



**Australian Government**  
**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Application No. 1598 – Genetic testing for diagnosis of inheritable cardiac rhythm disorders***

**Applicant: The Royal College of Pathologists of Australasia (RCPA)**

**Date of MSAC consideration: MSAC 80<sup>th</sup> Meeting, 26-27 November 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

#### **1. Purpose of application**

A clinical utility card (CUC) format application for genetic testing for the diagnosis of inheritable cardiac arrhythmias was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health.

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for germline genomic testing for inherited cardiac arrhythmias or channelopathies, based on the available evidence for comparative safety, clinical effectiveness and cost-effectiveness.

MSAC supported new items for testing of affected individuals, as well as cascade testing in biological relatives of those affected individuals who receive a positive genetic diagnosis. MSAC considered that the value of testing mainly arose from superior outcomes following cascade testing. MSAC also supported new items for reproductive partner testing for genes with autosomal recessive inheritance, and for subsequent re-analysis following a negative result of an affected individual if a virtual panel has been used on an exome background. MSAC recommended that utilisation of all these items should be reviewed after 2 years.

<b>Consumer summary</b>
<p>The Royal College of Pathologists of Australasia (RCPA) applied for public funding via the Medicare Benefits Schedule (MBS) for genetic testing for certain inherited heart rhythm problems.</p> <p>These problems include long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. In people with these problems, their heart can suddenly stop beating or they can die suddenly.</p>

### **Consumer summary**

This application involves testing a group of 20 genes that are known to be involved in inherited heart problems. The test is for people who could be at risk of having one of these heart conditions, perhaps because a family member develops heart symptoms. If the test shows a genetic variant related to one of these conditions, then their close family members may also be recommended to get tested, even if they don't have symptoms. This is called cascade testing. Cascade testing allows people to make more informed health and family planning decisions.

The main advantage of genetic testing is to find genetic variants in family members so that they can be monitored, or start treatment earlier. Earlier treatment can save their life. Family members who do not have the genetic variant do not need to be monitored or treated. This testing is also cost-effective for the health system.

People with some gene variants who are planning on having children will be advised to consider testing for their reproductive partner too. The need for this testing depends on the type of gene and how it is inherited.

New genes are often being discovered, and may be added in the future to the group of genes tested. Pathology laboratories can sequence the patient's whole exome (all of a person's genetic makeup), and reanalyse the same data later as new genes are identified.

### **MSAC's advice to the Commonwealth Minister for Health**

The Medical Services Advisory Committee (MSAC) recommended that genetic testing for 20 genes involved in inherited heart conditions be listed on the MBS. MBS items should address initial testing, cascade testing, reproductive partner testing and data reanalysis as new genes are identified. MSAC considered that this type of genetic testing is accurate, results in benefits for the consumer and is cost-effective.

### **3. Summary of consideration and rationale for MSAC's advice**

MSAC noted that application 1598 is for MBS listing of genetic testing for variants in a panel of 20 genes implicated in inherited cardiac arrhythmias or channelopathies.

MSAC noted the clinical claim is that testing clinically affected individuals helps to estimate their predisposition for further disease and to identify the pathogenic variant for cascade testing. Where appropriate, cascade testing would then be offered to asymptomatic family members to detect their future risk of developing the disease.

MSAC noted that genetic testing for inherited cardiac arrhythmias and channelopathies is already standard practice in genetic/cardiac genetic clinics, and not having an MBS item for such testing may result in issues of equity of access for some people. MSAC also noted that such testing is recommended in clinical guidelines.

MSAC supported the creation of an MBS item for genetic testing in the reproductive partners of probands, restricted to syndromes that have autosomal recessive inheritance patterns. MSAC noted that this type of genetic testing could inform reproductive decision-making, as testing for arrhythmia genes is clinically indicated for those genes with autosomal recessive inheritance and that have the potential to result in severe disease in children. MSAC noted the applicant's support in the pre-MSAC response for an additional item for embryo or fetus

testing. MSAC considered that testing of reproductive partners should be single gene sequencing for the gene in which their partner has a variant, and should not be the full panel test, which is intended only for affected individuals.

MSAC considered it could be beneficial to create a new item to reanalyse stored data, to look for changes in newly recognised genes associated with the phenotype that were not tested for initially. However, MSAC noted that this will only be possible if virtual panel testing has been performed on an exome background. MSAC encouraged this approach – as it is more cost-effective in the long term – by suggesting restricting item claiming to once per lifetime and adding the following explanatory note:

The rapidly expanding field of genomic medicine has resulted in recognition of an increasing number of genetic causes of cardiac diseases. Genomic testing methods that permit reanalysis of existing data for variants in newly described clinically relevant genes are recommended/encouraged.

MSAC noted that if amplicon-based testing (which only sequences the genes of current interest) is performed, then other genes will not be able to be analysed at a later time-point. MSAC also noted that utilisation of this reanalysis item would have to be reviewed over time, as genetic reanalysis is usually only recommended for childhood syndromes.

MSAC noted the likelihood for leakage, and recommended that the item descriptors need to include additional information that emphasises that testing should only be recommended for people who have clinical evidence that is suggestive of inherited cardiac arrhythmias or channelopathies, or if a multidisciplinary team has reviewed the case and recommended genetic testing.

MSAC noted that genetic testing has non-inferior safety and non-inferior effectiveness in affected individuals, but non-inferior safety and superior effectiveness in cascade testing of family members.

MSAC noted the clinical validity of the genetic testing, and that individuals with definite LQTS (defined clinically) were 10 times more likely to have at least one variant in the *KCNQ1*, *KCNH2* or *SCN5A* genes than healthy controls<sup>1</sup>. MSAC noted that no studies were informative about the accuracy of genetic testing against a clinical reference standard. However, MSAC considered that genotype may not correlate with disease status due to incomplete penetrance.

MSAC noted that genetic testing helped to reclassify patients: 4.4% (k = 5, 10/229) of patients with “LQTS” were reclassified as CPVT; and 7.1% (k = 3, 4/56) of patients with “CPVT” were reclassified as having LQT5 or LQT7 after genetic testing. MSAC acknowledged that for some of the genes identifying the pathogenic variant in the affected individual can assist clinicians with prognoses.

MSAC noted the main clinical utility comes from the cascade testing, as identification of genotype-positive family members allows early and targeted treatment, and identification of genotype-negative family members provides reassurance and enables avoidance of lifelong clinical surveillance and unnecessary prophylaxis.

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<sup>1</sup> Kapa, S, et al., 2009, 'Genetic testing for long-QT syndrome: Distinguishing pathogenic mutations from benign variants', *Circulation*, vol. 120, no. 18, 2009, pp. 1752-1760.

MSAC considered the testing to likely be cost-effective – albeit with uncertain incremental cost-effectiveness ratios (ICERs) – provided that the initial diagnostic testing is restricted to affected individuals with definite or probable inherited cardiac arrhythmia syndromes and other assumptions. However, MSAC considered the 40-year time horizon used in the economic model to be unrealistic, and considered 20 years to be more appropriate. However, MSAC did not consider this discrepancy to materially affect the cost-effectiveness.

Although there is a risk of leakage, MSAC acknowledged that the listing would have small overall financial impact, and that reviewing the items in two years would help to identify item usage and thus leakage. MSAC recommended the following be considered at the 2-year review:

- What is the diagnostic yield for the diagnostic test in affected individuals offered and proceeding with testing? (The economic model assumed it to be 26%; MSAC considered that it should be at least 20%)
- How many relatives access cascade testing if the genetic variant in their family is identified? (MSAC acknowledged there might not be enough data for this within 2 years.)
- What is the diagnostic yield in the standard setting versus an adjudicated model? (This would require analysis of laboratory reports.)
- What is the change in clinical practice after a positive or negative result? (MSAC considered this important as a negative test may not always lead to a decision to release an unaffected relative from monitoring, and to address the uncertain ICERs.)

MSAC suggested the Medical Research Future Fund (MRFF) may be a possible funding source to review the implementation strategy for this genetic testing and for the data collection, and recommended that the Department investigate this as an option. If the MRFF investigated this aspect of the review, it would be responsible for establishing a diagnostic yield methodology.

Although MSAC recommended this genetic testing for MBS listing, it acknowledged that out-of-session work with the Department is required regarding the MBS item descriptors, the need for genetic counselling, and the possible involvement of the MRFF.

Proposed descriptors for the MBS items supported by MSAC for affected individual testing (Table 1) and cascade testing (Table 2) are provided in subsequent sections of this document. MSAC supported the modification of the MBS descriptors for both item numbers. Item descriptors for reproductive partner testing for genes with autosomal recessive inheritance, and for reanalysis of stored exome data, are to be developed during implementation.

#### **4. Background**

In November 2010, the Pathology Services Table Committee (PSTC) lodged MSAC [application 1151](#), requesting public funding for testing of six genes associated with long-QT syndrome (LQTS; genes *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1* and *SCN5A*) in symptomatic patients and asymptomatic first- and second-degree relatives. This application was considered by PASC in February and April 2011, and then by ESC in February 2012. ESC advised that there were several uncertainties, particularly pertaining to the proposed item descriptor and fee for symptomatic patients. As the PSTC disbanded, the RCPA agreed in March 2013 to become the applicant. The RCPA advised on 11 February 2014 that they would like to place application 1151 on hold, as new technologies are now available.

Application 1598 builds significantly on application 1511, as it includes additional genes, and was submitted in CUC format, which is designed for use in MSAC applications related to genetic testing for heritable mutations. The CUC format has therefore also been used for application 1598's DCAR.

Related is MSAC [application 1599](#), for genetic testing for the diagnosis of heritable cardiomyopathies. Application 1599 is a CUC format application proposed to include 24 genes, of which one (*SCN5A*) overlaps with the genes proposed in this application.

Note the name of this application was changed after consideration by PASC from “Genetic testing for diagnosis of inheritable cardiac rhythm disorders” to “Clinical utility card for genetic testing for diagnosis of inheritable cardiac rhythm disorders”, to reflect the decision to use a CUC approach for assessment.

## **5. Prerequisites to implementation of any funding advice**

The DCAR stated that this test is already conducted in National Association of Testing Authorities (NATA) accredited Australian laboratories, and there is an existing quality assurance program. This was supported by the statement on application 1598 from the National Pathology Accreditation Advisory Council (NPAAC). The NPAAC further commented that the number of tests would not be expected to be high.

The NPAAC also noted that the item descriptor includes a risk cut-off of 10%, though if this was derived from early restrictions around access to *BRC A* testing, then it should not be directly transferred to other genetic tests. ESC noted that the 10% risk threshold is a standard feature of the CUC.

## **6. Proposal for public funding**

The DCAR proposed a new MBS item descriptor, XXXXX, for testing germline variants in patients with clinical suspicion of inheritable cardiac arrhythmia syndrome (Table 1). First and second-degree relatives of patients identified with a familial arrhythmia variant are proposed to have cascade testing under proposed item YYYYYY (Table 2).

**Table 1: Proposed item descriptor for diagnostic testing**

Category 6–Pathology services
MBS item XXXXX <del>Characterisation</del> Detection of germline gene variants, <del>requested by a specialist or consultant physician</del> , including copy number variation in at least <del>the following genes</del> <b>KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, RYR2, and CASQ2</b> , <del>genes and one or more of the following genes</del> <b>CAV3, SCN4B, AKAP9, SNTA1, KCNJ5, ALG10, CALM1, CALM2, ANK2, TECRL</b> <del>or and TRDN</del> in a patient for whom clinical and/or 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. <del>Requested by a specialist or consultant physician.</del>
Maximum of one service per lifetime
<u>MBS Fee: \$1,200 85% \$1,020 75% \$900</u>
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. <u>The rapidly expanding field of genomic medicine has resulted in recognition of an increasing number of genetic causes of cardiac diseases. Use of genomic testing methods that permit reanalysis of existing data for variants in newly described clinically relevant genes are recommended/encouraged.</u>

Source: DCAR Table 1, with ESC's changes (blue text)

**Table 2: Proposed item descriptor for predictive testing of family members**

Category 6–Pathology services
MBS item YYYYY Detection of <del>familial</del> germline variant(s), in a first or second-degree biological relative of a <del>patient</del> person with one or more documented pathogenic germline variants associated with a cardiac arrhythmia or channelopathy <del>identified from the genes listed in item XXXXX, where the patient has not previously received a service number item XXXXX. Requested by a specialist or consultant physician.</del>
<del>Applicable once per variant per lifetime.</del>
<u>MBS Fee: \$400 85% \$340 75% \$300</u>
Explanatory note: PN.0.23 Prior to ordering these tests (YYYYY) the ordering practitioner should ensure the patient (or appropriate 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.

