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Australia and New Zealand Horizon Scanning Network

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# **National Horizon Scanning Unit**

## **Horizon scanning prioritising summary**

**Volume 13, Number 5:**

**Genetic testing for Long QT syndrome to  
identify individuals at high-risk of sudden  
cardiac death**

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# PRIORITISING SUMMARY

**REGISTER ID:** 000210

**NAME OF TECHNOLOGY:** GENETIC TESTING FOR LONG QT SYNDROME

**PURPOSE AND TARGET GROUP:** IDENTIFYING INDIVIDUALS AT HIGH-RISK OF SUDDEN CARDIAC DEATH

## STAGE OF DEVELOPMENT (IN AUSTRALIA):

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established  |
| <input type="checkbox"/> Experimental             | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational          | <input type="checkbox"/> Should be taken out of use   |
| <input type="checkbox"/> Nearly established       |   |

## AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- |  |             |
|--|-------------|
| <input type="checkbox"/> Yes                       | ARTG number |
| <input type="checkbox"/> No                        |             |
| <input checked="" type="checkbox"/> Not applicable |             |

## INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
New Zealand		✓	
United States	✓		
Italy	✓		

## IMPACT SUMMARY:

Mutational analysis for long QT syndrome aims to identify individuals at high-risk of sudden cardiac death. Genetic testing for long QT syndrome is not currently conducted in Australia but is conducted in one centre in New Zealand. However, diagnostic laboratories would be able to provide mutational analysis of the gene sequences identified as implicated in inherited long QT syndrome, as mutational analyses for a number of genetic disorders, using similar techniques, is already well established in a number of pathology laboratories. Mutation analysis of these gene sequences is currently not funded by the Medicare Benefits Schedule (MBS).

## BACKGROUND

Long QT syndrome (LQTS) is a genetic disorder characterised by arrhythmias which may, if left untreated, result in sudden cardiac death, mostly in children and teenagers. Cardiac arrest usually occurs during periods of increased physical activity or at times of psychological or emotional stress but may occur in response to a loud noise such as a phone ringing or an alarm clock (Schwartz 2006 and CIDG 2006).

The main clinical feature of LQTS is the elongation of the QT interval on electrocardiograms. QT prolongation results in a fast, abnormal heart rhythm known as torsade de pointes (Schwartz 2006). The Q-T interval represents the time for both ventricular depolarisation and repolarisation to occur, estimating the duration of an average ventricular action potential. This interval can range from 0.2 to 0.4 seconds depending upon heart rate. After correction for heart rate, Q-T intervals are less than 44 milliseconds (ms) (Figure 1) (Klabunde 2005). Patients with LQTS will typically have a corrected QT interval of >480 ms. Patients deemed to have an intermediate or high risk of LQTS according to these diagnostic criteria would be candidates for screening by mutational analysis (Schwartz 2006). The majority of patients are asymptomatic and are diagnosed either by family history or by virtue of having survived an episode of syncope or severe ventricular arrhythmias (Roberts 2006). Rates of mortality in untreated individuals are high and patients who become symptomatic in the first year of life are at high risk of sudden cardiac death (Schwartz 2005).

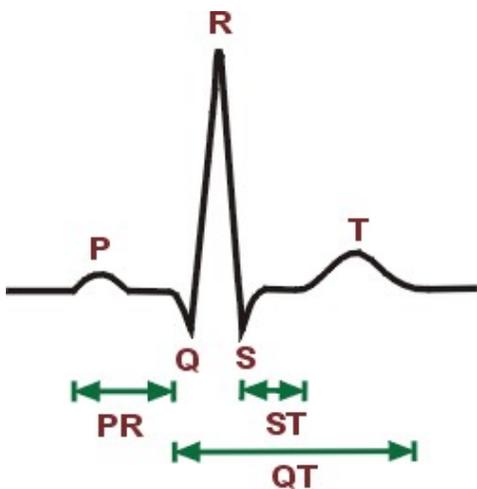


Figure 1 A normal ECG (printed with permission Klabunde 2005)

