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Polygenic Risk Score for Coronary Artery Disease: a Clinical Use Case

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Coronary Artery Disease PRS in a clinical pathway

OVERVIEW

This document outlines an approach for using a Polygenic Risk Score (PRS) in a Coronary Artery Disease (CAD) clinical pathway. Following a patient request for a CAD risk evaluation from his/her physician, an initial assessment based on traditional risk factors such as LDL/HDL cholesterol levels, age, family history of heart disease, and smoking status is performed. In addition, the physician will prescribe a genetic test, which identifies risk from common genome-wide variants via PRS. To enable genetic analysis, the physician collects a non-invasive saliva sample. The sample is sent to a lab, DNA is extracted and sequenced, and the resulting genetic data is analysed in combination with clinical risk information. The physician receives a Patient Report within 2 weeks, which provides information on the patient's PRS, their probability of disease by age 75, and their absolute 10 year risk of CAD. On the basis of this analysis the patient's risk is classified as low, average, or high. The physician communicates results to the patient and prescribes a prevention plan based on results.

ABSOLUTE RISK CLASSIFICATION

The risk classification for CAD in this use case is based on a new model that takes into account information on traditional risk factors and polygenic risk. These are identified through patient consultation and genetic analysis. Our research shows that combining PRS with clinical risk factors level can accurately stratify CAD risk. Full description found on Page 6.

PRECONDITIONS

- Healthcare provider offers cardiovascular disease risk assessment services and has the ability to measure blood lipids (LDL-C)
- Healthcare provider has an internal or partner laboratory equipped with technology necessary for sample processing: DNA extraction and sequencing
- Risk classification uses WGS or microarray genotyping data and all analyses are performed in a secure cloud computing environment or on premise
- Measurement of a patient's LDL cholesterol level is required

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MOTIVATING FACTORS

- Trigger 1: Patient is interested in understanding his/her CAD risk, for example because he/she has family history of disease, has a high cholesterol level, or has an active interest in personal heart disease prevention.
- Trigger 2: Patient has suffered a cardiac event with no clear indication of cause through normal clinical evaluation (e.g. no family history or low/average cholesterol level). He/she is interested in whether polygenic risk can explain the event.
- This test is not diagnostic and therefore not appropriate for individuals presenting with an indicator of acute disease.

OBJECTIVE OUTCOME

Physician uses comprehensive risk assessment to provide the patient with either (1) an actionable plan to manage his/her individual absolute risk of CAD and reduce likelihood of him/her contracting the disease or (2) an explanation for the cause of his/her cardiac event.

BASIC FLOW: SCENARIO 1

DESCRIPTION	This scenario describes the situation of a patient who has no history of coronary artery disease
1	Patient comes to physician for CAD risk assessment
2	Physician performs initial assessment for clinical risk factors, including cholesterol level, family history, smoking, and age, and communicates the additional potential value of incorporating genetic information
3	Physician prescribes polygenic assessment of the patient's DNA
4	Physician performs sampling and sends DNA to laboratory for analysis and sets 2 week follow up appointment
5	Physician receives patient result as a report and automatically to EHR
6	Patient identified as having **Population** risk of CAD
7	Physician provides patient with Population Risk Action Plan: for example communicating importance of maintaining a healthy lifestyle, regular cholesterol measurements according to national guidelines, etc

ALTERNATIVE FLOW A: Patient has Borderline risk

6A	Patient identified as having **Borderline** risk of CAD
7A	Physician provides patient with Borderline Risk Action Plan: for example 6 month healthy lifestyle program, regular cholesterol measurements according to national guidelines

ALTERNATIVE FLOW B: Patient has Intermediate risk

6B	Patient identified as having Intermediate risk of CAD
7B	Physician provides patient with Intermediate Risk Action Plan: for example behaviour change program, low-to-moderate statin dosage treatment, annual blood test to monitor cholesterol

ALTERNATIVE FLOW C: Patient has High risk

6C	Patient identified as having High risk of CAD
7C	Physician provides patient with High Risk Action Plan: for example, immediate therapeutic intervention, statin treatment, annual blood test to monitor cholesterol

NOTES

Risk classification is the result of cholesterol level, age, fixed risk elements (e.g. family history and genetics) and modifiable factors such as smoking and BMI. Absolute risk therefore changes over time and should be monitored.

The exact course of action for individuals at Population, Borderline, Intermediate and High risk is at the discretion of the physician and depends on availability of resources but should be based on current guidelines.

Although a patient's risk may be accurately estimated, these predictions do not allow one to say precisely which patient will develop CAD as some who do not develop CAD have higher risk estimates than those who do develop the disease.

This framework identifies individuals at Population, Borderline, Intermediate and High absolute risk of disease, but only recommends a change in clinical care pathway for individuals with High risk. Further personalisation for is possible.*

The effect of PRS on absolute risk depends on ancestry and is accounted for in the integrated model.

*Risk classifications & example action plans based on AAC & AHA guidelines (2021)

BASIC FLOW: SCENARIO 2

DESCRIPTION	This scenario describes the situation of a patient who has suffered a cardiac event but does not present any traditional risk factors
1	Patient comes to physician for assessment to understand cause of the cardiac event
2	Physician reviews patient's previous risk assessment test results
3	Physician prescribes polygenic assessment of the patient's DNA
4	Physician performs sampling and sends DNA to laboratory for analysis and sets 2 week follow up appointment
5	Physician receives patient result as a report and automatically to EHR
6	Physician communicates result to patient. Patient and physician discuss potential effect of polygenic risk to cardiac event

ABSOLUTE RISK CLASSIFICATION

POPULATION RISK	<5% 10 year risk / risk by age 75
BORDERLINE RISK	5 - 7.4% 10 year risk / risk by age 75
INTERMEDIATE RISK	7.5 - 19% 10 year risk / risk by age 75
HIGH RISK	>20% 10 year risk / risk by age 75

Benefit of integrating PRS into risk models

The addition of PRS into standard risk classification models increases the number of individuals identified at high risk of disease. These individuals are both more likely to get disease and are unlikely to be identified through traditional models. This so-called 'invisible' population is identified thanks to PRS picking up risk that is not captured in standard risk assessments. For CAD, models incorporating PRS have been shown to improve classification of absolute risk by around 10%. Targeting new interventions such as statin therapeutics at individuals with intermediate risk could help prevent 1 additional CVD event for 340 individuals screened, and help prevent 7% more CVD events than assessments without PRS.

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