



Australian Government

Department of Health

RATIFIED PICO

Application 1598:

Genetic testing for diagnosis of inheritable cardiac rhythm disorders

Summary of PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PPICO criteria for assessing safety and effectiveness of genetic testing in patients and family members suspected of, or at risk of, inheritable cardiac arrhythmias

Component	Description
Population	<ol style="list-style-type: none"> 1. Individuals strongly suspected of, or clinically diagnosed with, inheritable cardiac arrhythmia (ICA) syndromes^a or channelopathies 2. First- and second-degree family members of an index case with a pathogenic ICA variant
Prior tests	Clinical assessment, family history and electrocardiogram (ECG)
Intervention	<ol style="list-style-type: none"> 1. Characterisation of germline gene variants associated with ICA (<i>KCNQ1</i>, <i>KCNH2</i>, <i>SCN5A</i>, <i>KCNE1</i>, <i>KCNE2</i>, <i>KCNJ2</i>, <i>CACNA1C</i>, <i>RYR2</i>, <i>CASQ2</i>, <i>CAV3</i>, <i>SCN4B</i>, <i>AKAP9</i>, <i>SNTA1</i>, <i>KCNJ5</i>, <i>ALG10</i>, <i>CALM1</i>, <i>CALM2</i>, <i>ANK2</i>, <i>TECL1</i> and <i>TRDN</i> genes) (in population 1) 2. Testing for a specific (known) familial pathological variant for ICA (in population 2)
Comparator	Usual standard of care, without genetic testing.
Reference standard (for analytical validity)	Sanger sequencing
Outcomes	<p><u>Patient relevant outcomes</u></p> <p><i>Direct safety and effectiveness:</i></p> <ul style="list-style-type: none"> • Safety: physical and/or psychological harms from testing or no testing, adverse events from testing and consequences of true or false test results. • Effectiveness (primary outcomes): variants identified, cardiac events such as cardiac arrest, sudden cardiac death or syncope avoided and quality of life years (QALYs) gained. <p><i>Linked evidence:</i></p> <ul style="list-style-type: none"> • Analytical validity: test failure rate, sensitivity, specificity, concordance, unsatisfactory or uninterpretable results, diagnostic yield • Clinical validity: diagnostic, predictive or prognostic value • Therapeutic efficacy: change in patient management (e.g. commencement of appropriate medical therapy, cessation of harmful medical therapy, identification of patients requiring an implantable defibrillator, avoidance of surgical intervention), change in surveillance, ICA detection and treatment of family members • Therapeutic effectiveness: effect of change in management (e.g. reduction in cardiac events (ACA or SCD, syncope) and mortality, reduced clinical surveillance and associated testing such as ECG and exercise stress tests in asymptomatic family members of proband, improved quality of life, improved psychological health) <p><u>Healthcare system outcomes</u></p> <ul style="list-style-type: none"> • Cost, cost-effectiveness • Financial implications (financial impact, overall healthcare costs, etc.)

^a Long QT syndromes (LQT1-LQT13), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT) and Jervell and Lange-Nielsen syndrome (JLNS).

ACA = aborted cardiac arrest; SCD = sudden cardiac death

1. PICO or PPICO rationale for therapeutic and investigative medical services only

1.1 RESEARCH QUESTIONS

1. What is the safety, effectiveness and cost-effectiveness of testing for heritable variants in the *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2*, *CACNA1C*, *RYR2* and *CASQ2*, and one or more of *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *ALG10*, *CALM1*, *CALM2*, *ANK2*, *TECRL* and *TRDN* genes in individuals strongly suspected of, or clinically diagnosed with, inheritable cardiac arrhythmia (ICA) syndromes or channelopathies after clinical assessment (and/or a family history of arrhythmia), compared with usual standard of care without genetic testing?
2. What is the safety, effectiveness and cost-effectiveness of cascade testing for a known ICA variant in first- and second-degree family members of an index case with an identified pathogenic ICA variant in the *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2*, *CACNA1C*, *RYR2*, *CASQ2*, *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *ALG10*, *CALM1*, *CALM2*, *ANK2*, *TECRL* or *TRDN* gene, compared with no genetic cascade testing?

In case of a linked analysis:

(See section 1.6 for brief explanation of ‘linked evidence approach’)

Table 2 Research questions for linked analysis

Linked evidence step	Research question(s)
Analytical validity	<ul style="list-style-type: none"> • What is the analytical validity of testing for heritable variants in the <i>KCNQ1</i>, <i>KCNH2</i>, <i>SCN5A</i>, <i>KCNE1</i>, <i>KCNE2</i>, <i>KCNJ2</i>, <i>CACNA1C</i>, <i>RYR2</i>, <i>CASQ2</i> (<i>star performer genes</i>), <i>CAV3</i>, <i>SCN4B</i>, <i>AKAP9</i>, <i>SNTA1</i>, <i>KCNJ5</i>, <i>ALG10</i>, <i>CALM1</i>, <i>CALM2</i>, <i>ANK2</i>, <i>TECRL</i> and <i>TRDN</i> genes in individuals strongly suspected of or clinically diagnosed with inheritable cardiac arrhythmia (ICA), compared with the reference standard?
Clinical validity	<ul style="list-style-type: none"> • What is the clinical validity of testing for heritable variants in the <i>KCNQ1</i>, <i>KCNH2</i>, <i>SCN5A</i>, <i>KCNE1</i>, <i>KCNE2</i>, <i>KCNJ2</i>, <i>CACNA1C</i>, <i>RYR2</i>, <i>CASQ2</i> (<i>star performer genes</i>), <i>CAV3</i>, <i>SCN4B</i>, <i>AKAP9</i>, <i>SNTA1</i>, <i>KCNJ5</i>, <i>ALG10</i>, <i>CALM1</i>, <i>CALM2</i>, <i>ANK2</i>, <i>TECRL</i> and <i>TRDN</i> genes in individuals strongly suspected of or clinically diagnosed with inheritable cardiac arrhythmia (ICA)? • What is the clinical validity of testing for a known ICA variant in first- and second-degree family members of an index case with an identified pathogenic ICA variant? • Will the extra information generated as a result of the genetic test be of additional prognostic or predictive value in individuals strongly suspected of or clinically diagnosed with ICA, compared to clinical assessment alone?
Clinical utility (impact on patient management)	<ul style="list-style-type: none"> • Does the addition of genetic testing lead to a change in disease management in individuals strongly suspected of or clinically diagnosed with ICA? • Does the addition of genetic cascade testing of first- and second-degree family members of an index case with an identified pathogenic ICA variant lead to a change in surveillance, detection and management of ICA in family members?#
Therapeutic effectiveness (impact of the change in patient management)	<ul style="list-style-type: none"> • Does the change in disease management due to genetic testing in individuals strongly suspected of or clinically diagnosed with ICA lead to better health outcomes? • Does the change in surveillance, detection and management due to genetic cascade testing in first- and second-degree family members of an index case with an identified pathogenic ICA variant lead to better health outcomes?

