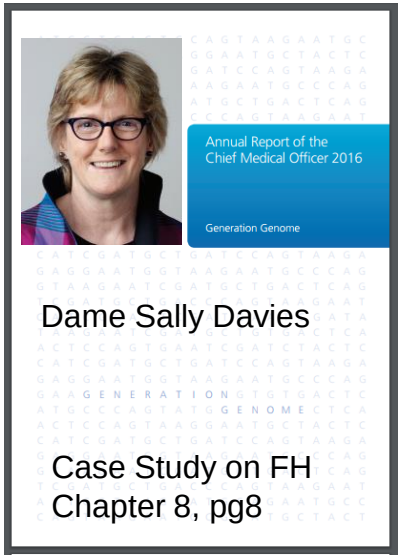
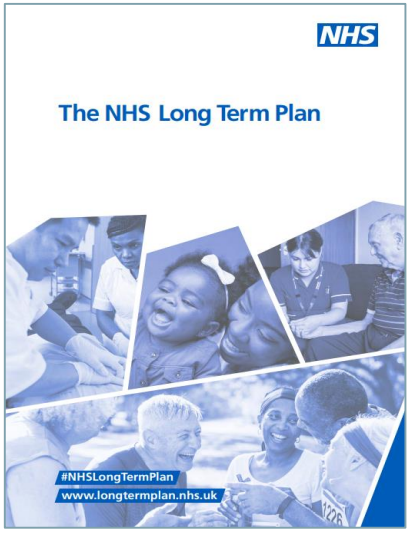
Familial Hypercholesterolaemia, Genomics and the NHS

CMO Report July 2017



"Genomics is not tomorrow. Its here today. I believe genomic services should be available to more patients, whilst being a cost-effective service in the NHS.

This is exciting science with the potential for fantastic improvements in prevention, health protection and patient outcomes. Now we need to welcome the genomic era and deliver the genomic dream!"



The NHS Long Term Plan – Jan 2019

PG 62 Cardiovascular disease

Expanding access to genetic testing for FH, which causes early heart attacks and affects at least 150,000 people in England, will enable us to diagnose and treat those at genetic risk of sudden cardiac death.

Currently only 7% of those with FH have been identified, but we will aim to improve that to at least 25% in the next five years through the NHS genomics programme.

How do we find 25% of the London FH patients?

Steve Humphries.
Emeritus Professor Cardiovascular Genetics UCL

British Heart Foundation

- FH key facts and Diagnostic criteria
- DNA tests for monogenic FH and polygenic hypercholesterolaemia
- NICE FH 2107 Guideline update – GP note searching for FH
- Universal Screening for childhood high cholesterol

CVG - Ros Whittall, Marta Futema, Sarah Leigh, Philippa Talmud; Royal Free Lipid Clinic - Devi Nair, Mahtab Sharifi; Bristol DNA Diagnostic Lab - Maggie Williams; Simon Broome Study Group - Andrew Neil, Nigel Capps, Ben Jones, Ian McDowell, Mary Seed, Handrean Soran, Paul Durrington; FH Child Register - Uma Ramaswami; HEARTUK - Jules Payne Simon Thompson; National Clinical Director CVD - Huon Gray; BHF- Jenney Hargrave, Jo Whitmore; PHE - Allison Streetly, Rhosyn Harris, Eleanor Wilkinson, Clare Thompson, Leah Desouza-Thomas

Public Health England

FH Diagnostic criteria – Simon Broome/DLCN?

