Cardiomyopathy: hidden in heart failure

Cardiomyopathy UK National clinical conference
Friday 22 September 2017
Implications of NHS strategy for Personalised Medicine for UK Cardiology

Professor Huon Gray
National Clinical Director for Heart Disease, NHS England, & Consultant Cardiologist, University Hospital, Southampton

Cardiomyopathy UK National Clinical Conference, London, 22nd September, 2017
Implications of NHS strategy for Personalised Medicine for English Cardiology

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“It is crucial that we continue to push the boundaries and this new plan will mean we are the first country in the world to use DNA codes in the mainstream of the health service.”

David Cameron announcing Government’s Life Sciences Strategy 2012
Principles for the NHS Genomic Medicine Service 2018/19 to 2020/12

1. To ensure comprehensive and equitable access to genomic medicine as part of routine clinical care for the population of England

2. To improve the quality, value and sustainability of care by providing - prompt and precise diagnosis - personalisation of interventions - a step change in prevention - active participation of patients.

3. To support learning, research & development through new collaborative partnerships between the NHS and with academia and UK life science sector and international collaborators; - new diagnostics, treatments & devices, better patient access to clinical trials.

4. To build the political, ethical and moral trust in genomic medicine - ensuring security of patient data & materials, - appropriateness of care, upholding the values of the NHS Constitution
Assembling all the building blocks

National Genomic Medicine Service

Genomic Medicine Centres providing population-based care

Informatics architecture & data store

Workforce development inc upskilling of existing staff

National Lab Network inc Genomic Laboratory Hubs

Whole Genome Sequencing Provider

National Testing Strategy from single gene - WGS

Clinical Interpretation Pipeline

Industry/academic/international partnerships supporting ongoing research & development through clinical care

Advances in genomic and informatics technologies
Transforming protocols and services across the NHS

• 13 NHS Genomic Medicine Centres (GMC)
  — Networks covering 3-7 million people (innovation, service transformation & workforce up-skilling)

• Brings together 91 NHS Trusts + outreach clinics to drive NHS contribution of 90,000 genomes to the 100k Genomes Project

• NHS GMCs define the genomic medicine service model currently including:
  – New ways of gaining consent
  – Standardisation of care models
  – Involvement of multiple clinical specialities
  – New sample handling & processing
  – Data collation & handling (new data hubs)
  – Genomic MDTs for Rare Disease and Cancer
  – Clinical Leadership for change
  – Patient and public involvement
13 NHS Genomic Medicine Centres

- North East and North Cumbria NHS GMC
- Greater Manchester NHS GMC
- North West Coast NHS GMC
- West Midlands NHS GMC
- Oxford NHS GMC
- West of England NHS GMC
- Wessex NHS GMC
- South West NHS GMC
- South London NHS GMC
- West London NHS GMC
- North Thames NHS GMC
- East of England NHS GMC
- Yorkshire and Humber NHS GMC
100,000 Genomes: a world-leading model for healthcare transformation

Key principles underpin the Project and the NHS contribution:

- **Whole Genome Sequencing** extends current NHS funded diagnostic repertoire
- **Participants consent** to sharing of de-identified data for R and D and for access to longitudinal records
- Recruitment of patients with Cancer and Rare Disease from routine care
- **Aligned to two major system priorities** (UK Rare Disease strategy and Cancer Taskforce)
- **A model for transformational change** in the NHS as well as delivering science and partnerships with industry
The 100,000 Genomes Project

- 100,000 genomes
- 70,000 patients and family members
- 21 Petabytes of data. 1 Petabyte of music would take 2,000 years to play on an MP3 player.
- 13 Genomic Medicine Centres, and 85 NHS Trusts within them are involved in recruiting participants
- 1,500 NHS staff (doctors, nurses, pathologists, laboratory staff, genetic counsellors)
- 2,500 researchers and trainees from around the world
NHS Genomic Medicine Centres

- Clinical samples and hospital data
- Laboratory processing including molecular pathology
- Broad consent for research and re-contact

Clinical Data
- Identifiable clinical data
- Longitudinal
- Linked to genomic data

Research Data
- Pseudonymised
- GeCIP and industry partners work within data centre

Existing Clinical Data
Cancer &RD registries, HES, Mortality data, etc

Diagnostic Analysis
Omicia
CONGENICA
Genome Based Medicine

Oversight:

Funding:

Participants

Biorepository
biocentre
DNA & samples for multi-omics

Sequencing
illumina

Clinicians & Academics
Training
Industry: GENE consortium

Clinicians & Academics
Training
Industry: GENE consortium

Data

Fire wall
The rare disease programme
The scale of rare diseases

1 in 17 people will suffer from a rare disease at some point in their lives.

Only a quarter of rare diseases have had their molecular basis defined, meaning many risk being undiagnosed and therefore untreated.

There are at least 6,000 rare diseases.

Seventy-five per cent of rare diseases affect children.

Many rare diseases (approximately 80%) are of genetic origin.

