




THE GENOMIC MEDICINE FOUNDATION (UK)

FELLOWSHIP, SCHOLARSHIP, EDUCATION AND PROMOTION OF GENOMIC APPLICATIONS IN MEDICINE,  
HEALTHCARE AND SOCIO-ECONOMIC PROGRESS



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# The IX International Cardiovascular Genomic Medicine Conference 23 & 24 October 2023, Edinburgh, Scotland, UK

## **Welcome- Introduction**

Welcome ALL to the IX International Cardiovascular Genomic Medicine Conference.

In 2007, the first cardiovascular genetics conference was held in Cardiff, Wales, UK. Around that time, the knowledge base and role of direct genetics input in managing the inherited cardiac conditions was very limited.

However, medical and health professionals, particularly cardiologists and related disciplines, recognised the relevance and scope of genetics and the emerging genomics in the future progression of cardiovascular medicine. The first conference was a tremendous success. The Wales Gene Park, under the auspices of the Institute of Medical Genetics, Cardiff University committed itself to the series. Since 2011 to 2017 this was held in Cardiff. All events were remarkably successful and brought forward the key advances and expanding knowledge base of cardiovascular genetics and genomics in clinical practice of cardiology, cardiovascular surgery and other related fields. The role of clinical genetics, genetic counselling and diagnostic genetic/ genomic testing got firmly rooted.

In 2019, the first conference outside Wales was held in York, England, UK. This conference (7th in the series) shifted the focus from limited genetics input to the wider genomic medicine. In recognition of the historical importance of Sir William Harvey in the development of cardiac sciences, large majority agreed to establish the William Harvey Oration as part of the biennial cardiovascular genomics conference series. The first oration was delivered by Professor William McKenna, one of the pioneers and global leaders of the cardiovascular genetics.

The next conference (8th in the series) was held virtually due to the Covid pandemic. It was remarkably successful with several key experts from world over. The second William Harvey Oration was delivered by Professor Dan Rodden of the Vanderbilt University, Nashville, TN, USA. This year, fortunately, we have managed to stage the IX International Cardiovascular Genomic Medicine Conference in the beautiful city of Edinburgh, Scotland hosted by the Scottish Royal College of Surgeons. The main theme of this major event is the “Precision & Personalised Cardiovascular Medicine’. The scientific programme, delivered by leading global experts in the field, includes plenary key note lectures, scientific oral and poster sessions. Professor Arthur Wilde from the University of Amsterdam, Netherlands is invited to deliver the Third William Harvey Oration.

## **Acknowledgements**

We gratefully acknowledge and appreciate support and guidance from several people, particularly members of the Organising and Scientific Committees. The educational relevance of this conference is acknowledged by the UK Federation of the Royal Colleges of Physicians with 13 hours of CPD credits. We gratefully appreciate our sponsors of this event without which the conference could not be presented in the current format.

### **Organising Committee**

Prof. Dhavendra Kumar, The Genomic Medicine Foundation UK (Chair)

Dr. Wayne Lam, University of Edinburgh, UK

Dr. John Dean, University of Aberdeen, Scotland, UK

Mr. Roan Fulton, RCS- Surgeons Quarter, Edinburgh, Scotland, UK

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Prof. Bill Newman (Centre for Genomic Medicine, Univ. Manchester, UK)

Prof. Christopher Semsarian (University of Sydney, Australia)

## Messages



**William J. McKenna, BA, MD, DSC, FRCP, FMEDSCI, FESC, FACC**

**Professor William McKenna is Emeritus Professor of Cardiology at University College London and Emeritus British Heart Foundation Chair of Molecular Cardiovascular Sciences. His main interests have been in clinical and basic research of the cardiomyopathies. His work has contributed to the identification of disease-causing genes in hypertrophic, dilated and arrhythmogenic right ventricular cardiomyopathy, to the establishment of new diagnostic criteria within the context of familial disease, and to the establishment of algorithms to identify patients at high risk of sudden death.**

**“Well done once again in putting together an outstanding program which brings the frontier of Cardiovascular Genomic Medicine to a growing community in the UK and globally. The increasing application of familial and genetic evaluation in the inherited cardiovascular diseases has taken us from a phenotypic to an etiological diagnosis and is now beginning to impact on management. Your initiative enabling quality genomics medicine meetings will be increasingly important going forward.**



**Professor Sue Hill DBE PhD DSc CBiol FRSB Hon FRCP Hon FRCPath is the Chief Scientific Officer for England and the head of profession for the healthcare science workforce in the NHS and associated bodies, providing professional leadership and expert clinical advice across the health and care system.**

**“This is an excellent conference which will be delivered by a world class faculty highlighting the important role that genomics will play in the care of cardiovascular patients.”**



**Sir Mark Jonathan Caulfield MD, FRCP, FESC, FPharm, FBHS, FMedSci  
Vice Principal for Health Queen Mary University of London Faculty of Medicine and  
Dentistry; Director of the NIHR Bart's Biomedical Research Centre; Formerly  
Director William Harvey Research Institute and Chief Scientist Genomics England.**

**“The organisers of the Ninth Cardiovascular Genomic Medicine conference have yet  
again created an excellent programme.”**



A Massive thanks to our Sponsors



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## Programme

The IX Biennial International Cardiovascular Genomic Medicine Conference

Theme: “PRECISION CARDIOVASCULAR MEDICINE”

Day 1 Monday 23rd October 2023

0800 Reception/ Registration

0900 Welcome/ Introduction

Professor Dhavendra Kumar, William Harvey Research Centre, Bart’s Medical School, QMUL, UK

0915- 1115 Session I: Diagnostic cardiovascular genomics

Chair- Professor Mary Porteous, Clinical Geneticist, Edinburgh, Scotland

1. Dr. Lorenzo Monserrat, Naevia Medical, La Coruna, Spain

‘Genomic evolution of diagnostic cardiology’

2. Prof. James Ware, Imperial, London

‘Genotype/phenotype in inherited cardiovascular conditions: do genomic biomarkers yield clinically-useful predictions?’

3. Dr. John Dean, University of Aberdeen, Scotland, UK

‘The sudden cardiac death- the Scottish experience

1115 Coffee break



1145-1330 Session II: Genotype-Phenotype ontology in cardiovascular genomics

Chair: Dr. John Dean, Clinical Geneticist, Aberdeen, Scotland

4. Dr. Farrah Khawaja, Deputy Director of Genomics Quality Assessment (GenQA), Royal Infirmary of Edinburgh, Scotland, UK.

‘Challenges of genome diagnosis in clinical cardiology’

5. Dr. Verity Harthill, Leeds Institute of Medical Research, University of Leeds, St James University Hospital, Beckett Street, Leeds, UK

‘Understanding the genetic basis of congenital heart disease; whole genome sequencing opens new avenues for investigation, but significant challenges remain’

1330- 1430 LUNCH

1430- 1500 Session III: Posters viewing

1500-1600 Session IV: ‘Multi-OMICS Cardiovascular Medicine’

Chair- Prof. Martin Denvir, Cardiologist, Edinburgh, Scotland

6. Prof. Seema Mittal, Hospital for Sick Children, Toronto, Canada

“A multi-omics approach to diastolic heart failure”

7. Dr. Anna Maria Choy, Cardiologist, Univ. Dundee, Scotland

‘ Multi-disciplinary management of arrhythmia syndromes’

1600-1630 TEA

1630-1730 Session V: Cardiovascular genomic precision medicine- back to the future’

Key Note Lecture: Chair- Prof. James Ware, Imperial College, London.

8. Prof. Perry Elliott, UCL, London, UK

‘Emerging novel treatment prospects for cardiomyopathies’

1730 Panel discussion- Reflections of the Day

**CLOSE OF DAY 1**

1930 Scottish Reception/ Welcome

2000 Conference Dinner (Smart casual / Traditional/ National)

Day 2 Tuesday 24th October 2023

0830-0930 Reception/ Registration

0930-1015 Key note lecture, Chair: Prof. Dhavendra Kumar

9. Prof. Sir Munir Pirmohamed, University of Liverpool, UK ‘Pharmacotherapy cardiovascular genomic medicine’

1015-1130 Session VI: ‘Oral Award presentations (10 minutes each with 5 minutes Q/A & Discussion)

Chairs: Dr. Claire Turner, Clinical Geneticist, Exeter, England. UK

Dr. Ruth McGowan, Clinical Geneticist, Glasgow, Scotland.

Judges: Dr. Wayne Lam, Edinburgh, Scotland; Dr. Catherine Mercer, Southampton, England; Dr. Siv Fokstuen, Geneva, Switzerland.

