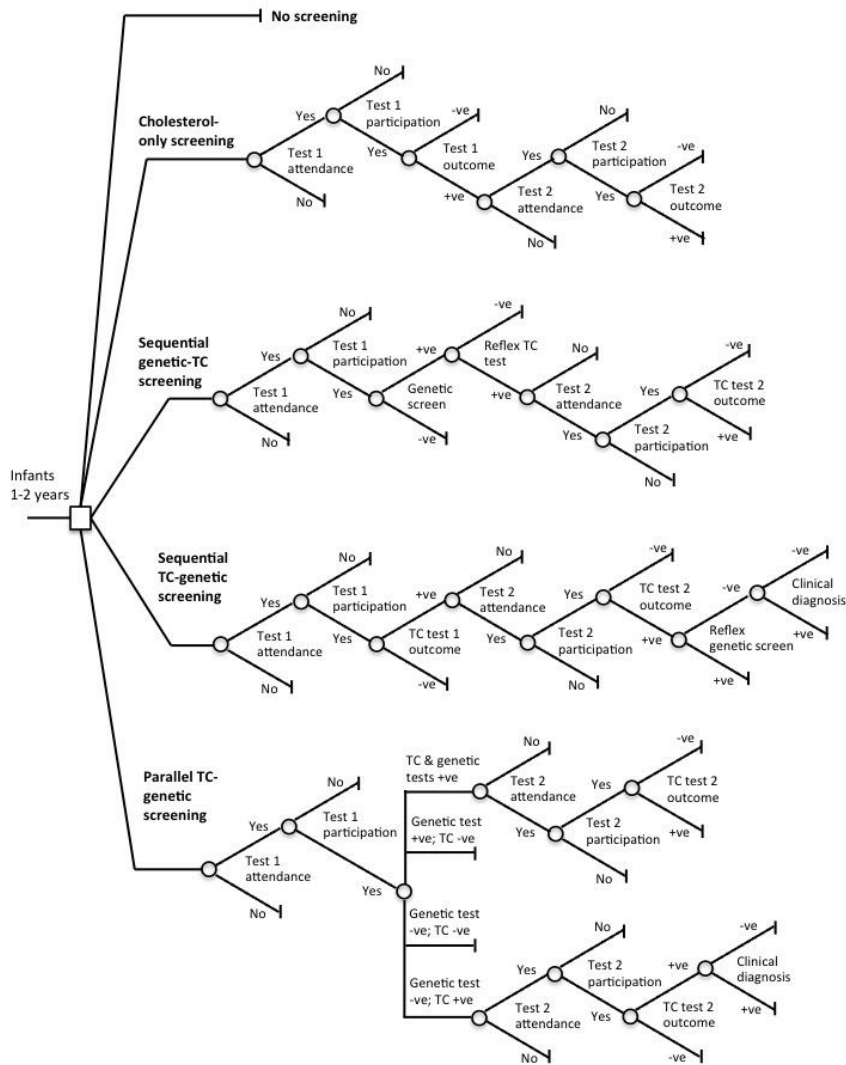


**Figure 1: Decision tree and Markov model structures**

**a. Tree used to estimate universal screening outcomes for each alternative**

Outcomes were modelled separately for the FH-positive and FH-negative individuals in each cohort, according to the probabilities and formulae described in Table 1 and Supplementary File 2, respectively. 'Reflex' testing (i.e. of samples already collected) applied where possible to minimize test requirements.

FH: familial hypercholesterolaemia; TC: total cholesterol



**b. Markov model health states and connections**

NB. 'Post-event' states accessible from associated event states only

CVD: cardiovascular disease; MI: myocardial infarction; TIA: transient ischaemic attack; CHD: coronary heart disease

**Entry state**

|                        |
|------------------------|
| Well (no existing CVD) |
|------------------------|

**Potential first transition states**

|               |                 |    |     |        |
|---------------|-----------------|----|-----|--------|
| Stable angina | Unstable angina | MI | TIA | Stroke |
|---------------|-----------------|----|-----|--------|

**Potential second transition states**

|                    |                      |         |          |             |                 |    |        |
|--------------------|----------------------|---------|----------|-------------|-----------------|----|--------|
| Post-stable angina | Post-unstable angina | Post-MI | Post-TIA | Post-stroke | Unstable angina | MI | Stroke |
|--------------------|----------------------|---------|----------|-------------|-----------------|----|--------|

**Potential third (and subsequent) transition states**

|                      |         |             |                 |    |        |
|----------------------|---------|-------------|-----------------|----|--------|
| Post-unstable angina | Post-MI | Post-stroke | Unstable angina | MI | Stroke |
|----------------------|---------|-------------|-----------------|----|--------|

**Dead states accessible from any other state:**

|           |                   |               |
|-----------|-------------------|---------------|
| CHD death | Non-CHD CVD death | Non-CVD death |
|-----------|-------------------|---------------|

**Table 1: Probabilities applied in calculation of decision tree outcomes**

<sup>a</sup>1/250 = estimated FH prevalence; 0.95 = estimated proportion of those mutation-positive with total cholesterol  $\geq 95^{\text{th}}$  percentile (Wald et al., 2007, Wald et al., 2016); <sup>a,b</sup>Estimated prevalence figures recalculated for threshold analyses; <sup>c</sup>full references in Supplementary File 9  
FH: familial hypercholesterolaemia; TC: total cholesterol; US: universal screening

| Probability  | Notation     | Value                     | Calculation/rationale   | References <sup>c</sup>  |
|--|--------------|---------------------------|---|--|
| <b>All scenarios</b>   |              |                           |   |  |
| FH-positive (undiagnosed) <sup>a,b</sup>                                 | p(FH+)       | 0.0034                    | 85% of estimated FH prevalence  | (Akioyamen et al., 2017, Nordestgaard et al., 2013)(Pedersen et al., 2010)               |
| FH-negative <sup>b</sup>   | p(FH-)       | 0.9966                    | 1 – p(FH+)  |  |
| Mutation-positive given FH+  | p(M+ FH+)    | 0.45                      | Probabilities reported from UK studies = 40.7% and 47.0%, within the range of values reported internationally (38.5-57.0%).                             | (Futema et al., 2015, Damgaard et al., 2015, Klančar et al., 2015, Civeira et al., 2008) |
| Mutation-negative given FH+  | p(M- FH+)    | 0.55                      | 1 – p(M+ FH+)   |  |
| Mutation-positive  | p(M+)        | 0.0019                    | (1/250)*p(M+ FH+)/0.95  |  |
| Mutation-positive given FH-  | p(M+ FH-)    | 9.51*10 <sup>-5</sup>     | p(M+) – (1/250)*p(M+ FH+)/p(FH-) (based on meta-analysis results indicative that $\geq 95\%$ of M+ infants exhibit hypercholesterolaemia).              | (Wald et al., 2007, Wald et al., 2016)   |
| Mutation-negative given FH-  | p(M- FH-)    | 1 - 9.51*10 <sup>-5</sup> | 1 – p(M+ FH-)   |  |
| First appointment attendance   | p(A1)        | 0.92                      | 2015-16 UK 24-month vaccination coverage  | NHS Immunisation Statistics  |
| First test participation   | p(P1)        | 0.94                      | As per recent UK US study   | (Wald et al., 2016)  |
| Second appointment attendance  | p(A2)        | 0.92                      | 2015-16 UK 24-month vaccination coverage  | NHS Immunisation Statistics  |
| Second test participation  | p(P2)        | 0.94                      | Willingness to participate in further screening reported in UK US study   | (Wald et al., 2016)  |
| Second elevated TC test following elevated first test                    | p(TC2+ TC1+) | 0.935                     | Pre-diagnosis duplication of elevated measurement recommended, in view of biological and analytical test variability                                    | (Nordestgaard et al., 2013, Watts et al., 2015)(NICE CG71, Neil, 1996)                   |
| <b>Cholesterol-only screening scenario</b>                               |              |                           |   |  |
| Positive TC tests given FH+  | p(TC+ FH+)   | 0.88                      | This threshold applied as post-test probability (=0.78) reasonably low (and 0.43 at next lowest threshold for which test performance figures described) | (Wald et al., 2007)  |
| Positive TC tests given FH-  | p(TC+ FH-)   | 0.001                     |   |  |
| <b>Sequential genetic-TC and parallel TC-genetic screening scenarios</b> |              |                           |   |  |
| Positive TC tests given FH+  | p(TC+ FH+)   | 1                         | By definition   |  |
| Positive TC tests given FH-  | p(TC+ FH-)   | 0                         | By definition   |  |
| Negative TC tests among FH-  | p(TC- FH-)   | 1                         | By definition   |  |
| <b>Sequential TC-genetic screening scenario</b>                          |              |                           |   |  |
| Positive TC tests among FH+  | p(TC+ FH+)   | 0.96                      | Lowest threshold for which test performance described. Found by UK US study to be above general population 95 <sup>th</sup> percentile.                 | (Wald et al., 2007, Wald et al., 2016)   |
| Positive TC tests among FH- <sup>a</sup>                                 | p(TC+ FH-)   | 0.045                     | 0.05 – (1/250)  |  |

Commented [SH1]: Shouldn't this now be 50%?

