Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK

Marion Kerr1, Robert Pears2, Zofia Miedzybrodzka3, Kate Haralambos4, Moyra Cather5, Melanie Watson6, and Steve E. Humphries7*

1Economics Department, Insight Health Economics Ltd., 16 Cambrian Road, Richmond, Surrey TW10 6JQ, UK; 2Public Health Department, Hampshire County Council, Elizabeth II Court South, Winchester SO23 8UJ, UK; 3Department of Medical Genetics, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, UK; 4Wales Heart Research Institute, Cardiff University, Heath Park, Cardiff CF14 4XN, UK; 5Northern Ireland Regional Genetics Centre, Regional Genetics Laboratories, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, UK; 6Wessex Clinical Genetics Service, University Hospital Southampton, Southampton NHS Foundation Trust, Princess Anne Hospital, Cosford Road, Southampton SO16 5YA, UK; and 7Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, University College London, 5 University Street, London WC1E 6JJ, UK

Received 21 September 2016; revised 6 January 2017; editorial decision 21 February 2017; accepted 28 February 2017

Aims
Familial hypercholesterolaemia (FH) is a vastly under-diagnosed genetic disorder, associated with early development of coronary heart disease and premature mortality which can be substantially reduced by effective treatment. Patents have recently expired on high-intensity statins, reducing FH treatment costs. We build a model using UK data to estimate the cost effectiveness of DNA testing of relatives of those with monogenic FH.

Methods and results
A Markov model was used to estimate the cost effectiveness of cascade testing, using data from UK cascade services. The estimated incremental cost effectiveness ratio (ICER) was £5806 and the net marginal lifetime cost per relative tested was £2781. More than 80% of lifetime costs were diagnosis-related and incurred in the 1st year. In UK services, 23% of 6396 index cases were mutation-positive. For each mutation-positive index case, 1.33 relatives were tested, resulting overall in a rate of 0.31 tested relatives per tested index case. If the number of relatives tested per tested index case rose to 3.2 (projected by National Institute for Health and Care Excellence in 2008) the ICER would reduce to £2280 and lifetime costs to £1092.

Conclusion
Cascade testing of relatives of those with suspected FH is highly cost effective. The current Europe-wide high levels of undiagnosed FH, and associated morbidity and mortality, mean adoption of cascade services should yield substantial quality of life and survival gains.

Keywords
Familial hypercholesterolaemia • Markov model • Cost effectiveness • Cascade testing

Introduction
Familial hypercholesterolaemia (FH) is an autosomal-dominant disorder associated with elevated low density lipoprotein cholesterol (LDL-C) and early development of atherosclerosis and coronary heart disease (CHD). Untreated, at least 50% of men with FH will develop CHD by age 50, and 30% of women by age 60.1,2 The risk of CHD death at age 20–39 is increased 80–84-fold FH.3 Treatment with statins reduces the risk of CHD to approximately general population levels.4 Historically it has been estimated that 1/500 people has FH, around 130 000 in the UK, 1.5 million in Europe and 15 million worldwide, although recent epidemiological data from Denmark5 and next

---

* Corresponding author. Tel: +44 207 679 6962, Fax: +44 207 679 6212, Email: steve.humphries@ucl.ac.uk
© The Author 2017. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
generation sequencing data suggest the frequency may be approximately 1/250. Although some countries such as the Netherlands have well established cascade testing programmes, most do not. The vast majority of those with FH, worldwide, are undiagnosed. In 2008, the National Institute for Health and Care Excellence (NICE) in England published guidelines for identification and management of FH. These guidelines, like those elsewhere in Europe, recommended cascade testing of relatives of index cases, and estimated the cost-effectiveness of such testing. Testing programmes were set up in Scotland, Wales, and Northern Ireland. No national programme exists in England; commissioning responsibility is divided between 211 local organizations. In much of the country there is no FH testing programme at all.

Since the NICE guideline, much has changed. Patents have expired on some high-intensity statins used to treat FH, leading to substantial cost reductions, while next generation sequencing has reduced the cost of DNA tests. There is now convincing evidence that in patients with a clinical diagnosis of FH but no mutation in any of the three known FH-causing genes (LDLR, APOB, and PCSK9), the most likely cause of elevated LDL-C is polygenic. In polygenic FH the risk of relatives having significantly raised LDL-C is much lower than the 50% observed for monogenic hypercholesterolaemia. Finally, the establishment of FH cascade services in parts of the UK provides an opportunity to use real-life data rather than projections in economic modelling. UK audit data, combined with new evidence on the association between LDL-C reduction and CHD risk allow for modelling based explicitly on observed LDL-C reductions in FH.

