Familial Hypercholesterolaemia: the case for finding the patients and finding their genes

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Familial Hypercholesterolaemia

Autosomal dominant disorder causing high levels of low density lipoprotein cholesterol which frequently leads to early coronary heart disease.

FH is caused by mutations in 3 genes identified so far:

• Low-density lipoprotein receptor gene (LDLR)
• Apolipoprotein B-100 gene (APOB) – involved in LDLR binding
• Proprotein convertase subtilisin/kexin type 9 (PCSK9) – cholesterol homeostasis
Signals for the growing protein chain to enter the rER

Has 7 cysteine rich repeats. DXSDE

Responsible for the dissociation of the receptor from its ligand during recycling.

Has YPXL domain responsible for internalisation of the receptor into clathrin coated pits.

Each receptor is recycled to the cell surface once every 10 mins and lasts about 24hrs
Stigmata of Familial Hypercholesterolaemia

Corneal Arcus

Xanthelasma

Tendon Xanthoma

Definite FH

With permission of HEART UK
"In children at risk of FH because of one affected parent, diagnostic tests should be carried out by the age of 10 years or at the earliest opportunity thereafter" 
NICE Guideline 1.1.15
Prior (%) probability that an individual has FH before measurement of cholesterol

LDL-C diagnostic criteria for family testing must take account of degree of relatedness, age & sex

1 in 500 for general population

12.5% for 1st cousins & sibs of grandparents

25% for each aunt, uncle, grandparent, niece, nephew

50% for each parent, sibling, child

Courtesy Professor Neil
Clinical diagnostic criteria: schematic frequency distributions of total cholesterol among a middle-aged unaffected population & an FH population.

NICE Guideline 1.1.12
“should offer people with a clinical diagnosis of FH a DNA test to increase the certainty of diagnosis and aid diagnosis among their relatives”
Mortality Rate in FH patients in the UK

With early identification and new more powerful STATIN drugs, life expectancy for FH patients may not be significantly reduced at all.

Before use of STATINS (pre1991)

After 1992

Kaplan-Meier curve estimates of cumulative CHD-free survival among 1950 Dutch FH patients followed for a mean 8.5 years from 1990 by statin treatment.

Statin treatment (7473 person-yrs)

76% (95% CI 70, 82) risk reduction

No statin treatment (9319 person-yrs)

Courtesy Professor Neil
Identification: extent of under-diagnosis based on UK lipid clinic survey conducted by HEART UK in 2001

Undiagnosed FH
~88%
~105,000 patients

Lack of systematic identification programme

~12% Diagnosed
5% definite FH
7% probable

Variable rate of identification
Oxford 34% J Med Screen 2006;13:156-9


Courtesy Professor Neil
The clinical syndrome of FH is readily identifiable by

- the presence of hypercholesterolaemia
- personal or family history of premature CHD
- characteristic tendon xanthomata in patient or first degree relative

It satisfies the main criteria for a screening programme

- the condition merits identification
- the natural history is known
- a definite diagnosis is possible
- pre-symptomatic treatment (e.g. statins) confers benefit

There are 2.5 million subjects in Greater Manchester

It is expected that there are 5000 subjects with FH

Only about 700 FH patients are known to lipid clinics in the region
In 1987 a case finding strategy to develop a genetic register of probands [FH] was initiated in Lipid Clinics at Manchester Royal Infirmary and University Hospital of South Manchester.

Secondary and tertiary referrals

Healthcare changes in NHS
262 probands with FH identified over 11 years

Simon Broome criteria

All were asked to provide detailed family history & names, addresses and telephone numbers of first degree relatives

3 patients refused to take part

Most relatives were sent a personalised standard letter

About 5% were asked to take part by telephone
89% of probands were already on lipid lowering agents
24% had angina
16% had had a myocardial infarction
18% had undergone CABG
216 out of 259 probands (83.4%) provided names of relatives

Further 59 out of 216 probands’ relatives could not take part

157 probands gave names of 233 relatives

74% provided the name of a single relative
26% provided names of 2 or more relatives

205 out of 233 relatives (80%) finally took part in the study
121 out of 205 relatives (59%) were diagnosed as having FH
79 out of 205 relatives (39%) were characterised as unaffected
4 out of 205 had missing blood samples (did not attend again)
12 affected relatives were below 16 years of age
From 1987-1998:

- 259 probands were detected
- 205 relatives entered the study
- A total of 121 relatives with heterozygous FH were detected

Total number of probands and relatives participating in the study over the last 11 years.
What does cascade testing involve?

