# NSW HEARTS:

# THE NSW INHERITED CARDIOMYOPATHY COHORT STUDY

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|---|---|
| **Sponsor** | Garvan Institute of Medical Research<br>384 Victoria St<br>Darlinghurst NSW 2010<br>Australia |
| **Protocol version and date** | Version 6, 15 March 2022 |
| **Coordinating Principal Investigator** | A/Prof Jodie Ingles |

### Document history

| Version number (date) | Summary of key changes |
|---|---|
| 3 (24 December 2020) | Revisions following HREC review of ethics application. |
| 4 (2 August 2021) | Amendment to reflect relocation of Clinical Genomics Laboratory, refinements in the study design and change in circumstances of cardiac imaging facilities. |
| 5 (8 December 2021) | Amendment to further detail contact with participants, use of scheduling software to arrange call appointments and add online CMRI PISCF option. |
| 6 (15 March 2022) | Add new investigators; add sponsor details; and amended section 10.1 to include RedCap as a platform for data transfer. |

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## 1. Background

In the 60 years since hypertrophic cardiomyopathy (HCM) was first described as a “tumour of the heart”, our understanding of the genetics and natural history of the disease has grown (1). The first gene for HCM was reported in 1990 (2) and since then, the genetic basis of other inherited cardiomyopathies has been described. These include dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM) and left-ventricular noncompaction cardiomyopathy (LVNC). Collectively, these diseases have a combined prevalence of 1 in 500 in the general population and show marked clinical and genetic heterogeneity. The key gaps in knowledge include an incomplete understanding of the genetic aetiology of disease, overly inclusive diagnostic criteria based on crude clinical measurements, and an inability to predict poor outcomes.

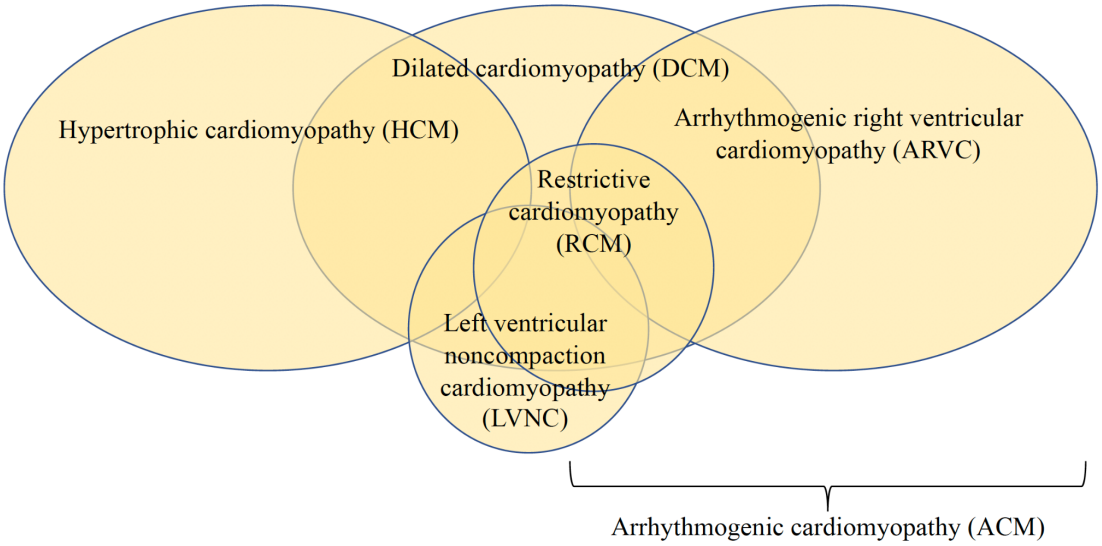


Figure 1. Inherited cardiomyopathies showing phenotype overlap

Inherited cardiomyopathies are typically inherited as an autosomal dominant trait. Clinical heterogeneity is a hallmark feature, with some patients presenting with minimal or no symptoms, while others can develop severe heart failure requiring cardiac transplantation, or sudden cardiac death. Sudden cardiac death can occur as one of the first presentations of disease. Amongst postmortem series, inherited heart diseases contribute to the majority of causes of sudden cardiac death in those aged <35 years (3), including 16% which are due to inherited cardiomyopathies.

Cardiac genetic testing is a two-step process (4). The first involves sequencing a DNA sample from an affected member of the family (proband, or index case) to identify a rare variant considered to be the cause of disease. If there is sufficient evidence the variant is causative, this can be used as

a tool to test for the presence of absence of the variant in asymptomatic relatives, allowing targeted clinical surveillance for those who are gene positive, while gene negative relatives can be released from future surveillance and worry (4, 5). For the most part, cardiac genetic testing is ordered by clinicians lacking disease specific expertise, resulting in sub-optimal and potentially harmful outcomes (6). There is growing evidence that classifying disease based on genotype and using a precision medicine-based approach to management will provide better outcomes.

Evidence to support clinical recommendations for patients with inherited cardiomyopathies is often derived from relatively small, tertiary-referred patient groups, lacking diversity. Indeed, management guidelines are based largely on expert consensus opinion rather than evidence-based recommendation (7, 8).

The investigators are international leaders in the field of inherited cardiomyopathies and improving patient care. This study will expand on previous work by collecting a comprehensive cohort of patients from a defined geographical location (NSW) and prospectively following them over time to gain critical clinical and genetic insights.

The **hypothesis** underlying these studies is that by better defining these diseases using genetics, we can provide tailored advice regarding management, treatments, prognosis and family screening.