Source: DCAR Table 2, with ESC's changes (blue text)

The applicant proposed cascade testing for asymptomatic family members in their application, though the HTA group also included symptomatic family members in the DCAR's cascade testing analysis, noting that the Cardiac Society of Australia and New Zealand (CSANZ) guidelines recommend testing of symptomatic relatives to confirm the genotype and exclude the possibility of a phenocopy.

The genes proposed for genetic testing are included below, with exemplar genes shown in bold font (Table 3). The DCAR stated that, based on articles identified during the systematic review, those with sufficient information on which to potentially make a decision are **KCNQ1, KCNH2, SCN5A** and **RYR2**.

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

Gene#	OMIM# of the genes	Inheritance	Protein	Functional effect	Phenotype	OMIM# of the disease	Frequency in disease <sup>c</sup>
<b>Long QT syndrome</b>							
<b>KCNQ1</b>	607542	AD	K <sub>v</sub> 7.1	Loss of function	LQT1	192500	38%
<b>KCNH2</b>	152427	AD	K <sub>v</sub> 11.1 or hERG	Loss of function	LQT2	613688	42%
<b>SCN5A</b>	600163	AD	Na <sub>v</sub> α5 subunit	Gain of function	LQT3	603830	12%
<b>ANK2</b>	106410	AD	Ankyrin B	Loss of function	LQT4	600919	1%
<b>KCNE1</b>	176261	AD	MinK	Loss of function	LQT5	613695	5%
<b>KCNE2</b>	603796	AD	MiRP1	Loss of function	LQT6	613693	1%
<b>KCNJ2</b>	600681	AD	Kir2.1	Loss of function	LQT7 (ATS1) <sup>a</sup>	170390	<0.1%
<b>CACNA1C</b>	114205	AD	Ca <sub>v</sub> 1.2	Gain of function	LQT8 (TS1) <sup>b</sup>	601005	<0.1%
<b>CAV3</b>	601253	AD	Caveolin 3	Gain of function	LQT9	611818	<0.1%
<b>SCN4B</b>	608256	AD	Na <sub>v</sub> β4 subunit	Gain of function	LQT10	611819	<0.1%
<b>AKAP9</b>	604001	AD	A-kinase anchor protein 9	Loss of function	LQT11	611820	<0.1%
<b>SNTA1</b>	601017	AD	Syntrophin α1	Gain of function	LQT12	612955	<0.1%
<b>KCNJ5</b>	600734	AD	Kir 3.4 subunit of I <sub>K<sub>ACh</sub></sub> channel	Loss of function	LQT13	613485	<0.1%
<b>CALM1</b>	114180	AD	Calmodulin 1	Loss of function	LQT14	616247	<0.1%
<b>CALM2</b>	114182	AD	Calmodulin 2	Loss of function	LQT15	616249	<0.1%
<b>JLNS</b>							
<b>KCNQ1</b>	607542	AR	K <sub>v</sub> 7.1	Loss of function	JLN1	220400	90%
<b>KCNE1</b>	176261	AR	MinK	Loss of function	JLN2	612347	<10%
<b>Brugada syndrome</b>							
<b>SCN5A</b>	600163	AD	Na <sub>v</sub> α5 subunit	Loss of function	BrS1	601144	20–30%
<b>CACNA1C</b>	114205	AD	Ca <sub>v</sub> 1.2	Gain of function	BrS3	611875	<1%
<b>CPVT</b>							
<b>RYR2</b>	180902	AD	Ryanodin receptor 2	Loss of function	CPVT1	604772	55–70%
<b>CASQ2</b>	114251	AR	Calsequestrin 2	Loss of function	CPVT2	611938	2–5%
<b>ANK2</b>	106140	AD	Ankyrin B	Loss of function	LQT4	600919	
<b>CALM1</b>	114180	AD	Calmodulin 1	Loss of function	CPVT4	614916	
<b>CALM2</b>	114182	AD	Calmodulin 2	Loss of function	LQT15	616249	
<b>KCNJ2</b>	600681	AD	Kir2.1	Loss of function	LQT7 (ATS1)	170390	
<b>TECRL</b>	617242	AR	Trans-2,3-enoyl-CoA reductase-like		CPVT3	614021	
<b>TRDN</b>	603283	AR	Triadin	Loss of function	CPVT5	615441	

<sup>#</sup> Exemplar genes are shown in bold font.

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

<sup>b</sup> Timothy syndrome type 1 (TS1) is a rare condition characterised by syndactyly, facial dysmorphism, autism and severe LQTS

<sup>c</sup> These frequencies are different to those discussed in section 2.1, as the denominator is those with disease, rather than those with pathogenic variants. Data sources<sup>2,3</sup>

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 in the *KCR1* gene is associated with reduced susceptibility for long QT syndrome 2. As this variant is not considered pathogenic, it is not included in the table.

Source: DCAR, Table 3.

<sup>2</sup> Waddell-Smith, KE & Skinner, JR 2016, 'Update on the Diagnosis and Management of Familial Long QT Syndrome', Heart Lung Circ, vol. 25, no. 8, Aug, pp. 769-776.

<sup>3</sup> Ackerman, MJ, et al. 2011, 'HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies', Heart Rhythm, vol. 8, no. 8, Aug, pp. 1308-1339.

In the pre-ESC response, the applicant stated that based on clinical evidence, especially for individuals suspected to have LQTS with early childhood cardiac arrest, extreme QT prolongation, and a negative family history, the College's expert cardiac arrhythmia panel recommend the addition of *CALM3* to the non-exemplar gene list above (non-bold genes, Table 3).

In the rejoinder, the HTA group responded that the proposed MBS item for affected individuals does not limit the number of genes to be tested, so *CALM3* may also be tested. The HTA group noted that variants in the *CALM1*, *CALM2* and *CALM3* genes are extremely rare but also very severe, with the median age of events being 4 years old<sup>4</sup>.

## **7. Summary of public consultation feedback/consumer Issues**

No consumer feedback/consumer comments were received for this application.

Feedback was received from two specialist organisations during targeted consultation, with both indicating strong support for application 1598. One organisation also provided unpublished data and results.

One organisation commented that while they endorse technology-agnostic approaches to providing genomic testing, in this case consideration should be given to a static panel versus whole genome/exome sequencing approach. Both organisations recommended that the MBS item descriptors be less technology-specific where possible, to future-proof against improvements in test technology.

Consultation feedback noted that currently, in some circumstances and locations, genetic counsellors are initiating the referral for cardiac genetic testing. The outcome of this application may have implications for this current pathway.

One organisation also commented that where a procedure results in DNA sequence data, item numbers for the reanalysis of stored genomic sequence data would also be useful.

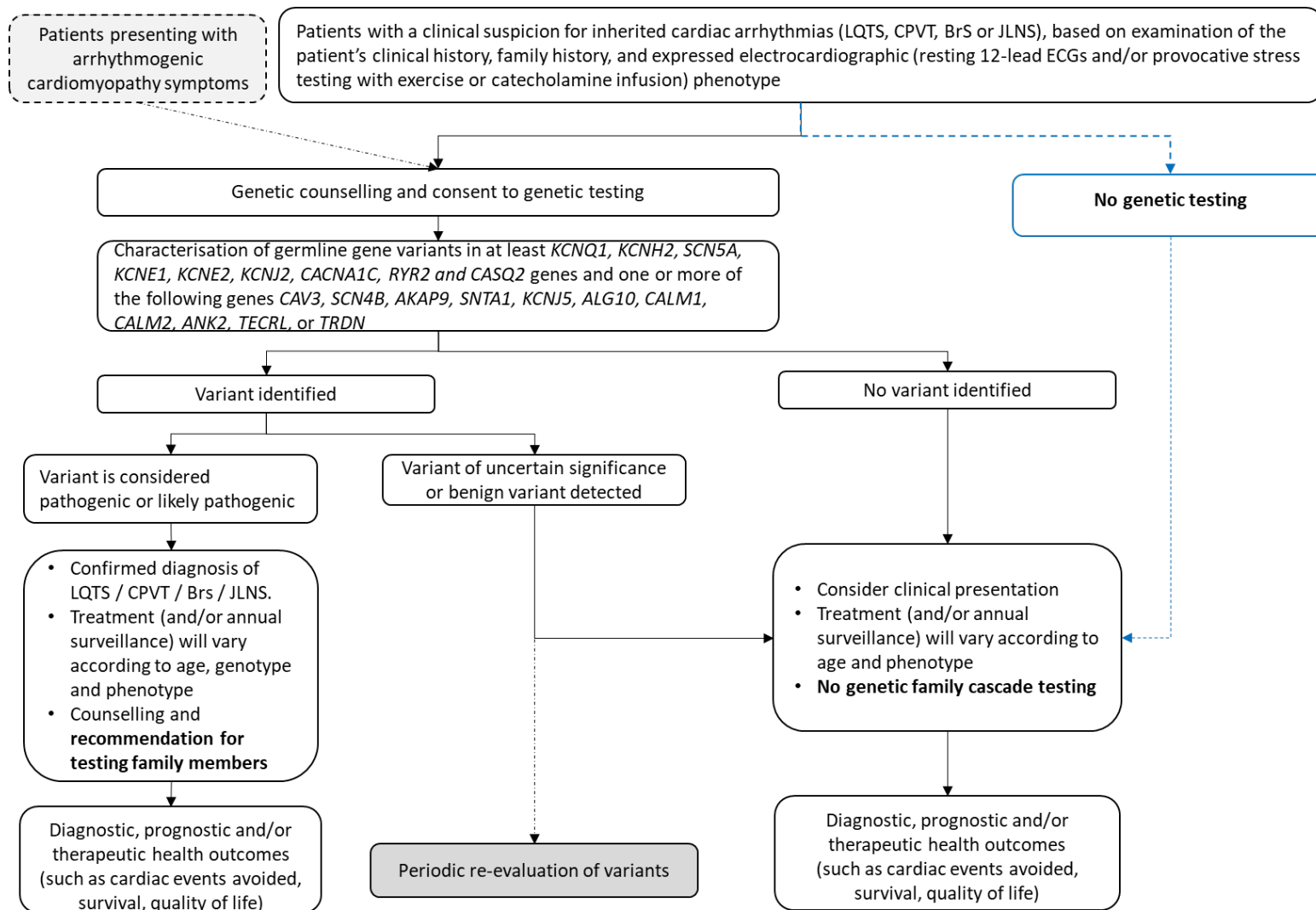
## **8. Proposed intervention's place in clinical management**

The DCAR provided the following clinical algorithms, encompassing both current (without genetic testing, blue lines) and proposed (with genetic testing, black lines) clinical management for affected individuals (Figure 1) and familial cascade testing (Figure 2).

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<sup>4</sup> Crotti L, et al. 2019, 'Calmodulin mutations and life-threatening cardiac arrhythmias: insights from the International Calmodulinopathy Registry', *Eur Heart J*, vol 40, no. 35, pp. 2964-2975.