10. ‘Double Trouble in the hypertrophic heart’

A. Kissopoulou, Department of Cardiology, County Hospital-Ryhov, Jönköping, 55185, Sweden

11. ‘One test, a lifetime of precision familial hypercholesterolemia report’

Aditi Babel, Imperial College, University of London, UK

12. ‘Distinct signaling events from the overexpression of the PRKAG2 R302Q variant of AMPK lead to Hypertrophic phenotype’

Vanya Vaidya, Department of Cardiology, PGIMER, Chandigarh, India

13. ‘WGS analysis reveals an Alu retrotransposon element insertion in the NEXN gene confirming a diagnosis of paediatric onset autosomal recessive dilated cardiomyopathy (AR DCM) in a family’

Mary Gable, Bristol Genetics Laboratory/South West Genomics Laboratory Hub, Southmead Hospital, Bristol, England, UK

14. ‘Prediction of Atrial Fibrillation using Polygenic Risk Scores for Cardiovascular Risk Factors’

Julia Ramirez, Aragon Institute of Engineering Research, University of Zaragoza, Zaragoza, Spain; Centre of Clinical Pharmacology and Precision Medicine, William Harvey Research Institute, Queen Mary University of London, U.K

1130 COFFEE

1145-1315 Session VII 'Genomic precision cardiovascular medicine

Chair: Prof. Sandi Deans, University of Edinburgh, Scotland

15. Prof. Nimesh Desai, Cardiovascular Surgery, University Pennsylvania, Philadelphia, USA

'Genotype driven surgical management of aortopathies'

16. Prof. Sandosh Padmanabhan, Glasgow, Scotland, UK

'Genomics and the cardiovascular continuum'

17. Dr. William Young, Bart's Heart Centre, Bart's Hospital & Queen Mary University of London, UK

'Molecular autopsy in sudden cardiac death'

1315-1430 LUNCH/ POSTERS

1430-1600 Session VIII: Personal genomics in preventive cardiology

Chair: Prof. Sandosh Padmanabhan, University of Glasgow

18. Prof. Manuel Mayr, Imperial College, London.

' Cardiovascular proteomics of coronary artery disease.'

19. Prof. Panagiotis Deloukas, Queen Mary University, London.

'Polygenic scoring systems in preventive cardiology'

20. Prof. Patricia Munroe, Queen Mary University, London

'Complex genomics of systemic hypertension'

1600-1630 TEA

1630-1730 'The Third William Harvey Oration'

Facilitator- Professor Sir Munir Pirmohamed

21. Invited speaker- Prof. Arthur A.M. Wilde, University Amsterdam, 'Evolution of channelopathies in clinical cardiology'

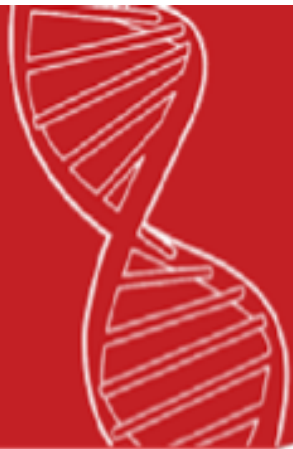
1730 Reflections of the Day ; Best Oral and Poster presentations awards

Vote of Thanks- Close and Bon Voyage



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## Posters & Abstracts

Distinct signaling events from the overexpression of the PRKAG2 R302Q variant of AMPK lead to Hypertrophic phenotype

Vanya Vaidya<sup>1</sup>, Zubin Singh Rana<sup>2</sup>, Pradeep Punnakal<sup>2</sup>, Madhu Khullar<sup>3</sup>, Ajay Bahl<sup>1\*</sup>, Anupam Mittal<sup>4\*</sup>

<sup>1</sup> Department of Cardiology, PGIMER, Chandigarh

<sup>2</sup> Department of Biophysics, PGIMER, Chandigarh

<sup>3</sup> Department of Experimental Medicine and Biotechnology, PGIMER, Chandigarh

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**Introduction:** The Protein Kinase AMP-Activated Non-Catalytic Subunit Gamma 2 (PRKAG2) cardiac syndrome is characterized by glycogen accumulation in the cardiac tissue that is often associated with unusual patterns of hypertrophy and conduction abnormalities. Variations in PRKAG2 have been associated with rare, early onset autosomal dominant inherited disease that involves ventricular pre-excitation, supraventricular arrhythmias and cardiac hypertrophy.

**Methods:** Using the Trio-exome sequencing, we have analysed a three generation family, which was reported to have a pathogenic variant in PRKAG2 gene that is c.905G>A (p.Arg302Gln) variant. The variant was reconfirmed by Sanger sequencing in the proband and the mother. The proband developed symptoms at the age of 29, while his mother at the age of 60 years. For functional studies, we have made clones for human WT PRKAG2 and the variant (Arg302Gln). To understand the mechanisms involved in disease pathogenesis, H9C2 cardiomyocyte cell line was transfected with mutated and wild PRKAG2 plasmid. We have analysed foetal genes through qRT-PCR, autophagy genes through immunostaining and Western blot and Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup> channels through transcriptomics and patch clamp.

**Results:** PRKAG2 p.Arg302Gln led to hypertrophic phenotype in H9C2 cardiomyocytes. We have observed the increase mRNA expression of foetal genes (ACTA1, MYH6, BETA-MHC, ANP, BNP) which indicates that cells have shifted to hypertrophic phenotype. Confocal microscopy data also corroborated with mRNA expression of foetal genes and the increase in the cell size of the cardiomyocytes was observed. Autophagy marker LC3 expression was found to be decreased as compared to control as was confirmed by confocal microscopy.

**Conclusion:** Using multi-omics approach, we were able to confirm the progression of hypertrophy due to the variant in the cardiomyocytes.

### KEYWORDS:

1. Hypertrophy
2. Glycogen accumulation
3. Conduction abnormalities
4. Autophagy

Understanding the genetic basis of congenital heart disease; whole genome sequencing opens new avenues for investigation, but significant challenges remain.

Verity Hartill<sup>1,2</sup>, Mitra Kabir<sup>3</sup>, Sunayna Best<sup>2</sup>, Kathryn E Hentges<sup>3</sup> and Colin A Johnson<sup>1</sup>

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This research was made possible through access to data and findings in the National Genomic Research Library via the Genomics England Research Environment.

Congenital heart disease (CHD) is the commonest congenital defect, affecting around 1 in 100 live births. CHD can be non-syndromic and isolated, or can present as part of a congenital anomaly or neurodevelopmental syndrome. The genetic aetiology of a large proportion of both syndromic and non-syndromic congenital heart disease remains unexplained. A recent focus on “de novo” genetic variants has been productive in CHD research, showing that, at least in some cases, heart defects are caused by a new mutation in the affected individual. It is expected that further investigation into the genetic basis of CHD will provide insight into the aetiology of this common congenital anomaly, thus benefitting the wider population.

Here we describe our previous progress using whole exome and whole genome sequencing in families with recurrence of CHD, for example in confirming the links between isolated CHD and motile ciliopathy genes. We discuss our recent study into the genetic causes of CHD within the 100,000 Genomes Project. In this study we have developed a Gene Discovery Pipeline, which combines de novo variant analysis with computer-assisted machine-learning, to identify and prioritise candidate genes for CHD (n=79).

Significant challenges remain in CHD genetics, including the confounding effects of genetic heterogeneity, incomplete penetrance, incomplete phenotyping and the complexities of working with large datasets. In spite of these challenges, large scale sequencing projects, such as the 100,000 Genomes Project present many opportunities for advancing our scientific understanding of this common condition.

One test, a lifetime of precision familial hypercholesterolemia reports  
Authors: Aditi Babel<sup>1</sup>, Mahmoud Barbir<sup>2</sup>, Emma Neves<sup>2</sup>, Riyaz Patel<sup>3</sup>, Steve E Humphries<sup>4</sup>, Cian Murphy<sup>4</sup>, Theodosia Charitou<sup>5</sup>, Mark Bartlett<sup>6</sup>

#### Affiliations

1 Imperial College Healthcare NHS Trust, London, U.K.

2 Royal Brompton Hospital, London, U.K.

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4 University College London Hospitals NHS Foundation Trust, London, U.K.

5 University of Thessaly, Thessaly, Greece

6 StoreGene Ltd, London, U.K.

#### Introduction

Familial hypercholesterolemia (FH) affects approximately 1 in 250 people in the UK, of which less than 10% are diagnosed<sup>1</sup>. Here, we evaluate the utility of the StoreGene whole genome sequencing (WGS) approach to comprehensively characterise individuals with FH.

#### Methods

Saliva samples from 16 participants who met the Simon-Broome FH diagnostic criteria were sent for DNA extraction and sequencing. Four StoreGene reports were generated: 1) FH 4-gene variant assessment, 2) LDL-C polygenic risk score (PRS), 3) SLCO1B1 variant linked to Simvastatin-induced myopathy, and 4) Lp(a) concentration gene scores. Results were compared to previous biochemical and panel tests by NHS-accredited laboratories.

#### Results

One sample per participant was used to carry out WGS, and StoreGene reports were generated in 22 days, vs. 2 samples and 42 days for comparator testing<sup>2</sup>. One sample was discarded due to low mapping quality. 15 WGS samples were analysed yielding 100% concordant results with comparators. Identical pathogenic variants were identified in 9 (60%) of cases, with 11 (73%) cases likely to have a polygenic aetiology (LDL-C PRS > 5th decile). The c-index for Lp(a) concentration between the two methods was 0.79. A pharmacogenomic risk variant in SLCO1B1 was identified in one participant.

#### Conclusions

StoreGene WGS showed significant benefits where multiple testing is required, including concordant outcomes with available panel tests, faster turnaround time, a wider range of available tests, and minimised sample collection with environmental savings on laboratory consumables. Further research should measure its cost-effectiveness and clinical utility.

