



PATHFINDER CHALLENGE
Cardiogenomics

CHALLENGE GUIDE
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EIC Programme Manager: Iordanis Arzimanoglou

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The EIC will hold an online Info Session on this Pathfinder Challenge call on 05/07/2022. Participation in the meeting, although encouraged, is optional and is not required for the submission of an application. Information about how to access the Info Session and on additional dissemination events can be found at [EIC Pathfinder Challenges Applicants' Day \(europa.eu\)](#) and [EIC Pathfinder \(europa.eu\)](#).

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1. About this document

The Challenge Guide serves as guidance and background for the common understanding, participation rules and obligations for the EIC beneficiaries that are involved in the Challenge Portfolio. Contractual Obligations are further detailed in the EIC Work Programme 2022 https://eic.ec.europa.eu/eic-work-programme-2022_en and collected in the Pathfinder Challenge guidance on contractual issues, available on the Challenge page.

The Challenge Guide is a guidance document accompanying a Pathfinder Challenge call for proposals to provide applicants with additional technical information to underpin the objectives and to provide further information about how portfolio considerations will be taken into account in the evaluation of proposals.

The Challenge Guide is prepared by and under the responsibility of the relevant EIC Programme Manager (information about the EIC Programme Managers is available on the EIC Website https://eic.ec.europa.eu/eic-communities/eic-programme-managers_en). It further details the intention of the call by complementing notably the Scope, Specific Objectives and/or Specific Conditions set out in the EIC Work Programme¹. In no case does the Challenge Guide contradict or supplant the Work Programme text.

Following the selection of a proposals to be funded under the Challenge, the Programme Manager will work together the selected projects to develop a common roadmap with a strategic plan for the Challenge. This roadmap/ strategy plan will integrate the activities and milestones of the individual projects into a shared set of objectives and cross-project activities. The roadmap serves as a common basis for implementing the projects - including possible adjustments, reorientations or additional support to projects - and can be updated in light of emerging results of difficulties during the implementation.

¹ [EIC Pathfinder Challenge: Cardiogenomics \(europa.eu\)](https://eic.ec.europa.eu/eic-communities/eic-programme-managers_en)

2 Background concerning the scope and objectives of the Challenge

This section provides additional information on the background in the relevant scientific and technological domains pertaining to Scope and Specific Objectives of the Challenges that applicants may wish to take into account. This section should be read as background to the Challenge call in the EIC Work Programme text (attached as Annex). Proposals to this Challenge are expected to explain how they relate to and intend to go beyond the state of the art, and how they interpret and contribute to the objectives of the Challenge.

Cardiogenomics: a relatively young field

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 with the most prominent ones being ischemic heart disease and stroke. An estimated 18M people died from CVDs in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke².

Cardiogenomics, the application of advanced genomics and genetics in cardiology is, a relatively young field, with the aim to improve patient care in CVDs. The initial rationale behind this field is that monogenetic or polygenetic polymorphisms are the root or contributors to several CVDs. The field of cardiogenomics gained importance when Brown and Goldstein received in 1985 the Nobel Prize for the discovery of the genetic mutations affecting the low-density lipoprotein (LDL) receptor cause hypercholesterolemia and early-onset myocardial infarction, which eventually led to LDL cholesterol-lowering therapies that reduce the risk of cardiovascular events. However, 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. Hence, the identification of critical single nucleotide polymorphisms (SNPs) is of high importance for the elucidation of the molecular mechanisms underlying the pathogenesis of various CVDs³. Deciphering the molecular pathogenesis underlying the pathology of a cardiac disease is key to apply precision cardiac care.

Scientists are still facing a big challenge in interpreting whether or not the function of a found variant is pathogenic⁴. Apparently, a pathogenic variant can be implicated in a pathway leading to an individual disease or a number of disorders (pathway-based classification of cardiac genetic diseases). 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. In addition, in the recent years, intense genome wide association studies have identified several loci that are associated with CVDs, which are used by the industry and clinical establishments to identify who among their patients is more likely to develop a condition or who is more likely to benefit from a specific treatment on the basis of SNPs. Therefore, it is crucial to better understanding the contribution of the variants to the molecular

² [Cardiovascular diseases \(CVDs\) \(who.int\)](#), [Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019 | Institute for Health Metrics and Evaluation \(healthdata.org\)](#)

³ [Genomics in Cardiovascular Disease - ScienceDirect](#)

⁴ [The most common technologies and tools for functional genome analysis | Acta medica Lituanica \(vu.lt\)](#)

mechanisms underlying the pathogenesis of a disease for both, designing more accurate diagnostic tools and more effective treatments.

