

Protocol to guide the
assessment of
molecular testing for
the diagnosis or
prediction of Long QT
Syndrome

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a decision analytic protocol that will be used to guide the assessment of molecular testing for (i) long QT syndrome in symptomatic patients, and (ii) clinically unaffected first or second degree family members of a patient with known¹ long QT syndrome. The protocol has been finalised after inviting relevant stakeholders to provide input, including Members of the Expert Standing Panel (MESP). It provides the basis for the evidence-based assessment of the intervention.

The protocol has been developed using the widely accepted "PICO" approach. This approach involves a clear articulation of the following aspects of the research questions that the assessment intends to answer:

Population – specification of the characteristics of the population or patients in whom the intervention is intended to be used;

Intervention – specification of the proposed intervention;

Comparator – specification of the therapy most likely to be replaced or added to, by the proposed intervention; and

Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

¹ The term 'known' is used primarily to describe the situation where a patient has a known mutation. However, there will be situations where the patient may have died of a sudden cardiac arrest before being diagnosed. In this case, the mutation may not be known, but the clinical diagnosis would be sufficient to warrant testing of close family members.

Purpose of application

In November 2010, an application from the Pathology Services Table Committee (PSTC) was received by the Department of Health and Ageing requesting a MBS listing of molecular testing for (i) long QT syndrome in symptomatic patients, and (ii) unaffected individuals with a relative who is known to have a pertinent mutation.

Adelaide Health Technology Assessment (AHTA), School of Population Health and Clinical Practice, University of Adelaide as part of its contract with the Department of Health and Ageing has developed this decision analytic protocol and will undertake an independent assessment of the safety, effectiveness and cost-effectiveness of genetic testing for Long QT syndrome in order to inform MSAC's decision-making regarding public funding of the intervention.

Intervention

Description

Long QT syndrome (LQTS) is an inherited cardiac conduction disorder and a leading cause of sudden death in apparently healthy individuals. LQTS manifests with recurrent episodes of syncope, polymorphous ventricular tachycardia (torsades de pointes) and sudden cardiac death defined by a natural and unexpected death due to cardiac events, within one hour of symptom onset. The main characteristics of the disease are the prolonged QTc interval and alteration of the T-wave morphology on electrocardiograms (ECG). The QT interval represents the time for both ventricular depolarisation and repolarisation to occur, estimating the duration of an average ventricular action potential. Depending on heart rate, a normal QT interval can range from 200 to 400 milliseconds (ms). After correction for heart rate, the normal corrected QT interval (QTc) is less than 440 ms. The T-wave represents the repolarisation (or recovery) of the ventricles and in the absence of a condition, shows a symmetrical morphology. However, patients with LQTS will present with either a flat, notched or peaked T-wave or T-waves with beat-to-beat variability (Goldenberg et al 2008b).

Long QT syndrome is caused by mutations in a set of genes which encode cardiac ion channel subunits or proteins involved in modulating ionic currents. At the present time (2011) mutations of 12 genes have been associated with LQTS (Ackerman & Mohler 2010; Bolik et al 2010). The genetic causes of LQTS involve mutations in the genes that regulate α -subunits (KCNQ1, KCNH2, SCN5A, CACNA1C and SNTA1), β -subunits (KCNE1, KCNE2, SCN4B, ANK2 and KCNJ2), Kir 2.1 subunits (KCNJ2), caveolin 3 membrane protein (CAV3) or

scaffolding protein (AKAP9). The twelve genes and associated long QT subtypes are as follows:

- KCNQ1 - LQT1 (Romano Ward syndrome);
- KCNH2 - LQT2 (Romano Ward syndrome);
- SCN5A - LQT3 (Romano Ward syndrome, Brugada syndrome);
- ANK2 - LQT4 (cardiac dysfunction);
- KCNE1 - LQT5 (Romano Ward syndrome, Jervell and Lange Nielsen syndrome);
- KCNE2 - LQT6 (Romano Ward syndrome);
- KCNJ2 - LQT7 (Anderson syndrome);
- CACNA1C – LQT8 (Timothy syndrome);
- CAV3 – LQT9
- SCN4B – LQT10 (Romano Ward syndrome);
- AKAP9 – LQT11; and
- SNTA1 – LQT12.

LQT1 and 2 account for 40% and 30-40% of all LQTS cases, respectively. LQT3 is less common with 10% of all cases. LQT4 to 12 make up the remaining 10%, of which some forms are known in only a single case or single family. In approximately 10% of cases the patient carries a second LQTS-causing mutation, in either the same gene or in another ion channel gene (Tester et al 2005).

Besides mutations, LQTS can also be acquired as an adverse response to drugs, metabolic abnormalities or bradyarrhythmias (Table 1). In general, genetic testing is not indicated for this particular group of patients.

Table 1 Causes of acquired long QT

Antiarrhythmic drugs	Quinidine Procainamide or N-acetylprocainamide Disopyramide Amiodarone and dronedarone Sotalol Dofetilide, Ibutilide, azimilide, sotalolide
Antimicrobial drugs	Erythromycin, clarithromycin, telithromycin, azithromycin (minor) Pentamidine Some fluoroquinolones (eg, sparfloxacin, gatifloxacin, evofloxacin, moxifloxacin) Other - Spiramycin, chloroquine, halofantrine mefloquine
Antihistamines	Terfenadine Astemizole
Psychotropic drugs	Thioridazine Phenothiazines Tricyclic or tetracyclic antidepressants Haloperidol and other butyrophenones
Other drugs	Selective serotonin reuptake inhibitors Risperidone Methadone Vasodilators; Prenylamine, bepridil, mibefradil Diuretics inducing electrolyte change (hypokalemia or hypomagnesemia) Serotonin antagonist; Ketanserin Motility drugs; Cisapride, domperidone Droperidol; safe at the low doses (0.625 to 1.25 mg) Ranolazine HIV protease inhibitors Miscellaneous; Organophosphate insecticides, probucol, cocaine, terodiline, papaverine, certain Chinese herbs, chloral hydrate, arsenic trioxide, cesium chloride, levomethadyl
Metabolic disorders	Hypokalemia, Hypomagnesemia, Hypocalcemia, Starvation, Anorexia nervosa, Liquid protein diets and Hypothyroidism
Bradycardias	Sinus node dysfunction AV block; second or third degree
Other factors	Myocardial ischemia or infarction Intracranial disease HIV infection Hypothermia Connective tissue diseases with anti-Ro/SSA antibodies

Source: (Berul et al 2010)

To identify the presence of an LQT mutation, genetic testing has to be performed, which requires a blood sample to isolate DNA, so that the genes of interest can be amplified from the patient's genome using specifically designed primer in a polymerase chain reaction (PCR). The PCR product is subjected to DNA sequencing to identify insertions, mis-sense and nonsense mutations, as well as multiplex ligation-dependent probe amplification (MLPA) to detect any large deletions and gene rearrangements. This technique allows the use of only one single primer for detection of genomic deletions and insertions (one or more entire exons). Any differences between the test and reference DNA can indicate a possible mutation in the patient's DNA. Only the genes linked to LQT types 1, 2, 3, 5, 6 and 7 are sequenced as the other types are very rare.

Administration, frequency of administration, duration of treatment

Molecular testing for LQTS is administered on one occasion, as the condition is hereditary and the test result is considered conclusive, regardless of whether it is being used for a diagnostic or predictive purpose. The tests should be ordered and interpreted by specialised cardiologists/electrophysiologists and clinical geneticists in the context of a specialty clinical service (eg Cardiac Genetic Clinics) and performed by an accredited molecular laboratory (eg Victorian Clinical Genetics Services). Although testing need only occur on one occasion, predictive tests are required to be analysed in duplicate (The Royal College of Pathologists of Australasia 2007).

In asymptomatic family members, genetic testing should only occur after genetic counselling. Testing should therefore be limited to centres which can provide accredited genetic counselling.

Co-administered interventions

In symptomatic patients, an indication for molecular testing for LQTS is based on the Schwartz score (Schwartz et al 1993). This score consists of a combination of points given for the clinical history, family history and electrocardiographic findings. A standard 12-lead electrocardiogram (ECG) is required to analyse the QTc interval² and T-wave morphology. To further improve diagnosis in borderline cases, additional methods of testing are used, like 24-hour Holter monitoring, exercise stress test ECGs, Adrenaline challenge test (non exercise stress test) or event ECG monitoring. Holter monitoring (ambulatory ECG) is used to detect extreme QTc interval events that happen infrequently during the day. Information regarding T-wave amplitude morphology is provided according to changing heart rates. The adrenaline challenge test is performed by intravenous administration of medication (such as epinephrine), to simulate intense exercise or emotional upset. During this procedure an ECG monitors the heart response, which may reveal concealed LQT. ² the QT interval is the time between the start of the Q wave and the end of the T wave in the electrical conduction of the heart. In general, the QT interval represents electrical depolarisation and repolarisation of the left and right ventricles. A prolonged QT interval is a biomarker for ventricular tachyarrhythmias that may lead to death.

In some LQTS patients, these sudden bursts of adrenaline can also trigger syncope. Patients with a Schwartz score of 3 or above are referred for genetic testing.

Unaffected individuals with a family member with a known mutation will be referred for genetic testing after genetic counselling. Based on a positive test result (mutation present), clinical assessment will be conducted with a standard 12-lead electrocardiogram (ECG), 24-hour Holter monitoring, exercise stress ECGs, adrenaline challenge test or event ECG monitoring.

The MBS/AR-DRG item numbers for these additional tests are listed in Table 6. Additional testing is required on at least one occasion, in the work-up to a possible diagnosis of LQTS of a symptomatic patient.

Background

Current arrangements for public reimbursement

Currently, there is no MBS listing for any test that detects germline mutations in the genes that are associated with LQTS.

There are MBS items that allow reimbursement for molecular tests that detect specific genetic mutations and/or monitor patients with disease (Table 2). The range of MBS fees associated with these items are indicative of the range of molecular methodologies used to detect the relevant mutations. Quantitative or semi-quantitative assays will incur greater costs than methods that are simply qualitative. However, the MBS items already listed for other heritable genetic diseases are classified as 'Level 1' under the current National Pathology Accreditation Advisory Council (NPAAC) guidelines, consisting of single PCR tests directed to the presence or absence of only one amplicon. Conversely, assessing for LQTS requires a 'Level 2' genetic test under the NPAAC guidelines, which is much more difficult to perform and interpret. The fees provided for the existing genetic tests are therefore not a good indicator of what would be proposed for genetic testing for LQTS.

Currently, molecular testing for LQTS is performed by the Victorian Clinical Genetics Service Pathology, at the Murdoch Institute and by LabPlus, at the medical laboratory of Auckland City Hospital, New Zealand.