Three main genes for LQTS (LQT 1-3) have been identified and all encode for cardiac ion channels involved in the control of ventricular repolarisation. At least three other genes have been associated with rarer forms of the disease (LQT 4-6), however this remains controversial. There are two forms of the disease, the most common form is autosomal dominant, also known as Romano Ward syndrome, and the other rare form, called the Jervell, Lange-Nielsen variant, is recessive and associated with congenital deafness (Roberts 2006). LQT1 results from a mutation in the gene (KCNQ1) coding for a cardiac potassium channel ( $I_{Ks}$ ) and is the most common form of LQTS. Untreated carriers of the KCNQ1 mutation have an annual risk of sudden death of approximately 0.3%. People with LQT2 have a defect in the HERG, or KCNH2 gene which encodes for a different cardiac potassium channel ( $I_{Kr}$ ) and is the second most common form of LQTS. Individuals with this mutation have a higher annual risk of sudden cardiac death of about 0.8% and 0.5% in females and males, respectively. LQT3 is a rare form of LQTS, and is a mutation in the SCN5A gene which encodes for a cardiac sodium channel ( $I_{Na}$ ). Unfortunately the first clinical presentation of patients carrying this mutation is often sudden death. For individuals with this mutation, the untreated annual risk of sudden death is 1% and 0.3% for males and females, respectively (CIDG 2006).

Genetic screening would require a small blood donation for DNA isolation and exons of interest would be amplified by polymerase chain reaction (PCR). In the New Zealand laboratory, there is currently a six month turnaround for LQT 1-3 analysis and LQT 5 and 6 are tested annually

(personal communication CIDG May 2006). It would not be practical to conduct universal population screening for LQTS, however screening of family members of individuals who have died from sudden cardiac failure should be recommended. PCR and DNA sequencing are robust techniques with high sensitivity and specificity and good reproducibility, however they are expensive and technically complex (Louie et al 2000).

Symptomatic patients should receive treatment and therapy options include  $\beta$ -blockers, left cardiac sympathetic denervation and implantable defibrillators. Asymptomatic patients should also be treated, usually with  $\beta$ -blockers (Schwartz 2006). Figure 2 describes the rate of survival of LQTS patients who don't receive treatment. Patients diagnosed with LQTS are advised to avoid competitive sports and vigorous activity, such as swimming, is contraindicated. In addition, some medications should be avoided in patients with LQTS including some antibiotics, antihistamines, vasodilators and decongestants (CIDG 2006).

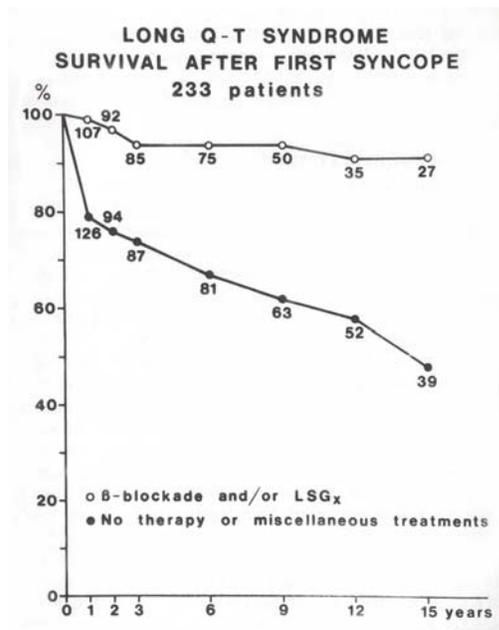


Figure 2 Long QT survival after first syncope (Schwartz & Locati 1985)

### CLINICAL NEED AND BURDEN OF DISEASE

It is difficult to estimate the prevalence of LQTS. It is a leading cause of sudden, unexplained cardiac death in children and young adults with a structurally normal heart and may be more common than previously thought. It is estimated that LQTS affects approximately 1:5,000 individuals in the United States and that it would be reasonable to expect that these estimates would hold true in Australia and New Zealand (Ackerman 2005 and SADS 2006).