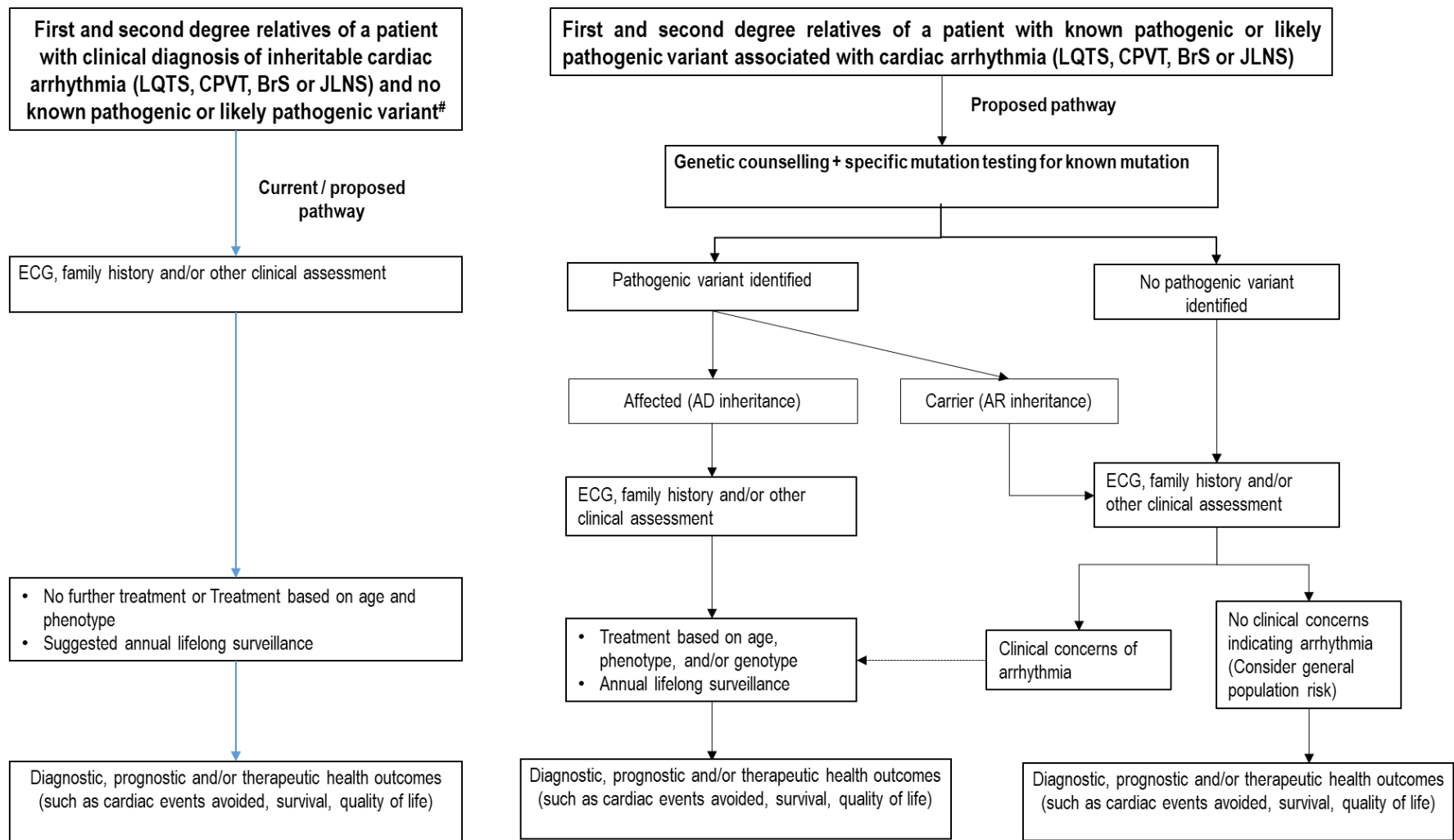


**Figure 1: Current and proposed clinical algorithm for testing of affected individuals**

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

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

Source: DCAR, Figure 1



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

<sup>#</sup> This includes affected individuals who have undergone genetic testing but were not identified with any pathogenic or likely pathogenic variants as well as those who have not undergone any genetic testing.

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

Source: DCAR, Figure 2

## Description of Proposed Intervention

Genetic testing of inherited cardiac arrhythmia disorders, for the following twenty genes: *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2*, *CACNA1C*, *RYR2*, *CASQ2*, *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *ALG10*, *CALM1*, *CALM2*, *ANK2*, *TECRL*, and *TRDN*.

Testing is proposed to be conducted for clinically affected individuals, to make a genetic diagnosis or confirm a phenotypic diagnosis, and thus estimate their disease severity and/or need for specific therapy. When a variant is identified in an affected individual, cascade testing is also offered to relevant family members to determine if they have inherited the variant. For any relatives of the proband who test positive to the familial variant an estimate of their predisposition to future risk of developing the clinical disease can be made (and, less commonly, future risk prediction if the disease has already been diagnosed phenotypically in a family member but they have not undergone genetic testing).

Genetic testing is proposed to be used in addition to current standard clinical practice.

## Description of Medical Condition(s)

Inherited cardiac arrhythmia syndromes (ICAs) or channelopathies occur when ion channel function is affected by variants in the set of genes encoding proteins or subunits of cardiac ion channels involved in the control of ventricular repolarisation<sup>5</sup>. ICAs include long QT syndrome (LQTS), Jervell and Lange-Nielsen syndrome (JLNS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT). The majority of ICA-associated variants are autosomal dominant with variable expressivity<sup>6</sup>. More than half of ICA patients are asymptomatic at the time of initial diagnosis and are diagnosed either by family history, incidentally, or by virtue of having survived an episode of syncope or severe ventricular arrhythmia<sup>7</sup>. Untreated individuals have an increased risk of syncope and sudden cardiac death<sup>8</sup>.

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<sup>9,10</sup>. Genes associated with ICAs are constantly being updated as new discoveries are made<sup>11</sup>.

LQTS is characterised by QT prolongation and T-wave abnormalities on the electrocardiogram (ECG) that are associated with tachyarrhythmias, typically torsades de pointes, 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

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<sup>5</sup> Kline, J & Costantini, O 2019, 'Inherited Cardiac Arrhythmias and Channelopathies', *Med Clin North Am*, vol. 103, no. 5, Sep, pp. 809-820.

<sup>6</sup> Mizusawa, Y et al. 2016, 'Prognostic significance of fever-induced Brugada syndrome', review of 1598, *Heart Rhythm*, vol. 13, no. 7, 2016, pp. 1515-1520.

<sup>7</sup> Hocini, M, et al. 2014, 'Diagnosis and management of patients with inherited arrhythmia syndromes in Europe: results of the European Heart Rhythm Association Survey', *EP Europace*, vol. 16, no. 4, pp. 600-603.

<sup>8</sup> Schwartz, PJ, et al. 2013, 'Impact of genetics on the clinical management of channelopathies', *J Am Coll Cardiol*, vol. 62, no. 3, Jul 16, pp. 169-180.

<sup>9</sup> Ackerman, MJ, et al. 2011, 'HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies', *Heart Rhythm*, vol. 8, no. 8, Aug, pp. 1308-1339.

<sup>10</sup> Hocini, M, et al. 2014, 'Diagnosis and management of patients with inherited arrhythmia syndromes in Europe: results of the European Heart Rhythm Association Survey', *EP Europace*, vol. 16, no. 4, pp. 600-603.

<sup>11</sup> Australian Genomics PanelApp [Arrhythmia super panel](#)

disease prevalence is estimated to be 1 in 2,500<sup>12</sup>. Variants in 15 genes have been associated with LQTS, most of which are autosomal dominant. Among patients with LQTS in whom a pathogenic variant is identifiable, variants are most commonly found in the *KCNQ1* gene (55%, LQTS type 1), *KCNH2* gene (35%, LQTS type 2) and *SCN5A* gene (9%, LQTS type 3)<sup>13</sup>. The 11 additional minor LQTS genes together comprise < 5% of LQTS cases. Genetic testing is recommended (Class 1 indication) for affected individuals clinically diagnosed with LQTS<sup>14</sup>. Approximately 5% of LQTS families carry two or more pathogenic variants either in the same gene (compound heterozygotes) or in different genes (digenic heterozygosity)<sup>15</sup>. The carriers of multiple variants in a single gene are 3.2 times more likely to have life-threatening cardiac event compared with probands with a single variant, and carriers of multiple variants across different genes have 1.7 times the risk of having a cardiac event than those with a single variant<sup>16</sup>.

The presence of biallelic (homozygous or compound heterozygous) variants in either the *KCNQ1* or *KCNE1* gene results in a severe autosomal recessive form of LQTS, called JLNS, with associated bilateral sensorineural deafness, long corrected QT (QTc) intervals (usually >500 ms), low gastric acid secretion and/or iron deficiency anaemia<sup>17</sup>. About 90% of cases of JLNS are caused by variants in the *KCNQ1* gene; *KCNE1* variants are responsible for the remaining cases.

BrS presents in adulthood, with a mean age of sudden death of 40 years<sup>18</sup>. 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)<sup>19,20</sup>. BrS is inherited in an autosomal dominant pattern. Variants in at least 12 genes have been reported for BrS with *SCN5A* identified as the most commonly mutated gene, having variants in 30% of affected individuals<sup>21</sup>. Variants in the calcium channel genes *CACNA1C* and *CACNB2b* also contribute to approximately 10 to 11.5% of BrS cases<sup>22,23</sup>. Variants in other genes account for less than two per cent of these cases<sup>24</sup>. Genetic testing for BrS is a Class 2A indication in the affected individual (i.e., not

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<sup>12</sup> Waddell-Smith, KE & Skinner, JR 2016, 'Update on the Diagnosis and Management of Familial Long QT Syndrome', *Heart Lung Circ*, vol. 25, no. 8, Aug, pp. 769-776.

<sup>13</sup> Earle, N et al. 2013, 'Community detection of long QT syndrome with a clinical registry: an alternative to ECG screening programs?', *Heart Rhythm*, 10: 233-238.

<sup>14</sup> Ackerman, MJ 2005, 'Cardiac causes of sudden unexpected death in children and their relationship to seizures and syncope: genetic testing for cardiac electropathies', *Semin Pediatr Neurol*, vol. 12, no. 1, Mar, pp. 52-58.

<sup>15</sup> Waddell-Smith, KE & Skinner, JR 2016, 'Update on the Diagnosis and Management of Familial Long QT Syndrome', *Heart Lung Circ*, vol. 25, no. 8, Aug, pp. 769-776.

<sup>16</sup> Mullally, J, et al. 2013, 'Risk of life-threatening cardiac events among patients with long QT syndrome and multiple mutations', review of 1598, *Heart Rhythm*, vol. 10, no. 3, 2013, pp. 378-382.

<sup>17</sup> Waddell-Smith, KE & Skinner, JR 2016, 'Update on the Diagnosis and Management of Familial Long QT Syndrome', *Heart Lung Circ*, vol. 25, no. 8, Aug, pp. 769-776.

<sup>18</sup> Brugada, R, et al. 2016, 'Brugada Syndrome'. University of Washington, Seattle, viewed 22nd May 2018, <<https://www.ncbi.nlm.nih.gov/books/NBK1517/>>.

<sup>19</sup> Szepesváry, DE & Kaski, DJP 2016, 'Genetic testing for inheritable cardiac channelopathies', *British Journal of Hospital Medicine*, vol. 77, no. 5, pp. 294-302.

<sup>20</sup> Vohra, J & Rajagopalan, S 2015, Position Statement on the Diagnosis and Management of Brugada Syndrome, The Cardiac Society of Australia and New Zealand, <<http://www.csanz.edu.au/resources/>>.

<sup>21</sup> U.S. National Library of Medicine 2019, Brugada syndrome, U.S. Department of Health & Human Services, viewed 6 November 2019, <<https://ghr.nlm.nih.gov/condition/brugada-syndrome#genes>>.

<sup>22</sup> Fukuyama, M, et al. 2016, 'Novel *SCN10A* variants associated with Brugada syndrome', *EP Europace*, vol. 18, no 6, pp 905-911.

<sup>23</sup> Mizusawa, Y & Wilde, AAM, 2012, 'Brugada syndrome', *Circulation: Arrhythmia and Electrophysiology*, vol. 5, no. 3, pp 606-616.

<sup>24</sup> U.S. National Library of Medicine 2019, Brugada syndrome, U.S. Department of Health & Human Services, viewed 6 November 2019, <<https://ghr.nlm.nih.gov/condition/brugada-syndrome#genes>>.

recommended in the absence of a diagnostic ECG but may be useful otherwise) but a Class 1 indication (recommended) in family members of an affected individual identified to have a pathogenic variant<sup>25</sup>.

