel are available or easily put in place?</i></p>	<ul style="list-style-type: none"> • It is envisaged that genetic testing for LQTS would be implemented through existing genetic services, such as Genetic Services of Western Australia. This service already performs a routine diagnostic service for genetic disorders and as such has in place procedures to guide administration, performance and follow-up pertaining to genetic tests. The service is monitored for laboratory quality assurance under the auspices of NATA and has in place counselling and medical facilities to ensure adequate treatment and referral for patients. • Specific equipment or reagents may need to be purchased for the laboratory testing procedure.
<p>Monitoring <i>What methods exist for long-term monitoring?</i></p>	<ul style="list-style-type: none"> • Long-term monitoring of patients include regular cardiologist visits, 6 to 12 monthly with ECG and/or Holter monitoring or ICD/pacemaker check and occasional exercise ECG testing (Dr. Luigi D’Orsogna, <i>personal comm.</i>). • Asymptomatic carriers require yearly reviews and family members in whom the diagnosis cannot be excluded require reviews every 1 to 5 years with ECGs (Dr. Luigi D’Orsogna, <i>personal comm.</i>).

<p>Education <i>What educational materials have been developed and validated and which of these are available?</i></p> <p><i>Are there informed consent requirements?</i></p>	<ul style="list-style-type: none"> • The Heart Foundation of Australia has published an educational brochure for use by the individuals and families affected by long QT syndrome (http://www.heartfoundation.com.au/downloads/Long_QT_Syndrome_04.pdf). This document covers diagnosis, inheritance, risks, treatment and links to a support group. • A support group, Sudden Arrhythmia Death Syndromes (SADS), provides support, information and links to research projects (www.sads.org.au). • Ethical guidelines such as those produced by the NHMRC or AHEC or by professional bodies with standing in the field, such as the Australian Medical Association or the Human Genetics Society of Australasia will guide clinical practice.
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Ethical, Legal and Social Issues

<p>Psychosocial <i>What is known about stigmatization, discrimination, privacy/confidentiality and personal/family social issues?</i></p>	<ul style="list-style-type: none"> • Preliminary research from the Netherlands demonstrates that the psychological impact of screening is high, especially in families with children. Twenty-four individual parents were informed that at least one of their children was a mutation carrier, while twelve parents were told that none of their children were mutation carriers. Distress in parents was already high prior to mutation detection, due to abnormal or indecisive results of ECG registrations at first consultation. Up to 50% of the parents of mutation carriers showed clinically relevant high levels of distress (Hendriks et al. 2005). • Factors that predicted high levels of distress were familiarity with LQTS for a longer time, experiences with (aborted) sudden cardiac death in the family, and receiving unfavourable results for all of the children. Parents of non-carrier children showed significantly less test-related and general anxiety (Hendriks et al. 2005). • It is concluded that psychosocial intervention right from the first consultation is necessary in LQTS, when abnormal or indecisive ECG results have been given and LQTS-carrier status may be expected (Hendriks et al. 2005). • The provision of psychosocial support to the immediate and extended family is probably best made available through the genetic counselling and clinical genetics facilities which are currently in place. This will allow the provision of support and follow-up of entire families (including asymptomatic members) in an appropriate manner and in accordance with recognised guidelines (such as the “Guidelines for the Practice of Genetic Counselling” from the Human Genetics Society of Australasia (HGSA)).
<p>Discrimination/Insurance</p>	<ul style="list-style-type: none"> • Due to legislation requiring health premiums to be based on a community rating and not individual risk, genetic testing cannot have an impact on health insurance in Australia. • Life insurance and income protection coverage may be affected by the availability of genetic information. • Pre-test counselling should include information on the possible implications of genetic testing on insurance for both themselves and other family members.
<p>Privacy <i>Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to</i></p>	<ul style="list-style-type: none"> • The Commonwealth Privacy Act 1988 protects the privacy of individuals who have genetic testing. • The Act sets standards as to the collection of personal information, storage and security, record keeping, access, alteration of records, and use and disclosure of information. • The release of genetic information is only through the consent of the individual tested, with one exception, being the release of information for law enforcement purposes.

<p><i>disclose, or reporting requirements?</i></p> <p><i>What safeguards have been described and are these safeguards in place and effective?</i></p>	<ul style="list-style-type: none">• Patents relating to testing for and sequences of genes implicated in LQTS have been issued to:<ul style="list-style-type: none">– the University of Utah Research Foundation (UURF) (WO/1996/028537, WO/2000/006600, WO/2000/006772, WO/2001/024681);– UURF with Yale University (WO/2000/063434);– UURF with Genzyme Corporation (WO/1997/023632, WO/2000/006199);– the Fondazione Salvatore Maugeri Clinica Lavoro e Della Riabilitazione I.R.C.C.S. with the Università' Degli Studi di Pavia (WO/2006/131528).
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