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

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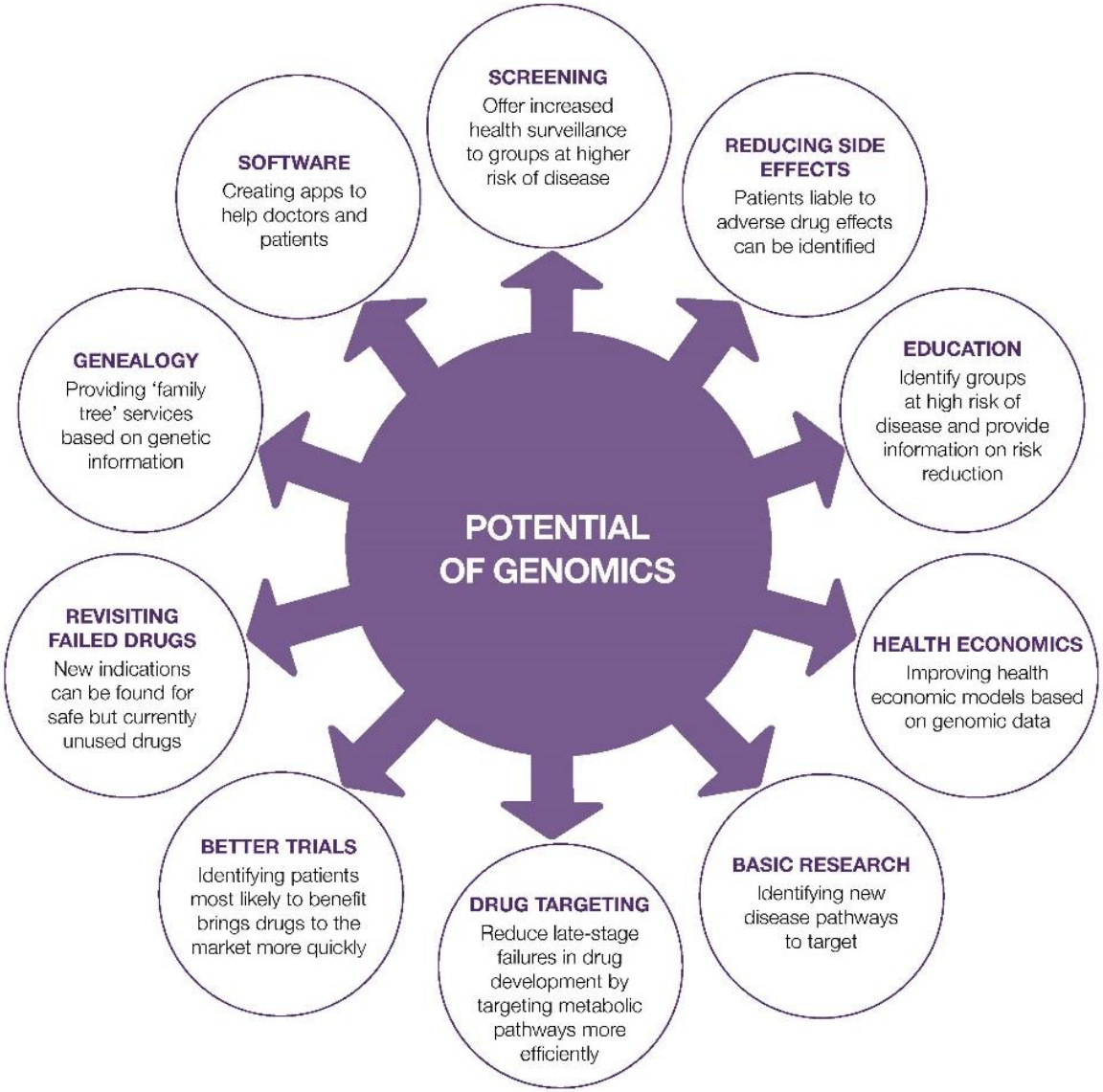
Background



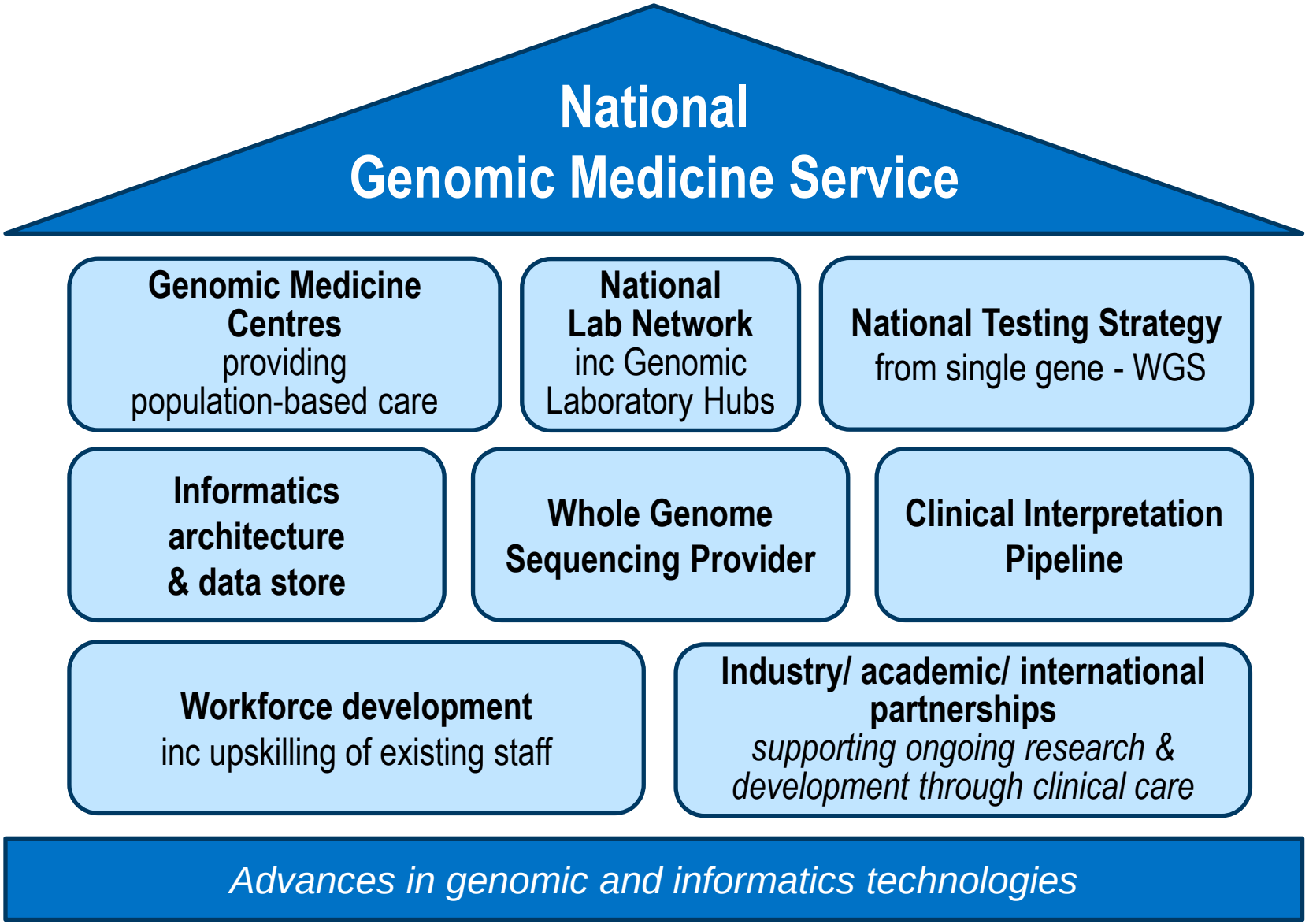
"It is crucial that we continue to push the boundaries and this new plan will mean we are the first country in the world to use DNA codes in the ***mainstream of the health service****."*