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 a clinical diagnosis<sup>26</sup>. CPVT is caused most commonly by autosomal dominant variants in the cardiac ryanodine receptor gene (*RYR2*), 50–55%, or less frequently by autosomal recessive variants in the cardiac calsequestrin gene (*CASQ2*), 2–5%. Variants in other genes, *CALMI*, *TECRL*, *TRDN*, *ANK2* and *KCNJ2*, have also shown to cause CPVT<sup>27</sup>. Genetic testing is recommended (Class 1 indication) for affected individuals clinically diagnosed with CPVT, especially to help predictive testing in the family members<sup>28</sup>.

## 9. Comparator

The DCAR stated that the comparator is the usual standard of care without genetic testing.

## 10. Comparative safety

The DCAR proposed that genetic testing has non-inferior safety both in affected individuals (proposed item XXXXX), and in family members (proposed item YYYYY). The DCAR identified no studies assessing the safety of cascade screening for ICAs (DCAR, section 6.4).

The DCAR stated that a clinical diagnosis of a cardiac arrhythmia may adversely affect mental health status<sup>29</sup>. Family members who are carriers for LQTS suffer fewer depressive symptoms than the affected individual or family members with LQTS who are both genotype and phenotype positive<sup>30</sup>. Younger adults with CPVT, including those with an implantable cardioverter-defibrillator (ICD), are at significant risk of poor psychosocial outcomes, including anxiety and post-traumatic stress symptoms. Additionally, patients with a genetic diagnosis experience more difficulties in adjusting, and parents of a child with CPVT generally considered that their child's quality of life was significantly worse than their peers<sup>31</sup>. Overall, children adapt to their genetic status and its implications<sup>32</sup>.

The DCAR's examination of ethical issues related to genetic testing for ICAs uncovered potential issues regarding equity of access to testing, patient motivations to test or not to test,

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<sup>25</sup> Priori, SG, et al. 2013, 'HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes', *Heart Rhythm*, vol. 10, no. 12, Dec, pp. 1932-1963.

<sup>26</sup> Pflaumer, A & Davis, AM 2019, 'An Update on the Diagnosis and Management of Catecholaminergic Polymorphic Ventricular Tachycardia', *Heart Lung Circ*, vol. 28, no. 3, Mar, pp. 366-369.

<sup>27</sup> Pflaumer, A & Davis, AM 2019, 'An Update on the Diagnosis and Management of Catecholaminergic Polymorphic Ventricular Tachycardia', *Heart Lung Circ*, vol. 28, no. 3, Mar, pp. 366-369.

<sup>28</sup> Priori, SG, et al. 2013, 'HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes', *Heart Rhythm*, vol. 10, no. 12, Dec, pp. 1932-1963.

<sup>29</sup> Ingles, J, et al. 2013, 'Health status of cardiac genetic disease patients and their at-risk relatives', *Int J Cardiol*, vol. 165, no. 3, 2013, pp. 448-453.

<sup>30</sup> Hintsä, T, et al. 2009, 'Depressive symptoms in the congenital long QT syndrome', *Ann Med*, vol. 41, no. 7, 2009, pp. 516-521.

<sup>31</sup> Richardson, E, et al. 2018, 'Psychosocial Implications of Living with Catecholaminergic Polymorphic Ventricular Tachycardia in Adulthood', review of 1598, *J Genet Couns*, vol. 27, no. 3, 2018, pp. 549-557.

<sup>32</sup> Meulenkamp, TM, et al. 2008, 'Predictive genetic testing for cardiovascular diseases: Impact on carrier children', review of 1598, *American Journal of Medical Genetics, Part A*, vol. 146, no. 24, 2008, pp. 3136-3146.

reproductive decision making, and issues of personal autonomy. Cascade testing also raises issues related to who ought to share the information with relatives (the affected individual or the doctor), how and why they ought to share it, what barriers and facilitators there are to sharing information, and under what circumstances it may be ethically justified to breach confidentiality of the affected individual.

## 11. Comparative effectiveness

### Clinical claim

The DCAR stated that compared to clinical screening (cardiology and family history) alone, genetic testing for ICAs and associated interventions has non-inferior safety and non-inferior effectiveness in affected individuals, and superior effectiveness and non-inferior safety in family members.

### Analytical validity

The DCAR stated that the reference standards for detection of variants are Sanger sequencing and validated NGS. Two small studies were available comparing the accuracy of three different NGS panels against Sanger sequencing, or a combination of denaturing high performance liquid chromatography plus Sanger sequencing to confirm variants in patients with LQTS ( $k=2$ ;  $n=47$ )<sup>33,34</sup>. The NGS panels were highly accurate, with sensitivity ranging from 97.1% to 100%, and specificity in one study of 100%. A total of nine false positive calls from 107 coding variants were reported in the other study.

For cascade testing, the DCAR stated that testing of family members would use a method of genetic testing suited to identifying the one or two familial pathogenic variants identified in the proband. As such, the analytical validity of the method chosen would be 100%.

### Clinical validity

#### Incremental diagnostic information

The DCAR stated that for affected individuals with a cardiac rhythm disorder, clinical validity includes how well the test classifies patients into the particular subtype of disorder (diagnosis), how this information can be used to predict their health outcomes (prognosis), and how well the test can predict response to treatment (predictive of benefit or harms). The reference standards used by the DCAR for these are outlined below (Table 4).

**Table 4: Reference standards for different forms of clinical validity information**

Type of clinical validity information	Reference standard
Diagnostic (cross-sectional accuracy)	Clinical diagnosis (for accuracy of genetic testing) OR Genetic variant status (for accuracy of clinical diagnosis)
Prognostic (longitudinal accuracy)	Cardiac events over follow-up (adjusting for treatment) Clinical outcomes subsequent to diagnosis
Predictive (longitudinal accuracy) <sup>a</sup>	Cardiac events over follow-up, considering differential response to treatment (benefits or harms)

<sup>a</sup> Studies reporting on differential response to treatment are incorporated into section 5.3 on clinical utility

Source: DCAR, Table 9

The DCAR stated that genetic testing is proposed to be used in addition to clinical diagnosis, and the resulting diagnosis is considered likely to concur with the phenotypic diagnosis. As such, no studies were informative about the accuracy of genetic testing against a clinical

<sup>33</sup> Chae, H, et al. 2017, 'Considerations when using next-generation sequencing for genetic diagnosis of long-QT syndrome in the clinical testing laboratory', *Clin Chim Acta*, vol. 464, 2017, pp. 128-135.

<sup>34</sup> Li, X, et al. 2013, 'Towards clinical molecular diagnosis of inherited cardiac conditions: a comparison of bench-top genome DNA sequencers', *PLoS ONE*, vol. 8, no. 7, p. e67744.

reference standard. However, studies were available regarding the accuracy of clinical diagnosis compared to pathogenic-variant status.

For LQTS, the DCAR stated that the gold-standard method of clinical diagnosis is through use of the Schwartz criteria, which provide a probability of having LQTS based on the combination of clinical history, family history and ECG findings. Of the four studies identified as assessing how well the Schwartz criteria predicted pathogenic status, Hayashi *et al.*<sup>35</sup> provided the most comprehensive evidence, as summarised below (Table 5).

**Table 5: Accuracy of Schwartz criteria for predicting LQTS pathogenic variant status**

Study	Population	Reference standard	Clinical	Sensitivity	Specificity	PPV	NPV
Hayashi, K <i>et al.</i> 2016	132 patients with prolonged QTc intervals and/or abnormal clinical history and familial findings during cardiac screening	LQTS pathogenic variant carrier status determined by HRM or dHPLC followed by Sanger sequencing	High probability of LQTS based on Schwartz score 2011 $\geq 3.5$ points	46/52 (88.5%)	64/80 (80.0%)	46/62 (74.2%)	64/70 (91.4%)

dHPLC = denaturing high performance liquid chromatography; HRM = high resolution melt; QTc = corrected QT  
Source: DCAR, Table 10

The DCAR identified two studies reporting on the accuracy of ECG in determining LQTS subtype (Table 6).

**Table 6: Accuracy of ECG data for predicting genotype of LQTS**

Study	Population	Reference standard	Clinical	Sensitivity	Specificity	PPV
Funasako <i>et al.</i> , 2016 <sup>36</sup>	Genotype-positive patients with LQTS	Genetic testing using DNA analyser, screened for <i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> using direct sequencing	12-lead ECG parameters and mexiletine test for distinguishing between LQT3 and LQT1/2 with optimal cut-off for change in QTc at 69 ms	86.7%	81.3%	81.3%
Gao <i>et al.</i> , 2016 <sup>37</sup>	200 individuals classified by ECG data as having LQT1, LQT2 or LQT3 (i.e. only test positives)	Direct sequencing of <i>KCNQ1</i> , <i>KCNH2</i> and <i>SCN5A</i>	Two investigators with 15 years experience in reading LQTS ECGs (n>300) performed prediction together, under consultation with an expert in LQT3 ECGs	-	-	LQT1: 67/85 (79%) LQT2: 86/110 (78%) LQT3: 4/5 (80%)

PPV = positive predictive value; QTc = corrected QT  
Source: DCAR, Table 11

The DCAR noted that while cascade screening is highly accurate at determining who does and does not carry LQTS-associated pathogenic variants (i.e. reference standard is the intervention of interest), genotype will not necessarily correlate with disease status due to

<sup>35</sup> Hayashi, K, *et al.* 2016, 'Impact of Updated Diagnostic Criteria for Long QT Syndrome on Clinical Detection of Diseased Patients: Results From a Study of Patients Carrying Gene Mutations', *JACC Clin Electrophysiol*, vol. 2, no. 3, 2016, pp. 279-287.

<sup>36</sup> Funasako, M, *et al.* 2016, 'Pronounced shortening of QT interval with mexiletine infusion test in patients with type 3 congenital long QT syndrome', *Circulation Journal*, vol. 80, no. 2, 2016, pp. 340-345.

<sup>37</sup> Gao, Y, *et al.* 2016, 'Common Genotypes of Long QT Syndrome in China and the Role of ECG Prediction', *Cardiology*, vol. 133, no. 2, 2016, pp. 73-78.

incomplete penetrance for variants in at least the *KCNQ1*, *KCNH2* and *SCN5A* genes<sup>38</sup>. Cascade screening has high specificity but it has very variable and often low sensitivity (19% to 100%), at determining who is at risk<sup>39,40,41,42</sup>.

For Brugada syndrome, the DCAR noted that diagnosing patients presents more difficulties both with, and without, genetic testing than for LQTS. ECG visual interpretation alone results in classification no better than chance (overall accuracy 53±33%)<sup>43</sup>. A new methodology of measuring the  $\beta$ -angle (angle between the upslope of the S-wave and the downslope of the r-wave) and length of the base of a triangle (between the upslope and the downslope of the r-wave at 0.5 mV from the high take-off) provides sensitivity of ECG criteria of only 60 to 80%, and specificity of 40 to 78%<sup>44</sup>. The poor accuracy of diagnostic methods for BrS in the absence of genetic testing means that genetic testing is likely to increase the sensitivity of diagnosis, although the lower diagnostic yield means that only a small proportion of patients are likely to benefit.

For cascade testing of patients with BrS, the DCAR noted that the ajmaline challenge test was 80% sensitive and 94% specific at predicting pathogenic variant status. There were two case reports of false negative results from cascade testing<sup>45</sup>. The penetrance of BrS in family members who carried pathogenic variants was 28.6% to 78.6%<sup>46,47</sup>. In those who had normal ECGs at screening but carried *SCN5A* variants, 27% develop the ECG phenotype over a mean of 5.9 years<sup>48</sup>.

For cascade testing of patients with CPVT, the DCAR stated that exercise stress testing in asymptomatic relatives was reasonably specific (91% to 97%), but not very sensitive (22-

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<sup>38</sup> Mazzanti, A, et al. 2018, 'Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome', review of 1598, *J Am Coll Cardiol*, vol. 71, no. 15, 2018, pp. 1663-1671.