[1] Familial Hypercholesterolemia Section (NHS England 2020) (accessed 21/08/2023)

[2] SouthWest Genomic Laboratory Hub Target Turnaround Times (accessed 21/08/2023)

Key words: familial hypercholesterolemia, cardiovascular disease, whole genome sequencing, personalised medicine, pharmacogenomics, diagnosis



## Double Trouble in the hypertrophic heart

A.Kissopoulou<sup>1</sup>, L.Guthreau<sup>1</sup>, T. Stumpf<sup>1</sup>, C.Gunnarsson<sup>2</sup>

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Key words: transthyretin cardiac amyloidosis, hypertrophy, genetic testing

Introduction: Cardiac amyloidosis and hypertrophic cardiomyopathy are associated with increased left ventricular wall thickness. Differential diagnosis of these entities can be challenging. To our knowledge, this is the first reported case of a patient with hereditary cardiac amyloidosis and hypertrophic cardiomyopathy.

Case presentation: A 45-year old man, from Nigeria was diagnosed with hypertrophic cardiomyopathy in 2000 when he experienced syncopal episodes during running. Echocardiography revealed a hypertrophied septum around 24mm without any outflow obstruction. He received an ICD and had several appropriate ICD discharges in 2014. No arrhythmias were noticed after increasing the beta-blocker. Regarding his family history, his father died suddenly at the age of 55 during exercise and his younger sister has sought for palpitations. Genetic testing performed in 2022 detected two pathogenic variants: one heterozygote in MYPBC3(c3330+5G>C) associated with familial hypertrophic cardiomyopathy and a heterozygote in TTR(c.424G>A p.(Val142Ile)) that has been reported to cause cardiac amyloidosis. This variant is found in 3.5% of African Americans and is defined as a late-onset cardiac amyloidosis. New echocardiography depicted a more pronounced concentric hypertrophy of the left ventricle, with some septal dominance. Cardiac technetium-99m pyrophosphate scintigraphy strongly suggested transthyretin amyloidosis. No peripheral nervous system involvement was noticed. Taking into account that our patient had obvious signs of cardiac amyloidosis, he received tafamidis, an amyloid stabilizer and keeps doing well.

Conclusion: Hereditary transthyretin cardiac amyloidosis and hypertrophic cardiomyopathy can co-exist. This case illustrates the importance of genetic testing to clarify the diagnosis of cardiac hypertrophy and its impact on therapeutic options.

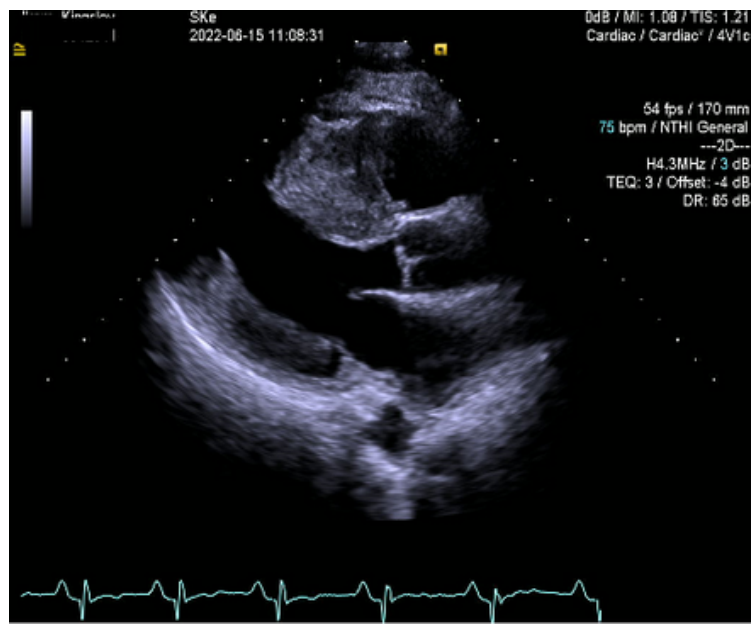


Figure 1, Echocardiography of the patient

## TITLE

Genetic analysis of Omani families with cardiomyopathies and arrhythmias.

## AUTHORS

Fahad Al Hattali<sup>1,2,3</sup>, Pier Lambiase<sup>2</sup>, Andrew Tinker<sup>3</sup>

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## ABSTRACT

Whole Exome Sequencing (WES) on trios i.e., patient and parents has proven an efficient way to identify variants in many families and thus in this study we performed trio-WES on five Omani families with cardiomyopathies and arrhythmias. The index patients were already subjected to an almost comprehensive panel of genes related to cardiovascular diseases. Nonacus Cell3 exome library preparation kit was used for the trio WES. Prioritization for rare and exonic variants were done using Exomiser and Qiagen softwares based on the hypothesis that the mode of inheritance is Autosomal Recessive (AR) since all families are of consanguineous marriages. Then final variants were confirmed using Sanger sequencing and segregated to the affected/ unaffected family members. The next step involved generating induced Pluripotent Stem cells (iPSc) and then differentiated them into cardiomyocytes and then we knockdown the genes of interest using siRNA and measure the effect using qPCR and Calcium Transient Assay.

One family showed a variant in the ALPK3 gene which already associated with HCM and DCM. Three families analysis showed three variants shared following AR inheritance which have never been associated with cardiovascular phenotype. One family showed no shared variants. Based on prediction of pathogenicity we selected, RAD9A, AFF4 and HMGA1 genes for siRNA knockdown using in vitro iPSc-CMs. Quantitative PCR (qPCR) showed that we successfully suppressed more than 80% of the genes at 80nM siRNA. The Calcium Transient imaging assays using Flu-4 is yet to be completed which will compare rise time, calcium transient duration at 50% and 90% of decay following the peak amplitude and change in amplitude.

Trio-WES revealed shared variants following AR inheritance that never been associated with cardiovascular phenotype. Functional characterization using iPSC-CMs followed by siRNA knockdown of novel genes is a great way to establish new causative genes in cardiovascular diseases.

## KEYWORDS

Trio-WES, siRNA, cardiovascular, arrhythmia, cardiomyopathy

## Prediction of Atrial Fibrillation using Polygenic Risk Scores for Cardiovascular Risk Factors

Julia Ramírez<sup>1,2</sup>, Stefan van Duijvenboden<sup>2,3</sup>, William J. Young<sup>2,4</sup>, Andrew Tinker<sup>2</sup>, Pier D. Lambiase<sup>4,5</sup>, Michele Orini<sup>5</sup>, Patricia B. Munroe<sup>2</sup>

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**Background:** Risk stratification for atrial fibrillation (AF) is suboptimal despite high cardiovascular comorbidity and mortality. Polygenic risk scores (PRSs) for AF predict risk independently from traditional risk factors. We assessed utility for risk stratification when including PRSs for multiple cardiovascular traits.

**Methods:** 379,574 European participants from UK Biobank without known cardiovascular conditions were included (median follow-up 11.5 years, 6.4% AF cases). In a training subset (50%), we built three scores using AF risk factors in Cox analyses. Score s1 included sex and age, score s2 included s1 and an AF PRS, and s3 included s2 and multiple PRSs for cardiovascular traits that remained independently associated with AF. In an independent test subset (50%), we evaluated performance using the area under the curve (AUC), hazard ratios (HRs) and net reclassification index (NRI).

**Results:** PRSs for coronary disease, body mass index, systolic blood pressure, tryglicerides, PR interval, QRS duration and heart rate were included in s3. Score s3 had a higher AUC than s2 (0.749 versus 0.747,  $P=1.6 \times 10^{-9}$ ). The HR (95% confidence interval) for individuals in the top versus bottom 20% of the s3 distribution was 4.81 (4.62–5.00), versus 4.76 (4.57–4.95) for s2. Mean NRI for s3 versus s2 was 1.8%. Score s3 reclassifies 1,757 individuals as  $\geq 10\%$  AF risk, where 168 would have an AF event within the follow-up period.

**Conclusions:** Although our results require validation, they suggest adding PRSs for multiple cardiovascular traits improves risk stratification for AF, potentially identifying individuals who may benefit from early prevention measures.

WGS analysis reveals an Alu retrotransposon element insertion in the NEXN gene confirming a diagnosis of paediatric onset autosomal recessive dilated cardiomyopathy (AR DCM) in a family

Gable M1;Pennock M1; Nash I1; Williams M1; Whittington R1; Archer B1; Stals K2; Shannon N3 Berry I1.

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We present a paediatric onset AR DCM family where genomic testing was requested in a 4 week old presenting with DCM and strong family history - one sibling died at 7 weeks (SIDS) and second died shortly after birth with DCM. NGS analysis of a bespoke paediatric cardiomyopathy gene panel (2015) revealed a heterozygous NEXN nonsense variant, c.424G>T p.(Glu142\*), reported as a VUS due to the uncertainty of the inheritance pattern.

With the evolution of genomic testing and increased sensitivity of technologies, trio WGS analysis of the Cardiomyopathies – including childhood onset gene panel (R135) (2022) revealed a heterozygous 299 bp AluYd8 retrotransposon element insertion in the final exon of NEXN. Parental testing confirmed the insertion was in trans with the nonsense variant; both were subsequently classified as likely pathogenic using ACMG/ACGS variant interpretation guidelines<sup>1,2</sup>. Testing DNA from deceased siblings confirmed the presence of both variants, hence confirming the diagnosis of AR NEXN-related DCM.

AR NEXN-related DCM is rare with only a small number of cases being reported to HGMDPro. Though AR DCM is a clearly emerging inheritance pattern, as demonstrated by this family, the consequence of heterozygous NEXN variants is unclear. The increasing sensitivity of genomic testing improves detection of complex and structural variants in suspected recessive disease, when only one variant has been identified. Trio WGS analysis is a valuable approach in such cases, to determine the inheritance of detected variants.