In this article, we use data from FH cascade services to inform an economic model re-examining the cost effectiveness in the UK of cascade testing for monogenic FH from known index cases, incorporating new study evidence, and changes in costs and clinical practice that have occurred since the 2008 guideline.

Methods

Data were collected from FH cascade services in Scotland, Wales and the Wessex region of England on people with clinically diagnosed FH who have had DNA tests, rates of monogenic FH diagnosis in this group (i.e. a detected FH-causing variant in LDLR, APOB, or PCSK9), and numbers of relatives DNA tested. Additional data were collected from Wales on the age-distribution and LDL-C levels at diagnosis of monogenic relatives, and resource use. Data on sections of the pathway were collected from Northern Ireland.

An economic model was developed to estimate the cost effectiveness of a cascade testing pathway with three steps: DNA testing of people who already have a clinical diagnosis of possible or definite FH (index cases), DNA testing of relatives of monogenic index cases, and treatment with high-intensity statins and, in some cases, ezetimibe for monogenic relatives, relative to no DNA tests, no cascade testing and no treatment of relatives (Figure 1).

It was assumed that, in both the intervention and non-intervention arms of the model, index cases are treated appropriately for FH. The outcome of the DNA test does not change the treatment of index cases. No costs or benefits were counted for identification or treatment of index cases, nor for treatment of relatives who do not carry the family mutation.

A Markov model was used to estimate the cost, adverse event, and Quality-adjusted-life-year (QALY) impacts of treatment for monogenic relatives, compared with no treatment. The cycle length was one year. Markov states are shown in Figure 2.

Pooled data from cascade services in Scotland, Wales and Wessex were used in base case analysis to estimate monogenic diagnosis rates in index cases and the number of relatives tested per monogenic index case. Northern Ireland data were excluded from the pool, as they do not cover the entire pathway, but were used in sensitivity analysis.

It was assumed in the base case that, once diagnosed, 86.25% of monogenic adult relatives take statins, and 46.43% also take ezetimibe, as reported in a recent FH audit in the UK. In sensitivity analysis, we modelled the impact of a 70% statin compliance rate, with a proportionate reduction in ezetimibe.

It was assumed that 72% of those treated take atorvastatin, 20% simvastatin and 8% rosuvastatin. The distribution of adult daily dosages for each medication was taken from the 2010 audit. In sensitivity analysis, we modelled the impact of a reduction in the price of rosuvastatin and ezetimibe when UK patent protection ends in 2017.

The model was run for seven representative patient groups, aged (at diagnosis) 20–24, 25–34, 35–44, 45–54, 55–64, 65–74, and 75+. The age distribution of patients at diagnosis was estimated from data supplied by the Welsh FH service. It was assumed that relatives diagnosed through cascade testing have no history of cardiovascular events.

Baseline (untreated) primary cardiovascular (CVD) risk by 5-year age-band and gender for the general population was estimated using the QRISK2-2016 calculator. The general population risk of individual cardiovascular events (MI, angina, TIA, stroke, CVD death) was estimated by applying the estimates of the distribution of these events from the NICE Clinical Guideline on Cardiovascular Disease 18118 to the QRISK estimates. CHD death risk was estimated by examining the proportion of CVD deaths attributed to CHD in ONS 2014 mortality data for England and Wales in each 5-year age-band, and applying this proportion to estimated CVD death risk. (CVD was identified by International Classification of Diseases-10 (ICD-10) codes I45, I20–25, I50, I60–64, and I73, and CHD by ICD-10 codes I20–25).
FH-specific primary risks of angina, MI and CHD death were estimated by applying the relative risks reported for the Simon Broome FH register population in 1980–92 to the general population baseline primary risks for each age-band (adjusting for the inclusion of the FH group in the general population figures). Simon Broome relative risks relate to CHD mortality rather than to total CHD events. They were used here as a proxy for CHD event relative risk. Simon Broome reported no increased risk of death from stroke or TIA in FH.20 Unadjusted general population risks were therefore used for stroke, TIA and non-CHD CVD death. For age >80, it was assumed that the risk of cardiovascular events in FH is as for the general population. Estimated baseline risks are given in Supplementary material online.