David Cameron announcing Government's Life Sciences Strategy 2012

Principles for the NHS Genomic Medicine Service 2018/19 to 2020/12

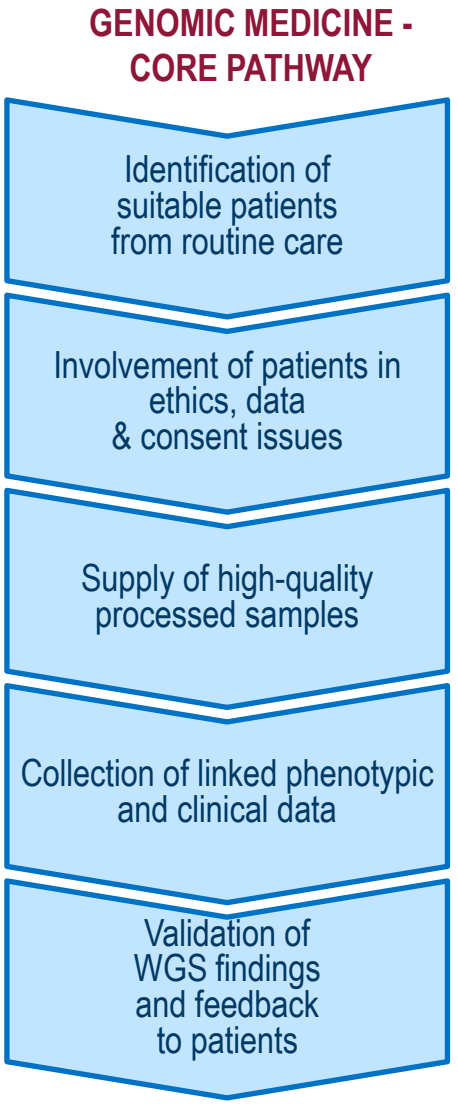
1. To ensure **comprehensive and equitable access** to genomic medicine as part of routine clinical care for the population of England
2. To improve the **quality, value and sustainability** of care by providing -
   prompt and precise diagnosis
   - personalisation of interventions
   - a step change 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

