Application Form

Genetic testing for the diagnosis of cardiomyopathies

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Phone: +61 2 6289 7550
Fax: +61 2 6289 5540
Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1.   Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):
Corporation name: The Royal College of Pathologists of Australasia
ABN: **REDACTED**
Business trading name: **REDACTED**

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business:
Mobile: **REDACTED**
Email: **REDACTED**

2.   (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes
☒ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. **Application title**

    Genetic testing for the diagnosis of cardiomyopathies

4. **Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)**

    Cardiomyopathies comprise a small group of related but clinically distinct primary diseases of the heart muscle and are one of the major causes of sudden cardiac death (SCD) and/or progressive heart failure (HF) (Szabadosova et al 2018). The most common cardiomyopathies are usually inherited as autosomal-dominant (Waldmuller et al 2015) and include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC. The phenotypic spectrum of many inherited cardiomyopathies can be varied and in some cases sub-classification by genotype is increasingly a more clinically useful approach, i.e. *LMNA*-cardiomyopathy. In many cases clinical management will not change for patients with a positive genetic diagnosis; however, identification of variant negative family members will represent significant savings to the health system by reducing the number of patients who require ongoing clinical monitoring.

5. **Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)**

    Diagnostic genetic testing of affected individuals: characterisation of germline gene variants for inherited cardiomyopathies in patients where clinical criteria or a family history indicate that genetic testing is warranted.

    HCM: *MYBPC3, MYH7, TNNI3, TNNT2, TPM1, ACTC1, MYL2, MYL3* plus "mimic" genes *PRKAG2, LAMP2, GLA*

    DCM: *LMNA, SCN5A, TTN, RBM20, PLN, DSP, MYH7*

    ARVC: *DSC2, DSG2, DSP, JUP, PKP2, and TMEM43*

    Predictive genetic testing of family members: detection of a clinically actionable pathogenic variant previously identified in a first-degree relative. Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of causative variant in an index case after clinical evaluation by a cardiologist (Ackerman et al 2011).

6. **(a) Is this a request for MBS funding?**

    ☒ Yes
    ☐ No

    (b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

    ☐ Amendment to existing MBS item(s)
    ☒ New MBS item(s)

    (c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

    (d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

i.	☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii.	☐ An amendment to the patient population under the existing item(s)
iii.	☐ An amendment to the schedule fee of the existing item(s)
iv.	☐ An amendment to the time and complexity of an existing item(s)
v.	☐ Access to an existing item(s) by a different health practitioner group
vi.	☐ Minor amendments to the item descriptor that does not affect how the service is delivered
vii.	☐ An amendment to an existing specific single consultation item
viii.	☐ An amendment to an existing global consultation item(s)

ix. ☐ Other (please describe below):

(e)   **If a new item(s) is being requested, what is the nature of the change to the MBS being sought?**

    i.   ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group

    ii.   ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)

    iii.   ☐ A new item for a specific single consultation item

    iv.   ☐ A new item for a global consultation item(s)

(f)   **Is the proposed service seeking public funding other than the MBS?**

☐ Yes
☒ No

(g)   **If yes, please advise:**

N/A

7.   **What is the type of service:**

☐ Therapeutic medical service
☒ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

8.   **For investigative services, advise the specific purpose of performing the service** *(which could be one or more of the following)*:

    i.   ☐ To be used as a screening tool in asymptomatic populations

    ii.   ☒ Assists in establishing a diagnosis in symptomatic patients

    iii.   ☒ Provides information about prognosis

    iv.   ☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy

    v.   ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

    vi.   ☒ A service that tests for heritable mutations in clinically affected individuals to make a genetic diagnosis and thus estimate their variation in (predisposition for) future risk of further disease and, when also appropriate, cascade testing of family members of those individuals who test positive for one or more relevant mutations, to make a genetic diagnosis and thus estimate each family member's variation in (predisposition for) future risk of developing the clinical disease.

9.   **Does your service rely on another medical product to achieve or to enhance its intended effect?**

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

10. (a)   **If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?**

☐ Yes
☐ No

(b)   **If yes, please list the relevant PBS item code(s):**

N/A

(c)   **If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?**

☐ Yes (please provide PBAC submission item number below)
☐ No

N/A

(d) **If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?**

Trade name:
Generic name:

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☐ Yes
☐ No

(b) If yes, please provide the following information (where relevant):

Billing code(s):
Trade name of prostheses:
Clinical name of prostheses:
Other device components delivered as part of the service:

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

☐ Yes
☐ No

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

☐ Yes
☐ No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: Laboratory consumables used for standard sequencing
Multi-use consumables:

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of genetic sequencing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, and specifically accredited to provide genetic testing via massively parallel sequencing with full whole exome analysis studies. This accreditation process covers the technical aspects of the laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. This allows any accredited laboratory to provide equivalent genetic variant analysis services to a minimum standard. There are no requirements for use of specific manufacturers, reagents, equipment or analysis pipelines.

13. **(a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:**

Type of therapeutic good: In-vitro diagnostic test
Manufacturer's name: N/A
Sponsor's name: Not applicable

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☒ Class III
☐ AIMD
☐ N/A

14. **(a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the _Therapeutic Goods Act 1989_?**

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☐ Yes (if yes, please provide details below)
☒ No

ARTG listing, registration or inclusion number:
TGA approved indication(s), if applicable:
TGA approved purpose(s), if applicable:

15. **If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?**

☐ Yes (please provide details below)
☒ No

Date of submission to TGA:
Estimated date by which TGA approval can be expected:
TGA Application ID:
TGA approved indication(s), if applicable:
TGA approved purpose(s), if applicable:

16. **If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?**

☐ Yes (please provide details below)
☒ No

Estimated date of submission to TGA:
Proposed indication(s), if applicable:
Proposed purpose(s), if applicable:

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	Clinical practice guidelines World-wide	2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy (Towbin et al 2019)	This expert consensus statement provides the clinician with guidance on evaluation and management of arrhythmogenic cardiomyopathy and includes clinically relevant information on genetics and disease mechanisms. PICO questions were utilised to evaluate contemporary evidence and provide clinical guidance related to exercise in arrhythmogenic right ventricular cardiomyopathy. Recommendations were developed and approved by an expert writing group, after a systematic literature search with evidence tables, and discussion of their own clinical experience, to present the current knowledge in the field.	https://www.sciencedirect.com/science/article/pii/S1547527119304382?via%3Dihub	2019
2.	Clinical practice guidelines Europe	HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) (Ackerman et al 2011)	This international consensus statement provides the state of genetic testing for the channelopathies and cardiomyopathies. It summarises the opinion of the international writing group members based on their own experience and on a general review of the literature with respect to the use and role of genetic testing for these potentially heritable cardiac conditions.	https://www.sciencedirect.com/science/article/pii/S1547527111006072?via%3Dihub	2011