A recent Australian study set out to determine the causes of sudden cardiac death in people aged  $\leq 35$  years. This cross sectional study (level IV aetiology evidence) was conducted on all autopsies performed on people  $\leq 35$  years at a major Sydney forensic unit from January 1994 and December 2002. During the study period there were 10,199 autopsies performed. Of these 2,986 (29.2%) were individuals aged  $\leq 35$  years of whom 193 were classified as sudden cardiac deaths. The cause of sudden death was as follows: not established but probable primary arrhythmia (31%), coronary artery disease (24%), hypertrophic cardiomyopathy / unexplained left ventricular

hypertrophy (15%), viral myocarditis (12%), congenital heart disease (7%) and other (11%). Of the 193 sudden cardiac deaths 22 and 38 per cent occurred during exercise and minimal exertion or at rest, respectively. Forty per cent were not witnessed. It may also be likely that a number of deaths in young people that have previously been attributed to causes including drowning, motor vehicle accidents and sudden infant death syndrome may be attributable to LQTS (Doolan et al 2004).

## **DIFFUSION**

The Cardiac Inherited Diseases Group in Auckland, New Zealand, conducts genetic testing for patients with overt LQTS, allowing identification of subtype, enabling patients to receive appropriate treatment and lifestyle advice. To date, over 100 patients have been screened, with 50 genetic mutations identified. In addition, 160 family members have been screened for the same mutations. Approximately 20 patient samples have been sent from Australia to New Zealand for genetic testing (personal communication CIDG May 2006).

A genetic lab has recently been set up at the Royal Children's Hospital in Melbourne for genetic studies to test for arrhythmia conditions such as Long QT Syndrome. The capacity for screening in this laboratory is limited due to lack of funding (personal communication Dr Andrew Davis, Royal Children's Hospital, May 2006)

## **COMPARATORS**

Diagnostic criteria for LQTS were developed in 1993. Patients suspected of having LQTS would undergo a full clinical examination where a number of points are assigned to the specific diagnostic criteria. The examination includes an electrocardiogram, clinical history (presence or absence of syncope and deafness) and family history (including unexplained sudden cardiac death in family members under the age of 30). A total of  $\geq 3.5$  points means that there is a high probability of LQTS,  $\geq 1-3$  points indicates an intermediate probability and  $\leq 1$  point means a low probability of LQTS (Schwartz 2005).

## **EFFECTIVENESS AND SAFETY ISSUES**

The study by Napolitano et al (2005) reported on the genetic screening of 430 LQTS probands with clinically defined Romano Ward syndrome and family members consecutively referred for genetic testing (level IV Screening evidence). Screening was conducted on five common mutations: KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5) and KCNE2 (LQT6). Of the 430 probands, 310 (72%) were identified as having a mutation associated with LQTS. Only the family members of these positive genotyped probands were screened (n=1,115) and 521 (46.7%) were genetically affected. Of the probands with a mutation, 296 (95.5%) were heterozygous carriers of a single mutation. Twelve patients were compound heterozygotes with 2 (n=11) or 3 (n=1) mutations, and two patients (0.6%) were homozygous. The most prevalent defect in those probands with a single mutation was on the KCNQ1 gene (49%) followed by defects in the KCNH2 gene (39%). Ten per cent of the probands had a mutation in the SCN5A gene, 1.7% in the KCNE1 gene and only 0.7% in the KCNE2 gene. Parental DNA was available from 247/310 (80%) of probands for genotyping, revealing that in the majority of cases that the mutation was inherited. Only 29 (12%) of cases were considered to be sporadic. Overall there were 235 different mutations detected, with 139 (59%) being considered novel mutations not previously reported. When clinical parameters were compared to the results of genetic testing the mean corrected QT interval for genetically affected individuals was 474 ms ( $\pm 46$  ms) (median =

467 ms, IQR<sup>1</sup> was 444-495 ms). The mean corrected QT interval amongst non-carrier family members was 406 ms ( $\pm$  27 ms) (median = 409 ms, IQR 390-425 ms). Amongst *probands*, the mean corrected QT interval was significantly longer ( $p < 0.001$ ) 496 ms ( $\pm$  46 ms) (median = 490 ms, IQR 462-520 ms) when compared to genetically affected family members, 461 ms ( $\pm$  40 ms) (median = 458 ms, IQR 436-484 ms).