## 2. Objectives

Specifically, the **aims** of this study are to:

(1) Comprehensively evaluate the underlying genetic architecture of disease
(2) Assess disease expression, natural history and clinical course of inherited cardiomyopathies, including genotype sub-groups and poorly represented populations
(3) Evaluate the non-familial HCM sub-group and develop family screening recommendations
(4) Describe patterns of care and burden of disease.

## 3. Study investigators

- A/Prof Jodie Ingles, Principal Investigator, Program Head and Cardiac Genetic Counsellor, Clinical Genomics Laboratory, Centre for Population Genomics (CPG), Garvan Institute of Medical Research & Centenary Institute
- Prof Christopher Semsarian, Cardiologist, Royal Prince Alfred Hospital (RPAH) & The University of Sydney
- Prof Diane Fatkin, Molecular Cardiologist, Victor Chang Cardiac Research Institute (VCCRI)
- A/Prof Saurabh Kumar, Cardiologist, Westmead Clinical School
- Prof Tim Driscoll, Epidemiologist, Sydney School of Public Health
- Dr Richard Bagnall, Senior Research Officer, Centenary Institute
- Dr Daniel MacArthur, Director of Centre for Population Genomics, Garvan Institute of Medical Research and the Murdoch Children's Research Institute
- Dr Jo Sweeting, Research Officer, CPG, Garvan Institute of Medical Research
- A/Prof Rajesh Puranik, Cardiologist, RPAH
- A/Prof Andrew Jabbour, Cardiologist, St Vincent's Hospital (SVH) & VCCRI
- Dr Cassia Iglesias, PhD Candidate and Cardiologist, VCCRI
- Dr Jim Pouliopoulos, Senior Postdoctoral Scientist, VCCRI & SVH
- Prof Martin Ugander, Professor and Director of Cardiac Imaging, The University of Sydney & Sydney Clinical Imaging Network (SCIN)
- A/Prof Ray Sy, Cardiologist, Concord Hospital
- Ms Felicity Leslie, Research Assistant, CPG, Garvan Institute of Medical Research
- Ms Sophie Hespe, MPhil Candidate, CPG, Garvan Institute of Medical Research
- Ms Alexandra Butters, Research Assistant and PhD Candidate, CPG, Garvan Institute of Medical Research
- Ms Judy Do, Junior Project Officer, CPG, Garvan Institute of Medical Research
- Ms Jaye Brown, Research Assistant, CPG, Garvan Institute of Medical Research
- Ms Laura Yeates, Genetic Counsellor and PhD Candidate, CPG, Garvan Institute of Medical Research & Centenary Institute
- Ms Neesha Krishnan, Research Assistant, CPG, Garvan Institute of Medical Research
- Mr Fergus Stafford, Research Assistant, CPG, Garvan Institute of Medical Research
- Ms Ebony Richardson, Research Assistant and Research Associate Genetic Counsellor, CPG, Garvan Institute of Medical Research
- Dr Renee Johnson, Genetic Counsellor, VCCRI
- Dr Charlotte Burns, Genetic Counsellor, Centenary Institute
- Ms Natalie Nowak, Genetic Counsellor, Centenary Institute

- Dr Belinda Gray, Cardiologist, RPAH and The University of Sydney
- Dr Julia Isbister, Cardiologist and PhD Candidate, Centenary Institute

## 4. Governance


Figure 2. Governance structure and working group (WG) composition

## 5. Study design

### 5.1 Type of study

This is a prospective cohort study with capacity to access retrospective medical data of enrolled patients. Study outcomes will be assessed prospectively depending on the specific study aim.

### 5.2 Number of participants

3000

### 5.3 Duration of study

Recruitment will be undertaken in 2021-2022. If recruitment is impacted significantly by COVID-19, we will consider expanding the recruitment period for an additional year, i.e. 2021-2023.

**Follow up will continue for 10 years subject to ongoing ethical approval.**

## 6. Study sites

- Royal Prince Alfred Hospital
- Garvan Institute of Medical Research
- St Vincent's Hospital
- Victor Chang Cardiac Research Institute
- Westmead Hospital
- Centenary Institute

## 7. Eligibility

Inclusion criteria:

(1) Diagnosis of an inherited cardiomyopathy that satisfies the criteria in Table 1 (below)
(2) Resident in NSW at time of consent
(3) Aged 17 years and older

Clinical diagnoses included in the eligibility criteria are shown below (Table 1). Where there is a question about the eligibility of a potential participant, the decision will be referred to the Clinical and Eligibility Working Group for adjudication. The eligibility criteria will be included as a study document to clinicians involved in recruitment (Table 1).

Table 1. Inherited cardiomyopathies eligibility criteria

| Phenotype | Abbreviation | Eligibility criteria |
|---|---|---|
| Hypertrophic cardiomyopathy | HCM | LV wall thickness of ≥15mm in one or more myocardial segments and where other causes have been excluded |
| Dilated cardiomyopathy | DCM | Dilated cardiomyopathy (LVEDD % predicted >112% + LVEF <45% where other causes have been excluded, as well as one of the following:<br>Positive family history<br>Diagnosed <50 years |
| Arrhythmogenic cardiomyopathy | ACM/ARVC | Ventricular dysfunction not explained by other causes, with evidence of arrhythmia (conduction disease, atrial or ventricular arrhythmias),<br>OR meets modified 2010 Taskforce Criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) |
| Left ventricular noncompaction | LVNC | >2.3:1 ratio of non-compacted to compacted myocardium in systole, as well as one of the following:<br>Positive family history<br>Impaired function on imaging<br>Conduction disease |
| Restrictive cardiomyopathy | RCM | Primary myocardial disease with LV diastolic dysfunction with normal/near normal wall thickness and systolic function |
| Undiagnosed but familial cardiomyopathy | - | Cardiomyopathy not meeting diagnostic criteria, as well as one of the following:<br>Positive family history<br>Young onset (<20 years)<br>Severe outcomes (resuscitated cardiac arrest or cardiac transplant <30 years) |
| Genetically confirmed heritable cardiomyopathy not already eligible | - | Genetically confirmed genocopy, for example: Danon disease, PRKAG2 cardiomyopathy, Fabry disease (cardiac form), Noonan syndrome, mitochondrial cardiomyopathy |
| Asymptomatic gene carrier | - | Family member who is genetically confirmed to have the gene variant causative of one of the above-listed conditions but has no clinical evidence of disease. |

## 8. Recruitment

The cohort will be drawn from multiple sources (as per Table 2).