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3.	Clinical practice guidelines USA	2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (Gersh et al 2011a)	Although the Task Force was aware of the lack of high levels of evidence regarding HCM provided by clinical trials, it was believed that a guideline document based on expert consensus that outlines the most important diagnostic and management strategies would be helpful.	http://circ.ahajournals.org/content/circulationaha/124/24/e783.full.pdf	2011
4.	Clinical practice guidelines USA	Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG) (Hershberger et al 2018)	Genetic testing is indicated for cardiomyopathy to assist in patient care and management of at-risk family members. A genetic evaluation of cardiomyopathy is indicated with a cardiomyopathy diagnosis, which includes genetic testing. Guidance is also provided for clinical approaches to secondary findings from cardiomyopathy genes. This is relevant as cardiomyopathy is the phenotype associated with 27% of the genes on the ACMG list for return of secondary findings. Recommendations herein are considered expert opinion per current ACMG policy as no systematic approach to literature review was conducted.	http://www.nature.com/articles/s41436-018-0039-z	2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
5.	Cost-effectiveness analysis Australia	A cost-effectiveness model of genetic testing and periodical clinical screening for the evaluation of families with dilated cardiomyopathy (Catchpool et al 2019)	The incremental cost per additional QALY of cascade genetic testing prior to periodical clinical surveillance of first-degree relatives compared with periodical clinical surveillance alone was approximately $6,100. At established thresholds of cost-effectiveness, there is a 90% probability that cascade genetic testing is cost-effective. Sensitivity analyses, including the addition of second-degree relatives, did not alter this conclusion. As the DCM pathogenic variant detection rate rises and new evidence for personalized treatment of at-risk individuals becomes available, the cost-effectiveness of cascade testing will further increase.	https://www.nature.com/articles/s41436-019-0582-2	2019
6.	Diagnostic yield The Netherlands	Toward an effective exome-based genetic testing strategy in pediatric dilated cardiomyopathy (Herkert et al 2018)	Diagnostic yield in paediatric DCM of combining exome sequencing (ES)-based targeted analysis and genome-wide copy-number variation (CNV) analysis. We reached a genetic diagnosis in 15/31 (48.4%) families. ES yielded a diagnosis in 13 probands (13/15; 86.7%), with most variants being found in genes encoding structural cardiomyocyte components. Two large deletions were identified using SNP array. This diagnostic approach yields the highest increase at each subsequent step and reduces analytic effort, cost, the number of variants of unknown clinical significance, and the chance of incidental findings.	https://www.nature.com/articles/gim20189	2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
7.	Cohort Spain	Additional value of screening for minor genes and copy number variants in hypertrophic cardiomyopathy (Mademont-Soler et al 2017)	Unrelated patients (n=223) clinically diagnosed with HCM screened for *MYBPC3, MYH7, TNNI3, TNNT2* and *TPM1*. First 84 patients underwent Sanger sequencing with remaining 303 using NGS panels. Each CNV identified by NGS was validated by MLPA or –qPCR. Family members of carriers of rare nonsynonymous variants, indels and/or CNVs were invited to undergo genetic analysis. 180 relatives were referred for genetic testing by Sanger sequencing or MLPA.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5542623/pdf/pone.0181465.pdf	2017
8.	Case series USA	Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity (Alfares & Kelly 2015)	We r`eport genetic testing results for HCM in 2,912 unrelated individuals with nonsyndromic presentations from a broad referral population over 10 years. Genetic testing was performed by Sanger sequencing for 10 genes from 2004 to 2007, by HCM CardioChip for 11 genes from 2007 to 2011 and by NGS for 18, 46, or 51 genes from 2011 onward. The detection rate is ~32% among unselected probands, with inconclusive results in an additional 15%. An expanded gene panel encompassing more than 50 genes identified only a very small number of additional pathogenic variants beyond those identifiable in our original panels, which examined 11 genes. Familial genetic testing in at-risk family members eliminated the need for longitudinal cardiac evaluations in 691 individuals. Data indicate that genetic testing resulted in a minimum cost savings of about $0.7 million.	https://www.nature.com/articles/gim2014205.pdf	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
9.	Cohort, clinical effectiveness The Netherlands	Outcomes of Contemporary Family Screening in Hypertrophic Cardiomyopathy (van Velzen et al 2018)	777 relatives of 209 probands underwent HCM screening. Genotype-positive relatives and relatives without genetic testing underwent repeated clinical evaluations. A pathogenic mutation was identified in 72% of probands. Genetic testing was performed in 620 (80%) relatives: 264 (43%) were genotype-positive and 356 (57%) were genotype-negative. At first screening, HCM was diagnosed in 98 (37%) genotype-positive relatives and 28 (17%) relatives without gene testing (p<0.001). During 9 years follow-up of relatives diagnosed with HCM, 8 (6%) underwent septal reduction therapy, 16 (16%) received primary prevention ICDs, and cardiac mortality was 0.3%/year. During 7 years follow-up of relatives without HCM, 29 (16%) developed HCM. Survival at 5/10 years was 99%/95% in genotype-positive relatives, 97%/94% in genotype-negative relatives (p=0.8), and 100%/100% in relatives without gene testing. HCM was identified in 30% of relatives at first screening, and 16% developed HCM during 7 years of repeated evaluation. GT led to a discharge from clinical follow-up in 46% of the study population.	https://www.ahajournals.org/doi/pdf/10.1161/CIRCGEN.117.001896	2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
10.	Cohort UK	Genetic complexity in hypertrophic cardiomyopathy revealed by high-throughput sequencing (Lopes et al 2013)	Unrelated patients (n=223) clinically diagnosed with HCM underwent MPS for 20 genes associated with HCM and DCM, 17 genes implicated in other inherited cardiomyopathies and arrhythmia syndromes, and a further four candidate genes. Sequencing results were compared to 1,287 control samples. All 50 variants were successfully validated by Sanger sequencing.	http://jmg.bmj.com/content/jmedgenet/50/4/228.full.pdf	2013
11.	Cohort Italy	A Next-Generation Sequencing Approach to Identify Gene Mutations in Early- and Late-Onset Hypertrophic Cardiomyopathy Patients of an Italian Cohort (Rubattu et al 2016)	Patients with a clinical diagnosis of HCM: Group 1 = early-onset mean age at diagnosis of 18.6 ± 8.5 years (n=35) Group 2 = late-onset mean age at diagnosis of 70.4 ± 4.8 years (n=35) 17 HCM phenotype causative genes sequenced on Personal Genome Machine (PGM) IonTorrent sequencer. The identified variants were validated by Sanger sequencing.	http://www.mdpi.com/1422-0067/17/8/1239/pdf	2016
12	Cohort Germany	Targeted 46-gene and clinical exome sequencing for mutations causing cardiomyopathies (Waldmuller et al 2015)	Consecutive patients clinically diagnosed with HCM (n =4), DCM (n = 7) or LVNC (n = 2) underwent NGS with either Illumina's TruSight Cardiomyopathy Enrichment Panel (tsCM, 46 genes) in conjunction with the MiSeq or Illumina's TruSight ONE Enrichment Panel (tsONE, 4813 genes). Relevant DNA sequence variants were confirmed by Sanger sequencing.	https://tinyurl.com/yctyya5p	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
13	Cohort Australia	Genome sequencing as a first-line genetic test in familial dilated cardiomyopathy (Minoche et al 2018)	42 patients with familial DCM underwent multigene panel sequencing and genome sequencing, and detection rates of rare single-nucleotide variants and small insertions/deletions in panel genes were compared. Loss-of function variants in 406 cardiac-enriched genes were evaluated, and an assessment of structural variation was performed.	https://www.nature.com/articles/s41436-018-0084-7.pdf	2018
14.	Observational study Italy	Targeted next-generation sequencing detects novel gene ± phenotype associations and expands the mutational spectrum in cardiomyopathies (Forleo et al 2017)	Unrelated patients (n=38) with a clinical diagnosis of DCM (n=16), HCM (n=14) and ARVC (n=8) underwent targeted NGS screening of 115 genes using the Illumina MiSeq platform	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5531468/pdf/pone.0181842.pdf	2017
15.	Cost-effectiveness analysis Australia	A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy (Ingles et al 2012)	The addition of genetic testing to the management of HCM families is cost-effective in comparison with conventional clinical screening. The ICER was $A785 per QALY, and $A12,720 per additional life-year gained. As the cost of proband genetic testing decreased, the ICER decreased and was cost saving when the cost fell below $A248. The mutation identification rate was also important in reducing the overall ICER.	https://heart.bmj.com/content/98/8/625.long	2012

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
16.	Diagnostic yield Australia	Whole Genome Sequencing Improves Outcomes of Genetic Testing in Patients With Hypertrophic Cardiomyopathy (Bagnall et al 2018)	WGS performed on 58 unrelated patients with HCM, 14 affected family members, and 2 unaffected parents of a severely affected proband. A pathogenic or likely pathogenic variant was identified in 9 of 46 families (20%) for which prior genetic testing was inconclusive. Three families had variants in genes not included in prior genetic testing. One family had a pathogenic variant that was filtered out with prior exome sequencing. Five families had pathogenic variants in noncoding regions, including 4 with deep intronic variants that activate novel splicing, and 1 mitochondrial genome variant. As a first-line genetic test, WGS identified a pathogenic variant in 5 of 12 families (42%) that had never received prior genetic testing.	https://www.ncbi.nlm.nih.gov/pubmed/30025578	2018
17.	Diagnostic case-control study USA, Australia	A gene-centric strategy for identifying disease-causing rare variants in dilated cardiomyopathy (Horvat et al 2019)	Cardiomyopathy gene panel testing was performed in 532 DCM patients and 527 healthy control subjects. Rare variants in 41 genes were stratified using variant-level and gene-level characteristics. Variants that met these criteria were found in 407 (77%) DCM cases and in 348 (66%) control subjects ($P = 0.0002$), with the number of rare variants per person ranging from 0 to 13 (mean 1.63) in DCM cases and from 0 to 8 (mean 1.24) in controls ($P < 0.0001$).	https://www.nature.com/articles/s41436-018-0036-2?WT.ec_id=GIM-201901&sap-outbound-id=61D1A794F6FCC7A9088C29632510134D82575B94	2019

