West Midlands Familial Hypercholesterolaemia Service

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Presentation Objectives

- What is Familial Hypercholesterolaemia (FH)
- What is the difference between FH and Hypercholesterolaemia.
- National Policy
- Case for change in the West Midlands
- Implementing a systems approach to the detection and management of FH in the West Midlands
- Challenges of implementation
- Case Studies
What is Familial Hypercholesterolaemia (FH)?

FH is an **autosomal dominant** Lipid Disorder affecting approximately 1:250 people.

**DEFINITION (SWAN UK)** - Some conditions are passed on through families in a **dominant** way. This means that if a person inherits one ‘normal’ copy of a gene and one ‘changed’ (mutated) copy, the ‘changed’ (mutated) gene is **dominant** over, or **overrides**, the normal copy. This causes the individual to become affected by the genetic condition.
Inheritance Pattern (Heterozygous)
Familial Hypercholesterolaemia

- Confers a lifelong risk of premature cardiovascular disease because of lifelong raised LDL-Cholesterol\(^1\) (Low Density Lipoprotein Cholesterol).
- Untreated FH leads to markedly increased risk of CHD.
  - Greater than 50% risk of CHD in men by the age of 50\(^2\).
  - At least 30% risk of CHD in women by the age of 60\(^2\).

**Effective treatment** reduces risk of mortality to almost that of the general population, especially in those that have not developed CHD\(^3\).

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1. Watts et al. *Int J Cardiology.* 2014; 171:

www.england.nhs.uk 5
Scope of the problem

• Most people with FH are undiagnosed (~8-15% cases known nationally) and are therefore untreated.
• Based on prevalence of 1 in 250 to 1 in 500 people; 130,000 – 260,000 are affected in the UK.
• Children of an individual with FH have a 50% chance of inheritance.
• Families are trapped in a cycle of: premature heart disease/premature death.
• No standard delivery model nationally.
• Variation of services locally, regionally nationally.
National Policy and Guidance

• NICE Quality Standard on FH (2013).
• DoH CVD Outcomes Strategy 2013.
• NHS RightCare CVD Prevention Pathway.
• NHS England Improving outcomes through personalised medicine (September 2016).
• PHE Implementing a systems approach to detection and management of FH (August 2018).
Former West Midlands Model

- Variation across region.
- Some availability of genetic testing.
- Lacked regional co-ordination.
- Patients referred to secondary care if (total) cholesterol elevated.
- Generally good uptake of NHS HC programme.
- No systematic case finding service.
- No systematic cascade screening service.
- Ambition for service redesign for many years.
West Midlands Region
- Population of 5.6 million
- Approx. 750 GP practices
- 20 CCG’s
- 11 acute trusts

DIVERSE!
West Midlands FH Prevalence

Total Population 5.6 million

1:500 – 11,000
1:250 – 22,000

identified 1,650 – 7.5%
(1:250)
West Midlands Case for Change

• 2015 - Business case developed by NHSE for regional FH service.
• Ambition for Primary Care delivery model.
• Grant application to BHF for nurse funding – approved.
• All 20 West Midlands CCG’s approved case for change and agreed funding (1:500).
• Nurses recruited in 2016.
• Open tender for genetic testing contract – awarded to Bristol Genetics Laboratory.
• Service mobilisation 1st November 2017.
<table>
<thead>
<tr>
<th>Area Covered</th>
<th>No of CCG’s</th>
<th>Population</th>
<th>Estimated number of FH cases 1:500</th>
<th>Estimated number of FH cases 1:250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham and Solihull</td>
<td>1</td>
<td>1,215,000</td>
<td>2430</td>
<td>4860</td>
</tr>
<tr>
<td>Black Country</td>
<td>4</td>
<td>1,376,000</td>
<td>2752</td>
<td>5502</td>
</tr>
<tr>
<td>Staffordshire and Shropshire</td>
<td>8</td>
<td>1,306,000</td>
<td>2612</td>
<td>5224</td>
</tr>
<tr>
<td>Hereford and Worcester</td>
<td>4</td>
<td>756,000</td>
<td>1512</td>
<td>3024</td>
</tr>
<tr>
<td>Coventry and Warwickshire</td>
<td>3</td>
<td>914,000</td>
<td>1828</td>
<td>3656</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td><strong>20</strong></td>
<td><strong>5,567,000</strong></td>
<td><strong>11,134</strong></td>
<td><strong>22,266</strong></td>
</tr>
</tbody>
</table>
Identification and management of familial hypercholesterolaemia