Table 2. Recruitment sources

| NAME | LOCATION | MODE | STUDY DOCUMENTS |
|---|---|---|---|
| TERTIARY HOSPITAL CLINICS | | | |
| HCM and Genetic Heart Disease clinics | Royal Prince Alfred Hospital, Camperdown | Face to face | Recruitment pack |
| HCM and Genetic Heart Disease clinics | Royal Prince Alfred Hospital, Camperdown | Mail out | Recruitment pack |
| Inherited Cardiomyopathy Clinics | St Vincent's Hospital | Face to face | Recruitment pack |
| Inherited Arrhythmia Clinics | Westmead Hospital | Face to face | Recruitment pack |
| PROFESSIONAL SOCIETIES & PATIENT SUPPORT GROUPS | | | |
| Cardiomyopathy Association of Australia | Email newsletter | Online | Invitation letter<br>Participant flyer<br>Social media posts |
| Cardiac Society of Australia and New Zealand (CSANZ) | Email newsletter | Online | Society advert |
| REGISTRY | | | |
| AGHDR | N/A | Mail out | Recruitment pack |
| AGHDR | N/A | Facebook | Social media posts |
| OTHER CLINICS | | | |
| Cardiologists | NSW | Mail out | Letter to health professionals<br>Recruitment pack |

| | | | |
|---|---|---|---|
| Clinical Genetics services | NSW | Mail out | Letter to health professionals<br>Recruitment pack |
| MISCELLANEOUS | | | |
| RPAH Patient Day | RPAH | Face to face | Recruitment pack |
| Facebook | Online | Online | Social media posts |

### 8.1 Recruitment through clinics and AGHD Registry

All new and existing patients presenting to clinics (including HCM and Genetic Heart Disease clinics at Royal Prince Alfred Hospital, Inherited Cardiomyopathy Clinics at St Vincent's Hospital and Arrhythmia Clinics at Westmead Hospital) or enrolling in the Australian Genetic Heart Disease (AGHD) Registry, who reside in NSW will be invited to participate.

Those attending the above-mentioned outpatient clinics who are eligible, will be provided with information about the research study by a member of their clinic team (Figure 3). Those who indicate interest will be given a "Recruitment Pack". All subsequent contact about the research study will be with a member of the research team.

The recruitment pack includes:

- Invitation letter
- Participant Information Sheet
- Consent form
- Participant withdrawal of consent form

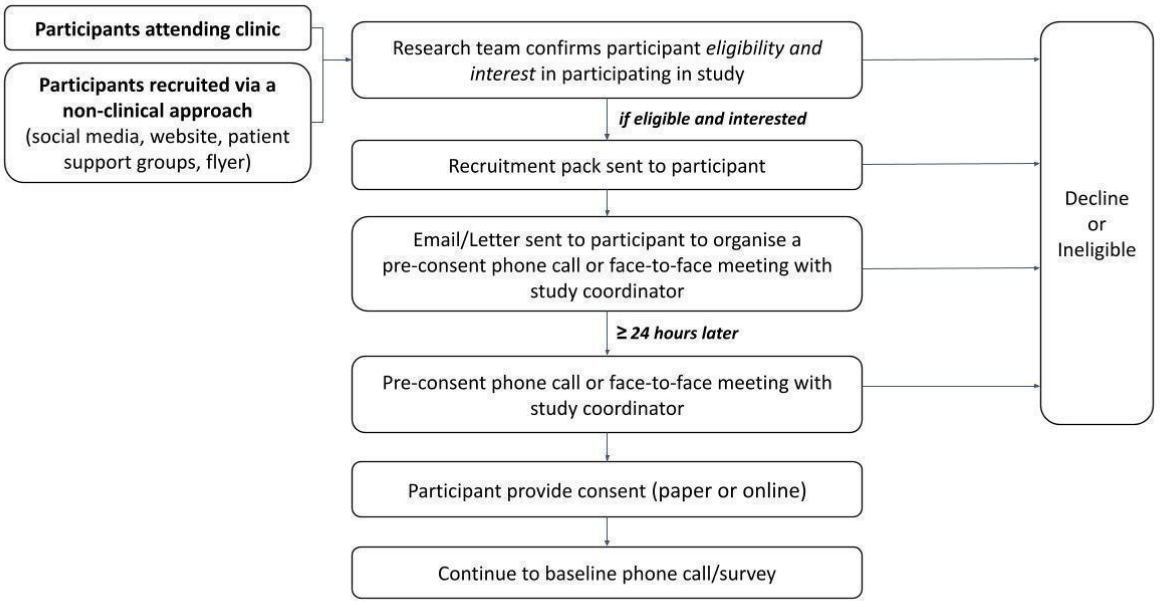


Figure 3. Participant Recruitment Flow

## 8.2 Recruitment through study advertisements

Recruitment will be undertaken through professional societies (for example Cardiac Society of Australia and New Zealand, and the Human Genetic Society of Australasia; Society advert), and patient support groups (such as the Cardiomyopathy Association of Australia; Support group advert). Social media posts (Facebook) will be provided to the relevant societies and Registry, advertising the study and providing an email to contact for more information or to enrol (Figure 3).