Simon Broome Criteria

- Cholesterol > 7.5mmol/l or LDL > 4.9mmol/l in adult
- Cholesterol > 6.7mmol/l or LDL > 4.0mmol/l if < 16 yrs

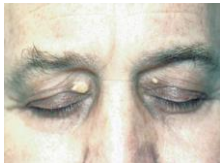
Possible FH

- PLUS family history of high cholesterol or MI (<55yrsM)
- OR PLUS Tendon Xanthoma
- OR FH-causing mutation

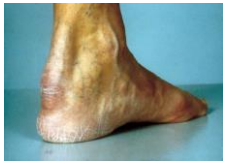
Definite FH

Corneal Arcus

Xanthelasma



Tendon Xanthoma



Dutch Lipid Clinic Criteria

Dutch Lipid Clinic Network Criteria		Points
Family history	1st-deg relative + known CVD (M 55yrs/F<60yrs)	1
	1st-degree relative with TX and/or arcus	2
Clinical history	Patient with premature CHD	2
	Patient with premature stroke or PVD	1
Physical examination	Tendon xanthomata	6
	Arcus cornealis prior to age 45 years	4
LDL-C levels	LDL-C >=8.5	8
	LDL-C 6.5-8.4	5
	LDL-C 5.0-6.4	3
	LDL-C 4.0-4.9	1
DNA analysis	Functional mutation in LDLR/APOB/PCSK9	8

>8 points = Definite FH
6 - 8 = Probable FH
3 - 5 = Possible FH

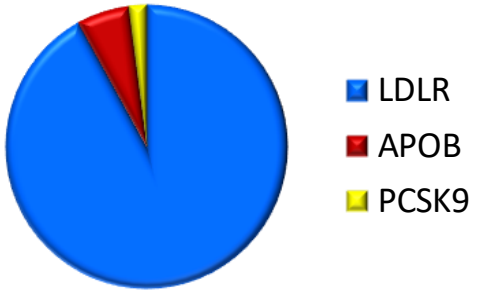
Welsh include –ve points for high TG – Haralambos et al 2014

NICE 2017 says evidence to support use of either

Genetic Causes of FH

Iacocca et al Hum Mut 2018

- *LDLR* – Commonest cause > 2300 world wide and >500 in UK
- *APOB* – One common mutation p.R3527Q
- *PCSK9* – Gain-of-Function – Least frequent/most severe
- *APOE* - Leu167del - frequency unknown
- *LIPA* - homozygosity → recessive pattern
- *LDLRAP1* – homozygosity (stop) – recessive pattern



DNA tests for FH - Offered by all 7 UK NHS Diagnostic Genomic Hub Labs

- Use NGS to capture and sequence exons of all genes in one run
- 96 samples can be handled in one run
- Costs now ~£250 for an index case, single mutation in relative ~ £70.
- Time taken to report now 4-6 weeks
- Costs for DNA tests covered by NHS from April 2019

Definite FH (~1/3rd of clinic load) → mutation in ~80%,
In Possible FH (~2/3rd of clinic load) detect in ~30%.
Remainder have a Polygenic Cause of their high LDL-C – Talmud et al Lancet 2013

UK FH NICE Guidelines 2008 – update 2017

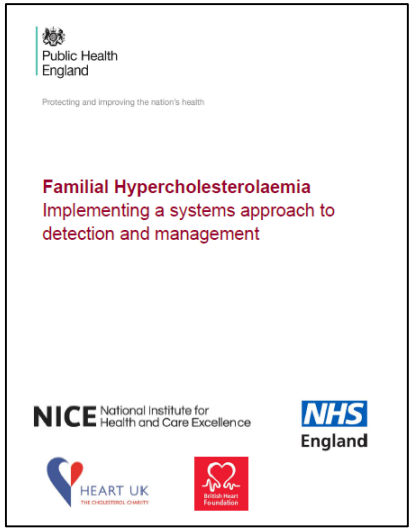
2008 →109 evidence-based recommendations - Several key changes in 2017

Treatment

- **Lower LDL-C by at least 50% from baseline.**
- **EAS target of <2.5mmol/ if no CHD and <1.8mmol/l if CHD**

Diagnosis

- **All individuals should be offered a DNA test to confirm the diagnosis and to assist in Cascade testing of relatives**
- **Systematically search GP notes for possible FH and refer**
- **In children aged 0–10 years at risk of FH (1 affected parent), offer a DNA test at the earliest opportunity (def by 10 years)**