Table 2 Current MBS items related to detection of genetic mutations

Item 73308	Characterisation of the genotype of a patient for Factor V Leiden gene mutation, or detection of the other relevant mutations in the investigation of proven venous thrombosis or pulmonary embolism - 1 or more tests Fee: \$36.70
Item 73317	Detection of the C282Y genetic mutation of the HFE gene and, if performed, detection of other mutations for haemochromatosis where: (a) the patient has an elevated transferrin saturation or elevated serum ferritin on testing of repeated specimens; or (b) the patient has a first degree relative with haemochromatosis; or (c) the patient has a first degree relative with homozygosity for the C282Y genetic mutation, or with compound heterozygosity for recognised genetic mutations for haemochromatosis (Item is subject to rule 20) Fee: \$36.70
Item 73320	Detection of HLA-B27 by nucleic acid amplification includes a service described in 71147 unless the service in item 73320 is rendered as a pathologist determinable service. (Item is subject to rule 27) Fee: \$40.80
Item 73314	Characterisation of gene rearrangement or the identification of mutations within a known gene rearrangement, in the diagnosis and monitoring of patients with laboratory evidence of: (a) acute myeloid leukaemia; or (b) acute promyelocytic leukaemia; or (c) acute lymphoid leukaemia; or (d) chronic myeloid leukaemia; Fee: \$232.50

Source: (Department of Health and Ageing 2009)

Clinical need and burden of disease

Data regarding the prevalence of Long QT Syndrome in Australia are scarce. However, it is estimated that 30% of unidentified sudden deaths in young Australians (aged <35 years), can be attributed to primary arrhythmogenic disorders, such as Long QT syndrome (Shephard & Semsarian 2009). The prevalence of LQTS is approximately 1 in 2,000 live births (Schwarz et al 2009), or close to 1 in 2,500 live births, which might be an underestimation as there are a significant number of silent mutation carriers (Crotti et al 2008). In 2007, the number of separations for other and unspecified disorders of the circulatory system was 126 (AIHW National Hospital Morbidity Database). However, this might also included other causes besides long QT syndrome. Similarly, there are minimal data regarding the incidence of LQTS.

The literature indicates that prior to the age of 20 years, boys have a higher risk of having an LQT-related cardiac event than girls. After the age of 20 years, the risk crosses over to

females being more prone to cardiac events than males. Similarly, males under the age of 26 are more likely to have an aborted cardiac event or a sudden cardiac death than females, whereas in the over 26 age bracket, females are more at risk (Goldenberg et al 2008a). There is no clear evidence for race-related differences in the occurrence of long QT syndrome.

Regulatory status

In vitro diagnostic medical devices (IVDs) are, in general, pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management (Therapeutic Goods Administration 2009).

The Therapeutic Goods Administration (TGA) regulatory framework for IVDs changed in July 2010, such that in-house laboratory tests now receive the same level of regulatory scrutiny as commercial kits. As testing for LQTS is currently only provided as an in-house IVD, it would be classified as a Class 3 in-house IVD (see Box 1).

Box 1 Classification of Class 3 in vitro diagnostic medical devices Therapeutic Goods (Medical Devices) Regulations 2002 –Schedule 2A

1.3 Detection of transmissible agents or biological characteristics posing a moderate public health risk or high personal risk

1. An IVD is classified as Class 3 IVD medical devices or a Class 3 in-house IVD if it is intended for any of the following uses:

- a. detecting the presence of, or exposure to, a sexually transmitted agent;
- b. detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation;
- c. detecting the presence of an infectious agent where there is a significant risk that an erroneous result would cause death or severe disability to the individual or foetus being tested;
- d. pre-natal screening of women in order to determine their immune status towards transmissible agents;
- e. determining infective disease status or immune status where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient;
- f. the selection of patients for selective therapy and management, or for disease staging, or in the diagnosis of cancer;
- g. human genetic testing;**
- h. to monitor levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient;
- i. the management of patients suffering from a life-threatening infectious disease;
- j. screening for congenital disorders in the foetus.

Note: For paragraph (f) An IVD medical device would fall into Class 2 under clause 1.5 if:

- k. a therapy decisions would usually be made only after further investigation; or
 - l. the device is used for monitoring.
2. Despite subsection (1) an IVD is classified as a Class 3 IVD medical device or a Class 3 in-house IVD if it is used to test for transmissible agents included in the Australian National Notifiable Diseases Surveillance System (NNDSS) list as published from time to time by the Australian government.

Source: <http://www.tga.gov.au/ivd/ivd-classification.htm> [accessed January 2011]

Laboratories that manufacture in-house Class 3 IVDs are required to notify the TGA of the types of IVDs manufactured in each laboratory for inclusion on a register. These laboratories must have NATA accreditation, with demonstrated compliance with the suite of standards on the validation of in-house IVDs, as published by the National Pathology Accreditation Advisory Committee (NPAAC), for each test manufactured. Manufacturers of Class 2, Class 3 and Class 4 IVDs must hold certification from a regulatory body to show compliance with a suitable conformity assessment procedure (Therapeutic Goods Administration 2009).

Patient population

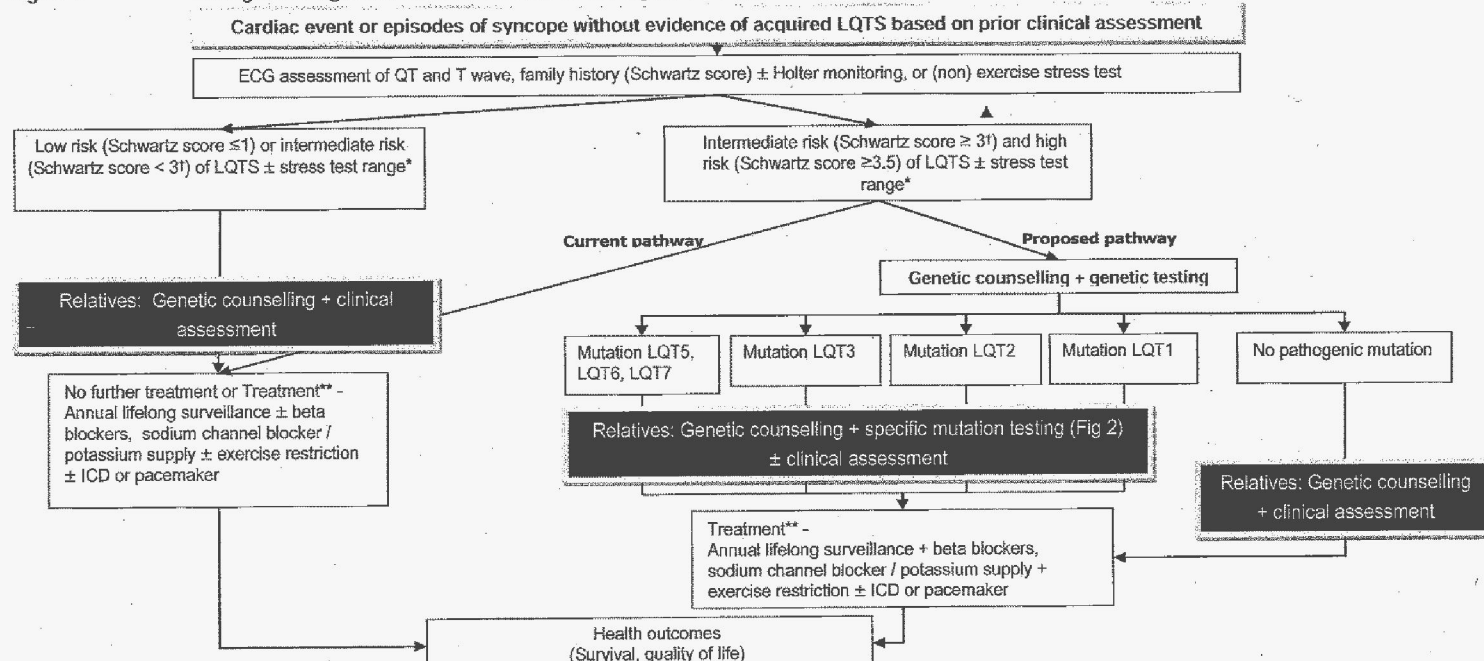
Clinical place for proposed intervention

Molecular testing for the detection of germline mutations in the genes associated with LQTS would be provided in addition to the current approaches to diagnosing LQTS in patients with signs or symptoms of the syndrome, and as a triage for clinical assessment and lifelong surveillance when predicting LQTS in asymptomatic family members. Molecular testing would only be conducted in those patients where acquired LQTS is ruled out.

One management algorithm is provided below for the diagnostic (Figure 1) and one for the predictive (Figure 2) use of molecular testing for LQTS. It is acknowledged that some patients currently receive genetic testing for LQTS, without it being listed on the MBS, however, for the sake of simplicity, the "current pathway" outlines the management approach taken for the diagnosis or prediction of LQTS without molecular testing. The "proposed pathway" outlines the approaches when molecular testing is available. Special emphasis should be given to material differences between the current and proposed clinical management of LQTS in the type of healthcare resources and the frequencies of their use. The main difference between the algorithms is the targeted use of genetic testing in unaffected family members, where those with a negative genetic test would no longer require clinical assessment, lifelong surveillance, or treatment.

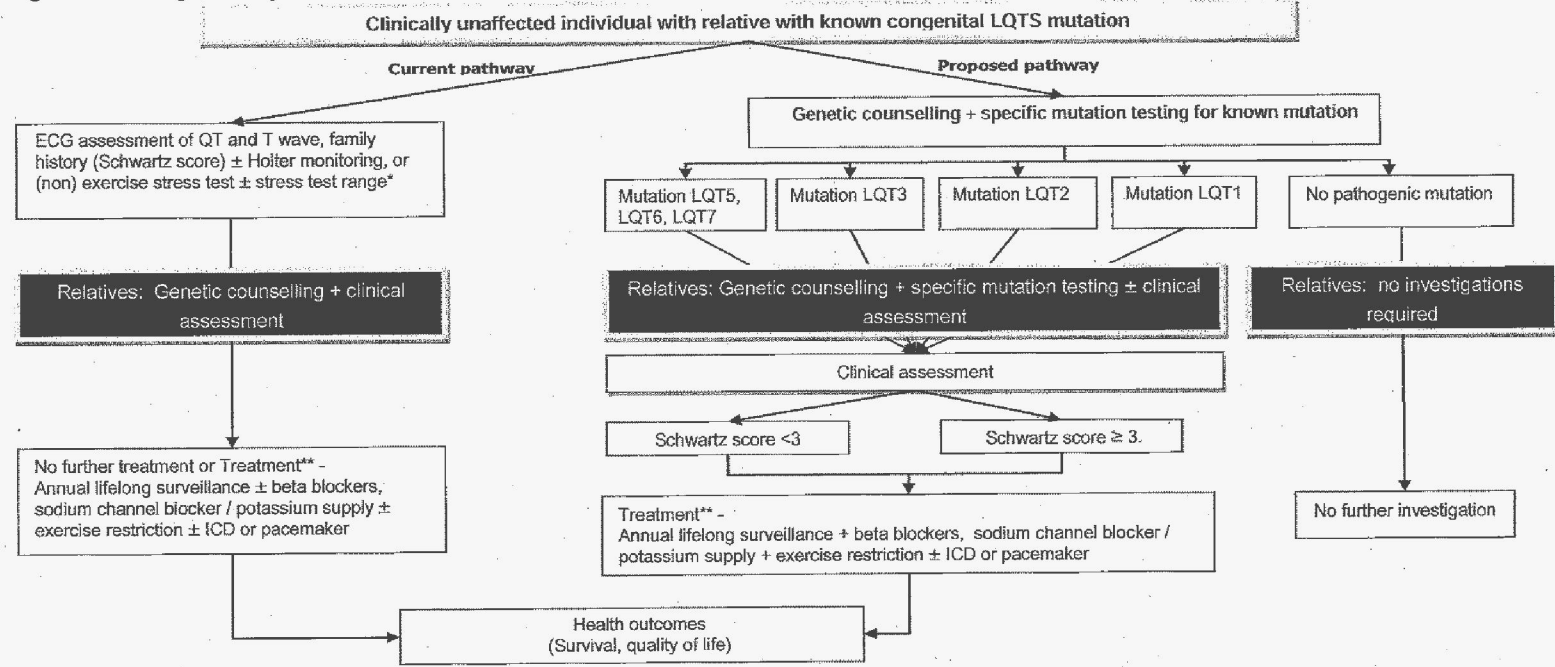
Figure 1

Management algorithm for use of molecular testing for the diagnosis of Long QT syndrome