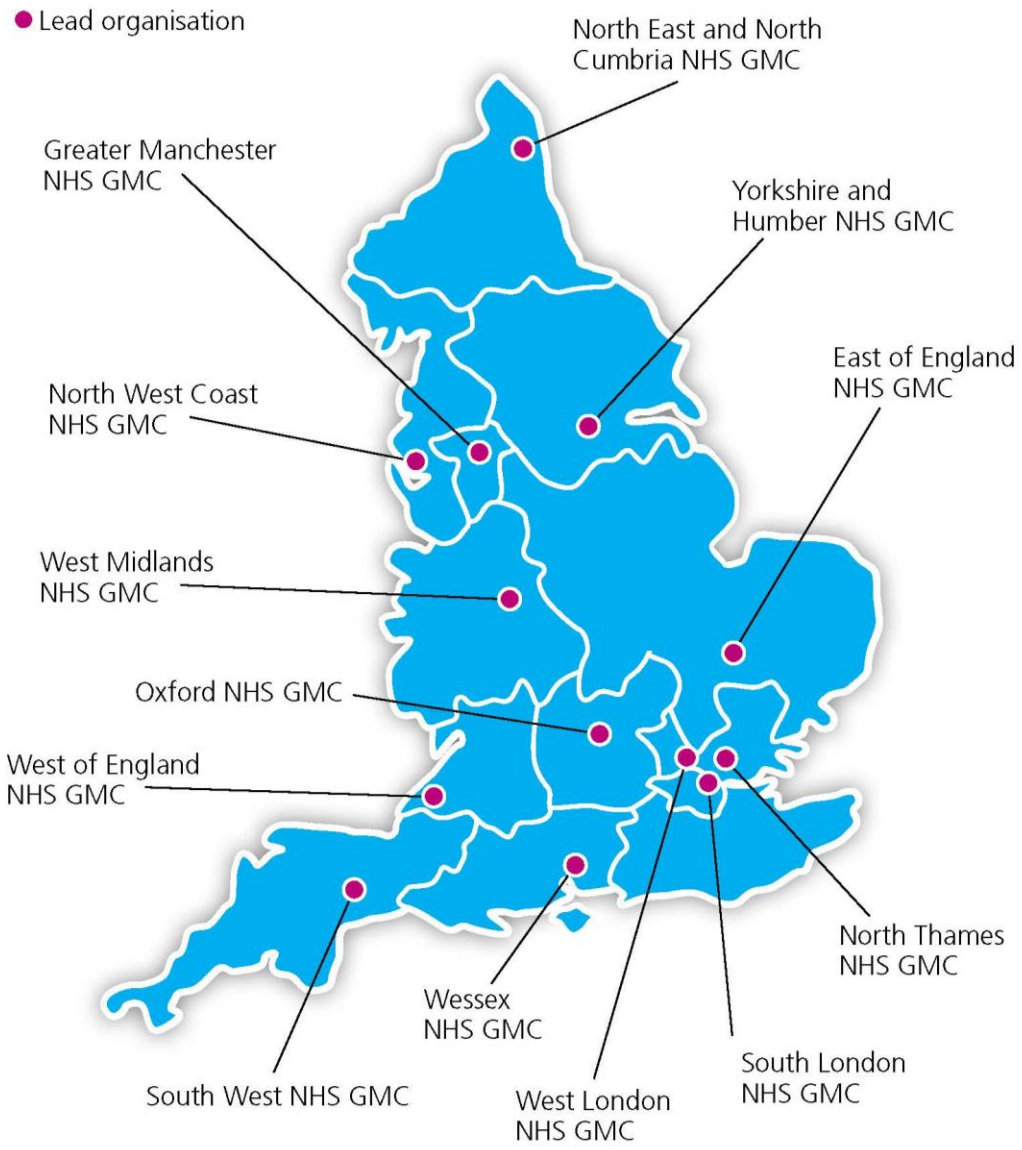


Transforming protocols and services across the NHS

- **13 NHS Genomic Medicine Centres (GMC)**
  - —Networks covering 3-7million 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

