# The cardiovascular genomic medicine- a global initiative

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**Abstract**

Strengths and weaknesses of any scientific development are judged by its translation and applications in real life. Applications in medicine and healthcare are prime examples and conveniently judged and appreciated by millions all over the World. Since the completion of the human genome sequencing, genomic advances in medicine and healthcare have moved ahead with jetting speed. The genomic medicine is no longer a hype but now a realty targeted at specific individual (personalized medicine), at specific molecular disease target (precision medicine), delivered in carefully stratified manner (stratified medicine), and based on the most up to date top class adequately validated evidence (evidence-based medicine).

The cardiovascular genomic medicine is by far one of the best examples of specialist genomic medicine. The field offers fresh opportunity to review and organize management and prevention of wide ranging inherited and familial cardiovascular conditions. By any conservative estimate based on the current incidence and prevalence data, the burden of these disorders is huge in any healthcare settings. In addition to highly sophisticated and specific diagnostic accuracy, applications of genomic and molecular laboratory technologies offer much needed insight into basic cellular and molecular pathology underpinning the rare and common cardiovascular conditions. There is urgent need to harmonize protocols and tools for systemic and globally acceptable definitions, criteria and algorithms utilizing the modern computational and bioinformatic software. The need for globally managed and accessible genomic database is not disputed for recording and annotating several hundred gene-specific variants and genomic variants.

The new emerging field of cardiovascular genomic medicine requires a concerted and coordinated effort involving the global cohort of like-minded clinical, health, nursing and scientific professionals. The global familial heart challenge (GFHC) is a global initiative aimed at achieving the ambitious globalized cardiovascular genomic medicine.

The GFHC is led by the Genomic Medicine Foundation (UK) and supported by the Global Variome. It has generated wide interest amongst the emerging developing countries including India, Asia Pacific, Middle East and Arab, Southern Africa, Europe and Latin America. The NIH funded *ClinVar* and *ClinGen* groups are associated with the powerful and undeniably essential cardiovascular genomic mutation and variants database. The globalization of cardiovascular genomic medicine is with us and needs serious collaboration and cooperation to make it useful to patients, families, and all professionals involved.

**Key words**: cardiovascular medicine; cardiology; genomic medicine; global health; familial heart disease; genomic database; preventive cardiology; genomic public health

## Introduction

During the last four decades, rapid progress in medical genetics and molecular medicine has revolutionized our approach for managing both communicable and non-communicable diseases. With better and effective control and prevention of communicable disorders, apparent rise in incidence and prevalence of a number of non-communicable diseases have attracted the attention of medical and public health professionals including the health planners and administrators [1].

Whilst communicable disorders remain significant in developing and less developed nations, collectively non-communicable disorders, particularly inherited and genetic conditions, contribute significantly to rising burden on mortality and morbidity in the developed world [2]. Non-communicable disorders are wide ranging and multi-system including birth defects contributing to significant neonatal and infant mortality and morbidity. However, most non-communicable disorders of public health importance, for example type 2 diabetes mellitus (DM2) and coronary heart disease (CHD) are late onset and remain a major cause for sustained morbidity and cause for early death. Major conditions in this category include obesity, diabetes mellitus, ischemic heart disease, stroke, common cancers (skin, lung, breast, colorectal and prostate), degenerative neurological diseases (motor neuron disease and multiple sclerosis) and neuropsychiatric diseases (dementia, bipolar depression, and schizophrenia).

A number of genetic and genomic studies have provided strong evidence for genetic factors contributing to the causation and natural history of many non-communicable diseases [3]. Whilst majority of the disorders are attributed to polygenic/ multifactorial inheritance with 50% or above heritability, a small but significant proportion is caused by high-risk Mendelian genetic conditions. Collectively are regarded familial with shared common life style and environmental factors.

**The contribution of high-risk genetic heart conditions**

A sizeable proportion, probably estimated to be about 10-15%, of all non-communicable diseases are accounted for high-risk genetic conditions with familial occurrence and recurrence following the Mendelian or monogenic inheritance pattern. Thus, most non-communicable diseases are familial and inherited with a significant genetic or genomic component measured in terms of low, medium and high genetic risk.