† a score of 2 may prompt for genetic testing in some cases; * Stress test range: LQT1 when ΔQT end ≥ 35 ms; LQT2 when ΔQT end ≥ 80 ms; LQT3 or control when ΔQT end ≥ 35 ms and < 80 ms
 ** Treatment will vary according to age and clinical presentation; ICD = implantable cardiac defibrillator

Figure 2 Management algorithm for use of molecular testing for the prediction of long QT syndrome in individuals with a relative with known long QT syndrome



Stress test range: LQT1 when Δ QT end ≥ 35 ms; LQT2 when Δ QT end ≥ 80 ms; LQT3 or control when Δ QT end ≥ 35 ms and < 80 ms;
 ** Treatment will vary according to age and clinical presentation; ICD = implantable cardiac defibrillator

Proposed MBS listing

The proposed MBS item descriptors and fees are provided in Table 3.

Table 3 Proposed MBS item descriptors for genetic testing for diagnosis and prediction of long QT syndrome

Category 6–Pathology services

MBS [item number]

Detection of germline mutations in the genes that regulate α -subunits (KCNQ1 (LQT1), KCNH2 (LQT2) and SCN5A (LQT3)) and β -subunits (KCNE1 (LQT5), KCNE2 (LQT6) and KCNJ2 (LQT7)) in:

- (a) Patients with symptoms and signs suggestive of intermediate or high risk of Long QT syndrome (Schwartz score >3)

-1 or more tests

Fee: \$3,730.00

Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the treating practitioner, a genetic counselling service or by a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

MBS [item number]

Detection of specific known mutation (α -subunits - KCNQ1 (LQT1) or KCNH2 (LQT2) or SCN5A (LQT3)) or β -subunits (KCNE1 (LQT5) or KCNE2 (LQT6) or KCNJ2 (LQT7)) in -

- (a) Relatives of patients with a known mutation associated with long QT syndrome

-1 or more tests

Fee: \$287.00

Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the treating practitioner, a genetic counselling service or by a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

NB: The phrase "1 or more tests" may describe a package of tests

Comparator

The current standard approach to the diagnosis of LQTS involves a clinical scoring system developed in 1993 (Schwartz et al 1993). The scoring system includes several clinical indicators and the patient's family history. The clinical indicators are: past episodes of syncope (fainting), either with or without stress; congenital deafness in the patient; length of the patient's QTc in milliseconds; torsade de pointes (TdP); T-wave alternans; notched T wave in 3 leads; and low heart rate for age. A family member with definite LQTS and/or unexplained sudden cardiac death in an immediate family member aged less than 30 years are relevant family history indicators. Based on the absence or presence of these indicators a clinical score is determined which corresponds to either a low probability of having LQTS (≤ 1 point); an intermediate chance of LQTS (2-3 points); or a high probability of having LQTS (≥ 3.5 points) (Table 4).

Table 4 Criteria for diagnosis of LQTS (Khan 2002)

CHARACTERISTICS	POINTS
Clinical history	
Syncope	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history*	
Family members with definite LQTS	1
Unexplained sudden cardiac death at age <30 y among immediate family members	0.5
Electrocardiographic findings†	
QTc	
≥480 ms	3
460-470 ms	2
450 ms (in males)	1
Torsade de pointes	2
T-wave alternans	1
Notched T wave in 3 leads	1
Low heart rate for age (<2nd percentile)	0.5

Scoring: ≤1 point = low probability, 2-3 points = intermediate probability, ≥3.5 points = high probability. Torsade de pointes and syncope are mutually exclusive.*The same family member cannot be counted twice, †In absence of medications or disorders known to affect these electrocardiographic features.

The use of standard 12-lead ECG assessment is required to analyse the QTc interval and T-wave morphology. LQTS patients present with a prolonged QTc interval and alterations in T-wave morphology.

Based on the ECG, QT interval durations may be identified as a normal range, borderline or prolonged range, depending on age and gender. Based on the ECG, QTc interval durations in adult males may be identified as within the normal range (<430 ms), borderline (430 – 450 ms) or in the prolonged range (>450). However, children and adult females present with QT intervals that are often longer than in adult males. In children a QT interval between 440 and 460 ms is defined as borderline and above 460 as prolonged. In adult

females, borderline values are between 450 and 470ms and prolonged above 470ms. In general, a QTc interval of more than 450 ms is indicative of possible LQTS (Goldenberg & Moss 2008). Table 5 provides an overview of the proportion of affected individuals with the different QTc intervals in males and females.

Table 5 Proportion of affected males and females with specific QTc intervals

Proportion of affected individuals	QTc (msec)	
	Resting QTc or max QTc on exercise	
	Male	Female
68%	> 470	> 480
20%	450 - 460	460 - 470
11% (LQT1 = 12%; LQT2 = 17%; LQT3 = 5%)	400 - 440	400 - 450
<< 1%	< 400	< 400

Source: (Vincent et al 1992)

Besides the QTc interval, careful analysis of T-wave morphology may be beneficial for the diagnosis of LQTS patients. Alterations in the pattern of repolarisation morphology in LQTS include notched T-waves, flat T-waves, broad-based T-waves with slow upslope of the initial segment, peaked T-waves, complex patterns of overlapping or merged T and U-waves and beat-to-beat variability in T-waves. It is even suggested that there is a relationship between T-wave morphology and genotype, where LQT1 presents with mainly wide, broad-based T-waves, LQT2 is identified by usually low amplitude and frequently notched T-waves, and LQT3 presents with peaked and frequently tall T-waves (Goldenberg & Moss 2008).

To further improve diagnosis in borderline cases, additional methods of testing are used, like 24-hour Holter monitoring, exercise stress ECG test, non exercise stress ECG test or sometimes event monitoring. Holter monitoring is used for the detection of extreme QTc interval events that happen infrequently during the day and give information regarding T-wave amplitude morphology with changing heart rates. Exercise stress testing, according to a standardised exercise protocol, may be used to observe QT prolongation during exercise and recovery periods. The presence of a QTc longer than 500ms at a heart rate of less than 100 beats per minute during either of these tests may be indicative of LQTS. ECG testing on its own is insufficient to determine the presence of LQTS as 50% of carriers and non carriers present with borderline QTc intervals.

The commonly occurring types of healthcare resources used currently for the diagnosis and prediction of LQTS are summarised in Table 6 below.

Table 6 Presenting commonly occurring types of healthcare resources required for the diagnosis and management of patients with long QT syndrome

Table 6 Presenting commonly occurring types of healthcare resources required for the diagnosis and management of patients with long QT syndrome

Type of resource and source	Identifier	Description	Quantity provided
Medicare Benefits Schedule (MBS)	MBS item number 23	LEVEL B CONSULTATION AT CONSULTING ROOMS Professional attendance at consulting rooms by a general practitioner (not being a service to which any other item in this table applies) lasting less than 20 minutes, including any of the following that are clinically relevant: a) taking a patient history; b) performing a clinical examination; c) arranging any necessary investigation; d) implementing a management plan; e) providing appropriate preventive health care; in relation to 1 or more health-related issues, with appropriate documentation.	Fee: \$34.90 Benefit: 100% = \$34.90
	MBS item number 104	SPECIALIST, REFERRED CONSULTATION - SURGERY OR HOSPITAL (Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred to him or her) INITIAL attendance in a single course of treatment, not being a service to which ophthalmology items 106, 109 or obstetric item 16401 apply.	Fee: \$82.30 Benefit: 75% = \$61.75 85% = \$70.00
	MBS item number 105	Each attendance SUBSEQUENT to the first in a single course of treatment	Fee: \$41.35 Benefit: 75% = \$31.05 85% = \$35.15
	MBS item number 110	CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY), REFERRED CONSULTATION - SURGERY OR HOSPITAL Professional attendance at consulting rooms or hospital by a consultant physician in the practice of his or her specialty (other than in psychiatry) where the patient is referred to him or her by a medical practitioner - INITIAL attendance in a single course of treatment	Fee: \$145.20 Benefit: 75% = \$108.90 85% = \$123.45
	MBS item number 116	CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY), REFERRED CONSULTATION - SURGERY OR HOSPITAL (Professional attendance at consulting rooms or hospital by a consultant physician in the practice of his or her specialty (other than in psychiatry) where the patient is referred to him or her by a medical practitioner) - Each attendance (other than a service to which item 119 applies) SUBSEQUENT to the first in a single course of treatment	Fee: \$72.65 Benefit: 75% = \$54.50 85% = \$61.80
	MBS item number 132	CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY) REFERRED PATIENT TREATMENT AND MANAGEMENT PLAN - SURGERY OR HOSPITAL	Fee: \$253.90 Benefit: 75% = \$190.45 85% = \$215.85

	<p>Professional attendance of at least 45 minutes duration for an initial assessment of a patient with at least two morbidities (this can include complex congenital, developmental and behavioural disorders), where the patient is referred by a medical practitioner, and where</p> <p>a) assessment is undertaken that covers:</p> <ul style="list-style-type: none"> - a comprehensive history, including psychosocial history and medication review; - comprehensive multi or detailed single organ system assessment; - the formulation of differential diagnoses; and <p>b) a consultant physician treatment and management plan of significant complexity is developed and provided to the referring practitioner that involves:</p> <ul style="list-style-type: none"> - an opinion on diagnosis and risk assessment - treatment options and decisions - medication recommendations <p>Not being an attendance on a patient in respect of whom, an attendance under items 110, 116 and 119 has been received on the same day by the same consultant physician.</p> <p>Not being an attendance on the patient in respect of whom, in the preceding 12 months, payment has been made under this item for attendance by the same consultant physician.</p>	
<p>MBS item number 133</p>	<p>CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY) REVIEW OF REFERRED PATIENT TREATMENT AND MANAGEMENT PLAN - SURGERY OR HOSPITAL</p> <p>Professional attendance of at least 20 minutes duration subsequent to the first attendance in a single course of treatment for a review of a patient with at least two morbidities (this can include complex congenital, developmental and behavioural disorders), where</p> <p>a) a review is undertaken that covers:</p> <ul style="list-style-type: none"> - review of initial presenting problem/s and results of diagnostic investigations - review of responses to treatment and medication plans initiated at time of initial consultation <p>comprehensive multi or detailed single organ system assessment,</p> <ul style="list-style-type: none"> - review of original and differential diagnoses; and <p>b) a modified consultant physician treatment and management plan is provided to the referring practitioner that involves,</p> <p>where appropriate:</p> <ul style="list-style-type: none"> - a revised opinion on the diagnosis and risk assessment - treatment options and decisions - revised medication recommendations <p>Not being an attendance on a patient in respect of whom, an attendance under item 110, 116 and 119 has been received on the same day by the same consultant physician.</p> <p>Being an attendance on a patient in respect of whom, in the preceding 12 months, payment has been made under item 132 by the same consultant physician, payable no more than twice in any 12 month period.</p>	<p>Fee: \$127.10 Benefit: 75% = \$95.35 85% = \$108.05</p>

