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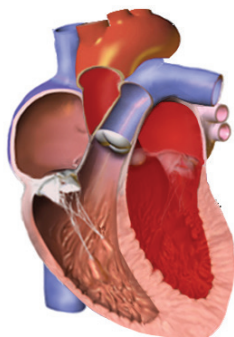
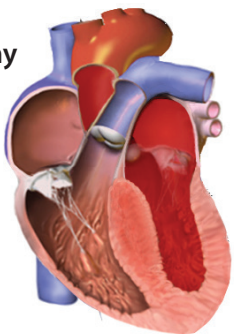
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Cardiovascular medicine and genomics

Clinicians have always personalised patient management. There is a growing momentum to improve this further through the integration of genomic information into clinical care. Here we present an overview of the current role of genetics and genomics in cardiovascular medicine, alongside our expectations for the future.

Advances in genetic technology and understanding, coupled with an increasing patient demand for genetic and genomic investigation, is driving this momentum. The healthcare workforce needs to be empowered to identify the opportunities for genomic medicine and feel confident in their skills to deliver personalised care effectively and compassionately.

Figure 1: Hypertrophic cardiomyopathy

Normal heart**Hypertrophic cardiomyopathy**

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Hypertrophic cardiomyopathy affects approximately 1:500 individuals (120,000 in the UK), and is defined by an increase in left ventricular wall thickness that is not solely explained by abnormal loading conditions (e.g. hypertension). It is an important cause of sudden death in the young.

Rare genetic diseases

To date, the most important contributions of genomic medicine in cardiology have been to the diagnosis and management of Inherited Cardiac Conditions (ICCs), such as hypertrophic cardiomyopathy (HCM) (see figure 1) and the long QT syndrome (LQT). Though such conditions are individually rare, collectively rare diseases (80% of which are genetic in origin) affect 1 in 17 people in the UK population, and therefore make up a proportion of the clinical caseload in all specialties. A rare genetic disease may be suspected either in the presence of a strong family history, or due to a characteristic phenotype.

Precision diagnosis

Although most inherited cardiac conditions in an index case are initially diagnosed on the basis of clinical evaluation, a precise molecular diagnosis can increase diagnostic certainty, inform prognosis, and guide management of the patient, and can also greatly facilitate evaluation of at-risk relatives. Molecular genetic testing is recommended in international guidelines and consensus statements, and is increasingly accessible as technological developments reduce the cost of gene sequencing. Deciding when to use these tests and how to interpret their results is becoming an important part of medical practice.

For those affected by an ICC, a molecular diagnosis may provide prognostic information. For example, for more than a decade the risk of life-threatening arrhythmia in LQT has been known to vary according to the underlying genetic aetiology, with LQT due to variants in the *KCNQ1* gene (encoding the alpha subunit of the slow delayed rectifier potassium channel) having a better prognosis than other subtypes. Prognosis can now be further refined on the basis of the precise molecular location of a variant, or its effects on the biophysical properties of the ion channel.

Figure 2: Fabry disease

Fabry disease, due to deficiency of the enzyme alpha galactosidase A and intracellular accumulation of glycolipids, has a prevalence of around 0.5-1% in HCM patients older than 35-40 years. Diagnosis is crucial as it enables specific treatment with enzyme-replacement therapy, as well as appropriate genetic and prognostic counselling.

Fabry disease may be diagnosed genetically, or through a specific enzyme test if the diagnosis is suspected clinically.

Clinical features that raise a suspicion of Fabry disease include:

Pain: neuropathic or gastrointestinal pain

Renal: renal impairment & proteinuria

Cardiac: conduction disease, concentric hypertrophy with impaired function, characteristic CMR appearances

Skin & eyes: angiokeratomata, hypohidrosis, cataracts, corneal opacities

Other: sensorineural deafness, stroke

Therapeutic stratification on the basis of genotype is also routine in the management of LQT. Patients are advised to avoid specific arrhythmia triggers dependent on the molecular aetiology (*e.g.* swimming in LQT1, alarm clocks in LQT2), or may be offered specific pharmacotherapy (mexilitine in LQT3). Examples of utility in the cardiomyopathies include the identification of specific treatable causes, such as Fabry disease (see figure 2) for which enzyme replacement therapy is available, or forms of DCM with a high arrhythmia burden where the specific diagnosis will influence ICD recommendations (*e.g.* LMNA).