Targeted recruitment strategies will be employed to accelerate recruitment of patients from other avenues, such as cardiology departments, cardiologists in private practice and clinical genetics units throughout NSW. We will also use social media to promote awareness of the cohort study directly to the public, including developing a simple Facebook page for the cohort study (*Social media posts*).

Table 3. Expected recruitment to the cohort study

| | Known patients | New patients | Total |
|---|---|---|---|
| HCM | 900 | 900 | 1800 |
| DCM | 400 | 400 | 800 |
| ARVC/ACM | 100 | 100 | 200 |
| All other groups | 100 | 100 | 200 |
| Total | 1500 | 1500 | 3000 |

## 9. Informed consent and withdrawal of consent

### 9.1 Informed consent

All potential participants will receive the Participant Information Sheet and Consent Form in person, by post or via email (*Online Consent Email*). An email (or letter) will also be sent to participants to organise a phone call or face to face meeting with a study coordinator to discuss the study (*Invitation letter/email*) and its requirements prior to consent taking place (*Pre-consent call script*). Phone calls could mean landline phone calls or zoom calls (https://zoom.us/) which may be audio or video calls. There will be no recording of the phone calls. For any phone calls with participants, we will use a scheduling software such as Calendly (https://calendly.com/) to arrange the appointment. Participants will only need to enter their name and phone number. This conversation will be an opportunity to ensure the eligibility of those people who have made direct contact having seen advertisements for the study.

There will always be at least 24 hours between receipt of a Participant Information Sheet and Consent Form and the phone call or meeting.

To enrol, participants are required to provide consent by either: completing the online consent form (*Online PISCF*), which has been developed on the Garvan RedCap, mailing a physical signed consent form, or scanning and emailing the consent form. It will always be made clear that participation in this study is voluntary and will have no impact on their clinical care.

As a future direction, we are interested in offering the existing cohort the option to move from this static model of consent to a dynamic consenting model. This platform is under development and will be submitted by way of a protocol amendment for review.

### 9.2 Withdrawal of consent

Participants are free to withdraw from the study at any time upon their request. Withdrawing from the study will not affect their relationship with, or care by, the hospital and affiliated healthcare professionals. Participants will need to complete the Participant Withdrawal of Consent Form (as received together with the Participant Information and Consent Form) and return it to A/Prof Jodie Ingles.

There will be different levels of withdrawal of consent options available to participants: (i) no further contact only or (ii) no further contact and no further use of data. If participants choose to withdraw with no further contact only, they will not be contacted again in the future; however, they agree to their samples and previously collected data to remain part of the study. If participants choose to withdraw with no further use of data, then their samples will be destroyed, their data deleted, and will not be made available for any future uses. Participants will be informed that it might not be possible to trace all distributed sample remnants, that some information would be archived for audit purposes, and that it would not be possible to remove information from analyses already undertaken. These details are outlined in the Participant Information Sheet and Consent Form.

## 10. Methods and data collection

The cohort study will form a resource that will allow us to answer many important research questions specifically relating to the aims described in Section 2 of this protocol.

Table 4. Schedule of assessments

| | T = 0 | T = 0 – 3 months | T < 3 years | Annually from date of consent | Every 3 years from date of consent |
|---|---|---|---|---|---|
| Informed consent | X | | | | |
| Baseline phone call | | X | | | |
| Clinical survey | | X | | | X |
| Environmental factors survey | | X | | | X |
| Health Status survey | | X | | | X |
| Follow-up clinical survey | | | | X | |
| Blood sample | | X | | | |
| Sleep apnoea monitor | | | X | | |
| Charlson Comorbidity index | | X | | | |
| CMR Imaging | | | X | | |
| Follow up phone call | | | | X | |

### 10.1 Baseline surveys, phone call and medical record requests

Following consent, an email containing unique RedCap survey links will be sent to participants by the research team (*Email to distribute surveys*). Surveys administered will include the Baseline clinical survey, Environmental factors survey and Health status survey. A phone call will be made to participants following the completion of these surveys. Areas requiring clarification or left missing will be clarified during this baseline post-consent phone call (*Baseline phone call script*). This document (*Baseline phone call script*) includes a data sheet which is not for circulation to participants or doctors, but to guide study investigators as to the information required.

A request letter (*Fax request letter*) will also be sent to the participant's regular cardiologist, clinical geneticist and/or general practitioner to request for medical records. The healthcare professional/ clinical team will provide the clinical information by either emailing, posting or faxing directly to the requesting study coordinator, or by uploading the files via the secure Garvan RedCap survey (*RedCap Clinical file upload*), which will then be imported to the NSW HEARTS database. Clinical information requested would include cardiac investigation reports performed as part of routine clinical care, including waist and neck circumference, body mass index, a digital ECG, echocardiogram reports, 24-hour ambulatory Holter monitoring, previous CMR reports, and exercise tests reports. Where available, we may request the DICOM image files for previously performed CMR imaging. If a participant dies during the follow up period of the study, a death certificate or post mortem report will be requested.