• Confirm clinical diagnosis of “definite” FH
• Invite index patient to discuss family tracing with the FH nurse
• Draw family pedigree – identify target relatives
• Contact 1st degree relatives
• Offer relatives point-of-care test at the clinic or at home (or visit GP)
• Fasting lipid profile offered to those above cut-off
• Inform GP & ask for patient referral.
Why do cascade testing?

• Autosomal Dominant disease - all 1st degree relatives are at 50% risk of having FH

• 1/500 of UK population is estimated to be affected, only 10% of 100,000 cases have been identified
• (Marks, Farrer Humphries et al 2004)


• Cascade testing for FH compares well with other screening/treatment programmes (Marks et al BMJ 2002)
Background of Study

- Funded by the Department of Health
- Announced in June 2003, “Our inheritance, our future”
- Audit and service development project.
- Builds on previous work at UCL, Oxford and Manchester
- Administered through the London IDEAS group
Five sites provided with nurse for 24 months.

Sites cover:
- Multi ethnic/social spread
- Single and Consortium of clinics
- Geographical spread
- All sites offer a service to children

Protocol:
- Audit of notes
- Cascade testing using LDL levels for diagnosis
Manchester region

• Dr D Bhatnagar (Project Lead) (Pennine Acute NHS Trust)

• Dr J Marples (Wrightington, Wigan and Leigh NHS Trust)

• Dr L N Sandle (Trafford Healthcare NHS Trust)

• Dr MF Stewart (Salford Royal Hospitals NHS Trust)

• Ms Ruth Eatough (Project Nurse)
Sites provided with:

- Full time research nurse
- Training in lipid biochemistry, genetics, informed consent, psychological impacts, ethnicity issues, counselling and testing children.
- Patient cholesterol testing equipment
- Laptop with biometric thumb print recognition for data protection and pedigree drawing software.
Cascade process - loop

National Roll-out

1. Audit current practice
2. Implement best Practice
3. Re-audit & feedback to DH

Best Practice Established
Audit current practice in each NHS Trust

• Diagnosis and management, (Simon Broome criteria) follow up, drug therapy.

• Family history taken or tracing recommended

• Pre treatment lipid profiles recorded.

• Clinic facilities, size, phlebotomy service, rooms

• Establish a database of FH index patients
Index Cases

![Index Cases Chart]

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<td>82</td>
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<td>Heartlands</td>
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Relatives contacted

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Greater Manchester Index cases

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<td>Wigan</td>
<td>52</td>
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Summary of results

High acceptance rate, but low pick up of new FH due to numbers tested already, out-of-catchment loss, and low LDL-C diagnostic specificity. 50% of new FH are under 24 years of age.
# Model assumptions

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<th>Pilot</th>
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<td>Number of 1st degree relative invited per index case</td>
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<td>Average number of letters per relative (cost = £0.5 per letter)</td>
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<td>Cholesterol test TC</td>
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<td>No. relatives screened to find one new case</td>
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Conclusions

• Cascade testing to identify FH patients is feasible and acceptable in the UK and is cost effective.

• DNA testing is essential for this to be efficient and this will improve cost effectiveness.

• Highlights infrastructure and staffing needs – NICE guidelines now available

Expect HEARTUK and patient voice to have major part in leveraging funding for roll-out
The pilot project reported here evaluates services against the NICE guidelines. The results do provide extremely helpful information, although care must be taken in interpretation as it is a pilot study. The current treatment of people identified with hypercholesterolaemia is good. However there are clearly apparent inadequacies in the screening programme, both in terms of cascade testing and in the use of DNA testing.
What did the audit find?

• The clinical management of patients with FH is of a good standard in lipid clinics

• Centres will need additional resources to cope with the identification of the predicted additional 100,000 FH cases UK wide. This includes access to trained staff (nurses), IT needs and pedigree drawing.

• There is a major lack of systematic family “cascade” testing, whether carried out on the basis of lipid levels, or by DNA testing.

