UNIVERSITY of TASMANIA
MENZIES
Institute for Medical Research

EDCAD-PMS Participant Information & Consent Form

Title	**Early detection of coronary artery disease by polygenic and metabolic risk scoring (EDCAD-PMS): an opportunity to start secondary prevention without a coronary event**
Principal Investigator	**Prof James Sharman**

1. Introduction

You are invited to take part in the "EDCAD-PMS" study project. You have been selected because you have a friend or family member with coronary heart disease. This research project is aiming to see whether genetic risk scores can improve patient selection for primary prevention strategies like coronary imaging or cholesterol reduction.

This Participant Information & Consent Form (PICF) tells you about the research project. It explains the tests and research involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read;
- Consent to take part in the research project;
- Consent to the tests and research described;
- Consent to the use of your personal and health information as described.

You will be given a copy of this PICF to keep.

2. What is the purpose of this research?

Coronary artery disease (CAD) is a major cause of sickness and death in Australia. The current approach to preventing its consequences (heart attacks and angina) is to determine the level of risk based on blood pressure, diabetes etc, and start treatment in those at high risk. Statins are a class of drugs often prescribed by doctors to help lower cholesterol levels in the blood. By lowering the levels, they help prevent heart attacks and stroke.

Traditional risk factors only allow us to identify some people at risk, and therefore we are missing some of those who need early treatment to prevent a heart attack/stroke and potentially unnecessarily treating others. We therefore need better ways of identifying those who would benefit from treatment. We are trying to improve the prediction process to better identify those who may benefit from treatment.

Our genes contain the instructions for how our body works, and this can be thought of as a book. While each of us have a very similar book of instructions or set of genes, there are some differences between us that can affect the way in which our body works. Sometimes these changes mean some of us are more likely to develop certain types of diseases. These differences between individuals are referred to as genetic variants. For CAD there are thought to be many genetic changes that may be associated with increased risk of having a serious cardiac event. Measurement of the many genetic changes associated

with a disease, is called a polygenetic risk score (PRS). We would like to examine your genes to see if the genetic changes that are associated with CAD are also associated with coronary calcium and who are most likely to benefit from medication such as statins.

Another way of measuring genetic and environmental effects is to measure metabolic markers. These are chemical signals that define how the chemical processes in the body are working. They can be combined with a metabolic risk score (MRS). We will also do this in this study.

To perform the genetic risk score, we would like to collect a blood sample for genetic and metabolic analysis, as well as ask you to have a standard "CAT" scan (CT) to identify if you have coronary calcification (a build up of calcium in the heart's arteries). If you have calcification, we will also ask you to undertake a CT coronary angiogram (which involves injection of a contrast dye). We are trying to find out if there is a relationship between genetic and metabolic changes and the presence coronary artery disease identified on CT.

Our main aims for this study are to identify whether:

- PRS and MRS can predict the presence of coronary calcium
- Knowledge of the PRS result is better or worse than knowledge of the CT scan result in guiding people to reduce their risk (by changing lifestyle and taking medications)

This research is being conducted at the Menzies Institute for Medical Research and the Baker Heart and Diabetes Institute and, together with the Australian Genomic Research Facility.

3. Why have I been invited to participate in the study?

You have close contact with a family member or friend who has CAD – as a result, we think you will be interested to engage with this trial.

4. What does participation in this research involve?

Participant Information & Consent Form (PICF)
If you decide to participate in this study, you will be asked to sign the PICF. Before we perform any assessments you will have an opportunity to read this PICF and ask our experienced research staff any questions in relation to this study.

Clinical review and questionnaires
You will be asked questions about your past medical history and we will ask you to complete a number of questionnaires about your current wellbeing, activity level, health status and need for medical resources.

Coronary CT scan
All participants in this study will undertake an X-ray (CT) scan to obtain detailed images of the heart and arteries and to detect any calcium at baseline**. Some people will have very low levels of calcium (no treatment is warranted) and others will have very high levels (treatment is needed). If you fall into either of these two categories, you will not be eligible for the study. If your calcium levels are found to be high, you will be referred for appropriate treatment**. People with scores in between will be suitable for the study and will undergo a coronary CT angiogram. This is a test based on X-ray dye administered through a small butterfly needle placed in a vein of the arm that shows any narrowing in the coronary arteries. Again, any subjects with a serious narrowing will be excluded as treatment is needed.

If plaque is detected during the coronary CT angiogram we will suggest that you commence a statin under the guidance of your GP.