Identifying people with FH using cascade testing

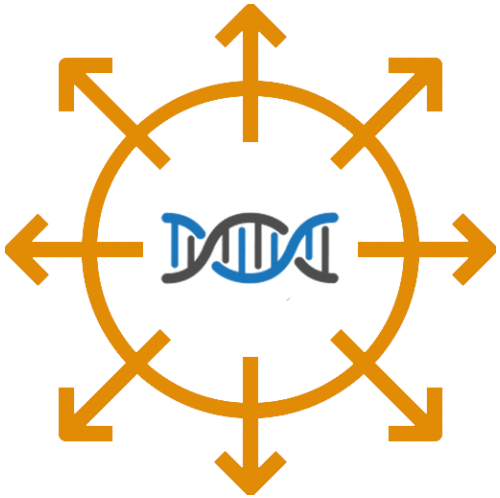
- **Systematic Cascade testing using DNA information is recommended to identify affected relatives of those with a clinical FH.**

Knowing the family mutation is a key piece of information for cascade testing and for starting statin therapy in childhood.

https://www.gov.uk/government/publications/familial-hypercholesterolaemia-implementation-guide

NHS Genomic Medicine Service: vision

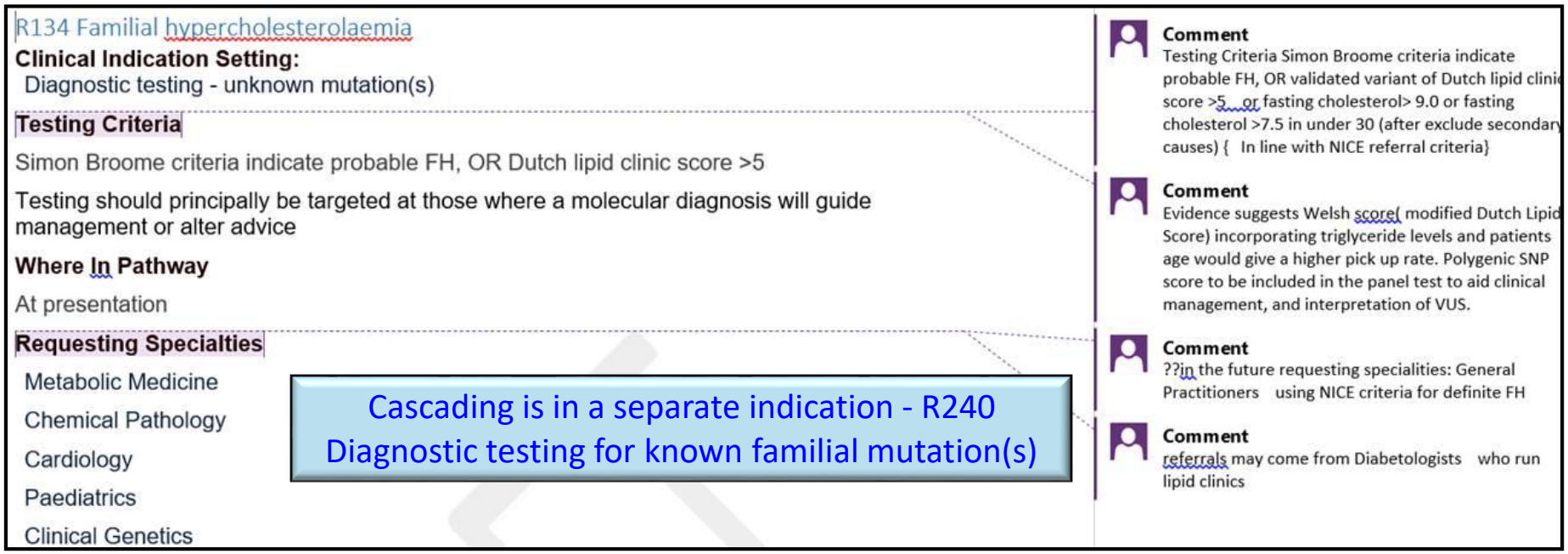
The NHS will have:



- A national Genomic Medicine Service providing **consistent & equitable care** for the country's 55 million population
- Operating to **common national standards**, specifications & protocols
- Delivering to a single **national testing directory** – covering use of all technologies from single gene to whole genome sequencing
- All patients to be given **the opportunity to participate in research** *(for individual benefit and to inform future care)*
- Building a **national genomic knowledge base** to provide real world data to inform academic & industry research & discovery *inc. clinical trials recruitment*

https://www.england.nhs.uk/genomics/nhs-genomic-med-service/

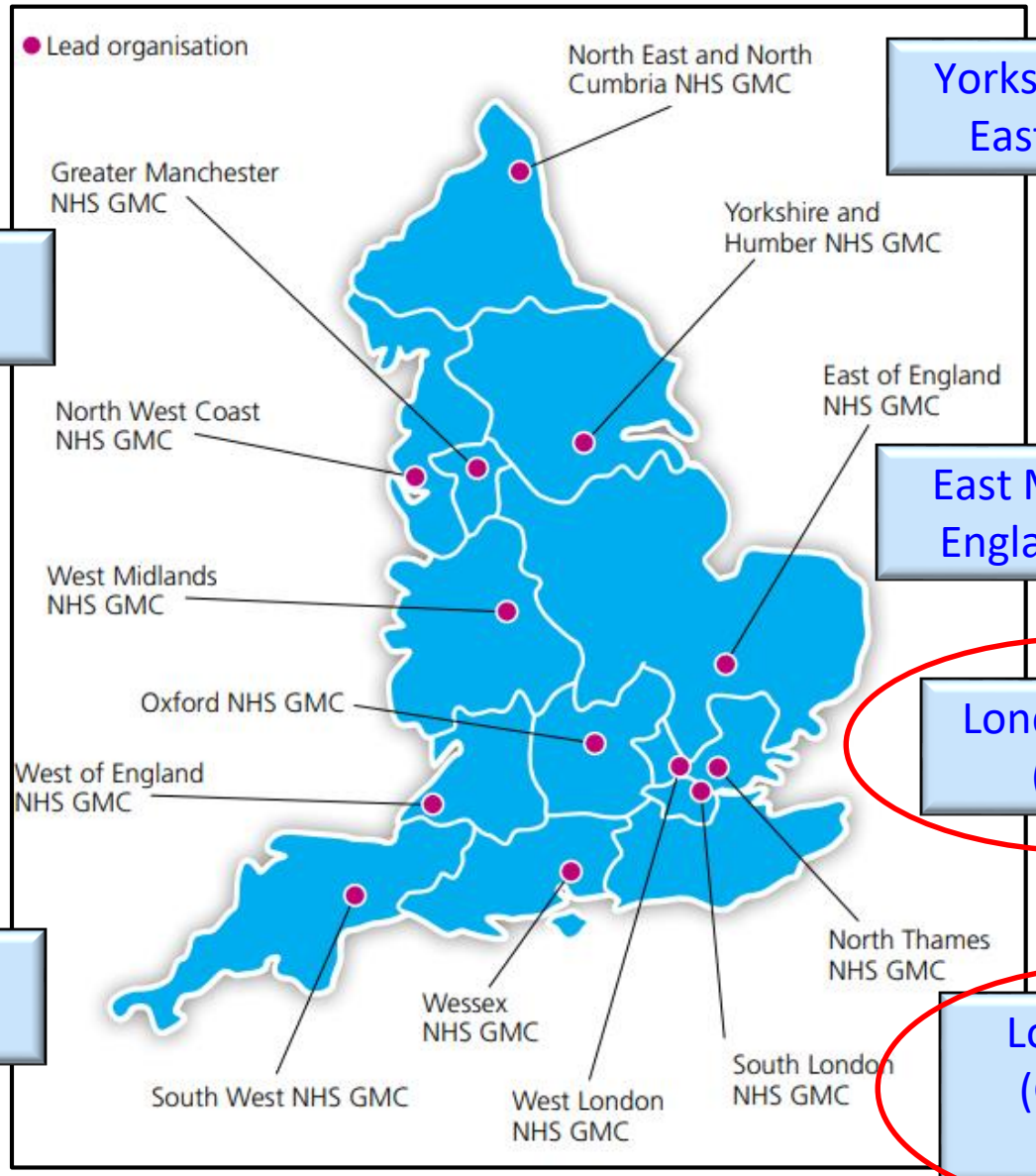
FH Eligibility Criteria



Diagnostic Test (NGS) as used by Bristol

- **v3 Gene panel (48/96 patients)**
  - Monogenic *LDLR, APOB, PCSK9, LDLRAP1 (APOE)*
  - Polygenic SNP score (reported in deciles as low, medium, and high likelihood)
  - *SLCO1B1* SNPs
- **Bespoke FH Bioinformatics Pipeline** (>8000 cases tested)