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
18	Diagnostic yield Portugal	Molecular characterization of Portuguese patients with dilated cardiomyopathy (Sousa et al 2019)	A multicentre study of 107 unrelated patients. Variants in 15 genes were screened using PCR with direct sequencing (NGS with at least 30-fold coverage combined with Sanger sequencing). 31 rare variants in 8 genes (mainly in *MYBPC3, TNNT2* and *LMNA*) were identified, in 28 patients (26%). Only 4 variants had been previously described in association with DCM, 11 with HCM, and 9 variants were novel.	https://www.sciencedirect.com/science/article/pii/S0870255118302269?via%3Dihub	2019
19.	Diagnostic yield Spain	Clinical and Genetic Diagnosis of Non-ischemic Sudden Cardiac Death (Jimenez-Jaimez et al 2017)	56 families with at least 1 index case of SCD (resuscitated or not). Survivors were studied with ECG, cardiac imaging, exercise testing, familial study, genetic testing and, in some cases, pharmacological testing. Families with deceased probands were studied using the post-mortem findings, familial evaluation, and molecular autopsy with NGS.A positive diagnosis was obtained in 80.4% of the cases, with no differences between survivors and non-survivors (P=.53). Cardiac channelopathies were more prevalent among survivors than non-survivors (66.6% vs 40%, P=.03). Among the 30 deceased probands, the definitive diagnosis was given by autopsy in 7. A diagnosis of cardiomyopathy tended to be associated with a higher event rate in the family. Genetic testing with NGS was performed in 42 index cases, with a positive result in 28 (66.6%), with no differences between survivors and non-survivors (P=.21).	https://www.sciencedirect.com/science/article/pii/S1885585717302281?via%3Dihub	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
20.	Diagnostic yield Denmark	Diagnostic Yield, Interpretation, and Clinical Utility of Mutation Screening of Sarcomere Encoding Genes in Danish Hypertrophic Cardiomyopathy Patients and Relatives (Andersen et al 2009)	Family screening combining clinical evaluation and screening for sarcomere gene mutations in a cohort of 90 Danish HCM patients and their close relatives (n= 451). Index patients were screened for mutations in all coding regions of 10 sarcomere genes and five exons of TTN. Relatives were screened for minor or major diagnostic criteria for HCM. The genetic diagnostic yield was almost 2x in familial HCM (53%) vs. HCM of sporadic or unclear inheritance (19%). The yield was highest in families with an additional history of HCM-related clinical events. In relatives, 29.9% of mutation carriers did not fulfil any clinical diagnostic criterion, and in 37.5% of relatives without a mutation, one or more criteria was fulfilled. A total of 60% of family members had no mutation and follow-up ceased.	https://onlinelibrary.wiley.com/doi/abs/10.1002/humu.20862	2009
21	Cohort Italy	Targeted next-generation sequencing helps to decipher the genetic and phenotypic heterogeneity of hypertrophic cardiomyopathy (Cecconi et al 2016)	Unrelated patients (n=92) with a clinical diagnosis of HCM underwent sequencing using NGS: Ion AmpliSeq™ Custom Panel for the mutational screening of 19 genes, compared to Sanger sequencing.	https://www.spandidos-publications.com/ijmm/38/4/1111/download	2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
22.	Cohort Abstract in English, body in Portuguese	Clinical and genetic diagnosis of familial hypertrophic cardiomyopathy: Results in pediatric cardiology (Cardoso et al 2017)	Outcome of clinical screening and genetic testing of child probands and relatives (<18 years of age) from families with HCM and assessed the age-related penetrance of HCM during the follow-up. 20 patients from 10 families consisting of three probands and 17 first-degree relatives. 14 child relatives were mutation carriers (70%), 7 (50%) of the 14 mutation carriers were diagnosed with HCM at initial assessment. At-risk child relatives were defined as those with a positive mutation but negative phenotype at enrolment. At 3.5±0.8 years follow-up, 2 of the phenotype-negative mutation carriers developed HCM at 10 and 15 years of age (28% penetrance rate), underlining the need for long-term monitoring of mutation carriers.	https://tinyurl.com/y7fuymbl	2017
23.	Diagnostic case-control study Russia	Targeted next-generation sequencing (NGS) of nine candidate genes with custom AmpliSeq in patients and a cardiomyopathy risk group (Glotov et al 2015)	A genetic analysis of student cohorts (with and without cardiomyopathy risk in their medical histories) and patients with cardiomyopathies was performed using a custom AmpliSeq panel for NGS sequencing of the coding sequences of *ACTC1, MYBPC3, MYH7, MYL2, MYL3, TNNI3, TNNT2, TPM1*, and *CASQ2*.	https://www.sciencedirect.com/science/article/pii/S0009898115002053	2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
24.	Cohort Denmark	Penetrance of hypertrophic cardiomyopathy in children and adolescents: a 12-year follow-up study of clinical screening and predictive genetic testing (Jensen et al 2013)	90 probands and 361 relatives were included in a family screening program for HCM. 12 child relatives were carriers, and 26 had unknown genetic status. 28 non-carriers served as control subjects. Two of 38 child relatives (5%) at risk of developing HCM fulfilled diagnostic criteria for HCM at inclusion. After 12 ± 1 years of follow-up, 2 of the 36 (6%; 95% confidence interval, 2-18) at-risk child relatives who were phenotype negative at inclusion had developed the HCM phenotype at 26 and 28 years of age. During follow-up, none of the child relatives experienced serious cardiac events. Forty-two percent of the child relatives were non-carriers, and repeat clinical follow-up could be safely limited to the remaining children	https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.111.090514	2013

MLPA = Multiplex ligation dependent probe amplification, qPCR = quantitative polymerase chain reaction (PCR), HCM = hypertrophic cardiomyopathy, DCM = dilated cardiomyopathy, ARVC = arrhythmogenic right ventricular cardiomyopathy, NGS = next generation sequencing, WGS = whole genome sequencing, CNV = copy number variant, WGS = Whole genome sequencing

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.

*** If the publication is a follow-up to an initial publication, please advise.

18. **Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only).** *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.					

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

***Date of when results will be made available (to the best of your knowledge).

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. **List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

    Royal College of Pathologists of Australasia

20. **List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

    Other medical professionals may request the medical service and would perform evaluation of patients prior, and subsequent to the test. Some patients may require, or become exempt from, longitudinal evaluation after the test. Organisations impacted by this medical service would include Fellows of Royal Australasian College of Physicians, the Royal Australasian College of General Practitioners and the Cardiac Society of Australia & New Zealand.

21. **List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

    Cardiomyopathy Association of Australia Ltd

22. **List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

    N/A

23. **Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

    Name of expert 1: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**

    Name of expert 2: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**.

    Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

24. **Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease in terms of both morbidity and mortality:**

Cardiomyopathies comprise a small group of related but clinically distinct primary diseases of the heart muscle and are one of the major causes of sudden cardiac death (SCD) and/or progressive heart failure (HF) (Szabadosova et al 2018). Cardiomyopathies are usually inherited as autosomal-dominant (Waldmuller et al 2015) and include:

- Hypertrophic cardiomyopathy (HCM), is a common cardiac genetic disease, with an estimated prevalence of 1 in 200 to 1 in 500 (Burns et al 2017). HCM is characterised by the presence of unexplained left ventricular hypertrophy (LVH). The LVH associated with HCM usually develops during adolescence or young adulthood. HCM was initially thought to be associated with high mortality, however, the majority of individuals with HCM will experience a normal life expectancy and manageable symptoms. Individuals with HCM are at an increased risk for atrial fibrillation (AF), which is associated with significant morbidity due to increased risk of thromboembolism and symptomatic deterioration. Approximately 5%-10% of individuals with HCM progress to end-stage disease with impaired systolic function and, in some cases, left ventricular dilatation and regression of LVH. The annual mortality rate in individuals with end-stage disease is estimated at 11% and cardiac transplantation may be required. A small number of individuals with HCM are at increased risk for SCD related to ventricular tachycardia / ventricular fibrillation. SCD may be the first manifestation of disease, usually occurring in adolescents or young adults (Cirino & Ho 2014). Patients can be risk stratified clinically for SCD via holter, echo, and family history; however, specific variants may add additional clinical information and assist risk stratification.
- Dilated cardiomyopathy (DCM) is characterised by LV enlargement and systolic dysfunction, a reduction in the myocardial force of contraction. Onset may occur at any time in life but is more common in adults aged 40-60 years. Few estimates of the prevalence of DCM exist; however, it has been estimated to be twice that of HCM (1:250) (Hershberger & Morales 2015).
- Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterised by progressive fibro-fatty replacement of the myocardium, predisposing young individuals and athletes to ventricular tachycardia and SCD affecting the right and/or left ventricle. The mean age at diagnosis is 31 ± 13 years (range 4-64 years). The prevalence of ARVC is estimated at 1:1,000 to 1:1,250 in the general population (McNally et al 2017).

25. **Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:**

Diagnostic genetic testing of affected individuals: characterisation of germline gene variants for inherited cardiomyopathies in patients where clinical criteria or a family history indicate that genetic testing is warranted. The 2019 HRS guidelines recommends (Class I)[1] genetic testing of established arrhythmogenic cardiomyopathy (ACM) susceptibility genes for individuals and decedents with either a clinical or necropsy diagnosis of ACM. In addition, it is recommended (Class I) that for genetic testing of the established ACM-susceptibility genes, a comprehensive analysis of all established genes with full coverage should be conducted (Towbin et al 2019).

---

[1] Class I recommendation = strong: Benefit >>> Risk, Class IIa = moderate: Benefit >> Risk, Class IIb = weak: Benefit ≥ Risk, Class III = no benefit: Benefit = Risk, Class III = Harm: Risk > Benefit Towbin, J. A., McKenna, W. J. et al (2019). '2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy', *Heart Rhythm*.