Both scans are normally performed in the one appointment (approximately 1-2 hours). You will be required to fast from food and fluids for two hours before your scheduled appointment. Prior to your appointment we will provide you with a prescription for metoprolol 50mg (or diltiazem 120 mg tablets if you cannot take metoprolol) – these medications are used to lower your heart rate. They are both widely-used, safe and well-tolerated generic medications that are used in "apparently healthy" people with high blood pressure and other situations. By taking this medication the day before and the morning of your scan appointment we are able to achieve the best quality images during your scan.

DNA collection for analysis and further information
We are seeking a standard venous blood sample for this analysis.

Timing of study measures

Study procedure	**Baseline**	**12 months**
Informed consent	X	
Clinical review - Medical history - Clinical examination - Medication adherence - Physical activity levels - Sociodemographic factors - Comorbidities	X	X
Blood test	X	X
CT imaging	CCS/CTCA	
DNA testing	X	
Metabolic score	X	
Genomic risk score calculation	X	
Medication compliance		X
Questionnaires • Resource use questionnaire • Assessment of quality of life (AqoL-4D) • Charleston comorbidity index • Health questionnaire (5Q-5D-5L) • Simple physical activity questionnaire (SIMPAQ)	X	X
Pregnancy test (if applicable)	X	
5 year Aus risk calculation	X	X

Participants in this study will be randomised (see definition below) to either receive the genetic risk score result or the CT scan result. The aim is to identify whether one is better than the other in informing you about your risk and changing your behaviour. To measure this, we will check your adherence to medications and your cholesterol and risk levels at baseline and 12 months.

'Randomised trial':
Sometimes doctors don't know the best way of treating patients with a particular condition so comparisons need to be made between different approaches. To do this, study participants are put into groups and given different treatments, and the results are compared to see whether one treatment is better. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the doctor nor the study participant can decide which treatment the participant receives.

Results
Genetic risk scores for CAD are new tools and more research needs to be performed before we can use the score to make clinical recommendations. For the duration of the study, we will provide either the genetic score, or the CT scan results, because we want to see the relative ability to encourage adherence to treatment. Please indicate in the consent form whether in the future you would like to be contacted to discuss obtaining the results of your genetic analysis. You can always change this decision at any time in the future by informing the research team.

We will also not be looking for genetic changes that are associated with diseases other than CAD and therefore we will not be aware of abnormal genetic findings which might increase your risk of other diseases.

5. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the study at any stage.

If you decide to take part, you will be given the PICF to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment or your relationship with those treating you.

6. What are the possible benefits of taking part?

This study aims to further medical knowledge and may improve future care of coronary artery disease. We cannot guarantee or promise that you will receive any benefits from this research.

7. What are the possible risks and disadvantages of taking part?

Radiation

The CT scans are a source of X-ray exposure, and there is concern that this could be harmful. The radiation dose of a coronary CT scan is ~2 mSv, equivalent to 20 chest X-rays. The risk of cancer from this dose in a 55 year old man is 0.0088%, meaning that 1 in 11346 men might develop cancer due to this test. In a 55 year old woman it would be 0.011%, meaning that 1 in 8768 women might develop cancer due to this test (http://www.xrayrisk.com/calculator/calculator-normal-studies.php). It is important that women participating in this study are not pregnant and do not become pregnant during the study because of radiation exposure. If you are a woman of childbearing age and there is any possibility that you are pregnant, the researchers will need to perform a urine pregnancy test before you start in the study. If necessary, you should use reliable contraception (such as oral or implanted contraception, an IUD or have had a tubal ligation if you are female, or condoms if you are male) during the course of the study. If at any time you think you, or your sexual partner may be pregnant, it is important to let the researchers know immediately.

Medication

Metoprolol and diltiazem are medications often used to prevent heart attacks, reduce blood pressure, reduce chest pain and manage heart rate. In this study it is important to have consistent and regular heart rate during the x-ray scans, therefore metoprolol is used for heart rate control over the 24 hours before the scan. If you cannot take metoprolol (e.g. because of asthma), then we will provide diltiazem. If you have had problems with either medication or their class of drugs (beta blockers or calcium channel blockers), have problems with asthma, slow heart rate or low blood pressure, please let the researchers know.

The common significant side effects seen in <20% of those taking beta-blockers include diarrhoea, dizziness, cold hands/feet, decreased heart rate and dulling of warning signs of low blood sugar in diabetic patients. Other uncommon side effects (<5%) are abdominal pain, nausea, and positional decrease in blood pressure, dyspnoea, impotence, palpitation, depression and insomnia. However due to the short duration of treatment any side effects are unlikely to be experienced. If you are someone who suffers from asthma then metoprolol may not be advised, so please make sure the researcher is made aware.

