Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Accelerating the identification and treatment of patients with familial hypercholesterolaemia (FH) through the establishment of a DNA diagnostic service: a paradigm example of Personalised Genomic Medicine

Period when the underpinning research was undertaken: 2013-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Steve Humphries	**Emeritus Professors of cardiovascular genetics**	**(1991-2015)**
Philippa Talmud		**2015- present**
		2015-present

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Research at UCL to develop genetic tests for Familial Hypercholesterolaemia (FH) has led to a significant increase in the number of patients with FH identified and treated for high cholesterol, thereby reducing cases of avoidable cardiovascular disease. The UCL research led to specific recommendations in national and international guidelines for diagnosis and treatment of adults and children with FH and to BHF-funded FH nurses being deployed throughout the UK to accelerate the diagnostic programme. Over 9,000 FH patients have been diagnosed since 2013. The work has led NHS England and Public Health England to set a target in the NHS Long Term Plan to identify at least a quarter of the expected 200,000 FH patients in the UK by 2024.

2. Underpinning research

Familial Hypercholesterolemia (FH) is a genetically inherited condition affecting up to 1 in 250 people in the UK, which causes build-up of LDL cholesterol in the blood, increasing the risk of heart and circulatory disease at a young age. Professor Humphries's research at UCL has identified the common mutations in the genes involved, developed tests to diagnose the condition, built data registries to follow disease progression and is informing developments in healthcare to reduce the number of adults and children with FH developing heart disease and dying prematurely.

Genetics of FH: UCL research on FH led to the establishment of a DNA diagnostic service at Great Ormond Street Hospital (GOSH) and the adoption in 2008 of FH testing as a recognised diagnostic test within the UK Genetic Testing Network "Gene Dossier". Humphries set up the UCL *LDLR* mutation database, curated by the UCL Cardiovascular Genetics Group until 2018, which has now been subsumed into the Global ClinVar database. Although many mutations causing FH have been identified, in at least 60% of clinical cases, no mutation can be found. Research at UCL demonstrated for the first time that in at least 80% of these patients. A polygenic cause of their elevated cholesterol level is likely, based on 12 single nucleotide polymorphisms (SNPs) associated with raised blood cholesterol. This finding has been confirmed in samples from 6 other countries (**R1**) and the SNP test has been adopted by the DNA diagnostic laboratory in Bristol and is being rolled-out across the UK.

The UCL team produced several lines of evidence to show that patients with a single mutation in one of the four known FH-related genes have higher levels of atherosclerotic disease and are more likely to die from coronary heart disease than those with a polygenic cause (**R2**). Recently

the team demonstrated that a total cholesterol cut-off of >9.3mmol/l can give a high degree of specificity and sensitivity for identifying patients in general practice likely to have FH (**R3**), and this is now the recommended cut-off in the NICE FH guideline.

Coronary Heart Disease (CHD) mortality in FH: Analysis of the Simon Broome UK FH register (based at UCL and used to track progression of FH in UK patients), demonstrated that FH patients treated with high-potency statins had a significantly increased life expectancy compared to untreated patients. The analysis also showed that FH patients on the register with no evidence of heart disease can, when treated with high intensity statins, have a life expectancy similar to the general population (**R4**).

Health Economic Studies: In cases where FH is a monogenic disorder, half of all first degree relatives are at risk of also having the faulty gene, and "cascade-testing" these relatives could be an effective way of identifying new patients. Humphries directed studies, which found that the cost per quality adjusted life year gained (QALY) was well below the accepted NICE threshold for recommendation for adoption. These papers were used to support recommendations in the NICE FH guideline 2017 update for DNA-based cascade testing from lipid clinic FH patients (**R5**) and from patients found by electronic note searching in general practice (**R6**).

Use of statins in children with FH: In 2012, the UCL team established the UK Paediatric Register for FH to collect baseline and follow-up data on any child with FH identified in the UK, and by November 2020, the register held 650 patient data sets. NICE recommends statin treatment for children with FH, however many parents and clinicians have concerns about its safety in children. Analysis of data from the UK Paediatric Register for FH showed that at 1 year follow up, growth rates were identical in children taking a statin, compared to those who were not, with no evidence of any clinical side effects (**R7**).

3. References to the research

1. Futema M, Shah S, Cooper JA, Li K, Whittall RA, Sharifi M, Goldberg O, Drogari E, Mollaki V, Wiegman A, Defesche J, D'Agostino MN, D'Angelo A, Rubba P, Fortunato G, Waluś-Miarka M, Hegele RA, Aderayo Bamimore M, Durst R, Leitersdorf E, Mulder MT, Roeters van Lennep JE, Sijbrands EJ, Whittaker JC, Talmud PJ, Humphries SE (2015). Refinement of variant selection for the LDL cholesterol genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolemia and replication in samples from 6 countries. *Clin Chem.* Jan;61(1):231-8. doi: 10.1373/clinchem.2014.231365.