<sup>39</sup> Benhorin, J, et al. 2002, 'Variable expression of long QT syndrome among gene carriers from families with five different HERG mutations', *Ann Noninvasive Electrocardiol*, vol. 7, no. 1, 2002, pp. 40-46.

<sup>40</sup> Jeyaraj, D, et al. 2008, 'I(Kr) channel blockade to unmask occult congenital long QT syndrome', *Heart Rhythm*, vol. 5, no. 1, 2008, pp. 2-7.

<sup>41</sup> Jiménez-Jáimez, J, et al. 2013, 'Low clinical penetrance in causal mutation carriers for cardiac channelopathies', *Rev Esp Cardiol (Engl Ed)*, vol. 66, no. 4, 2013, pp. 275-281.

<sup>42</sup> Vink, AS, et al. 2018, 'Determination and Interpretation of the QT Interval', review of 1598, *Circulation*, vol. 138, no. 21, 2018, pp. 2345-2358.

<sup>43</sup> Gottschalk, BH, et al. 2016, 'Expert cardiologists cannot distinguish between Brugada phenocopy and Brugada syndrome electrocardiogram patterns', *Europace*, vol. 18, no. 7, 2016, pp. 1095-1100.

<sup>44</sup> Gottschalk, BH, et al. 2016, 'New methodologies for measuring Brugada ECG patterns cannot differentiate the ECG pattern of Brugada syndrome from Brugada phenocopy', *J Electrocardiol*, vol. 49, no. 2, pp. 187-191.

<sup>45</sup> Hong, K, et al. 2004, 'Value of electrocardiographic parameters and ajmaline test in the diagnosis of Brugada syndrome caused by *SCN5A* mutations', *Circulation*, vol. 110, no. 19, 2004, pp. 3023-3027.

<sup>46</sup> Hong, K, et al. 2004, 'Value of electrocardiographic parameters and ajmaline test in the diagnosis of Brugada syndrome caused by *SCN5A* mutations', *Circulation*, vol. 110, no. 19, 2004, pp. 3023-3027.

<sup>47</sup> Jiménez-Jáimez, J, et al. 2013, 'Low clinical penetrance in causal mutation carriers for cardiac channelopathies', *Rev Esp Cardiol (Engl Ed)*, vol. 66, no. 4, 2013, pp. 275-281.

<sup>48</sup> Baruteau, AE, et al. 2018, '*SCN5A* mutations in 442 neonates and children: genotype-phenotype correlation and identification of higher-risk subgroups', *Eur Heart J*, vol. 39, no. 31, 2018, pp. 2879-2887.



63%)<sup>49</sup>. Penetrance at the time of cascade screening is reported at 57-80%<sup>50,51,52</sup>. Half of those family members who were genotype positive, but did not show signs of CPVT at the point of cascade screening, developed the CPVT phenotype over a median of only 1.6 years<sup>53</sup>.

#### Incremental prognostic information

The DCAR also examined incremental prognostic information gained with the addition of genetic testing, though noted this was not one of the clinical claims made by the applicant.

For patients with LQTS, the DCAR stated that patients with *KCNH2* variants have a significantly higher hazard of further cardiac events and seizures than patients with *KCNQ1* variants (k=4)<sup>54,55,56,57</sup>. The exception was a subgroup of patients aged under 14 years, where those with *KCNQ1* variants had a higher risk of having a cardiac event than those with *KCNH2* variants<sup>58</sup>. Patients with *KCNH2* variants also had a higher risk of cardiac events and seizures than patients with *SCN5A* variants<sup>59,60</sup>. Those with multiple pathogenic variants were significantly more likely to experience cardiac events than those with single variants, particularly if the two variants were within the same gene<sup>61</sup>.

The DCAR stated that for LQTS cascade testing, knowledge of having the familial pathogenic variant clearly provides prognostic information for family members. Family members with normal QTc interval (i.e. who would not have been detected through clinical assessment alone) but were genotype-positive had 10.3 times the hazard of having a life-threatening cardiac event than family members who were genotype-negative<sup>62</sup>.

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<sup>49</sup> Hayashi, M, et al. 2012, 'The role of stress test for predicting genetic mutations and future cardiac events in asymptomatic relatives of CPVT probands', *Europace*, vol. 14, no. 9, 2012, pp. 1344-1351.

<sup>50</sup> Broendberg, AK, et al. 2017, 'Nationwide experience of catecholaminergic polymorphic ventricular tachycardia caused by RyR2 mutations', *Heart*, vol. 103, no. 12, 2017, pp. 901-909.

<sup>51</sup> Postma, AV, et al. 2005, 'Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients', review of 1598, *J Med Genet*, vol. 42, no. 11, 2005, pp. 863-870.

<sup>52</sup> van der Werf, C, et al. 2012, 'Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives', review of 1598, *Circ Arrhythm Electrophysiol*, vol. 5, no. 4, 2012, pp. 748-756.

<sup>53</sup> van der Werf, C, et al. 2012, 'Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives', review of 1598, *Circ Arrhythm Electrophysiol*, vol. 5, no. 4, 2012, pp. 748-756.

<sup>54</sup> Goldenberg, I, et al. 2010, 'Beta-blocker efficacy in high-risk patients with the congenital long-QT syndrome types 1 and 2: implications for patient management', *J Cardiovasc Electrophysiol*, vol. 21, no. 8, pp. 893-901.

<sup>55</sup> Auerbach, DS, et al. 2016, 'Genetic biomarkers for the risk of seizures in long QT syndrome', *Neurology*, vol. 87, no. 16, 2016, pp. 1660-1668.

<sup>56</sup> Koponen, M, et al. 2018, 'Clinical and molecular genetic risk determinants in adult long QT syndrome type 1 and 2 patients : Koponen et al. Follow-up of adult LQTS patients', *BMC Med Genet*, vol. 19, no. 1, 2018, p. 56.

<sup>57</sup> Sauer, AJ, et al. 2007, 'Long QT syndrome in adults', review of 1598, *J Am Coll Cardiol*, vol. 49, no. 3, 2007, pp. 329-337.

<sup>58</sup> Goldenberg, I, et al. 2010, 'Beta-blocker efficacy in high-risk patients with the congenital long-QT syndrome types 1 and 2: implications for patient management', *J Cardiovasc Electrophysiol*, vol. 21, no. 8, pp. 893-901.

<sup>59</sup> Auerbach, DS, et al. 2016, 'Genetic biomarkers for the risk of seizures in long QT syndrome', *Neurology*, vol. 87, no. 16, 2016, pp. 1660-1668.

<sup>60</sup> Sauer, AJ, et al. 2007, 'Long QT syndrome in adults', review of 1598, *J Am Coll Cardiol*, vol. 49, no. 3, 2007, pp. 329-337.

<sup>61</sup> Mullally, J, et al. 2013, 'Risk of life-threatening cardiac events among patients with long QT syndrome and multiple mutations', review of 1598, *Heart Rhythm*, vol. 10, no. 3, 2013, pp. 378-382.

<sup>62</sup> Goldenberg, I, et al. 2011, 'Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals', *J Am Coll Cardiol*, vol. 57, no. 1, 2011, pp. 51-59.

The DCAR stated that in patients with Brugada syndrome, having a pathogenic variant in the *SCN5A* gene was associated with a significantly higher risk of arrhythmic events than BrS patients without an identified pathogenic variant<sup>63</sup>.

No studies were identified that reported on the prognostic value of genetic testing in patients with CPVT.

### **Clinical utility**

For each of the ICAs, the DCAR examined published evidence for a change in diagnosis of the affected individual as a result of genetic testing.

The DCAR identified three studies reporting the rate of change in diagnosis after using genetic testing in patients with clinically diagnosed LQTS. In those thought to have LQTS, the addition of genetic testing resulted in a change in diagnosis in 6.2% of cases (10/162) to CPVT<sup>64,65,66</sup>.

The DCAR identified no evidence reporting on the proportion of patients with phenotypic BrS who had a change in diagnosis subsequent to genetic testing. One study reported on the impact of a large cardiac panel (75 or 115 genes) in patients who were re-analysed after no variants were found on phenotype-guided Sanger sequencing<sup>67</sup>. Of the seven patients with a presumed diagnosis of BrS, none of them were identified as having rare variants, or had a change in diagnosis.

The DCAR stated that no studies were available on the accuracy of either genetic testing or clinical diagnosis for CPVT. However, three studies were available that suggested genetic testing in patients classified as having CPVT may result in a change in diagnosis in 0-36.3% of cases<sup>68,69,70</sup>. After genetic testing, patients were reclassified as having Andersen-Tawil syndrome (LQT7) or LQT5<sup>71</sup>.

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<sup>63</sup> Chen, C, et al. 2020, 'Brugada syndrome with *SCN5A* mutations exhibits more pronounced electrophysiological defects and more severe prognosis: A meta-analysis', *Clin Genet*, vol. 97, no. 1, 2020, pp. 198-208.

<sup>64</sup> Burgos, M, et al. 2016, 'Semiconductor Whole Exome Sequencing for the Identification of Genetic Variants in Colombian Patients Clinically Diagnosed with Long QT Syndrome', *Mol Diagn Ther*, vol. 20, no. 4, 2016, pp. 353-362.

<sup>65</sup> Fukuyama, M, et al. 2020, 'High Prevalence of Late-Appearing T-Wave in Patients With Long QT Syndrome Type 8', *Circ J*, vol. 84, no. 4, 2020, pp. 559-568.

<sup>66</sup> Ozawa, J, et al. 2018, 'Differential Diagnosis Between CPVT and Long QT Syndrome Type 1 - Modified Schwartz Score', review of 1598, *Circ J*, vol. 82, no. 9, 2018, pp. 2269-2276.

<sup>67</sup> Broendberg, AK, et al. 2018, 'Targeted next generation sequencing in a young population with suspected inherited malignant cardiac arrhythmias', *European Journal of Human Genetics*, vol. 26, no. 3, pp. 303-313.

<sup>68</sup> Tester, DJ, et al. 2006, 'Genotypic heterogeneity and phenotypic mimicry among unrelated patients referred for catecholaminergic polymorphic ventricular tachycardia genetic testing', review of 1598, *Heart Rhythm*, vol. 3, no. 7, 2006, pp. 800-805.

<sup>69</sup> Burns, C, et al. 2016, 'Clinical and genetic features of Australian families with long QT syndrome: A registry-based study', *J Arrhythm*, vol. 32, no. 6, 2016, pp. 456-461.

<sup>70</sup> Ozawa, J, et al. 2018, 'Differential Diagnosis Between CPVT and Long QT Syndrome Type 1 - Modified Schwartz Score', review of 1598, *Circ J*, vol. 82, no. 9, 2018, pp. 2269-2276.

<sup>71</sup> Tester, DJ, et al. 2006, 'Genotypic heterogeneity and phenotypic mimicry among unrelated patients referred for catecholaminergic polymorphic ventricular tachycardia genetic testing', review of 1598, *Heart Rhythm*, vol. 3, no. 7, 2006, pp. 800-805.

For cascade testing, the DCAR stated that the identification of genetic variants in family members would lead to:

- enabling cascade testing of further family members
- early detection of inheritable cardiac arrhythmia in relatives (to direct early commencement of lifestyle changes and/or drug/device therapy)
- reassuring family members who have not inherited the condition
- reducing, or obviating, the requirement for genotype-negative family members to have lifelong surveillance

### Translation issues

Australian Genomics data on diagnostic yield for LQTS, BrS and CPVT (Austin *et al.*, 2021; Table 7) were used in the DCAR’s economic and financial analyses.

**Table 7: Diagnostic yields for patients clinically diagnosed with the different arrhythmias**

Inheritable arrhythmia disorder	Systematic review of literature mean (range), %	Clinical Audit data – Austin <i>et al.</i> , 2021 <sup>72</sup>
LQTS	46 (18–90)	33.7%
BrS	22 (9.5–45))	12.8%
CPVT	42 (13–77)	20.0%
Combined	-	26.3%

BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; LQTS = long QT syndrome  
Source: DCAR CUC technical document, Table 93 (as updated in HTA group’s rejoinder to applicant’s pre-ESC response).