  - **SNP/indel** (binning system)
    - Pathogenic/likely pathogenic variants/VUS/New variants requiring classification
  - **CNV** (2 algorhythms - concordance)
    - MLPA confirmation (positives and poor quality (low numbers))
    - *LDLR* validated (but other genes detected)

Genomic Medicine Centres/Genomic Laboratory Hubs (GLH)



Yorkshire and North East (Newcastle)

North West (Manchester)

East Midlands/East of England (Cambridge)

Wessex and West Midlands (Birmingham)

London North (GOSH)

South West (Bristol)

London South (Guy's and St Thomas')

NHS England

FH DNA "Steering Group" to curate VUS etc

GP note searching for FH

2017 NICE FH Guideline update recommends:

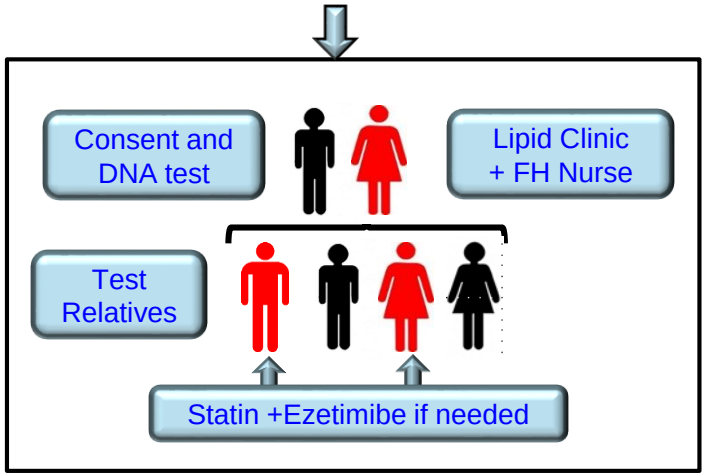
Crosland et al 2018

- Finding new index cases by electronic search of GP records for likely FH.

Systematically search primary care records for those at high risk of FH:

- <30 years, with a T-Cholesterol concentration > 7.5 mmol/l
- >30 years, with T-cholesterol concentration > 9.0 mmol/l

