Backing visionary entrepreneurs

EIC Pathfinder Challenge Cardiogenomics

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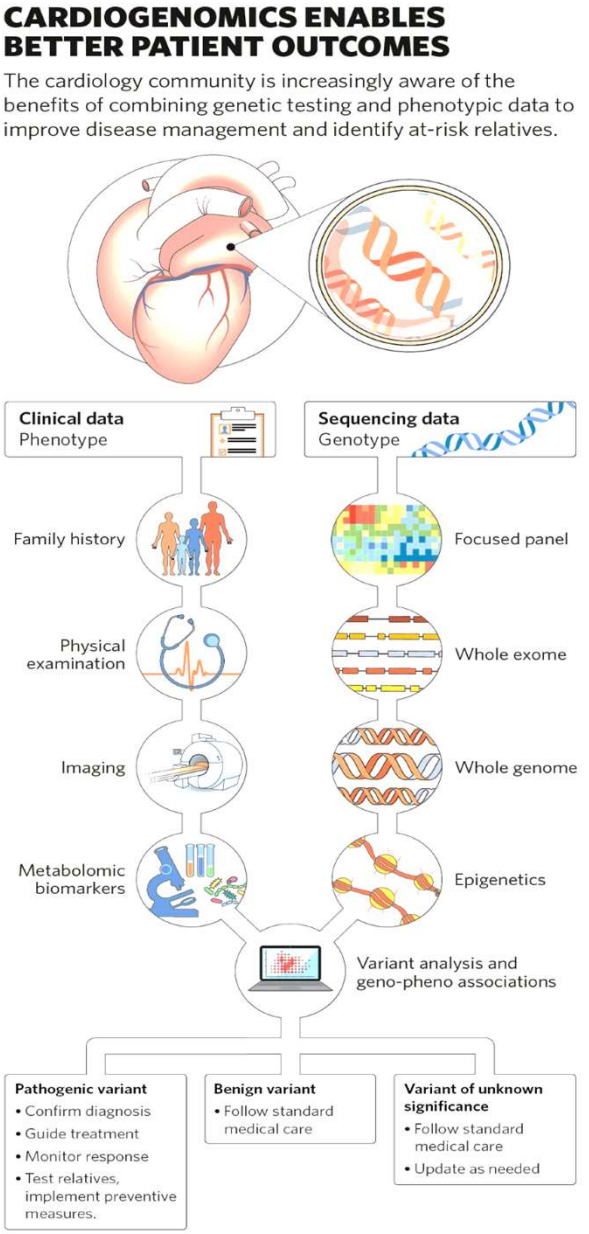
Scope of the Cardiogenomics Challenge (I)

Cardiogenomics is the application of advanced genomics and genetics in cardiology

Cardiogenomics holds the potential to address existing gaps in the diagnosis and treatment of cardiovascular (CVS), which would enable better patient outcome. Combining genetic testing with clinical phenotype can improve clinical management of the CVS diseases and identify who is likely to be at risk



Infographic: https://www.nature.com/

Scope of the Cardiogenomics Challenge (II)

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To address the current lack of Calls from basic to translational research in the CVD area

In the next two years alone, the Commission plans to open 18 health research calls covering 48 topics in mental health, obesity, pandemics, and cancer

➔ *"But cardiovascular diseases are not mentioned,"* according to the advocacy committee chair at the European Society of Cardiology (ESC). The ESC wants to see calls covering the chain from basic to translational clinical research, and work on infrastructure for health data sharing https://sciencebusiness.net/news/call-targeted-eu-research-heart-disease

Specific Objectives (I)
Identifying or confirming gene variants of high biological significance

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- Identifying **new single or multiple gene variants of high biological significance or other key molecules associated with the CVDs** that would allow for accurate stratification of patients and guide the physician in their clinical management and monitoring of these CVDs

  - A genome wide study examining the genomes of more than 25,000 initially healthy US women aimed to identify potential gene variants associated with major health incidents, including myocardial infarction and stroke was not very informative. Understandably, other co-expressed or modifier genes and gene-environment interactions, play a role *https://www.nature.com/articles/d42473-020-00278-7?twclid=1137867443604861 33*

- Confirming the potential pathogenicity of already identified gene variants of unknown significance and thus of limited clinical utility

Specific Objectives (II)

Identifying novel targets based on pathogenic variants and seeking for novel solutions, leading to first in class therapies

- To identify **novel targets based on these variants** for specific CVD indication(s) that would allow for the development of first in class therapies for the same indication

- To seek for **novel technological solutions** that could contribute to the development and acceleration of first in class therapies for major CVD conditions for which no effective treatments are currently available