	MBS item 11700	TWELVE-LEAD ELECTROCARDIOGRAPHY, tracing and report	Fee: \$30.05 Benefit: 75% = \$22.55 85% = \$25.55
	MBS item number 11709	CONTINUOUS ECG RECORDING (Holter) of ambulatory patient for 12 or more hours (including resting ECG and the recording of parameters), NOT IN ASSOCIATION WITH AMBULATORY BLOOD PRESSURE MONITORING, utilising a system capable of superimposition and full disclosure printout of at least 12 hours of recorded ECG data, microprocessor based scanning analysis, with interpretation and report by a specialist physician or consultant physician	Fee: \$161.15 Benefit: 75% = \$120.90 85% = \$137.00
	MBS item number 11712	MULTI CHANNEL ECG MONITORING AND RECORDING during exercise (motorised treadmill or cycle ergometer capable of quantifying external workload in watts) or pharmacological stress, involving the continuous attendance of a medical practitioner for not less than 20 minutes, with resting ECG, and with or without continuous blood pressure monitoring and the recording of other parameters, on premises equipped with mechanical respirator and defibrillator	Fee: \$146.35 Benefit: 75% = \$109.80 85% = \$124.40
	MBS item number 38350	SINGLE CHAMBER PERMANENT TRANSVENOUS ELECTRODE, insertion, removal or replacement of, including cardiac electrophysiological services where used for pacemaker implantation	Fee: \$614.45 Benefit: 75% = \$460.85
	MBS item number 38353	PERMANENT CARDIAC PACEMAKER, insertion, removal or replacement of, not for cardiac resynchronisation therapy, including cardiac electrophysiological services where used for pacemaker implantation	Fee: \$245.80 Benefit: 75% = \$184.35
	MBS item number 38356	DUAL CHAMBER PERMANENT TRANSVENOUS ELECTRODES, insertion, removal or replacement of, including cardiac electrophysiological services where used for pacemaker implantation	Fee: \$805.65 Benefit: 75% = \$604.25
Pharmaceutical Benefits Schedule (PBS)	PBS item numbers:	BETA-ADRENERGIC BLOCKERS Beta blocking agents, non-selective	DPMQ:
	2043M	SOTALOL HYDROCHLORIDE, 160 mg	\$26.50 - \$31.50
	8398B	SOTALOL HYDROCHLORIDE, 80 mg	\$15.78 - \$20.78
	2565B	PROPRANOLOL HYDROCHLORIDE, 10 mg	\$10.19 - \$13.33
	2566C	PROPRANOLOL HYDROCHLORIDE, 40 mg	\$10.58 - \$13.70
	2899N	PROPRANOLOL HYDROCHLORIDE, 160 mg	\$11.01
	3062E	PINDOLOL, 5 mg	\$11.48 - \$14.19
	3065H	PINDOLOL, 15 mg	\$13.71 - \$16.40
	2942W	OXPRENOLOL HYDROCHLORIDE, 20 mg	\$10.00
	2961W	OXPRENOLOL HYDROCHLORIDE, 40 mg	\$11.78

	1324Q 1325R 9310B 9311C 9312D 9316H 8604W 8605X 8606Y 1081X 8732N 8733P 8734Q 8735R	Beta blocking agents, selective METOPROLOL TARTRATE, 50 mg METOPROLOL TARTRATE, 100 mg NEBIVOLOL, 1.25 mg (as hydrochloride) NEBIVOLOL, 5 mg (as hydrochloride) NEBIVOLOL, 10 mg (as hydrochloride) NEBIVOLOL, 1.25 mg (as hydrochloride) BISOPROLOL FUMARATE, 2.5 mg BISOPROLOL FUMARATE, 5 mg BISOPROLOL FUMARATE, 10 mg ATENOLOL, 50 mg METOPROLOL SUCCINATE, 23.75 mg METOPROLOL SUCCINATE, 47.5 mg METOPROLOL SUCCINATE, 95 mg METOPROLOL SUCCINATE, 190 mg	\$10.84 - \$14.09 \$12.03 - \$15.28 \$29.25 \$60.94 \$68.02 \$50.62 \$49.16 \$59.00 \$72.13 \$10.27 - \$13.81 \$21.04 \$72.46 \$88.96 \$109.60
	1088G 1090J	FLECAINIDE ACETATE, 50mg FLECAINIDE ACETATE, 50mg	\$37.75 \$44.69
	2642C	POTASSIUM CHLORIDE, 600 MG	\$13.02 - \$15.74
	2875H 2876J 3474W	Class TB anti arrhythmia LIGNOCAINE HYDROCHLORIDE, injection 100mg/5mL LIGNOCAINE HYDROCHLORIDE, infusion 500mg/5mL LIGNOCAINE HYDROCHLORIDE, injection 100mg/5mL (emergency drug supplies)	\$37.33 \$29.59 \$37.33
	ARTG 17933 17931	MEXITIL, mexiletine hydrochloride 50mg MEXITIL, mexiletine hydrochloride 200mg	
Prosthesis List (PL)	PL item number SJ053 SJ067 BT062 / 080/ 106/ 109/ 113 BS124/ 145/ 147/ 149/ 152 GU124/ 126/ 139 MC728 SA137/ 142/ 143	Single chamber pacemaker	\$4.264 - \$ 5.928

	SJ060/ 077/ 090/ 105/ 131/ 205 BT108/ 110 SJ200		min benefit \$5.928 max benefit \$ 8.928 min benefit \$5.928 max benefit \$7.928
	GU 149 / 150 SA 140 MC 721 / 938 SJ 115 / 123 BS 128 SA 147	ICD	\$ 43.686 - \$ 45.760
Private hospital admission	AR-DRG F73A F73B F70A F70B F71A F71B	Syncope & Collapse + CSCC Syncope & Collapse - CSCC Mjr Arrhythmia&Crdc Arrst+CSCC Mjr Arrhythmia&Crdc Arrst-CSCC N-Mjr Arythm&Conductn Dsrst+CSCC N-Mjr Arythm&Conductn Dsrst-CSCC	4,485 (8.35 ALOS) 2,201 (3.43 ALOS) 4,957 (6.77 ALOS) 2,243 (2.97 ALOS) 4,260 (7.35 ALOS) 2,209 (2.25 ALOS)
Public hospital admission	AR-DRG F73A F73B F70A F70B F71A F71B	Syncope & Collapse + CSCC Syncope & Collapse - CSCC Mjr Arrhythmia&Crdc Arrst+CSCC Mjr Arrhythmia&Crdc Arrst-CSCC N-Mjr Arythm&Conductn Dsrst+CSCC N-Mjr Arythm&Conductn Dsrst-CSCC	4,991 (5.37 ALOS) 1,877 (1.94 ALOS) 6,378 (4.75 ALOS) 2,379 (2.06 ALOS) 5,843 (5.86 ALOS) 2,160 (2.18 ALOS)
Public hospital emergency care	ATS** number	Cardiac arrest Cardiac arrhythmia	

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; DPMQ = Dispensed price for maximum quantity; AR-DRG = Australian Refined Diagnosis Related Group; ALOS = Average length of stay

*AR-DRG = Australian Refined Diagnosis Related Group

** ATS = Australian Triage Scale

Outcomes³

The health outcomes upon which the comparative clinical performance of molecular testing for LQTS (in addition, or as a triage for the current diagnostic approaches for LQTS), versus the comparator of current LQTS diagnostic approaches alone, will be measured are:

Effectiveness

Primary (patient relevant)

- mortality/survival
- incidence of life-threatening events, ie. cardiac arrest
- quality of life

Secondary

- incidence of symptoms, including arrhythmia (eg tachycardia), length of the patient's QTc in milliseconds, torsade de pointes (TdP), T-wave alternans, notched T wave in 3 leads, low heart rate for age, ventricular fibrillation and syncope
- patient anxiety
- age at diagnosis

Safety

- psychological and physical harms from testing

Summary of PICO to be used for assessment of evidence (systematic review)

Table 7 provides a summary of the PICO used to:

- (1) define the question for public funding,
- (2) select the evidence to assess the safety and effectiveness of molecular testing for LQTS, and
- (3) provide the evidence-based inputs for any decision-analytic modelling to determine the cost-effectiveness of molecular testing for LQTS.

The methodology for undertaking this evidence-based assessment of molecular testing in the diagnosis of LQTS is outlined in detail in the "Assessment methodology" section of the protocol.

³ These will be assessed in the event that there is direct evidence of the effect of molecular testing on health outcomes (eg randomised controlled trials or intervention studies). In the absence of this evidence, a linked evidence approach will be used – the PICO criteria that are relevant to this type of evidence are given in Appendix A.

Table 7 Summary of PICO to define the clinical questions that the assessment will investigate

Patients	Intervention	Comparator	Reference Standard	Outcomes to be assessed
Patients suspected of having long QT syndrome, who are classified as intermediate or high risk (Schwartz score ≥ 3)	ECG (Schwartz score) \pm exercise stress test \pm Holter monitoring plus molecular genetic testing for LQTS	ECG (Schwartz score) \pm exercise stress test \pm Holter monitoring	Clinical diagnosis determined from long term follow-up	<p>Safety: Psychological and physical harms from genetic and clinical testing</p> <p>Effectiveness: <i>Direct evidence</i> Primary outcomes – Mortality/survival; quality of life; incidence of life-threatening events including cardiac arrest and ventricular fibrillation Secondary outcomes – incidence of symptoms, age at diagnosis <i>Plus linked evidence ^a</i></p>
Clinically unaffected relatives of a patient with a known long QT syndrome	Molecular genetic testing for LQTS \pm ECG (Schwartz score) \pm exercise stress test \pm Holter monitoring	ECG (Schwartz score) \pm exercise stress test \pm Holter monitoring	Clinical diagnosis determined from long term follow-up	<p>Safety: Psychological and physical harms from genetic and clinical testing</p> <p>Effectiveness: <i>Direct evidence</i> Primary outcomes – Mortality/survival; quality of life; incidence of life-threatening events including cardiac arrest and ventricular fibrillation Secondary outcomes – incidence of symptoms, age at diagnosis <i>Plus linked evidence ^a</i></p>
<p>Clinical Questions</p> <p>1. <i>Is molecular testing for the genetic mutations associated with LQTS safe and effective when used in addition to clinical diagnostic approaches in the diagnosis of patients presenting with symptoms suggestive of long QT syndrome?</i></p> <p>2. <i>Is molecular testing for the genetic mutations associated with LQTS safe and effective when used as a triage test for clinical assessment, treatment and life-long monitoring of family members of patients who are known to have LQTS?</i></p>				

^a See Appendix A for outcomes if a linked evidence approach is needed.