### 10.2 Surveys

We will longitudinally assess clinical course and outcomes of patients to (1) Describe the clinical profile of these groups and, (2) Determine whether minority or under-represented groups bear a disproportionate burden of poor health outcomes. A number of demographic variables will be collected at baseline with a Clinical survey and a Health status Survey. Variables will include ethnic background, country of birth, country where the participant spent most of their childhood, language spoken at home, whether a translator is required, current residential postcode, sex and gender.

a. Clinical survey: will be administered online within a month of consent and every 3 years until close of the study. It will take approximately 15-20 mins to complete.
b. Environmental factors survey: will be administered online within three months of consent and every 3 years until close of the study. It will take approximately 15-20 mins to complete.

c. Health status survey: will be administered online within 3 months of consent and every 3 years until close of the study. It will take approximately 15-20 mins to complete.
d. Follow up clinical survey: will be administered online annually from the 1-year time-point from consent. It will take approximately 15-20 mins to complete. The follow up phone call listed in the schedule of assessments will only be made if there has been a significant clinical outcome listed in the follow up clinical survey completed.

Survey reminders: Participants are given 3 months to complete the surveys distributed. If the survey is not completed after 2 weeks, participants will be sent an email reminder, including an offer to contact the genetic counsellor if they require assistance (*Email reminder surveys 14 days*). If the survey is still not completed 2 weeks after the first reminder, a second email reminder and offer for assistance will be sent (*Email reminder surveys 28 days*). If not complete by this point, the study coordinator will contact the participant to determine their interest in continuing in the study (*Survey reminder phone script)*.

### 10.3 Blood sample

Following consent, a pathology request form, developed by NSW Health, will be sent to the participant for blood collection, including local sites across NSW. The blood sample required is 20 mls. Storage of DNA, plasma and serum will be at the NSW Health Statewide Biobank and, from time to time, at the location of the sequencing provider(s). Research-focused genomic sequencing, such as whole-genome sequencing, will be performed (as per section 10.4).

### 10.4 Genetic analysis

All participants will undergo research-based genome sequencing during the study period. Samples will be submitted to a suitably accredited sequencing provider for genomic sequencing. The samples will be de-identified and the identifiers will not be shared with the sequencing provider. The samples will be stored by the sequencing facility for the duration of the sequencing process. These sequencing providers may include the Kinghorn Centre for Clinical Genomics (KCCG) at the Garvan Institute of Medical Research (Garvan), the Garvan-Weizmann Centre for Cellular Genomics (GWCCG) at Garvan, the Victorian Clinical Genetics Service (VCGS) at the Murdoch Children's Research Institute (MCRI), and/or the Center for Mendelian Genomics (CMG) at the Broad Institute. We will analyse the genomic and other de-identified data available for the cases with the aim of identifying novel disease-causing genes and genetic diagnoses, facilitated by analytical platforms such as seqr. This will involve triangulation with relevant external datasets pertinent to understanding the likely functional impact of individual variants. The data will also be

used to test newly developed methods for analysis, including the incorporation of new external reference data sets, and the use of improved analysis algorithms.

Analysis of Tier 1 (high confidence genes) and Tier 2 (research genes) will be included as routinely performed by A/Prof Jodie Ingles' team. Variant classification will be performed according to current practice with variants in established genes relevant to the clinical diagnosis classified using the modified American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG/AMP) standards. Where required, variants will be discussed (de-identified) at our multidisciplinary pathogenicity meeting chaired by A/Prof Ingles and consensus classification (pathogenic, likely pathogenic, VUS, likely benign and benign) reached.

In those where a heritable basis is strongly suspect (i.e. positive family history, young onset, severe presentation) and a causative variant is not identified, additional efforts to identify the cause will be made such as analysis of expanded gene lists, , or genome trio analysis where the case appears to be de novo and sporadic. It is likely that participants would become candidates for other research studies with more comprehensive gene discovery ethics approval, or additional ethics amendment to cover more comprehensive approaches will be sought. Any research variants identified will be classified as per current practice in A/Prof Ingles' group and reported back to the participant and the referring cardiologist if considered clinically significant.

Clinically actionable variants unrelated to the inherited cardiomyopathy will not be actively sought, but may be identified and would be returned to the participant and their nominated healthcare professional. These variants will be reviewed by an expert panel and we will seek multidisciplinary expertise in their interpretation. In such instances, we will directly link participants with a genetic service who can perform clinical confirmation of the result. Discussion of incidental findings is also included in the Sample Biobanking section, given this is a requirement for inclusion of the sample collection in the NSW Health Statewide Biobank.

All variant classifications performed (as above) will be included as the genotype status for enrolled participants. Further, we will upload very basic and de-identified data to NCBI ClinVar, a freely accessible, public archive of variants and phenotypes (gene, variant details, number of probands, phenotype of probands, and number of informative segregations that are known).

Analysis of common variants i.e. single nucleotide polymorphisms (SNP) will be performed using the genome sequencing data generated. At present, we can use genome wide association studies to identify how common genetic variation relates to disease risk, severity and outcomes. However, this is a fast-moving field and by the time we have such data, the most effective ways we can

contribute to understanding the impact of common variants will likely have evolved significantly. Further, typically such studies require extremely large sample sizes to be informative, and we aim to contribute anonymised data to larger international efforts, as per the participant information statement and consent form regarding data sharing with international collaborators to answer important research questions.

### 10.5 Sleep apnoea monitor

ApneaLink is a take home simple to use device that measures blood oxygenation and breathing during sleep. Used clinically as a screening tool for sleep apnoea. Where an individual has an AHI >5 they will receive a phone call to complete the Stop-Bang questionnaire (5 items) which allows determination of need for referral to a sleep physician. An ApneaLink set includes clear instructions on its use, which will be posted to the participant along with a return post envelope. A zoom or phone call would be scheduled between the study coordinator and the participant on the day of use to ensure they understand how to use the equipment accurately.

### 10.6 Charlson Comorbidity Index

The Charlson Comorbidity Index is a short survey recording an individual's health conditions. The survey will be administered over the phone by the study coordinator during the baseline phone call following consent. It will take approximately 5 minutes.