HCM: Class I (is recommended): Comprehensive or targeted (*MYBPC3, MYH7, TNNI3, TNNT2, TPM1*) HCM genetic testing is recommended for any patient in whom a cardiologist has established a clinical diagnosis of HCM based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype (Ackerman et al 2011).

DCM: Class I (is recommended): Comprehensive or targeted (*LMNA* and *SCN5A*) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease and/or a family history of premature unexpected sudden death (Ackerman et al 2011).

ARVC: Class I (is recommended): Comprehensive or targeted (*DSC2, DSG2, DSP, JUP, PKP2*, and *TMEM43*) ACM/ARVC genetic testing is recommended for patients satisfying task force diagnostic criteria for ACM/ARVC. (Towbin et al 2019)

Predictive genetic testing of family members: detection of a clinically actionable pathogenic variant previously identified in a first-degree relative.

HCM: Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the HCM-causative variant in an index case (Ackerman et al 2011).

DCM: Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of a DCM-causative variant in the index case (Ackerman et al 2011).

ARVC: Class I (is recommended): Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the ACM/ARVC causative variant in an index case (Ackerman et al 2011).

26. **Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):**

    Patients would normally undergo diagnosis on the basis of clinical criteria.

    The diagnosis of HCM is most often established with non-invasive cardiac imaging, including echocardiography and/or cardiac magnetic resonance imaging (cardiac MRI). HCM can also be diagnosed by pathognomonic histopathologic findings in cardiac tissue, including myocyte disarray and fibrosis. Clinical cardiovascular screening by ECG and echocardiography in relatives at risk for HCM should be performed in accordance with published recommendations (Cirino & Ho 2014).

    The position statement of the Cardiac Society of Australia and New Zealand states that "The diagnosis of DCM is made using echocardiography or other imaging modalities such as magnetic resonance imaging. Approximately 25% patients with "idiopathic" DCM are likely to have a genetic basis for disease and a detailed three-generation family history needs to be taken in all newly-diagnosed cases. First-degree family members of individuals with known or suspected familial DCM should undergo clinical screening with physical examination, 12-lead ECG and transthoracic echocardiography. A detailed medical history needs to be taken to identify any co-morbidities or acquired factors that might contribute to DCM development or exacerbate disease severity. In female family members, DCM may present during pregnancy or in the postpartum period. It has been recommended that all first-degree family members of individuals with "idiopathic" DCM, and of individuals with suspected familial DCM on the basis of a positive family history, should undergo clinical screening with physical examination, 12-lead ECG and transthoracic echocardiography to identify familial disease and to determine the number of affected individuals within families" (CSANZ 2016).

    The diagnosis of DCM is established by the presence of both of the following:

    - Left ventricular enlargement, most commonly assessed in adults by 2D echocardiography
    - Systolic dysfunction, a reduction in the myocardial force of contraction
        - An ejection fraction of less than 50% is considered systolic dysfunction. LVEF is the most commonly used clinical measure of systolic dysfunction, and is usually estimated from a 2D-echocardiogram, from other non-invasive studies (e.g., cardiac nuclear or MRI studies), or from a left ventricular angiogram.

- o Fractional shortening is another clinical measure of systolic function. A fractional shortening of less than 25% is considered systolic dysfunction (Hershberger & Morales 2015).

ARVC is a primary cardiomyopathy that is most commonly diagnosed after an individual presents with arrhythmia findings. Diagnostic criteria rely on a combination of ECG and signal averaged ECGs, imaging studies that include 2D echocardiography, cardiac MRI or RV angiography, and arrhythmia presence documented by telemetric monitoring, genetic testing, and family history. ARVC should be suspected in individuals with any of the following: syncope, palpitations, SCD, abnormal ECG, or abnormal right ventricle observed by cardiac imaging (McNally et al 2017).

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

Figure 1 outlines the pathway for the genetic and clinical screening of probands and relatives.
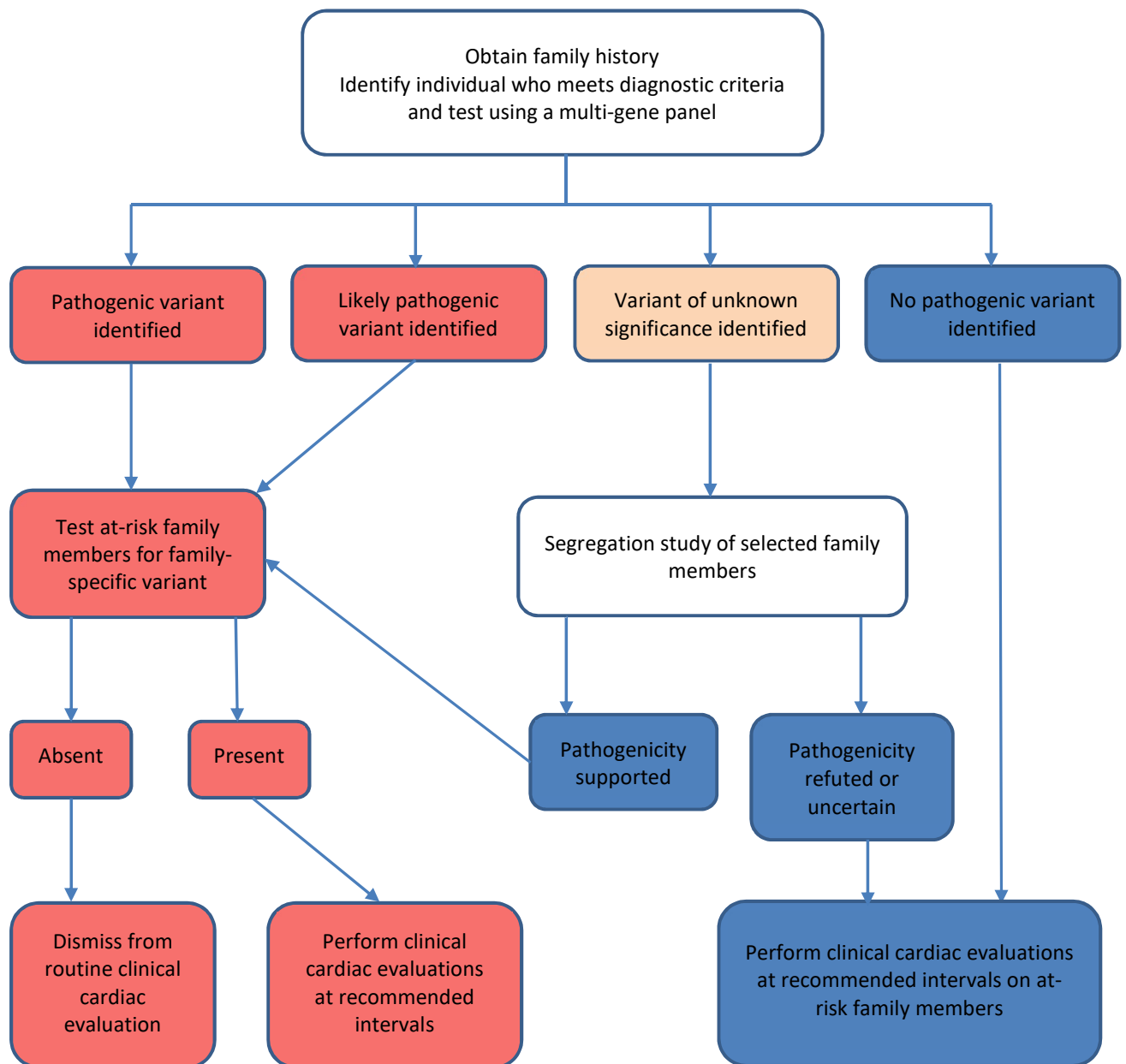

Figure 1   Flow chart for the genetic and clinical screening of probands and relatives

Once a clinical diagnosis has been made, a confirmatory genetic diagnosis is recommended and requested from a specialist cardiologist. The HRS guidelines recommend (Class I) that a detailed ≥ 3-generation family history from the proband be obtained by a genetic counsellor or an appropriately experienced clinician, which would be used to determine the existence of familial disease and identify relatives who should be informed of the need for cardiac evaluation (Towbin et al 2019).

For the genetic test, the patient would be required to provide a blood sample, from which DNA is extracted for analysis by a gene panel. The samples analysed are most commonly blood samples from affected individuals except in the case of cascade testing where duplicate and independent blood samples from affected and/or unaffected family members are submitted for specific analysis. Interpretation of variants should only be performed where there is high-level of disease-specific expertise.