Clinical claim

The PSTC application claims that: (i) molecular testing for LQTS ensures identification of all patients with LQTS and so there can be accurate targeting of treatment appropriate to the specific LQTS mutation; and (ii) molecular testing for LQTS ensures identification of all family members with LQTS so that lifelong prophylaxis can be provided and unnecessary monitoring of family members who have not inherited the condition can be avoided.

These claims suggest that molecular testing (i) as an addition to current diagnostic approaches to identify LQTS in symptomatic patients; and (ii) as triage for clinical assessment and lifelong monitoring of family members of a LQTS proband, would result in superior health outcomes for the individuals affected. Relative to the comparator, molecular testing would therefore be considered non-inferior in terms of safety. In the diagnostic setting (as an additional test), molecular testing would be considered superior in terms of effectiveness. As such, the type of economic evaluation required is a cost-effectiveness analysis or cost-utility analysis (green shading in Table 8). In the predictive setting (as a triage test), molecular testing could potentially be superior, non-inferior or inferior to the comparator (green, orange and blue shading in Table 8). If superiority is demonstrated in the literature, a cost-effectiveness analysis or cost-utility analysis will be performed. If non-inferiority is demonstrated, a cost-comparison will be performed with sensitivity analyses to examine the uncertainties around the conclusion of non-inferiority, for which an assessment will be provided by presentation of cost-effectiveness or cost-utility analysis. In the situation where triaging with molecular testing is found to be inferior to clinical assessment, a simple cost comparison is all that would be provided. Should superiority in health outcomes be unable to be demonstrated due to a lack of evidence, it would be treated as non-inferiority and the analysis will be performed as the above mentioned cost-comparison and sensitivity analysis with cost-effectiveness analysis (orange shading in Table 8).

Table 8 Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator				
		Superior		Non-inferior	Inferior	
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA	Net clinical benefit	CEA/CUA
					Neutral benefit	CEA/CUA*
					Net harms	None [^]
	Non-inferior	CEA/CUA		CEA/CUA*	None [^]	
		Inferior	Net clinical benefit	CEA/CUA	None [^]	None [^]
			Neutral benefit	CEA/CUA*		
Net harms	None [^]					

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is

often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

[^] No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes for economic evaluation

Ideally the health outcomes used in the economic evaluation are life-years gained and/or quality-adjusted life-years gained. However, these outcomes might not be available for a diagnostic or predictive test. In the case of absence of primary outcomes, some secondary outcomes will be used instead.

The health outcomes upon which the comparative clinical performance of molecular testing for LQTS in addition to current LQTS diagnostic approaches versus the comparator (current LQTS diagnostic approaches alone) will be measured are:

Effectiveness

Primary (patient relevant)

- mortality/survival
- quality of life
- incidence of life-threatening events, including cardiac arrest and ventricular fibrillation.

Secondary

- incidence of symptoms, including arrhythmia (eg tachycardia), length of the patient's QTc in milliseconds, torsade de pointes (TdP), T-wave alternans, notched T wave in 3 leads, low heart rate for age, and syncope
- age at diagnosis

Health care resources

Given that it is proposed that genetic testing will be used in addition to the current clinical assessment for the diagnosis of long QT syndrome, the cost of clinical assessment will be incurred in both comparative arms and therefore will not be considered in this economic

evaluation. However, it is proposed that genetic testing among at-risk family members, for the prediction of long QT syndrome, will be a triage for clinical assessment, prophylactic treatment and lifelong monitoring. The cost of lifelong clinical assessments and prophylactic treatment will therefore be estimated in this economic evaluation.

Cost-effectiveness analyses for genetic testing in the index case and first degree relatives will be conducted incorporating the probability of a mutation. The cost-effectiveness analysis of the genetic test in both first and second degree relatives will incorporate the average probability of a mutation in these relatives (based on the estimated proportion of first and second degree relatives tested).

More information is being sought from the Applicant on the costs of performing genetic testing for LQTS. If it is determined that the risk of multiple mutations within a single symptomatic patient is low (<5% of those with LQTS) then the potential for cascade testing will be assessed (testing for the most common mutation first, and only if negative, testing further).

Clinical advice will be used to estimate the type of tests and the frequency of each test used in the life-long clinical assessment. Clinical advice will also be sought to estimate the type of resources involved in the treatment package and its frequency of use. The table below will be completed upon receiving clinical input.

Table 9 lists the health care resources whose utilisation is likely to be impacted should LQTS molecular testing be made available as requested, regardless of whether the utilisation of the resource will be impacted due to differences in outcomes or due to availability of the proposed intervention itself. The disaggregated unit costs will be obtained during the assessment.

Table 9 List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS or PBS or PL or AR-DRG	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
<u>Resources provided to deliver clinical assessment of LQTS</u>										
-consultation	GP	outpatient	Clinical advice	Clinical advice	MBS Item 23 (\$34.9)					
-consultation	Cardiologist	outpatient	80% without comorbidities	Clinical advice	MBS Item 110					
			20% with comorbidities	Clinical advice	MBS Item 132 (\$253.9) Item 133 (\$127.10)					
-ECG		outpatient	Clinical advice	Clinical advice	MBS Item 11700 (\$30.05) Item 11709 (\$161.15) Item 11712 (\$146.35)					
<u>Resources provided in association with treatment of LQTS</u>										
-Beta blockers		outpatient	Clinical advice	Clinical advice						
-ICD		Inpatient	Clinical advice	Clinical advice						
-Pacemaker		Inpatient	Clinical advice	Clinical advice						
-Pacemaker implantation		Inpatient	Clinical advice	Clinical advice	AR-DRG F12Z (\$18,418) F17Z (\$14,053)					
-Potassium	GP	outpatient	Clinical advice	Clinical advice	PBS 2642C (\$13.02)					
- Sodium channel blocker	GP	outpatient	Clinical advice	Clinical advice	PBS 2875H (\$37.33)					
-Doctor consultation	GP	outpatient	Clinical advice	Clinical advice	MBS Item 23 (\$34.9)					
<u>Resource provided to deliver the proposed test</u>										
-Diagnostic genetic test	Specialist ^a	outpatient	Clinical advice	Clinical advice	Proposed fee (\$3,730)					
-Predictive genetic test	Specialist ^a	outpatient	Clinical advice	Clinical advice	Proposed fee (\$287)					

^aSpecialists may include cardiologists, electrophysiologists and clinical genetists

Proposed structure of economic evaluation (decision-analytic)

The extended PICO to be used for the economic evaluation are provided in Table 10.

Table 10 Summary of extended PICO to define research questions that economic evaluation will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Patients suspected of having long QT syndrome, who are classified as intermediate or high risk (Schwartz score ≥ 3)	ECG (Schwartz score) \pm exercise stress test \pm Holter monitoring plus molecular genetic testing for LQTS	ECG (Schwartz score) \pm exercise stress test \pm Holter monitoring	Effectiveness: <i>Direct evidence</i> Primary outcomes – Mortality/survival; quality of life; incidence of life-threatening events including cardiac arrest and ventricular fibrillation. <i>Linked evidence</i>	see Table 9
Clinically unaffected relatives of a patient with a known long QT syndrome	Molecular genetic testing for LQTS \pm ECG (Schwartz score) \pm exercise stress test \pm Holter monitoring	ECG (Schwartz score) \pm exercise stress test \pm Holter monitoring	Effectiveness: <i>Direct evidence</i> Primary outcomes – Mortality/survival; quality of life; incidence of life-threatening events including cardiac arrest and ventricular fibrillation. <i>Linked evidence</i>	see Table 9
Research Questions				
<p>1. Is molecular testing for the genetic mutations associated with LQTS cost-effective when used in addition to clinical diagnostic approaches in the diagnosis of patients presenting with symptoms suggestive of long QT syndrome?</p> <p>2. Is molecular testing for the genetic mutations associated with LQTS cost-effective when used as a triage for clinical assessment, treatment and life-long monitoring of family members of patients who are known to have LQTS?</p>				

Two main analyses will be performed, assessing: 1) the consequences of adding the genetic test into clinical practice for the proband (index case) alone (diagnostic setting; Figure 3); and 2) the consequences of using the genetic test for both the proband and their family members (predictive setting; Figure 4). A stepped analysis will be performed to determine whether the genetic test is cost-effective when restricted to index cases and first degree relatives alone, and subsequently, if it is cost-effective when broadened to the index case plus first and second degree relatives.

Figure 3 Decision tree representing the decision options available when using genetic testing for the diagnosis of long QT syndrome