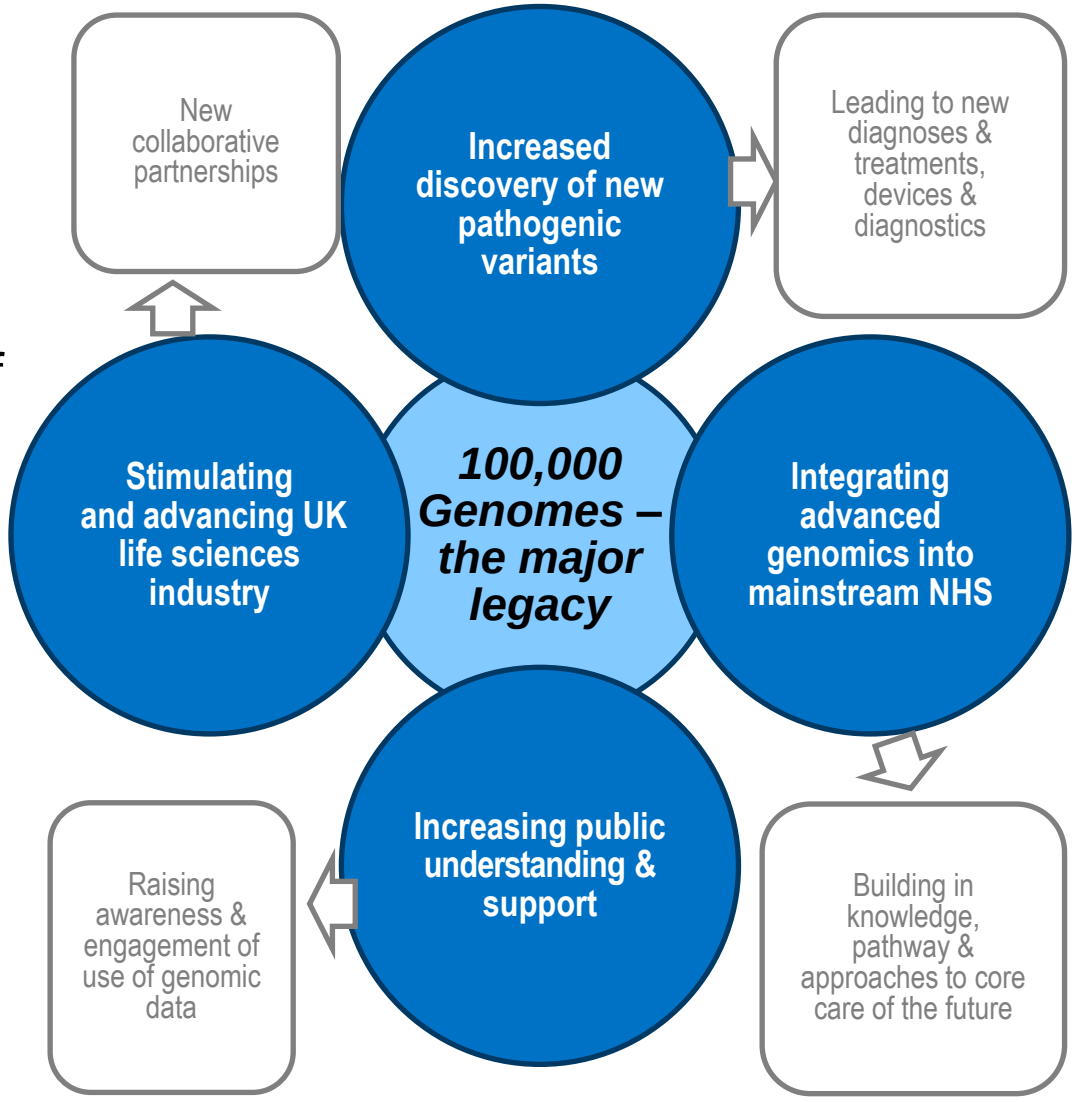


100,000 Genomes: a world-leading model for healthcare transformation

NHS England

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

Genomics england

100,000 genomes

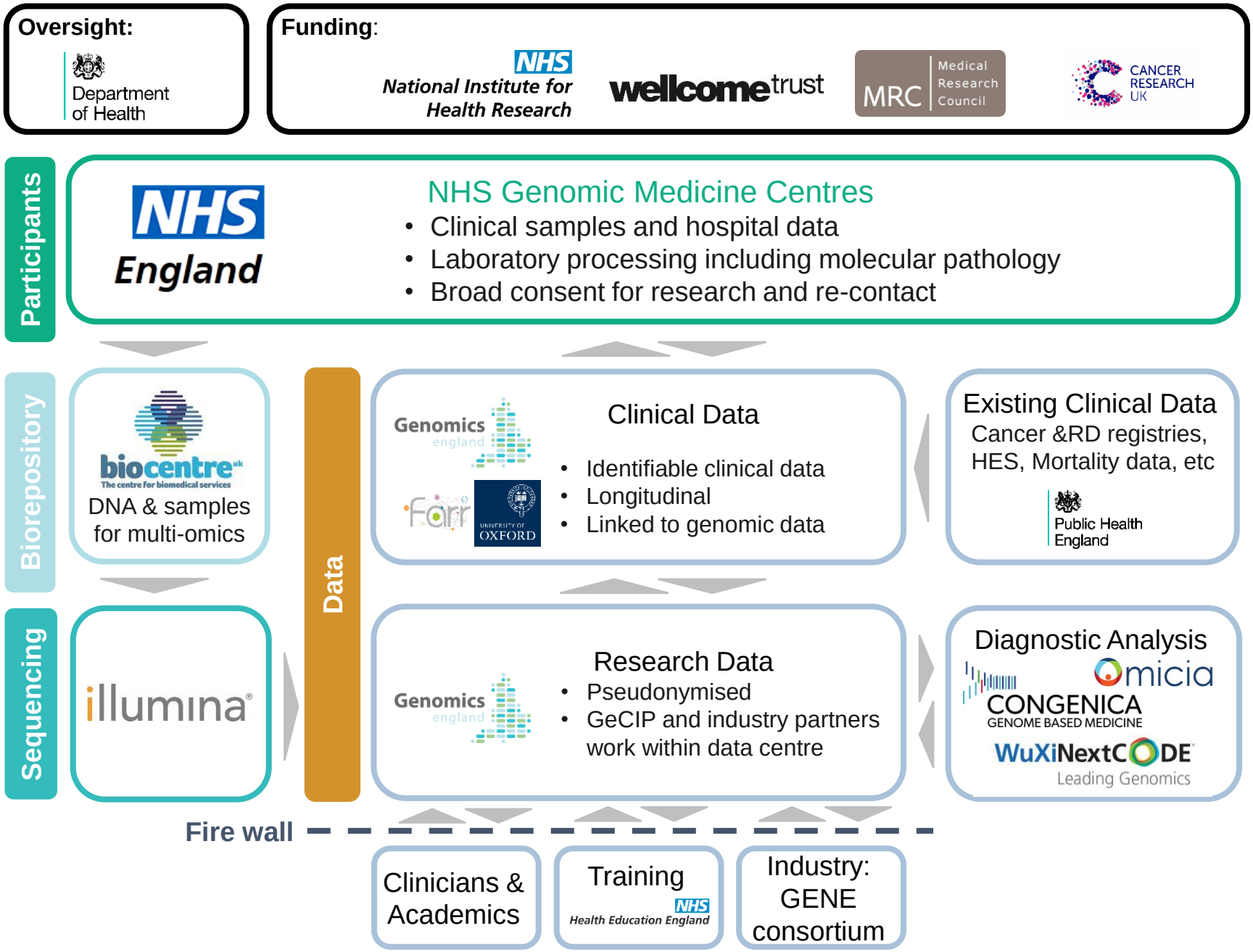
70,000 patients and family members

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


Oversight:
Department of Health
Funding:
National Institute for Health Research
wellcome trust
MRC Medical Research Council
CANCER RESEARCH UK
Participants
NHS England
NHS Genomic Medicine Centres
• Clinical samples and hospital data
• Laboratory processing including molecular pathology
• Broad consent for research and re-contact
Biorepository
biocentre
The centre for biomedical services
DNA & samples for multi-omics
Sequencing
illumina
Data
Genomics england
Farr
UNIVERSITY OF OXFORD
Clinical Data
• Identifiable clinical data
• Longitudinal
• Linked to genomic data
Existing Clinical Data
Cancer &RD registries, HES, Mortality data, etc
Public Health England
Genomics england
Research Data
• Pseudonymised
• GeCIP and industry partners work within data centre
Diagnostic Analysis
omicia
CONGENICA
GENOME BASED MEDICINE
WuXiNextCODE
Leading Genomics
Fire wall
Clinicians & Academics
Training
NHS Health Education England
Industry: GENE consortium

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.

In the UK alone that equates to approximately **3.5 million** people.

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

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

Seventy-five per cent of rare diseases affect children.

30% of rare disease patients die before their fifth birthday.

Category	Subcategory	Disease
Cardiovascular disorders	Arteriopathies	Familial cerebral small vessel disease
		Familial hypercholesterolaemia
	Connective tissues disorders and Aortopathies	Familial Thoracic Aortic Aneurysm Disease
	Cardiac arrhythmia	Brugada syndrome
		Long QT syndrome
		Catecholaminergic Polymorphic Ventricular Tachycardia
		Unexplained sudden death in the young
	Cardiomyopathy	Arrhythmogenic Right Ventricular Cardiomyopathy
		Left Ventricular Noncompaction Cardiomyopathy
		Dilated Cardiomyopathy
		Dilated Cardiomyopathy and conduction defects
		Hypertrophic Cardiomyopathy
	Congenital heart disease	Fallots tetralogy
		Hypoplastic Left Heart Syndrome
		Pulmonary atresia
		Transposition of the great vessels
		Left Ventricular Outflow Tract obstruction disorders
		Isomerism and laterality disorders
	Lymphatic disorders	Meige disease
		Milroy disease
		Lymphoedema distichiasis

Genomics england

Additional findings

- Information about ‘serious and actionable’ conditions (optional)
- Carrier status for adults who might have future children (optional)