### 10.7 Cardiac Magnetic Resonance (CMR) Imaging

CMR Imaging studies and analysis will be overseen by A/Prof Rajesh Puranik (RPAH) and A/Prof Andrew Jabbour (SVH). Enrolled participants will complete an *CMRI Safety Questionnaire and Consent Form*. Those participants who do not have any contraindications for CMR will be invited to undergo a research-focused scan at either the St Vincent's Hospital (Jabbour) or I-MED Radiology Network (Puranik). The scan protocol is included in the appendix (*NSW HEARTS CMR protocol*).

Participants will be provided with an additional participant information statement (*CMR participant information statement*) and consent form (*CMR consent form*) focused specifically on the benefits and risks of CMR. To provide consent, participants can either: complete the online CMR consent form (Online CMR PISCF), which has been developed on the Garvan RedCap, mail a physical signed consent form, or scan and email the consent form. We will apply novel analytic approaches to: (1) Extract high-dimensional quantitative imaging features from CMR imaging digital files; (2) Characterise associations between raw imaging features and conventional phenotypic

manifestations of disease; (3) Assess whether high-resolution image analysis can predict key clinical outcomes. Aspects of this work may form part of a larger international collaboration, in which case de-identified information about participants may be shared.

Any clinically significant findings will be interpreted by experienced cardiologists (Puranik & Jabbour) and communicated to the patient and their nominated doctor.

## 11. Longitudinal follow up

There will be longitudinal assessment of disease expression and clinical course of patients to determine whether genotype sub-groups demonstrate different expression and outcomes. We will use the comprehensive genotype data acquired in the genome sequencing. Baseline variables will be compared with follow-up data from each additional time point of data collection. Within the disease groups, there will be assessment of whether variants in specific genes give rise to varying disease expression and/or worse outcomes. In larger genotype groups, there will be assessment of whether location of the variant in the gene is associated with different clinical outcomes. Descriptive statistics will be used initially to describe the groups, then Cox regression models will be developed to show independent predictors of event-free survival. Clinical outcomes to be analysed include; atrial fibrillation, ventricular arrhythmias, severe heart failure and all-cause mortality.

## 12. Data linkage

Informed consent will include permission to link the cohort data to routinely collected datasets. We will provide the Centre for Health Record Linkage (CHeReL) with our cohort dataset, to be linked to the NSW Admitted Patient Collection (NSW APDC), NSW Emergency Department Data Collection (NSW EDDC), and NSW Mortality dataset. Ethics approval will be sought from NSW Population & Health Services Research Ethics Committee (PHSREC), followed by custodian approval for the various datasets, prior to this work being performed. We have previous experience linking our Australian Genetic Heart Disease Registry population to these NSW Health linked datasets.

We will aim to examine associations between patterns of care and serious outcomes such as death, implantation of cardioverter defibrillator and heart failure requiring cardiac transplantation. For those with a hospital admission or ED presentation, we will report the reason for admission/presentation, frequency of admission/presentations, length of stay per episode of care and the number and type of procedures involved in care. We will examine whether patient demographic factors such as age, relative sociodemographic disadvantage, geographic

remoteness, patient education level or family history of cardiac events are associated with differing patterns of care or increased interactions with the health care system.

## 13. Data storage

### 13.1 Clinical data

All patient data will be stored within the NSW HEARTS: The NSW Inherited Cardiomyopathy Cohort Study Filemaker Pro database (requiring password-protected computer, access limited to approved investigators), which will exist on a secure server, developed, managed and housed at the Garvan Institute of Medical Research, Sydney. Filemaker Pro was chosen as the database for storage of information given our previous extensive experience with this program and using it securely for other studies, and the ability to create a functional relational database. The database is currently being finalised and will be ready by mid-2021.

### 13.2 Survey data

Information to be obtained from participants themselves will be collected via secure Garvan Redcap surveys, which will then be imported to the NSW HEARTS database. This will include:

a. Clinical patient survey: This closely resembles the intake survey provided to participants who join the Australian Genetic Heart Disease Registry and will gather clinical and demographic information.
b. Health status survey: We will record information about health-related quality of life using the Medical Outcomes Short Form-12, the Depression Anxiety and Stress Scale and the Health Literacy Questionnaire.
c. Environmental factors survey: A comprehensive survey comprising questions about non-genetic factors that may influence their disease severity and outcomes. This includes the International Physical Activity Questionnaire.

### 13.3 Genomic data

All genomic data will be stored on infrastructure developed and managed by the Garvan Institute of Medical Research (Garvan) in a cloud computing and storage environment such as the Google Cloud Platform (GCP). The GCP is an ISO/IEC 27001 compliant cloud infrastructure platform (https://cloud.google.com/security/compliance) that has also undergone third-party attestation and follows the European Union (EU) Data Protection Directive. All data in transit and at rest will be encrypted. The investigators listed in this protocol will have access to the data through GCP. These

investigators will access the GCP by obtaining an authenticated Google account. The Google Access Control List (ACL, https://cloud.google.com/storage/docs/access-control/lists) will be used to facilitate the authorisation of user permissions. The ACL maintains a complete audit trail history of permissions authorisation, removal, and delegation that can be reviewed at any time. No third party will be given access without written permission from the data owners. The data collected and generated through this study will be analysed using best practice analytical tools and techniques including cloud-based analytical platforms such as seqr.