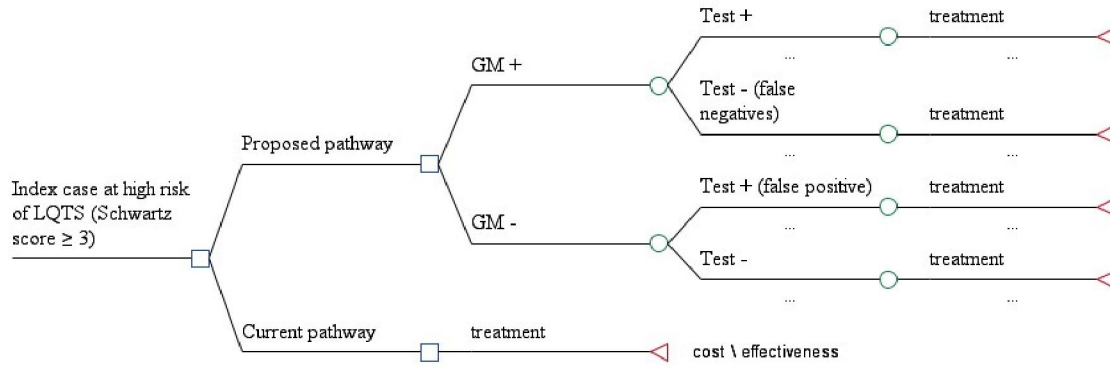
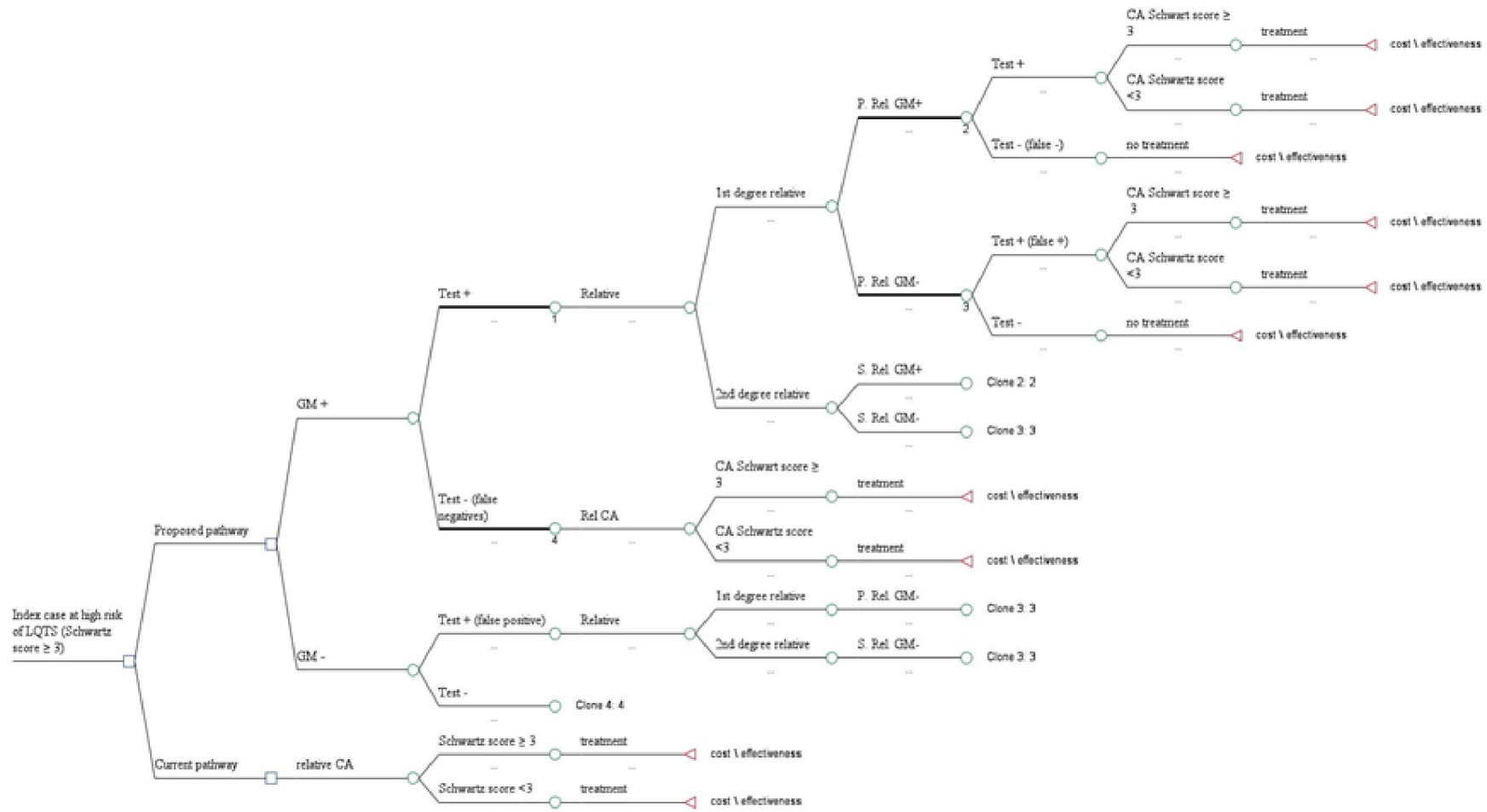


Figure 4 Decision tree representing the decision options available when using genetic testing for index and family members for LQT syndrome
 GM = pathological genetic marker; CA = clinical assessment; P. Rel = primary relatives; S. Rel. = secondary relatives



Assessment methodology

Clinical need for molecular testing for LQTS in Australia will be determined using available national data collections such as the AIHW National Hospital Morbidity and Mortality Database, as well as published literature concerning the incidence and prevalence of the condition.

A systematic literature review will then be undertaken to assess the safety and effectiveness of molecular testing for LQTS in (1) symptomatic patients with suspected long QT syndrome, and (2) clinically unaffected family members of individuals with known LQTS. A systematic literature review is undertaken because it is a method that is transparent and reduces bias in the selection and reporting of pertinent evidence. This review of evidence will then be used to provide the inputs and derive the transition probabilities needed for the decision-analytic model to determine the cost-effectiveness of the use of LQTS molecular testing in each of the two funding scenarios.

The effectiveness of a diagnostic test depends on whether it improves patient health outcomes. This can be assessed by studies that directly investigate the impact of the test on health outcomes or alternatively, in some situations, by linking evidence from studies.

Should there be no direct evidence (eg clinical trials) available assessing the impact of molecular testing for LQTS on patient outcomes, either for prediction or for diagnosis in a population presenting with symptoms, a linked evidence approach will be undertaken using the methods outlined in the MSAC (2005) Guidelines for the assessment of diagnostic technologies.

A linked evidence approach involves narratively linking evidence reporting on three aspects of a diagnostic test intervention, if certain conditions are met. These aspects are:

test accuracy - measured for example, by sensitivity, specificity, positive or negative predictive values or likelihood ratios. This involves comparing the LQTS test results against a reference standard ('truth'), which may be determined by life-long follow-up of the patient to determine whether they truly have or develop the syndrome

impact on clinical decision making - measured as the change in treatment decision made by clinicians in response to the information provided by the LQTS test

effectiveness of treatment – measured as the impact of available treatment on the health outcomes of those people with a LQTS diagnosis

Information provided from a linked evidence approach feeds directly into the development of decision analytic models. However, because the approach is pre-specified and there are

criteria for selecting the evidence, it means that the model (and model results) is less likely to be open to bias and the inputs are the best available evidence that is applicable to the question for public funding. Further, the full range of possible results is provided in the evidence-base so that uncertainty can be explored within a known range. In instances where the test will not affect the type of treatment a patient would receive, or if treatment is not likely to be received any earlier than currently, then the linkage to assess the effect of treatment on patient health outcomes may not be necessary. Any cost-effectiveness analysis would simply be reduced to the incremental cost per correct diagnosis.

Literature search

An initial search will be conducted to identify if there are any existing health technology assessment (HTA) reports on molecular testing for LQTS. The electronic databases and websites of international HTA agencies to be searched are given in Appendix B.

Search strategies are generally developed using the key elements of the research question, outlined in Table 7 and Table 10. Table 11 outlines the search terms for this review, based on a PubMed search platform and initial searching for direct evidence. Should direct evidence be unavailable, a literature search will be undertaken for evidence appropriate for linkage.

Appendix C lists the databases and websites that will be searched for appropriate literature.

Table 11 Search terms for LQTS genetic testing (direct evidence)

Element of clinical question	Suggested search terms
Population	((long QT syndrome [MeSH] OR LQTS [Text Word] OR long QT syndrome [Text Word] OR (LQTS [text word] AND (gene* OR mutat*)) OR KNCE1 [Text Word] OR KCNE2[Text Word] OR KCNH2[Text Word] OR KCNJ2[Text Word] OR KCNQ1[Text Word] OR SCN5A[Text Word] OR LQT1 [Text Word] OR LQT2 [Text Word] OR LQT3 [Text Word] OR LQT5 [Text Word] OR LQT6 [Text Word] OR LQT7 [Text Word] OR 'romano-ward syndrome' [Text Word] OR 'Jervell and Lange-Nielsen syndrome' [Text Word] OR 'sudden cardiac death' [text word] OR (prolonged [text word] AND QT interval [text word]))
Intervention/test	AND 'Molecular Diagnostic Techniques' [MeSH] OR 'molecular test' [Text Word] OR molecular test* [Text Word] OR 'genetic testing' [MeSH] OR 'genetic test' [Text Word] OR genetic test* [Text Word] OR 'genetic screening' [Text Word] OR 'genetic analysis'[Text Word] OR (gene* [Text Word] AND screen* [Text Word] OR ((diagno* OR diagnosis [MeSH]) AND (gene* OR genes [MeSH] OR screen*))
Comparator	N/A
Outcomes	N/A
Limits	Human, 1991 – May 2011

NA = not applicable

Selection criteria for evidence

Table 7 provides the PICO to be addressed by the research questions and also outlines the selection criteria that will be applied to the articles identified by the literature search. Studies that do not address the PICO, as described, will be excluded. In instances where direct evidence is lacking or is insufficient to answer the research questions, the literature search will be re-conducted according to the search terms given in Appendix B and the PICO applied to the results of that search according to the criteria outlined in Appendix A.

All literature must also meet the following criteria:

- Fall within the search period from 1991 – May 2011;
- Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified;
- Conducted on human subjects;
- Provide data or patients that are not duplicated in other articles. Where this occurs, only the most recent and/or comprehensive information will be selected;
- Provide data that can be extracted (ie not described graphically); and
- Have study designs that are relevant to the aspect being assessed – namely,
 - Safety: All of the relevant study designs are given in the Intervention column of Table 13. If large numbers of case series are identified, all will be reviewed but only those that are large case series and/or with long-term follow-up will have data extracted.
 - Effectiveness:
 - Direct evidence - All of the relevant study designs are listed in the Intervention column of Table 13. However, post-test case series will be excluded. If large numbers of pre-test/post-test case series are identified, all will be identified and reviewed but only those that are large case series and/or with long-term follow-up will have data extracted.
 - Linked evidence –
 - Diagnostic accuracy: All of the relevant study designs are listed in the Diagnostic accuracy column of Table 13.

- Change in management (impact on clinical decision-making): All of the relevant study designs are listed in the Intervention column of Table 13. However, post-test case series will be excluded. If large numbers of pre-test/post-test case series are identified, all will be identified and reviewed but only those that are large case series and/or with long-term follow-up will have data extracted.
- Treatment effectiveness: Level I, II, III-1 and III-2 evidence listed in the Intervention column of Table 13. Should there be sufficient good quality evidence available from Level I, II and III-1 evidence, then level III-2 evidence will be identified and reviewed but data will not be extracted.

Initial eligibility on the basis of the collated study citations will be conservatively determined by two reviewers (ie if unclear from the abstract, or if the reviewer is unsure, the full text paper will be ordered anyway). One reviewer will then assess each of the retrieved full text articles for eligibility, with another assessing those over which there is doubt. When consensus cannot be reached, a third reviewer will independently assess the paper in question and the majority decision will prevail. A PRISMA flowchart will be used to describe the selection process for all the included studies. A list of studies which met the inclusion criteria but were subsequently excluded from the review will be appended to the final report.

Critical appraisal of individual eligible studies

Evidence retrieved from the above searches will be assessed according to the NHMRC Dimensions of Evidence which are listed in Table 12.

There are three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified for a particular intervention. The last two require expert clinical input as part of their determination. Study quality will be evaluated and reported using an appropriate instrument for quality assessment, eg quality checklists published by the Centre for Reviews and Dissemination (Khan 2001), National Health and Medical Research Council (NHMRC 2000), Downs and Black (Downs & Black 1998), and the QUADAS instrument (Whiting et al 2003).

Table 12 **NHMRC dimensions of evidence**

Type of evidence	Definition
Strength of the evidence Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality Statistical precision	The methods used by investigators to minimise bias within a study design. The <i>p</i> -value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the “null” value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 13

Table 13 Designations of levels of evidence* according to type of research question (including tablenotes) (Merlin T et al 2009; NHMRC 2009)

Level	Intervention ¹	Diagnostic accuracy ²	Prognosis	Aetiology ³	Screening Intervention
I ⁴	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among consecutive persons with a defined clinical presentation ⁶	A prospective cohort study ⁷	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among non-consecutive persons with a defined clinical presentation ⁶	All or none ⁸	All or none ⁸	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial ⁹ <ul style="list-style-type: none"> ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study¹⁰ ▪ Interrupted time series without a parallel control group 	Diagnostic case-control study ⁶	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ¹¹	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

¹ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b) and in the accompanying Glossary.