Targeted panel testing of genes as stipulated should be undertaken, and if negative for a variant, then review by a multidisciplinary, specialised cardiac genetic team should be undertaken. The 2019 HRS guidelines recommends (Class IIa) that the interpretation of a cardiac genetic test by a team of providers with expertise in genetics and cardiology can be useful. This expert team should therefore consist, at minimum, of cardiologists, clinical and molecular geneticists, genetic counsellors, and pathologists, or individuals with expertise that encompass these subspecialties.(Towbin et al 2019)

28. **Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?**

    No

29. **If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?**

    No

30. **If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):**

    Once off diagnostic test

31. **If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:**

    Consultation with clinical geneticists / genetic counsellor with expertise in genetic counselling. The delivery of results to the patients and / or family would require a formal consultation with the referring cardiologist with expertise in the condition, and clinical geneticist / genetic counsellor.

32. **If applicable, advise which health professionals will primarily deliver the proposed service:**

    This test is usually requested by a cardiologist with experience in the genetic management of cardiac disease or a clinical geneticist.

    A pathologist would perform the service and provide the clinical report, including interpretation of the results.

33. **If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:**

    No

34. **If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:**

    Consideration should be given to restricting this service to a specialised setting.

35. **If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:**

Testing would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

☐ Inpatient private hospital
☐ Inpatient public hospital
☐ Outpatient clinic
☐ Emergency Department
☐ Consulting rooms
☐ Day surgery centre
☐ Residential aged care facility
☐ Patient's home
☒ Laboratory
☐ Other – please specify below

Specify further details here

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

N/A

37. Is the proposed medical service intended to be entirely rendered in Australia?

☒ Yes
☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. **Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):**

No genetic testing – clinical diagnosis alone. Usual standard of care, without genetic testing.

The 2019 HRS guidelines recommends (Class I) that cardiovascular evaluation should include 12-lead ECG, ambulatory ECG, and cardiac imaging (echocardiogram, cardiac MRI, or CT depending on availability and institutional expertise). In addition, exercise stress testing may be useful when evaluating family members (Class IIb recommendation) (Towbin et al 2019).

In the absence of a genetic diagnosis, the frequency of clinical screening for asymptomatic HCM family members ranges from 1 to 5 times per year (**Error! Reference source not found.**) (CSANZ 2016). It is strongly recommended that all first-degree relatives of an affected individual be clinically screened for HCM. Screening of at-risk, asymptomatic family members is important due to incomplete penetrance or age-related and varied expression. At-risk relatives who undergo clinical evaluation may be clinically affected, have borderline disease (incomplete penetrance), or be clinically unaffected. Serial evaluation can define ongoing disease expression and risk stratification (Towbin et al 2019).

Clinical evaluation involves a physical examination by a cardiologist, an ECG and an echocardiogram. The suggested time intervals for clinical screening of unaffected family members should follow the format shown in Table 1 but should be individually tailored to each person. The HRS guidelines recommends that first-degree relatives undergo clinical evaluation every 1-3 years starting at 10-12 years of age (Class I, level of evidence B-NR)[2] (Towbin et al 2019).

Table 1   Recommended frequency of clinical screening of asymptomatic HCM family members (CSANZ 2016)

Age (years)	Frequency of screening (years)
0-10	Optional: unless clinical suspicion, symptoms, malignant family history of HCM1
11-20	1 – 1.5
21 -30	2 -3
31+	3 - 5

39. **Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?**

☒ Yes (please provide all relevant MBS item numbers below)
☐ No

Item number 57360: COMPUTED TOMOGRAPHY OF THE CORONARY ARTERIES performed on a minimum of a 64 slice (or equivalent) scanner, where the request is made by a specialist or consultant physician, and:
a) the patient has stable symptoms consistent with coronary ischaemia, is at low to intermediate risk of coronary artery disease and would have been considered for coronary angiography; or
b) the patient requires exclusion of coronary artery anomaly or fistula; or
c) the patient will be undergoing non-coronary cardiac surgery (R) (K)
Fee: $700.00 Benefit: 75% = $525.00 85% = $618.30

---

[2] Strength of recommendation = Class I = strong, Level of evidence = B-NR from non-randomised studies: Moderate-quality evidence from 1 or more well-designed, well-executed non-randomised studies, observational studies, or registry studies. Or a meta-analyses of such studies.

Item number 55116: EXERCISE STRESS ECHOCARDIOGRAPHY performed in conjunction with item **11712**, with two-dimensional recordings before exercise (baseline) from at least three acoustic windows and matching recordings from the same windows at, or immediately after, peak exercise, not being a service associated with a service to which an item in Subgroups 1 (with the exception of item 55054) or 3, or another item in this Subgroup applies (with the exception of items 55118 and 55130). Recordings must be made on digital media with equipment permitting display of baseline and matching peak images on the same screen (R)
Fee: $261.65 Benefit: 75% = $196.25 85% = $222.45

Item number 55122: EXERCISE STRESS ECHOCARDIOGRAPHY performed in conjunction with item 11712, with two-dimensional recordings before exercise (baseline) from at least three acoustic windows and matching recordings from the same windows at, or immediately after, peak exercise, not being a service associated with a service to which an item in Subgroups 1 (with the exception of items 55026 and 55054) or 3, or another item in this Subgroup applies (with the exception of items 55118, 55125, 55130 and 55131). Recordings must be made on digital media with equipment permitting display of baseline and matching peak images on the same screen (R) (NK)
Fee: $130.85 Benefit: 75% = $98.15 85% = $111.25

Item number 11700: TWELVE-LEAD ELECTROCARDIOGRAPHY, tracing and report
Fee: $31.25 Benefit: 75% = $23.45 85% = $26.60

Item number 11709: Continuous ECG recording (Holter) of ambulatory patient for 12 or more hours (including resting ECG and the recording of parameters), not in association with ambulatory blood pressure monitoring, utilising a system capable of superimposition and full disclosure printout of at least 12 hours of recorded ECG data, microprocessor based scanning analysis, with interpretation and report by a specialist physician or consultant physician.
Fee: $167.45 Benefit: 75% = $125.60 85% = $142.35

Item number 11712: MULTI CHANNEL ECG MONITORING AND RECORDING during exercise (motorised treadmill or cycle ergometer capable of quantifying external workload in watts) or pharmacological stress, involving the continuous attendance of a medical practitioner for not less than 20 minutes, with resting ECG, and with or without continuous blood pressure monitoring and the recording of other parameters, on premises equipped with mechanical respirator and defibrillator.
Fee: $152.15 Benefit: 75% = $114.15 85% = $129.35

40. **Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):**

Many treatment options are currently available for HCM patients. This ranges from no treatment; lifestyle modifications, eg avoiding competitive sports in all patients with HCM; use of pharmacological agents eg beta-blockers, calcium channel blockers, and diuretics; to dual chamber pacing, septal myotomy-myectomy and trans-coronary alcohol septal ablation of the myocardium for individuals with significant left ventricular outflow tract obstruction with symptoms unresponsive to drug therapy. The most important advance in the clinical management of HCM has been the use of ICD therapy to prevent sudden death. Recent studies indicate that treatment of individuals at highest risk of sudden death with an ICD is the most definitive form of therapy in preventing sudden death, surpassing preventative strategies previously used such as amiodarone and beta blockers (Semsarian 2011). See Figure 2.
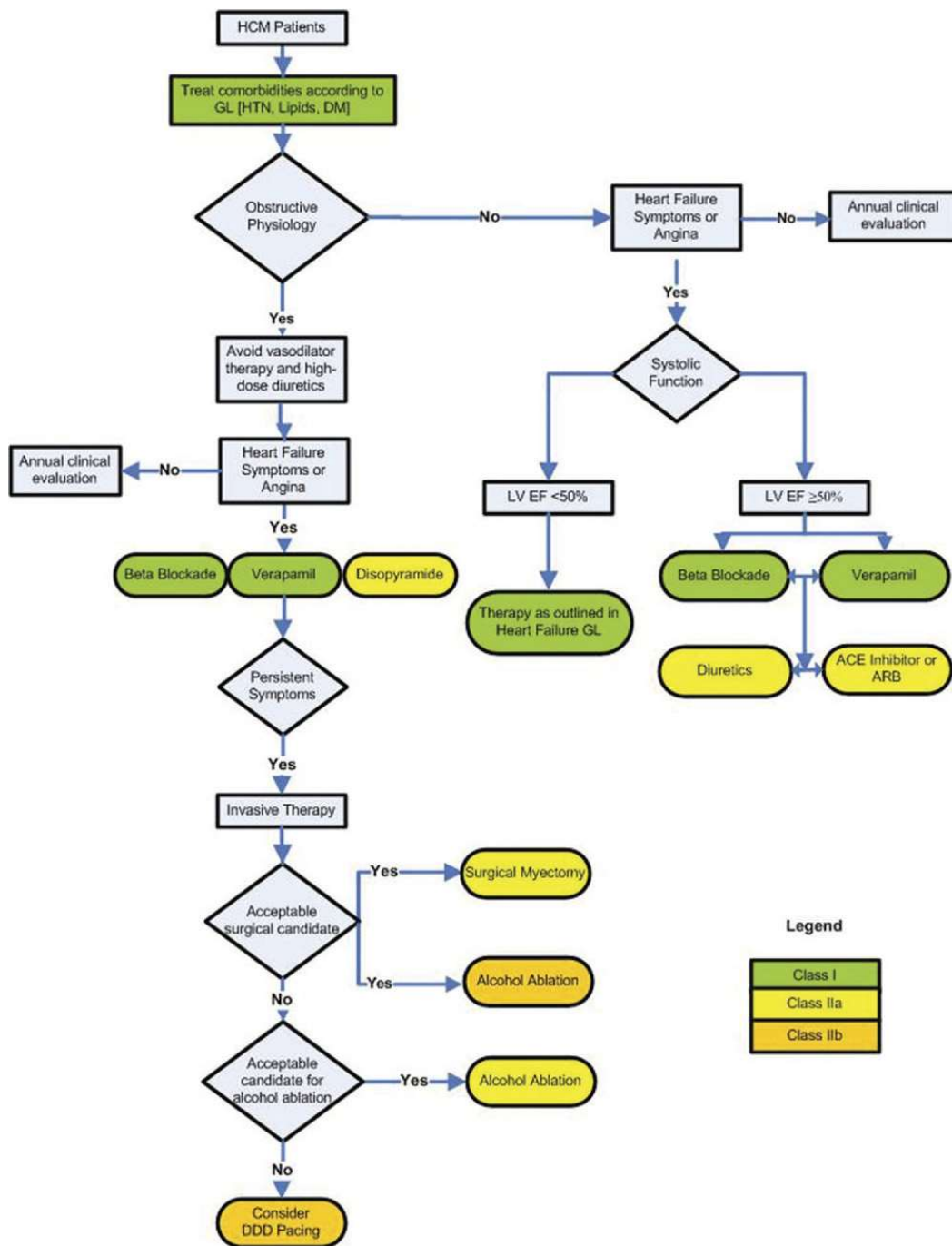
Figure 2   Treatment algorithm for hypertrophic cardiomyopathy (Gersh et al 2011b)