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**Table 2: Base case screening, treatment and health state costs**

<sup>a</sup>Staff time costed using 2017-18 band midpoint salaries plus oncosts, assuming full-time working with 80% (nursing, phlebotomy) and 90% (administration) clinical time (NHS Staff Council, 2017; HMRC, 2017; NHS Business Services Authority, 2017); <sup>b</sup>Originally calculated based on guideline-recommended management; interim updates have been few, the main update being extension of stroke thrombolysis window from 3 to 4.5 hrs (NICE CG68); <sup>c</sup>full references in Supplementary File 9

US: universal screening; (R)CT: (reverse) cascade testing; NGS: next generation sequencing; LMT: lipid modification therapy; GDG: guideline development group; CPI: consumer price index; FH: familial hypercholesterolaemia; NICE: National Institute for Health and Care Excellence; MFF: market forces factor; GP: general practitioner; PSSRU: Personal Social Services Research Unit

|   | Cost/item<br>(as listed) | Details and references <sup>c</sup>   |
|---|--------------------------|---|
| <b>Screening</b>                                  |                          |   |
| Nursing time:                                     |                          |   |
| - first US appointment                            | £17.07                   | On local clinical expert advice, 30 min allocated for first US appointment, 15 min for second; 45 min for RCT consultation with index case, 30 min for consultation with relatives. Time costed for band 7 nurse specialist. <sup>a</sup> |
| - second US appointment                           | £8.54                    |   |
| - index case consultation for CT                  | £25.61                   |   |
| - initial relative CT appointment                 | £17.07                   |   |
| NGS screen  | £263                     | 2017-18 local laboratory NHS costs (Bristol Genetics Laboratory, 2017)  |
| Genetic <del>test</del> screen for known mutation | £79                      |   |
| Lipid profile test                                | £3                       | 2014 CG181 GDG estimate (in keeping with recently published values)   |
| Results/appointment invitation letter             | £1.09                    | CPI-uplifted 2009 NICE FH costing template values   |
| Administrator time per letter                     | £4.92                    | Time costed for band 5 administrator <sup>a</sup>   |
| Initial specialist review (paediatric)            | £316.70                  | 2017-18 National Tariff first endocrinology outpatient review*mean MFF (NHS England)  |
| Initial specialist review (adult)                 | £239.96                  |   |
| <b>Treatment</b>                                  |                          |   |
| Average annual LMT (8-9 years)                    | £10.31                   | September 2017 Drug Tariff (NHS Business Services Authority)  |
| Average annual LMT (10-17 years)                  | £17.14                   |   |
| Average annual LMT (adult)                        | £204.11                  |   |
| Lipid profile test                                | £3                       | 2014 NICE CG181 GDG estimates (in keeping with recently published values)   |
| Liver function tests                              | £1                       |   |
| Creatine kinase test                              | £2                       |   |
| Blood sampling appointment (paediatric)           | £5.01                    | 20 min (paediatric) or 15 min (adult) of band 3 phlebotomist time <sup>a</sup>  |
| Blood sampling appointment (adult)                | £3.76                    |   |
| Secondary care follow-up (paediatric)             | £156.73                  | 2017-18 National Tariff follow-up endocrinology outpatient review*mean MFF (NHS England)  |
| Secondary care follow-up (adult)                  | £100.52                  |   |
| Primary care follow-up (adult)                    | £36.89                   | CPI-adjusted 2016 face-to-face GP consultation cost (PSSRU)   |
| <b>Health state costs (annual)</b>                |                          |   |
| Well and dead states                              | £0                       | CPI-adjusted CG181 estimates <sup>b</sup>   |
| Stable angina                                     | £8280                    |   |
| Post-stable angina                                | £252.95                  |   |
| Unstable angina                                   | £3694.70                 |   |
| Post-unstable angina                              | £405.78                  |   |
| Myocardial infarction                             | £3932.37                 |   |
| Post-myocardial infarction                        | £830.53                  |   |
| Transient ischaemic attack                        | £674.54                  |   |
| Post-transient ischaemic attack                   | £130.69                  |   |
| Stroke  | £4394.53                 |   |
| Post-stroke                                       | £163.37                  |   |

**Table 3: Summary of deterministic sensitivity analyses**

<sup>a</sup>It was assumed that transition probabilities reverted to untreated values immediately on treatment discontinuation – likely conservative in view of treatment legacy effects.(Ford et al., 2016); <sup>b</sup>Current costs of simvastatin regimes with equivalent LDL-C-reducing potency used to estimate off-patent rosuvastatin costs. Off-patent ezetimibe cost estimated using value recently predicted by Kerr *et al* (10% of current cost); <sup>c</sup>80% of secondary prevention patients, and 20, 30, 40 and 50% of those that reached 40, 50, 60 and 70 years, respectively, were treated (regardless of diagnosed/undiagnosed status); <sup>d</sup>full references in Supplementary File 9; DSA: deterministic sensitivity analysis; M+: mutation-positive; (R)CT: (reverse) cascade testing; LMT: lipid modifying therapy; LDL-C: low density lipoprotein cholesterol; CVD: cardiovascular disease; US: universal screening; NICE: National Institute for Health and Care Excellence; TC: total cholesterol

| DSA-specific adjustment  | Rationale  | References <sup>d</sup>  |
|--|--|--|
| All M+ defined as FH+  | Both extent and duration of raised LDL-C influence CVD risk; hence M+ status associated with relatively high risk for given current LDL-C  | (Khera et al., 2016, Damgaard et al., 2005)  |
| RCT case yield/index = 0.5   | Reflective of current CT achievement   | (Hadfield et al., 2009, Kerr et al., 2017, Marks, 2006)                                    |
| RCT case yield/index = 6.1   | Theoretical maximum achievable under current UK approach to CT.  | (Morris et al., 2012)  |
| RCT case yield/index = 8.6; probability relative M+ = 0.21                         | Achieved in The Netherlands; theoretical maximum achievable in UK If first- to third- degree relatives screened unconditionally. Cases (n=2.5) identified with probability of second- versus third- degree relatives unclear, therefore analysed assuming all second-degree, repeated assuming all third-degree. | (Umans-Eckenhausen, 2001, Morris et al., 2012)   |
| RCT case yield/index = 8.6; probability relative M+ = 0.31                         |  |  |
| 100% of diagnosed adults treated   |  |  |
| 100% of diagnosed treated from 8 years   |  |  |
| 15% discontinue LMT at 10 years  | Potential LMT discontinuation/reduced adherence (reportedly, 84%+ treated, with ≥80% regime-adherent, at 10 years, but rates may fall over time) <sup>a</sup>  | (Kusters et al., 2014) (Galema-Boers et al., 2014)   |
| 50% LDL-C reduction achieved with LMT  | NICE CG71 recommendation   |  |
| Estimated off-patent LMT costs applied   | Patents protecting rosuvastatin and ezetimibe due to expire this year <sup>b</sup>   | September 2017 Drug Tariff (NHS Business Services Authority)(Kerr et al., 2017)            |
| Discount rate = 1.5%   |  |  |
| Discount rate = 5.0%   |  |  |
| CVD risks 90% of base case estimates   | It has not been possible to obtain unbiased estimates of untreated secondary event risks since LMT introduction. General population CVD risk has fallen in the meantime, and a continuing downward trajectory is predicted.  | (Bhatnagar et al., 2016)   |
| CVD risks 80% of base case estimates   |  |  |
| Undiagnosed cases treated at background rate                                       | Treatment prior to diagnosis plausible <sup>c</sup>  | (Nanchen et al., 2015, Carey et al., 2012, O’Keeffe et al., 2016, Fleetcroft et al., 2014) |
| Cholesterol test sensitivity in sequential cholesterol-genetic US strategy = 62.5% | Recent finding detection rates with LDL-C threshold at approx. general population 95 <sup>th</sup> percentile could be as low as 62.5% (lower using TC) (NB. n=6 mutation-positive children identified in study)   | (Futema et al., 2017)  |
| Time for first US appointment 40 min   | Expert clinician suggestion  |  |