Familial and inherited non-communicable disorders are now fast emerging as the global phenomenon. The combined burden on any healthcare settings and the socio-economic impact is likely to be huge. Most currently available data is probably inaccurate and seriously underestimated. The collection, by any epidemiologic tools, is questionable since the variation in the geographic and population-specific distribution remains unclear. In part this might reflect lack of awareness or insufficient numbers probably due to regional or country based epidemiology data surveillance system or strategic health policy focused on other common conditions, notably malnutrition, common infections, tuberculosis, human immunodeficiency virus (HIV) and other local health priorities. Thus, available data might not indicate clearly the incidence and prevalence of familial or inherited life-long disorders (Table 1). Nevertheless, it should not escape the attention of public health professionals and healthcare planners that the burden, by any measures, of familial and inherited cardiovascular conditions is certainly considerably large. Perhaps the best example is chronic heart failure of which at least 30% is caused by non-ischemic and non-inflammatory myocardial diseases, predominantly the heterogeneous inherited cardiomyopathies estimated to affect 1 in 300 individuals in the general population irrespective of geographic and ethnic variables. This alone would amount to around 5000 cases per million population. Each such individual requires whole life general and

specialist healthcare including targeted health surveillance in close relatives, deemed to be at high recurrence risk. This would be real challenge in developing and under-developed nations.

**Table 1: Familial and Inherited Cardiovascular Conditions***

| Condition | Incidence @1000 births | Prevalence @1000 living | Burden @ million |
|---|---|---|---|
| Congenital heart disease[1] | 5 | 7 | 7,000 |
| Aortic/Arterial disease [2] | 0.3 | 0.5 | 500 |
| Inherited cardiomyopathies[3] | 3 | 5 | 5000 |
| Inherited arrhythmias & cardiac Conduction diseases[4] | 1 | 3 | 3000 |
| Atrial fibrillation | N/A | 5 | 5,000 |
| Familial hypercholesterolemia | 2 | 4 | 4,000 |
| Systemic hypertension | N/A | 10 | 10,000 |
| Pulmonary hypertension[5] | 0.2 | 0.3 | 300 |
| Rare cardiovascular disease | 0.5 | 1.5 | 1500 |

**Data extracted from various resources; figures rounded to near best possible estimate. This data is for discussion only and should not be used for any healthcare planning or administration.*

*1.* ***Congenital heart disease****- sporadic single cardiac anomaly, multiple cardiac anomalies, cardiac anomalies within the spectrum of inherited Mendelian disorders*

*2.* ***Aortic and arterial disease****- Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic dilatation and dissection (TAAD), vascular Ehlers Danlos syndrome, hereditary haemorrhagic teleangiectasia, and other rare inherited angiopathies.*

*3.* ***Inherited cardiomyopathies****- hypertrophic cardiomyopathy (HCM); dilated cardiomyopathy (DCM); arrhythmogenic cardiomyopathy (ACM); restrictive cardiomyopathy (RCM), and other inherited myocardial diseases associated with metabolic storage diseases (Pompe's and Fabry's), auto-immune/ inflammatory diseases (Sarcoidosis and Amyloidosis).*

*4.* ***Inherited arrhythmias and cardiac conduction diseases****- Long QT syndrome, short QT syndrome, Brugada syndrome, familial cardiac conduction, and other rare inherited cardiac electrical disorders.*

*5.* ***Pulmonary hypertension****- pulmonary arterial hypertension (PAH); secondary to inherited left-sided heart disease; secondary to chronic interstitial lung disease; secondary to chronic pulmonary embolization caused by inherited clotting disorders; secondary to reversal of the left-right shunt of the untreated congenital cardiac anomalies, such as ventricular septal defects; and rare inherited metabolic diseases, for example glycogen storage disease*

In the context of familial and inherited long-term conditions, many cardiovascular diseases deserve special consideration. These are collectively more prevalent and impose a huge burden on health resources with significant morbidity and young age mortality [4]. In some conditions, risk for sudden unexplained death remains relatively high. Moreover, with increasing diagnostic and therapeutic avenues, most are amenable to specific diagnosis and targeted medical and surgical treatment. Most developed nations now enjoy benefits with improved survival rate and symptom free prolonged working long life contributing to positive socio-economic gains. Apart from complex polygenic inherited cardiovascular diseases (ischemic/coronary artery disease, hypertension, stroke), a number of high-risk cardiovascular genetic conditions are now managed by general or specialist clinical and health professionals, including primary care.