According to the 2016 CSANZ guidelines, "clinically-affected family members with DCM should receive standard pharmacological, device, and surgical management (circulatory support and transplantation) as indicated by the severity of symptoms and signs of heart failure, the electrocardiographic findings and the degree of left ventricular dysfunction. In families with DCM and conduction-system disease, young family members who present with conduction-system disturbances (sinus bradycardia, atrioventricular conduction block, ± atrial fibrillation) should be followed for arrhythmias that might necessitate pacemaker implantation and for the onset of DCM in later life. Electrophysiological studies/review ± ICD implantation should be considered in individuals with syncopal episodes, and/or a strong family history of sudden death, particularly in those families with LMNA variants. In most families, however, treatment choices for affected individuals are not currently altered by the discovery of a causative gene variant. In selected cases, elucidation of the molecular mechanisms underpinning disease may permit specific gene-targeted intervention. The natural history of familial DCM varies widely. It is likely that family genotype

will be a very important determinant of prognosis but genotype-phenotype correlations in large populations of family members have yet to be performed. Recent data suggest that patients with genetic causes of DCM have a worse long-term outcome if there are co-existent non-genetic environmental factors including viral infection, immune-mediated cardiac inflammation and toxic exposure."(CSANZ 2016)

In asymptomatic (DCM) family members, the CSANZ recommend "Periodic cardiac screening (ECG and transthoracic echocardiography) of family members of probands with familial DCM is recommended, to identify arrhythmias and asymptomatic abnormalities of left ventricular size and function. The frequency of follow-up assessments should be determined in each individual case by factors such as the typical age of onset of disease in symptomatic family members, and "suspicious" echocardiographic changes that may be indicative of early disease and may range from 6-12 months to 5 years. Familial DCM exhibits age-related penetrance, i.e. family members who are born with a gene defect may not develop manifestations of disease until later in life. Young family members with a normal ECG and echo, particularly offspring of an affected parent, should not be dismissed as "unaffected" and require ongoing medical surveillance. In the case of an affected child, all first-degree relatives, including parents, should be screened and siblings are offered ongoing screening into adult life."(CSANZ 2016)

As with HCM, a recent international task force consensus statement recommends that patients with a definitive diagnosis of ARVC avoid competitive and/or endurance sports and should have restricted participation in athletic activities, with the possible exception of recreational low-intensity sports. In addition, family members with a negative ARVC phenotype (Health gene carriers or those with unknown genotype) should consider restriction from competitive sports. Treatment with anti-arrhythmic drugs such as amiodarone alone or in conjunction with beta blockers is recommended for some ARVC patients, and are recommended as an adjunct to therapy with an ICD. Anti-arrhythmic drugs and beta blockers are not recommended for use in healthy gene carriers. For ARVC patients who develop right- and/or left-sided heart failure treatment with ACE inhibitors, angiotensin II receptor blockers, beta-blockers, and diuretics is recommended. In addition, catheter ablation is an option for ARVC patients who have ventricular tachycardia. ICD implantation (single chamber) should only be considered in high-risk ARVC patients, that is those patients who have experienced an aborted SCD event due to ventricular fibrillation, those with sustained ventricular tachycardia or those with severe left or right (or both) ventricular dysfunction (Corrado et al 2015).

41. **(a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?**

⊠ Yes   In addition to
☐ No

(b) **If yes, please outline the extent of which the current service/comparator is expected to be substituted:**

Genetic diagnosis will be used in conjunction with the usual clinical diagnosis.

42. **Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):**

The key role of genetic testing for many ACM conditions is to identify asymptomatic carriers who can be targeted for closer surveillance or gene-negative relatives who are unlikely to develop disease and can be released from future screening (Towbin et al 2019).

The CSANZ guidelines state that "In most families, treatment choices are not currently altered by the discovery of a causative gene variant and clinically-affected individuals should receive standard pharmacological and device management. Asymptomatic family members should have baseline cardiac assessment and ongoing periodic cardiac screening for early detection of pre-clinical disease. When a pathogenic genetic variant has been identified in an affected individual, appropriate family members should be offered predictive genetic testing and genetic counselling"(CSANZ 2016). The greatest benefit of genetic testing is the cascade testing of family members of the proband.

A genetic diagnosis delivers increased certainty – gene negative relatives may avoid inappropriate treatments and can be released from future clinical surveillance if variant interpretation has been performed robustly, delivering savings to the health system. The 2019 HRS guidelines recommends (Class IIb) that in families with a variant classified as pathogenic, it is reasonable for asymptomatic members of a family who are negative for the familial variant and have a normal cardiovascular evaluation to be released from regular screening (Towbin et al 2019).

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. **Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):**

Public funding of genetic testing for the diagnosis of cardiomyopathies would provide equity of access for all Australian patients. Identifying the disease-causing gene variant can be valuable for a family, as it allows the earlier identification, treatment and management of affected probands in addition to at-risk family members, avoiding unnecessary screening of non-carriers. Genetic testing may also help to discriminate between all causes of left ventricular hypertrophy, including hypertension and "athlete's heart" (Semsarian 2011). The diagnostic, prognostic and therapeutic impact of variant analysis for the genes involved in the various cardiomyopathies is summarised in Table 2.

Although clinical management may not change in all patients who already have a clinical diagnosis that is then confirmed by genetic testing, the value in testing lies in confirming variant-negative family members, who may then avoid clinical monitoring, representing ongoing cost-savings to the health system. Clinical screening may involve a consultation with a cardiologist, an ECG and possibly an exercise stress test conducted on average every two years (item number: **55116** Fee: $261.65 or **55122** Fee: $130.85 in conjunction with 11712 Fee: $152.15, plus consultation 105 Fee $43.65)

In addition, evidence is emerging that genotype knowledge may expedite treatments such as heart transplantation for some patients with high-risk genotypes with truncating variants (Towbin et al 2019).

HCM

Knowledge of the underlying gene and variant may have a limited role in risk assessment and management of the individual patient, which instead is based largely on clinical diagnosis. However, validated clinical risk factors including a family history of SCD, suggest that a greater knowledge of genotype–phenotype correlations is useful in HCM. For example, patients with features of HCM but without pathogenic sarcomere variants have a lower likelihood of a positive family history and, on average, a milder phenotype; thus, a negative genetic test may be of prognostic significance. There are only a few specific variants that carry a prognostic implication, and ordinarily a genetic test result in isolation will not constitute an indication for an ICD for primary prevention. Many families have a previously unrecorded variant. Long-term efforts are needed to accumulate reliable evidence on genotype–phenotype correlations, especially those pertaining to specific variants. Within typical, sarcomeric HCM, no HCM variant-specific therapeutic implications exist, as therapy in HCM is not disease modifying and treatment response is not influenced by variant type (Ackerman et al 2011).