Secondary risk was estimated for seven age-bands, 20–24, 25–34, 35–44, 45–54, 55–64, 65–74, and 75+. Secondary risks for those aged 45–74 were taken from NICE 181.18 Risks for ages <45 and >74 were not provided in NICE 181. To estimate risk for ages 20–24, 25–34, and 35–44, we examined the per capita rate of hospital admissions with cardiovascular events as primary diagnoses, in hospital episode statistics (HES), for England in 2014–15, for each of these age-bands, relative to the per capita rate for age 45–54. Cardiovascular events were identified by ICD-10 codes as above. Population by age-band was taken from Office for National Statistics (ONS) 2014 mid-year population estimates for England.21 The ratio of per capita events in each age-band relative to the per capita rate for age 45–54 was applied as a scaling factor to the age 45–54 transition probabilities in NICE 181 to estimate risks for ages 20–24, 25–34, and 35–44. For ages 75+, the ratio of per capita events in this age group, relative to that for age 65–74 was applied as a scaling factor to the age 65–74 transition probabilities. It was assumed that, in general, secondary risks in FH do not differ from secondary risks in the general population. However, in cases where the general population secondary risk was lower than the FH primary risk, the primary risk estimate was used.

Non-CVD mortality was estimated from ONS mortality data, by 5-year age-band.

Given that there are no large-scale studies of treatment effects in FH, treatment risk ratios were estimated using evidence from the cholesterol treatment trialists’ collaborators (CTTC) study, which linked absolute reductions in LDL-C to cardiovascular relative risk.13 While CTTC focused on primary events, we assumed that the relative risk reduction is the same for secondary events. Rate ratios for MI were applied also to angina, and those for stroke were applied also to TIA. Model outputs were sense-checked against existing small-scale FH studies.

It was assumed that mean baseline levels of LDL-C, for monogenic relatives by age-band, are as observed by the Welsh FH cascade service. In the base case it was assumed that the mean reduction in LDL-C for treated patients is 37%, as observed in the 2010 UK FH audit.15 In sensitivity analysis we modelled the impact of a 50% reduction in LDL-C, the target recommended by NICE. In the base case it was assumed that the 37% reduction in LDL-C is achieved after cascade testing, for all treatment-compliant monogenic relatives. It is known, however, that some relatives are already taking cholesterol-lowering medication before receiving their DNA test results (though it is not known whether they started statins before the cascade-testing process began, or whether treatment was changed after monogenic diagnosis). In sensitivity analysis we modelled the impact of assuming no change in treatment after cascade testing for those already on statins before monogenic diagnosis (and thus no reduction in LDL-C associated with cascade testing). Some monogenic relatives are normocholesterolemic at diagnosis. In sensitivity analysis we modelled the impact of assuming no treatment and no health impact for this group.

The net cost and QALY impacts of testing and treatment, per relative participating in cascade testing, were estimated. The cost of DNA testing for index cases was apportioned across tested relatives.

Figure 2 Markov model health states.
Table 1  Costs of testing, treatment and adverse events

