Institution: Queen's University Belfast

Unit of Assessment: 2

Title of case study: Identifying patients and families at risk of inherited high cholesterol

1. Summary of the impact

A routine service for genetic diagnosis of familial hypercholesterolaemia (FH) was developed and commissioned by the Northern Ireland Department of Health, based on the identification by the Queen's team of a series of mutations causing this condition. The team then developed novel diagnostic strategies that led to over 900 affected individuals being identified so that treatment could be delivered to them. Samples are received for diagnosis from the UK and Ireland and the work of the Centre helped to inform recent NICE guidance. The laboratory is recognised as an expert laboratory for the diagnosis of inherited lipid disorders by the International Federation for Clinical Chemistry and Laboratory Medicine.

2. Underpinning research

Resulting from research by Professor Young and his colleagues at Queen's University Belfast, a service has been set up to test patients and their families for inherited high cholesterol (familial hypercholesterolaemia - FH). FH is the most common significant inherited clinical disorder in the UK. It affects somewhere between 1 in 200 and 1 in 500 of the population, meaning that there are over 110,000 affected individuals in the UK, and approximately 3,800 in Northern Ireland. Traditional diagnosis of the condition relies on measuring serum cholesterol, but this is unreliable, especially in children and adolescents. If FH is not identified and treated, 50% of men will have a heart attack before the age of 50, and 50% of women before the age of 60. The majority of individuals suffering from FH currently remain unidentified.

The key pathways of importance to the regulation of serum cholesterol and the relevant genes controlling them were identified by Brown and Goldstein in the USA in work originating in the 1970s. FH usually arises as a result of a defect in one of three genes[1,2]. In a programme of work originating in the early 1990s, researchers from Queen's (Young and Nicholls) published a series of papers describing the identification of genetic defects causing FH in the Northern Ireland population, and a number of methodology papers describing improved methods for testing for the condition[2]. Young is Professor of Medicine and the Director of the Centre for Public Health, Queen's University Belfast, while Nicholls is an Honorary Professor of Medicine.

The impact reported derives from ten papers published between 1995 and 2008. Initial research was funded by the Northern Ireland Chest Heart and Stroke Association and subsequently by the British Heart Foundation. This involved the clinical identification of families with suspected FH. In these families cholesterol levels were measured and this was correlated with assessments of heart disease in family members[3,4,5]. Once a potential family had been identified, DNA was collected from them to start a screening process. The majority of cases of FH result from a defect in the low density lipoprotein receptor gene. A relatively small number of cases result from defects in two other genes (known as ApoB and PCSK9). Young and his colleagues identified over 20 novel genetic defects in the Northern Ireland population as well as a number of mutations which had been previously described in other populations, and the relationship between these defects, gene expression and clinical presentation was established. In parallel with the clinical work, a laboratory-based program

developed increasingly sophisticated methods of genetic diagnosis. The most recent evolution of the laboratory methodology was published in *Clinical Genetics* in 2008 and now provides the basis of the routinely offered genetic approach[6]. This is followed by sequencing of the relevant genes if a defect is not identified in a family with a high degree of clinical suspicion.
In summary, the research led to the identification of new mutations involved in FH and these were incorporated into a diagnostic screening programme.

3. References to the research

1. Graham CA, Wright WT, McIlhatton BP, **Young IS**, **Nicholls DP**. The LDLR variant T705I does not cause the typical phenotype of familial hypercholesterolaemia. *Atherosclerosis.* 2006 Sep; 188(1):218-9. Doi: 10.1016/j.atherosclerosis.2006.04.014 (cited 2 times)

2. Ward AJ, O'Kane M, **Nicholls DP**, **Young IS**, Nevin NC, Graham CA. A novel single base deletion in the LDLR gene (211delG): Effect on serum lipid profiles and the influence of other genetic polymorphisms in the ACE, APOE and APOB genes. *Atherosclerosis.* 1996 Feb; 120(1-2):83-91. Doi: 10.1016/0021-9150(95)05685-8 (cited 31 times)

3. Graham CA, McIlhatton BP, Kirk CW, Beattie ED, Lyttle K, Hart P, Neely RD, **Young IS, Nicholls DP.** Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate. *Atherosclerosis*. 2005 Oct; 182(2):331-40. Doi: 10.1016/j.atherosclerosis.2005.02.016 (cited 3 times)

4. Graham CA, McClean E, Ward AJ, Beattie ED, Martin S, O'Kane M, **Young IS**, **Nicholls DP**. Mutation screening and genotype: phenotype correlation in familial hypercholesterolaemia. *Atherosclerosis*. 1999 Dec; 147(2):309-16. Doi: 10.1016/S0021-9150(99)00201-4 (cited 43 times)

5. **Nicholls P, Young IS**, Graham CA. Genotype/phenotype correlations in familial hypercholesterolaemia. *Curr Opin Lipidol.* 1998 Aug; 9(4):313-7. Doi: 10.1097/00041433-199808000-00005 (cited 12 times)

6. Wright WT, Heggarty SV, **Young IS, Nicholls DP**, Whittall R, Humphries SE, Graham CA. Multiplex MassARRAY spectrometry (iPLEX) produces a fast and economical test for 56 familial hypercholesterolaemia-causing mutations. *Clin Genet.* 2008 Nov; 74(5):463-8. Doi: 10.1111/j.1399-0004.2008.01071.x (cited 14 times)

Funding:

1992 – 1995 Graham, **Nicholls, Young**. **NI Chest Heart & Stroke Association** "Molecular genetics of familial hypercholesterolaemia – in depth family studies and evaluation of a screening program to improve detection of FH in NI." £81,236.