To achieve this aim, it is necessary to perform large-scale data analysis that involves different fields of study: genomics, transcriptomics, proteomics, and metabolomics. By combining the above categories of data with cardiac functional analysis, we can explore and establish the relationship between the genotype and cardiac phenotype, potentially leading to better understanding the role and impact of known genes on susceptibility, timing of onset, and clinical progression of the cardiac disease. In that regard, cardiogenomics is a timely call with potential to empower our ability to effectively treat heart diseases for which previously no treatment options were available.

Selected examples of pathogenic gene variants

According to the American Heart Association, a different set of genes is correlated to different clinical forms of cardiomyopathies such as, general, arrhythmogenic right ventricular cardiomyopathy, hypertrophic, restrictive and others⁵. One example of gene variants, likely to be pathogenic is the TTN gene. TTN variants leading to premature stop codons or causing frameshift mutations that disrupt canonical splice sites in the TTN protein, are present in up to 25% of dilated cardiomyopathy cases and thus, deemed to be associated with the development of this condition⁶. On the other hand, TTN variants are also found in approximately 1% of healthy individuals. However, it is far from known why some individuals with TTN variants are healthy while others are not. Ongoing RNA sequencing work will determine exon-level expression in human heart tissue shedding light on the role of TTN variants in cardiomyopathies⁷. The list of single genes contributing to a specific cardiac condition could end up being much longer, if one takes into account the very many genes currently under investigation for their potential role in certain cardiac conditions. In that regard, our call is timely and highly relevant as it aims, among others, at providing insights in the genotype-phenotype relationship in cardiomyopathies.

A second example of a key pathogenic gene is the FBN1 (MIM 134797) encoding the extracellular matrix protein fibrillin-1. Previous evidence has demonstrated that a specific pathogenic variant in FBN1 can be detected in over 90% of patients exhibiting Marfan Syndrome (aortic root dilatation, ectopia lentis and skeletal features), consistent with the view that FBN1 is likely to be a causal gene for Marfan syndrome⁸.

Selected examples of new targets and enabling technologies, potentially leading to the development of new CVD drugs

In mouse and rhesus monkey preclinical models of cerebral ischemia/reperfusion injury, administration of the peptide targeting the TLR4 ligand LY96, immediately after stroke and

⁵ [Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association | Circulation: Genomic and Precision Medicine \(ahajournals.org\)](#)

⁶ [Truncations of Titin Causing Dilated Cardiomyopathy | NEJM](#)

⁷ [EMBL-EBI: EMBL's European Bioinformatics Institute | EMBL's European Bioinformatics Institute](#)

⁸ [Marfan's syndrome - The Lancet](#)

then again at 6- and 24- hours post-reperfusion reduced neurological deficits and infarct volume⁹. Therefore, it has been proposed as a peptide that could treat ischemic and hemorrhagic stroke if administered early.

Recently, preclinical data obtained from a study involving 36 non-human primates assessing the potency of a lead compound for atherosclerotic cardiovascular disease demonstrated that even a single gene editing application at the PCSK9 gene level sustainably lowered the blood PCSK9 protein and low-density lipoprotein cholesterol (LDL-C), with no evidence of adverse events or significant off-target editing¹⁰. As a result, it has been proposed as potential breakthrough new treatment for this very frequent cardiac condition.

Furthermore, sequencing whole genomes which is required to identify new genomic variants has been to a large extent facilitated with new technologies that have been developed and through which, long strands of DNA can be reliably sequenced meaning no longer remain as challenge in the technically demanding process of identifying single base changes.

Cardiogenomics: impact on the practice of cardiology

Cardiogenomics holds the potential to address existing gaps in the diagnosis, treatment and prognosis of CVDs, which would enable better patient outcome. Combining multi-omics testing with clinical phenotype can improve clinical management of the CVDs and identify who is likely to be at risk¹¹.

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. In this context, the identification of pathogenic mutations associated with major complex CVDs that have actionable effects, will have a substantive impact on the practice of cardiology. To accomplish that, several stakeholders try to combine human genetic data with genomic tools and computational technologies to identify undiscovered connections between genes and their impact on disease progression¹². The outcome of these processes are platforms that can help to find variants within the same gene. In this context risk-enhancing variants are the ones that are of most importance. Such platforms try to classify variants with possible cardiovascular disorders and give a help for clinical genome interpretation.¹³

Fostering initiatives like that, could have a major impact on clinical decision making in terms of cardiovascular diseases. In the same line, the American Heart Association issued <https://www.ahajournals.org/doi/10.1161/HCG.0000000000000067> for patients diagnosed with all forms of cardiomyopathy, arrhythmic disorders, vascular disorders and lipid

⁹ [BioCentury - Peptide inhibitor of LY96 for ischemic and hemorrhagic stroke](#)

¹⁰ [Verve Therapeutics Reports New Preclinical Data with VERVE-101 Demonstrating Robust, Durable and Precise Editing of the PCSK9 Gene for the Treatment of Cardiovascular Disease | Verve Therapeutics \(vervetx.com\)](#)

¹¹ [Genomic discoveries at the heart of cardiovascular disease \(nature.com\)](#)

¹² [BridgeBio Pharma and Maze Therapeutics Establish Joint \(globenewswire.com\)](#)

¹³ [CardioClassifier: disease- and gene-specific computational decision support for clinical genome interpretation | Genetics in Medicine \(nature.com\)](#)

disorders such as familial hypercholesterolemia and also pointed to the need that health care providers should become more literate in cardiogenomics¹⁴.