DNA collection

The risk of harm or discomfort to you in this study will be minimal, since the procedures undertaken in this study are all standard procedures. However, having a blood sample taken may cause some discomfort, bruising, bleeding or minor infection. If this happens, it can be easily treated. Should you feel any anxiety, faintness or nausea during the blood test, the researcher in attendance will have the option of ceasing the blood test and will be trained in providing you with any support as required.

Genetic analysis results

You should be aware that if you decide you want to know the results of your genetic tests, the information we give you could affect your future applications for insurance other than medical insurance. An employer might also ask for the results of your tests.

When you apply for some kinds of insurance, including life insurance, you must reveal all that you know about your health, including the results of any genetic tests. The law allows private insurers to distinguish between their customers on the basis of this information except in the case of medical insurance. For

example they might offer a different price for the insurance (higher or lower) or even refuse to offer insurance depending on what you tell them about your health or genetic tests.

From 1 July 2019, the Financial Services Council (FSC) introduced a moratorium to ensure people can access a level of life insurance without being asked about the result of a previously taken genetic test. However; for applications over the stated limits (https://www.australiangenomics.org.au/financial-services-council-introduces-a-moratorium-on-genetic-tests-in-life-insurance/), life Insurance providers can ask the applicant to disclose the result of any genetic test they have had. Genetic results obtained as part of a research study are treated the same as a clinical test results and must be disclosed as part of applications for cover over the financial limits.

For more information visit or contact Australian Genomics (https://www.australiangenomics.org.au/financial-services-council-introduces-a-moratorium-on-genetic-tests-in-life-insurance/)

Other considerations:
Inconvenience associated with a visit to the site for blood testing

8. 'What happens if I suffer injury or complications as a result of the study?'

It is unlikely that you will suffer any injuries or complications as a result of this study. However, if this occurs, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies. You do not give up any legal rights to compensation by participating in this study.

If you are not eligible for compensation for your injury or complication under the law, you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

9. How is this study being paid for?

The study is being supported by the Heine trust, a research funding body that is not a commercial entity and has no financial interests in the study findings. None of the investigators have any duality or conflict of interest. All of the money being paid to run the trial will be deposited into an account managed by the institution of chief investigators. No money is paid directly to individual researchers.

10. 'Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything and you will not be paid. You will be reimbursed for parking expenses.

11. What will happen to my test samples?

Your samples will be given a unique identifier code and will be stored securely at the Baker Institute until they are transported to Australian Genomic Research Facility (AGRF) in Adelaide, Australia. At AGRF, part of your sample will have DNA extracted and genetic analysis performed. The processed samples will be transported back to the Baker Heart and Diabetes Institute in Melbourne, Australia. We plan to hold your remaining samples and genetic analysis data in the Baker Heart and Diabetes Institute indefinitely. If you want us to destroy your data and test sample after 15 years following completion of the project, please indicate on the consent form.

Only authorised staff will have access to your samples. Your samples will be stored and labelled with your unique study number only, not your name or other identifiable information. Storing your samples will allow for future research to be performed on the samples, if you consent. Any research undertaken in the future that requests the use of the samples collected in this study will require additional approval from an appropriate ethics committee. This research may involve sending the samples to other institutions in

Australia or overseas and may include further genetic research. Samples will not be released until ethics approval has been received.

When you provide consent to take part in this study, you are consenting for the collection of your blood sample as well as for the use of your samples in future research activities. This research may involve but is not limited to cardiovascular research.

12. Will I get results of the research done on my DNA?

As stated on page 3, the clinical implications of genetic risk scores are uncertain at this time, we will not be communicating the results of the genetic analysis on your sample to you. We will also not be able to inform you if there are genetic changes associated with diseases other than CAD as we will not be looking for these changes and the results will not be available to us.
Participants randomized to the group who are provided the genetic risk score will receive a percentage risk from this score – **this is not the same as the individual genetic profile results**. As stated above, because the clinical implications of genetic risk scores are uncertain at this time, we will not be communicating the results of individual gene analysis on your sample to you.