- These are then referred to a lipid clinic for confirmation, DNA and CT



Cost Effectiveness → ICER vs CT no DNA ~ £3000/QALY

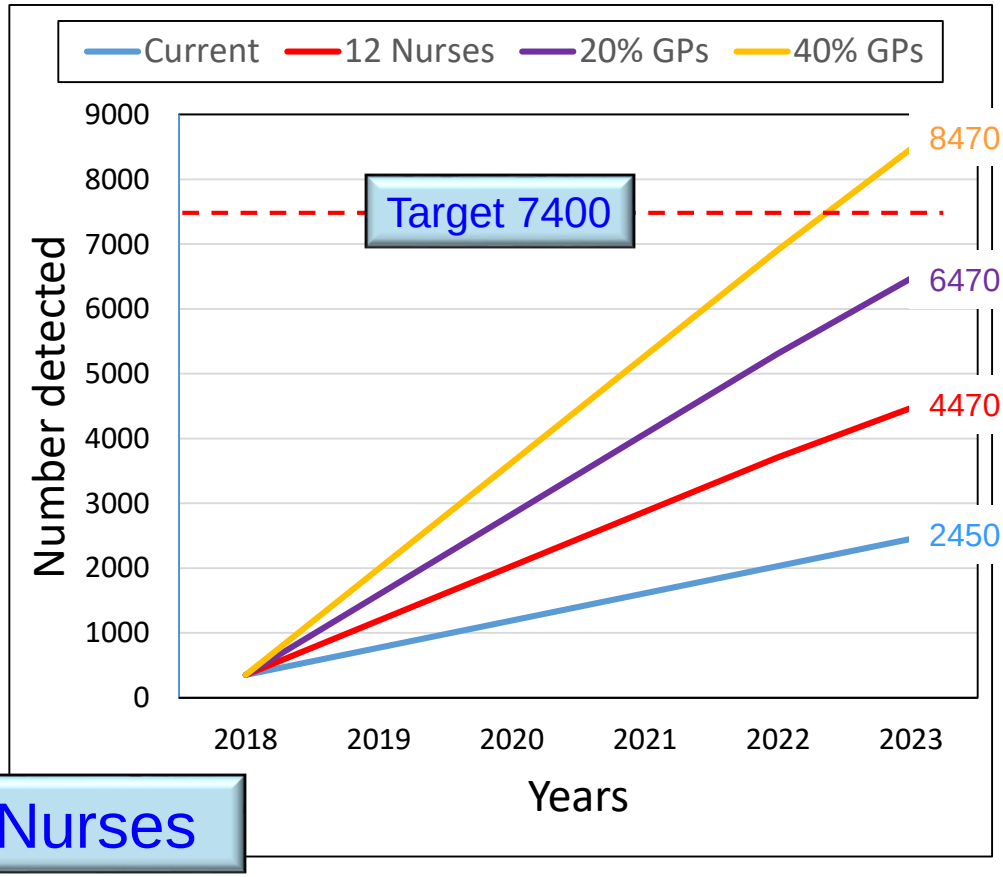
Health Check programme → many 40-74year olds have FIRST EVER lipid profile and can be identified as possible FH if TC>9.0mmol/l

FAMCAT programme being tested in S London

Needs Nurses!

Ambition : → 25% of M+ve GLondon FH patients by 2023

- If FH = 1/270, 8 Million in M25 → 30,000 GLondon, so 25% = 7400. Currently 350 known.
- Each Nurse finds 70 index+relatives pa. currently 6 Nurses in GLondon → ~420 new pa
- If we could → 12 Nurses to cover GLondon could find ~840 new pa
- ~1000 GP in GLondon. If 20% each finds 3 possible FH pa → referral → 1 M+ve = 200 index
- each → one M+ve relative = total 400 new M+ve FH pa
- If 40% GPs each finds 3 possible FH pa → referral → 1 M+ve. = 400 index
- each → one M+ve relative = total 800 new M+ve FH pa



Incentivise GPs + Train Nurses

Universal Screening for high Chol

Child–Parent Familial Hypercholesterolemia Screening in Primary Care

David S. Wald, F.R.C.P., Jonathan P. Bestwick, M.Sc., Joan K. Morris, Ph.D., Ken Whyte, Lucy Jenkins, F.R.C.Path., and Nicholas J. Wald, F.R.S.

- Measured cholesterol in 10,094 children at time of routine immunisation (median age 12.7 months). NEJM 2016
- Used diagnostic criteria of *either* total chol >5.31mmol/l (95th percentile) plus one mutation, *or* two cholesterol values of ≥5.90mmol/l (99th percentile).
- Selected samples sent for FH-mutation chip plus sequencing
- Identified 45 children with "FH", 37 with a detected mutation and 8 with repeated LDL-C over the pre-specified threshold but with no identified mutation.