30% of rare disease patients die before their fifth birthday.
<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategory</th>
<th>Disease</th>
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<tr>
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<td>Tachycardia</td>
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<td>Unexplained sudden death in the young</td>
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Additional findings

- Information about ‘serious and actionable’ conditions (optional)

- Carrier status for adults who might have future children (optional)

NB FH is the only cardiovascular condition on AF list at present
Already changing lives

**CHILD D**
10 year old girl admitted with life-threatening chicken pox
Previous unusual infections
Detailed immune testing not found cause
Mutations found in CTSP1 gene – not familiar to immunologists
Curative bone marrow transplant
No risk to siblings
New testing planned to identify others with condition

**PATIENT J**
24-year-old with intellectual disability & visual problems
Undiagnosed for 20 years
Defect identified in SRD5A3 gene
End of ‘diagnostic oddessy’
Follow-up modified to reflect risk of coagulopathy
Will help diagnose other families

**INFANT P**
‘Failure to thrive’
Unclassified immune deficiency
Recruited with consaguinous parents
Died age 5 months
Mother pregnant
Defect identified in TCN2 gene – transcobalamin deficiency
Sibling also affected – condition can be treated with Vit B12
Sibling responding well
Genomics England
Clinical Interpretation Partnership (GeCIP)

Driving research & development across academia & beyond

2600+ researchers

341 academic institutions world-wide

1056 researchers have been verified by 54 institutions with a signed Participant Agreement

683 researchers have been verified and have ARC approval
# Clinical Interpretation Partnership (GeCIP) - Domains

## Rare
- **Cardiovascular**
- Endocrine and Metabolism
- Gastroenterology and Hepatology
- Hearing and Sight
- Immunology and Haematology
- Inherited Cancer Predisposition
- Musculoskeletal
- Neurological
- Paediatric Sepsis
- Paediatrics
- Renal
- Respiratory
- Skin

## Cancer
- Breast
- Colorectal
- Lung
- Renal Cell
- Sarcoma
- Ovarian
- Prostate
- Childhood Solid Cancers
- Haematological Malignancy
- Pan Cancer

## Functional
- Electronic Records
- Validation and Feedback
- Ethics and Social Science
- Functional Effects
- Health Economics
- Machine Learning, Quantitative Methods and Functional Genomics
- Population Genomics
- Enabling Rare Disease Translational Genomics via Advanced Analytics and International Interoperability
- Functional Cross Cutting
- Education and Training
# Cardiovascular GeCIP domain

## Lead: Bernard Keavney (Manchester)

<table>
<thead>
<tr>
<th>Subdomain</th>
<th>Lead(s)</th>
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<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>Hugh Watkins, Perry Elliott, Stuart Cook</td>
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<tr>
<td>Arrhythmias</td>
<td>Elijah Behr, Andrew Grace, Clifford Garratt</td>
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<tr>
<td>Familial thoracic aortic aneurysms and dissection</td>
<td>Paul Clift, University Hospitals Birmingham</td>
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<tr>
<td>Congenital Heart Disease</td>
<td>Bernard Keavney</td>
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<tr>
<td>Familial hypercholesterolaemia</td>
<td>Steve Humphries</td>
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<tr>
<td>CADASIL negative small vessel cerebral disease</td>
<td>Hugh Markus</td>
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<tr>
<td>Primary lymphoedema</td>
<td>Pia Ostergaard, Sahar Mansour</td>
</tr>
<tr>
<td>Functional Genomics</td>
<td>Panos Deloukas</td>
</tr>
</tbody>
</table>
Personalised Medicine
Figure 7: Burden of disease attributable to 20 leading risk factors for both sexes in 2010, expressed as a percentage of UK disability-adjusted life-years. The negative percentage for alcohol is the protective effect of mild alcohol use on ischaemic heart disease and diabetes.
Coronary Heart Disease (n=302,430)


Ischaemic Stroke (n=173,312)
FH Key Facts

• Heterozygous FH is common (1:250-1:500 in UK)
  – 120,000-240,000 people in UK (>1m in Europe)

“The current estimate of prevalence of Type 1 diabetes in children in the UK is one per 700–1,000. This gives a total population of 25,000 under-25s with Type 1 diabetes.”
Diabetes in the UK 2010: Key statistics on diabetes.
Diabetes UK (2010)
Heterozygous FH is common (1:250-1:500 in UK)
- 120,000-240,000 people in UK (>1m in Europe)

It runs in families as autosomal dominant
- 50% of offspring affected

It is serious
- 50% of men have MI by age 50, and 60% of women by age 60

It is under diagnosed (especially in those under 35 yrs)
- Only ≈15% of all cases known
  - Cascade testing is effective

Treatment is proven to be safe & effective (statins)
Familial hypercholesterolaemia

List of quality statements

Statement 1. Adults with a baseline total cholesterol above 7.5 mmol/l are assessed for a clinical diagnosis of familial hypercholesterolaemia (FH).

Statement 2. People with a clinical diagnosis of familial hypercholesterolaemia (FH) are referred for specialist assessment.

Statement 3. People with a clinical diagnosis of familial hypercholesterolaemia (FH) are offered DNA testing as part of a specialist assessment.