In the pre-ESC response, the applicant commented that the figures from the systematic review provide a combined diagnostic yield for cardiac arrhythmias of 36.7%, compared to the relatively low combined rate from clinical audit data, which was used in the economic analysis. The applicant also asserted that the DCAR did not consider the relative frequencies of the three conditions when calculating the combined diagnostic yield, with LQTS being the most prevalent inherited arrhythmia syndrome (65%), followed by CPVT (27%) and BrS (8%). Further data analysis by the Genomics Cardiovascular Genetic Disorders Flagship<sup>73</sup> indicates a 49% diagnostic rate for LQTS, and a 41% overall diagnostic rate for all ICAs (i.e. LQTS, CPVT and BrS) patients. As indicated by the sensitivity analysis in the CUC, a higher diagnostic yield in affected individuals will result in a higher uptake of cascade genetic testing in family members which, all else being equal, will result in more cost-savings to the health system. In the rejoinder, the HTA group responded that the Australian Cardiac Genomic Flagship audit data figures reflected current clinical practice and were within the published range – which in any case varies widely, perhaps due to ethnicity differences between countries. The HTA group also clarified that estimating a combined diagnostic yield using relative proportions of published prevalence may be less appropriate due to the possibility of misdiagnosis or overlapping syndromes.

The DCAR examined potential translation issues regarding the applicability and/or extrapolation of the evidence to the proposed setting (Table 8).

<sup>72</sup> Austin, R, et al. 2021 ‘Investigation of current models of care for genetic heart disease in Australia: A national clinical audit’, *Int J Cardiol*, [in press](#).

<sup>73</sup> Austin, R, et al. 2021 ‘Investigation of current models of care for genetic heart disease in Australia: A national clinical audit’, *Int J Cardiol*, [in press](#).

**Table 8: Summary of results of pre-modelling studies and their uses in the economic evaluation**

Translation issue	Results used in Section 10	Results used in Subsection 10.6
Applicability		
Diagnostic yield in affected individuals	The diagnostic yield of genetic tests in affected individuals varied from 10–90% according to potential causative family history. Data on diagnostic yield reported in the Australian National clinical audit report is identified and used in the base case.	Sensitivity analyses are conducted assuming lower and higher values of diagnostic yield (10–90%) in affected individuals.
Adherence to surveillance	The clinical algorithm recommends family members adhere to recommended surveillance and prophylactic treatments where indicated, and no evidence was identified to suggest that this does not occur. Therefore the approach used in the economic model is to assume that clinical algorithms are followed and recommended surveillance and/or prophylactic management is conducted as required.	Sensitivity analyses are conducted where 50% of the family members who do not receive testing do not adhere to surveillance recommendations.
Transformation		
The impact of the clinical findings on patient-relevant health outcomes and quality of life.	There was no clinical evidence identified that enabled incremental final health outcomes to be quantified. The limited evidence available that directly compared psychological health related to genetic testing suggests that predictive genetic testing for inherited rhythm disorders does not inflict psychological harm and in fact can invoke significant benefits by providing reassurance or alleviating uncertainty. Therefore, neither health benefits nor disutility associated with genetic testing are modelled in the economic analysis.	Not tested

Source: DCAR, Table 12

## 12. Economic evaluation

The DCAR presented a cost-effectiveness evaluation of genetic testing for affected individuals, and for cascade testing a cost comparison analysis primarily with secondary cost-effectiveness analysis (Table 9).

**Table 9: Population and type of economic analysis**

Genetic test purpose	Population	Intervention	Comparator	Type of analysis	Outcome measure
Diagnosis	Patients with cardiac arrhythmias clinically assessed as likely to have been inherited (affected individuals)	Gene panel testing for inheritable cardiac arrhythmias	No genetic test	Cost-effectiveness	Incremental cost per positive genotyping
Diagnosis and cascade family testing	Affected individuals and at-risk family members of the proband	Genetic testing in affected individuals and known familial variant testing in family members + clinical assessment	Clinical assessment	Cost-effectiveness analysis and cost-comparison analysis	Incremental cost per positive genotyping and cost per affected individual

Source: DCAR, Table 13. The definition of the population of affected individuals has been updated in line with terminology as specified in the [CUC pro forma](#).

Cost-effectiveness and cost-comparison analyses were presented comparing genetic testing with no genetic testing, as summarised below (Table 10).

**Table 10: Summary of the economic evaluation**

<b>Perspective</b>	Australian health care system
<b>Population</b>	People with clinical diagnosis of inheritable cardiac rhythm disorders, and their first- and second-degree relatives.
<b>Prior testing</b>	Clinical diagnosis incorporating a combination of clinical assessment of symptoms, family history, and investigations such as ECGs, with or without exercise stress tests or sodium channel blockers such as flecainide.
<b>Comparator</b>	Usual standard of care, without genetic testing
<b>Type of economic evaluation</b>	Cost-effectiveness analysis and cost-comparison analysis
<b>Outcomes</b>	Cost per positive genotyping and costs/cost-savings associated with surveillance
<b>Sources of evidence</b>	Systematic review of the literature, additional sources
<b>Methods used to generate results</b>	Decision tree and Markov cohort analysis
<b>Cohorts modelled</b>	Affected individuals Family members
<b>Time horizon</b>	Immediate to test result (affected individuals), 40 years (for cascade testing)
<b>Health states</b>	In the decision tree: genotype status unrevealed, genotype positive (identified) and genotype negative (identified). In the Markov model: surveillance, no surveillance and dead.
<b>Cycle length</b>	One year (for cascade testing)
<b>Discounting</b>	5%
<b>Transition probabilities</b>	Based on Australian life tables and literature search
<b>Software packages used</b>	TreeAge Pro 2020

Source: DCAR, Table 14

Key assumptions included:

- Affected individuals are treated irrespective of variant status. There is no difference in measurable health outcomes between the two comparative pathways, therefore the only difference is in the cost per person.
- Testing has been assumed to be 100% accurate (for known variants) in both affected individuals and relatives, based on the results of the clinical assessment which showed that tests currently used are sensitive and specific in the populations that they were tested in, and detect almost all genetic variants they are designed to detect.
- Compliance with the recommended periodical surveillance post-screening is assumed to be 100% in all family members, as per the clinical algorithm. (This is tested in sensitivity analysis).

The DCAR summarised the benefits and outcomes for each modelled subgroup (affected individual subgroups in Table 11, and family member subgroups in Table 12) based on the clinical evidence and the reasons for including or excluding the related costs and health outcomes.

**Table 11: Summary of the consequences for each modelled subgroup (affected individuals) based on the clinical evidence**

Population subgroup	Test Outcome	Disease management	Clinical consequences	Modelled costs/outcomes
Affected individual (genotype positive)	Knowledge of genotype	Patient management based on genotype Allow cascade genetic testing in addition to clinical screening in family members	Avoiding genotype specific triggers Treatment adjustments based on disease reclassification (for those with LQTS, 6.2% change to CPVT and for those clinically diagnosed with CPVT, 7.5% get changed to LQTS) Lack of evidence to suggest improvement in health outcomes related to disease reclassification Greater participation of family members for clinical assessment if affected individual has a positive result for a pathogenic gene variant rather than a negative result (83% vs 54%)	Only the costs associated with genetic test considered in the model. Health outcomes and costs associated with patient management are assumed to be similar across both strategies; therefore these are not modelled. Cascade genetic testing in addition to clinical screening in family members is modelled.
Affected individual (genotype negative)	Genetic test inconclusive	Patient management continues based on phenotypic presentation Cascade clinical screening in family members	No change in health outcomes Family members go through clinical assessment	Only the costs associated with the genetic test considered in the model. Health outcomes and costs associated with patient management are assumed to be similar across both strategies; therefore not modelled
Affected individual, no genetic testing	Clinical diagnosis based on clinical assessment alone	Patient management continues based on phenotypic presentation Cascade clinical screening in family members	No change in health outcomes Family members go through clinical assessment	No costs associated with the affected individual

Source: DCAR, Table 16

**Table 12: Summary of the benefits and outcomes for each modelled subgroup (family members) based on the clinical evidence**

<b>Population subgroup</b>	<b>Test Outcome</b>	<b>Disease management</b>	<b>Clinical consequences</b>	<b>Modelled costs/outcomes</b>
Family member, genotype positive	Familial variant identified	Patient management based on genotype and phenotype Genotype specific triggers can be avoided Allow cascade genetic testing in addition to clinical screening in subsequent family members	Symptomatic family members have little incremental benefit from genetic testing as management is based on their phenotype Treatment decisions in asymptomatic family members (around 25%) may be guided by the presence of genotype Cardiac events avoided due to periodic surveillance and prophylactic treatment such as initiation of beta-blockers Subsequent family members tested for known variant(s)	Compliance with the recommendations are unknown. These are assumed to be 100% in all family members Health outcomes (such as cardiac event rates) associated with uptake of cascade testing/screening, compliance to periodic surveillance and treatment adherence are not modelled due to lack of evidence. Costs associated with genetic testing, clinical screening and periodical surveillance are modelled.
Family member, genotype negative	Absence of familial variant	No need of periodical clinical surveillance and prophylactic treatment No need of cascade clinical screening in offspring	Risk of cardiac events is similar to the general population No need of periodic surveillance and prophylactic treatment	Costs associated with unnecessary lifelong periodical surveillance are avoided Only costs associated with genetic testing and clinical screening are modelled
Variant status unknown in family member	Familial variant status unknown	Lifelong periodical clinical surveillance	Lifelong periodical clinical surveillance in all family members and prophylactic treatment based on clinical assessment	Costs associated with clinical screening are included for all Costs associated with periodical clinical surveillance are modelled for family members of affected individuals who would have had a positive test result if the test was available Family members of the affected individuals who would have had an inconclusive genetic test results are assumed to have health outcomes and patient management similar to the family members of the affected individuals without genetic testing. Therefore, only costs associated with initial clinical assessment are included in the model for this subgroup.

Source: DCAR, Table 17

The inputs used in the DCAR’s economic evaluation are provided in Table 13.

**Table 13: Summary of the inputs used in the economic evaluation**

Parameter	Value	Source
Diagnostic yield in affected individuals	26.3%	The yield in affected individuals in National clinical audit report is used (Australian Cardiac Genomic Flagship audit data <sup>74</sup> ). Sensitivity analyses were conducted using the yield reported in literature (10–90%)
Disease reclassification	6.5%	Clinical assessment identified that positive genetic results in affected individuals result in reclassification of approximately 6–7% of the affected individuals with clinical diagnosis of ICAs.
Uptake of cascade testing per index case	FDR: 3 SDR: 0	Total number of relatives tested per index case was based on Burns <i>et al.</i> <sup>75</sup> . The base case analysis assumes only FDR (assuming that SDRs are only eligible for testing, if a variant has been found in the FDR). Scenario analysis is presented with both FDR and SDR (assuming SDR are eligible without testing in FDR). Sensitivity analysis varied number of family members tested per index case (1–6 first-degree family members, and 0–4 second-degree family members).
Yield in cascade genetic screening	FDR: 50% 3FDR+1SDR: 43.8%	Assuming Mendelian inheritance patterns, weighted by the relationship to index cases of those who undertook cascade screening. A sensitivity analysis is presented assuming the yield reported in CIDRNZ (53%) <sup>76</sup> .
Mean cohort age of the family members	25 years	The mean age of the family members participating in cascade testing is assumed to be 25 years as reported <sup>77</sup> . Sensitivity analysis presents the results with mean cohort age of 8 years for the family members.
Surveillance interval	Biennial	The PICO suggested annual lifelong surveillance for family members who are genotype positive or in family members where the familial variant is unknown. As a conservative approach, the base-case analysis assumes clinical screening for monitoring occurs every two years as some of the MBS items in the surveillance are limited to one claim per two years. Surveillance interval varying from 1–5 years is assessed in the sensitivity analysis.
Mortality	Age-specific	In the base-case analysis age-specific mortality rate observed in the general population is applied to all modelled subgroups (Australian Bureau of Statistics [ABS] 2019).
Genetic counselling uptake rate	Affected individuals: 26.3%. Relatives: pre-test 100%, post-test 50%	Affected individuals: those who test positive (i.e. index cases). Family members: pre-test for all undergoing testing, post-test for those who test positive (DCAR technical document, p 161).
<b>Costs</b>		
Proposed genetic testing	Affected individuals: \$1,200 Relatives: \$400	Proposed fees.
Genetic counselling	Initial: \$157.95 Subsequent: \$79.05	Based on MBS items 110 and 116.
Clinical screening or surveillance	\$354.26	Calculated using fee and estimated use of resources (one unit each of MBS items 23, 110, 116 and 11704; and 11.75% and 16.53% units of MBS items 11716 and 11729 respectively). <sup>a</sup>

<sup>a</sup> Use of MBS items 11709 and 11712 relative to MBS 11700 (11.75% and 16.53% respectively), estimated using Medicare statistics data for years 2017–20 (all of these MBS items have been redefined in the MBS August 2020 schedule as 11704, 11716 and 11729).