ARVC

Left ventricular involvement is more marked in families with chain-termination variants and/or desmoplakin disease, while individuals harbouring *PKP2* variants may have earlier onset of both symptoms and ventricular arrhythmia. Intra-familial phenotype diversity, however, is prominent. Variance component analysis suggests that both genetic and environmental modifiers contribute significantly to varying disease penetrance and phenotypic manifestations, including arrhythmic outcome, between family members who carry a gene variant in arrhythmogenic cardiomyopathy (Ackerman et al 2011).

DCM

There is no *prognostic* role of genetic testing for DCM except for the increased risk of sudden cardiac death in LMNA- and DES mediated disease. A *therapeutic* role for DCM genetic testing exists for patients with DCM and prominent cardiac conduction system disease that often stems from variants in LMNA. Because cardiac conduction disease (e.g., first-, second-, or third-degree heart block) and supra-ventricular arrhythmias commonly precede life-threatening ventricular arrhythmias, early or pre-emptive use of an implantable cardiac defibrillator (rather than a pacemaker) has been advocated prior to the occurrence of life-threatening syncope or SCD. It is unknown whether early pharmacological treatment of variant-positive, pre-clinical subjects can prevent or delay manifestation of the disease. Genetic testing also has a therapeutic role for syndromic disease (e.g., muscular dystrophy) with known arrhythmia and/or conduction system disease (e.g., LMNA, DES variants) in terms of possible consideration of a prophylactic pacemaker and/or ICD (Ackerman et al 2011).

Table 2   Impact of genetic testing for the index case (Semsarian 2011)

Disease	Diagnostic	Prognostic	Therapeutic
HCM	+++	++	+
ACM/ARVC	+	+/-	-
DCM	-	-	-

Relative strength: - = negligible to +++ = strong

44. Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Direct evidence

Safety Outcomes: Physical and/or psychological harms from testing or no testing, adverse events from testing

Clinical Effectiveness Outcomes: Quality of life, reduced morbidity, mortality

Cost-effectiveness

Indirect evidence

Analytical validity: test failure rate, sensitivity, specificity, concordance, unsatisfactory or uninterpretable results, diagnostic yield

Clinical validity: predictive or prognostic value

Therapeutic efficacy: change in patient management, change in detection and treatment of family members

Therapeutic effectiveness: effect of change in management (e.g. reduction in mortality, increased quality of life)

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

Australian prevalence and incidence data for the cardiomyopathies are not well defined. The National Australian Childhood Cardiomyopathy Study (NACCS) is a population-based cohort study comprising all Australian children under the age of 10 years who were diagnosed with cardiomyopathy over a 10-year period (January 1, 1987 to December 31, 1996). A total of 314 new cases of cardiomyopathy were reported during the 10-year study period: 184 cases of DCM (58.6%), 80 cases of HCM (25.5%), 42 cases of unclassified cardiomyopathy (13.4%), and 8 cases of restrictive cardiomyopathy (2.5%). Of 42 children with unclassified cardiomyopathy, 29 had LVNC (9.2% of all cases), 9 had cardiac hypertrophy with initially impaired systolic function, 2 had familial neonatal cardiomyopathy that caused death within hours after delivery, 1 had oncocytic cardiomyopathy, and 1 had left ventricular dysfunction associated with a congenital left ventricular diverticulum. The annual incidence of each type of cardiomyopathy is summarised in Table 3. The overall annual incidence for all cardiomyopathies combined was 1.24 per 100,000 children younger than 10 years of age (Nugent et al 2003). Based on ABS population data, the number of children aged 10 years and under in the year ending June 2017 was 3,474,771, which would result in an expectation of 43 new paediatric cases per year (ABS 2018). However, the issue of age-related penetrance, and variable penetrance makes cardiomyopathies more complex. Relying on the potential incidence in a paediatric population will be misleading as cardiomyopathies are generally later onset diseases, and although they may present in childhood, more often they will not.

HCM

The estimated prevalence of HCM of 1 in 500 is based on data originally collected almost 20 years ago in the landmark CARDIA (Coronary Artery Risk Development in Young Adults) cohort study conducted in the US, which reported standard echocardiographic analyses in 4,111 unrelated people 23 to 35 years of age (Maron et al 1995; Semsarian 2011). Probable or definite echocardiographic evidence of HCM was present in 7 subjects (0.17%) on the basis of identification of a hypertrophied, non-dilated left ventricle and maximal wall thickness ≥15 mm that were not associated with systemic hypertension. Prevalence was higher in men compared to women (0.26% vs 0.09%) and in African-Americans compared to Caucasians (0.24% vs 0.10%) (Maron et al 1995). Semsarian et al (2015), however, re-examined data on the variant analysis of asymptomatic individuals in the general population and has estimated that the prevalence of HCM gene carriers could be more than 1 in 200 people or greater (Semsarian et al 2015).

Few estimates of the *prevalence* of DCM exist; however, it has been estimated to be twice that of HCM (1:250) (Hershberger & Morales 2015).

The *prevalence* of ARVC is estimated at 1:1,000 to 1:1,250 in the general population (McNally et al 2017).

Table 3   Annual incidence of each type of cardiomyopathy in a paediatric population, according to the age at presentation (Nugent et al 2003)

Type of cardiomyopathy	Age at presentation				
	0 to <1 year	1 to < 2 year	2 < 5 year	5 to <10 year	Total
Dilated cardiomyopathy					
Number of children	121	29	18	16	184
Annual incidence/100,000 children	4.76	1.14	0.24	0.13	0.73
95 % CI	3.95, 5.69	0.77, 1.64	0.14, 0.37	0.07, 0.21	0.63, 0.84
Hypertrophic cardiomyopathy					
Number of children	48	9	10	13	80
Annual incidence/100,000 children	1.89	0.36	0.13	0.10	0.32
95 % CI	1.39, 2.51	0.16, 0.67	0.06, 0.24	0.06, 0.18	0.25, 0.39
Restrictive cardiomyopathy					
Number of children	0	1	4	3	8
Annual incidence/100,000 children	0	0.04	0.05	0.02	0.03
95 % CI	0, 0.15	0, 0.22	0.01, 0.13	0.01, 0.07	0.01, 0.06
Unclassified					
Number of children	30	5	4	3	42
Annual incidence/100,000 children	1.18	0.20	0.05	0.02	0.17
95 % CI	0.80, 1.69	0.06, 0.46	0.01, 0.13	0.01, 0.07	0.12, 0.22

Type of cardiomyopathy	Age at presentation				
	0 to <1 year	1 to < 2 year	2 < 5 year	5 to <10 year	Total
Total					
Number of children	199	44	36	35	314
Annual incidence/100,000 children	7.84	1.73	0.47	0.28	1.24
95 % CI	6.79, 9.0	1.26, 2.33	0.33, 0.65	0.19, 0.39	1.11, 1.38

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

The test would be conducted once per patient lifetime. Cascade testing would also be a one-off single gene investigation for first-degree relatives of the affected patient, where clinically indicated.

48. How many years would the proposed medical service(s) be required for the patient?

N/A - testing would be conducted once per lifetime. Testing may be repeated in variant-negative patients if, in the future, new genes are added to the panel.

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

Initially there may be some "catch up", with testing of the prevalent (those with a clinical diagnosis) rather than the true incident population. It would therefore be expected that testing numbers may be slightly higher in the first year, compared to following years. Incidence data has been difficult to obtain.

The RCPA conducted a survey, on behalf of the Commonwealth Department of Health, of all Australian laboratories (n=87) known to offer genetic/ genomic tests that yielded results with medical utility during the 2016/17 financial year. **This data remains confidential until such time that the Department publishes the report.**

Participation in the survey was 96.6% of all public and private sector laboratories. The private and public sector delivered 71% and 29% of all genomic tests for heritable conditions, respectively; however, the data is unclear which sector provided testing for cardiovascular indications. It should be noted that those tests conducted in the private sector would be on a user-pays basis, and would therefore represent an underestimation of the true number as many patients would be unable to meet the cost of testing. Similarly, the number of tests conducted in the public sector would also represent an underestimation of the true number due to long waiting lists and limited funding.

During the one year sample period, cardiologists requested a total of 2,324 tests. It would also be expected that a proportion of 40,579 tests requested by clinical geneticists would be for cardiology indications. In addition, a total of 244 samples were referred to international laboratories for genetic testing for cardiac disorders.

The number of tests conducted with targeted multi-gene panels (testing ≥3 genes) were:

- Panel – Cardiomyopathy (11-50 genes)   86
- Panel – Cardiomyopathy (51+ genes)   159.

However, it is possible that some cardiomyopathy tests may have been conducted in the following:

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

In addition, targeted analysis of single genes took place:

- Cardiomyopathy, dilated, *RBM20*   6
- Cardiomyopathy, dilated, *TTN*   5

These figures may be used to approximate a potential upper and lower utilisation estimation, both of which would be an *underestimation o*f usage:

- Lower limit (# of cardiomyopathy tests only)   256
- Upper limit   417[3]

It should also be noted that the Australian Genomics Cardiac Flagship is currently conducting an audit of flagship sites in Queensland, Victoria and New South Wales to ascertain the number of cardiac diagnostic

---

[3] There were a total of 1,692 genetic tests for all cardiovascular conditions. Specific testing for cardiomyopathies represented 14.5% of these tests. If a similar proportion was applied to the generic – Cardiac panels (11-50 genes) and (51+ genes), in addition to the cardiac tests conducted overseas, this would represent 14.5% of 1,108 = 160 tests, in addition to the 256 cardiomyopathy specific tests conducted.

genetic tests being conducted – this data will be available in the near future and would inform costing calculations for the assessment.