Issued: August 2008

NICE clinical guideline 71
guidance.nice.org.uk/cg71
Systematic approach to commissioning FH services

There are broadly five objectives of an FH service:-

• To identify those at risk of carrying an FH gene (detection).
• To undertake genetic testing for those considered appropriate.
• To undertake ‘cascade’ genetic testing for appropriate relatives of those with confirmed monogenic FH.
• To manage those with monogenic FH (treat) and to do so with most cost-effective use of primary and specialist care.
• To manage the majority of those with polygenic hypercholesterolaemia in primary care (as per NICE guidance).
Delivery Model

- Clinical Programme Manager and 5 FH Specialist Nurses – funded by British Heart Foundation.
- Eligibility Criteria TC >9.0 mmol/L and/or Simon Broome criteria*.
- Referrals from all specialities.
- Patient invited to appointment at location of their choice.
- A bespoke West Midlands FH database is currently in use.
- Assessment includes family history, family pedigree drawing, medications, physical presentation, lifestyle etc., BP, pulse, BMI.
- Give lifestyle advice.
- Receive written consent and obtain blood sample for genetic testing.

*CG71 (2008)
Physical presentation of FH
Genetic Results

- FH Confirmed.

- FH Not Confirmed.

  Low Likelihood of Polygenic Hypercholesterolaemia.
  Medium Likelihood of Polygenic Hypercholesterolaemia.
  High Likelihood of Polygenic Hypercholesterolaemia.

- Variant of Uncertain Significance (VUS)
FH Confirmed

Clinical Summary: Total cholesterol 6.2, LDL-C 3.9. Positive family history. For FH NGS analysis.

Familial Hypercholesterolaemia Results

<table>
<thead>
<tr>
<th>Sequence Analysis</th>
<th>LDLR Dosage Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene : LDLR</td>
<td>No Duplications or Deletions Detected</td>
</tr>
<tr>
<td>Location : Exon 13</td>
<td></td>
</tr>
<tr>
<td>DNA Description : c.[1897C&gt;T];[1897=]</td>
<td></td>
</tr>
<tr>
<td>Protein Description : p.[(Arg633Cys)];[Arg633=]</td>
<td></td>
</tr>
</tbody>
</table>

Report Summary: Diagnosis of FH confirmed

Analysis of four genes associated with Familial Hypercholesterolaemia (FH) has been undertaken using next generation sequencing.

Sequence analysis of the LDLR gene in this patient revealed the presence of a heterozygous likely pathogenic missense variant in exon 13; c.1897C>T, p.(Arg633Cys).

This result is consistent with a diagnosis of Familial Hypercholesterolaemia in this patient.

Any offspring of this patient are at 50% risk of inheriting this likely pathogenic FH variant. Cascade testing is available for relatives if appropriate.

In addition, no pathogenic variants were detected in the APOB, PCSK9 or LDLRAP1 genes.
Genetic Test Results
FH Confirmed

• If +ve – TREAT – in accordance with NICE CG71(2017) guidelines (Managing FH).
• MECC, lifestyle advice and refer to relevant lifestyle services.
• Refer to lipid clinic for cardiac risk assessment; (echocardiogram, calcium scoring if indicated, prescription of additional lipid lowering therapy (in addition to statins e.g. PCSK9-inhibitor drugs).
• Manage majority in General Practice.
• INITIATE FAMILY CASCADE SCREENING.
Clinical Summary: TC 9.8mmol/L. Welsh Score 10. ? Familial Hypercholesterolaemia. For FH NGS analysis.