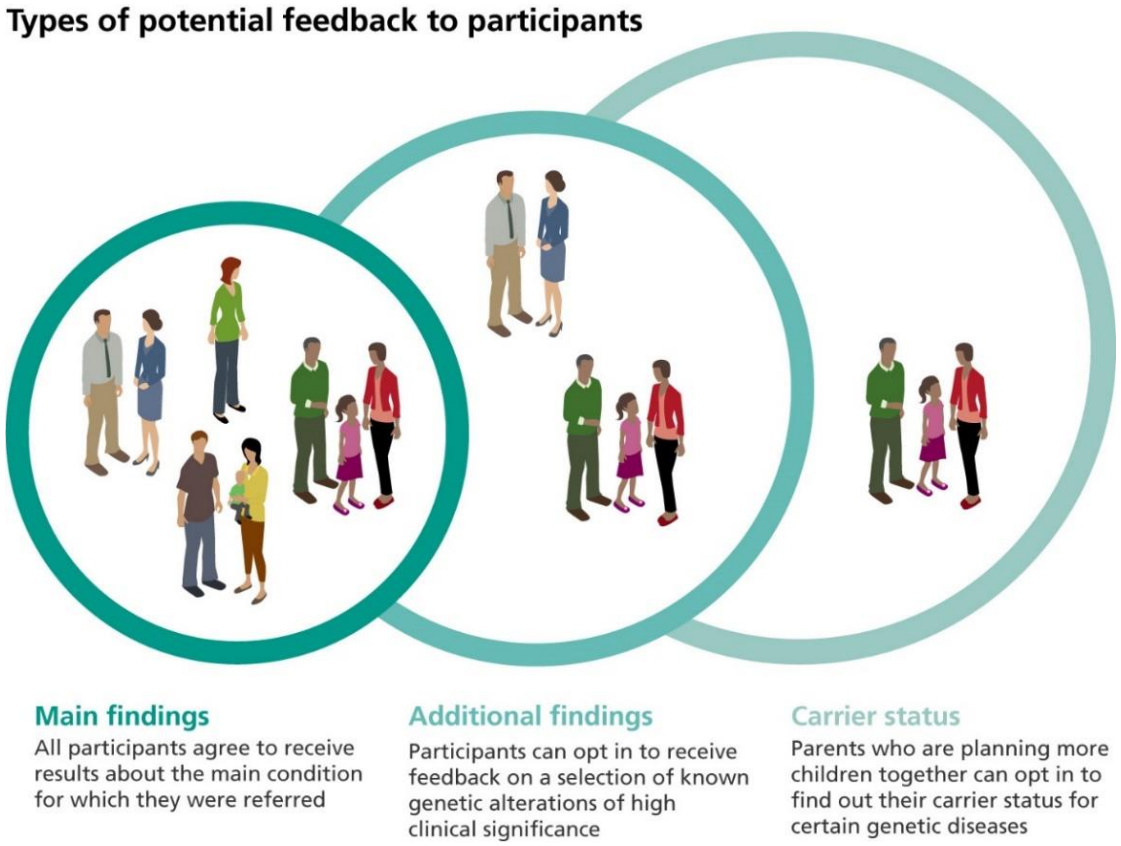


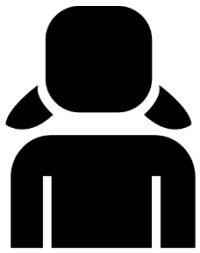
Image courtesy of Health Education England

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

Already changing lives

NHS England

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

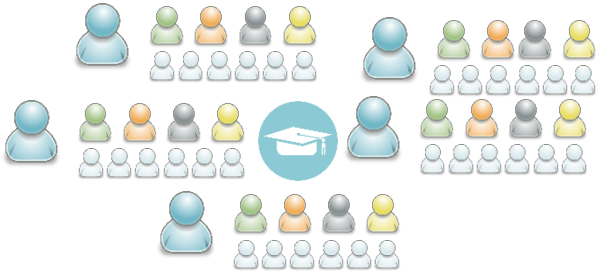
Genomics England
Clinical Interpretation Partnership (GeCIP)

NHS England

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

Queen Mary University of London
University of Oxford
Newcastle University
Manchester 1824 The University of Manchester
King's College London University of London
University of Southampton
Central Manchester University Hospitals NHS Foundation Trust
University of Cambridge
UCL
wellcome trust sanger institute
The University Of Sheffield.

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)

Subdomain	Lead(s)
Cardiomyopathy	Hugh Watkins, Perry Elliott, Stuart Cook
Arrhythmias	Elijah Behr, Andrew Grace, Clifford Garratt
Familial thoracic aortic aneurysms and dissection	Paul Clift, University Hospitals Birmingham
Congenital Heart Disease	Bernard Keavney
Familial hypercholesterolaemia	Steve Humphries
CADASIL negative small vessel cerebral disease	Hugh Markus
Primary lymphoedema	Pia Ostergaard, Sahar Mansour
Functional Genomics	Panos Deloukas

Personalised Medicine

DALYs Attributable to top 20 (of 67) Risk Factors (UK)