We present this family and review the AR NEXN-related DCM published families to date.

Key words: paediatric onset AR DCM, trio WGS, NEXN gene, Alu retrotransposon.

References:

- 1) Richards et al (2015) Genet Med 17(5):405.
- 2) Ellard et al (2020) ACGS guidelines.

# Risk stratification for advanced atrioventricular block using electrocardiogram trait polygenic risk scores.

William J. Young<sup>1,2</sup>, Julia Ramírez<sup>1,3</sup>, Helen R. Warren<sup>1</sup>, Stefan van Duijvenboden<sup>1,4</sup>, Andrew Tinker<sup>1</sup>, Pier D. Lambiase<sup>1,5</sup>, Patricia B. Munroe<sup>1</sup>

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3. Aragon Institute of Engineering Research, University of Zaragoza, Zaragoza, Spain
4. Nuffield Department of Population Health, University of Oxford, Oxford, U.K.
5. Institute of Cardiovascular Science, University College London, London, U.K.

**Background:** Every year, >1 million pacemakers are implanted worldwide for advanced (2nd/3rd degree) atrioventricular block (AV-block), a potentially life-threatening cardiac rhythm disturbance. Electrocardiogram trait polygenic risk scores (PRS) are associated with AV-block independent of age and sex. However, to determine clinical utility, we must assess their performance alongside other risk predictors.

**Methods:** PRSs for PR-interval, spatial QRS-T angle (spQRSTa), P-wave and QRS-duration were constructed in European ancestry participants from UK-Biobank using previously reported lead genome-wide significant variants. 10-year AV-block risk (5,991 cases; 351,460 controls) was evaluated in Cox regression models adjusted for covariates age, sex, systolic blood pressure, prevalent diabetes, coronary disease and heart failure. Hazard ratios were calculated for all individuals, and after stratifying for sex and age. A Bonferroni-corrected significance threshold was applied ( $P < 0.0125$ ). Area under the curve (AUC) was calculated to compare performance when adding a PRS to the clinical predictors alone.

**Results:** Each PRS was independently associated with incident AV-block (hazard ratios [HR] range between 1.05-1.24). Comparing top vs bottom PRS deciles, HRs were: PR-interval 2.18 (1.86-2.56); P-wave 1.26 (1.08-1.47); spQRSTa 1.25 (1.07-1.45); QRS-duration 1.19 (1.03-1.39). Significant stratified analyses results were: QRS-duration and spQRSTa PRS for individuals <60 years; P-wave duration if >60 years; P-wave and spQRSTa PRS for males. The PR-interval PRS was significant in all analyses. AUCs did not significantly differ vs covariates alone.

**Conclusions:** Our findings highlight age and sex-specific associations for AV-block risk using electrocardiogram PRS. Larger case sample sizes in younger cohorts may identify applications for risk stratification earlier in life.

**Key words:** Polygenic risk scores, conduction disease, atrioventricular block, risk stratification

## -Identification of a novel founder nonsense variant in DSP causes Familial Cardiomyopathy in Multiplex Arabian Consanguineous Family with Four Affected Siblings

### Abstract

Introduction: Familial dilated cardiomyopathies (DCM) are a heterogeneous group of diseases that often have a genetic cause, and can lead to arrhythmia, heart failure and sudden death. Familial DCM is diagnosed when two or more family members meet the criteria for DCM. Methods: a multiplex family with four affected daughters all having familial DCM.

Autozygosity mapping and exome sequencing was conducted in the two of the affected siblings (the other two were deceased) followed by segregation analysis. Echocardiographic findings showed arrhythmogenic right ventricular cardiomyopathy. Results: Autozygosity mapping confirmed the two affected individuals shared IBD across the DSP gene (encoding Desmoplakin) locus at Chr 6. Analysis of exome data interestingly led to identification of homozygous nonsense mutation (c.4297C>T; p.Gln1433\*) rs1554108283 in exon 23 of DSP gene. It is a loss-of-function mutation that predicts a premature termination of translation. The parents are heterozygous carriers for the mutation which confirms the mutation is segregated with the disease phenotype. Remarkably, according to ACMG guidelines this mutation is classified as pathogenic. However, it is not cited in any genome browsers up to date. Conclusion: we reported a rare novel pathogenic nonsense variant causing desmosomal familial DCM in multiplex Arabian family with four affected siblings.

Keywords: Familial dilated cardiomyopathies; DSP gene; Consanguinity, sudden cardiac death

# CARDIAC GENETICS REFERRALS: SRI LANKA'S SINGLE CENTRE EXPERIENCE OVER 7 YEARS

## INTRODUCTION

Genetics is an evolving field in Sri Lanka. Genetic testing facilities have gradually developed, but it is not yet available for free of charge for patients in the government sector, despite free health in the island. Cost of testing is the main obstacle for more testing opportunities. Significant proportion of referrals for whole exome sequencing are directed to a university centred laboratory located in the financial capital of Sri Lanka.

## METHODS

Patients who were referred with cardiac phenotype and those who have been identified with variants in genes related to cardiac phenotype were filtered using the local Clinical Genetics Database for whole exome sequencing. Demographic data, phenotypic and genotypic data were analysed using electronic performance.

## RESULTS

Total of 13 referrals were included: 46 % of the referrals received in the last 2 years. Cohort comprises 61 % females. The Ages range from 8 months to 32 years. Number referred with primary cardiac phenotype was 10: no variant identified in 1 (10%) . Out of those where variant was identified, 66.6 % were cardiomyopathies (50 %; likely pathogenic, 50 %; variant of uncertain significance [VUS]), 1(11.11%) each with valvular pathology, and arrhythmogenicity. Detection of paternally inherited 2 VUS in cardiomyopathy related genes among one patient (11.11%) with cardiomyopathy and dysmorphism. Incidental detection of variants in cardiac genes were seen in 3 patients over the study period.

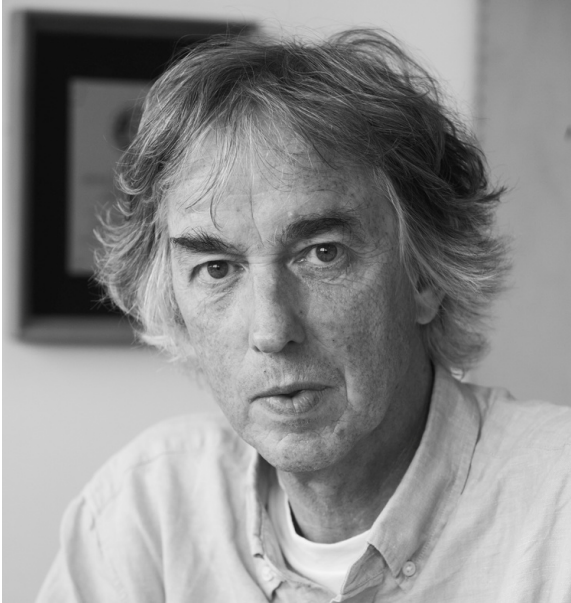
## CONCLUSION

Recent increasing trend in receiving referrals noted. Variant detection rate is satisfactory. Non availability of a wide range of testing for example microarray creates the gap in evaluating individuals with inherited variants of uncertain significance which are phenotypically not fully correlated.



### **The Third William Harvey Oration**

The 3rd William Harvey Oration is delivered by Professor Arthur A.M Wilde from the Academic Medical Centre, the University of Amsterdam, The Netherlands. He is one of the outstanding globally acclaimed cardiologists with special interests in genetic and molecular cardiology. He will speak on the 'Evolution of channelopathies in clinical cardiology'.



Arthur A.M. Wilde got his M.D. at the University of Amsterdam in 1983. After his Ph.D. in 1988, he started his Fellowship training in Cardiology at the Academic Medical Centre, and was registered as such in 1994. Afterwards he specialized in clinical electrophysiology at the Academic Hospital Utrecht. From the Netherlands Heart Association he was awarded a grant as Clinical Established Investigator for five years. In 1999, he became head of the Laboratory of Experimental Cardiology, and in 2003 head of the Department of Clinical and Experimental Cardiology (Academic Medical Centre). His major focus is on different aspects of inherited arrhythmia syndromes. In more recent years also genetic factors contributing to sudden cardiac death in the general population became a focus.

In 2011 he was appointed as member of the Dutch Academy of Science and in 2012 he received the Distinguished Investigator award of the Heart Rhythm Society.

Recent contributions include-

1. Cardiac Hypertrophy Modulates Risk in Patients With Inherited Cardiac Sodium Channelopathy
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**The Faculty**  
**Speakers; Session Chairs; Poster presenters**



**Professor Dhavendra Kumar, Chair Organising/ Scientific Committees**

An alumnus (Graduate, MBBS); Postgraduate, MD and Honorary Doctorate in Science, DSc) of the King George's Medical University, Lucknow, UP, India. He holds Fellowship of the Royal Colleges of Physicians (FRCPI & FRCP London) and Paediatric-Child Health (FRCPC). In addition, he is a Fellow of the American College of Genetics and Genomics (FACMG). He is one of the globally acknowledged genetic and genomic clinician. His special interests in clinical genetics include genetic diseases of children, inherited conditions of heart and blood vessels, genomic medicine and genomic applications in global healthcare.