The results of a study by Tester et al (2006) were similar (level IV Screening evidence). Unrelated consecutive patients (n=541) were referred for LQTS genetic testing and screening was conducted on five common mutations: KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5) and KCNE2 (LQT6). Blinded to genotype, clinical phenotype was established. Of the 541 referred patients, 269 (50%) were genotype negative. Of the 272 patients who were genotype positive, the majority had a single mutation, with 29/272 (10.8%) having multiple mutations. The most prevalent defect in patients with a single mutation was on the KCNQ1 gene (120/272, 44%) followed by defects in the KCNH2 gene (93/272, 34%). A mutation in the SCN5A gene was found in 9.6% of patients, 1.1% in the KCNE1 gene and only 0.4% in the KCNE2 gene (Table 1). There was no significant association between syncope, previous cardiac arrest or family history with a positive genetic genotype. It would appear that clinical diagnosis based on the Diagnostic Criteria points allocation system and a corrected QT interval  $>480$  ms are an accurate basis for diagnosis for LQTS as both of these factors were statistically significant in the genotype positive group ( $p < 0.0001$ ).

Table 1 Comparison of Genotype-Positive and Genotype-Negative Subsets (Tester et al 2006)

	Total Cohort	Genotype-Positive	Genotype-Negative	p Value
Number of unrelated patients	541	272	269	NS
Age at diagnosis (yrs) (range)	24 $\pm$ 16 (0-78)	23 $\pm$ 16 (0-75)	25 $\pm$ 16 (0-78)	NS
Gender (male/female)	183/358	94/178	89/180	NS
Ethnicity (% white)	93	90	96	NS
Average QTc (ms) (range)	482 $\pm$ 57	494 $\pm$ 51	470 $\pm$ 60	<0.0001
% with QTc $>480$ ms	46	57	35	<0.0001
% with syncope	42	46	38	0.067
% with cardiac arrest	12	13	12	NS
% with positive family history	42	46	38	0.067
% with Diagnostic criteria score $\geq 4$ <sup>a</sup>	29	41	17	<0.0001

QTc = corrected QT interval, <sup>a</sup> see Comparator section for description

The group of patients screened in the study by Tester et al (2006) had their DNA samples probed for LQT4, or the ANK2 gene, which encodes for the membrane adaptor protein ankyrin-B. As this gene does not code for a cardiac ion channel, many researchers in the field are reluctant to include it in the LQT family of mutations. However, patients who satisfy clinical diagnostic

<sup>1</sup> IQR = inter-quartile range

criteria but who are genotype negative for the traditional LQT mutations may carry a mutation in the ANK2 gene, which would explain their clinical symptoms. The study by Sherman et al (2005) screened the same 541 patients and 200 control DNA samples for ANK2 (level III-2 Screening evidence). Of the previous genotype *negative* group, 9/269 (3.3%) patients were genotype positive for ANK2. Five patients in the genotype positive group (5/272, 1.8%) were also positive for the ANK2 gene defect. Interestingly, an unexpectedly high number of controls were also genotype positive (13/200, 6.5%), which the authors reported warranted further investigation considering that LQTS affects only 1:5,000 (0.02%) individuals.

None of these studies reported on the subsequent treatment of the genotype positive patients and their outcomes.