The high-risk cardiovascular genetic conditions include [5]:

1. structural developmental cardiac anomalies (e.g., ventricular septal defect, Fallott's tetralogy, atrio-ventricular septal defect, truncus arteriosus etc.);
2. cardiac muscle disease (e.g., hypertrophic and dilated cardiomyopathy);
3. cardiac arrhythmic disease (e.g., long QT and Brugada syndromes);
4. arterial and aortic vascular conditions (e.g., aortic/ arterial dilatation and aneurysm with dissection), and
5. other multi-system genetic disorders with significant cardiovascular manifestations, for example familial hypercholesterolemia, Duchene/Becker muscular dystrophy, Marfan syndrome, Ehlers-Danlos syndrome, Fabry's disease and systemic amyloidosis.

The remit and scope of GFHC include above inherited cardiovascular conditions (ICCs). Most ICCs can be diagnosed early with precision and managed by a combination of drugs and devices and surgical intervention. Advances in cardiovascular imaging combined with reliable properly validated biochemical and immunological biomarkers are routinely employed by cardiovascular and general physicians in the diagnosis and stratification of wide range of familial cardiovascular conditions. There are now several ***gene-molecule*** families etiologically associated with most monogenic/ Mendelian cardiovascular disorders. There are several next generation genome sequencing based diagnostic multi-gene panels available for confirmation of the disease causing specific

gene mutation or pathogenic variants in major inherited cardiovascular conditions. Many genetic/genomic laboratories offer these services and have developed ***gene-disease*** specific genotype-phenotype databases [6].

Most leading regional and teaching cardiovascular units in developed countries have multi-disciplinary teams (MDTs) managing patients and families with familial cardiovascular diseases. One of the important tasks of these dedicated MDTs includes advising and supporting the 'at-risk' healthy asymptomatic family members. Through systemic evaluation and genetic counseling processes, these anxious relatives are prepared and offered accurate predictive genetic testing [7]. Those found to share the inherited specific gene mutation or the pathogenic variant are offered long term clinical surveillance (clinical examination, 12 lead electrocardiogram and ultrasound echocardiography), prophylactic medication (e.g., beta blockers), interventional cardiac (external or internal) devices (e.g. implantable cardioverter device- ICD) and in some cases by preventive surgical procedure.

Familial and inherited cardiovascular diseases are global and affect all irrespective of geographic and ethnic origin. It is a global phenomenon and requires a world wide high level strategic health approach. The whole group of conditions poses a major global challenge. The proposed *Global Familial Heart Challenge (GFHC)* is a new international initiative for raising awareness and developing regional and country specific health information, data resource and targeted specialist health service provision in cardiovascular medicine targeting the inherited or likely genetic cardiovascular conditions. This ambitious project entails to deliver the cardiovascular genomic medicine within the broad remit of genomics led global health [8].

**The Global Familial Heart Challenge**

The overriding aim of this novel initiative is to set up and develop the coordinated global network to deal with medical and health challenges of the familial and inherited heart disease. This aim is targeted through several key objectives-

1. To assist clinicians, health professionals, laboratory scientists and patient & family support groups for the key health challenges of the familial and inherited

heart disease- clinical diagnosis, laboratory genetic/genomic diagnosis, multi-disciplinary care and health surveillance, prevention and support.

2. To develop a fully accessible clinically oriented database to include fully validated evidence-based information for clinical applications.

3. To set up on-line access for the consumer (professionals, partners, patient and public) on qualified and validated information related to the key familial heart health challenges.

4. To encourage and engage in applied research on management and treatment of familial/ inherited conditions in a cost-effective manner, including prevention; providing data for bio molecular research for a 'cure'.

5. To strengthen the emphasis in public health to make sure that it encompasses some aspects of mapping genetic mutation and genomic variant patterns across various populations, and from this being able to provide some evidence to service providers regarding public health messages as opposed to individual case treatment.

The Global Familial Heart Challenge (GFHC) [9] is a network of a number of clinical establishments, genetic/genomic laboratories, research centers and patient/ family support groups committed to caring and supporting patients and families affected with a familial/ inherited heart disease organized on the following principles (Figure 1):

- Each individual center, partner or professional of GFHC contributes on voluntary basis.
- GFHC does not have direct access to any patient clinical or research data or information.
- GFHC ensures that any information or data shared by the partner or participating organization is kept undisclosed as far as possible to avoid any breech of confidentiality or identity.
- GFHC supports the consumer- patient, family member, clinician, health professional, researcher or student engaged and/or committed to caring or supporting any one affected with a familial / inherited heart disease.
- GFHC functions through the consortium of several clinicians, health professionals, laboratory scientists, researchers and patient/ family support workers with these

groups making recommendations for action on a participative and consultative basis

- The GFHC consortium is arranged on Regional and Country node basis to ensure that national regulatory and legal requirements are adhered to as well as all relevant social, cultural and religious norms are taken into account;
- Day-to-day administration will be under the supervision of the executive team selected from the consortium membership.