Background to Cardiogenomics (I)
The root or contributors to several CVDs are monogenetic or polygenetic polymorphisms

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- Cardiovascular Diseases (CVDs) are the leading cause of death globally and a major contributor to disability

- CVDs can be categorized in different disorders and comprise a vast spectrum of diseases. Most prominent ones being ischemic heart disease and stroke. The genetic basis of, not just classic inherited cardiovascular conditions, but major common diseases such as heart attack and atrial fibrillation is yet to be uncovered

- **Rationale behind this field**: The root or contributors to several CVDs are monogenetic or polygenetic polymorphisms

Background to Cardiogenomics (II)
A relatively young field

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- Most of the complex CVDs are polygenic disorders arising as a result of DNA variants in multiple genes contributing to the development of the disease

  ➔ identification of critical single nucleotide polymorphisms (SNPs) is of high importance for the elucidation of the molecular mechanisms underlying the pathogenesis of various CVDs

- Scientists facing a big challenge in interpreting whether or not the function of a found variant is pathogenic

Background to Cardiogenomics (III)
Large scale data and multi-omics analysis

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- Our ability **to sub-classify diseases according to their underlying molecular mechanisms**, has been enhanced by technological approaches such as spatial transcriptomics, single-cell and others

- Necessary to perform **large-scale** data analysis that involves different fields of study: genomics, transcriptomics, proteomics, and metabolomics

Background to Cardiogenomics (IV)
More valuable targets if genomic interpretation is applied right at the beginning

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- **Target identification**: The challenge for pharma companies in the drug discovery process is, that they are often confronted with massive amounts of information from which they struggle to gain insights/potential new targets

- On the positive side, it is accepted that there are more valuable targets-requiring less time to market with lower risk-if genomic interpretation is applied right at the beginning. Combining sequencing data with that from electronic medical records can result in more effective genomic interpretation: https://liebertpub.com/doi/10.1089/genbio.2022.29036.gil

Specific condition for the Cardiogenomics Challenge

Applicants must convincingly demonstrate that they have access to a large cohort of genomic and/or transcriptomics and/or proteomics and/or metabolomics database from CVD patients

Expected outcomes from the Challenge (I)
Substantive impact on the practice of cardiology

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- Identifying potentially pathogenic mutations that have actionable effects (by disrupting normal biochemical pathways associated with the cause and/or progression of the disease), will have a substantive impact on the practice of cardiology

- Performing targeted DNA sequencing on CVD patient(s) to identify previously characterized pathogenic mutations, is expected to become part of the daily clinical routine in the CVD clinics.

Expected Outcomes from the Challenge (II)
Accelerating the implementation of personalised care in CVD

Deciphering the molecular pathogenesis underlying the pathology of a disease is key for personalized care. Targeted genetic testing is envisaged to serve a triple purpose:

- To achieve an early and more accurate diagnosis
- To guide the physician to administer the right treatment for the right patient (personalised treatment); and
- To make more accurately prognosis of post treatment clinical course (favorable or non- clinical prognosis)

Expected Outcomes from the Challenge (III)
Advancing Cardiovascular disease modelling

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Gathering the necessary knowledge and data that would enable to apply disease modelling for CVD, including through 3D in-vitro models, to be used for screening drugs/therapies for CVDs.

Portfolio Considerations

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Cardiogenomics Challenge Guide: file:///C:/Users/arzimio/Downloads/Challenge%20Guide%202022_Cardiogenomics.pdf

For building the portfolio of projects to be funded, the evaluation committee will apply the following portfolio considerations:

1. All proposals will be mapped against **well defined building blocks**
2. **Shared components implying shared objectives will be identified** that are common to several proposals coming from different building blocks (e.g. several projects addressing different cardiac clinical indications, but using the same technological approach)

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Portfolio proposal selection using building blocks (I) Technological approaches/-omics analysis with exemplary list of activities (non-exhaustive list):

- Genetic testing approaches leading to the identification of new or interpretation of the role of gene variants of uncertain significance
- Transcriptomics approaches including spatial and single-cell transcriptomics
- Proteomics approaches
- Metabolomics approaches
- Novel technological approaches based on variants or other key molecules associated with the complex molecular pathogenesis of the CVDs, leading to potential new targets
- Disease modelling for CVDs, including 3D in-vitro models for testing drugs/therapies.