• There is limited access to DNA diagnosis and that which is available is being carried out in a research environment.

• There is a shortfall in child-focused services throughout the country, so that the ability to diagnose and treat FH in children and young persons in the health service is limited.
KEY RECOMMENDATIONS

Acute trusts (England) / Integrated Trusts (Wales)

• Care pathways for FH patients need to be implemented. This must include shared care arrangements between hospital and primary care and better links between with several other specialities, including paediatrics.

• Additional resources (clinic sessions) will be needed to cope with the identification of the predicted additional 100,000 FH cases UK wide. At present there is a shortage of both specialists and lipid clinic nurses.

• Systems need to be developed and implemented to carry out systematic family “cascade” testing. This will require trained nursing/genetic services to follow up the families of index patients, improved IT needs, including an FH patient database, and pedigree drawing.

• Resources are needed for DNA diagnosis and Clinical Genetics input.
Key priorities for implementation

– Diagnosis

– Identifying people with FH using cascade testing

– Management

– Information needs and support

– Ongoing assessment and monitoring
Identification and Management of Familial Hypercholesterolaemia
– the NICE Guidance

1.1 Diagnosis – 13 recommendations

1.2 Identifying individuals with FH using cascade testing – 8 recommendations

1.3 Management – 56 recommendations

1.4 Information needs and support – 14 recommendations

1.5 Ongoing Assessment and Monitoring – 8 recommendations

A total of 99 recommendations

courtesy Dr Neely
Diagnosis

– Always take a family history of premature coronary heart disease.

– In children, by the age of 10 years:
  – offer a DNA test if the family mutation is known
  – measure LDL-C concentration if the family mutation is not known.

– Do not use coronary heart disease risk estimation tools such as those based on the Framingham algorithm.
Identifying people with FH using cascade testing

– Offer all people with FH a referral to a specialist for confirmation of diagnosis and initiation of cascade testing.

– Conduct cascade testing:
  – using a combination of DNA testing and LDL-C concentration measurement
  – including at least first-, second- and, when possible, third-degree biological relatives of index individuals.

– Nationwide family-based follow-up system is recommended (currently unavailable).
Management

Adult
– Consider prescribing a high-intensity statin to achieve a reduction in LDL-C concentration of greater than 50% from baseline.

Children and young people
– Offer referral to a specialist with expertise in FH in children and young people, in an appropriate child/young person-focused setting.
Information needs and support

• For women and girls with FH:
  – Provide information and counselling on contraception.

  – Discuss risks for future pregnancy and the fetus while taking lipid-modifying drug therapy at least annually.
Ongoing assessment and monitoring

– Offer all people with FH a regular structured review that is carried out at least annually.
Lifestyle advice

– Smoking

– Diet

– Physical activity

– Weight management

– Alcohol consumption
Impact on workload for GP’s

• Likely to have 1 or 2 FH families on register

• Important that FH patients are referred to a clinic to ensure family tracing is initiated

• Patients in your area maybe relatives of FH patients. They will present with a letter and information pack from the FH Nurse

• Important that they have a cholesterol test and are referred to a lipid clinic if positive
Questions patients ask

- What is the benefit to me?
- What about my family?
- Can they refuse to take part?
- What is entailed in the test?
- Who will know the results of the tests?
- Will my insurance premiums increase?
Logistical issues

• Time taken by grading panels to assess job description (repeated at each trust)

• Shortage of nurses

• Space for the nurses

• Access to Medical Records for audit

• IT support

• Honorary contracts

• Extended CRB checks
Logistics: Cascade testing

• Nurses are working in “lipid clinics” not “FH clinics”, reduces efficiency.

• Some index cases unaware that they have a genetic disorder.

• Letter to the index patient prompts them to contact their relatives immediately, they go to the GP (we get feedback on ~ 30%).

• Children & adolescents with FH need support (~50% of new FH are <18).

• Management of Family Files – no system in Lipid Clinics.
Logistics: Cascade testing

- Patients discharged back to GPs (and lots have been in recent months to reduce waiting times) are less likely to come forward for cascade testing.

- GPs don’t always refer new FH to a lipid clinic, this blocks the cascade testing, even though GP may treat, but they don’t always.