He has authored/edited many textbooks and monographs in the field of clinical genetics, cardiovascular genetics and genomic medicine & healthcare. Main titles include 'Genetic Disorders of the Indian Subcontinent', 'Principles and Practice of Genomic Medicine', 'Genomics and Health in Developing World' and 'Clinical Molecular Medicine-Principles & Practice'. His books 'Oxford Specialist Handbook Inherited Cardiac Disease' and 'Medical & Health Genomics' received Highly Commended award at the British Medical Association Annual Medical Book Awards. Since 2016, he has served as the Serial Editor for 'Advances in Genetics' and serves on the editorial board of many biomedical journals.

He is passionate for raising awareness and promoting importance of the inherited cardiovascular conditions (ICC) in clinical cardiology and genetic/genomic in modern medicine. He is acknowledged with the benchmark practice of 'multi-disciplinary care for inherited/familial heart disease'. He founded and leads the 'Global Familial Heart Challenge' project for promotion; early detection, management and prevention of familial/ inherited heart diseases globally. He is an international authority in cardiovascular genomic medicine (CVGM) and leads the Global Network comprising of leading CVGM Centres. Since 2007, he has organized and led the Biennial International Cardiovascular Genetics and Genomics Conferences. He is the Founding Editor in Chief of the new biomedical journal 'Genomic and Molecular Cardiology' and co-author/co-editor of 'Cardiovascular Genetics & Genomics- Principles and Clinical Practice' and the 'Oxford Specialist Handbook Inherited Cardiac Disease'.

Professor Kumar is passionate for high quality healthcare in developing nations. His new project, the Global Consortium for Genomic Education (GC4GE) aims to enhance and empower healthcare providers in the developing world through genetic/genomic education and training. Pursuant to this initiative he is actively engaged with a number of global genomic medicine initiatives of the Human Genome Organization International (HUGO), Human Variome Project (Global Variome), Global Genomic Medicine Collaborative (G2MC) and Genomic Alliance for Global Health (GA4GH). He is the first Chair of the HUGO Genomic Education Committee. He founded and leads the Genomic Medicine Foundation (UK), a 'not-for-profit' organization that aims to support genomic and OMIC applications in medicine, healthcare and socio-economic welfare through scholarship, fellowship and mutually beneficial collaboration.

**Dr. Lorenzo Monserrat, MD, PhD, Cardiologist, La Coruna, Spain**



**Lorenzo Monserrat, MD, PhD Founder and Medical Director , Dilemma Solutions Researcher in University of A Coruña Founder of Health in Code Medical degree in Santiago de Compostela, Research Fellowship in Cardiomyopathies at St George's University Hospital in London. Specialist in Cardiology and PhD in A Coruña University. Diplomature in Design and Statistics in Health Sciences (Autonoma University, Barcelona). Former researcher of the Galician Health Service and Chief of the Inherited Cardiovascular Diseases Reference Unit in A Coruña University Hospital. Author of >150 papers focused on inherited cardiovascular diseases and cardiovascular genetics. Participation and leadership in multiple research projects on the field of cardiovascular genetics.**



**Dr Sandi Deans, National Laboratory & Scientific Lead (Genomics)  
NHS England**

Sandi Deans is the National Laboratory and Scientific Lead within the NHS England Genomics Team providing scientific oversight and leadership for the delivery of the NHS National Genomic Medicine Service and the NHS contribution to the 100,000 Genomes Project.

Dr Deans is a Consultant Clinical Scientist with an international reputation in the delivery and assessment of a wide range of molecular and genomic technologies in modern healthcare. She is also the Director of Genomics Quality Assessment (GenQA) part of the UK National External Quality Assessment Service (UK NEQAS) based in the Department of Laboratory Medicine, Royal Infirmary of Edinburgh.

Dr Deans is an Honorary Reader in Genomic Medicine at Edinburgh University and a Senior Honorary Lecturer in the Medical School, University of St. Andrews.

## **Catherine Mercer, MD FRCP**



**Dr Catherine Mercer is a Consultant Clinical Geneticist at University Hospital Southampton NHS Foundation Trust and an Honorary Senior Lecturer at the University of Southampton. She works as the Wessex Cardiac Genetics Lead, and along with the team, covers a population of 3.5 million. Dr Mercer has expertise in caring for families with isolated familial cardiac disease as well as those with syndromic diagnoses that include a cardiovascular component. Dr Mercer is active in research regarding gene identification, including the discovery of both NR2F2 in patients with left ventricular outflow tract obstruction and more recently a novel monogenic cause of familial Ebstein's anomaly.**

## Prof. James Ware, Cardiovascular Genomic Medicine, Imperial/ Brompton, London, UK



**Dr. James Ware** is a Reader in Genomic Medicine at Imperial College London and the MRC London Institute of Medical Sciences, and Consultant Cardiologist at Royal Brompton and Harefield Hospitals. He graduated from the University of Cambridge, trained clinically in London & Geneva, and pursued research training at Imperial College London, Harvard Medical School, and the Broad Institute of MIT & Harvard.

James' research aims to understand the impact of genetic variation on the heart and circulation, and to use genomic information for precision medicine. Clinical interests include the management of Inherited Cardiac Conditions, and the broader application of genetics and genomics to healthcare.



**Professor Seema Mital, Sick Kids, Univ. Toronto, Canada**



**Dr. Seema Mital is a Heart Failure and Transplant Cardiologist and Head of Cardiovascular Research at the Hospital for Sick Children, Toronto. She is Professor of Paediatrics at the University of Toronto and a Senior Scientist at the SickKids Research Institute. She is also the Heart and Stroke Foundation of Ontario Chair of Cardiovascular Science, and the Scientific Co- Lead of the Ted Rogers Centre for Heart Research.**

**Seema Mital has a strong translational research program focused on genomics, pharmacogenomics and stem cell applications to model childhood heart disease and discover new therapies. She has extensive experience in the genetics/genomics of congenital heart disease and heart failure, personalized medicine and clinical trials. She established the SickKids Heart Centre Biobank, a multi-centre biorepository of children and adults with childhood onset heart disease for genomics research, one of the largest international repositories of its kind.**

**She is the Scientific Co-lead of the Ted Rogers Centre for Heart Research Cardiac Precision Medicine Program established in November 2014. Mital is a Principal Investigator of the CIHR-funded Canadian National Transplant Research Program, the NIH-funded Pediatric Heart Network, and leads the ERAPerMed funded PROCEED network for Personalized Genomics in congenital heart disease. She serves on the Leadership Committee of the Functional Genomics and Translational Biology Council of the American Heart Association, and the Heart and Stroke Foundation**



**Dr. Anna Mario Choy, MD FRCP, Honorary Reader Cardiology, University of Dundee, Scotland.**



**Dr Anna Maria Choy is a Honorary Reader and a consultant cardiologist with interests in inherited and acquired arrhythmias. She is also the lead for international medical students at the medical school.**

**Prior to her appointment in 2004 to University of Dundee, she was an associate professor in Cardiology, and head of the Arrhythmia Service at the University of Malaya, an American Heart Association Fellow at Vanderbilt University, USA. Her research interests are arrhythmia related; focusing on implantable cardiac electronic devices for arrhythmia management, the familial arrhythmias, anti-arrhythmic drugs and atrial fibrillation. Dr Choy is also the national lead clinician for FANS (the Familial Arrhythmia Network for Scotland), a national specialist network for patients with malignant arrhythmias due to genetic disease. She was awarded the National Award for Outstanding Contribution to the Management of Inherited Cardiac Conditions from the Arrhythmia Alliance in 2009.**

#### **Impact of Research**

**Maintaining serum potassium in drug induced long QT syndrome. Her research on the importance of potassium in drug induced arrhythmias is cited as the supporting evidence in the recommendation of current American Heart Association and the American College of Cardiology on the Prevention of torsade de pointes in hospital settings. Dr Choy's work with FANS was recognized by the National Award for Outstanding Contribution to the Management of Inherited Cardiac Conditions from the Arrhythmia Alliance in 2009.**



**Prof. Perry M. Elliott (H-index 83, 37,824 citations) is Professor of Cardiovascular Medicine at University College London (UCL). He is director of the UCL Centre for Heart Muscle Disease, Head of Clinical Research at the Institute of Cardiovascular Science UCL and a consultant cardiologist in the Centre for Inherited Cardiovascular Disease at the Bart's Heart Centre, St. Bartholomew's Hospital London, UK. He studied medicine at St. Thomas's Hospital Medical School, London. After qualifying in 1987 he trained in general medicine, gaining membership of the Royal College of Physicians in 1991, and completed his general cardiology training at St. George's Hospital Medical School, London. He was appointed as Senior Lecturer first at St. George's Hospital in 1999 and then at UCL in 2003. He was promoted to Reader in Inherited Cardiac Disease in 2005 and became a full Professor at UCL in 2012. He was elected as a Fellow of the European Society of Cardiology (ESC) in 2005, is past Chairman of the ESC Working Group on Myocardial and Pericardial Diseases (2010–2012), and chairs the ESC Guideline Task Force on Hypertrophic Cardiomyopathy and the Executive Committee for the European Outcomes Research Programme registry on cardiomyopathies. He is cardiovascular lead for the North Thames NHS Genomic Medicine Centre and is President of Cardiomyopathy UK, Europe's foremost charity for patients with heart muscle disease. From 2009 to 2013, he was Deputy Editor of The Heart Journal and is currently Deputy Editor for the International Journal of Cardiology. Over the past 25 years, Prof. Elliott has established an international reputation in the field of heart muscle disease, authoring more than 300 peer-reviewed papers on the subject. He develops diagnostic standards, risk stratification tools and clinical service models based on some of Europe's largest inherited heart disease cohorts, fostering industry collaborations in sequence interpretation, therapeutic trials and multicentre research partnerships. In the NIHR-BRC funded programme Prof. Elliott has used hypertrophic cardiomyopathy (HCM) as a model for translation. HCM is a genetic disorder (1:500 adults) that causes sudden cardiac death, stroke and heart failure. It is characterised by marked variability in disease expression and despite 20 years of research, an understanding of genotype-phenotype relations in HCM had remained elusive. Professor Elliott's work shows that genetic heterogeneity causes different but predictable effects on cardiac phenotype and that creation of an integrated genetic testing pipeline can be used to guide therapy and counselling strategies in patients with this and other inherited cardiac diseases. These results are used in national and international guidance on genetic testing in families affected by inherited heart muscle disease:**