² These levels of evidence apply only to studies of assessing the accuracy of diagnostic or screening tests. To assess the overall effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002). The evidence hierarchy given in the 'Intervention' column should be used when assessing the impact of a diagnostic test on health outcomes relative to an existing method of diagnosis/comparator test(s). The evidence hierarchy given in the 'Screening' column should be used when assessing the impact of a screening test on health outcomes relative to no screening or opportunistic screening.

³ If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (eg. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

⁴ A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

⁵ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

⁶ Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

⁷ At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

⁸ All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

⁹ This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

¹⁰ Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

¹¹ Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within randomised controlled trials, in which case lower levels of evidence may be the only type of evidence that is practically achievable; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Note C: Each individual study that is attributed a “level of evidence” should be rigorously appraised using validated or commonly used checklists or appraisal tools to ensure that factors other than study design have not affected the validity of the results.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001

Data extraction and synthesis of evidence

Data will be extracted by the evaluators using a standardised data extraction form which will be designed specifically for this review.

Evidence tables will be developed for each study – outlining the level of evidence, quality assessment, authors, publication year, location, study design, study population characteristics, type of intervention, inclusion/exclusion criteria, outcomes assessed and follow-up period.

Descriptive statistics will be extracted or calculated for all safety and effectiveness outcomes in the individual studies – including numerator and denominator information, means and standard deviations, medians and inter-quartile ranges.

Relative risk/rate ratio (RR), absolute risk differences, number needed to diagnose or screen and associated 95% confidence intervals will be calculated from individual comparative studies containing count data. Mean differences and 95% confidence intervals will be extracted or calculated for normally distributed continuous outcomes in individual studies using the independent t-test. In the analysis of diagnostic accuracy, calculations of sensitivity, specificity, negative and positive predictive values of tests, likelihood ratios and diagnostic odds ratios, as well as 95% confidence intervals, will be undertaken where possible.

Meta-analyses of randomised controlled trials will be conducted, where appropriate, and tested for heterogeneity and publication bias. Sensitivity analyses (particularly analysing the impact of study quality) and stratification on known confounders will occur where necessary. Subgroup analyses will be undertaken according to those delineated in Table 7. Meta-analyses and all statistical calculations and testing will be undertaken using the biostatistical computer package, Stata version 11 (Stata Corporation 2010).

Where meta-analysis cannot or should not be conducted, a narrative meta-synthesis of the data will be undertaken.

Assessment of the body of evidence

In addition to the individual studies, the overall body of evidence will be assessed. An evidence level from A (excellent) to D (poor) will be assigned considering each of the components outlined in the body of evidence matrix outlined in Table 14.

Table 14 Body of evidence assessment matrix, adapted from NHMRC FORM framework (Hillier et al 2011)

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base¹	one or more level I studies with a low risk of bias or several level II studies with a low risk of bias	one or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency²	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population ³	population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

SR = systematic review; several = more than two studies

¹ Level of evidence determined from the NHMRC evidence hierarchy –Table 13

² If there is only one study, rank this component as 'not applicable'.

³ For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

Decision analytic modelling methodology

A decision analytic model is a means of summarising the comparison/s that the assessment report will investigate and present. It is used to identify the extent of substitution of current technologies by the proposed technology in a specific patient group (whereas this patient

group may relate to one region of a management algorithm). The decision analytic will also show how various outcomes and utilisation of health care resources are related and how they are integrated into the economic evaluation. The final model will include specification of all relevant variables and transition probabilities to permit estimation of costs and outcomes associated with the proposed intervention and the comparator.

There will be two decision analytic models included in the economic evaluation, one for the genetic test as a means of diagnosis of LQTS, and the other one incorporating the test as both a diagnostic tool (for the index case) and as a means of predicting LQTS in family members. Both models will take a societal perspective, which means any additional resources incurred associated with genetic test relative to currently used clinical assessment will be estimated, regardless who pays for it. Both models will take a life-time horizon. The mean age of patients suspected of LQTS entering the model is 10.7 years (± 7.6 ; range 1.5 to 39 years) (Vincent et al 1992). The age of family members entering the model has to be determined by consulting the literature.

In the diagnostic genetic test model, genetic testing will be used in addition to the currently used clinical assessment, and treatment may be initiated according to the gene involved. Thus the corresponding cost and health outcomes are expected to vary, compared with those patients diagnosed via clinical assessment and treated accordingly.

In the diagnostic and predictive genetic test model, genetic testing in family members will be a triage for clinical assessment and an overall lifelong screening program. For those family members who have a mutation, subsequent investigations and prophylactic treatment are expected to be the same as in the current clinical scenario. However, for those family members who are found not to have the LQT mutation found in the index case, they may avoid subsequent clinical assessment and lifelong screening. Without genetic testing, at-risk family members of patients with long QT syndrome remain in a lifelong screening program given the high false negative rate of ECG screening. Predictive genetic testing may accurately establish risk status of family members of patients with long QT syndrome, and therefore may improve risk management for affected individuals, and remove unnecessary anxiety for unaffected individuals, along with the need for lifelong screening.

Appendix A

Selection criteria for linked evidence

In the absence of direct evidence, a linked evidence approach will be attempted, where evidence of diagnostic accuracy, change in clinical management and treatment effectiveness are linked to provide an assessment of the effectiveness of using molecular testing in the diagnosis of long QT syndrome. The inclusion criteria for a linked assessment of diagnostic genetic testing are outlined in Table 15 to Table 17.

Table 15 Inclusion criteria for identification of studies relevant to an assessment of the diagnostic accuracy of molecular testing for long QT syndrome (index case)

Characteristic	Criteria
Study design	Studies of test accuracy where patients are cross-classified on the test and reference standard. Case-control diagnostic studies will only be acceptable if studies of test accuracy are not available or are limited. Systematic reviews of these study designs are also acceptable.
Population	Patients with a history of recurrent syncope or cardiac event (cardiac arrhythmia or non-fatal cardiac arrest)
Intervention/test	Molecular testing for clinical relevant mutations, ie KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1 or SCN5A mutations + ECG (Schwartz score) ± exercise stress test and Holter monitoring
Comparator	ECG (Schwartz score) ± exercise stress test and Holter monitoring
Reference standard	Clinical diagnosis determined from long term follow-up
Outcome	Diagnostic accuracy outcomes: Sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values, diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy
Search period	1991 – May 2011
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified

Table 16 Inclusion criteria for identification of studies relevant to an assessment of a change in patient management as a result of molecular testing for long QT syndrome (index case)

Characteristic	Criteria
Study design	Randomised or non-randomised controlled trials or cohort studies, uncontrolled before-and-after case series, or systematic reviews of these study designs
Population	Patients with a history of recurrent syncope or cardiac event (cardiac arrhythmia or non-fatal cardiac arrest)
Intervention/test	Molecular testing for clinical relevant mutations, ie KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1 or SCN5A mutations + ECG (Schwartz score) ± exercise stress test and Holter monitoring
Comparator	ECG (Schwartz score) ± exercise stress test and Holter monitoring
Outcome	Rates of treatment, method of treatment, rates of referral, type of referral, rate of hospitalisation, rates of consultation
Search period	1991 – May 2011
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified

Assessing the health benefits from a particular change in patient management can only be performed once knowledge regarding what change occurs is available. Table 17 outlines the proposed broad inclusion criteria for studies assessing the health impact from a range of possible changes in patient management. Table 18 and Table 19 outline the inclusion criteria for assessing the health benefits of two particular forms of targeted treatment that may occur as a result of genetic testing of LQT syndrome which were identified in scoping searches of the literature (targeted potassium supplementation for those with LQT2, and targeted sodium channel blockers for those with LQT3).

Table 17 Inclusion criteria for identification of studies relevant to an assessment of treatment effectiveness following a change in patient management as a result of molecular testing for long QT syndrome (index case)

Characteristic	Criteria
Study design	Randomised or non-randomised controlled trials or cohort studies, uncontrolled before-and-after case series, or systematic reviews of these study designs
Population	Patients with a history of recurrent syncope or cardiac event (cardiac arrhythmia or non-fatal cardiac arrest)
Intervention/test	<i>Treatment that may have been based on knowledge of genetic mutation:</i> Lifelong surveillance + β blockers + exercise restriction, sodium channel blocker, ICD/ pacemaker or Lifelong surveillance + β blockers + exercise restriction +potassium supply \pm ICD/ pacemaker
Comparator	<i>Treatment that may have been based on clinical assessment:</i> No further treatment or annual lifelong surveillance \pm beta blockers, sodium channel blocker / potassium supply \pm exercise restriction \pm ICD or pacemaker
Outcome	Primary health outcomes: mortality; quality of life; reduction in symptoms or life-threatening events, including syncope, cardiac arrhythmia, cardiac arrest; avoidance of unnecessary treatments Secondary health outcomes: length of hospital stay, hospital admission Safety: adverse events
Search period	1991 – May 2011
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified

Table 18 Inclusion criteria for identification of studies relevant to assessment of treatment effectiveness following a change in patient management for long QT2 syndrome as a result of molecular testing

Characteristic	Criteria
Study design	Randomised or non-randomised controlled trials or cohort studies, uncontrolled before-and-after case series, or systematic reviews of these study designs
Population	Patients (index and family members) who are found to have LQT2 syndrome
Intervention/test	Potassium supplementation
Comparator	Beta blockers
Outcome	Primary health outcomes: mortality; quality of life; reduction in symptoms or life-threatening events, including syncope, cardiac arrhythmia, cardiac arrest; avoidance of unnecessary treatments Secondary health outcomes: length of hospital stay, hospital admission Safety: adverse events
Search period	1991 – May 2011
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified

Table 19 Inclusion criteria for identification of studies relevant to assessment of treatment effectiveness following a change in patient management for long QT3 syndrome as a result of molecular testing

Characteristic	Criteria
Study design	Randomised or non-randomised controlled trials or cohort studies, uncontrolled before-and-after case series, or systematic reviews of these study designs
Population	Patients (index and family members) who are found to have LQT3 syndrome
Intervention/test	Sodium channel blocker
Comparator	Other forms of beta blockers
Outcome	Primary health outcomes: mortality; quality of life; reduction in symptoms or life-threatening events, including syncope, cardiac arrhythmia, cardiac arrest; avoidance of unnecessary treatments Secondary health outcomes: length of hospital stay, hospital admission Safety: adverse events
Search period	1991 – May 2011
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified

The inclusion criteria for a linked assessment of predictive genetic testing are outlined in Table 20 to Table 23.