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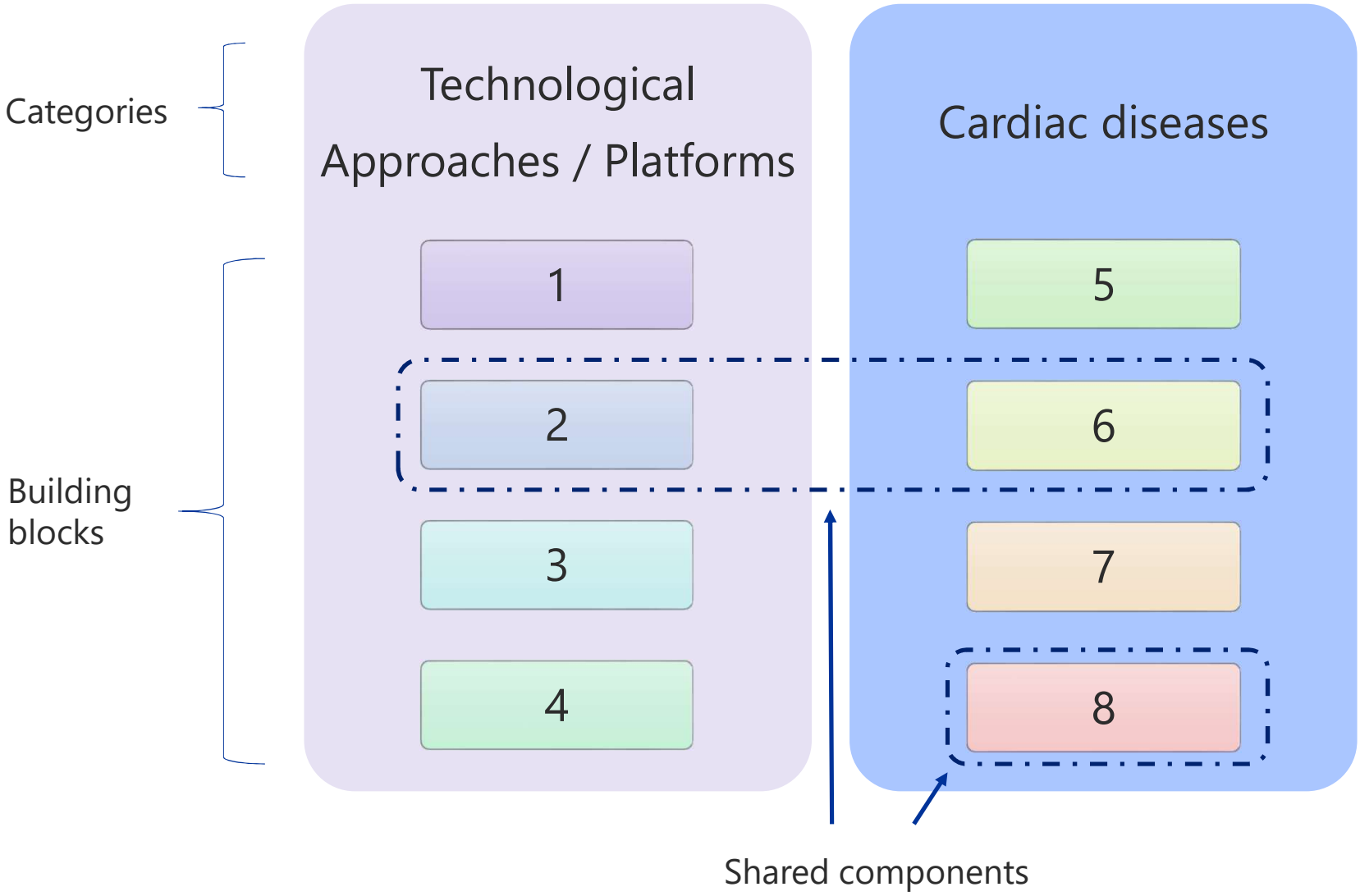
Portfolio proposal selection using building blocks (II)
Cardiac clinical indications with exemplary list of activities (non-exhaustive list):

- Haemorrhagic and ischemic stroke
- Aortic aneurysm
- Cardiomyopathies
- Arrhythmias
- Myocardial infarction, myocardial ischemia
- Heart failure including hypertrophy associated failure and the role of autophagy in that, and affecting cardiomyocyte contractility


Categories
Technological
Approaches / Platforms
Cardiac diseases
Building
blocks
1
2
3
4
5
6
7
8
Shared components

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Rationale behind the proposal selection to establish the portfolio: Shared component

- A portfolio of proposals will be selected based on **maximising the shared component** enabling the evaluation committee to group the projects and to identify a **recognisable transversal pattern constituting the portfolio**

- If the shared component from the first category is lacking in a proposal originally ranked among the top ones, and which is found in the further proposals down the list, this will result in its displacement by another one clearly aligning with the already identified pattern shared among top ranked proposals, that will eventually define the actual portfolio

- **Funding list of projects**: Projects selected for funding after the second step of evaluation are expected to differ from the original ranking list, established from the first evaluation step