2. Sharifi M, Higginson E, Bos S, Gallivan A, Harvey D, Li KW, Abeysekera A, Haddon A, Ashby H, Shipman KE, Cooper JA, Futema M, Roeters van Lennep JE, Sijbrands EJG, Labib M, Nair D, Humphries SE (2017). Greater preclinical atherosclerosis in treated monogenic familial hypercholesterolemia vs. polygenic hypercholesterolemia. *Atherosclerosis*. Aug;263:405-411. doi: 10.1016/j.atherosclerosis.2017.05.015.

3. Futema M, Kumari M, Boustred C, Kivimaki M, Humphries SE (2015). Would raising the total cholesterol diagnostic cut-off from 7.5 mmol/L to 9.3 mmol/L improve detection rate of patients with monogenic familial hypercholesterolaemia? *Atherosclerosis*. Apr;239(2):295-8. doi: 10.1016/j.atherosclerosis.2015.01.028.

4. Humphries SE, Cooper JA, Seed M, Capps N, Durrington PN, Jones B, McDowell IFW, Soran H, Neil HAW; Simon Broome Familial Hyperlipidaemia Register Group (2018). Coronary heart disease mortality in treated familial hypercholesterolaemia: Update of the UK Simon Broome FH register. *Atherosclerosis*. Jul;274:41-46. doi: 10.1016/j.atherosclerosis.2018.04.040.

5. Kerr M, Pears R, Miedzybrodzka Z, Haralambos K, Cather M, Watson M, Humphries SE (2017). Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on

data from familial hypercholesterolaemia services in the UK. *Eur Heart J.* Jun 14;38(23):1832-1839. doi: 10.1093/eurheartj/ehx111.

6. Crosland P, Maconachie R, Buckner S, McGuire H, Humphries SE*, Qureshi N* (2018). Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales. *Atherosclerosis.* Aug;275:80-87. doi: 10.1016/j.atherosclerosis.2018.05.021. * equal contribution.

7. Humphries SE, Cooper J, Dale P, Ramaswami U (2018) FH Paediatric Register Steering Group. The UK Paediatric Familial Hypercholesterolaemia Register: Statin-related safety and 1-year growth data. J Clin Lipidol. Jan - Feb;12(1):25-32. doi: 10.1016/j.jacl.2017.11.005.

4. Details of the impact

If left untreated, people with FH are 80 times more likely to die of a heart attack before they reach 40 years old than people without the condition, according to the BHF. Diagnosing FH in childhood and young adulthood allows earlier treatment with appropriate lipid-lowering therapy and reduces risk of avoidable heart attacks and death by at least 50%. Research at UCL has made it possible to identify and treat all the 200,000 FH patients predicted to be in the UK and the NHS has now set a target to find and treat at least a quarter (50,000) of patients who are at high risk of heart disease, within the next five years.

National and international guidelines updated for diagnosis and treatment for FH
Research led by Professor Humphries at UCL has informed the NICE (CG71) 2017 update to support intensive statin treatment for patients with FH. Updated recommendations to identify FH patients were informed by UCL's finding that cascade testing from index cases in lipid clinics combined with note searching in General Practice are highly cost effective (**S1**). Also, the demonstration that a total cholesterol cut-off of >9.3mmol/l would give an appropriate specificity and sensitivity for identifying likely FH patients, was directly incorporated in the NICE 2017 cholesterol cut-off recommendation. These recommendations are fully supported by the NHSE/PHE implementation guideline 'Familial Hypocholesterolaemia: Implementing a systems approach to detection and management' (**S2**) and have directly informed the UK FH identification strategy. The research also informed international consensus guidelines produced by the International Atherosclerosis Society that have had a significant influence on improving FH identification and the clinical pathway for management of many thousand FH patients world-wide (**S3**).

Targeting high-intensity statin treatment for high-risk patients:
As a direct result of research carried out at UCL, current NICE guidelines recommend that monogenic FH patients should be treated with high intensity statins and monitored in tertiary referral lipid clinics while polygenic patients should be referred back to GPs for treatment (**S1**). This has informed targeted treatment of the 40% of clinical FH patients who are 'monogenic' with high intensity statins to reduce their risk of CHD, while the 60% lower-risk 'polygenic' patients avoid the potential side effects of being inappropriately treated with high intensity statins. In 2016, the Academy of Medical Sciences used this as an exemplar of the use of genomic information for personalised medicine (**S4**). Already 10,000 patients with DNA confirmed FH have been offered high intensity statins by their lipidologist to substantially lower their high CHD risk and the 17,000 index cases, where no FH mutation was found, are being managed by their GP.

