1) Introduction

- FH is an autosomal co-dominant condition that leads to high blood cholesterol from birth.
- The FH service was launched in 2010 with the introduction of a diagnostic service for FH combined with family cascade testing.
- Strong R&D aspect of the FH service:
  - FH R&D committee
  - Several areas of the service in development
  - Research studies integrated into the clinical service.
- Multidisciplinary service as shown by the spider diagram.

2) Genetic Testing

A total of 120 different variants have been identified in 3 genes: • 88% in LDLR
• 11% in APOB
• 1% in PCSK9
1 homozygous patient & 3 compound heterozygotes.

Clinical scoring system developed for Wales FH service as a guide for clinicians to determine whether lipid clinic patients with a clinical diagnosis of possible FH are suitable for FH genetic testing. This is based on a modification of the Dutch Lipid Clinic Network scoring criteria.

3) Currently Active Studies

- Commercial Trials:
  - REALIZE – Study of Anacetrapib (Merck).
  - FOCUS FH – Study of Mipomersen (antisense inhibitor of apolipoprotein B synthesis (Genzyme)).
  - REGN72 – 2nd generation of the human monoclonal antibody REGN72 that binds PCSK9 (Sanofi).
- Cardiff University/FH NHS Service R&D projects:
  - Variants of Uncertain Significance in FH: Can family cosegregation analysis help determine pathogenicity?
  - Short title ‘Family studies in FH’ (See box #4)
- Development and evaluation of Genotype Scoring Criteria for FH in Wales (See box #2).
- NEUS – Validation/application of a novel technique for assessment of endothelial function: vascular endothelial function validation study.

Development within FH Service:
- Genetic testing of indexes to be developed and brought in house (AWMG Biochemical Service).
- Identifying FH patients in primary care – GP search strategy currently being piloted.

4) R&D study – Family Studies in FH

- In 9% (n=80) of the Welsh FH patients tested to date (n=910, June 2013), DNA testing has identified a variant of uncertain significance (VUS) in one of the 3 known genes associated with FH.
- A VUS is a DNA sequence variant for which it is unclear whether it is causing the clinical condition (hypercholesterolaemia) or else may be an incidental variant that is of no functional significance.
- Family testing studies to assess whether or not the VUS co segregates with the condition (raised LDL-C) in families may provide evidence about whether or not the variant is disease-causing.
- FH is a very well suited for this type of study because there is a simple test for phenotype (LDL-C) which can be measured alongside the genotype. This allows researchers to quantify the degree of association and calculate the likelihood of the variant is disease-causing.
- An all Wales study has been set up to coordinate the family testing of families with VUS. This is carried out by a partnership between the FH Service and Cardiff University. Recruitment for this commenced May 2013.
- This is a pathway to portfolio study and grants to extend this study are in the process of being applied for.

5) FH Database

Bespoke software – PASS CLINICAL – developed for the Service

Clinical aspects:
- Register individuals & families with FH
- Co-ordinate cascade testing
- Pedigree creation and storage
- Database of clinical & contact information

Research aspects:
- Records patients’ consent to be contacted for research.
- Records which studies patients recruited to.
- Enables efficient recruitment with the ability to create reports based on inclusion/exclusion criteria.

In patients who scored 13 or more a pathogenic variant was identified in 81%. This decreased progressively with lower scores to 6% in those who scored 5 or less. Risk scores of 5, 7-8, 9-10, 11-12 the pickup rate was 9%, 16%, 38%, and 51% respectively.

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The Team

6) Evaluation of the service

- Questionnaires were developed in conjunction with Cardiff University to enable the service to be evaluated by the patients.
- The questionnaires were piloted: 75 were sent out across Wales. Of these 34 were returned (45%).
- Patients were asked to rate their overall experience of the service and the results of this are shown in the graph below (5: very bad; 10: very good).
- There was room for free text and patients wrote:
  - ‘An evaluation into the non-responding relatives (those who don’t contact the service after they receive an invitation letter) is about to commence.

7) NHS FH Service – Cardiff University Synergy

R&D Clinical Service

New research

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Familial Hypercholesterolaemia (FH) in Wales – Integrating R&D with Service Delivery

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