Table 20 Inclusion criteria for identification of studies relevant to assessment of the diagnostic accuracy of molecular testing for long QT syndrome (family members)

Characteristic	Criteria
Study design	Studies of test accuracy where patients are cross-classified on the test and reference standard. Case-control diagnostic studies will only be acceptable if studies of test accuracy are not available or are limited. Systematic reviews of these study designs are also acceptable
Population	Patients with a relative with a known LQTS mutation
Intervention/test	Molecular testing for clinical relevant mutations, ie KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1 or SCN5A mutations ± ECG (Schwartz score) ± exercise stress test and Holter monitoring
Comparator	ECG (Schwartz score) ± exercise stress test and Holter monitoring
Reference standard	Clinical diagnosis determined from long term follow-up
Outcome	Diagnostic accuracy outcomes: Sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values, diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy
Search period	1991 – May 2011
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified

Table 21 Inclusion criteria for identification of studies relevant to assessment of a change in patient management as a result of molecular testing for long QT syndrome (family members)

Characteristic	Criteria
Study design	Randomised or non-randomised controlled trials or cohort studies, uncontrolled before-and-after case series, or systematic reviews of these study designs
Population	Patients with a relative with a known LQTS mutation
Intervention/test	Molecular testing for clinical relevant mutations, ie KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1 or SCN5A mutations + ECG (Schwartz score) ± exercise stress test and Holter monitoring
Comparator	ECG (Schwartz score) ± exercise stress test and Holter monitoring
Outcome	Rates of treatment, method of treatment, rates of referral, type of referral, rate of hospitalisation, rates of consultation
Search period	1991 – May 2011
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified

Broad inclusion criteria for studies assessing the health impact of a change in patient management in family members is outlined in Table 22. Targeted treatment with potassium supplementation or sodium channel blockers would be assessed using the inclusion criteria outlined in Table 18 and Table 19.

In the proposed pathway, some family members will be ruled out of having a pathogenic mutation. They therefore may avoid the need for prophylactic treatment and lifelong surveillance. Table 23 outlines the inclusion criteria for assessing the health impact of no treatment versus treatment within the population with no pathogenic mutation. However, it would be unethical to treat asymptomatic family members who are known to be free from a pathogenic mutation. Studies meeting the PICO criteria in Table 23 are therefore unlikely to exist, unless they provide retrospective data, ie evaluating treatment prior to knowledge of mutation status.

Table 22 Inclusion criteria for identification of studies relevant to assessment of treatment effectiveness following a change in patient management as a result of molecular testing for long QT syndrome (family members)

Characteristic	Criteria
Study design	Randomised or non-randomised controlled trials or cohort studies, uncontrolled before-and-after case series, or systematic reviews of these study designs
Population	Patients with a relative with a known LQTS mutation
Intervention/test	Lifelong surveillance + β blockers + exercise restriction, ICD/ pacemaker
Comparator	No further treatment or annual lifelong surveillance \pm beta blockers \pm exercise restriction \pm ICD or pacemaker
Outcome	Primary health outcomes: mortality; quality of life; reduction in symptoms or life-threatening events, including syncope, cardiac arrhythmia, cardiac arrest; avoidance of unnecessary treatments Secondary health outcomes: length of hospital stay, hospital admission Safety: adverse events
Search period	1991 – May 2011
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified

Table 23 Inclusion criteria for identification of studies relevant to an assessment of treatment effectiveness following a change in patient management as a result of molecular testing for long QT syndrome (family members)

Characteristic	Criteria
Study design	Retrospective cohort studies, historically controlled studies, or systematic reviews of these study designs
Population	Patients with a relative with a known LQTS mutation
Intervention/test	<i>Treatment that may have been based on knowledge of the absence of a pathogenic mutation:</i> No treatment
Comparator	<i>Treatment that may have been based on clinical assessment:</i> Annual lifelong surveillance \pm beta blockers, sodium channel blocker / potassium supply \pm exercise restriction \pm ICD or pacemaker
Outcome	Primary health outcomes: mortality; quality of life; reduction in symptoms or life-threatening events, including syncope, cardiac arrhythmia, cardiac arrest; avoidance of unnecessary treatments Secondary health outcomes: length of hospital stay, hospital admission Safety: adverse events
Search period	1991 – May 2011
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified

Appendix B

Table 24 Health Technology Assessment Agency Websites

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
Centre for Clinical Effectiveness, Monash University	http://www.southernhealth.org.au/page/Health_Professionals/CCE/
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita
Agence d’Evaluation des Technologies et des Modes d’Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/publications/
Alberta Institute of Health Economics	http://www.ihe.ca/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database	http://www.ryerson.ca/library/info/databases/cabot.html
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.sst.dk/english/dacehta.aspx?sc_lang=en
Danish Institute for Health Services Research (DSI)	http://dsi.dk/
Finnish Office for Health Technology Assessment (FINOHTA)	http://finohta.stakes.fi/EN/index.htm
L’Agence Nationale d’Accréditation et d’Evaluation en Santé (ANAES)	http://www.anaes.fr/
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en/index.html
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Health Council of the Netherlands Gezondheidsraad	http://www.gezondheidsraad.nl/en/
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
Norwegian Knowledge Centre for the Health Services	http://www.kunnskapssenteret.no
Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud “Carlos III”/Health Technology Assessment Agency (AETS)	http://www.isciii.es/
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.hta.ac.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry [note: cannot locate this [9MAR2010]	http://www.tufts-nemc.org/cearegistry/index.html
Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services	http://www.nlm.nih.gov/hsrph.html
Research and Health Care Technology (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
Oregon Health Resources Commission (US)	http://www.nlm.nih.gov/hsrph.html
Office of Health Technology Assessment Archive (US)	http://fas.org/ota
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/blueresources/tec/
Veteran’s Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm

Appendix C

Literature sources

Electronic bibliographic databases will be searched to find relevant studies (those meeting the inclusion criteria) addressing each of the research questions developed for this MSAC assessment. These databases are described in Table 25. Molecular testing for Long QT Syndrome has only been described in the literature after 1991, therefore the search period will be restricted from 1991 (or if inception of the database is later, from that date) until May 2011.

Table 25 Bibliographic databases

Electronic database	Time period
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1991– May 2011
Current Contents	1991 – May 2011
Embase.com (including Embase and Medline)	1991 – May 2011
Pubmed	1991– May 2011
ProceedingsFirst	1991 – May 2011
Web of Science – Science Citation Index Expanded	1991 – May 2011
EconLit	1991 – May 2011

Additional sources of literature – peer-reviewed or grey literature – will be sought from the sources outlined in Table 26, and from the health technology assessment agency websites provided in Table 24. Websites of specialty organisations will also be searched for any potentially relevant information.

Table 26 Additional sources of literature

Source	Location
Internet	
NHMRC- National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	http://www.update-software.com/National/
Google Scholar	http://scholar.google.com/
Hand Searching (Journals from 2010-2011)	
	Library or electronic access
Expert Clinicians	Library or electronic access
Studies other than those found in regular searches	MSAC Experts Standing Panel
Pearling	
All included articles will have their reference lists searched for additional relevant source material	

Specialty websites

Sudden Arrhythmic Death Syndrome Australia (SADS) organisation	http://www.sads.org.au/
The Australian Sudden Arrhythmia Death Syndromes (SADS) Foundation	http://wallcannrewards.com/fundraising/sads
VCGS Pathology The Victorian Clinical Genetics Services (VCGS)	http://www.vcgspathology.com.au/sections/MolecularGenetics/?docid=9a38bbfc-144f-4c95-b25f-992e00efe8cd
GeneTests Laboratories offering clinical testing for LQTS syndrome	http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2171?db=genetests
The Royal College of Pathologists of Australasia Catalogue of Genetic Tests and Laboratories	http://genetictesting.rcpa.edu.au/
National Genetic Heart Disease Registry, Long QT syndrome	http://www.registry.centenary.org.au/p/resources/lqts/
Romano-Ward syndrome National Center for Biotechnology Information, U.S. National Library of Medicine	http://www.ncbi.nlm.nih.gov/books/NBK1129/
E- medicine; LQT syndrome	http://emedicine.medscape.com/article/157826-overview

Search terms for a linked evidence approach (if required)

The search terms developed to assess the direct evidence of the safety and effectiveness of genetic testing for LQT syndrome would also be used to capture studies assessing the diagnostic accuracy of genetic testing, and studies assessing the change in management resulting from the genetic testing. As discussed in Appendix A, the impact of the change in patient management can only be evaluated after a change in management has been detected. Studies assessing the health impact of the use of targeted treatment with potassium supplements and sodium channel blockers (the changes in management identified through scoping searches) will be retrieved using the search terms shown in Table 27. The assessment of any other change in management that is identified may require a protocol variation and additional literature searches.

Table 27 Suggested search terms for LQTS genetic testing (linked evidence)

Element of clinical question	Suggested search terms
Direct evidence, diagnostic accuracy and change in patient management	<p>((long QT syndrome [MeSH] OR LQTS [Text Word] OR long QT syndrome [Text Word] OR (LQTS [text word] AND (gene* OR mutat*)) OR KNCE1 [Text Word] OR KCNE2[Text Word] OR KCNH2[Text Word] OR KCNJ2[Text Word] OR KCNQ1[Text Word] OR SCN5A[Text Word] OR LQT1 [Text Word] OR LQT2 [Text Word] OR LQT3 [Text Word] OR LQT5 [Text Word] OR LQT6 [Text Word] OR LQT7 [Text Word] OR 'romano-ward syndrome' [Text Word] OR 'Jervell and Lange-Nielsen syndrome' [Text Word] OR 'sudden cardiac death' [text word] OR (prolonged [text word] AND QT interval [text word]))) AND [humans]/lim AND [1991-2011]/py</p> <p>AND</p> <p>'Molecular Diagnostic Techniques' [MeSH] OR 'molecular test' [Text Word] OR molecular test* [Text Word] OR 'genetic testing' [MeSH] OR 'genetic test' [Text Word] OR genetic test* [Text Word] OR 'genetic screening' [Text Word] OR 'genetic analysis'[Text Word] OR (gene* [Text Word] AND screen* [Text Word] OR ((diagno* OR diagnosis [MeSH]) AND (gene* OR genes [MeSH] OR screen*)) Limits: Humans, Publication Date from 1991 to 2011/05</p>
Treatment of LQT syndrome	<p>(long QT syndrome [MeSH] OR LQTS [Text Word] OR long QT syndrome [Text Word] OR romano-ward syndrome [Text Word] OR Jervell and Lange-Nielsen syndrome [Text Word] OR sudden cardiac death [text word] OR (prolonged [text word] AND QT interval [text word]))) AND (gene* OR mutat* OR genetic mutation OR KNCE1 [Text Word] OR KCNE2[Text Word] OR KCNH2[Text Word] OR KCNJ2[Text Word] OR KCNQ1[Text Word] OR SCN5A[Text Word] OR LQT1 [Text Word] OR LQT2 [Text Word] OR LQT3 [Text Word] OR LQT5 [Text Word] OR LQT6 [Text Word] OR LQT7 [Text Word])) AND [humans]/lim AND [1991-2011]/py</p> <p>AND</p> <p>(Adrenergic beta-Antagonists [MeSH] OR beta blocker [Text Word] OR Channel Blockers, Sodium[MeSH] OR sodium channel blocker[Text Word] OR Channel Blockers, Potassium[MeSH] OR potassium supplements[Text Word] OR mexitil OR atenolol OR lignocaine hydrochloride OR nebivolol OR metoprolol OR propranolol hydrochloride OR pindolol OR flecainide acetate OR potassium chloride OR bisoprolol fumarate OR oxprenolol hydrochloride OR sotalol hydrochloride) AND [humans]/lim AND [1991-2011]/py</p>

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