PASC advised there is little role for partner testing. PASC also advised the assessment report should include justification of including second-degree relatives in familial cascade testing.

1.2 POPULATION

PASC confirmed the proposed population, as detailed in this PICO.

PASC considered the proposed number of diagnostic tests (200) to be an underestimate. PASC noted the Australian Genomics Cardiac Flagship is auditing the number of cardiac genetic tests being conducted. This should provide the accurate figures required to inform costing calculations for the assessment report. PASC's view is that predictive test numbers would be about 3x the diagnostic test numbers.

PASC advised there is little role for partner testing.

PASC also advised the assessment report should include justification of including second-degree relatives in familial cascade testing.

The applicant has advised that the issue of whether to test second-degree relatives (in addition to first-degree relatives) is a complex one. The applicant notes that, whilst limiting testing for pathogenic/like pathogenic variants to first-degree relatives is reasonable, there may be some circumstances where no living first-degree relative is available for testing, in which case, a second-degree relative may be tested. The proposed item could attempt to capture this by inclusion of a statement such as "at the discretion of the cardiac genetic clinic, in order to determine if this information is useful or if no living first-degree relative is available".

Inherited cardiac arrhythmia syndromes (ICA) or channelopathies, such as long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), occur when ion channel function is affected by variants in set of genes encoding proteins or subunits of cardiac ion channels involved in the control of ventricular repolarisation (Kline & Costantini 2019). The majority are autosomal dominant with variable expressivity (Mizusawa 2016).

ICA syndromes are characterised by conduction abnormalities that may predispose the patient to life threatening arrhythmias (Kline & Costantini 2019). More than half of the patients are asymptomatic at the time of initial diagnosis and are diagnosed either by family history or by virtue of having survived an episode of syncope or severe ventricular arrhythmia (Hocini et al. 2014). Untreated individuals have high risk of syncope and sudden cardiac death (SCD) (Schwartz 2005).

Management of patients suspected of having an inherited arrhythmia include avoiding disease-specific triggers, lifestyle modifications, annual clinical review, medication and, in those considered to be at highest risk, implantation of an implantable cardioverter defibrillator (Ackerman et al. 2011; Hocini et al. 2014).

Long QT syndrome

Long QT syndrome (LQTS) is characterised by QT prolongation and T-wave abnormalities on the electrocardiogram (ECG) that are associated with tachyarrhythmias, typically torsades de pointes (TdP), which are usually self-terminating, causing syncope. Cardiac events usually occur during exercise, loud noise, during sleep or emotional stress, and often without warning. The disease prevalence is estimated to be 1 in 2,500 (Waddell-Smith & Skinner 2016).

Variants in 15 genes have been associated with LQTS, all of which are autosomal dominant. The most common genotypes are long QT subtypes 1 and 2 (*KCNQ1* and *KCNH2*); next in frequency are subtypes 3 and 5 (*SCN5A* and *KCNE1*) (Waddell-Smith & Skinner 2016). The eleven additional minor LQTS

genotypes comprise < 5% of LQTS cases. Genetic testing is recommended (Class 1 indication) for index patients clinically diagnosed with LQTS (Ackerman 2005).

Approximately 5% of LQTS families carry two or more pathogenic variants either in the same gene (compound heterozygotes) or in different genes (digenic heterozygosity). The carriers of two variants have longer QTc intervals and are 3.5-fold more likely to have cardiac arrest compared with probands with one or no identified pathogenic variant.

The presence of two variants on opposite chromosomes in either the LQT1 or LQT5 gene results in a severe autosomal recessive form of LQTS, **Jervell and Lange-Nielsen syndrome (JLNS)**, with associated bilateral sensorineural deafness, long QTc (usually >500 msec), low gastric acid secretion and/or iron deficiency anaemia (Waddell-Smith & Skinner 2016). About 90% of cases of JLNS are caused by variants in the *KCNQ1* gene; *KCNE1* variants are responsible for the remaining cases. 50% of individuals with JLNS have cardiac events before age of three years, and >50% of untreated children with JLNS die before age 15 years (Tranebjærg, Samson & Green 2017).

Brugada syndrome (BrS)

BrS diagnosis is established in individuals presenting with type 1 ECG (elevation of the J wave ≥ 2 mm with a negative T wave and ST segment that is coved type and gradually descending) in more than one right precordial lead (V1–V3) with or without administration of a sodium channel blocker, and at least one of the following:

- Recurrent syncope or nocturnal agonal respiration
- Documented ventricular fibrillation
- Self-terminating polymorphic ventricular tachycardia
- Cove-shaped ECGs in family members
- A family history of sudden cardiac death
- Electrophysiologic inducibility (Brugada et al. 2016)

The incidence of BrS is variable, being higher in South East Asians and is generally quoted as 1 in 2000 (ranges from 1:1000 to 1:10 000) (Szepesváry & Kaski 2016; Vohra & Rajagopalan 2015). It is eight to ten times more prevalent in males than in females (Priori et al. 2013). BrS is responsible for 20% of sudden cardiac deaths in those without structural heart disease. Typical presentation is syncope or aborted cardiac arrest and symptoms usually occur at sleep or at rest (Brugada et al. 2016).