**Professor Sir Munir Pirmohamed, MB ChB (Hons), MRCP, PhD, FRCP, FRCP(E), FBPharmacolS**



**Professor Sir Munir Pirmohamed is a British clinical pharmacologist and geneticist. Since 2007 he has been the NHS Chair of Pharmacogenetics at the University of Liverpool. He studied medicine at the University of Liverpool from 1980 to 1985.**

**He was awarded a PhD in pharmacology in 1993, and began working as a consultant physician at the Royal Liverpool University Hospital in 1996. Pirmohamed gained the position of Personal Chair in Clinical Pharmacology at The University of Liverpool in 2001. He went on to become the NHS Chair of Pharmacogenetics in 2007 and the David Weatherall Chair of Medicine at the University of Liverpool in 2013. He was a member of the Commission on Human Medicines and Chair of its Pharmacovigilance Expert Advisory Group from 2005 to 2020 and was appointed Chair of the Commission in 2021.**

**He is Director of the Centre for Drug Safety Science, Director of the Wolfson Centre of Personalised Medicine, [6] and Director of the MRC Clinical Pharmacology Training Scheme, all at the University of Liverpool. In addition, he is Director of HDR North, part of HDR UK. Alongside these responsibilities, Pirmohamed is a Non-Executive Director for NHS England/Improvement, a member of the governing council of the Medical Research Council, a medical trustee for the British Heart Foundation, and was President of the British Pharmacological Society from January 2020 to December 2021. He is President-Elect of the Association of Physicians for 2022, and will become President in 2023. In 2022, he chaired a committee that produced a report, Personalised prescribing, on behalf of the Royal College of Physicians of London and the British Pharmacological Society, which advocates the implementation of pharmacogenomics into the UK NHS.**

**Dr. Nimesh Desai, MD, PhD, Cardiovascular Surgeon, University of Pennsylvania, Philadelphia, USA**



**Nimesh Desai, MD, PhD is a cardiovascular surgeon who serves as Co-Director of the Penn Aorta Center. He is an Associate Professor of Surgery at the Hospital of the University of Pennsylvania. He also serves as Associate Director of the Cardiovascular Outcomes, Quality, and Evaluative Research (CAVOQER) Center at Penn.**

**Dr. Desai's research interests include organizing large multi-center clinical trials to assess new cardiovascular technologies and health process evaluations using big-data and novel statistical approaches to improve quality of care for cardiac patients. Dr. Desai is the primary investigator of over 10 clinical trials currently ongoing at Penn, holds grants for database and registry development, and was recently awarded funding from the NHLBI to develop and direct a Clinical and Implementation Research Skills Program (CIRSP) for surgical trainees as part of a successful Penn U01 submission. Dr. Desai's clinical focus is on advanced aortic surgery, both endovascular and open, percutaneous valve replacement, complex valve surgery, multiple arterial grafting, and arrhythmia surgery.**

**Dr. Desai holds several national leadership positions in cardiovascular surgery including Co-Chair of the Society of Thoracic Surgeons Aortic Surgery Task Force and Co-Chair of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry Risk Modelling Sub-Committee. He received his medical degree from the Schulich School of Medicine at Western University in Ontario and his PhD in Clinical Epidemiology from the University of Toronto. He completed an integrated Cardiac Surgery Residency at the University of Toronto and is a Fellow of the Royal College of Surgeons of Canada.**

## **Prof. Sadnosh Padmanabhan, Academic Cardiologist, University of Glasgow, Scotland**



**Prof Sandosh Padmanabhan completed his MBBS and MD at JIPMER, Pondicherry, India and was awarded the Gold Medal for MD General Medicine in 1995. His PhD (1999-2003) on G-protein signalling in hypertension was awarded the Bellahouston Medal by the University of Glasgow in 2004. He received the Austin Doyle Award from the International Society of Hypertension in 2004. His pharmacogenetic genomewide linkage study led to a BHF Intermediate Fellowship (2006-2009). He was the lead on a genome wide association analysis of Hypertension between 2008 and 2010 resulting in the discovery of a new gene and pathway for hypertension. He was a visiting fellow to the Broad Institute of Harvard and MIT (2010-2012). He is a Fellow of the Royal College of Physicians, the British Hypertension Society and the American Heart Association.**

# **Professor Manuel Mayr, MD, PhD, BHF Professor of Cardiovascular Medicine, King's College, London, UK**

**Manuel Mayr qualified in Medicine from the University of Innsbruck (Austria) in 1999. He then moved to London to undertake a PhD. Upon completion of his PhD, he achieved promotion to Professor in 2011. He has been awarded a prestigious British Heart Foundation Personal Chair in 2017. His academic achievements have been recognised by the inaugural Michael Davies Early Career Award of the British Cardiovascular Society (2007), the inaugural Bernard and Joan Marshall Research Excellence Prize of the British Society for Cardiovascular Research (2010), and the Outstanding Achievement Award by the European Society of Cardiology Council for Basic Cardiovascular Science (2013).**

## **Prof. Panagiotis Deloukas, PhD, FMedSci, Queen Mary University, London, UK**

**Panos Deloukas obtained his BSc in Chemistry from the Aristotelian University of Thessaloniki, Greece and MSc in Microbiology from University Paris 7, France. He received his PhD from the Biozentrum University of Basel, Switzerland in 1991. He joined the Sanger Centre in 1994 where he set up a high-throughput pipeline for radiation hybrid mapping, leading an effort to map 30,000 gene markers, GeneMap98. Panos was an active member of the Human Genome Project coordinating the sequencing and analysis of chromosomes 10 and 20. After the completion of the HGP he joined the International HapMap project constructing SNP maps of the human genome. Since 2005 he is studying the molecular basis of common disease and variable response to drugs in humans through large-scale genetic studies. He joined the William Harvey Research Institute at Queen Mary University London in September 2013 working on the genomics of coronary artery disease and lipid levels. Panos is a member of many consortia including CARDIoGRAMplusC4D, Global Lipids Genetics Consortium, GIANT, the UK Biobank Cardiometabolic Consortium, and the Cardiovascular Genomics England Clinical Interpretation Partnership. He has authored over 400 publications (H-index 121) and is listed by Thomson Reuters among the 1% highly cited researchers in Molecular Biology & Genetics since 2012.**



## **Prof. Arthur A.M. Wilde**



**Arthur A.M. Wilde got his M.D. at the University of Amsterdam in 1983. After his Ph.D. in 1988, he started his Fellowship training in Cardiology at the Academic Medical Centre, and was registered as such in 1994. Afterwards he specialized in clinical electrophysiology at the Academic Hospital Utrecht.**

**From the Netherlands Heart Association he was awarded a grant as Clinical Established Investigator for five years. In 1999, he became head of the Laboratory of Experimental Cardiology, and in 2003 head of the Department of Clinical and Experimental Cardiology (Academic Medical Centre). His major focus is on different aspects of inherited arrhythmia syndromes. In more recent years also genetic factors contributing to sudden cardiac death in the general population became a focus.**

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- 4. Nadolol Decreases Incidence and Severity of Ventricular Arrhythmias During Exercise Testing Compared With Beta-1 Selective Beta Blockers in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia**

## Mary Porteous



**I was appointed as the first NHS funded Consultant Clinical Geneticist in Edinburgh in 1992 and am currently Service lead for the SE Scotland Genetic Service and an honorary Professor at the Institute of Genetics and Cancer at the University of Edinburgh. I was the Clinical Genetic Adviser on implementation of the Scottish Government Calman report which led to a significant increase in funding for Genetic Services and in 2009 chaired the Scottish Government Molecular Pathology Review Group establishing the principle of central funding via the Scottish Genetic Consortium.**

**My first exposure to Genetics was in 1987 as an MSc student in Glasgow where I spent many hours clinically characterising Aarskog syndrome (an X-linked short stature syndrome) and mapping the FDG1 gene responsible. I moved to Newcastle in 1989 as the “Catherine Cookson Research Fellow” under the supervision of Professor John Burn where my research initially focussed on linkage analysis and clinical characterisation of Hereditary Haemorrhagic Telangiectasia, collaborating with Doug Marchuk (Duke university) in the mapping and cloning of ENG and ACVRL1, the major genes involved. At that time it was possible to complete higher specialist training concurrently with a research job and I attended cardiac genetic clinics at the Freeman Hospital in Newcastle. Since moving to Edinburgh I have been fortunate to combine translational research with my clinical role and have been a Principal Investigator with Malcolm Dunlop and Harry Campbell on two MRC Programme grants focussed on genetic epidemiology of colorectal cancer. The NHS Genetic Laboratory in Edinburgh provides a diagnostic service for cardiomyopathy patients across Scotland and I have maintained an interest in Cardiac Genetics, the molecular epidemiology of which has similarities to cancer genetics in terms of complexity, working closely with my colleague Dr Wayne Lam to support the Cardiac Genetic Service that he leads.**