Familial Hypercholesterolaemia Results

<table>
<thead>
<tr>
<th>Sequence Analysis</th>
<th>LDLR Dosage Analysis</th>
<th>LDL-c raising SNP score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pathogenic Variant Detected</td>
<td>No Duplications or Deletions Detected</td>
<td>Score: 1.055 Decile: 8</td>
</tr>
</tbody>
</table>

Report Summary

FH not confirmed
High Likelihood of Polygenic Hypercholesterolaemia

SLCO1B1 polymorphisms:
- rs2306283 genotype G/G
- rs4149056 genotype T/T

Please refer to the suggested references below for further guidance.

Report

Analysis of four genes associated with Familial Hypercholesterolaemia has been undertaken using next generation sequencing. This patient was also genotyped for 12 LDL-C raising SNPs.

No pathogenic variants or variants of uncertain significance have been detected. No duplications or deletions within the LDLR gene have been detected.

These results do not confirm a diagnosis of Familial Hypercholesterolaemia in this patient.

These results virtually exclude a pathogenic variant of the APOB, LDLR, PCSK9, and LDLRAP1 genes as the cause of the phenotype in this patient.

The LDL-C 12 SNP score for this patient is 1.055, which is in the 8th decile; therefore there is a high likelihood that the elevated LDL-C levels in this patient have a polygenic aetiology.
FH Not Confirmed

• If –ve TREAT – in accordance with NICE CG181 guidelines (CVD Risk Assessment and Reduction).

• MECC, lifestyle advice and refer to relevant lifestyle services.

• Offered referral to 100,000 genome project (if eligible).

• Manage in General Practice but refer to lipid clinic where lipid lowering therapy does not reduce to TC to <5.0 mmol/L or LDLc to <2.5 mmol/L.

• Advise family members to have cholesterol checked.
Patient Eligibility

• Identify Patients via data extraction or opportunistic review of GP clinical Systems.

• Criteria TC greater than or equal to 9.0 mmol/L & triglyceride ≤5.0 mmol/L.

AND NO HISTORY OF

• Diagnosis/Treatment for nephrotic syndrome.
• Diagnosis/Treatment for CKD 4 and above.
• Diagnosis/Treatment for chronic liver disease.

• TC 7.5 – 8.9 mmol/L – risk stratify using Welsh Scoring Criteria
12 months on……………

- Paediatric service developed in conjunction with Birmingham Children's Hospital.
- First paediatric patient seen on 21st June 2018.
- Service delivered from 60 sites across West Midlands.
- Patient experience surveys –positive.
- Engaged with a wide range of stakeholders.
- Nominated for Building Healthier Lives award.
- Multiple abstracts accepted for presentation.
12 months on………..

- In excess of 1520 referrals to date (since 1\textsuperscript{st} November 2017).
  - 52\% from General Practice.
  - 48\% from Consultants.
- 664 genetic tests sent.
- 526 results received.
- 115+ve (22\%).
- 16 Paediatric samples sent; 12 results, 4+ve (33\%).
- 49 Cascade samples sent; 23 +ve (47\%).
- 111 referred to 100 000 genome project (results awaited!).
- 14 VUS.
Challenges to implementation

- IT.
- Clinic space.
- Administration.
- Incomplete referral information.
Case Study 2
Case Study 1

ANON 1

- Familial Hypercholesterolaemia
- Raised TC
- FH -ve
- Condition 4

The diagram illustrates a family tree with various details indicated by colored icons.
Paediatric Case Study*

Seconds after finishing a cross country run and telling her friend "Oh God, I think I am going to die", 11 year old Rianna Wingett's heart stopped beating.

Despite her positive family history, Rianna had undiagnosed FH.

Estimated 56,000 children with FH in the UK.

*HEART UK Case study
Acknowledgements

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Questions....