### **COST IMPACT**

Phillips et al (2005) conducted a cost-effectiveness analysis of genetic testing for familial LQTS in symptomatic index cases. The population in this study was aged 15-40 years as little is known about LQTS after the age of 40 years. Index cases were assumed to have a compatible family history and clinical presentation consistent with LQTS. The expected cost-effectiveness of genetic testing of first-degree relatives or more distant relatives was not included in this analysis. The three most common mutations were examined in the KCNQ1, KCNH2 and the SCN5A genes. Genetic testing was found to be cost-effective compared to no genetic testing, at a cost per year life saved of US\$2,500, well below the standard threshold of US\$50,000 per life-year saved often used to define a cost-effective intervention. An extensive sensitivity analysis was conducted and the results were generally robust. If the mortality rate for untreated individuals *increases*, the cost-effectiveness of testing *increases* eg if the mortality rate doubles to 30%, cost-effectiveness of testing *decreases* to US\$1,200 per year of life saved. However, testing becomes both more costly and less effective if the mortality rate falls below 1.5%. In addition, as the cost of implantable cardiac defibrillators (ICD) increases, mutational analysis becomes more cost-effective. This is due to the fact that with a definitive diagnosis only a small proportion of patients will receive an ICD, however based on a clinical diagnosis alone, many “borderline” patients would receive an ICD although it is unlikely they will benefit from this preventative therapy. The benefit of mutational analysis for LQTS is that patients are more accurately diagnosed and therefore treated appropriately. A further cost-effectiveness analysis is required to consider the benefits of genetic testing of family members of the proband (Phillips et al 2005).

In New Zealand, the cost of a five gene scan is NZ\$3,000 (screening for LQT 1-3,5,6). If a mutation is found in the proband, the cost of familial screening is markedly reduced (NZ\$300) as only the one target mutation is screened for. In New Zealand the cost for screening is covered by the health service. Patients referred from Australia are not directly billed, however the referring clinician or hospital are billed, which may result in the patient bearing the cost (personal communication CIDG May 2006).

A commercial test, FAMILION<sup>®</sup>, is available in the United States produced by Genaisance Pharmaceuticals Inc. FAMILION<sup>®</sup> is designed to identify mutations in five of the major cardiac ion channel genes. Physicians in the United States take a blood sample from patients, which are then shipped back to Genaisance Pharmaceuticals Inc for analysis. It is stressed that FAMILION<sup>®</sup> should not be used to exclude the diagnosis of LQTS and that the test is expected to identify up to 75% of mutations that cause LQTS. The cost of full five gene analysis is US\$5,400 (Familion 2005).

## **ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

Probands and family members should receive appropriate genetic counselling on the potential risks, benefits and implications (especially for medical and life insurance) of a positive test. A negative test may reassure the patient and extended family, however a negative genetic test does not mean the family does not have LQTS. A positive test will have implications for further clinical follow-up and treatment options. Counselling is extremely important for both the proband and other family members and a full explanation of the inheritance of LQTS and its consequences should be an integral part of genetic counselling (CIDG 2006).

## **OTHER ISSUES**

No other issues were identified in the sources examined.

## **CONCLUSION:**

Studies assessed in this summary indicate that genetic screening is a potentially useful tool in diagnosing asymptomatic patients who may be carriers of an undetected genetic defect. These defects may only become apparent at first clinical presentation, which may in some cases be a cardiac event that results in death. A single cost-effectiveness study indicated that screening probands was cost-effective, however this study was not extended to include screening for family members. The number of potential individuals who would require genetic screening for long QT syndrome would be small if screening was limited to only family members of probands and as such would not incur a great financial burden on the health system. However the benefit of identifying an undetected mutation to these individuals would be far reaching.

## **HEALTHPACT ACTION:**

Given the potential health benefits of testing for long QT syndrome, an horizon scanning report, taking into account a broad range of clinical views, is recommended by HealthPACT.

## **SOURCES OF FURTHER INFORMATION:**

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#### **LIST OF STUDIES INCLUDED**

Total number of studies	
Level IV Screening evidence	2
Level III-2 Screening evidence	1
Level IV Aetiology evidence	1

#### **SEARCH CRITERIA TO BE USED:**

Long QT Syndrome/diagnosis/\*economics/\*genetics/therapy  
 Potassium Channels  
 \*Mutation  
 Sequence Analysis, DNA  
 DNA Mutational Analysis  
 Exons  
 Genetic Screening/\*economics