On the other hand, support targeted to unravelling the complex genetic basis of CVDs in the European continent, appears not to be not equally strong. According to the advocacy committee chair at the European Society of Cardiology, the EC plans to open 18 health research calls covering a wide spectrum of topics (48) but Calls on CVDs are not evident^{15 16}. Hence, there is clear need for this Challenge Call.

3 Portfolio considerations for the evaluation of applications to the Challenge

This section describes how portfolio considerations will be taken into account in the second stage of the evaluation of applications. In the first stage, all applications will be evaluated individually by external experts and scored against the evaluation criteria set out in the Work Programme. All applications that pass the defined thresholds against the criteria will be included in the second stage of the evaluation. At the second stage, all above threshold applications will be considered collectively by an evaluation panel chaired by a relevant Programme Manager. At this stage, the Evaluation Committee will consider which applications to recommend for funding in terms of a coherent portfolio of projects that can interact, reinforce, or compete with each other to increase the overall impact.

Portfolio considerations

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 categories/ building blocks which comprise a non-exhaustive list (see below).
- 2) Shared components/ shared objectives will be identified that are common to several proposals coming from different categories/ building blocks (e.g., several projects addressing different cardiac clinical indications, but using the same technological approach).
- 3) Starting from the most highly ranked proposal, a portfolio of proposals will be selected based on maximising the shared components/ objectives enabling the evaluation committee to group the projects and to identify a recognisable

¹⁴ [Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association | Circulation: Genomic and Precision Medicine \(ahajournals.org\)](#)

¹⁵ [Call for targeted EU research into heart disease | Science|Business \(sciencebusiness.net\)](#)

¹⁶ [Establishment of Specialized Clinical Cardiovascular Genetics Programs: Recognizing the Need and Meeting Standards: A Scientific Statement From the American Heart Association | Circulation: Genomic and Precision Medicine \(ahajournals.org\)](#)

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 shared category-pattern shared among top ranked proposals, that will eventually define the actual portfolio. Consequently, this means that the projects selected for funding after the second step is expected to differ from the ranking list established from the first step.

Categories/ Building blocks

The building blocks can be divided in two major categories in terms of nature (I, II) Technological approaches/-omics analysis with exemplary list of activities (non-exhaustive list):

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

II. Cardiac clinical indications with exemplary list of activities (non-exhaustive list):

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

4 Implementation of the Challenge portfolio

Once selected, projects will be expected and obliged to work collectively during the implementation of their projects under the guidance of an EIC Programme Manager. This section summarises some of the key aspects of this pro-active management which applicants should take into account in preparing their proposals.

Grant negotiations

Applicants may be requested to make amendments to their proposed project in order to take into enhance the portfolio. Such changes may include: additional activities to undertake

common/ joint activities (workshops, data exchanges, joint research, etc) with other projects in the portfolio;

Challenge portfolio roadmap/ strategy plan

This Challenge aims at:

1. **Enhancing the clinical development potential of the portfolio individual project, as a result of its active participation in the portfolio activities:** Ensuring that portfolio members, can access a much higher number of relevant clinical establishments to explore key partnerships
2. **Enhancing the commercialisation potential of the portfolio individual project, as a result of its active participation in the portfolio activities:** Ensuring that portfolio members, can access the right industry partners to explore key partnerships

In order to accomplish the above the Programme Manager needs to develop and agree on a strategy plan for the cardiogenomics portfolio with the portfolio projects

Portfolio Strategy Plan

Following the selection of a proposals to be funded under the Challenge, the Programme Manager will work together the selected projects to develop a common strategy plan/roadmap for the Challenge. This plan will integrate the activities and milestones of the individual projects into a shared set of specific objectives and cross-project activities. The roadmap serves as a common basis for implementing the projects - including possible adjustments, reorientations, or additional support to projects - and can be updated in light of emerging results of difficulties during the implementation. The objectives can be revised, for instance based on projects' unexpected achievements, new technology trends, external inputs (other projects, new calls...).