**Table 4: Case yields, costs per diagnosis and cost-effectiveness of screening alternatives**

US: universal screening; RCT: reverse cascade testing; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; RCS: reverse cascade screening; SD: strongly dominated

|   | FH cases identified per 10,000 screened |       |       | Screening costs per diagnosis (£) |       |         | ICER (£/QALY) |           |                     |                         |                             |
|---|---|-------|-------|-----------------------------------|-------|---------|---------------|-----------|---------------------|-------------------------|-----------------------------|
|   | US                                      | RCT   | total | US                                | RCT   | total   | QALYs         | Costs (£) | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 0                                       | 0     | 0     | n/a                               | n/a   | n/a     | 992.2         | 225,834   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 22.38                                   | 0     | 22.38 | 11,788                            | n/a   | 11,788  | 1,009.5       | 560,929   | 19,410              | 19,410                  | ED                          |
| Sequential cholesterol-genetic screening          | 24.41                                   | 0     | 24.41 | 13,785                            | n/a   | 13,785  | 1,011.0       | 640,147   | 21,999              | 50,476                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 24.41                                   | 15.38 | 39.79 | 13,785                            | 1,110 | 8,886   | 1,027.7       | 672,309   | 12,562              | 1,925                   | 12,562                      |
| Sequential genetic-cholesterol screening          | 11.44                                   | 0     | 11.44 | 217,036                           | n/a   | 217,036 | 1,001.0       | 2,745,746 | 285,445             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 11.44                                   | 19.67 | 31.11 | 217,036                           | 1,110 | 80,519  | 1,022.4       | 2,786,887 | 84,799              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 25.43                                   | 0     | 25.43 | 98,959                            | n/a   | 98,959  | 1,011.8       | 2,823,202 | 132,399             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 25.43                                   | 19.67 | 45.10 | 98,959                            | 1,110 | 56,279  | 1,033.2       | 2,864,342 | 64,368              | 402,285                 | 402,285                     |

## Supplementary File 1: Systematic literature search – summary and example database search strategy

Search terms were chosen with the aim of identifying information related to FH screening, diagnostics, treatment, and CVD and mortality outcomes, as well as previous economic evaluations of FH screening. Results were limited to those published since 1999, and to systematic reviews and meta-analyses, clinical trials, observational studies, other evaluations including economic evaluations, case series, registry data, guidelines, government publications and technical reports, published in English. Reference lists of included papers were also searched and further searches were carried out using the names of authors active in the field.

The Medline (via Pubmed), Embase (via Ovid), Cochrane Library, Health Management Information Consortium, NICE Evidence, Cost-Effectiveness Analysis Registry, Paediatric Economic Database Evaluation, and Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effect, NHS Economic Evaluation Database, and Health Technology Assessment databases were searched on 08/08/2017.

### Keywords and additional terms used to generate database search strategies:

|                     | Keyword                         | Additional terms  |
|---------------------|---------------------------------|---|
| <b>Population</b>   | Familial hypercholesterolaemia  | Fredrickson hyperlipoproteinaemia, type IIa; Hyperbetalipoproteinaemia; Hyperlipidaemia, group A; Low-density-lipoprotein-type hyperlipoproteinaemia                              |
| <b>Intervention</b> | Mass screening[mesh]            | Case-finding  |
| <b>Outcomes</b>     | Diagnostic tests, routine[mesh] | Symptom assessment[mesh]; Physical examination[mesh]; Medical history taking[mesh]; Clinical laboratory techniques[mesh]; Diagnostic errors[mesh]; Clinical decision-making[mesh] |
|                     | Genetic techniques[mesh]        | Genotype[mesh]; Phenotype[mesh]; Genetic heterogeneity[mesh]; Mutation[mesh]; Polymorphism, genetic[mesh]; Genetic Counseling[mesh]   |
|                     | CVD, mortality                  | Myocardial ischaemia[mesh]; cerebrovascular disorders[mesh]; peripheral arterial disease[mesh]; vital statistics[mesh]; death[mesh]   |
|                     | Anticholesteremic agents[mesh]  | Treatment outcome[mesh]   |

### Example search strategy:

Terms and filters used to search the Medline database via Pubmed

1. familial hypercholesterolaemia[Title/Abstract] OR familial hypercholesterolemia[Title/Abstract]

2. cost and cost analysis[MeSH Terms] OR mass screening[MeSH Terms] OR diagnostic tests, routine[MeSH Terms] OR clinical chemistry tests[MeSH Terms] OR genetic testing[MeSH Terms] OR genotype[MeSH Terms] OR phenotype[MeSH Terms] OR genetic heterogeneity[MeSH Terms] OR mutation[MeSH Terms] OR polymorphism, genetic[MeSH Terms] OR genetic counseling[MeSH Terms] OR myocardial ischemia[MeSH Terms] OR cerebrovascular disorders[MeSH Terms] OR peripheral arterial disease[MeSH Terms] OR life expectancy[MeSH Terms] OR life tables[MeSH Terms] OR mortality[MeSH Terms] OR death[MeSH Terms] OR anticholesteremic agents[MeSH Terms] OR treatment outcome[MeSH Terms]
3. 1 AND 2

Filters applied:

1. Dates: 1999 – present
2. Article types: Clinical study, clinical trial (all phases), comparative study, consensus development conference, dataset, evaluation studies, government publications, guidelines, meta-analysis, multicenter study, observational study, practice guideline, pragmatic clinical trial, randomised controlled trial, systematic review, technical report, twin study, validation study



## Supplementary File 2: Formulae applied in decision tree calculations

Formulae presented only for outcomes not equal to zero

FH+: familial hypercholesterolaemia (FH)-positive, as per base case definition

FH-: FH-negative, as per base case definition

M+: FH mutation-positive

M-: FH mutation-negative

TC+: total cholesterol test results positive

TC-: total cholesterol test results negative

A1: first screening appointment attendance

P1: screening participation at first appointment

A2: second screening appointment attendance

P2: screening participation at second appointment

### Branch 1: No screening

| Mutation status | Mutation status determined | Formula                                     |
|-----------------|----------------------------|---|
| False negatives |                            |   |
| M+              | No                         | $p(\text{FH+}) * p(\text{M+}   \text{FH+})$ |
| M-              | No                         | $p(\text{FH+}) * p(\text{M-}   \text{FH+})$ |
| True negatives  |                            |   |
| M+              | No                         | $p(\text{FH-}) * p(\text{M+}   \text{FH-})$ |
| M-              | No                         | $p(\text{FH-}) * p(\text{M-}   \text{FH-})$ |