| Test/Treatment/Event                  | Cost per person | Cost type | Source                                      | Notes                                                                 |
|--------------------------------------|-----------------|-----------|---------------------------------------------|----------------------------------------------------------------------|
| Genetic scanning, index cases        | £353            |           | UK Genetic Testing Network                  | Range £255-£450, mean used.                                           |
| Genetic testing, relatives           | £120            |           |                                             | Range £65-£175, mean used.                                            |
| Staff inputs, index case testing     |                 | Mutation-positive £371 | Welsh FH service, PSSRU                      | Costs are higher for those with positive results owing to family tree drawing, cascade test planning and (for relatives) treatment planning. See supplementary material online. |
|                                      |                 | Mutation-negative £174 |                                             |                                                                      |
| Staff inputs, relative testing       |                 | Mutation-positive £257 |                                             |                                                                      |
|                                      |                 | Mutation-negative £179 |                                             |                                                                      |
| Atorvastatin                         | £20             |           | Unit cost: NHS Electronic Drug Tariff.       | Dose details, see supplementary material online.                       |
| Simvastatin                          | £12             |           |                                             |                                                                      |
| Rosuvastatin                         | £20             | sensitivity analysis | Recurring (annual) |                                             |
|                                      | £316            |           | Unit cost: NHS Electronic Drug Tariff.       |                                                                      |
| Rosuvastatin                         | £20             | sensitivity analysis | Recurring (annual) | National FH audit Sensitivity analysis estimates for post-patent expiry. |
| Ezetimibe                             | £34             | sensitivity analysis | Recurring (annual) |                                             |
| Statin monitoring year 1             | £120            |           | Non-recurring                               | NICE CG181                                                            |
| Statin monitoring subsequent years   | £101            | Recurring (annual) | NICE CG181                                  |                                                                      |
| MI                                   | £3,731          |           |                                             |                                                                      |
| Stable angina                        | £7,736          | Non-recurring (year 1 cost) | Saka 2009 |                                                                      |
| Unstable angina                      | £3,313          | Non-recurring | Saka 2009                                  |                                                                      |
| Stroke                               | £13,697         |           |                                             |                                                                      |
| TIA                                  | £640            | Recurring (annual) | NICE CG181                                  |                                                                      |
| Post-MI                               | £788            |           |                                             |                                                                      |
| Post-stable angina                   | £240            |           |                                             |                                                                      |
| Post-unstable angina                 | £385            |           |                                             |                                                                      |
| Post-stroke                          | £3,301          |           |                                             |                                                                      |
| Post-TIA                             | £124            |           |                                             |                                                                      |

See references 15, 16, 18, 22, 23 and 24.
A UK NHS perspective was used for costs. We examined costs and benefits over a lifetime perspective, and also their profile over time. All costs were expressed in 2014-15 UK pounds. Costs and benefits were discounted at 3.5% in the base case, and adjusted in sensitivity analysis. Cost sources are given in Table 1.

It was assumed that clinical effectiveness of statins continues undiminished throughout life. Health state utilities were taken from NICE 181. It was assumed that statin treatment does not of itself reduce utility,25 and that the same is true of ezetimibe.

## Results

Since the Welsh, Scottish and Wessex FH services were established, 6,396 clinically diagnosed FH index cases have had DNA tests. Of these, 22.98% had an FH-causing monogenic mutation. On average, 1.33 relatives were tested per monogenic index case. In Northern Ireland, no data were available on index cases tested. The number of relatives tested per monogenic index case was 5.63 (Supplementary material online).

In Wales, mean baseline LDL-C in monogenic relatives was 5.82 mmol/L, and levels ranged from 5.56 to 6.08 (Table 2). Estimated relative risks associated with 37% and 50% reductions in LDL-C, respectively, based on CTTC estimates of the impact of absolute reductions in LDL-C on cardiovascular relative risk, and Welsh data on baseline LCL-C, are shown in Supplementary material online. In Wales, 41.66% of diagnosed monogenic relatives were taking cholesterol-lowering medication before receiving their DNA results. Of those aged ≥20, 8.89% were normocholesterolemic.

The economic model estimates that, for every 1,000 relatives tested, over 20 years 46 MIs, 50 cases of angina, 8 strokes and 16 deaths are averted (Table 3).

The estimated incremental cost effectiveness ratio (ICER) of DNA testing, cascade testing and treatment of relatives ranges from £4889 per relative tested in those aged 20-34, to £11 072 in those aged ≥75 (Table 4). For a cohort with the age-distribution observed in the Welsh cascade service the ICER is £5806 and the overall net marginal lifetime cost per relative tested is £2781.

The net annual cost per tested relative is £2268 in year 1. Net annual costs drop to £96 per tested relative in year 2, and are negative or <£2 from year 18 (Supplementary material online). Four fifths of total lifetime costs are for the initial tests, and almost two thirds are for DNA tests in index cases. The total cost per tested relative is highly sensitive to the ratio of relatives tested to index cases tested. If the number of relatives tested per tested index case rose from 0.31 (Scotland, Wales and Wessex mean) to 3.2 (projected by NICE in 2008) the ICER would reduce to £2280 and lifetime costs to £1092.