BrS is inherited most commonly in an autosomal dominant pattern. Around 12 genotypes have been reported for BrS with *SCN5A* identified as the most commonly mutated gene. Variants in other genes account for less than two percent of these cases (U.S. National Library of Medicine 2019). Genetic abnormalities are found in around 20–30% of the genotyped patients. Genetic testing for BrS is a Class 2A indication in the index patient (i.e., not recommended in the absence of a diagnostic ECG but may be useful otherwise) but a Class 1 indication (recommended) in family members of a proband identified with pathogenic variant (Priori et al. 2013).

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

CPVT is a highly lethal inherited arrhythmia, characterised by polymorphic ventricular tachycardia induced by adrenergic stress. CPVTs often present with exercise or emotion induced syncope with a mean age of onset between 6 and 10 years. The true prevalence of CPVT is unknown with estimates of approximately 1:10,000, however, this may be an underestimate. Genetic variants are identified in approximately 55–70% of patients with clinical diagnosis (Pflaumer & Davis 2019).

CPVT is inherited most commonly in an autosomal dominant mode due to variants in the cardiac ryanodine receptor gene (*RYR2*), 50–55%, or less frequently in an autosomal recessive mode due to variants in the cardiac calsequestrin gene (*CASQ2*), 2–5%. Variants in other genes, *CALM1*, *TECRL*, *TRDN*, *ANK2* and *KCNJ2*, have also shown to cause CPVT (Pflaumer & Davis 2019). Genetic testing is recommended (Class 1 indication) for index patients clinically diagnosed with CPVT, especially to help predictive testing in the family members (Priori et al. 2013).

The most common genes associated with inheritable cardiac arrhythmias and associated subtypes are summarised in Table 3.

Table 3 Genes commonly associated with cardiac channelopathies and suggested for variant analysis in the proposed listing

Gene#	Inheritance	Protein	Functional effect	Phenotype	Frequency in disease
Long QT syndrome					
KCNQ1	AD	K _v 7.1	Loss of function	LQT1	38%
	AR			JLN1	
KCNH2	AD	K _v 11.1 or hERG	Loss of function	LQT2	42%
SCN5A	AD	Na _v α5 subunit	Gain of function	LQT3	12%
ANK2	AD	Ankyrin B	Loss of function	LQT4	1%
KCNE1	AD	MinK	Loss of function	LQT5	5%
	AR			JLN2	
KCNE2	AD	MiRP1	Loss of function	LQT6	1%
KCNJ2	AD	Kir2.1	Loss of function	LQT7 (ATS1) ^a	<0.1%
CACNA1C	AD	Ca _v 1.2	Gain of function	LQT8 (TS1) ^b	<0.1%
CAV3	AD	Caveolin 3	Gain of function	LQT9	<0.1%
SCN4B	AD	Na _v β4 subunit	Gain of function	LQT10	<0.1%
AKAP9	AD	A-kinase anchor protein 9	Loss of function	LQT11	<0.1%
SNTA1	AD	Syntrophin α1	Gain of function	LQT12	<0.1%
KCNJ5	AD	Kir 3.4 subunit of I _K Ach channel	Loss of function	LQT13	<0.1%
CALM1	AD	Calmodulin 1	Loss of function	LQT14	<0.1%
CALM2	AD	Calmodulin 2	Loss of function	LQT15	<0.1%
Brugada syndrome					
SCN5A	AD	Na _v α5 subunit	Loss of function	BrS1	20–30%
CPVT					
RYR2	AD	Ryanodin receptor 2	Loss of function	CPVT1	55–70%
CASQ2	AR	Calsequestrin 2	Loss of function	CPVT2	2–5%
ANK2	AD	Ankyrin B	Loss of function	LQT4	
CALM1	AD	Calmodulin 1	Loss of function	CPVT4	
CALM2	AD	Calmodulin 2	Loss of function	LQT15	
KCNJ2	AD	Kir2.1		LQT7 (ATS1)	
TECRL	AR	Trans-2,3-enoyl-CoA reductase-like		CPVT3	
TRDN	AR	Triadin	Loss of function	CPVT5	

Star performer genes are presented in the bold text.

^a Anderson-Tawil syndrome type 1 (ATS1) is a rare neurological disorder characterised by periodic paralysis, skeletal developmental abnormalities, and QT prolongation.

^b Timothy syndrome type 1 (TS1) is a rare condition characterised by syndactyly, facial dysmorphism, autism and severe LQTS.

Source: Data sourced from Waddell-Smith 2016 (Waddell-Smith & Skinner 2016); Ackerman 2011 (Ackerman et al. 2011)

AD = autosomal dominant; AR = autosomal recessive; ATS = Andersen-Tawil syndrome; BrS = Brugada syndrome; CPVT = Catecholaminergic polymorphic ventricular tachycardia; JLNS = Jervell and Lange-Nielsen syndrome; LQT = long QT syndrome; TS = Timothy syndrome

NB: Variant ALG10B on the *KCR1* gene has been found to be associated with reduced susceptibility for long QT syndrome 2. As this variant is not considered pathogenic, it is not included in the table above.

1.3 PRIOR TESTS

Genetic testing is proposed to be used in addition to standard clinical practice. Patients are required to have a clinical assessment based on clinical presentation, standard 12-lead ECG and family history.

Additional methods of testing include 24-hour Holter monitoring, exercise (stress) ECGs and cardiac electrophysiology.

Table 4 summarises the clinical criteria used to estimate the probability of underlying LQTS. Patients scoring < 1 point have a low probability of LQTS, those with 2–3 points have an intermediate probability, with those scoring > 3.5 points having a high probability of LQTS (Steinberg 2018). The Schwartz scoring tool has high specificity (99%) but a very low sensitivity (19%), and LQTS cases with normal resting ECG and an absence of positive family history are unlikely to be detected, which makes diagnosis of LQTS challenging. In these ‘concealed’ cases additional investigations, including exercise testing, adrenaline challenge and Holter monitoring, may increase diagnostic sensitivity (Steinberg 2018; Waddell-Smith & Skinner 2016).