Global Burden of Disease Study. Lancet 2013;381:997-1020

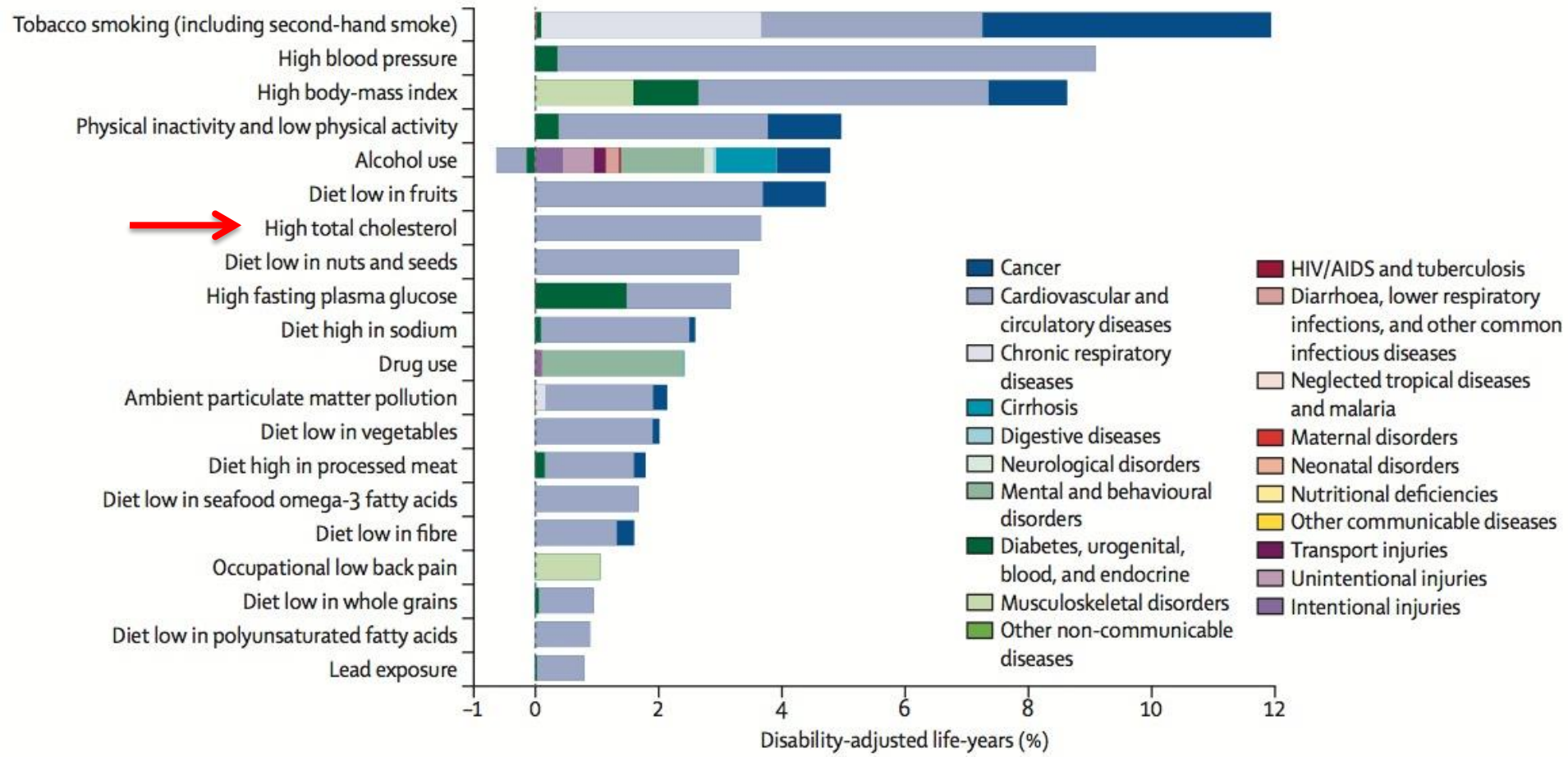
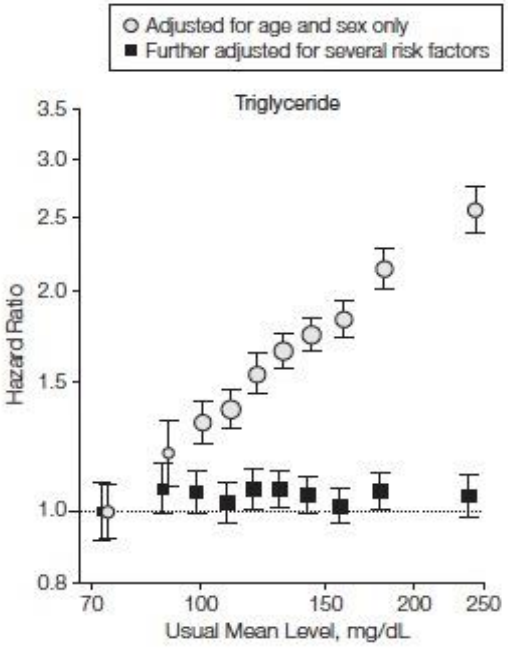
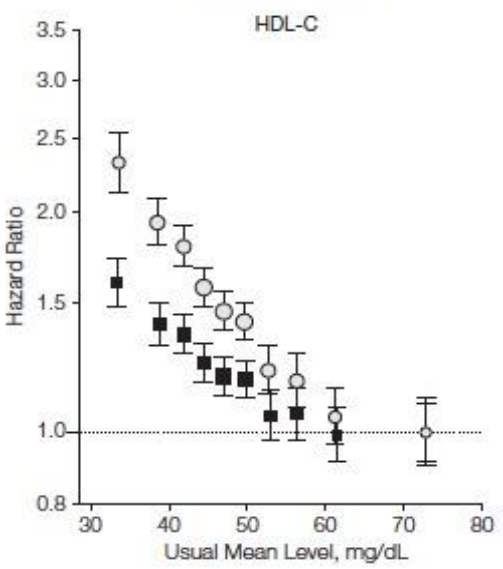
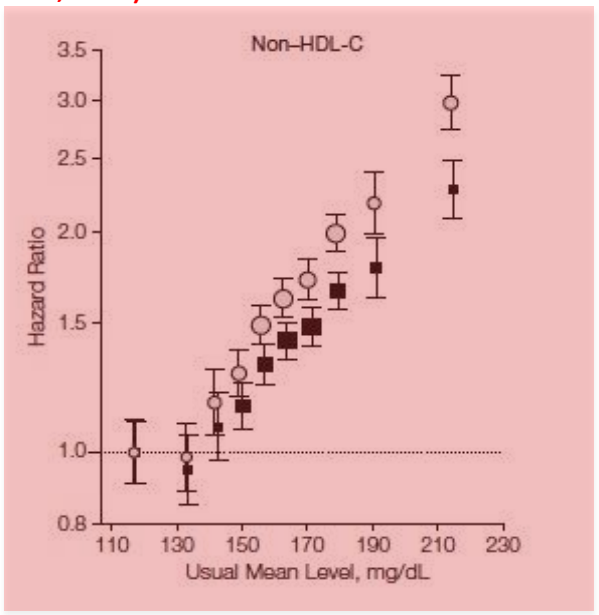


Figure 7: **Burden of disease attributable to 20 leading risk factors for both sexes in 2010, expressed as a percentage of UK disability-adjusted life-years**
The negative percentage for alcohol is the protective effect of mild alcohol use on ischaemic heart disease and diabetes.

Coronary Heart Disease (n=302,430)