## Table 2 Age distribution and mean LDL-C (mmol/L) at diagnosis, mutation-positive relatives, Wales

| Age | 0–19 | 20–24 | 25–34 | 35–44 | 45–54 | 55+ |
|-----|------|-------|-------|-------|-------|-----|
| % of all mutation-positive relatives | 26.64% | 8.30% | 18.78% | 19.21% | 13.97% | 13.10% |
| Mean LDL-C (95% CI) | 5.59 (5.33–5.86) | 5.89 (5.13–6.64) | 6.54 (6.04–7.03) | 7.27 (6.62–7.92) | 7.03 (6.26–7.79) | 8.30 (7.35–9.25) |
| Normocholesterolemia, % of age group | 13.11% | 21.05% | 11.63% | 6.82% | 15.63% | 0.00% |
| Mean LDL-C (95% CI) excluding normocholesterolemic | 5.82 (5.56–6.08) | 6.36 (5.54–7.18) | 6.90 (6.45–7.35) | 7.51 (6.88–8.15) | 7.57 (6.71–8.42) | 8.30 (7.35–9.25) |

## Table 3 Estimated adverse events averted (cumulative) per 1000 relatives tested

| Years after testing | Years | Myocardial infarction | Stroke | Unstable angina | Stable angina | Deaths |
|--------------------|-------|-----------------------|--------|-----------------|---------------|--------|
|                    | 5     | 10                    | 1      | 3               | 12            | 2      |
|                    | 10    | 22                    | 3      | 8               | 22            | 7      |
|                    | 20    | 46                    | 8      | 14              | 36            | 16     |
|                    | 30    | 67                    | 13     | 17              | 42            | 23     |

## Table 4 Lifetime net cost, ICER and QALY impacts of cascade testing per tested relative

| Age     | Lifetime cost | Lifetime QALY gain | ICER     |
|---------|---------------|--------------------|----------|
| 20–34   | £2722         | 0.56               | £4889    |
| 35–44   | £2943         | 0.46               | £6369    |
| 45–54   | £2789         | 0.48               | £5770    |
| 55–64   | £2732         | 0.36               | £7587    |
| 65–74   | £2495         | 0.31               | £8056    |
| 75+     | £2285         | 0.21               | £11072   |
| Cohort  | £2781         | 0.48               | £5806    |

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted-life-year.
normocholesterolemia at DNA diagnosis increases the ICER by 5% (Table 5 and Supplementary material online).

The reduction in CHD mortality in treated relatives is estimated at 44%, based on a mean LDL-C reduction of 37%, and 55% with a mean 50% LDL-C reduction. The Simon Broome study reported a 48% reduction in CHD mortality for those without prior CHD. Our model estimates a 60.7% reduction in myocardial infarction (MI) over 8 years for treated relatives achieving a 37% reduction in LDL-C, and 68.6% for a mean 50% LDL-C reduction. Versmissen did not report specifically on MI risk, but found an overall CHD risk reduction of 76% (hazard ratio 0.24 (95% CI 0.18-0.30), over mean follow-up time of 8.5 years.

Discussion

The reduction in unit costs for genetic testing and the expiry of patients for high-intensity statins make re-examination of the cost effectiveness of cascade testing for FH important for all countries. We were able to use data from UK FH cascade services to replace key assumptions of the NICE 2008 model, and to use the findings of recent clinical studies examining the link between cardiovascular risk and treatment-induced reductions in LDL-C, an approach which is likely to be more appropriate to FH than the use of population-level relative risks. However, in common with all economic studies of FH, we are restricted by the lack of large-scale studies on treatment effects in FH. We have assumed that FH patients respond to statins in the same way as non-FH patients, and also that treatment effects are undiminished over time. We have also assumed that compliance rates are the same across all age groups, and are sustained over a lifetime. We have sense-checked our model outputs against data from existing small-scale FH studies, and believe that our findings are compatible with those results.

Our economic model suggests that cascade testing in families with FH is highly cost effective. Our base case estimates the cost per QALY (ICER) of DNA cascade testing at £5806 per tested relative, considerably below the cost effectiveness threshold of £20 000–£30 000 commonly used in the English NHS. Over a 30-year perspective, we estimate that 139 adverse CVD events and 23 deaths are averted per 1,000 relatives tested, at a cost of £2.8 million (Figure 3).

Health gains and cost effectiveness are negatively related to age at diagnosis. The cost per QALY is 57% higher in those aged > 55 than in those aged 20-54.