Examples

- GP to 32 year old sister of FH patient “You’re a young woman, you don’t want to be taking tablets for the rest of your life”. Her cholesterol was 9.

Referral times can be very lengthy – slows down the cascade process (one took from Nov. 05 to Mar. 06, presumably due to financial constraints).
Recommendations

Cascade Testing is feasible and cost effective in UK

- Integrated national infrastructure needed so that relatives wherever they live, have access to the service.
- DNA testing should underpin FH cascade testing, as LDL-C measurements have a poor diagnostic sensitivity and specificity.
- Specialist services needed for young people with FH - not currently available in most areas of the country.
- Education and incentives needed for Primary Care Teams, so new FH patients offered appropriate care.

Will DNA testing improve cost-effectiveness?
Finding all the FH patients

Cascade Testing
Each FH $\rightarrow$ 5 living relatives of whom 50% have FH so 15,000 known $\rightarrow$ ~30,000 new

From Young MI
All MIs on MINAP register. 5-10% of those <45yrs may be FH $\rightarrow$ 1000/yr? Piloting offering DNA test, and then cascading $\rightarrow$ 10,000 /10 years?

From General Practice
Each will have 2-3 families. Find by note search Grey et al 2008
Would help if Chem Path “flags” extreme values. 1000/yr? $\rightarrow$ 10,000/10 years

National Health Check will find >40 yrs with Chol > 7.5 $\rightarrow$ Lipid Clinics

What about general population screening of children?
LDL-C Diagnostic Tables for 1º relatives

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Legend

- Red = Likely FH
- Grey = Uncertain
- Green = Unlikely FH
DNA vs Cholesterol – Testing Relatives

Summary

How does this affect costs?
DH FH DNA Cascade Testing Pilot Study

Newcastle patients - Mutation Status by Simon Broome Diagnosis

Definite FH 77% positive, Possible FH 38% positive

Overall, mutations were detected in 75/145 (52%)

courtesy Dr Neely
Model 1 – Genetics Centre Based

1st care

Relatives

Cascade testing not required

Assessment
Specialist lipid clinic
Management

New Definite FH Case

Offered gene test and cascade testing

GENETICS SERVICE

Counsel
Consent
Test
Contact relatives
Test relatives
Deal with results

Possible FH Case

2nd care

Definite or Possible FH by Simon Broome criteria

Yes

No

?
Model 2 – Outreach Service

courtesy Dr Neely
Study costs of screening

Laboratory & clinical consumables       £5.00

Nurse time spent with relative @ 1 hour (including questionnaire & telephone calls)   £13.00

Nurse time with proband @ 30 minutes   £7.50
## Costs to identify FH relatives
### Cholesterol vs DNA

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>No rel’s/1000 probands</th>
<th>Costs to find one (FH)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chol true</td>
<td>Chol false</td>
<td>Mut +ve</td>
</tr>
<tr>
<td>A 2002 model, DNA= £1000 5 1st degree, 2 2nd degree</td>
<td>2537</td>
<td>0</td>
<td>2500</td>
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<tr>
<td>B DNA = £250, Sens/spec = 70/85 Nurse time 0.5hr→2hr/1hr</td>
<td>1630</td>
<td>852</td>
<td>2500</td>
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<tr>
<td>B but DNA = £500</td>
<td>1630</td>
<td>852</td>
<td>2500</td>
</tr>
<tr>
<td>B but nurse time = £50</td>
<td>1630</td>
<td>852</td>
<td>2500</td>
</tr>
<tr>
<td>B but family size larger 7 1st degree, 3 2nd degree</td>
<td>2751</td>
<td>1407</td>
<td>4358</td>
</tr>
</tbody>
</table>

If DNA costs reduce to £250/proband, will be comparable to Cholesterol
As nurse costs, or family size increase, DNA testing becomes more cost-effective
What is “value” of False Positive and False Negative?
How much will the guideline cost the NHS?