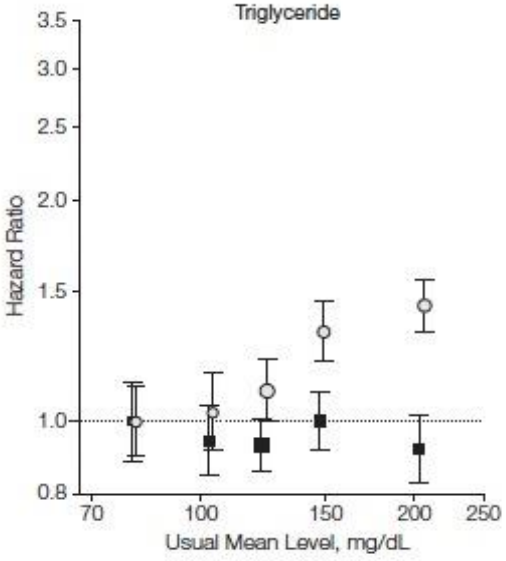


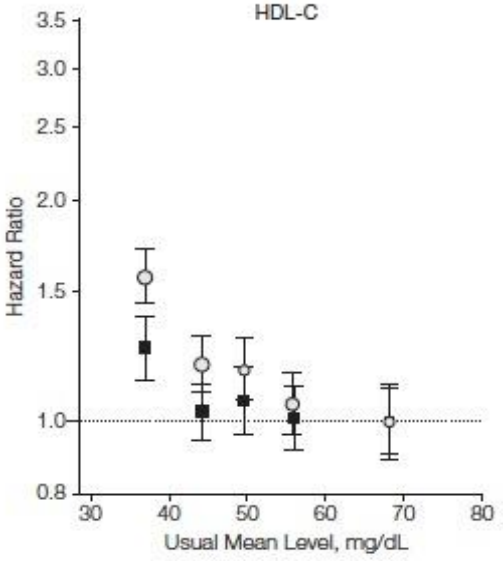


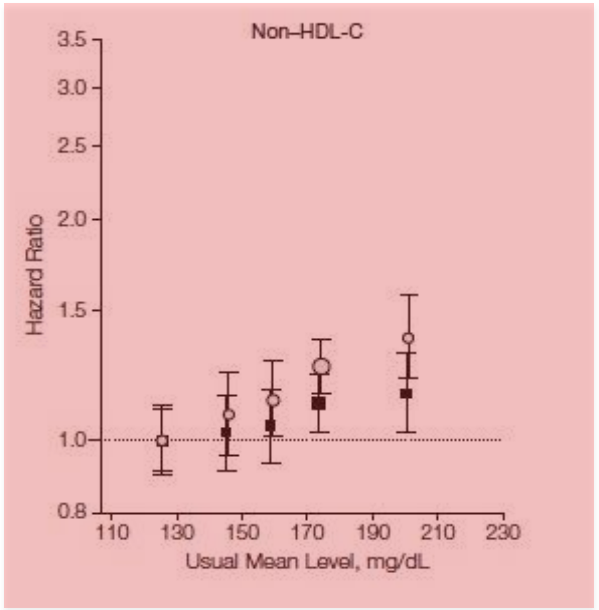


JAMA. 2009;302(18):1993-2000

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)

FH Key Facts

- 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)

NICE National Institute for Health and Care Excellence

Identification and management of familial hypercholesterolaemia

Issued: August 2008

NICE clinical guideline 71

guidance.nice.org.uk/cg71

NICE National Institute for Health and Care Excellence

Familial hypercholesterolaemia

Issued: August 2013

NICE quality standard 41
guidance.nice.org.uk/qs41

NB: Excludes Homozygous FH

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.

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Familial hypercholesterolaemia

Issued: August 2013

NICE quality standard 41
guidance.nice.org.uk/qs41

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Statement 1:

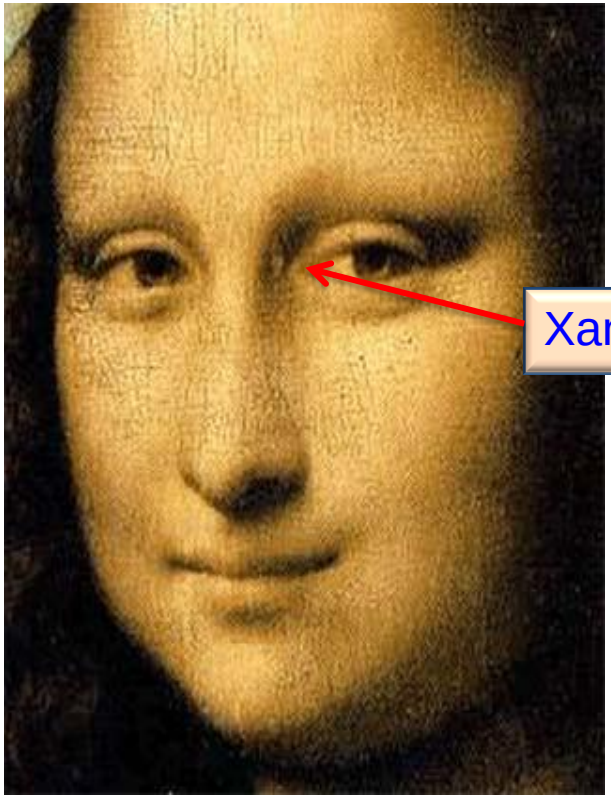
"Adults with a baseline cholesterol above 7.5mmol/l are assessed for a clinical diagnosis of FH"

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, 1st or 2nd 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 2nd degree relative <50 yrs or 1st degree relative <60 yrs
    - Family history of TC as above in 1st degree relative

Dutch Lipid Clinical Network criteria offers similar predictive model

Madonna Lisa Maria di Gherardini
Born Florence 1479
Died 1516 age 37 years



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NB: Excludes Homozygous FH

List of quality statements

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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