### Table 5  Sensitivity analyses: lifetime net cost, QALY and ICER impacts

| Sensitivity analysis | Lifetime cost | Lifetime QALY gain | ICER  |
|---------------------|---------------|--------------------|-------|
| 1: 50% LDL-C reduction | £2560         | 0.57               | £4503 |
| 2: Northern Ireland relative: monogenic proband ratio | £1277         | As base case       | £2667 |
| 3: 70% compliance | £2672         | 0.39               | £6874 |
| 4: Rosuvastatin and ezetimibe cost reduction | £1882         | As base case       | £3929 |
| 5: Discount rate 1.5% | £2773         | 0.85               | £3278 |
| 6: Discount rate 5% | £2771         | 0.33               | £8387 |
| 7: No treatment change if already on statins | £2615         | 0.26               | £9954 |
| 8: No treatment change if normocholesterolemic | £2686         | 0.44               | £6069 |

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted-life-year.

Figure 3  Adverse events averted, net cost and incremental cost effectiveness ratio after 30 years per 1000 relatives tested.
These estimates are highly sensitive to the number of relatives tested per index case tested. Increasing the yield of monogenic diagnoses in index cases would significantly increase cost effectiveness, all other things equal. Currently 65% of lifetime costs are for index case testing and the monogenic detection rate is 22.98%. Increasing the number of relatives tested per monogenic index case would also increase cost effectiveness. Data from Northern Ireland indicate a considerably higher yield of tested relatives than elsewhere in the UK, with corresponding reductions in net costs, as shown in sensitivity analysis. In regions of Europe where there has been less family dispersion than in the UK, or where families are larger, cost effectiveness may be higher other things equal.

All the UK cascade services are relatively new, and it is likely that the yield of relatives will increase over time. It is also likely that the incompleteness of UK cascade services impacts testing rates for existing services; some relatives identified in the Welsh, Scottish and Northern Irish services live in England, where there is very little provision.

It is also important to note that many families with FH are completely undetected. There is a need for further study on the cost effectiveness of strategies for index case finding, and of approaches such as reverse cascade testing from children identified at immunization as having FH.27

The expiry of patents on atorvastatin and simvastatin has substantially reduced the cost of statin treatment since the NICE guidance of 2008. UK patents for ezetimibe and rosuvastatin will expire in 2017. These estimates are highly sensitive to the number of relatives outside the scope of the model. It is likely, however, that in practice cascade testing would lead to changes in some cases and this could have an impact on overall cost effectiveness. Further work is needed on the impact of cascade testing on these groups.

It is hoped that the current study will lay the foundation for future work, and will support commissioning decisions on FH services in Europe and elsewhere.

Supplementary material

Supplementary material is available at European Heart Journal online.

Funding

Funding was provided by the British Heart Foundation (M.K., K.H, M.W and S.E.H.), by the National Institute for Health Research University College London (S.E.H.), Hospitals Biomedical Research Centre (S.E.H.), and the Scottish Government Health Department (Z.M.). Open Access funding was provided by the British Heart Foundation.

Conflicts of interest: None declared.