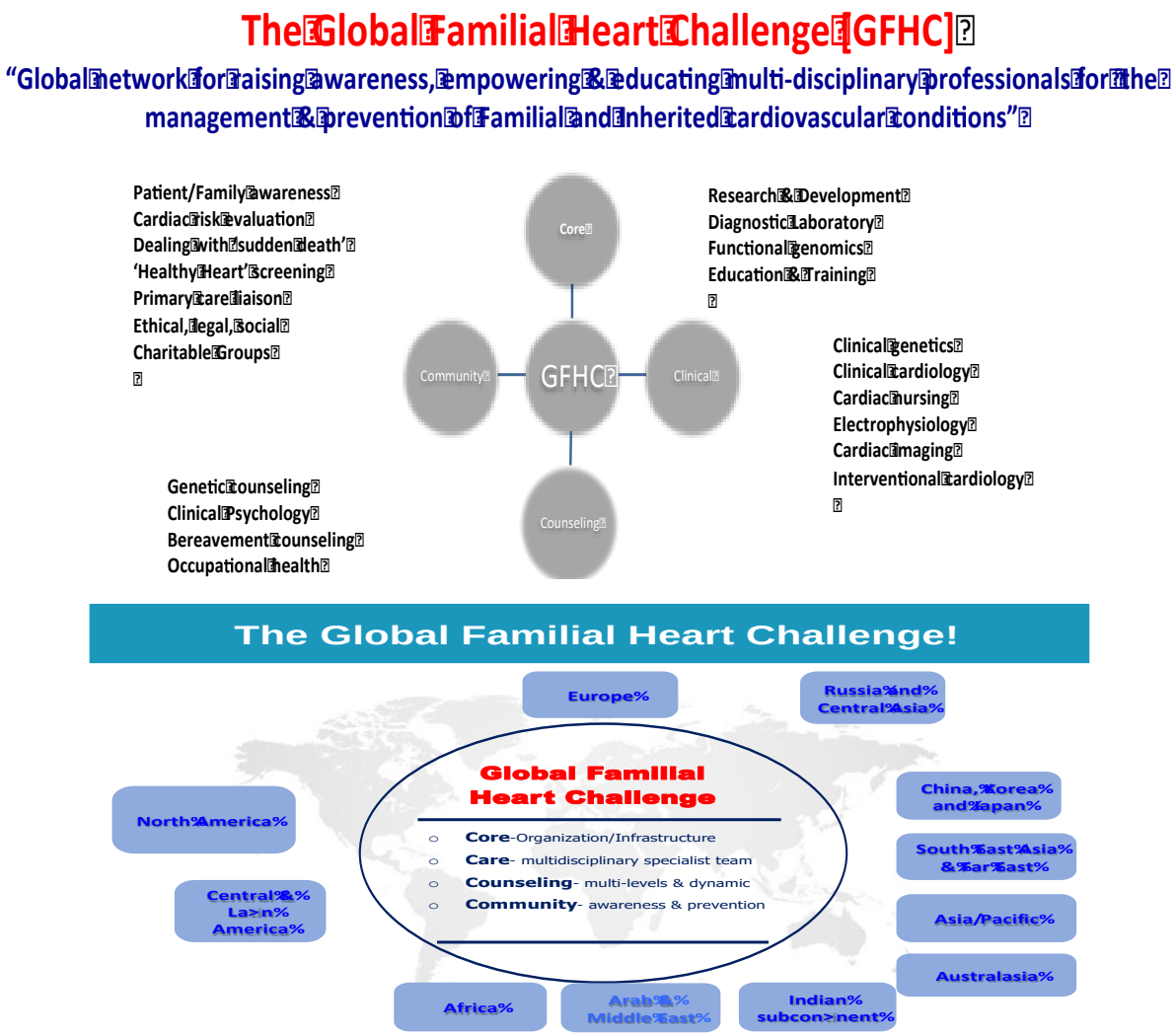


**Figure 1: Principles and functional organization of the Global Familial Heart Challenge**

The GFHC is administered by the central Executive team selected from the Consortium membership. The GFHC has its own website page (www.genomicmedicine.org/GFHC ) with information on aims, objectives, consortium, membership, affiliations, consumer information and questionnaire. The GFHC will ensure working in parallel and partnership with already established databases network for ICCs, for example ClinGen, ClinVar (USA). The GFHC is financed through voluntary contributions and funding from leading professional and health organizations.