Estimated annual cost impact of fully implementing the guideline in England

<table>
<thead>
<tr>
<th>Recurrent costs</th>
<th>Year 1 (£000s)</th>
<th>Year 2 (£000s)</th>
<th>Year 3 (£000s)</th>
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</thead>
<tbody>
<tr>
<td>Cascade testing*</td>
<td>5,151</td>
<td>5,151</td>
<td>5,151</td>
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<tr>
<td>Drug therapy for people diagnosed with FH through cascade testing</td>
<td>2,553</td>
<td>5,106</td>
<td>7,659</td>
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<tr>
<td>Specialist referrals for people diagnosed with FH through cascade testing</td>
<td>693</td>
<td>693</td>
<td>693</td>
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<tr>
<td>Annual review meetings</td>
<td>0</td>
<td>596</td>
<td>1,194</td>
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<tr>
<td>Coronary events avoided</td>
<td>-452</td>
<td>-908</td>
<td>-1,361</td>
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<tr>
<td>Net resource impact of FH guideline</td>
<td>7,945</td>
<td>10,638</td>
<td>13,336</td>
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</tbody>
</table>

* INCLUDES COSTS FOR DNA TESTING (£400 and £50)

Based on average of 100,000 subjects, each PCTs costs = £16,000 in year 1

Courtesy Professor Humphries
Efficiency of CT based on assumption that 50% of 1st degree relatives will be FH

A Mutation identifies best families for cascade testing - Humphries et al 2006

- Mutation +ve probands ➔ 50% relatives will be FH
- Mutation -ve families ➔ only 25-30% have high cholesterol,

Those with a detected mutation have higher rate of CHD – Humphries et al 2006

- DNA - CT programme running in Netherlands for >10 years - Uman-Eckens et al 2002
- Modelling suggests Is Cost Effective Marks et al Humphries BMJ 2000
- CT acceptable and feasible in UK Manchester/Oxford, DH Project, Hadfield et al 2008

Allows unambiguous diagnosis in relatives and for further cascading

Courtesy Professor Humphries
Who should take care of the FH patient?

Hospital-based Lipid Clinic

- Fasting Sample
- Take Pedigree
- Confirm Diagnosis
- Offer DNA test
- Start Treatment
- Start Cascading
- Achieve 50% LDL lowering
- Request GPs to refer relatives

What is cascade testing and why does DNA help?

Courtesy Professor Humphries
What do we need for an integrated effective FH Management Programme?

National Register, IT Software

Referral shared care annual review

Tool kit

RCP AUDIT

DNA Diagnostic Laboratory

Clinical Geneticist

Interpretation of novel mutations

FH Genetic Nurse

Train Support

“FH-Clinic”

Joint clinics Must expand

Pediatric input

Lipidologist

GP


May need ~60 CT clinics ie 1/million population, each → 2000 FH

Courtesy Professor Humphries
Service Development

Planning the service

Staffing issues

Stakeholder involvement

Working with genetics departments

Working across specialties

Working with healthcare organisations

Working with communities

Communication

Providing online Information

Providing Education for Health Professionals
## Who will should pay for implementing CG71?

HEARTUK FG Implementation Team

<table>
<thead>
<tr>
<th>Recurrent costs</th>
<th>Commissioning Level</th>
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<tbody>
<tr>
<td>Identification of Simon Broome PFH and DFH in Secondary Care</td>
<td>Local FTs</td>
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<tr>
<td>Identification of Simon Broome PFH and DFH in Primary Care</td>
<td>Local PCTs</td>
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<tr>
<td>Specialist Clinical Assessment for Simon Broome PFH and DFH</td>
<td>Local PCTs/FTs</td>
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<tr>
<td>FH Mutation screening (probands)</td>
<td>SCG</td>
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<tr>
<td>Family Cascade testing</td>
<td>SCG</td>
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<tr>
<td>FH Mutation testing (relatives)</td>
<td>SCG</td>
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<td>Specialist referrals for people diagnosed with FH through cascade testing</td>
<td>Local PCTs/FTs</td>
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<td>Drug therapy for people diagnosed with FH through cascade testing</td>
<td>Local PCTs</td>
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<td>Annual Structured review for diagnosed FH</td>
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<td>Specialist referrals for FH diagnosed with vascular complications</td>
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<td>LDL Apheresis for HoFH and severe FH with CVD</td>
<td>SCG</td>
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<tr>
<td>National FH Register</td>
<td>NCG</td>
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</table>

Commissioning Guide from NICE?

Courtesy Professor Humphries
Charioteer 474 B.C., Delphi

Courtesy Professor Neil