In particular, the Challenge roadmap/ strategy plan will include activities on the transition to innovation and commercialisation, and to stimulate business opportunities. These activities may be reinforced during the implementation with additional funding and expertise through pro-active management.

Non-exhaustive examples of activities towards the above-mentioned aims are:

- **Regulatory framework: Contributing to improve the current regulatory framework concerning new cardiovascular therapeutics linked to companion diagnostics/predictive biomarkers or new more accurate diagnostics:** Effectively communicating to EMA/Competent Authorities novel research data collectively produced by the portfolio members that can be potentially used to tackle current regulatory challenges.
- **Investors: Effectively communicate of any key outcome of the research work of the portfolio members collectively and/or an individual project, to early stage private and corporate investors focused on the same field.**

- **Market analysis:** Map the targeted biotech and pharma players and exchange the market research analysis results with other the portfolio projects to identify specific biotech and pharma *players* of common interest with which the entire portfolio can establish partnership(s) of much higher impact (clinical or commercial) as opposed to that of the individual project.

These tasks require the active participation of portfolio members to a series of meetings called for and steered by the Programme Manager. Portfolio projects will be expected to exchange information about the accessed clinical databases in order to collectively use the available resources in their entirety. This exchange of CVD data between portfolio members can enhance the potential of individual projects, use of results originating from the analysis of CVD databases, as well as their chances to establish key partnerships.

Tools though which projects can receive additional support

Projects in the portfolio may be offered additional support, either individually or collectively, in order to reinforce portfolio activities or explore the transition to innovation. Such additional support includes:

- Booster grants of up to €50k (see Annex 6 of the EIC Work Programme)
- Access to additional EIC Business Acceleration Services (see https://eic.ec.europa.eu/eic-funding-opportunities/business-acceleration-services_en)
- Access to the Fast Track to the EIC Accelerator, which would follow a project review (see Annex 4 of the EIC Work Programme)
- Access to the EIC Market Place, once operational, to connect with innovators, investors and other selected partners
- Interactions with relevant projects and initiatives outside the portfolio, including other EU funding initiatives as well as those supported by national, regional or other international bodies.

ANNEX Extract of EIC work programme

II.2.3 EIC Pathfinder Challenge: Cardiogenomics

Cardiogenomics holds the potential to address existing gaps in the diagnosis and treatment of cardiovascular diseases (CVD), which would enable better outcome for the patient. Advanced genetic testing taking into account complex inheritance, or combining genetic testing, transcriptomics, proteomics and metabolomics analysis with clinical phenotype can improve clinical management of the CVD and identify more accurately, who is likely to be at risk for major cardiovascular events such as heart failure or sudden death . Many gene variants associated with CVD are of unknown significance and thus of limited clinical utility. Our ability to sub-classify CVD diseases according to their underlying molecular mechanism has been enhanced due to technological approaches such as, spatial or single-cell transcriptomics, and others.

There has been considerable funding in the past directed to support and improve the quality of life of patients with severe heart and other CVD conditions (e.g. development of bio-electronic implants/devices). On the other hand, there has been considerably less public funding allocated to demanding research targeted to the actual cause of major CVDs and their complex genetic basis and as a result, limited progress has been made in this front. Although, the complex genetic basis of some of the inherited cardiovascular conditions, such as, the cardiomyopathies is widely accepted, it remains far from being elucidated. In addition, already identified gene variants can demonstrate variable expressivity (clinical phenotype severity), challenging the clinical interpretation of the variants identified in a patient and the selection of the therapeutic tool. As per the major common diseases such as heart attack and atrial fibrillation, the genetic basis is incompletely understood.

Companies are therefore increasingly raising funding to support their preclinical CVD programs aimed to develop key molecules that can disrupt signalling pathways that regulate key cardiovascular processes including rhythm, hypertrophy, contractility, and autophagy and others, potentially leading to new therapies for heart failure or other CVD conditions. The overall aim of this Challenge is to pave the way for novel therapies for major CVD conditions including hemorrhagic and ischemic stroke, aneurysm, cardiomyopathy and certain types of arrhythmias and other conditions, for which no effective treatments are currently available.

The gender dimension in research content should be considered, where relevant. See also the Gendered Innovation 2 report.

Specific objectives

- to identify 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
- 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.

Expected outcomes and impacts

- impact on the practice of cardiology: identification of pathogenic mutations or multiple variants 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;
- accelerating the implementation of personalised care in CVD: deciphering the molecular pathogenesis underlying the clinical pathology of a CVD disease, is key for implementing personalised care. Performing targeted DNA sequencing on CVD patient(s) to identify previously characterised pathogenic mutations, is expected to become part of the daily clinical routine in the CVD clinics. 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 predict more accurately post treatment clinical course (favorable or non-clinical prognosis).
- 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.

Specific conditions

- 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.