The GFHC works in close partnership with the Human Variome Project (HVP) through the International Scientific Advisory Committee (ISAC). It is anticipated that membership of the HVP/ ISAC will actively contribute to GFHC through discussions and advising based on the experience on similarly aimed projects like *BRCA Challenge* and *Globin2020.* The GFHC is affiliated with a number of national Institutes, Professional Organizations and Patient/ Family Support groups who are able to become partners/ collaborators of GFHC (Table 2)

**Table 2: Partners and collaborators of the Global Familial Heart Challenge**

| |
|---|
| **A. Partners** |
| Human Variome Project through the International Scientific Advisory Committee |
| **B. Collaborators** |
| Asia-Pacific Society of Human Genetics |
| European Rare Diseases Network |
| European Human Genetics Society |
| British Heart Foundation |
| NIH ClinGen/ ClinVar |
| Department of Molecular Cardiology, Academic Medical Center, Amsterdam, The Netherlands |
| Center for Medical Genetics, University of Gent, Belgium |
| Department of Medical Genetics, University of Antwerp, Belgium |
| Health-n-Code, Center for Cardiovascular Genomics, La Coruna, Spain |
| Department of Cardiology, Post Graduate Institute for Medical Education & Research, Chandigarh, India |

## Functions and Roles

GFHC is planned to be supportive and advisory working with our partners and collaborators to organize and deliver the multidisciplinary integrated and

comprehensive service for wide ranging inherited, familial and genetic cardiovascular conditions. The main components of GFHC include core facilities, clinical service development, genetic and clinical counselling support and community service for predominantly prevention and targeted health surveillance (Figure 1).

The individual consumer, a researcher, patient or clinician, can approach GFHC with a specific enquiry or service. The consumer provides information and relevant professional input in relation to the question or service. The Executive team then, through an expert or the working group reviews the individual enquiry. The executive team may reply direct or refer to a participating center or a specific professional to deal with the specific enquiry or question. Enquiries on clinical care matters, health management and support, are referred to the lead regional executive.

## CARDIOVASCULAR GENOMIC MEDICINE

It is widely accepted that genetic and genomic factors have key roles in the etiology, pathogenesis and outcomes in several common and rare cardiovascular diseases. Inherited cardiovascular conditions represent selected diseases that impact on individual patient and closely related family members. In contrast, there are several complex cardiovascular diseases caused by mutations and pathogenic variations spread across the human genome. These individually carry low risk but collectively predispose the individual for adversely interacting with environmental and life style factors resulting in the complex cardiovascular phenotype. The emergence of cardiovascular genomic medicine as a distinct sub-specialty has now set out the scientific basis of targeted and precision clinical diagnosis, pharmaco-therapy, best case selection for devices, and clinical surveillance for '*at-risk*' family members. Families affected or aggrieved from sudden unexplained death in the family can now hope to have positive applications from cardiovascular genomic medicine.

The whole field of cardiovascular genomic medicine is new with limited genomic understanding and data applicable for wider clinical use. Recent reports have set the scene. And necessary agenda for genomic applications in precision and personalized cardiovascular medicine [10;11]. There are only few research centers engaged in structured genomic research, mostly located in developed nations. It is extremely

important to raise awareness, develop integrated cardiovascular genomic research infrastructure and enhance capacity for translational and applied research. Similar approach and initiatives in other field, such as cancer research and neuro-muscular diseases, have led to development of multi-center International network. These facilities also provide opportunity for systematic clinical genomic research fellowships targeted at different levels.

The GFHC aims to establish the ***International Centre for cardiovascular genomic medicine*** (ICCVGM) leading and coordinating with partner and collaborating centers in key emerging nations of the developing world. Currently, leading academic centers in India, Sri Lanka, Egypt, South Africa and Brazil have agreed to join and collaborate with the proposed ICCVGM (Figure 2). In addition, these collaborating units have also pledged to support the GFHC. It is anticipated that such a move would be supported and funded by participating countries. Clinical and academic leaders in human genomics, genomic technology, bio-informatics, health data management, cardiovascular medicine and public health are willing to join and steer through this ambitious and wholly justified project.