Statement 4. Children at risk of familial hypercholesterolaemia (FH) are offered diagnostic tests by the age of 10 years.

Statement 5. Relatives of people with a confirmed diagnosis of monogenic familial hypercholesterolaemia (FH) are offered DNA testing through a nationwide, systematic cascade process.

Statement 6. Adults with familial hypercholesterolaemia (FH) receive lipid-modifying drug treatment to reduce LDL-C concentration by more than 50% from baseline.

Statement 7. Children with familial hypercholesterolaemia (FH) are assessed for lipid-modifying drug treatment by a specialist with expertise in FH in a child-focused setting by the age of 10 years.

Statement 8. People with familial hypercholesterolaemia (FH) are offered a structured review at least annually.

NB: Excludes Homozygous FH
Statement 1:

“Adults with a baseline total cholesterol above 7.5 mmol/l are assessed for a clinical diagnosis of familial hypercholesterolaemia (FH)”
Clinical Diagnosis of FH
Simon Broome Criteria

• **Definite FH**
  – TC >6.7 mmol/l or LDL >4.0 mmol/l in a child (<16 yrs)
  – TC >7.5 mmol/l or LDL >4.9 mmol/l in an adult
  – *Plus:*
    • tendon xanthomas in patient, 1\textsuperscript{st} or 2\textsuperscript{nd} degree relative
    • DNA evidence (LDL receptor, apo B-100, PCSK-9)

• **Possible FH**
  – Cholesterol as above
  – *Plus at least one of the following:*
    • MI in 2\textsuperscript{nd} degree relative <50 yrs or 1\textsuperscript{st} degree relative <60 yrs
    • Family history of TC as above in 1\textsuperscript{st} degree relative

Dutch Lipid Clinical Network criteria offers similar predictive model
Madonna Lisa Maria di Gherardini
Born Florence 1479
Died 1516 age 37 years
List of quality statements

Statement 1. Adults with a baseline total cholesterol above 7.5 mmol/l are assessed for a clinical diagnosis of familial hypercholesterolaemia (FH).

Statements 2-8:
Those with clinical diagnosis of FH

• Refer to specialist
• Offer DNA testing
• Test children at risk by age 10 yrs
• Relatives of those with FH are offered DNA testing
• Adults receive lipid-lowering Rx
• Children are treated by specialist
• People with FH have annual ‘structured review’
FH Barriers

• Costs of diagnosis, cascade testing and treatment misunderstood
• Commissioning
• Lack of clear pathways for referral, diagnosis and Rx
• System change

“The quality standard for FH specifies that services should be commissioned from and coordinated across all relevant agencies encompassing the whole FH care pathway. A person-centred, integrated approach to providing services is fundamental to delivering high-quality care to people with FH”. NICE Quality Standard 41 (2013)
Progress with FH

• FH Steering Group
• Meetings with Bruce Keogh (NHSE) & Duncan Selbie (PHE)
• Meetings
  – NHSE Senior Management Team 9th (April 2014)
  – Kings Fund FH Meeting for Commissioners (24th November 2014)
  – FH Session at BCS Annual Conference (Manchester, June 2015)
  – PHE/NHSE FH Conference (5th November 2015)
  – Academy of Med Sciences Stratified Medicine Roundtable (17th March 2016)
  – NHSE Board (25th May 2016)
  – NHS Expo presentation (7th September 2016)
  – Deputy CMO Roundtable Meeting on Cholesterol (14th Nov 2016)
  – NHSE FH Roundtable meeting (10th March 2017)
  – NHSE Medical Directorate MAG (20th June 2017)
• PASS Software / National Data collection
• Genomic Centres & the 100k Genome Project
• BHF Funding of FH Nurses (£1.5m+)
FH Genetic Diagnoses by year

Data from Wales and English services who use PASS
Courtesy: Kate Haralambos
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• PASS Software / National Data collection
• Genomic Centres & the 100k Genome Project
• BHF Funding of FH Nurses (£1.5m+)
• NICE Guidance and Cost effectiveness
Recommendations (for heterozygous FH):

- Consider FH if TC >7.5mmol/l and/or family history of premature CVD
- Family history = coronary event <60yrs in 1º relative or index case
- Systematically search 1º care records for people with TC >9.3mmol/l & refer to specialist
- Specialist to refer for DNA testing, then cascade test 1st, 2nd (& 3rd) degree relatives
- DNA test (and treat where indicated) before aged 10

NB: Total recommendations cover whole of FH pathway in adults & children (diagnosis, treatments & lifestyle etc.) Total = 105.
Conclusions

• The Genomics ‘revolution’ is underway
• Relevance of FH to CVD risk and the Personalised Medicine agenda will help drive change
• Refreshed NICE Guidance should raise profile of FH
• Challenge is to establish consistent pathways for detection & management of high cholesterol/FH in an increasingly devolved system of health & social care
• The same challenges apply to other genetically determined CVD conditions
Recorded at
Cardiomyopathy: hidden in heart failure.
Cardiomyopathy UK national clinical conference.
22 September 2017

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