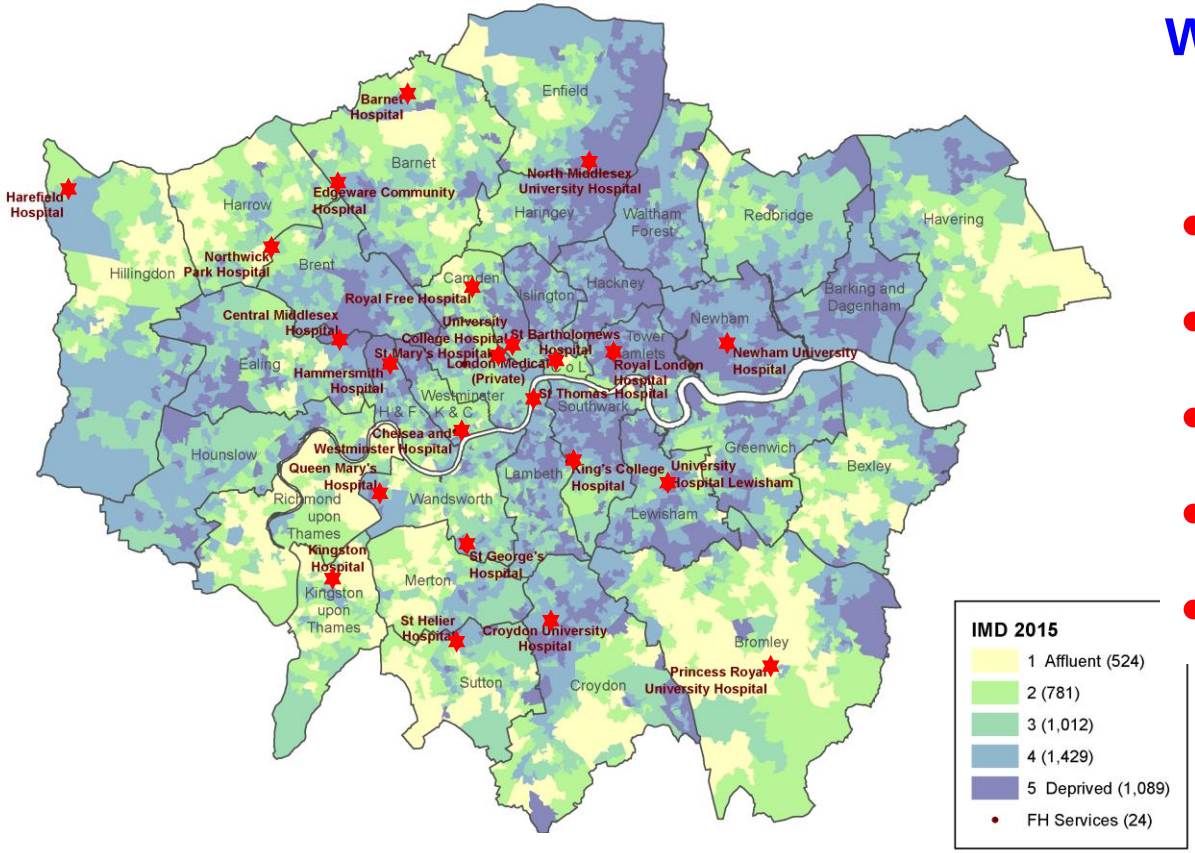
Prevalence of mutation carriers was 1/273 (37/10,940).

- The 8 with no mutation likely to have a polygenic aetiology for their FH
- Testing parents of the confirmed FH children identified 40 parents who also met the criteria for FH diagnosis. Offered statin.

Supports the feasibility and acceptability of US to identify new FH index cases

- HEARTUK Application to National Screening Committee for US rejected in 2018
- NCS are re-examining case in 2019 → updated HEARTUK application
- If approved unlikely to start before 2020?

Location of Glondon Lipid clinics



Well covered (except NE)

What do we need to do to → 25% FH by 2023?

- Increase clinic capacity
- Find funds for Nurses
- Find and train Nurses
- Incentivise GPs
- Increase Paed's capacity

We intend this Pan-London group to be a networking-sharing support group to help achieve this ambition