Cascade screening in families

Once an individual is diagnosed with an inherited cardiac condition, it is also necessary to consider whether their relatives are at risk of developing the condition. Most ICCs follow an autosomal dominant inheritance pattern, and so first degree relatives each have a 50% risk of carrying the causative genetic variant. Once the causative genetic abnormality has been identified in one family member, molecular genetic testing has a much higher sensitivity and specificity than clinical evaluation. A negative genetic test result allows an unaffected relative to be confidently discharged from the cardiology clinic, rather than embarking on a programme of expensive and time intensive clinical surveillance. After a sudden cardiac death with normal cardiac findings at post-mortem, a 'molecular autopsy' can provide a precise diagnose and tool for family screening. Genetic testing can also reveal other inheritance patterns, *e.g.* X-linked or matrilineal (mitochondrial) inheritance, with important implications for relatives.

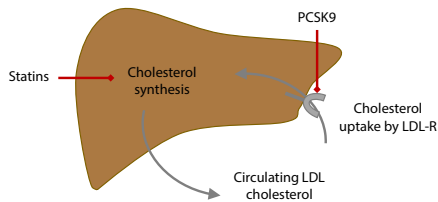
Specialist ICC services are becoming widely established across the UK to co-ordinate counselling and interpretation of clinical and genetic tests.

Enabling technology

Advances in genetic knowledge and sequencing have led to the development of new genetic tests for rare monogenic diseases. With older technologies, these tests were expensive and time-consuming, and some important cardiovascular genes, such as Titin, were too large to be routinely sequenced at all. Tests were usually offered for single-genes, tested sequentially. Although a single gene mutation is typically responsible for disease in an individual patient or family, the causal mutations in any particular inherited disease may be found in one of several different genes – for example at least 15 genes have been reported in association with the Long QT syndrome.

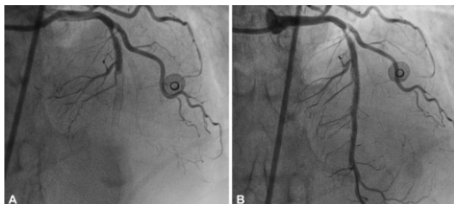
New technologies allow for many genes related to the suspected condition to be gathered together into 'panels' of genes and tested in parallel, at vastly reduced time and expense, though an important increase in the complexity of interpretation. It is likely that clinicians across multiple specialties will have access to these tests, and eventually routine access to tests for all genes or even the whole genome (already available in selected circumstances through the Genomics England 100,000 genomes project). The UKGTN website provides information on

Figure 3: Genetic variation in *PCSK9* identifies a new target for cholesterol-lowering drug therapy



PCSK9 encodes an enzyme that binds the LDL receptor. In 2003 gain-of-function genetic variants in *PCSK9* were linked to familial hypercholesterolaemia: when *PCSK9* binds the LDL receptor it is broken down and can no longer remove LDL cholesterol from the blood. Subsequently loss-of-function variants in the same gene were found to be associated with very low cholesterol, without obvious adverse effects. The study of natural genetic variation therefore identified inhibition of *PCSK9* as an attractive therapeutic target, and the first inhibitors received FDA approval in 2015.

Figure 4: Predicting response to antiplatelet therapy



Stent thrombosis. A: coronary angiogram showing total occlusion at a previous stent site in the mid left anterior descending artery and the diagonal branch. B: coronary angiography after balloon angioplasty

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Clopidogrel is an antiplatelet agent, usually administered in combination with aspirin after coronary stent implantation to prevent potentially fatal in-stent thrombosis. Common genetic variants in the cytochrome P450 enzyme *CYP2C19* can alter the conversion of the inactive prodrug to its active metabolite. About 1 in 4 caucasians have intermediate enzyme activity, and 1 in 50 have little or no enzyme activity, in which case an alternative antiplatelet is recommended. The proportion of individuals at risk is even higher in other ethnicities.

genetic tests that are currently listed on the NHS directory of genetic tests, most of which are now based on panel tests.

Use of genetic testing will be supported by clinical guidelines, published testing criteria and educational resources (useful contact details for support are provided at the end of this document). However, it is recognised that expert support will still be required to help with interpreting the results from larger panels, as there is a greater risk of finding changes that are of uncertain significance. Complex ethical issues involving family members may also need to be addressed.