## **Farrah Khawaja**



**Farrah Khawaja is a Deputy Director of Genomics Quality Assessment (GenQA), which is based in the Royal Infirmary of Edinburgh, Scotland, UK.**

**She is a Principal Clinical Scientist and has been working with GenQA for 10 years, coordinating the assessment of monogenic disorders, newborn screening, prenatal diagnosis, preimplantation genetic diagnosis, and next generation sequencing EQAs.**

**GenQA is part of the UK NEQAS External Quality Assessment Service (UK NEQAS). The EQA Scheme delivers assessment of the standard of the full clinical genomic pathway through 120 different schemes.**

**Farrah provides laboratories with an external measure of quality and education as well as support and guidance with molecular genetic testing.**

## **Dr. Verity Hartill**



**Dr. Verity Hartill is a Consultant in Clinical Genetics at Leeds Teaching Hospitals NHS Trust and is an active member of the Yorkshire Inherited Cardiac Conditions team. She is also a researcher at the University of Leeds with funding from an MRC/NIHR Clinical Academic Research Partnership (CARP) award. Verity completed her PhD in 2017, which focused on genetic causes of congenital heart disease using whole exome sequencing. Her current research interests remain in the genetics of rare disease, syndromic and non-syndromic congenital heart disease, abnormalities of methylation and ciliopathies. Verity is co-chair of the national Genetics Research and Audit Collaborative.**

## Dr Ruth McGowan



**Dr Ruth McGowan is a Consultant in Clinical Genetics (West of Scotland, Centre for Genomic Medicine), Honorary Clinical Associate Professor (University of Glasgow) and part of the Developmental Endocrinology Group (DERG), affiliated to University of Glasgow. She is an active member of the Network for Inherited Cardiac Conditions Scotland (NICCS) and Deputy Chair of the Rare Diseases Implementation Board. Her key research interests are Inherited Cardiac Conditions, Disorders of Sex Development (DSD) and rare conditions. She is the Lead Clinical Geneticist for the West of Scotland ICC service, Chair of the West ICC MDT meetings and has a key role in ICC clinics, overseeing genetic testing and research projects. Dr Ruth McGowan has been Chief or Principal Investigator of numerous research projects including the MRC/CSO funded ‘Scottish Genomes Partnership’, the ‘Scottish Participation in the 100K Genomes Knowledgebase’ and the ‘Genetic Investigation of Rare Disorders’ study.**

## **Antheia G. Kissopoulou**



**I work as a Consultant Cardiologist in the Inherited Cardiovascular Diseases Unit at Ryhov County Hospital Jönköping Sweden in collaboration with Linköping University Hospital. I have a special interest on congenital heart disease and cardiogenetics. I trained at the Department of Cardiology at the Linköping University Hospital in Sweden and even at SÖS Hospital in Stockholm, one of the largest emergency departments in Scandinavia with expertise in acute cardiovascular care. I am a PhD student, working my thesis on the genetic background of hypertrophic cardiomyopathy in the Swedish population and genes associated with sudden cardiac death.**

**Sub-specialties Congenital Heart Disease, Cardiomyopathies and Imaging**

## **Dr. Aditi Babel**



**Dr. Aditi Babel is a General Practice specialty registrar with the St. Mary's (Imperial) training program. She has an MSc in Genomic Medicine and a special interest in Digital Health and Precision Medicine. She is also the author of [GenomicsForDummies.com](https://www.genomicsfordummies.com).**

## **Melanie Pennock-Jones**



**I have worked at Bristol Genetics laboratory for the last 22 years (since 2001), firstly as a trainee clinical scientist, and then a State registered Clinical Scientist in Molecular Genetics since 2004. As a trainee, I worked on setting-up the first UK molecular genetic testing service for Barth syndrome. Post-training, I moved on to setting up a QF-PCR service in Bristol for detection of trisomies in pregnancy, which I worked on for a number of years. Subsequently, I have run the services in Bristol for Haemochromatosis, Polycythemia Vera, Cystic Fibrosis, MCADD, Congenital Central hypoventilation syndrome, Galactosaemia, and worked in the familial hypercholesterolaemia NGS and cascade services. I have only recently, in 2023, joined the cardiac team at Bristol.**



## **Dr William J Young**



**Dr William J Young is an Electrophysiology Cardiology Registrar at St Bartholomew's Hospital, London and a NIHR-funded Clinical Lecturer at Queen Mary University of London. His PhD thesis investigated the genetics of ventricular depolarisation and repolarisation. He has a special interest in inherited arrhythmia syndromes and the role of monogenic and polygenic contributions to arrhythmic risk.**

## **Professor Patricia Munroe**



**Patricia Munroe is Professor of Molecular Medicine at Queen Mary University of London. She holds a BSc in Biochemistry and MSc in Biotechnology from Galway University Ireland, and a PhD in Medicine from the University of London. Following post-doctoral research at University College London on rare neurogenerative diseases identifying genes for Batten disease she moved to complex trait research. Her lab investigates the molecular basis of hypertension, cardiac arrhythmia and heart failure. Her work is funded by the BHF and NIHR. She is a co-founder of several international genetic disease consortia, research which has led to the discovery of over 2000 genes for cardiovascular risk factors and she has published over 250 original publications. Professor Munroe is the Director of the Genome Centre at Queen Mary and was elected to the Academy of Medical Sciences in 2021.**

## **Dr Siv Fokstuen, MD**



**Dr Siv Fokstuen is a clinical geneticist working as Associate Professor at the Institute of Medical Genetics of the University Hospitals in Geneva, and as senior consultant at the University Heart Center in Zurich, Switzerland. Her main academic interest is focused on mendelian cardiac disorders, in particular on hypertrophic cardiomyopathy.**

**Dr Wayne Lam**



**Became a consultant in Clinical Genetics in 2001. His main interest is Paediatric Genetics. He helped develop multidiscipline clinics in the diagnosis and management of patients with Marfan syndrome for both paediatric and adult population and which has been running since 2004.**

**As part of the FANS (Familial Arrhythmia Network of Scotland) steering group, he helped develop cardiac genetics services in the Lothian region and is the Clinical Genetics lead for ICC for South East of Scotland. This involved developing patients care pathway for families with ICC.**

# Certificate of Attendance



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**Consultant in  
Clinical Genetics &  
Genomic Medicine**  
**Professor Dhavendra  
Kumar, MBBS MD**  
MedSci DCH FRCPI FRCP  
FRCPCH FACMG DSc (Hon)

- Consultant in Clinical Genetics & Genomic Medicine
- Wide clinical experience in medical/clinical genetics
- Special interests in Pediatric genetic diseases, clinical dysmorphology, neurogenetics and inherited cardiovascular conditions
- Author/ Editor of many books and journals on genetics and genomics;

### Genetic & Genomic Services

- Comprehensive clinical genetics service covering wide-ranging specialist areas:
- Genetic disease diagnosis with diagnostic genetic testing
- Detailed assessment of birth anomalies
- In depth review and analysis of the family history
- Specialist advice on cousin marriages (consanguinity)
- Genetic risk review and assessment
- Genetic & Genomic counselling
- Predictive or pre-symptomatic genetic testing
- Genetic & genomic screening for life style and health counselling
- Prenatal screening and testing for chromosomal abnormality or specific genetic disease
- Pre-implantation genetic diagnosis for preventing recurrence of high risk genetic disease
- Medical-legal review and Expert Witness reports related to genetic or possible genetic condition

### Genetic/Genomic Tests (by Accredited Genetic Laboratories in UK/Europe)

- Chromosome (cytogenetic) analysis including Fluorescent Insitu Hybridisation (FISH)
- Microarray chromosome analysis (MCA)/ Array Comparative Genomic Hybridization (aCGH)
- Single gene mutation testing for specific diseases, for example Cystic Fibrosis, Duchenne Muscular Dystrophy, Hypertrophic Cardiomyopathy and many more
- Gene panel testing for complex undiagnosed possible genetic conditions, for example familial cardiomyopathy, breast/ ovarian cancer, colo-rectal cancer, diabetes/obesity, infantile epilepsy, inherited blindness, floppy child etc.
- Copy number variation analysis
- Deletion/ Duplication testing (MLPA)
- Mitochondrial genetic analysis
- Pharmacogenetic testing for targeted and personalised drug prescribing
- Next generation sequencing- clinical exome sequencing (CES); whole exome sequencing (WES); whole genome sequencing (WGS)
- RNA sequencing and related functional genetic testing
- Preconception/Prenatal genetic screening for carrier status of common genetic diseases in minority ethnic groups
- Genome testing for selection and health surveillance for common diseases
- Genetic/ genomic advice for life style modification and health enhancement