CIDRNZ = Cardiac Inherited Diseases Registry New Zealand; FDR = first-degree relative; MBS = Medicare Benefits Schedule; SDR = second-degree relatives

Source: DCAR, Table 18 (as updated in HTA group’s rejoinder to applicant’s pre-ESC response), including genetic counselling uptake rates used in modelling (DCAR, Table 26)

<sup>74</sup> Austin, R, et al. 2021 ‘Investigation of current models of care for genetic heart disease in Australia: A national clinical audit’, *Int J Cardiol*, [in press](#).

<sup>75</sup> Burns, C, et al. 2016, 'Factors influencing uptake of familial long QT syndrome genetic testing', *Am J Med Genet A*, vol. 170, no. 2, 2016, pp. 418-425.

<sup>76</sup> Earle, N et al. 2013, ‘Community detection of long QT syndrome with a clinical registry: an alternative to ECG screening programs?’, *Heart Rhythm*, 10: 233-238.

<sup>77</sup> Burns, C, et al. 2016, 'Factors influencing uptake of familial long QT syndrome genetic testing', *Am J Med Genet A*, vol. 170, no. 2, 2016, pp. 418-425.



The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, using the base case assumptions, are shown in Table 14.

**Table 14: Incremental cost-effectiveness and cost-savings of genetic testing across various cohorts**

	Genetic test available	Genetic test not available	Increment	ICER
Affected individuals only				
Costs	\$1,242	\$0	\$1,242	
Variants identified <sup>a</sup>	0.263	0.00	0.263	\$4,721 / positive genotyping
Misdiagnosis averted	0.065	0.00	0.065	\$19,101 / misdiagnosed affected individual identified
Affected individuals +FDR				
Short-term costs <sup>b</sup>	\$2,682	\$1,063	\$1,619	
Affected individuals cost	\$1,242	\$0	\$1,242	
FDR	\$1,441	\$1,063	\$378	
Ongoing Surveillance <sup>c</sup>	\$1,066	\$2,726	-\$1,661	
Total costs (testing + ongoing surveillance) over modelled time horizon <sup>c</sup>	\$3,748	\$3,789	-\$41	-\$41 (cost-savings)
Variants identified <sup>a</sup>	0.656	0.000	0.656	Testing strategy is dominant <sup>d</sup>
Affected individuals +FDR + SDR				
Short-term costs <sup>b</sup>	\$3,152	\$1,417	\$1,735	
Affected individuals cost	\$1,242	\$0	\$1,242	
FDR + SDR	\$1,911	\$1,417	\$493	
Ongoing Surveillance <sup>c</sup>	\$1,217	\$3,635	-\$2,418	
Total costs (testing + ongoing surveillance) over modelled time horizon <sup>c</sup>	\$4,370	\$5,052	-\$683	-\$683 (cost-savings)
Variants identified <sup>a</sup>	0.723	0.000	0.723	Testing strategy is dominant <sup>d</sup>

<sup>a</sup> Pathogenic or likely pathogenic

<sup>b</sup> Short-term costs include immediate costs associated with testing, counselling and clinical screening (in family members only) in affected individuals and family members.

<sup>c</sup> Discounted at 5% per annum

<sup>d</sup> Testing strategy is dominant as it results in cost-savings due to unnecessary surveillance avoided in genotype negative family members and informs about variant status for both affected individuals and family members tested.

FDR = first-degree relatives; SDR = second-degree relatives

Source: DCAR, Table 19 (as updated in HTA group's rejoinder to applicant's pre-ESC response).

The DCAR's sensitivity analyses indicated that the economic model was very highly sensitive or highly sensitive to all factors examined (Table 15).

**Table 15: Univariate sensitivity analyses**

Description	Method/value	Increment in average cost per affected individual and family members (lower value, higher value) (base-case: -\$41)	Impact
Diagnostic yield in affected individuals (base case: 26.3%)	Values changed over range: 10% to 90%	\$728, -\$3,048	Very high impact; higher diagnostic yield in affected individuals results in higher uptake of genetic testing in family members and therefore more cost-savings
Number of FDR screened per index case (base case: 3)	Values changed over range: 1 to 6	\$814, -\$1,324	Very high impact; increased uptake of genetic testing in family members increases the cost saving associated with testing.
Number of SDR screened per index case (base case: 0)	Values changed over range: 0 to 4	-\$41, -\$2,607	Very high impact; increased uptake of genetic testing in family members increases the cost saving associated with testing.
Recommended surveillance interval (base case: 2 years)	Values changed over range from 1 year to 5 years	-\$1,253, \$684	High impact; the cost-saving associated with genetic testing increases if the surveillance interval is shorter
Cost of surveillance (base case: \$354)	Values changed over range from \$177 to \$709.	\$601, -\$1,326	High impact; the cost-saving associated with genetic testing are increased if the cost of surveillance is higher.
Uptake of surveillance in no testing arm (base case: 100%) <sup>a</sup>	Value changed to 50%	\$1,242	High impact; the cost-savings are not observed if uptake of surveillance is lower in the non-testing arm. However, this is likely an underestimate, as health benefits associated with surveillance are not quantified in the model.

FDR = first-degree relatives; SDR = Second-degree relatives

Source: DCAR, Table 20 (as updated in HTA group's rejoinder to applicant's pre-ESC response).

### 13. Financial/budgetary impacts

The DCAR noted that genetic testing for ICAs is currently provided by the States/Territories through public hospitals, or, is privately funded by the populations eligible for MBS funding. Should listing on the MBS be recommended, it is expected that the cost of testing will shift from the States/Territories or the public, to the MBS (with no cost-offsets to the MBS anticipated).

The DCAR therefore reported changes in the use of other medical services associated with this application as the sum of additional genetic counselling services for affected individuals, and pre- and post-test genetic counselling for family members receiving cascade tests (counselling uptake rates as in Table 13). In the pre-ESC response, the applicant comments that as recommended by the 2015 ESC guidelines, genetic testing may also deliver additional benefits by the avoidance of other cardiac investigations in patients suspected of a ventricular arrhythmia, such as echocardiograms (MBS item number 55126, fee \$234) or cardiac MRI (not currently funded by the MBS). In the rejoinder, the HTA group responded that there is a lack of real-world data on resource use associated with the clinical assessment and/or surveillance in Australian clinical practice.

The DCAR estimated the total financial implications to the MBS of introducing genetic testing for ICAs (Table 16). The DCAR noted that the net costs to the MBS associated with the proposed listing would be expected to be associated with a commensurate reduction in public hospital expenditure.

**Table 16: Total cost to MBS (proposed tests and co-administered services) for affected individuals and FDRs**

Row	Description	2021–22	2022–23	2023–24	2024–25	2025–26
	<i>Affected individuals</i>					
B	Number of diagnostic tests	437	671	758	857	968
C	Number of affected individuals testing positive, i.e. probands (= B × 26.3%)	115	177	199	225	255
G	Cost to MBS (= B × \$1,115.30)	\$445,970	\$684,563	\$773,557	\$874,119	\$987,754
	<i>Cascade testing</i>					
F	Number of predictive tests, for 3 FDRs per proband (= C × 3)	345	530	598	676	764
H	Cost to MBS (= F × \$340)	\$117,290	\$180,040	\$203,445	\$229,893	\$259,779
I	<b>Cost to MBS of the proposed tests (affected individuals and FDRs) (= G + H)</b>	<b>\$563,260</b>	<b>\$864,604</b>	<b>\$977,002</b>	<b>\$1,104,012</b>	<b>\$1,247,534</b>
M	Number of genetic counselling services in probands (= C × 1)	115	177	199	225	255
N	Cost to MBS (= M × \$134.30)	\$15,443	\$23,705	\$26,787	\$30,269	\$34,204
O	Number of pre-test genetic counselling services in FDRs (= F × 1)	345	530	598	676	764
P	Cost to MBS (= O × \$134.30)	\$46,330	\$71,116	\$80,361	\$90,808	\$102,613
Q	Number of post-test genetic counselling services in FDRs (= O × 50%)	172	265	299	338	382
R	Cost to MBS (= Q × \$67.20)	\$11,591	\$17,792	\$20,105	\$22,719	\$25,672
S	<b>Cost to MBS of co-administered services (= N + P + R)</b>	<b>\$73,364</b>	<b>\$112,613</b>	<b>\$127,253</b>	<b>\$143,796</b>	<b>\$162,489</b>
X	<b>Total costs to MBS (= I + S)</b>	<b>\$636,623</b>	<b>\$977,217</b>	<b>\$1,104,255</b>	<b>\$1,247,808</b>	<b>\$1,410,023</b>

FDR = first-degree relative; MBS = Medicare Benefits Schedule

Source: DCAR, Tables 24, 26, and 28 (as updated in HTA group's rejoinder to applicant's pre-ESC response).

The DCAR summarised the estimated costs associated with the proposed testing for affected individuals and first- and second-degree relatives, to the MBS (Table 17) and to the public via co-payments (Table 18).

**Table 17: Estimated cost to MBS (proposed tests and co-administered services) for affected individuals, FDRs and SDRs**

Row	Description	2021–22	2022–23	2023–24	2024–25	2025–26
I	Cost to MBS of genetic testing in affected individuals, FDRs and SDRs (= G + H)	\$602,356	\$924,617	\$1,044,817	\$1,180,643	\$1,334,127
S	Cost to MBS of co-administered services in affected individuals, FDRs and SDRs (= N + P + R)	\$92,677	\$142,444	\$160,637	\$181,581	\$205,328
X	<b>Total cost to MBS (= I + S)</b>	<b>\$695,033</b>	<b>\$1,067,061</b>	<b>\$1,205,454</b>	<b>\$1,362,224</b>	<b>\$1,539,455</b>

Note: Rows may not add up due to rounding-off errors.

FDR = first-degree relative; MBS = Medicare Benefits Schedule; SDR = second-degree relatives;

Source: DCAR, Tables 26 and 29 (as updated in HTA group's rejoinder to applicant's pre-ESC response). In order to include co-administered services in this scenario for consistency with the base case presented in Table 16, the Department has updated the calculation of co-administered services (S) in this table to also include SDRs (italics). Calculations used 1 SDR per proband, as per DCAR Table 29.

**Table 18: Estimated co-payments (proposed tests and co-administered services) for affected individuals, FDRs and SDRs**

Row	Description	2021–22	2022–23	2023–24	2024–25	2025–26
L	Co-payments for genetic testing in affected individuals, FDRs and SDRs (= J + K)	\$64,631	\$99,208	\$112,105	\$126,679	\$143,147
W	Co-payments for other co-administered services in affected individuals, FDRs and SDRs (= M + U + V)	\$16,325	\$25,089	\$28,294	\$31,983	\$36,166
	<b>Total co-payments (= L + W)</b>	<b>\$80,956</b>	<b>\$124,297</b>	<b>\$140,399</b>	<b>\$158,662</b>	<b>\$179,313</b>

Note: Rows may not add up due to rounding-off errors.