1995 – 1998 Graham, **Nicholls, Young**. **NI Chest Heart & Stroke Association** "LDL receptor mutations and other genetic lipid markers in FH: genotype – phenotype study" £33,244.

1999 – 2002 Graham, **Nicholls, Young**. **British Heart Foundation** "Genetic basis of Familial Hypercholesterolaemia: Families without LDLR/FDB point mutations" £ 87,000.

2002 – 2008 Graham, **Nicholls, Young**. **NI Health and Social Care R&D office RRG 7.8 [5.28]** "The genetic basis of hyperlipidaemia and vascular disease in Northern Ireland" £ 545,000.

4. Details of the impact

Of the 3,800 individuals who are suspected to suffer from FH in Northern Ireland, less than 200 had been identified at the start of this programme of research. A clinical register of families that appeared to have an inherited problem with levels of lipids in the blood was established in Belfast from the early 1970s, and research into the causes of these disorders began in Queen's in the late 1980's. As a result of the programme of work, which has been outlined here, the number of identified individuals is now approximately 1,100. Having initially been funded as a research project, a fully funded laboratory and clinical service covering the entire Northern Ireland population has now been established with the support of the Department of Health and Social Care.

The service offers testing in individual and families with suspected FH after the identification of index cases which are referred from primary or secondary care to the specialist clinics according to agreed local guidelines. The service is now embedded within the Northern Ireland Cardiovascular Care Framework. The Service Framework for Cardiovascular Health and Wellbeing [DHSSPS June 2009] recognises the importance of familial hypercholesterolaemia in Overarching standard 12, which states[1]:

"*All people with genetically linked high cholesterol (FH) should be identified and treated and their names entered on a regional register so that other family members can be identified in order that measures can be introduced to prevent the development of cardiovascular disease".*

Patients are offered lipid lowering therapy aimed at achieving a 50% reduction in pre-diagnosis LDL cholesterol, in line with NICE guidance. Audit has shown that this standard is met in over 70% of cases.

The expertise of the genetic testing laboratory is widely recognised: samples are routinely received and tested from a number of regions in England and Scotland, as well as the Republic of Ireland. In addition, the world's leading laboratory medicine organisation The International Federation for Clinical Chemistry and Laboratory Medicine has recognised the Belfast laboratory as an expert laboratory in this area, one of only two global laboratories so recognised. As a result of this, the laboratory provides advice and guidance on genetic diagnosis of inherited lipid disorders to clinical laboratories throughout the world.

The NICE guidance on FH (CG71: Identification and management of familial hypercholesterolaemia, August 2008) was significantly informed by the Northern Ireland experience (references 54 and 55; cited on pages 59, 71 and 104; table 6 extracted from these papers), and the recommendations in the NICE guidance for England and Wales are very similar to established practice in Northern Ireland[2].

Currently, around 700 samples for genetic testing for FH are received by the genetics laboratory each year[5]. A Northern Ireland target has been agreed for the identification of 200 new cases of familial hypercholesterolaemia per year. Furthermore, recent research work in collaboration with the local biotechnology company Randox has developed a test for common polymorphisms on a chip which has been commercially launched on the international market this year[6].

Thus the development of the diagnostic service based on the identification of specific mutations in FH has led to the identification of 900 more people in Northern Ireland who carry a high risk of cardiovascular disease. A pro rata number in England would be 32,000 people who could be offered behaviour modification or treatment with statins or other drugs to reduce their risk of serious morbidity and mortality.

5. Sources to corroborate the impact

1) The Northern Ireland Department of Health, Social Services and Public Safety. Service framework for cardiovascular health and well-being, 2009. http://www.dhsspsni.gov.uk/service_framework_for_cardiovascular health_and_wellbeing.pdf

2) NICE clinical guideline 71. 2008. Identification and management of familial hypercholesterolaemia. http://www.nice.org.uk/nicemedia/live/12048/41700/41700.pdf.

3) International Federation for Clinical Chemistry and Laboratory Medicine molecular diagnostics centres. www.ifcc.org.

4) Royal College of Physicians of London familial hypercholesterolaemia audit, 2010. http://www.rcplondon.ac.uk/resources/audits/FH.

5) Genetic Testing for Familial Hypercholesterolaemia. Leaflet from genetic laboratory indicating testing approach and current price list. Northern Ireland Regional Genetics Centre, Belfast Health and Social Care Trust, Belfast City Hospital. This leaflet can be supplied on request.

6) Randox website : (http://www.randox.com/fh-genetic-molecular-test.php)