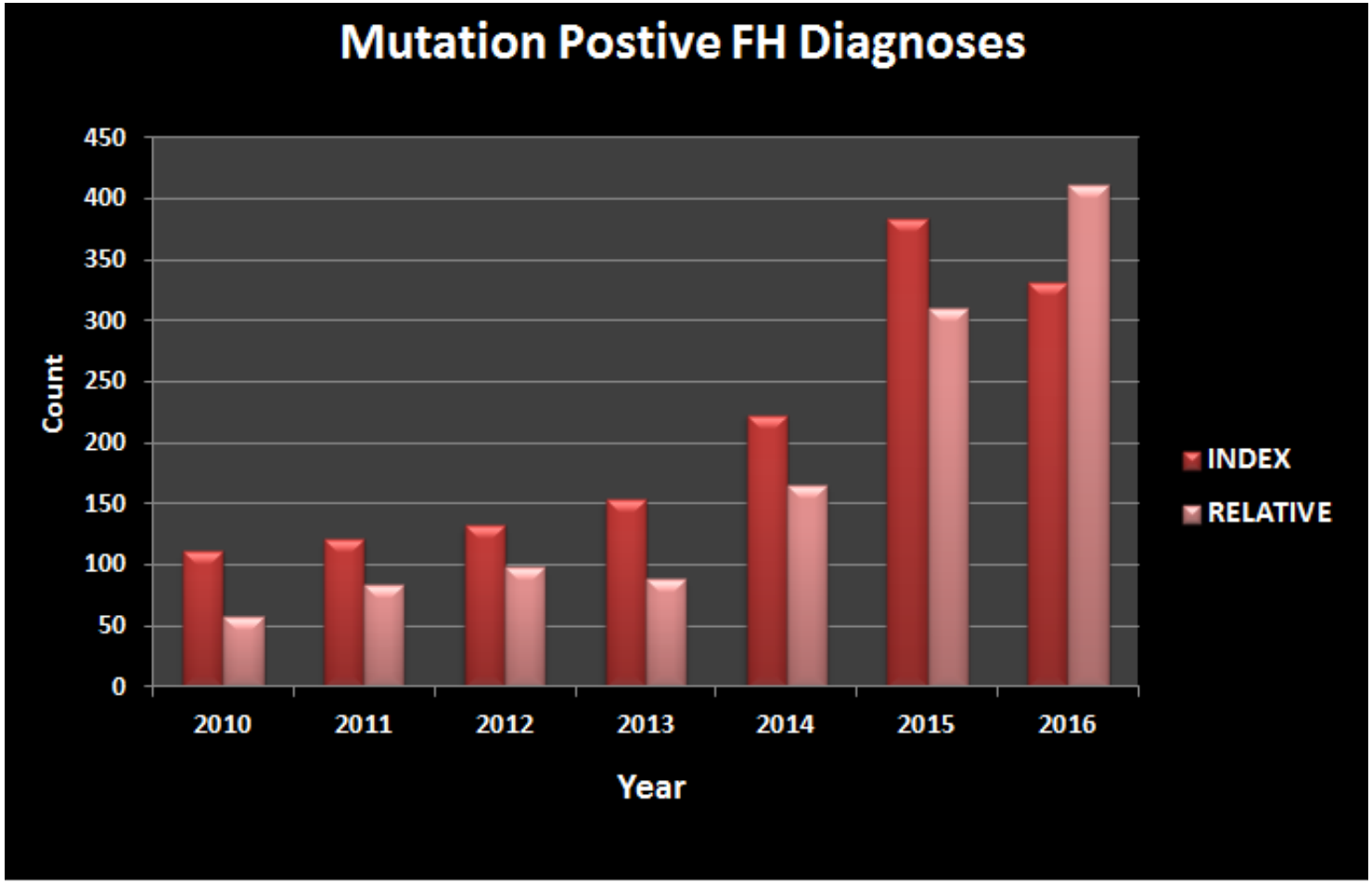
"The quality standard for FH specifies that services should be commissioned from and coordinated across all relevant agencies encompassing the whole FH care pathway. A person-centred, integrated approach to providing services is fundamental to delivering high-quality care to people with FH".

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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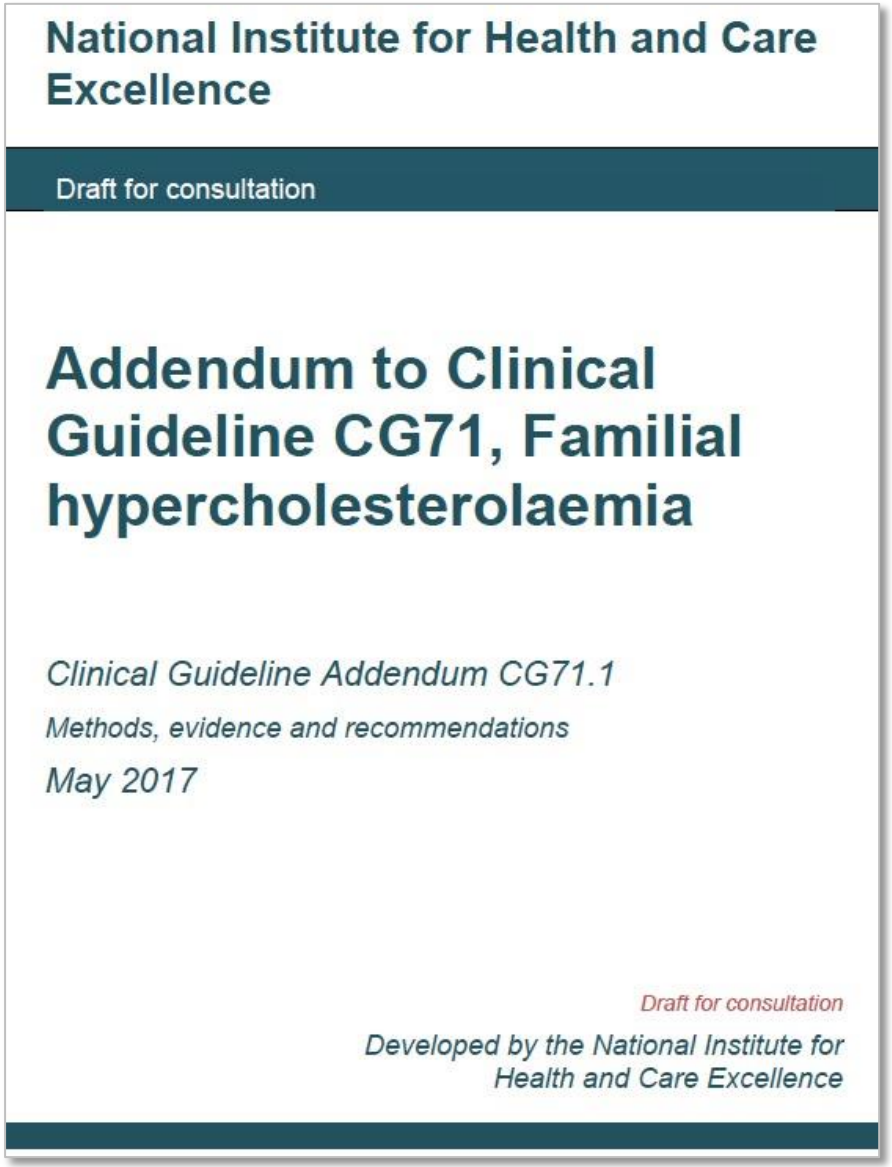
- NICE Guidance and Cost effectiveness



Recommendations (for heterozygous FH):

- Consider FH if **TC >7.5mmol/l** and/or family history of premature CVD
- Family history = coronary event <60yrs in 1^{o} relative or index case
- Systematically search 1^{o} 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