FDR = first-degree relative; SDR = second-degree relatives;

Source: DCAR, Tables 27 and 30 (as updated in HTA group's rejoinder to applicant's pre-ESC response). In order to include co-administered services in this scenario for consistency with the base case presented in Table 16, the Department has updated the calculation of co-administered services (W) in this table to also include SDRs (italics). Calculations used 1 SDR per proband, as per DCAR Table 29.

The DCAR's sensitivity analyses of the forward estimates found that the cost to the MBS is primarily sensitive to higher increases in the number of family members tested per proband, higher growth rate of genetic testing and higher diagnostic yield in affected individuals (Table 19).

**Table 19: Sensitivity analyses** (results presented as net costs to MBS for proposed tests and co-administered services)

	Net costs to MBS, by year				
	2021–22	2022–23	2023–24	2024–25	2025–26
<b>Base-case</b>	<b>\$636,623</b>	<b>\$977,217</b>	<b>\$1,104,255</b>	<b>\$1,247,808</b>	<b>\$1,410,023</b>
Diagnostic yield in affected individuals – 10%	\$518,462	\$795,838	\$899,297	\$1,016,206	\$1,148,313
Diagnostic yield in affected individuals – 50%	\$808,429	\$1,240,939	\$1,402,261	\$1,584,555	\$1,790,547
Diagnostic yield in affected individuals – 90%	\$1,098,397	\$1,686,039	\$1,905,224	\$2,152,904	\$2,432,781
Genetic testing growth rate (before listing) – 5%	\$474,598	\$728,508	\$764,934	\$803,180	\$843,339
Genetic testing growth rate (before listing) – 10%	\$571,662	\$877,502	\$965,252	\$1,061,777	\$1,167,955
Genetic testing growth rate (before listing) – 20%	\$809,643	\$1,242,803	\$1,491,363	\$1,789,636	\$2,147,563
Constant growth rate for genetic testing – 15%	\$511,623	\$588,366	\$676,621	\$778,114	\$894,831
Relatives tested per proband – 1	\$519,816	\$797,918	\$901,647	\$1,018,862	\$1,151,314
Relatives tested per proband – 5	\$753,430	\$1,156,516	\$1,306,863	\$1,476,755	\$1,668,733
Relatives tested per proband – 10	\$1,045,448	\$1,604,763	\$1,813,382	\$2,049,122	\$2,315,507
Higher genetic counselling costs – Fee for MBS items 132 and 133	\$691,566	\$1,061,553	\$1,199,555	\$1,355,498	\$1,531,712
MBS rebate – 75%	\$627,993	\$963,970	\$1,089,286	\$1,230,893	\$1,390,909

MBS = Medicare Benefits Schedule

Source: DCAR, Table 31 (as updated in HTA group's rejoinder to applicant's pre-ESC response).

## 14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Additional MBS items	Consider further items to cover testing in reproductive partners, and in embryos/fetuses, and additional genes rather than a full alternative panel.
Uncertain clinical utility and therapeutic effectiveness	Consider monitoring data on adherence to recommended management (including advice to cease lifelong surveillance), particularly for family members (key potential benefits of genetic testing). Recommend accessing registry data to help address this.
Limitations of the modelled evaluation	A number of benefits are suggested but not demonstrated and/or quantified. Substantial model improvements are unlikely. Consider what value to place on the benefits that are not modelled, such as personal or perceived utility, behaviour change, and the potential of treatment adjustments or prevention to affect health outcomes. Consider if the limited approach to modelling is useful, and the plausibility and value of these potential consequences.
Key drivers of model results	Diagnostic yield, number of relatives screened and surveillance (frequency, cost and uptake). Dominance is highly uncertain and appears optimistic. Consider what base case inputs are conservative and realistic. Further explore uncertainty in multivariate analysis.
Rationale for listing (economic)	There is considerable risk of adding more cost to the system hoping for unlikely cost-savings and without any demonstrated health gains.
Budget impacts reflect testing only	Moderate uncertainty of results that are presented. Only “short-term” costs are included. The long-term impacts of services associated with changed prevention and surveillance are uncertain.
Policy	Ensure descriptor is technology-agnostic, reanalysis of stored genomic sequence data, and information sharing to avoid duplication of testing.
Related Applications	To note related application 1599, genetic panel testing for diagnosis of cardiomyopathies, is scheduled for the February 2021 ESC meeting

### ESC discussion

ESC noted that this clinical utility card (CUC) application from the Royal College of Pathologists of Australasia (RCPA) is for testing for inherited cardiac arrhythmia disorders, for the following 20 genes: *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *KCNJ2*, *CACNA1C*, *RYR2*, *CASQ2*, *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *ALG10*, *CALM1*, *CALM2*, *ANK2*, *TECL1* and *TRDN*.

ESC noted that this application builds on application 1152 lodged in 2010 by the Pathology Services Table Committee (PSTC), which was for testing of six genes associated with long QT syndrome (LQTS). In 2011, ESC advised that the application contained several uncertainties, particularly relating to the proposed item descriptor and fee for symptomatic patients. The PSTC disbanded and the RCPA took over as applicant in 2013, advising in 2014 that it wished to place application 1152 on hold, as new technologies were now available.

ESC noted that a related application – 1599, genetic panel testing for diagnosis of cardiomyopathies – is scheduled for the February 2021 ESC meeting.

ESC noted the lack of consumer feedback for this application.

ESC noted the two proposed populations:

- population 1 – clinically affected individuals, to make a genetic diagnosis and estimate risk of further disease
- population 2 – cascade testing of family members of an individual who has a pathogenic variant, to (i) confirm or refute the inheritance of the familial variant, and (ii) estimate the risk of the disease in those inheriting the variant according to the penetrance of the inherited variant.

ESC agreed with the Department’s request to include “requested by a specialist or consultant physician”, to ensure consistency among all proposed items and align with the associated practice note (PN.0.23) requiring appropriate genetic counselling. ESC also agreed with the Department’s request to include a practice note on both proposed items to ensure that the testing methodology used is appropriately sensitive to detect the clinically relevant variants in the Australian population. This is consistent with the practice notes for the existing MBS items 73345–73350.

ESC considered the current restriction to first- and second-degree biological relatives to be appropriate.

ESC queried whether cascade testing should include reproductive partner testing if a recessive pathogenic variant was identified in an affected patient. ESC noted that the inheritance pattern of most of the variants was dominant, but agreed that, for recessive inheritance patterns, partner testing would be appropriate.

ESC noted that some evidence on comparative safety in terms of psychological outcomes was provided by a study in a large LQTS-genotyped patient cohort. This study found that depressive symptoms were associated with arrhythmic events in patients with LQTS, rather than having a confirmed pathogenic gene variant. Depressive symptoms did not differ between asymptomatic LQTS variant carriers and their non-carrier relatives. In addition, ESC noted that no studies were identified that assessed the safety (e.g. adverse psychological outcomes) of cascade screening for cardiac arrhythmias.

ESC noted that testing of the affected patient leads to a clinical claim of non-inferiority compared with no genetic testing. ESC noted that therapeutic effectiveness of genetic testing for inherited cardiac arrhythmia disorders is uncertain. There is evidence for potential clinical utility arising from a change in a diagnosis from LQTS to catecholaminergic polymorphic ventricular tachycardia (CPVT) and vice versa, and clarification of LQTS subtype with more certainty. There was also potential to decrease both underdiagnosis and overdiagnosis of LQTS. Knowledge of which particular type of cardiac disorder or subtype of LQTS may influence the lifestyle modifications recommended for those patients, and treatment options considered. But it is unclear how often treatment based on clinical assessment plus genotype information differs to that based on clinical assessment alone. In addition, ESC noted that there is no evidence on whether management of affected individual Brugada syndrome (BrS) or CPVT cases are changed by identifying the genotype.

ESC noted the claim of superiority for cascade testing, in which relatives of the proband who test positive can begin early management and/or prophylactic beta-blockers, and relatives of

the proband who do not inherit the pathologic variant can be spared ongoing cardiac surveillance and therapy. ESC noted that the penetrance of the pathogenic genetic variants for LQTS, BrS and CPVT is uncertain and variable. ESC noted that symptomatic family members will likely have little incremental benefit from undergoing genetic testing, whereas asymptomatic people who carry pathogenic variants may benefit from commencing prophylactic treatment to reduce their risk of having cardiac events. For LQTS, treatment with beta-blocker therapy is associated with a 25% reduction in aborted cardiac arrest and has similar effects in those with prolonged QTc (corrected QT) intervals and those without prolonged QTc intervals. For CPVT, the effectiveness of prophylactic treatment is unclear.

ESC noted that the pre-ESC response regarding benefits of genetic testing (including avoided cardiac magnetic resonance imaging scans and echocardiograms) assumed this would be primarily in the family members who are found to not inherit the familial variant; however, ESC agreed with the rejoinder in that although this hypothesis appears reasonable, there is no real world evidence currently available to support these claims.

Consumer issues noted by ESC were that if testing remains unfunded, people unable to afford testing would not receive a potentially life-saving diagnosis – an ethical discussion alongside the economic evaluation would allow further examination of this issue. Genetic testing may facilitate probands to join communities of shared interest. Referral for genetic testing should be relatively easy in order to prevent delay in appropriate diagnosis and treatment. Patients with one of the variants detectable by NGS but not Sanger sequencing may be disadvantaged. As with other heritable conditions, those unable to know their family history (e.g. donor-conceived) would not be fully able to participate in cascade testing. Ethnic differences should be considered when using panels of genetic tests, including populations currently under-represented in genomic databases.

ESC queried whether Centres of Excellence (CoEs) could be asked to contribute data to help determine how genetic analysis changes patient management. Patients with such cardiac conditions are currently referred to CoEs for genetic testing (including cascade testing of family members) and data are centralised. These data may provide information regarding patient management with and without genetic testing.

ESC noted the approach in the economic evaluation was a cost-effectiveness analysis (CEA) of genetic testing in affected patients, and a cost-comparison and secondary CEA for cascade testing. ESC noted that a number of anecdotal benefits were presented but not modelled. ESC considered that the 40-year time horizon used in the modelling was unlikely to be justified, and queried the starting age. ESC considered if the 40-year time horizon would account for the potential to develop another cardiac-related condition, the management of which would make dedicated surveillance no longer required.

ESC noted that there was no information presented about treatment or management adherence. The economic model was based on clinical guidelines and adherence was assumed to be 100% for all relatives, which ESC considered to be overly optimistic.

ESC noted that the incremental cost-effectiveness ratios (ICERs) of \$4,721 per positive genotyping and \$19,101 per misdiagnosis identified, which was considered to be high given limited usefulness of this information in affected patients, but acknowledged that this did not account for the key benefit of enabling cascade testing. The stepped analysis suggested that testing was dominant for the index case plus first-degree relative testing, and for index case plus first- and second-degree relative testing, with higher cost-savings when the testing was expanded to include second-degree relatives. However, ESC considered these outcomes to be highly uncertain, and noted that dominance represented circumstances that favoured the

proposed intervention, including 100% testing uptake among relatives and the avoided costs of surveillance that assumed maintenance of perfect adherence over a long period of 40 years.

ESC noted the pre-ESC response, which queried whether the assessment group used an appropriate diagnostic yield and whether using data from the Australian Cardiac Genomic Flagship Audit was appropriate. ESC agreed with the rejoinder, which stated that the economic evaluation included a range of estimates, and the values used reflect current Australian clinical practice and the literature. ESC also agreed with the presented sensitivity analyses.

ESC noted that the financial impacts accounted for short-term (i.e. testing and counselling) costs only and did not reflect the changing cost of surveillance captured in the economic model. Financial impacts were driven by uptake and diagnostic yield, and varied considerably depending on these two factors. ESC noted that while the minimum 10% diagnostic yield threshold is the same as that used in *BRCA* analyses, this is a standard feature of the CUC and the 10% threshold was determined independently of *BRCA* analyses.

#### **15. Other significant factors**

Nil.

#### **16. Applicant comments on MSAC's Public Summary Document**

The Royal College of Pathologists of Australasia (the College) would like to take this opportunity to thank the Department and the MSAC for their assistance in moving this application forward to a successful outcome, which will provide certainty of knowing for patients with an inheritable cardiac disorder and, importantly, their family members.

#### **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)