50. **Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:**

    Testing levels are likely to be slightly less in the second and third years of implementation due to the likely testing of some of the prevalent population in year 1 of funding.

PART 8 – COST INFORMATION

51. **Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:**

    The estimated cost of providing the test is $1,800, with cascade testing of a known variant in a relative costing $400.

52. **Specify how long the proposed medical service typically takes to perform:**

    It would be expected that a test would be performed and reported on within a 4-8 week turnaround time.

53. **If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.**

Item descriptor diagnostic genetic testing of affected individuals

Category 6 – PATHOLOGY SERVICES
Proposed item descriptor: AAAA Characterisation of germline variants for inherited cardiomyopathies in a patient who fulfils diagnostic criteria for cardiomyopathy, as assessed by specialist or consultant physician such as a cardiologist with experience in the genetic management of cardiac disease. Fee: $1800

Item descriptor predictive genetic testing of family members

Category 6 – PATHOLOGY SERVICES
Proposed item descriptor: BBBB Request by a clinical geneticist, or a medical specialist providing professional genetic counselling services, for the detection of a clinically actionable pathogenic variant previously identified by Item AAAA in a first- or second-degree relative. Fee: $400

References

ABS (2018). *3101.0 - Australian Demographic Statistics, Dec 2017: TABLE 59. Estimated Resident Population By Single Year Of Age, Australia* [Internet]. Australian Bureau of Statistics. Available from: [Accessed 26th June 2018].

Ackerman, M. J., Priori, S. G. et al (2011). 'HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)', *Heart Rhythm,* 8 (8), 1308-1339.

Alfares, A. A. & Kelly, M. A. (2015). 'Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity', 17 (11), 880-888.

Andersen, P. S., Havndrup, O. et al (2009). 'Diagnostic yield, interpretation, and clinical utility of mutation screening of sarcomere encoding genes in Danish hypertrophic cardiomyopathy patients and relatives', *Hum Mutat,* 30 (3), 363-370.

Bagnall, R. D., Ingles, J. et al (2018). 'Whole Genome Sequencing Improves Outcomes of Genetic Testing in Patients With Hypertrophic Cardiomyopathy', *J Am Coll Cardiol,* 72 (4), 419-429.

Burns, C., Bagnall, R. D. et al (2017). 'Multiple Gene Variants in Hypertrophic Cardiomyopathy in the Era of Next-Generation Sequencing', *Circ Cardiovasc Genet,* 10 (4).

Cardoso, B., Gomes, I. et al (2017). 'Clinical and genetic diagnosis of familial hypertrophic cardiomyopathy: Results in pediatric cardiology', *Rev Port Cardiol,* 36 (3), 155-165.

Catchpool, M., Ramchand, J. et al (2019). 'A cost-effectiveness model of genetic testing and periodical clinical screening for the evaluation of families with dilated cardiomyopathy', *Genet Med.*

Cecconi, M., Parodi, M. I. et al (2016). 'Targeted next-generation sequencing helps to decipher the genetic and phenotypic heterogeneity of hypertrophic cardiomyopathy', *Int J Mol Med,* 38 (4), 1111-1124.

Cirino, A. L. & Ho, C. (2014). *Hypertrophic Cardiomyopathy Overview* [Internet]. University of Washington. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1768/?report=reader [Accessed 19 June 2018].

Corrado, D., Wichter, T. et al (2015). 'Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement', *Eur Heart J,* 36 (46), 3227-3237.

CSANZ (2016). *Diagnosis and Management of Familial Dilated Cardiomyopathy – Position Statement* [Internet]. Cardiac Society of Australia and New Zealand. Available from: http://www.csanz.edu.au/wp-content/uploads/2016/11/Familial-Dilated-Cardiomyopathy_25-Nov-2016-1.pdf [Accessed 5th September 2018].

Forleo, C., D'Erchia, A. M. et al (2017). 'Targeted next-generation sequencing detects novel gene-phenotype associations and expands the mutational spectrum in cardiomyopathies', *PLoS One,* 12 (7), e0181842.

Gersh, B. J., Maron, B. J. et al (2011a). '2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines', *Circulation,* 124 (24), e783-831.

Gersh, B. J., Maron, B. J. et al (2011b). '2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons', *J Am Coll Cardiol,* 58 (25), e212-260.

Glotov, A. S., Kazakov, S. V. et al (2015). 'Targeted next-generation sequencing (NGS) of nine candidate genes with custom AmpliSeq in patients and a cardiomyopathy risk group', *Clin Chim Acta,* 446, 132-140.

Herkert, J. C., Abbott, K. M. et al (2018). 'Toward an effective exome-based genetic testing strategy in pediatric dilated cardiomyopathy', *Genet Med,* 20 (11), 1374-1386.

Hershberger, R. E., Givertz, M. M. et al (2018). 'Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)', *Genet Med*.

Hershberger, R. E. & Morales, A. (2015). *Dilated Cardiomyopathy Overview* [Internet]. University of Washington. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1309/?report=classic [Accessed 19 June 2018].

Horvat, C., Johnson, R. et al (2019). 'A gene-centric strategy for identifying disease-causing rare variants in dilated cardiomyopathy', *Genetics in Medicine,* 21 (1), 133-143.

Ingles, J., McGaughran, J. et al (2012). 'A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy', *Heart,* 98 (8), 625-630.

Jensen, M. K., Havndrup, O. et al (2013). 'Penetrance of hypertrophic cardiomyopathy in children and adolescents: a 12-year follow-up study of clinical screening and predictive genetic testing', *Circulation,* 127 (1), 48-54.

Jimenez-Jaimez, J., Alcalde Martinez, V. et al (2017). 'Clinical and Genetic Diagnosis of Nonischemic Sudden Cardiac Death', *Rev Esp Cardiol (Engl Ed),* 70 (10), 808-816.

Lopes, L. R., Zekavati, A. et al (2013). 'Genetic complexity in hypertrophic cardiomyopathy revealed by high-throughput sequencing', *J Med Genet,* 50 (4), 228-239.

Mademont-Soler, I., Mates, J. et al (2017). 'Additional value of screening for minor genes and copy number variants in hypertrophic cardiomyopathy', *PLoS One,* 12 (8), e0181465.

Maron, B. J., Gardin, J. M. et al (1995). 'Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults', *Circulation,* 92 (4), 785-789.

McNally, E., MacLeod, H. & Dellefave-Castillo, L. (2017). *Arrhythmogenic Right Ventricular Cardiomyopathy* [Internet]. University of Washington. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1131/?report=classic [Accessed 19 June 2018].

Minoche, A. E., Horvat, C. et al (2018). 'Genome sequencing as a first-line genetic test in familial dilated cardiomyopathy', *Genet Med*.

Nugent, A. W., Daubeney, P. E. et al (2003). 'The epidemiology of childhood cardiomyopathy in Australia', *N Engl J Med,* 348 (17), 1639-1646.

Rubattu, S., Bozzao, C. et al (2016). 'A Next-Generation Sequencing Approach to Identify Gene Mutations in Early- and Late-Onset Hypertrophic Cardiomyopathy Patients of an Italian Cohort', *Int J Mol Sci,* 17 (8).

Semsarian, C. (2011). 'Guidelines for the diagnosis and management of hypertrophic cardiomyopathy', *Heart Lung Circ,* 20 (11), 688-690.

Semsarian, C., Ingles, J. et al (2015). 'New perspectives on the prevalence of hypertrophic cardiomyopathy', *J Am Coll Cardiol,* 65 (12), 1249-1254.

Sousa, A., Canedo, P. et al (2019). 'Molecular characterization of Portuguese patients with dilated cardiomyopathy', *Rev Port Cardiol,* 38 (2), 129-139.

Szabadosova, V., Boronova, I. et al (2018). 'Analysis of selected genes associated with cardiomyopathy by next-generation sequencing', *J Clin Lab Anal,* 32 (2).

Towbin, J. A., McKenna, W. J. et al (2019). '2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy', *Heart Rhythm*.

van Velzen, H. G., Schinkel, A. F. L. et al (2018). 'Outcomes of Contemporary Family Screening in Hypertrophic Cardiomyopathy', *Circ Genom Precis Med,* 11 (4), e001896.

Waldmuller, S., Schroeder, C. et al (2015). 'Targeted 46-gene and clinical exome sequencing for mutations causing cardiomyopathies', *Mol Cell Probes,* 29 (5), 308-314.