Table 4 Diagnostic criteria for long QT syndrome in adults #

Characteristics	Points
Clinical history	
Syncope ^a	
With stress	2
Without stress	1
Congenital deafness	1
Family history^b	
Family members with definite long QT syndrome	1
Unexplained sudden cardiac death at age <30 years among immediate family members	0.5
Electrocardiographic findings^c	
A resting QTc interval ^d	
≥480 ms	3
460–479 ms	2
450–459 ms (in males)	1
QTc at 4 min of recovery from exercise stress test ≥480 ms	1
Torsade de pointes ^a	2
T-wave alternans	1
Notched T wave in 3 leads	1
Sinus bradycardia (resting heart rate < 2nd percentile for age)	0.5

QTc = corrected QT interval; RR = the time interval between 2 consecutive QRS complexes on electrocardiogram).

Source: Schwartz et al 2013 and Szepesvary et al 2016 (Schwartz et al. 2013; Szepesváry & Kaski 2016).

Patients scoring <1 point have a low probability of LQTS, those with 2–3 points have an intermediate probability, with those scoring >3.5 points having a high probability of LQTS.

^a Torsade de pointes and syncope are mutually exclusive.

^b The same family member cannot be counted twice.

^c In the absence of medications or disorders known to affect these electrocardiographic features.

^d Corrected QT interval (calculated by the Bazett formula $QTc = QT / \sqrt{RR}$; where R-R is the time interval between 2 consecutive QRS complexes on electrocardiogram).

The diagnosis of JLNS is based on three-generation family history, formal audiology evaluation for extent of hearing loss, complete blood count to screen for anaemia, screening for iron deficiency (if anaemia is present) and cardiac examination including calculation of QTc using standard 12-lead ECG (Tranebjærg, Samson & Green 2017).

BrS is diagnosed based on family history, clinical history and ECG pattern (Brugada et al. 2016). CPVT is diagnosed based on family history, exercise or emotional stress-induced symptoms and most importantly, exercise stress testing or catecholamine infusion. In patients who are not able to perform exercise testing (such as children), Holter ECG and event recorders may be useful in the diagnosis.

Further details regarding diagnosis and management of inheritable arrhythmias are available through guidelines published by Cardiac Society of Australia and New Zealand (CSANZ) (Pflaumer & Davis 2019; Vohra & Rajagopalan 2015; Waddell-Smith & Skinner 2016) and Expert Consensus Statement on Inherited Arrhythmia Syndromes (Priori et al. 2013).

1.4 INTERVENTION

PASC confirmed the intervention (as presented in this PICO).

PASC queried if the ALG10 gene should be included in the analysis (and added to Table 3). The ALG10 (alpha-1,2-glucosyltransferase) gene is listed as one of the non-star performer genes. The assessment group has confirmed there is evidence that a mutation in the [KCR1 gene \(ALG10B; OMIM 603313\)](#), on chromosome 12q12, confers reduced susceptibility to acquired long QT syndrome-2 (i.e. it is protective rather than pathogenic), so should not be included.

Ongoing challenges in the clinical diagnosis of inherited arrhythmia syndromes and the discovery of clinically meaningful genotype–phenotype correlations, supports the role of genetic testing as outlined by expert consensus documents (Priori et al. 2013). Furthermore, there is growing evidence for genotype specific management and risk. For example, in long QT syndrome, genetic testing can differentiate types of LQTS, which can be indistinguishable by diagnostic criteria including electrocardiography, clinical symptoms, and family history (Napolitano et al. 2015). There is substantial genetic heterogeneity, with different variants in the same cardiac ion channel genes resulting in different phenotypes, depending on their functional effect. For example, gain of function variants in *SCN5A* gene cause LQT3 syndrome, while loss of function variants may be responsible for BrS type 1. Similarly, abnormal changes in intracellular Ca²⁺ channels can cause Timothy syndrome (LQT8), Brugada syndrome, and CPVT (Szepesváry & Kaski 2016).

Genetic testing in index cases is useful to confirm diagnosis, inform prognosis, reduce risk through tailored patient management and allow genetic screening of potentially affected family members. When a familial pathogenic variant is identified in the proband, predictive cascade family testing can reveal family members who are affected (variant positive) and those who are not (variant negative). Variant negative family members are considered not at risk of inheritable arrhythmias, and do not require any special management or annual surveillance (Waddell-Smith & Skinner 2016).

Appropriate genetic counselling should be provided to the patient and at-risk relatives either by the treating practitioner, a specialist cardiac genetic clinic or by a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

Method

Given the clinical overlap between different arrhythmia conditions, comprehensive testing (gene panel testing; usually performed using massively parallel sequencing) allows for a more efficient evaluation of multiple conditions based on a single indication for testing. The proposed listing covers most common genetic causes of LQTS, BrS and CPVT (variants in *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2*, *CACNA1C*, *RYR2*, *CASQ2* (star performer genes), *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *ALG10*, *CALM1*, *CALM2*, *ANK2*, *TECL1* and *TRDN* gene).

The clinical sensitivity of this test would vary based on the patient's phenotypic presentation and family history. For each syndrome, the table below shows the probability of identifying a pathogenic variant by the suspected clinical condition, through analysis of the genes on the proposed panel. 'Pathogenic variant' includes class 4 variants (likely pathogenic) and class 5 variants (pathogenic).

Table 5 Estimated prevalence and clinical sensitivity for different arrhythmia syndromes

	Underlying condition			
	BrS	CPVT	LQTS	JLNS
Clinical sensitivity	20%–30%	65%	70%	Unknown
Prevalence of variants in unselected population	1:2000	1:10,000	1:2,534	1:200,000

BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; JLNS = Jervell and Lange-Nielsen syndrome; LQTS = long QT syndrome

Source: Priori et al 2013 (Priori et al. 2013); Vohra et al 2015 (Vohra & Rajagopalan 2015); Waddell-Smith 2016 (Waddell-Smith & Skinner 2016); Pflaumer et al 2019 (Pflaumer & Davis 2019); Tranebjærg et al 2017 (Tranebjærg, Samson & Green 2017)

Frequency of testing

The test would be done once per lifetime for index patients, as the condition is hereditary and the test result is considered conclusive. Although it is expected that family members would only be tested once per lifetime, if another relative of theirs is found to have a different germline variant, they should be able to receive cascade testing for that particular variant as well.