You will be able to obtain overall research results of the study based on your genetic analysis on the trial's website: https://www.menzies.utas.edu.au/research/participant-based-studies

13. What if new information arises during this research project?

During the research project, new information about the risk and benefits of the project and use of genetic risk scores may become known to the researchers. Developments that meaningfully change the clinical impact of genomic risk scores in cardiovascular disease may be published through the trial's website: https://www.menzies.utas.edu.au/research/participant-based-studies. We will be able to offer you the option of being told about this new information and the researcher will discuss whether this new information affects you. If you do want to be offered the option to be told new information in future, please indicate this in your consent form. You can always change this decision at any time in the future by informing the research team.

14. Can I have other treatments during this research project?

This research will not interfere with any current treatment you may be receiving.

15. What if I withdraw from this research project?

Participation is entirely voluntary. You are not obliged to participate and, if you do participate, you can withdraw at any time. If you withdraw and want your remaining DNA to be destroyed, you must request this in writing by emailing: kristyn.whitmore@utas.edu.au or by letter to Kristyn Whitmore, EDCAD-PMS study, The Menzies institute for Medical Research, Private Bag 23, Hobart TAS 7001, Australia . Otherwise the DNA will be kept and used as stated.

If you do withdraw your consent during the research project, the relevant study staff will not collect additional personal and health information from you, although the personal and health information already collected will be retained to ensure that the results of the research project can be measured properly. Once your genetic information has been obtained from your sample and combined with that from other participants, it will not be possible to withdraw this information. If your sample is shared with other researchers, it will be coded, and therefore it may not be possible to withdraw your genetic sample. If you do not want them to do this, you must tell the research team before you join the research project.

16. What will happen with the results and to the information about me?

If you give us your permission by signing the consent document, we plan to publish the results in peer-reviewed journals and present the findings at scientific conferences. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided through the website https://www.menzies.utas.edu.au/research/participant-based-studies

We may need to share our study results with other researchers and upload our results in forums accessible to the public (like the internet) to ensure compliance with publishing or funding requirements. In these situations, and wherever possible, we would share a general summary of the data (e.g. how common each

genetic variant was in this study) and not individual-level data. When it is required to share individual-level data, the data will be submitted to a controlled access repository that meets international security and safety standards. The data will be coded and confidential, subject to a data-sharing agreement and limited to the minimum information required. Information that can link your coded genetic data to your personal identity will be safely and securely stored separately, to minimise the possibility of genetic information to be re-identified.

By signing this form, you consent to the relevant research staff collecting and using your personal and health information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential and securely stored. All datasets used for analyses will have identifying data removed (such as name and address), using only a study ID number. Your information will only be used for the purpose of this research project. It will be disclosed only with your permission, or in compliance with the law.

17. What happens when the research project ends?

Your DNA and genetic information will be stored indefinitely at Baker Heart and Diabetes Institute in Melbourne. If you want us to destroy your data and test sample after 15 years following completion of the project, please indicate on the consent form. Results of the study will be provided through the website https://www.menzies.utas.edu.au/research/participant-based-studies.
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18. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Tasmanian Health and Medical Human Research Ethics Committee

19. What should I do if I want to discuss this study further before I decide?

When you have read this information, the researcher will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact the study coordinator Kristyn Whitmore, email Kristyn.whitmore@utas.edu.au or ph 6226-4235

20. Who should I contact if I have concerns about the conduct of this study?

The person you may need to contact will depend on the nature of your query.
If you would like any further information concerning this project you can contact any of the following people:

Name: Kristyn Whitmore
Position: Study coordinator
Telephone: 03 6226 4235
Email: Kristyn.whitmore@utas.edu.au

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns or complaints about the conduct of the study, you can contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 6254 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You need to quote H0024000.

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EDCAD- PMS Consent Form (participant copy)

Title	**Early detection of coronary artery disease by polygenic and metabolic risk scoring (EDCAD-PMS)**
Principal Investigator	Prof James Sharman
Associate Investigator	Prof Thomas Marwick
Ethics Project Number	24000
Location	Menzies Institute for Medical Research

Declaration by Participant

I have read the Participant Information & Consent Form.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I understand that the researchers may contact me to request data about my health or to collect an additional sample.

I understand that my DNA will only be used for ethically-approved research.

I request my sample and data be destroyed after 15 years and understand that choosing to not tick the box allows for indefinite storage of my sample and data:	☐
If in future the clinical value of the genetic results justifies disclosing my genetic score results to me, I want to be contacted to discuss the option of obtaining my results.	☐

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Researcher _____

Signature _____ Date _____

Note: All parties signing the consent section must date their own signature

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Signature _____ Date _____

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