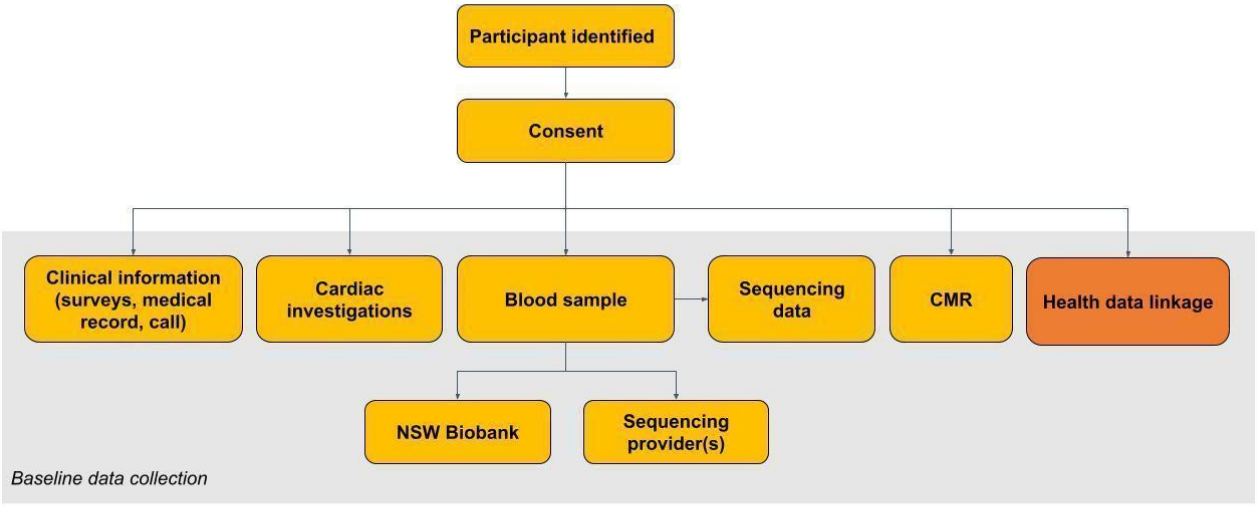


Figure 4. An overview of the different datasets that will be generated from NSW HEARTS

## 14. Sample Biobanking

Biological samples will be stored at the Garvan Institute of Medical Research and the NSW Health Statewide Biobank (henceforth referred to as the NSW Biobank) (https://biobank.health.nsw.gov.au/). The Biobank was launched in 2018 and it supports the collection, processing and storage of biospecimens for researchers. The facility is located in the Professor Marie Bashir Centre at 67-73 Missenden Road, Camperdown, NSW, 2050.

Following informed consent, participants will be asked to attend one of 200 designated collection centres across NSW. These are NSW Health Pathology affiliated centres and therefore have vast experience with phlebotomy procedures, as well as existing agreements with the NSW Biobank regarding specimen collection and expedient courier networks.

Following receipt of the sample, the NSW Biobank will remove personal information from the sample and assign a unique code for each participant. Samples will be processed according to purpose i.e. aliquots for biochemistry and/or DNA extracted for sequencing. Samples will be submitted to a suitably accredited sequencing provider, such as the Kinghorn Centre for Clinical Genomics (KCCG) at the Garvan Institute of Medical Research (Garvan), for genomic sequencing such as whole-genome sequencing (WGS).

We will store DNA, plasma and serum. Specimens collected for the study will be stored at NSW Biobank for future use and, from time to time, at the location of the sequencing provider(s) such as the Garvan Institute of Medical Research. The NSW Biobank has a rigorous governance procedure and has access request forms available for collaborators to use if they wish to obtain these biospecimens.

As this study involves sample biobanking, it requires participants to also consent to receiving any incidental findings that may be found during the course of gene analysis. In the event where an incidental finding is confirmed to be clinically significant and clinically actionable, we will notify participants (as per section 10.4).

The biobank protocol (*NSW HEARTS Biobank protocol*) and ethically defensible plan (*NSW HEARTS Biobank Ethically Defensible plan*) are included in the appendix.

## 15. Study database and hardcopy data

Dedicated study coordinators will recruit participants and perform data entry.

The security of the database will be paramount. To ensure security of the stored data, only a limited number of individuals at each site will have an access code to use the database.

The Filemaker Pro database will be housed on Pandora, a secure server at the Garvan Institute of Medical Research, Sydney. Hard copy data, such as consent forms, echocardiogram reports and pedigrees, will be stored at the site the patient was recruited from in a key-locked filing cabinet. Any other paper forms from participants recruited via other means (i.e. recruitment via study advertisements) will be stored at the central study site (the Garvan Institute of Medical Research, Sydney) in a key-locked filing cabinet. Copies of all consent forms will be digitally saved onto the database and a de-identified copy of the pedigree will be uploaded to the database.

We will collect individually identifiable information from participants, however we will use individually identifiable, re-identifiable and non-identifiable information. Sensitive and health

information will be collected from the participant and entered into the secure study database. Data used will include identifiable (especially where we need to link to follow-up data), re-identifiable (where we will code all participants and store data for analysis) and non-identifiable (where we share minimal datasets with external collaborators for a specific purpose).

Study data will be collected and analysed by A/Prof Jodie Ingles and the study team, including Ms Alexandra Butters as part of the requirements for a PhD degree and by Ms Sophie Hespe as part of the requirements for a research degree. Both students will conduct their research under the supervision of A/Prof Jodie Ingles. They will have access to data collected as ethics approved researchers on this study.

## 16. Confidentiality

Confidentiality of the information held by the NSW HEARTS database is paramount.

The identifiable clinical patient data will be securely stored in a database and only investigators who are authorised and directly involved in the Study will be given password access to the Study database. Strict protocols will be followed at each site, including hard copy data being stored in secure key-locked filing cabinets. Each site will follow their governance policy for releasing information, and in general will require signed consent from the person the information relates to.

If the participant requests to see the information held about themselves, this is permitted.