It is recommended that results from a commercial kit which identify a mutation being present should be confirmed using a second validated testing method. The proposed fee covers the entire testing process and the confirmatory testing is at the discretion of specific laboratory. This would not involve a second sample for repeat testing; the initial tests and confirmatory tests would be performed on the same DNA sample.

The Royal College of Pathologists of Australasia (RCPA) conducted a survey, on behalf of the Commonwealth Department of Health, of all Australian laboratories (n=87) known to offer genetic or genomic tests that yielded results with medical utility during the 2016–17 financial year (RCPA 2019). The private and public sector delivered 71% and 29% of all genomic tests for heritable conditions, respectively; however, the data are unclear which sector provided testing for cardiovascular indications.

Data from this survey indicated that during the one-year sample period, cardiologists requested a total of 2,324 genetic/genomic tests. A proportion of 40,579 tests requested by clinical geneticists would also be expected for cardiology indications. Additionally, 244 samples were referred to overseas laboratories for genetic testing for cardiac disorders.

The number of cardiovascular tests conducted with targeted multi-gene panels (testing ≥three or more genes) for arrhythmia was estimated to be 106:

- Panel – Arrhythmia (11–50 genes) 96
- Panel – Arrhythmia (51+ genes) 10

However, some arrhythmia tests may have been conducted under the other generic cardiac panels:

- Panel – Cardiac (11–50 genes) 403
- Panel – Cardiac (51+ genes) 461

According to data provided by the applicant in the Clinical Utility Card, a total of 1,692 genetic tests were performed for all cardiovascular conditions and 6.2% of these tests were specific to arrhythmia^[1]. If this similar proportion is applied to the generic cardiac panels (864 tests) and cardiac tests referred to overseas laboratories (244), an additional 69 arrhythmia tests (6.2% of 1,108 tests) may have been conducted. Therefore an estimated 175 cardiac arrhythmia genetic tests would have been performed during the survey period.

Of note, as genetic testing for cardiac arrhythmia is not currently MBS funded, tests conducted in the private sector would be privately funded, and would therefore be a likely underestimate of the true number as many patients would be unable to afford it. Similarly, the number of tests conducted in the public sector would also represent an underestimation of the true number due to long waiting lists and limited funding. Therefore, the number of diagnostic tests performed per year for inheritable arrhythmias might increase due to higher uptake as a result of availability and affordability.

For financial estimates, therefore it may be appropriate to assume that approximately 200 diagnostic tests would be performed for the arrhythmic conditions. When the disease distribution as reported in the literature is applied (Hocini et al. 2014), around 75% of these would be attributed to the proposed indications (LQTS, BrS and CPVT); that is 149 tests. Out of these 149 tests approximately 78 tests would be positive for pathogenic or likely pathogenic variants (after applying the diagnostic yield in different syndromes, Table 5).

The average number of first- and second-degree relatives are assumed to be 11.5 per proband, based on a survey undertaken by the South Australian Clinical Genetics Service in 2006 (Suthers et al. 2006). If uptake of cascade testing is assumed to be around 50%, approximately 449 relatives would undergo the proposed familial testing for cardiac arrhythmias.

As stated above, PASC considered the proposed number of diagnostic tests (200) to be an underestimate. PASC noted the Australian Genomics Cardiac Flagship is auditing the number of cardiac genetic tests being conducted. This should provide the accurate figures required to inform costing calculations for the assessment report. PASC's view is that predictive test numbers would be about three times the diagnostic test numbers.

1.5 COMPARATOR

PASC confirmed the comparator is “no genetic testing” (usual standard of care).

The proposed test is an addition to current practice (see section 1.3). In the absence of genetic testing for inheritable cardiac arrhythmia, there would be usual standard of care (without the proposed test).

^[1] MSAC 1598 Clinical Utility Card for Inheritable Cardiac Arrhythmia Disorders, 2019.

This means that without genetic testing, treatment is based on the phenotype / symptoms, and there would be no genetic family cascade testing. Family members or children of a diagnosed patient may have phenotypic testing (such as ECG, Holter monitoring and stress test), and will also be treated based on phenotype. If no familial variant is found through genetic testing (but there is a clinical diagnosis), family members of an inheritable cardiac arrhythmia patient are still advised to undergo clinical assessment.

1.6 OUTCOMES

PASC confirmed the proposed outcomes.

PASC added that, similar to Application 1599 (Genetic testing for diagnosis of cardiomyopathies), PICO 1598 should state that the main benefit is for cascade testing – these are people whose management may be altered by results of the test (given a negative test would obviate the need for lifelong surveillance or preventive intervention). PASC recommended this should be reflected in the economic evaluation, which has been actioned in Section 3 below.

The applicant stated that identification of FH variants in affected individuals and family members would lead to:

- Confirming the type of arrhythmia diagnosis
- Tailored patient management
- Improved medication compliance
- Enabling cascade testing of family members
- Early detection of inheritable cardiac arrhythmia in relatives (early commencement of lifestyle changes and drug/device therapy)
- Reassuring family members who have not inherited the condition

The assessment aims to determine the safety, effectiveness and cost-effectiveness of the test. Direct evidence would include evidence on whether genetic testing leads to better quality of life / survival (in both the index case and family members), compared to no genetic testing. In the absence of sufficient direct evidence, a linked evidence approach should be conducted, including evidence on analytical validity, clinical validity, therapeutic efficacy and therapeutic effectiveness. Outcomes related to these linked evidence steps are shown below in ‘patient relevant outcomes’.

To show clinical utility, evidence on change in management should be provided. Changes in management due to genetic cascade testing could be earlier detection of cardiac arrhythmia and earlier management/treatment of relatives due to genetic testing, and possible lifestyle changes (in case of a positive result, such as stopping sporting activities, or avoiding loud noises).