References

1. Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. Lancet 1969;2:1380–1382.
2. Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. Circulation 1974;49:476–488.
3. Scientific Steering Committee on behalf of the Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Atherosclerosis 1999;142:105–112.
4. Versmissen J, Oosterweel DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, Heerings J, Witteman JC, Lansberg PJ, Kastelein JJ, Sijbrands EJ. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008;337:a2422.
5. Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Familial hypercholesterolaemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012;97:3956–3964.
6. UK10K Consortium, Verstas J, Eaves C, Cai Y, Min J, Huang J, Crooks L, Menn TP, McCarthy S, Perry JR, Xu C, Futema M, Lawson D, Itochovica S, Schifflers S, Hendricks AE, Danek P, Li R, Floyd J, Wain LV, Barroso I, Humphries SE, Hurles ME, Zeggini E, Barrett JC, Plagnol V, Richards JB, Greenwood CM, Timpson NJ, Durbin R, Soranzo N. The UK10K project identifies rare variants in health and disease. Nature 2015;526:82–90.
7. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wegman J, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averma M, Borén J, Bruckert E, Catapano AL, Kuijvenhoven JA, Plevnaj P, Roy K, Stalenhoef AF, Stroes ES, Taskinen MR, Tybjærg-Hansen A; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478–3490.
8. DeMott K, Nherera L, Shaw EJ, Minhas R, Humphries SE, Kathoria M, Ritchie G, Nunes V, Davies D, Lee R, McDowell I, Neil A, Qureshi N, Rowlands P, Seed M, Stracey H, Thorogood M, Watson M. Clinical Guidelines and Evidence Review for Familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2008. (PMID: 21678927).
9. Taylor A, Wang D, Patel K, Whittall R, Wood G, Farrer M, Neely RD, Fairgrieve S, Nair D, Barbir M, Jones JL, Egan S, Everts R, Lolin Y, Hughes E, Cooper JA, Hadfield SG, Norbury G, Humphries SE. Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade study. Clin Genet 2010;77:572–580.
10. Pears R, Griffin M, Futema M, Humphries SE. Improving the cost-effectiveness equation of cascade testing for familial hypercholesterolaemia. Curr Opin Lipidol 2015;26:162–168.
11. Talmud PJ, Shah S, Whittall R, Futema M, Howard P, Cooper JA, Harrison SC, Li K, Drenos F, Karpe F, Neil HA, Descamps OS, Langenborg C, Lench N, Kivimaki M, Whittal J, Hingorani AD, Kumari M, Humphries SE. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case–control study. Lancet 2013;381:1293–1301.
12. Hadfield SG, Horara S, Starr BJ, Yazdgerdi S, Marks D, Bhatnagar D, Cramb R, Egan S, Evertelle R, Berns G, Jones A, Marenah CB, Marples D, Pinson P, Snyder A, Stewart MF, Sandle L, Wang T, Watson MS, Humphries SE. Steering Group for the Department of Health Familial Hypercholesterolaemia Cascade Testing Audit Project. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Ann Clin Biochem 2009;46(Pt 1):24–32.
13. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bha A, Petru R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–1681.
14. Sonnenberg FA, Beck JR, Marks models in medical decision making: a practical guide. Med Decis Making 1993;13:322–338.
15. The National Audit of the Management of Familial Hypercholesterolaemia. National Report 2010. Royal College of Physicians, London.
16. Pears R, Griffin M, Watson M, Wheeler R, Hilder D, Meeson B, Bacon S, Byrne CD. The reduced cost of providing a nationally recognised service for familial hypercholesterolaemia. Open Heart 2014;1:e000015.

17. https://www.qrisk.org/2016/ (6 March 2017).

18. National Institute for Health and Care Excellence, Clinical Guideline 181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London: National Clinical Guideline Centre (UK) and National Institute for Health and Care Excellence (UK); 2014. (PMID: 25340243).

19. http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2015-07-15 (6 March 2017).

20. Huxley RR, Hawkins MH, Humphries SE, Karpe F, Neil HA. Simon Broome Familial Hyperlipidaemia Register Group and Scientific Steering Committee. Risk of fatal stroke in patients with treated familial hypercholesterolaemia: a prospective registry study. Stroke 2003;34:22–25.

21. https://www.ons.gov.uk/peoplepopulationandcommunity/populationestimates (6 March 2017).

22. Curtis L, Burns A. Unit Costs of Health and Social Care 2015, Personal Social Services Research Unit, University of Kent. 2015. http://www.pssru.ac.uk/project-pages/unit-costs/2015/ (6 March 2017).

23. NHS Electronic Drug Tariff. 2016. http://www.nhsbsa.nhs.uk/PrescriptionServices/4940.aspx (6 March 2017).

24. Saka O, McGuire A, Wolfe C. Cost of stroke in the United Kingdom. Age Ageing 2009;38:27–32.

25. Ward S, Lloyd Jones M, Pandor A, Holt JM, Ara R, Ryan A, Yeo W, Payne N. Statins for the Prevention of Coronary Events: Technology Assessment Report. London: National Institute for Health and Clinical Excellence, 2005.

26. Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P, Seed M, Humphries SE. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008;29:2623–2633.

27. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child-parent familial hypercholesterolaemia screening in primary care. N Engl J Med 2016;375:1628–1637.

28. Ademi Z, Watts GF, Juniper A, Liew D. A systematic review of economic evaluations of the detection and treatment of familial hypercholesterolaemia. Int J Cardiol 2013;167:2391–2396.

29. Chen CX, Hay JW. Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolaemia in the United States. Int J Cardiol 2015;181:417–424.

30. Catapano AL, Graham ID, Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2016;37:3099–31058.