Genetics of Common Complex Disease

Most common diseases such as hypertension or coronary artery disease are complex in aetiology, caused by a combination of environmental risk factors and underlying genetic susceptibility conferred by many genes each of small effect. Recent advances in genomics have led to a more comprehensive understanding of the contribution to different diseases of genetic factors and normal genetic variation between individuals. As well as contributing to a greater understanding of pathways involved in disease mechanisms (which are potential targets for drug development – see figure 3), investigation of rare cases of ‘genetic’ disease has been important for understanding the more common forms of a disease.

Pharmacogenetics and treatment

Even after taking into account disease sub-phenotypes, there is considerable variability in individual responses to medicines which can be due to differences in the way a drug is handled in the body (pharmacokinetics) and / or variation in the drug targets (for example, receptors, enzymes, ion channels etc.). Knowledge of the genomic influences in these processes, when combined with clinical risk factors can provide insights into how a patient will respond in terms of efficacy to a given drug which may alter drug choice and / or dose. For example, up to half of the population have a reduced capacity to convert the pro-drug clopidogrel into its active metabolite, with an increased risk of thrombosis after coronary stent insertion (see figure 4). Pharmacogenetic testing can identify potential non-responders, in which case an alternative antiplatelet is recommended.

This information can also predict susceptibility to adverse drug reactions, such as statin-induced myopathy. With the development of rapid sequencing assays, and multiple gene panels, it is anticipated that testing for relevant genetic variants that influence both drug efficacy and drug safety may be increasingly used to aid both drug and dosage selection. Such information is being incorporated into the summary of product characteristics of individual drugs, and is reflected in the guidance provided by regulatory agencies such as the European Medicines Agency and the FDA. However, many believe that it will only be when systematic genomic data is available ahead of the point of prescription (e.g. with genome sequence as part of the electronic patient record) that any broad application of pharmacogenetics will be feasible.

Further Information and Resources

Association for Inherited Cardiac Conditions
theaicc.org

British Heart Foundation
www.bhf.org.uk

HEE Genomics Education Programme
Health Education England
Information on genomics education including HEE sponsored MSc., Diploma, PG Certificate and CPPD genomics courses
0121 695 2374
genomicseducation@wm.hee.nhs.uk
www.genomicseducation.hee.nhs.uk

Online module, St George's, University of London, The Genomics Era: the future of genetics in medicine
www.futurelearn.com/courses/the-genomics-era

UK Genetic Testing Network (UKGTN)
0203 350 4999
SECSU.UKGTN@nhs.net
ukgtn.nhs.uk

Genomics England
www.genomicsengland.co.uk

Perry M Elliott et al., 2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy. *European Heart Journal* 2014;35:2733.

SG Priori et al., Executive Summary: HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes. *Europace* 2013;15:1389.

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline information for clopidogrel and CYP2C19

Ethical, legal, social and organisational implications

There are a number of broader challenges that will influence the use of genomic medicine. These include:

- Developing skills and expertise in genetics and genomics within the wider health professional workforce
- Issues relating to patient communication, privacy and consent (particularly for genetic testing in children)
- Handling uncertain, unexpected or incidental findings from genomic tests in clinical practice
- Implications of significant results for other family members
- Bioinformatics provision and secure genomic data storage and access within the health service
- Impact of genomics on current healthcare services, resources and patient pathways (including equity of access to genomic tests)
- Developing intelligent decision support systems that allow the use of genomic and clinical information to aid in the prescribing of drugs at the right dose
- Clarifying risks and benefits associated with using genomic tests for opportunistic screening

The future

The last two decades have seen unprecedented investment in life sciences in the UK. Advanced technologies are now available to sequence the entire genome at a cost of a few thousand pounds in as little as 24 hours, and it is envisaged that this cost will fall considerably over the next few years. Achieving the benefits of these technologies will depend on the ability of clinicians to use them effectively, efficiently and responsibly, for the population as a whole. Genomics can no longer be left to specialists and enthusiasts, but must be grasped by every clinician throughout the NHS for their patients.

Through the 'Clinical Champions' network, the Royal College of Physicians aims to promote education and training in genomics within every specialty. This will ensure that clinicians of the future are ready to capitalise on all of these new developments to provide personalised care for their patients.



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