### Branch 2: cholesterol-only screening

| Mutation status | Mutation status determined | Formula  |
|-----------------|----------------------------|--|
| True positives  |                            |  |
| M+              | No                         | $p(\text{FH+}) * p(\text{M+}   \text{FH+}) * p(\text{A1}) * p(\text{P1}) * p(\text{TC+}   \text{FH+}) * p(\text{A2}) * p(\text{P2})$ |
| M-              | No                         | $p(\text{FH+}) * p(\text{M-}   \text{FH+}) * p(\text{A1}) * p(\text{P1}) * p(\text{TC+}   \text{FH+}) * p(\text{A2}) * p(\text{P2})$ |
| False negatives |                            |  |
| M+              | No                         | $p(\text{FH+}) * p(\text{M+}   \text{FH+}) - p(\text{true positive, M+ status undetermined})$  |
| M-              | No                         | $p(\text{FH+}) * p(\text{M-}   \text{FH+}) - p(\text{true positive, M- status undetermined})$  |
| True negatives  |                            |  |
| M+              | No                         | $p(\text{FH-}) * p(\text{M+}   \text{FH-}) - p(\text{false positive, M+ status undetermined})$                                       |
| M-              | No                         | $p(\text{FH-}) * p(\text{M-}   \text{FH-}) - p(\text{false positive, M- status undetermined})$                                       |
| False positives |                            |  |
| M+              | No                         | $p(\text{FH-}) * p(\text{M+}   \text{FH-}) * p(\text{A1}) * p(\text{P1}) * p(\text{TC+}   \text{FH-}) * p(\text{A2}) * p(\text{P2})$ |
| M-              | No                         | $p(\text{FH-}) * p(\text{M-}   \text{FH-}) * p(\text{A1}) * p(\text{P1}) * p(\text{TC+}   \text{FH-}) * p(\text{A2}) * p(\text{P2})$ |

### Branch 3: genetic-only screening

| Mutation status | Mutation status determined | Formula  |
|-----------------|----------------------------|--|
| True positives  |                            |  |
| M+              | Yes                        | $p(\text{FH+}) * p(\text{A1}) * p(\text{P1}) * p(\text{M+}   \text{FH+}) * p(\text{TC+}   \text{FH+}) * p(\text{A2}) * p(\text{P2})$ |
| False negatives |                            |  |
| M+              | Yes                        | $p(\text{FH+}) * p(\text{A1}) * p(\text{P1}) * p(\text{M+}   \text{FH+}) - p(\text{true positive, M+ status determined})$            |

|                       |     |   |
|-----------------------|-----|---|
| M+                    | No  | $p(\text{FH}+) * p(\text{M}+   \text{FH}+) - p(\text{true positive, M+ status determined}) - p(\text{false negative, M+ status determined})$  |
| M-                    | Yes | $p(\text{FH}+) * p(\text{A1}) * p(\text{P1}) * p(\text{M-}   \text{FH}+)$   |
| M-                    | No  | $p(\text{FH}+) * p(\text{M-}   \text{FH}+) - p(\text{false negative, M- status determined})$  |
| <b>True negatives</b> |     |   |
| M+                    | Yes | $p(\text{FH-}) * p(\text{M}+   \text{FH-}) - p(\text{true negative, M+ status undetermined})$   |
| M+                    | No  | $p(\text{FH-}) * p(\text{M}+   \text{FH-}) * (1 - p(\text{A1})) + p(\text{FH-}) * p(\text{M}+   \text{FH-}) * p(\text{A1}) * (1 - p(\text{P1})) + p(\text{FH-}) * p(\text{A1}) * p(\text{P1}) * p(\text{M}+   \text{FH-}) * p(\text{TC}+   \text{FH-}) * (1 - p(\text{A2})) + p(\text{FH-}) * p(\text{A1}) * p(\text{P1}) * p(\text{M}+   \text{FH-}) * p(\text{TC}+   \text{FH-}) * p(\text{A2}) * (1 - p(\text{P2}))$ |
| M-                    | Yes | $p(\text{FH-}) * p(\text{A1}) * p(\text{P1}) * p(\text{M-}   \text{FH-})$   |
| M-                    | No  | $p(\text{FH-}) * p(\text{M-}   \text{FH-}) - p(\text{true negative, M- status determined})$   |

#### Branch 4: sequential cholesterol-genetic screening

| Mutation status        | Mutation status determined | Formula  |
|------------------------|----------------------------|--|
| <b>True positives</b>  |                            |  |
| M+                     | Yes                        | $p(\text{FH}+) * p(\text{A1}) * p(\text{P1}) * p(\text{TC}+   \text{FH}+) * p(\text{A2}) * p(\text{P2}) * p(\text{M}+   \text{FH}+)$ |
| M-                     | Yes                        | $p(\text{FH}+) * p(\text{A1}) * p(\text{P1}) * p(\text{TC}+   \text{FH}+) * p(\text{A2}) * p(\text{P2}) * p(\text{M-}   \text{FH}+)$ |
| <b>False negatives</b> |                            |  |
| M+                     | No                         | $p(\text{FH}+) * p(\text{M}+   \text{FH}+) - p(\text{true positive, M+ status determined})$  |
| M-                     | No                         | $p(\text{FH}+) * p(\text{M-}   \text{FH}+) - p(\text{true positive, M- status determined})$  |
| <b>True negatives</b>  |                            |  |
| M+                     | No                         | $p(\text{FH-}) * p(\text{M}+   \text{FH-})$  |
| M-                     | Yes                        | $p(\text{FH-}) * p(\text{A1}) * p(\text{P1}) * p(\text{TC}+   \text{FH-}) * p(\text{A2}) * p(\text{P2}) * p(\text{M-}   \text{TC}+)$ |
| M-                     | No                         | $p(\text{FH-}) * p(\text{M-}   \text{FH-}) - p(\text{true negative, M- status determined})$  |

#### Branch 5: parallel cholesterol-genetic screening

| Mutation status        | Mutation status determined | Formula  |
|------------------------|----------------------------|--|
| <b>True positives</b>  |                            |  |
| M+                     | Yes                        | $p(\text{FH}+) * p(\text{A1}) * p(\text{P1}) * p(\text{M}+   \text{FH}+) * p(\text{TC}+   \text{FH}+) * p(\text{A2}) * p(\text{P2})$         |
| M-                     | Yes                        | $p(\text{FH}+) * p(\text{A1}) * p(\text{P1}) * p(\text{M-}   \text{FH}+) * p(\text{TC}+   \text{FH}+) * p(\text{A2}) * p(\text{P2})$         |
| <b>False negatives</b> |                            |  |
| M+                     | Yes                        | $p(\text{FH}+) * p(\text{A1}) * p(\text{P1}) * p(\text{M}+   \text{FH}+) - p(\text{true positive, M+ status determined})$                    |
| M+                     | No                         | $p(\text{FH}+) * p(\text{M}+   \text{FH}+) - p(\text{true positive, M+ status determined}) - p(\text{false negative, M+ status determined})$ |
| M-                     | Yes                        | $p(\text{FH}+) * p(\text{A1}) * p(\text{P1}) * p(\text{M-}   \text{FH}+) - p(\text{true positive, M- status determined})$                    |
| M-                     | No                         | $p(\text{FH}+) * p(\text{M-}   \text{FH}+) - p(\text{true positive, M- status determined}) - p(\text{false negative, M- status determined})$ |
| <b>True negatives</b>  |                            |  |
| M+                     | Yes                        | $p(\text{FH-}) * p(\text{A1}) * p(\text{P1}) * p(\text{M}+   \text{FH-}) * p(\text{TC-}   \text{FH-})$                                       |
| M+                     | No                         | $p(\text{FH-}) * p(\text{M}+   \text{FH-}) - p(\text{true negative, M+ status determined})$  |
| M-                     | Yes                        | $p(\text{FH-}) * p(\text{A1}) * p(\text{P1}) * p(\text{M-}   \text{FH-})$  |
| M-                     | No                         | $p(\text{FH-}) * p(\text{M-}   \text{FH-}) - p(\text{true negative, M- status determined})$  |

**Supplementary File 3: Formulae applied to calculate annual probabilities from 10-year cardiovascular disease risk estimates**

10-year risks ( $P_{10\text{-year}}$ ) were converted to rates using the formula:

$$\text{rate } (r) = (-\ln(1 - P_{10\text{-year}})) / 10$$

The calculated rates were converted into annual risks ( $P_{\text{annual}}$ ) using the formula:

$$P_{\text{annual}} = 1 - e^{-r}$$

#### Supplementary File 4: Details of modeled treatment

\*40mg/day atorvastatin substituted for 80mg/day simvastatin regimes observed in audit on which modelled treatment based (Pedersen et al, 2010), given recent Medicines and Healthcare products Regulatory Agency guidance to limit use of 80mg/day simvastatin (MHRA, 2010).