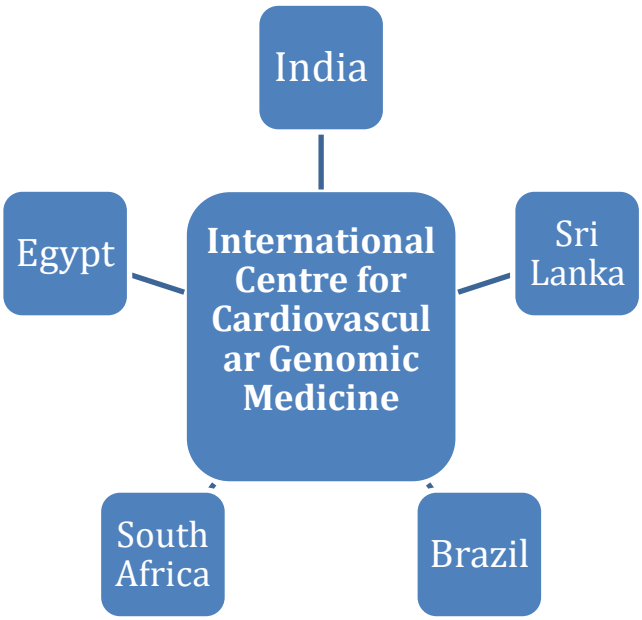


**Figure 2: International Centre and Collaborating Countries for Cardiovascular Genomic Medicine.**

It is envisaged that the proposed cardiovascular genomic medicine initiative is recognized as one of the major global activities within the broader global genomic initiatives led by the key global genomic organizations, specifically the Genomic Alliance for Global Health (GA4GH; www.ga4gh.org ); the Global Genomic Medicine Collaborative (G2MC; www.g2mc.org ); the Global Genomic Nursing Alliance (www.g2na.org ), and the International Federation of Human Genetic Societies (www.ifhgs.org ). In addition, the center would work in close liaison with the Sanger- Wellcome Genome Centre (www.sanger.ac.uk ), the Genomics England Ltd (www.genomicsengland.co.uk ), and the NIH funded ClinVar-ClinGen (www.clinicalgenome.org) .

The ICCVGM has set out the following objectives-

- Develop a transcontinental cardiovascular genomics research and capacity building partnership in genomic and precision medicine
- Enhance number of cardiovascular disease patients with an accurate genetic and genomic diagnosis
- Develop and maintain comprehensive and integrated cardiovascular genomic database to assist researchers for new drug and devices discovery and development
- Create and maintain "clinical trial ready" cohorts for new cardiovascular drug and devices development
- Develop and sustain the clinical capacity in cardiovascular genetic diseases by training a cohort of clinical academic researchers.
- Ensure governance and ethical standards as per international standards.

**Scope of Cardiovascular conditions**

The International Centre for Cardiovascular Genomic Medicine (IC-CVGM) in collaboration with the overseas collaborating centers aims to focus on developing the cutting edge applied clinically oriented research projects related to the whole range of cardiovascular diseases. The following groups of cardiovascular genetic and genomic disorders are of interest. However, several other disorders could also be included. Examples include-

- Clinical and genomic studies in anatomic cardiovascular anomalies- fetal, pediatric and adult
- Mendelian and/or structural genome disorders of heart and blood vessels; for example, microdeletion (22q deletion) disorders. Congenital heart defects in children and adults
- Single gene (Mendelian) cardiac diseases of heart muscle (inherited cardiomyopathies), and cardiac electrical current and rhythm (inherited cardiac conduction diseases and cardiac arrythmias/ ion channelopathies)
- Single gene (Mendelian) vascular diseases of the pulmonary vasculature (for example, primary pulmonary arterial hypertension) and systemic vasculature including syndromic (Marfan, Loeys-Dietz, vascular Ehlers-Danlos) and non-syndromic aortopathies and arteriopathies (for example hereditary hemorrhagic telangiectasia)
- Non-cardiac genetic diseases with secondary cardiovascular structural and functional manifestations;