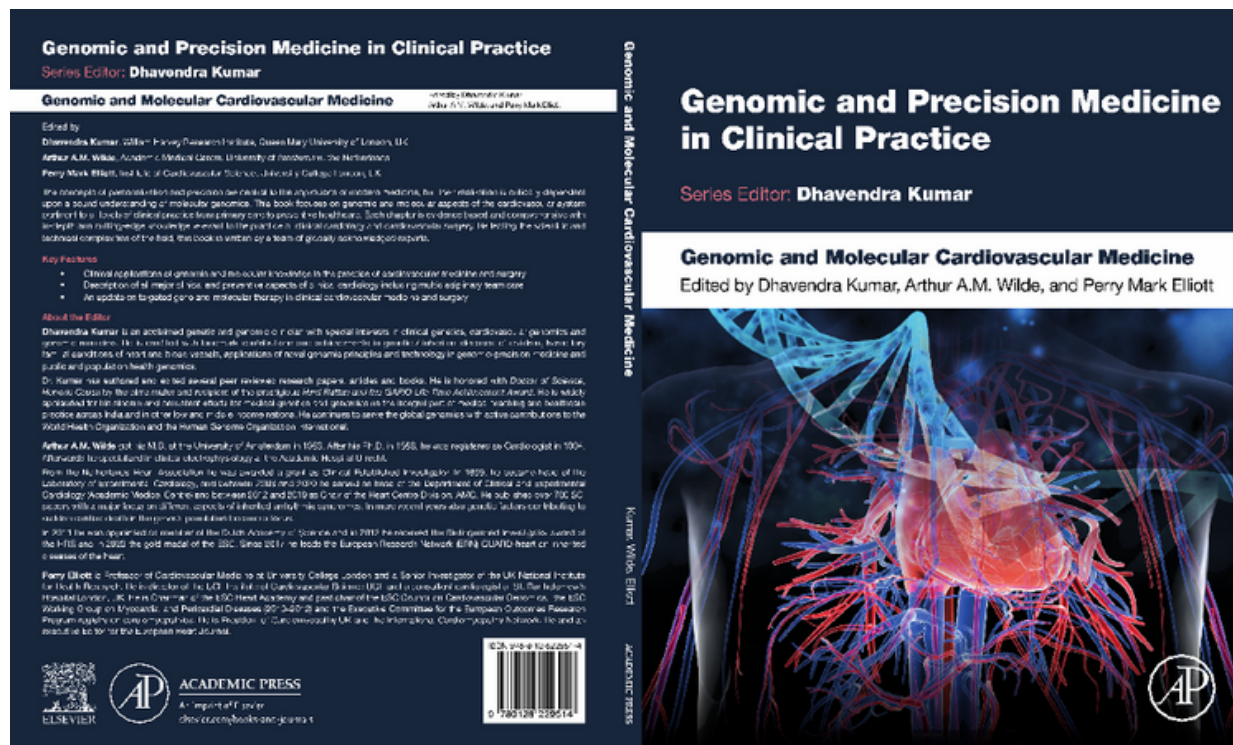
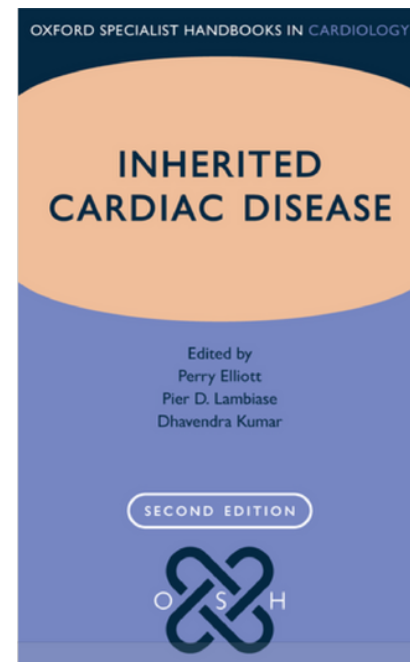
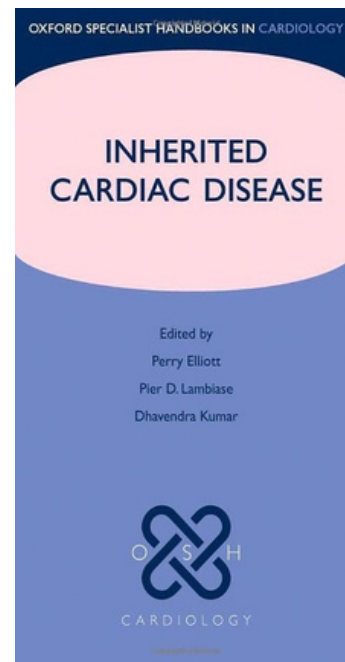
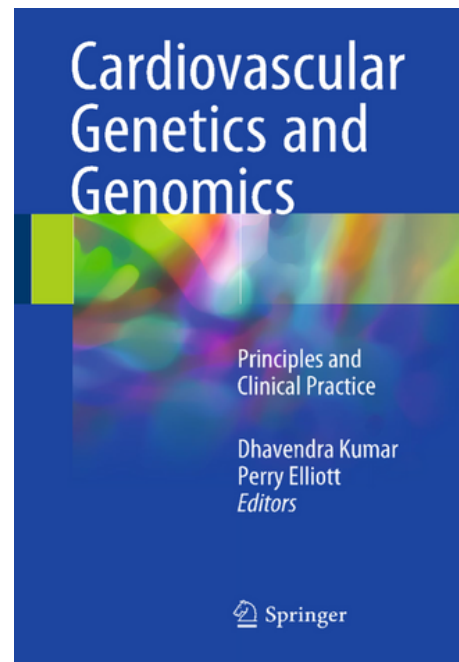
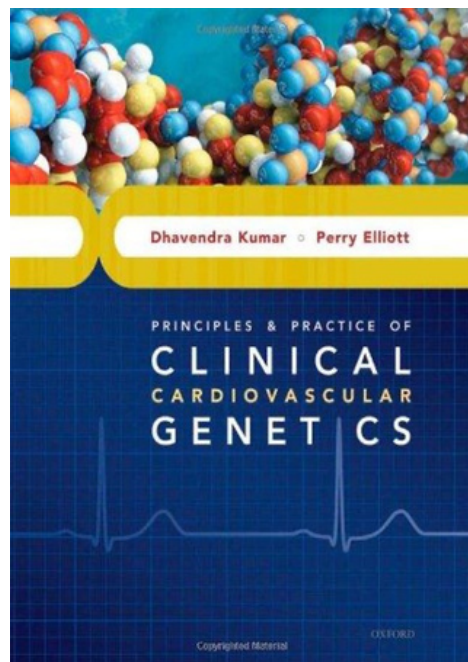
### Medico-Legal Genetic/ Genomic Service

- specialist medico-legal services including expert medical reports with clinical review and genetic testing
- advisor on adoption and child protection cases related to an inherited disease
- joint expert witness either through written evidence of Court attendance
- genomic testing for disputed paternity or identity.

### Genome Clinic appointments

Spire Cardiff Hospital, Croescadarn Road, Pentwyn,  
Cardiff, CF2 3BX, UK ; Tele: +44 (0) 2920735515 or +44 (0) 2920736011  
[cardiffhospitaloutpatients@spirehealthcare.com](mailto:cardiffhospitaloutpatients@spirehealthcare.com) ; [genomeclinic@gmail.com](mailto:genomeclinic@gmail.com)  
Direct Mobile: +44 (0) 7766310291/ 7498168507







# Genomic and Molecular Cardiovascular Medicine

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**AUDIENCE:** Students and Trainees in General Medicine, Cardiology, Cardiovascular surgery, Pathology, Preventive & Public health Practicing clinical cardiologists and cardiac surgeons, Academic cardiologists and cardiac surgeons Investigators in cardiovascular science, Practitioners and professionals in cardiovascular preventive and public health

**SHELVING CLASSIFICATIONS:**

Life Sciences (General)

**BISAC CODES:** MED010000,

SCI008000, SCI086000

**THEMA CLASSIFICATION:**

THEMAPS

**An up-to-date, authentic resource on the genomic and molecular basis of cardiovascular medicine and surgery**

A Volume in the *Genomic and Precision Medicine in Clinical Practice Series*

## KEY FEATURES

- Includes clinical applications of genomic and molecular new knowledge, along with advances in the practice of cardiovascular medicine and surgery
- Provides wide coverage of all major clinical and preventive aspects of clinical cardiology, including multi-disciplinary team care
- Focuses on targeted gene and molecular therapy in clinical cardiovascular medicine and surgery

## DESCRIPTION

*The Genomic and Molecular Cardiovascular Medicine* largely focuses on pertinent genomic and molecular aspects of cardiovascular medicine relevant to all levels of clinical practice, from primary care to preventive healthcare. The book also focuses on practice applications of translational genomic and molecular developments and advances that impact on cardiovascular system structure and function. Each chapter is evidence-based and comprehensive, with in-depth, cutting-edge knowledge relevant to the practice of clinical cardiology and cardiovascular surgery. The book aims to fill a major gap of knowledge resource focused on genomic and molecular aspects of contemporary cardiovascular medicine and surgery practice.

In view of scientific and technical complexities of the field, the book is written by a team of globally acknowledged experts in respective clinical, investigative, therapeutic and preventive aspects. The current practices within cardiovascular medicine and surgery offer excellent opportunity for genomic and molecular applications to achieve the high order effectiveness with maximum efficiency.

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