[Patient-relevant outcomes](#)

Safety

- Physical and/or psychological harms from testing or no testing
- Adverse events from testing and consequences of true or false test results.

Effectiveness

- Cardiac events (such as: cardiac arrest, sudden cardiac death or syncope) avoided
- Quality of life years (QALYs) gained.

For a linked evidence approach:

Analytical validity

- Test failure rate (and re-testing rate)
- Analytical performance (sensitivity, specificity)
- Concordance (per cent positive agreement)
- Unsatisfactory or uninterpretable test results
- Diagnostic yield

Clinical validity

- Predictive and prognostic value

Clinical utility – therapeutic efficacy

- Change in patient management (management after genetic testing vs no genetic testing),
- Change in surveillance, detection and treatment of family members

Clinical utility – therapeutic effectiveness

- Effect of change in management (e.g. reduction in cardiac events (ACA or SCD, syncope) and mortality)
- Effect of change in management due to cascade testing (uptake of genetic testing in family members, reduced clinical surveillance and associated testing such as ECG and exercise stress tests in asymptomatic family members of proband, improved quality of life, improved psychological health, reduction in cardiac events, etc.)

Healthcare system outcomes

Cost-effectiveness

- Cost
- Cost per life year gained (LYG)
- Cost per quality adjusted life year (QALY) or disability adjusted life year (DALY)
- Incremental cost-effectiveness ratio (ICER)

Financial implications / healthcare resources

- Cost of test: variant analysis in proband and predictive genetic testing of family members
- Estimated number of patients / family members undergoing genetic testing
- Test turn-around time
- Net overall healthcare costs
- Net cost to the MBS
- Estimated cost of subsequent treatment, monitoring and counselling after genetic testing
- Estimated cost of subsequent treatment, monitoring and counselling after no genetic testing

Estimation of changes in use, and cost of other medical services may include:

- Changes in β -blocker prescriptions and other pharmaceuticals
- Change in the rate of ICD implantation
- Reduction in number of services currently provide to asymptomatic family members of proband, such as:
 - Clinical surveillance by cardiologists and associated testing such as ECG and exercise stress tests
 - Pharmaceuticals
- Reduction in hospitalisations for cardiac events

2. CURRENT AND PROPOSED CLINICAL MANAGEMENT ALGORITHM FOR IDENTIFIED POPULATION

PASC noted the clinical management of some people may change after having a genetic test diagnose their condition, which has been included in the clinical management algorithm.

PASC noted there is some evidence to suggest, for example, that genetic diagnosis of LQTS does affect subsequent management.

PASC also noted that, currently, there are clinical misdiagnoses that could be clarified after genetic testing, which could affect management. PASC considered the clinical benefits need to be clarified in the management algorithms (affected individual, familial cascade testing), so it can be included in the economic modelling. This has been actioned.

The applicant did not provide a clinical management algorithm. The clinical management algorithms presented below are based on Australian clinical practice and a teleconference with the applicants, clinical experts and the Department of Health.

Genetic testing for cardiac arrhythmias currently happens in Australia through familial genetic clinics or private funding. In the absence of genetic testing it is assumed that patients and family members would be managed based on the clinical diagnosis of the index case. This is the comparator.

Identification of a pathogenic variant causing inherited arrhythmia syndrome has important diagnostic, prognostic, and therapeutic implications, facilitating appropriate medical advice and therapy to affected individuals in order to prevent cardiac arrhythmia and sudden cardiac death (Ackerman et al. 2011; Priori et al. 2013).

Identification of variants has treatment implications in index patients with respect to triggers to avoid arrhythmias and provide maximally beneficial medications. Once a precise diagnosis is established, more targeted and efficacious prevention, surveillance, and treatment can be established, and ineffective treatments can be avoided (Ackerman et al. 2011; Priori et al. 2013).

Identification of a pathogenic variant in the probands allows an efficient, effective method for identifying other at-risk family members who can then make an informed decision regarding their risk, and whether to commence appropriate treatment.

A negative pathogenic variant analysis doesn't necessarily exclude disease (Anderson et al. 2016). Management of these individuals should follow phenotypic guidelines and their at-risk relatives should still receive careful clinical screening and appropriate prevention strategies and interventions (Alders, Bikker & Christiaans 2018).

The current and proposed approaches for management (and any downstream services and outcomes) of the proposed populations are explained in two different algorithms on: (1) individuals suspected of or diagnosed with inheritable cardiac arrhythmias after clinical assessment (Figure 1), and (2) first- and second-degree family members of an index case with/without identified pathogenic variant (Figure 2).