| Daily therapy       | Proportions of treated persons using therapy |             |           |
|---------------------|--|-------------|-----------|
|                     | ≥18 years                                    | 10-17 years | 8-9 years |
| Atorvastatin 10 mg  | 0.08   | 0.366       | 0         |
| Atorvastatin 20 mg  | 0.112  | 0.113       | 0         |
| Atorvastatin 40 mg* | 0.32   | 0.038       | 0         |
| Atorvastatin 80 mg  | 0.288  | 0.013       | 0         |
| Rosuvastatin 5 mg   | 0.014  | 0.029       | 0         |
| Rosuvastatin 10 mg  | 0.025  | 0           | 0         |
| Rosuvastatin 20 mg  | 0.031  | 0           | 0         |
| Rosuvastatin 40 mg  | 0.03   | 0           | 0         |
| Simvastatin 10 mg   | 0.008  | 0.162       | 0         |
| Simvastatin 20 mg   | 0.017  | 0.054       | 0         |
| Simvastatin 40 mg   | 0.075  | 0           | 0         |
| Simvastatin 80 mg*  | 0  | 0           | 0         |
| Pravastatin 10 mg   | 0  | 0.169       | 1.0       |
| Pravastatin 20 mg   | 0  | 0.056       | 0         |
| Pravastatin 40 mg   | 0  | 0           | 0         |
| Ezetimibe 10 mg     | 0.463  | 0           | 0         |

### Supplementary File 5: Probability distributions assigned to sampled parameters and associated statistics

<sup>a</sup>Standard errors estimated as 10% of the point estimate, as per previous models (NICE CG181; Ward et al, 2005); <sup>b</sup>Normal distribution was assigned to pre-treatment LDL-C estimates, as studies indicate such distribution, (Starr et al., 2008, Wald et al., 2007) and CI limits were sufficiently high to avoid risk of impossible negative values; SE: standard error; MI: myocardial infarction; TIA: transient ischaemic attack; FH: familial hypercholesterolaemia; CHD: coronary heart disease; LDL-C: low density lipoprotein cholesterol; LL: lower limit; UL: upper limit; CI: confidence interval; SB: Simon Broome

| Parameter  | Distribution        | Statistics         |                              |                        |                       | References                     |
|--|---------------------|--------------------|------------------------------|------------------------|-----------------------|--------------------------------|
|  |                     | Point estimate (E) | SE                           | Alpha                  | Beta                  |                                |
| <b>Transition probabilities</b>                        | Beta                | As per text        | 0.1*annual risk <sup>a</sup> | $E*(E*(1-E)/(SE^2)-1)$ | $(\alpha/E) - \alpha$ |                                |
| <b>Health states</b>                                   |                     |                    |                              |                        |                       |                                |
| Well   |                     | 1                  | -                            | -                      | -                     |                                |
| (Post) stable angina                                   |                     | 0.808              | 0.038                        | 86.00                  | 20.44                 |                                |
| Unstable angina  |                     | 0.770              | 0.038                        | 93.67                  | 27.98                 |                                |
| Post-unstable angina                                   |                     | 0.880              | 0.018                        | 285.93                 | 38.99                 | NICE CG181                     |
| MI   | Beta                | 0.760              | 0.018                        | 427.09                 | 134.87                |                                |
| Post-MI  |                     | 0.880              | 0.018                        | 285.93                 | 38.99                 |                                |
| TIA/post-TIA   |                     | 0.900              | 0.025                        | 128.70                 | 14.30                 |                                |
| Stroke/post-stroke                                     |                     | 0.628              | 0.040                        | 91.07                  | 53.94                 |                                |
| Dead states  |                     | 0                  | -                            | -                      | -                     |                                |
| <b>FH-associated relative risk CHD</b>                 |                     |                    |                              |                        |                       |                                |
|  |                     |                    | <b>LL 95% CI</b>             | <b>UL 95% CI</b>       | <b>Ln(mean)</b>       | <b>Ln(SE)</b>                  |
| <39 years  | Log-normal          | 84.3               | 33.8                         | 173.3                  | 4.43                  | 0.42 (SB Register Group, 1991) |
| 40-59 years  |                     | 5.3                | 2.7                          | 9.2                    | 1.67                  | 0.31                           |
| <b>Relative risk of outcome per mM LDL-C reduction</b> |                     |                    |                              |                        |                       |                                |
| Non-fatal CHD  |                     | 0.74               | 0.69                         | 0.78                   | -0.30                 | 0.03                           |
| Ischaemic stroke                                       | Log-normal          | 0.8                | 0.73                         | 0.88                   | -0.22                 | 0.05 (CTT, 2010)               |
| Fatal CHD  |                     | 0.8                | 0.73                         | 0.86                   | -0.22                 | 0.04                           |
| <b>Pre-treatment LDL-C (mM)</b>                        |                     |                    |                              |                        |                       |                                |
|  |                     |                    | <b>LL 95% CI</b>             | <b>UL 95% CI</b>       | <b>SE</b>             |                                |
| 0 -19 years  |                     | 5.82               | 5.56                         | 6.08                   | 0.13                  |                                |
| 20-24 years  |                     | 6.36               | 5.54                         | 7.18                   | 0.42                  |                                |
| 25-34 years  | Normal <sup>b</sup> | 6.9                | 6.45                         | 7.35                   | 0.23                  | (Kerr et al., 2017)            |
| 35-44 years  |                     | 7.51               | 6.88                         | 8.15                   | 0.32                  |                                |
| 45-54 years  |                     | 7.57               | 6.71                         | 8.42                   | 0.44                  |                                |
| 55+ years  |                     | 8.3                | 7.35                         | 9.25                   | 0.48                  |                                |

**Supplementary File 6: Familial hypercholesterolaemia case yields and costs per diagnosis under each screening strategy, as modelled in deterministic sensitivity analyses**

Results are presented for all scenarios where screening outcomes differ from the base case scenario

US: universal screening; RCT: reverse cascade testing

a. DSA adjustment: All M+ defined as FH+

|   | FH cases identified per 10,000 screened in US |       |       | Screening costs per diagnosis (£) |     |         |
|---|---|-------|-------|-----------------------------------|-----|---------|
|   | US  | RCT   | total | US                                | RCT | total   |
| No screening                                      | 0   | 0     | 0     | n/a                               | n/a | n/a     |
| Cholesterol-only screening                        | 22.38   | 0     | 22.38 | 11,788                            | n/a | 11,788  |
| Sequential genetic-cholesterol screening          | 14.05   | 0     | 14.05 | 176,742                           | n/a | 176,742 |
| Sequential cholesterol-genetic screening          | 24.41   | 0     | 24.41 | 13,785                            | n/a | 13,785  |
| Parallel cholesterol-genetic screening            | 28.04   | 0     | 28.04 | 89,751                            | n/a | 89,751  |
| Sequential genetic-cholesterol screening plus RCT | 14.05   | 28.10 | 42.15 | 176,742                           | 777 | 59,432  |
| Sequential cholesterol-genetic screening plus RCT | 24.41   | 21.97 | 46.38 | 13,785                            | 777 | 7,624   |
| Parallel cholesterol-genetic screening plus RCT   | 28.04   | 28.10 | 56.14 | 89,751                            | 777 | 45,212  |

b. DSA adjustment: RCT case yield/index = 0.5

|   | FH cases identified per 10,000 screened |      |       | Screening costs per diagnosis (£) |       |         |
|---|---|------|-------|-----------------------------------|-------|---------|
|   | US                                      | RCT  | total | US                                | RCT   | total   |
| No screening                                      | 0                                       | 0    | 0     | n/a                               | n/a   | n/a     |
| Cholesterol-only screening                        | 22.38                                   | 0    | 22.38 | 11,788                            | n/a   | 11,788  |
| Sequential genetic-cholesterol screening          | 11.44                                   | 0    | 11.44 | 217,036                           | n/a   | 217,036 |
| Sequential cholesterol-genetic screening          | 24.41                                   | 0    | 24.41 | 13,785                            | n/a   | 13,785  |
| Parallel cholesterol-genetic screening            | 25.43                                   | 0    | 25.43 | 98,959                            | n/a   | 98,959  |
| Sequential genetic-cholesterol screening plus RCT | 11.44                                   | 4.92 | 16.36 | 217,036                           | 1,165 | 152,146 |
| Sequential cholesterol-genetic screening plus RCT | 24.41                                   | 3.84 | 28.26 | 13,785                            | 1,165 | 12,068  |
| Parallel cholesterol-genetic screening plus RCT   | 25.43                                   | 4.92 | 30.35 | 98,959                            | 1,165 | 83,110  |