  **for example**, Duchenne muscular dystrophy, myotonic dystrophy, familial hypercholesterolemia (risk for early onset coronary heart disease), adult onset polycystic kidney disease (risk for early onset systemic hypertension), and metabolic storage diseases.
- Inherited metabolic diseases complicating cardiovascular manifestations and/or secondary functional disruption.
- Mitochondrial genome (mtDNA) disorders with cardiovascular involvement
- Genetic susceptibility or host resistance to cardiovascular involvement in chronic inflammatory or auto-immune diseases; **for example**, amyloidosis and sarcoidosis
- Design, planning and conducting the population specific large-scale genome wide association studies (GWAS) in complex cardiovascular phenotypes including systemic hypertension and coronary artery disease.
- Design, planning and participating in the multi-center studies related to pharmacogenomics of cardiovascular adverse drug reactions (ADRs).

- Design, planning and participating in the multi-center genomic studies related to cardiovascular manifestations in nutritional disorders; for example, vitamin D deficiency.
- Set out protocols, clinical pathways and surveillance guidance for the early diagnosis, management and prevention of life- threatening complications, for example sudden unexplained death, and early onset of clinical manifestations [12; 13].

**Role of the International Centre**

- Development and/or endorsement of the evidence-based clinical protocols for the diagnosis and management of single gene (Mendelian), oligogenic or multigenic, or mitochondrial inherited cardiovascular diseases.
- Facilitating and coordinating guidelines on the diagnosis and management of congenital heart defects in children and adults.
- Development and implementation of the up to date guidelines on the diagnostic genomic analysis with particular reference to whole genome sequencing and the variant interpretation.
- Central coordinating center of excellence for cardiovascular genomic medicine (CVGM) research and academic training.
- Design and planning research projects focused on applied and translational aspects of cardiovascular genomics.
- Facilitate and coordinate genomic laboratory analysis for the overseas collaborating centers.
- Provide and lead the bioinformatic/computational biology input for the overseas collaborating centers.
- Host the cardiovascular genomic medicine database with active input from the overseas collaborating centers.
- Lead on the 'clinical trial' ready selected cohorts for cardiovascular drug and devices testing.
- Lead and/or coordinate the multi-center clinical trials for drug development and licensing.

**Role of the Overseas collaborating Centre**

- Development and implementation of the evidence-based clinical protocols for the diagnosis and management of broad range of inherited cardiovascular conditions (ICC) in line with the international protocols.
- Adopting and promoting the diagnostic genomic testing for single gene (Mendelian), oligogenic or multigenic, or mitochondrial inherited cardiovascular diseases including complex disorders with particular reference to congenital heart defects.
- Development of the regional/ national classified clinical genomic database for ICC in line with international gene/genome nomenclature and the human phenotype ontology.
- Development and implementation of the local/ regional/ national approved (legal and ethical) guidelines for providing access and/or sharing the epidemiological, clinical and genomic data with the central and other collaborating CVGM centers.
- Aim for developing the Centre of Excellence for CVGM research and academic training.
- Development and funding for conducting applied and translational CVGM research on regional and/or national basis.
- Identification and development of the 'clinical trials' ready cohorts for new drug or devices development and licensing.
- Design, project development and conducting the multi-center clinical trials (Phase II or III) in collaboration with the Central and other country nodal collaborating centers.
- Participation and active engagement in the clinical research and academic training with the main emphasis at Masters (MSc) or Doctoral level (PhD/MD).
- Active participation with the post-doctoral and senior clinical scientist training programs

**Summary**

Significantly higher global incidence and prevalence of genetic, inherited and familial cardiovascular conditions (IFCC) pose a huge challenge and implications for developing clinical and preventive cardiovascular healthcare. The huge burden of these conditions and extremely limited resources together with comparatively lower standard of the healthcare infrastructure in most developing and under developed nations remain a massive challenge. It becomes more complicated when faced with priorities set for nutritional and infectious diseases in the developing world. The Global Familial Heart Challenge (GFHC) aims to support and assist in developing targeted medical and healthcare facilities for wide ranging heterogenous IFCC. The advances in genomics and related *omics* disciplines have enabled precision and personalized medical care including the prevention. The new emerging field of cardiovascular genomic medicine is included in most tertiary cardiology services. There is global need for the network of dedicated CVGM collaborating centers coordinated by an international base and centrally managed public accessible clinical and genomic database. It is achievable with proper planning and investments for establishing the core genomic medicine infrastructure shared by leading specialist healthcare services. The global drive for genomic medicine and healthcare is the main focus of leading global genomic initiatives and alliances [14].

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