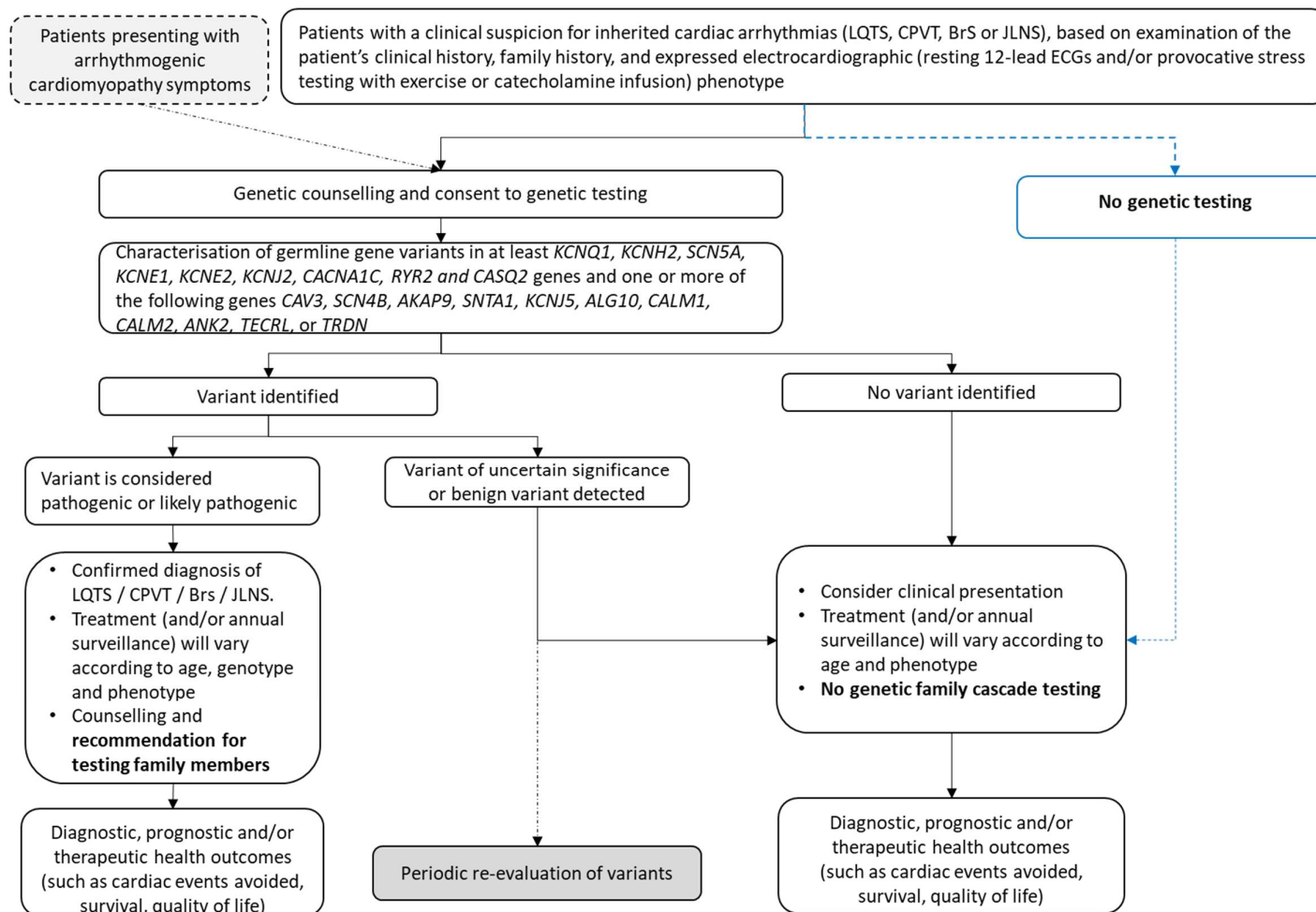


Figure 1 Current and proposed clinical algorithm in the index cases

BrS = Brugada syndrome; CPVT = Catecholaminergic polymorphic ventricular tachycardia; JLNS = Jervell and Lange-Nielsen syndrome; LQT = long QT syndrome

*The diagnostic, prognostic, and therapeutic contribution of a genetic test result is disease dependent.

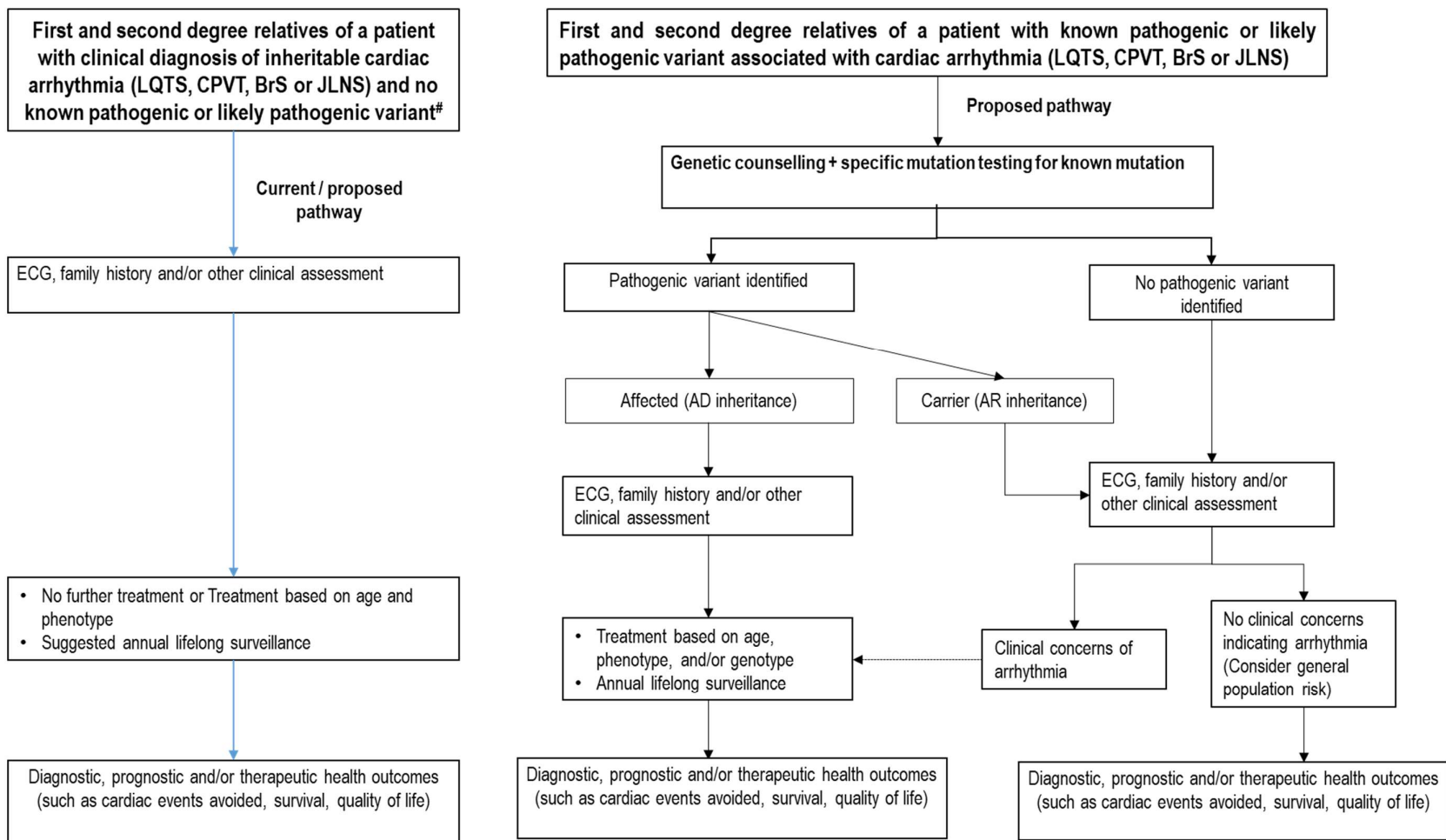


Figure 2 Current and proposed clinical algorithm for proposed familial cascade testing