c. DSA adjustment: RCT case yield/index = 6.1

|   | FH cases identified per 10,000 screened |       |       | Screening costs per diagnosis (£) |       |         |
|---|---|-------|-------|-----------------------------------|-------|---------|
|   | US                                      | RCT   | total | US                                | RCT   | total   |
| No screening                                      | 0                                       | 0     | 0     | n/a                               | n/a   | n/a     |
| Cholesterol-only screening                        | 22.38                                   | 0     | 22.38 | 11,788                            | n/a   | 11,788  |
| Sequential genetic-cholesterol screening          | 11.44                                   | 0     | 11.44 | 217,036                           | n/a   | 217,036 |
| Sequential cholesterol-genetic screening          | 24.41                                   | 0     | 24.41 | 13,785                            | n/a   | 13,785  |
| Parallel cholesterol-genetic screening            | 25.43                                   | 0     | 25.43 | 98,959                            | n/a   | 98,959  |
| Sequential genetic-cholesterol screening plus RCT | 11.44                                   | 60.00 | 71.44 | 217,036                           | 1,098 | 35,684  |
| Sequential cholesterol-genetic screening plus RCT | 24.41                                   | 46.91 | 71.32 | 13,785                            | 1,098 | 5,441   |
| Parallel cholesterol-genetic screening plus RCT   | 25.43                                   | 60.00 | 85.43 | 98,959                            | 1,098 | 30,227  |

d. DSA adjustment: RCT case yield/index = 8.6; probability relative M+ = 0.31

|   | FH cases identified per 10,000 screened in US |       |        | Screening costs per diagnosis (£) |       |         |
|---|---|-------|--------|-----------------------------------|-------|---------|
|   | US  | RCT   | total  | US                                | RCT   | total   |
| No screening                                      | 0   | 0     | 0      | n/a                               | n/a   | n/a     |
| Cholesterol-only screening                        | 22.38   | 0     | 22.38  | 11,788                            | n/a   | 11,788  |
| Sequential genetic-cholesterol screening          | 11.44   | 0     | 11.44  | 217,036                           | n/a   | 217,036 |
| Sequential cholesterol-genetic screening          | 24.41   | 0     | 24.41  | 13,785                            | n/a   | 13,785  |
| Parallel cholesterol-genetic screening            | 25.43   | 0     | 25.43  | 98,959                            | n/a   | 98,959  |
| Sequential genetic-cholesterol screening plus RCT | 11.44   | 84.59 | 96.03  | 217,036                           | 1,414 | 27,106  |
| Sequential cholesterol-genetic screening plus RCT | 24.41   | 66.13 | 90.54  | 13,785                            | 1,414 | 4,749   |
| Parallel cholesterol-genetic screening plus RCT   | 25.43   | 84.59 | 110.02 | 98,959                            | 1,414 | 23,959  |

e. DSA adjustment: RCT case yield/index = 8.6; probability relative M+ = 0.21

|   | FH cases identified per 10,000 screened in US |       |        | Screening costs per diagnosis (£) |       |         |
|---|---|-------|--------|-----------------------------------|-------|---------|
|   | US  | RCT   | total  | US                                | RCT   | total   |
| No screening                                      | 0   | 0     | 0      | n/a                               | n/a   | n/a     |
| Cholesterol-only screening                        | 22.38   | 0     | 22.38  | 11,788                            | n/a   | 11,788  |
| Sequential genetic-cholesterol screening          | 11.44   | 0     | 11.44  | 217,036                           | n/a   | 217,036 |
| Sequential cholesterol-genetic screening          | 24.41   | 0     | 24.41  | 13,785                            | n/a   | 13,785  |
| Parallel cholesterol-genetic screening            | 25.43   | 0     | 25.43  | 98,959                            | n/a   | 98,959  |
| Sequential genetic-cholesterol screening plus RCT | 11.44   | 84.59 | 96.03  | 217,036                           | 2,049 | 27,666  |
| Sequential cholesterol-genetic screening plus RCT | 24.41   | 66.13 | 90.54  | 13,785                            | 2,049 | 5,213   |
| Parallel cholesterol-genetic screening plus RCT   | 25.43   | 84.59 | 110.02 | 98,959                            | 2,049 | 24,448  |

f. DSA adjustment: Cholesterol test true positive rate for sequential cholesterol-genetic US strategy = 62.5%

\*NB. Cholesterol-only cholesterol threshold not adjusted in DSA as not clear that performance would be acceptable even using thresholds of highest described post-test probability (=0.53) in recent analysis, and not of concern as strategy dominated even at base case performance for this strategy (see Supplementary File 7, Table r)

|   | FH cases identified per 10,000 screened in US |       |       | Screening costs per diagnosis (£) |       |         |
|---|---|-------|-------|-----------------------------------|-------|---------|
|   | US  | RCT   | total | US                                | RCT   | total   |
| No screening                                      | 0   | 0     | 0     | n/a                               | n/a   | n/a     |
| Cholesterol-only screening*                       | 22.38   | 0     | 22.38 | 11,788                            | n/a   | 11,788  |
| Sequential genetic-cholesterol screening          | 11.44   | 0     | 11.44 | 217,036                           | n/a   | 217,036 |
| Sequential cholesterol-genetic screening          | 15.89   | 0     | 15.89 | 21,023                            | n/a   | 21,023  |
| Parallel cholesterol-genetic screening            | 25.43   | 0     | 25.43 | 98,959                            | n/a   | 98,959  |
| Sequential genetic-cholesterol screening plus RCT | 11.44   | 19.67 | 31.11 | 217,036                           | 1,110 | 80,519  |
| Sequential cholesterol-genetic screening plus RCT | 15.89   | 10.01 | 25.90 | 21,023                            | 1,110 | 13,327  |
| Parallel cholesterol-genetic screening plus RCT   | 25.43   | 19.67 | 45.10 | 98,959                            | 1,110 | 56,279  |



g. DSA adjustment: Universal screening appointment duration = 40 minutes

|   | FH cases identified per 10,000 screened in US |       |       | Screening costs per diagnosis (£) |       |         |
|---|---|-------|-------|-----------------------------------|-------|---------|
|   | US  | RCT   | total | US                                | RCT   | total   |
| No screening                                      | 0   | 0     | 0     | n/a                               | n/a   | n/a     |
| Cholesterol-only screening                        | 22.38   | 0     | 22.38 | 14,127                            | n/a   | 14,127  |
| Sequential genetic-cholesterol screening          | 11.44   | 0     | 11.44 | 221,611                           | n/a   | 221,611 |
| Sequential cholesterol-genetic screening          | 24.41   | 0     | 24.41 | 15,930                            | n/a   | 15,930  |
| Parallel cholesterol-genetic screening            | 25.43   | 0     | 25.43 | 101,018                           | n/a   | 101,018 |
| Sequential genetic-cholesterol screening plus RCT | 11.44   | 19.67 | 31.11 | 221,611                           | 1,110 | 82,201  |
| Sequential cholesterol-genetic screening plus RCT | 24.41   | 15.38 | 39.79 | 15,930                            | 1,110 | 10,202  |
| Parallel cholesterol-genetic screening plus RCT   | 25.43   | 19.67 | 45.10 | 101,018                           | 1,110 | 57,439  |