Increased use of statins to treat children with FH:
Analysis using the UCL based UK Paediatric Register for FH informed the NICE (CG71) 2017 update to support recommendations for statin treatment for FH children. The UCL team carried out Cochrane reviews that demonstrated short-term safety and efficacy of statin treatment in children and is widely cited by clinicians (**S5**). The Medical Director at the BHF stated in a press release: "Children with FH are at very high risk of developing early heart attack or stroke ….. and

lowering their cholesterol is so vital. However, we should never assume that drugs that are safe in adults are also safe in children. That is why this research … is so important and provides reassurance that they are safe to use in this age group" (**S6**). To provide information for parents of a child with FH the UCL team worked with HEARTUK in 2017 to develop leaflets and videos for children of different ages and statin information leaflets for parents (**S7**). These have been translated into 10 languages, including French, Portuguese, Czech, Arabic, Russian and Mandarin, and are being disseminated widely across the globe. A Consultant Paediatrician of Inherited Metabolic Disease said, "(Professor Humphries') research has supported the use of cascade testing to identify children as well as adults with FH … Early identification of these children by cascade screening allows us to get them established on statins during childhood; starting treatment is sometimes harder in adolescents and young adults" (**S8**).

Accelerated access to genetic testing for FH supported by BHF and NHS

The research at UCL to develop effective testing for FH has led the BHF to invest more than GDP1,200,000 in 28 FH nurse-led clinics UK-wide (**S9**). As a result, since 2014, more than 22,000 index cases and 10,000 relatives have had a DNA test for FH, and more than 10,000 FH cases have been diagnosed and treated. In a BHF press release, BHF's Medical Director said, "Although testing has been recommended in the NHS for some time, its application is patchy and…the research does not only have implications for the NHS but for health systems internationally."

Humphries's research has also directly informed the **NHS Long Term Plan (S10)**, which states in its implementation plan to address cardiovascular disease, published in January 2019: 'Expanding access to genetic testing for FH….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'. The FH genetic test is now offered as part of the 'core' DNA tests in all seven Genomic Laboratory Hubs (GLHs), with costs covered by the NHS (**S11**). The National Clinical Director for Heart Disease, NHS England (2013-2019) commented: "The Academy of Medical Sciences meeting in 2016 (and a publication which followed) used presentations that (Professor Humphries) and I both gave on FH, demonstrating FH as a model exemplar of the use of genomic information for personalised medicine. This report, and Steve Humphries' publications on finding FH patients through GP electronic note searching (with the demonstration of cost effectiveness of DNA-based cascade testing from index cases) was an important factor in our preparation of the 2019 NHS Long Term Plan. … This will enable thousands of newly identified clinical FH patients to have a free (NHS funded) DNA test over the next 5 years, and ensure they are then appropriately treated, and their at-risk relatives identified" (**S12**).

5. Sources to corroborate the impact

S1 National Institute for Health and Care Excellence, Clinical Guidelines (CG71) – Familial Hypercholesterolaemia. Initially published 2008, and updated 2017. https://www.nice.org.uk/guidance/cg71/evidence

S2 Public Health England and National Institute for Health and Care Excellence Implementation Guideline 'Familial Hypercholesterolaemia: Implementing a systems approach to detection and management': https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/731873/familial_hypercholesterolaemia_implementation_guide.pdf

S3 Santos RD et al., (2016). Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol*. Oct;4(10):850-61. doi: 10.1016/S2213-8587(16)30041-9.

S4 Exemplar clinical pathways for a stratified approach to cardiovascular disease. Summary report of a meeting held on 17 March 2016 by the Academy of Medical Sciences, and supported by NHS England: https://acmedsci.ac.uk/viewFile/57cfd5170e1de.pdf

S5 2017 Cochrane review of safety of statin use in children: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006401.pub4/full. Update 2019: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006401.pub5/full
S6 https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2018/january/new-research-shows-statins-safe-for-children-with-high-cholesterol
S7 Statin leaflet for parents: https://www.heartuk.org.uk/downloads/paediatric-fh-registry/why-should-my-child-start-taking-statin.pdf
S8 Testimonial letter from Paediatrician, Manchester.
S9 https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2017/april/our-research-shows-targeted-genetic-testing-for-inherited-condition-is-lifesaving-and-cost-effective
S10 NHS Long term plan January 2019: https://www.longtermplan.nhs.uk/ (p.63).
S11 National Genomic Test Directory FAQ August 2020: https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-Inherited-Disease-Eligibility-Criteria-November-2020-21.pdf https://www.england.nhs.uk/genomics/genomic-laboratory-hubs/
S12 Testimonial letter from National Clinical Director, 2013-2019.