As outlined in the NHMRC guidelines, if a registrant is deceased his/her information may be released with the authorisation of the spouse/next of kin.

In accordance with the NSW State Records Act and the recommendations of the Australian Code for the Responsible Conduct of Research, study records will be maintained for at least 15 years post the completion of the study.

## 17. Benefits and risks of participation

Blood collection involves some discomfort at the site from which the blood is taken. There is also a risk of some minor bruising at the site, which may last one to two days. Most other tests that we will perform are those performed routinely. While we intend that this research study furthers medical knowledge about inherited cardiomyopathies and may improve treatment in the future, there may be no direct benefit to the participants themselves.

## 18. Education, raising awareness and engagement of participants over the long term

We are in the process of creating a website that will be an informative resource for helping to identify participants, provide reliable information to them and their families and educate health professionals about inherited cardiomyopathies. We will include information sheets (adopted from the Australian Genetic Heart Disease Registry website) and aim to provide a regular newsletter to keep participants up to date about the progress and any research outcomes from the study. We strongly believe such a study will heavily rely on the motivation and participation of our patients, therefore additional effort is needed to keep them engaged.

## 19. Further use of samples and data

### 19.1 Data

The CPG is committed to broad data availability to encourage collaborative discovery. After a period of time (to be agreed with each investigator), de-identified genomic data, and phenotype and participant variant/gene information, will be uploaded to international genomic reference databases, to the degree that this sharing is compatible with the participant informed consent.

### 19.2 Samples

Following completion of any biochemistry analyses and/or genome sequencing, all remaining samples and product will be stored at the NSW Biobank facility, indefinitely (unless a participant wishes to withdraw from the study) for future use. These samples will remain in the possession of the Principal Investigator (A/Prof Jodie Ingles) and will be identified using an identification number. The code linking the sample identification number to information that identifies a participant will be securely stored in the database.

The remaining samples may be made available, in a de-identified manner, for subsequent, unspecified health and medical research projects as approved by a Human Research Ethics Committee and the NSW HEARTS Access Committee.

The NSW HEARTS Access Committee will consist of the study lead (A/Prof Jodie Ingles), other NSW HEARTS investigators, a consumer and a Biobank representative. All ethics approved requests to the Biobank for access to the NSW HEARTS collection will be forwarded to the Access committee for approval, prior to release of any specimens.

### 19.3 External requests

NSW HEARTS data will be made available for use by research groups at a later date. This will be possible in two ways:

(1) External researchers wishing to access this dataset must make a preliminary application to the study lead (A/Prof Jodie Ingles) to discuss feasibility of the study. If preliminary approval is granted, then they will then need to seek appropriate Human Research Ethics Committee (HREC) approval. Once HREC approval is granted, the research group will make a full application to the advisory committee. Only when all approvals have been granted will secondary use data and/or samples be shared. Excess sample materials obtained as part of this study, de-identified data generated as part of this study, and limited phenotype information may be provided to requesting researchers. No personal identifiable information will be shared with external researchers. Investigators with whom we share materials must also agree to never attempt to access identifiable health/medical information or attempt to identify the subject(s) who provided the sample.
(2) As above, however, where a researcher wishes to approach the NSW HEARTS cohort for additional information, this request will be made by us on behalf of the researcher. Therefore, no personal information is provided to the researcher and if participants wish to participate, they can connect with the researcher.

This model of access to study data closely aligns with existing methods used by the Australian Genetic Heart Disease Registry.

## 20. Funding arrangements

The NSW Cardiomyopathy Study is currently funded by NHMRC Clinical Trials and Cohort Studies Grant (CIA: J Ingles, APP1186500, $2,173,950, 2020-2024), a NSW Ministry of Health Biospecimens Collection Grant (CIA: J Ingles, $100,000, 2021-2025) and previously by a NSW Health EMCR Fellowship, Cardiovascular Health (CIA: J Ingles, $250 000, 2018-2020).

## 21. Outcomes and significance

The study will comprehensively address current gaps in clinical and genetic basis of inherited cardiomyopathies. We will leverage unique national and international datasets. By aligning with international organisations, we can ensure our study outcomes are world class and rapidly translated to clinical care. The outcomes of this study are highly significant, and include:

- The genetic analyses proposed have potential to solve the genetic basis of disease for many families and will be directly translated to improved classification criteria
- Determination of polygenic disease risk will lead to a major shift in the field, unlike other cross-sectional studies we will have future opportunity to assess long-term outcomes.
- Use of a cohort to address clinical course and outcomes will remove some of the inherent biases of observational, cross-sectional studies.
- By understanding disease by genotype sub-groups, we can provide an evidence-base for tailored clinical management, which will have a major impact in the field.
- Seek to understand this new paradigm of non-familial disease and allow a precision-based approach to care of families. By better targeting advice and resources we can improve clinical outcomes and screening advice for family members, and ultimately reduce healthcare costs.
- Evaluate how patients with inherited cardiomyopathies interact with the healthcare system, especially those from under-represented patient sub-groups, allowing a deeper appreciation of the real-world burden of inherited cardiomyopathies.
- Provide an invaluable resource for numerous other research projects using the existing data sets, as well as opportunity for future data collection waves, extending follow-up even further.
- Very significant findings resulting in high impact publications.

## 22. References


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## 23. Appendices

(1) NSW Hearts CMR protocol, v2 15/02/2022

(2) NSW Hearts Biobank Lab Processing Instructions, v1 17/11/2020

(3) NSW Hearts Biobank Ethically Defensible Plan, v1 17/11/2020

(4) Biobank feasibility letter, v1 17/11/2020

(5) Centre for Health record linkage feasibility letter, v1 17/11/2020