### Supplementary File 7: Deterministic sensitivity analysis incremental cost effectiveness ratio comparisons

QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; RCT: reverse cascade testing; SD: strongly dominated

a. DSA adjustment: Costs for treatment of false positives included

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 992.2   | 225,834   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,009.5 | 601,028   | 21,733              | 21,733                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,011.0 | 640,147   | 21,999              | 24,926                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,027.7 | 672,309   | 12,562              | 1,925                   | 12,562                      |
| Sequential genetic-cholesterol screening          | 1,001.0 | 2,745,746 | 285,445             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,022.4 | 2,786,887 | 84,799              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,011.8 | 2,823,202 | 132,399             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,033.2 | 2,864,342 | 64,368              | 402,285                 | 402,285                     |

b. DSA adjustment: All M+ defined as FH+

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 1,215.4 | 284,695   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,231.7 | 622,603   | 20,733              | 20,733                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,233.2 | 702,077   | 23,475              | 53,638                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,256.0 | 743,929   | 11,327              | 1,839                   | 11,327                      |
| Sequential genetic-cholesterol screening          | 1,225.7 | 2,814,688 | 247,203             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,254.8 | 2,868,223 | 65,649              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,235.8 | 2,893,902 | 127,771             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,265.0 | 2,947,437 | 53,749              | 244,955                 | 244,955                     |

c. DSA adjustment: RCT case yield/index = 0.5

|   | QALYs | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|-------|-----------|---------------------|-------------------------|-----------------------------|
|   |       |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 715.2 | 136,036   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 732.5 | 471,131   | 19,410              | 19,410                  | ED                          |
| Sequential cholesterol-genetic screening          | 734.0 | 550,349   | 21,999              | 50,476                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 738.2 | 558,600   | 18,364              | 1,975                   | 18,364                      |
| Sequential genetic-cholesterol screening          | 724.0 | 2,655,948 | 285,445             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 729.4 | 2,666,503 | 178,563             | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 734.8 | 2,733,403 | 132,399             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 740.2 | 2,743,958 | 104,479             | 1,120,252               | 1,120,252                   |

d. DSA adjustment: RCT case yield/index = 6.1

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 1,749.3 | 471,283   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,766.6 | 806,378   | 19,410              | 19,410                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,768.1 | 885,596   | 21,999              | 50,476                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,819.1 | 983,114   | 7,333               | 1,914                   | 7,333                       |
| Sequential genetic-cholesterol screening          | 1,758.1 | 2,991,195 | 285,445             | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,768.9 | 3,068,651 | 132,399             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,823.3 | 3,115,936 | 35,731              | 505,301                 | ED                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,834.1 | 3,193,391 | 32,098              | 7,179                   | 147,247                     |

e. DSA adjustment: RCT case yield/index = 8.6; probability relative M+ = 0.31

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 2,210.9 | 620,947   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 2,228.2 | 956,042   | 19,410              | 19,410                  | ED                          |
| Sequential cholesterol-genetic screening          | 2,229.8 | 1,035,260 | 21,999              | 50,476                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 2,301.6 | 1,193,623 | 6,315               | 2,204                   | 6,315                       |
| Sequential genetic-cholesterol screening          | 2,219.8 | 3,140,859 | 285,445             | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 2,230.6 | 3,218,314 | 132,399             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 2,311.7 | 3,343,430 | 27,027              | 213,885                 | ED                          |
| Parallel cholesterol-genetic screening plus RCT   | 2,322.5 | 3,420,885 | 25,106              | 7,179                   | 106,869                     |

f. DSA adjustment: RCT case yield/index = 8.6; probability relative M+ = 0.21

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 2,210.9 | 620,947   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 2,228.2 | 956,042   | 19,410              | 19,410                  | ED                          |
| Sequential cholesterol-genetic screening          | 2,229.8 | 1,035,260 | 21,999              | 50,476                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 2,301.6 | 1,235,611 | 6,778               | 2,789                   | 6,778                       |
| Sequential genetic-cholesterol screening          | 2,219.8 | 3,140,859 | 285,445             | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 2,230.6 | 3,218,314 | 132,399             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 2,311.7 | 3,397,138 | 27,560              | 215,052                 | ED                          |
| Parallel cholesterol-genetic screening plus RCT   | 2,322.5 | 3,474,593 | 25,588              | 7,179                   | 107,432                     |

g. DSA adjustment: 100% of diagnosed adults treated

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 992.2   | 225,834   | -                   | -                       |                             |
| Cholesterol-only screening                        | 1,012.3 | 565,638   | 16,874              | 16,874                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,014.2 | 645,283   | 19,094              | 43,507                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,033.8 | 679,458   | 10,904              | 1,741                   | 10,904                      |
| Sequential genetic-cholesterol screening          | 1,002.5 | 2,748,154 | 244,946             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,027.6 | 2,791,868 | 72,461              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,015.1 | 2,828,552 | 113,739             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,040.2 | 2,872,267 | 55,136              | 342,833                 | 342,833                     |

h. DSA adjustment: 100% of diagnosed treated from 8 years

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 992.2   | 225,834   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,013.1 | 566,487   | 16,301              | 16,301                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,015.0 | 646,210   | 18,439              | 41,963                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,034.7 | 680,410   | 10,688              | 1,733                   | 10,688                      |
| Sequential genetic-cholesterol screening          | 1,002.9 | 2,748,589 | 236,067             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,028.1 | 2,792,335 | 71,430              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,016.0 | 2,829,518 | 109,638             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,041.2 | 2,873,264 | 54,038              | 339,512                 | 339,512                     |

i. DSA adjustment: 15% discontinue LMT at 10 years

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 992.2   | 225,834   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,007.1 | 558,168   | 22,305              | 22,305                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,008.5 | 637,135   | 25,304              | 58,299                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,023.8 | 668,581   | 14,016              | 2,051                   | 14,016                      |
| Sequential genetic-cholesterol screening          | 999.8   | 2,744,335 | 330,547             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,019.4 | 2,784,559 | 93,954              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,009.1 | 2,820,065 | 153,219             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,028.7 | 2,860,289 | 72,086              | 442,080                 | 442,080                     |

j. DSA adjustment: 50% LDL-C reduction achieved with LMT

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 992.3   | 225,114   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,017.9 | 539,005   | 12,241              | 12,241                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,020.3 | 616,295   | 13,984              | 33,155                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,044.7 | 629,187   | 7,713               | 528                     | 7,713                       |
| Sequential genetic-cholesterol screening          | 1,005.4 | 2,734,183 | 191,342             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,036.6 | 2,750,647 | 56,951              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,021.4 | 2,798,386 | 88,307              | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,052.7 | 2,814,877 | 42,896              | 273,840                 | 273,840                     |

k. DSA adjustment: Estimated off-patent LMT costs applied

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 992.7   | 224,041   | -                   | -                       |                             |
| Cholesterol-only screening                        | 1,009.9 | 519,499   | 17,275              | 17,275                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,011.4 | 595,113   | 19,888              | 48,633                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,028.0 | 598,023   | 10,611              | 175                     | 10,611                      |
| Sequential genetic-cholesterol screening          | 1,001.5 | 2,723,684 | 285,812             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,022.7 | 2,727,407 | 83,553              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,012.2 | 2,776,366 | 131,326             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,033.4 | 2,780,089 | 62,878              | 403,544                 | 403,544                     |

l. DSA adjustment: Discount rate = 1.5%

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 1,554.0 | 455,562   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,602.2 | 808,339   | 7,330               | 7,330                   | ED                          |
| Sequential cholesterol-genetic screening          | 1,606.5 | 889,164   | 8,259               | 18,474                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,637.2 | 920,123   | 5,586               | 1,010                   | 5,586                       |
| Sequential genetic-cholesterol screening          | 1,578.6 | 2,984,516 | 102,760             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,617.9 | 3,024,117 | 40,243              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,608.7 | 3,073,022 | 47,860              | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,647.9 | 3,112,624 | 28,295              | 204,037                 | 204,037                     |

m. DSA adjustment: Discount rate = 5.0%

|   | QALYs | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|-------|-----------|---------------------|-------------------------|-----------------------------|
|   |       |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 765.7 | 145,874   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 774.3 | 469,310   | 37,830              | 37,830                  | ED                          |
| Sequential cholesterol-genetic screening          | 775.0 | 547,467   | 43,057              | 100,557                 | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 786.4 | 579,142   | 20,932              | 2,785                   | 20,932                      |
| Sequential genetic-cholesterol screening          | 770.1 | 2,659,824 | 575,009             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 784.6 | 2,700,340 | 135,026             | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 775.4 | 2,729,992 | 265,977             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 790.0 | 2,770,508 | 108,179             | 615,027                 | 615,027                     |