This includes index cases who have undergone genetic testing but were not identified with any pathogenic or likely pathogenic variants as well as those who haven't undergone any genetic testing.
 BrS = Brugada syndrome; CPVT = Catecholaminergic polymorphic ventricular tachycardia; JLNS = Jervell and Lange-Nielsen syndrome; LQT = long QT syndrome

3. PROPOSED ECONOMIC EVALUATION

PASC confirmed the economic evaluation should be a cost-effectiveness/cost-utility analysis.

The clinical utility card (CUC) application suggested the proposed genetic testing for variants responsible for inherited cardiac arrhythmias or channelopathies in patients with a strong clinical and/or family history and their unaffected first and second-degree relatives, is superior in effectiveness and non-inferior in safety to the management of these people in the absence of genetic testing.

Table 6 classifies the type of economic evaluation that should be presented, based on the assessed evidence profile. According to this classification, if there is enough data to reach a conclusion regarding superior/non-inferior safety and effectiveness of specified genetic testing (diagnostic and predictive) for inheritable cardiac arrhythmia, a cost-effectiveness/cost-utility analysis is the most appropriate type of economic evaluation to present. PASC confirmed this, as stated above.

The main benefit of the proposed listing is for cascade testing – these are people whose management may be altered by results of the test (given a negative test would obviate the need for lifelong surveillance or preventive intervention). Therefore, the economic model should aim to investigate the incremental value of cascade testing. Cascade testing would include first- and second-degree family members. PASC also advised the assessment report should include justification of including second-degree relatives in familial cascade testing. PASC advised there is little role for partner testing.

Table 6 Classification of an intervention for determination of economic evaluation to be presented

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

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

4. PROPOSED MBS ITEM DESCRIPTOR/S AND MBS FEES

PASC noted the type of requestor in the descriptor was overly-detailed, compared to similar descriptors. PASC recommended this detail be moved to the MBS Explanatory Notes.

PASC noted anyone with an autosomal recessive condition may not have a family history of ICA (and this also applies to autosomal dominant conditions, since up to 30% of these may be de novo mutations). PASC therefore recommended the descriptor should read “...clinical and/or family history criteria ...”

PASC noted the wording “usual practice guidelines” is vague, albeit current standard wording for MBS item descriptors (i.e. it is similar to BRCA gene testing wording). PASC recommended the Department assess this wording (for this and similar items).

PASC recommended that family members should have pre- and post-test genetic counselling (recognising it is outside the scope of the MBS), and the recommendation for counselling should be reflected in the practice note.

PASC advised that co-claiming of cardiac panels (relating to this application and Application 1599) is an implementation issue the Department will need to resolve. PASC noted the panels are largely different, but there is some overlap. PASC considered that most laboratories would process the full panel, then analyse only the required genes. The cost could therefore be 2 x \$1,200, or 1 x \$1,200 (plus another fee to analyse additional genes not included in the panel).

The applicant agreed with PASC that the proposed restrictor on the requestor group is unworkable, and should be amended in line with similar MBS items.

The proposed new MBS descriptor for testing germline variants in patients with clinical suspicion of inheritable cardiac arrhythmia syndrome is presented in

Table 7. First and second-degree relatives of patients identified with a familial arrhythmia variant can have cascade family testing under the proposed item YYYYY (Table 88).

Table 7 Proposed item descriptor for diagnostic testing

Category 6–Pathology services
<p>MBS item XXXXX</p> <p>Characterisation of germline gene variants, requested by a specialist or consultant physician, including copy number variation in at least <i>KCNQ1</i>, <i>KCNH2</i>, <i>SCN5A</i>, <i>KCNE1</i>, <i>KCNE2</i>, <i>KCNJ2</i>, <i>CACNA1C</i>, <i>RYR2</i> and <i>CASQ2</i> genes and one or more of the following genes <i>CAV3</i>, <i>SCN4B</i>, <i>AKAP9</i>, <i>SNTA1</i>, <i>KCNJ5</i>, <i>ALG10</i>, <i>CALM1</i>, <i>CALM2</i>, <i>ANK2</i>, <i>TECRL</i> or <i>TRDN</i> in a patient for whom clinical and/or relevant family history criteria suggestive of inherited cardiac arrhythmias or channelopathies place the patient at >10% risk of having a pathogenic variant identified in one of the genes specified above</p> <p>Maximum of one service per lifetime</p> <p><u>MBS Fee:</u> \$1,200</p> <p>Explanatory note: PN.0.27 Patients who are found to have any form of affected allele should be referred for post-test genetic counselling as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral.</p>

Table 8 Proposed item descriptor for predictive testing of family members

Category 6–Pathology services
<p>MBS item YYYYYY</p> <p>Characterisation of one or more germline gene variants, in a first or second-degree biological relative of a patient with pathogenic variants associated with cardiac arrhythmia or channelopathy identified from item XXXXX, who has not previously received a service under item XXXXX.</p> <p><u>MBS Fee: \$400</u></p> <p>Explanatory note: PN.0.23 Prior to ordering these tests (YYYYY) the ordering practitioner should ensure the patient (or approximate proxy) has given informed consent. Testing should only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.</p>

CONSULTATION FEEDBACK

PASC noted the consultation feedback, including the letter of support from Australian Genomics.

NEXT STEPS

Upon ratification of PICO 1598, the application can PROCEED to the pre-Evaluation Sub-Committee (ESC) stage.

The applicant has elected to progress this application through a DCAR (Department-contracted assessment report).

PASC recommended it is appropriate for the assessment to follow the clinical utility card (CUC) approach.

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