n. DSA adjustment: CVD risks 90% of base case estimates

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 1,002.1 | 210,445   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,018.1 | 547,894   | 20,986              | 20,986                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,019.6 | 627,325   | 23,766              | 54,339                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,035.1 | 661,757   | 13,644              | 2,216                   | 13,644                      |
| Sequential genetic-cholesterol screening          | 1,010.3 | 2,731,561 | 306,613             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,030.2 | 2,775,604 | 91,297              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,020.3 | 2,810,487 | 142,295             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,040.2 | 2,854,531 | 69,314              | 432,665                 | 432,665                     |



o. DSA adjustment: CVD risks 80% of base case estimates

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 1,012.4 | 192,560   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,027.1 | 532,932   | 23,052              | 23,052                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,028.5 | 612,629   | 26,079              | 59,374                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,042.6 | 650,193   | 15,149              | 2,664                   | 15,149                      |
| Sequential genetic-cholesterol screening          | 1,019.9 | 2,715,171 | 334,100             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,037.9 | 2,763,220 | 100,461             | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,029.1 | 2,795,924 | 155,158             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,047.2 | 2,843,974 | 76,153              | 476,121                 | 476,121                     |

p. DSA adjustment: Undiagnosed cases treated at background rate

|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 1,009.9 | 263,749   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1,023.2 | 585,152   | 24,159              | 24,159                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,024.4 | 663,125   | 27,518              | 64,471                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1,036.3 | 683,821   | 15,940              | 1,748                   | 15,940                      |
| Sequential genetic-cholesterol screening          | 1,016.7 | 2,776,660 | 369,384             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,031.9 | 2,803,133 | 115,699             | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1,025.0 | 2,845,558 | 170,780             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,040.2 | 2,872,031 | 86,187              | 559,669                 | 559,669                     |

q. DSA adjustment: Cholesterol test true positive rate for sequential cholesterol-genetic US strategy = 62.5%

\*NB. Cholesterol-only cholesterol threshold not adjusted in DSA as not clear that performance would be acceptable even using thresholds of highest described post-test probability (=0.53) in recent analysis, and not of concern as strategy dominated even at base case performance for this strategy

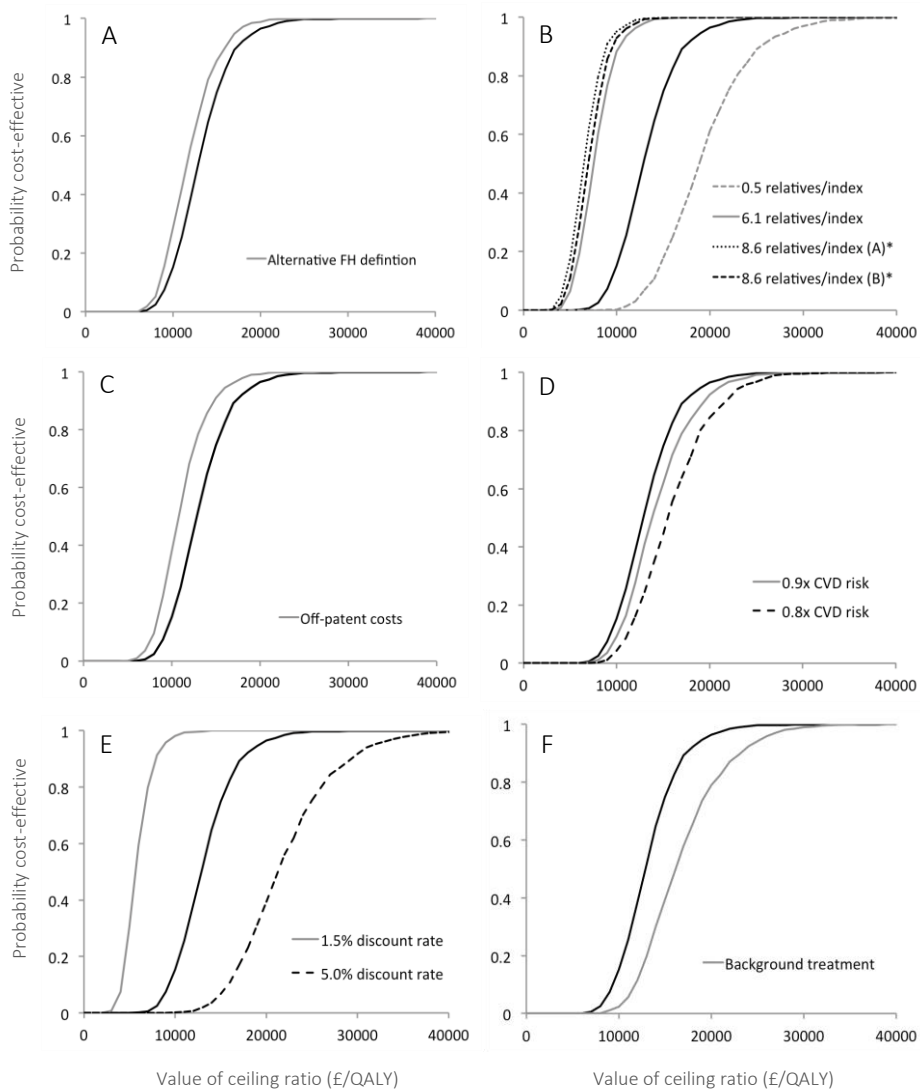
|   | QALYs   | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|---------|-----------|---------------------|-------------------------|-----------------------------|
|   |         |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 992.2   | 225,834   | -                   | -                       | -                           |
| Cholesterol-only screening*                       | 1,009.5 | 560,929   | 19,410              | 19,410                  | ED                          |
| Sequential cholesterol-genetic screening          | 1,004.5 | 610,592   | 31,380              | SD                      | SD                          |
| Sequential cholesterol-genetic screening plus RCT | 1,015.3 | 631,531   | 17,533              | 12,016                  | 17,533                      |
| Sequential genetic-cholesterol screening          | 1,001.0 | 2,745,746 | 285,445             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1,022.4 | 2,786,887 | 84,977              | 305,210                 | SD                          |
| Parallel cholesterol-genetic screening            | 1,011.8 | 2,823,202 | 132,399             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1,033.2 | 2,864,342 | 64,499              | 7,179                   | 125,076                     |

r. DSA adjustment: Universal screening appointment duration = 40 minutes

|   | QALYs  | Costs (£) | ICER (£/QALY)       |                         |                             |
|---|--------|-----------|---------------------|-------------------------|-----------------------------|
|   |        |           | versus no screening | versus next lowest cost | versus relevant alternative |
| No screening                                      | 992.2  | 225,834   | -                   | -                       | -                           |
| Cholesterol-only screening                        | 1009.5 | 613,277   | 22,443              | 22,443                  | ED                          |
| Sequential cholesterol-genetic screening          | 1011.0 | 692,495   | 24,779              | 50,476                  | ED                          |
| Sequential cholesterol-genetic screening plus RCT | 1027.7 | 724,657   | 14,035              | 1,925                   | 14,035                      |
| Sequential genetic-cholesterol screening          | 1001.0 | 2,798,094 | 291,375             | SD                      | SD                          |
| Sequential genetic-cholesterol screening plus RCT | 1022.4 | 2,839,235 | 86,533              | SD                      | SD                          |
| Parallel cholesterol-genetic screening            | 1011.8 | 2,875,550 | 135,067             | SD                      | SD                          |
| Parallel cholesterol-genetic screening plus RCT   | 1033.2 | 2,916,690 | 65,645              | 402,285                 | 402,285                     |

### Supplementary File 8: Cost-effectiveness acceptability curves

Probability of cost-effectiveness of sequential cholesterol-genetic plus reverse cascade testing (RCT) versus no screening is displayed for the base case (black line) and deterministic sensitivity analysis scenarios that modelled a definition of familial hypercholesterolaemia that included all mutation-positive individuals (A), different RCT yields (B), off-patent drug costs (C), lower cardiovascular (CVD) risk estimates (D), alternative discount rates (E) and background lipid modifying treatment (F); \*A: 6.1 relatives identified with probability = 0.4; 2.5 with probability = 0.2; B: 6.1 identified with probability = 0.4; 2.5 with probability = 0.1



## Supplementary File 9: Additional references

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