Familial hypercholesterolaemia (standing committee update)

Consultation on draft addendum - Stakeholder comments table

12 May 2017 to 09 June 2017

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
AMGEN	Short	4	10 - 12	Having a threshold of 9.3mmol/L seems extremely cautious. In the draft guideline we note that the NICE committee itself suggested that: - the threshold was high and would likely miss a large number of cases - given the highly cost-effective nature of primary care case finding in populations with total cholesterol above 9.3mmol/L, it is likely that conducting case finding in lower thresholds would still represent a cost-effective use of NHS resources. We would therefore challenge this high threshold level as not being aligned to a patient-centric approach. FH patients deserve to be identified and lack of specificity of a lower threshold should not be reason to deny them screening and thus a chance of diagnosis. In the context of Recommendation 1.1.5, this threshold is also somewhat counter-intuitive, as SB possible/definite or DLCN of >5 have much lower thresholds (e.g. SB is 7.5mmol/l). We would strongly urge that the threshold should be 7.5mmol/L to avoid inaccurate identification of FH patients. Patients above this threshold could then be considered for referral if they meet the appropriate criteria, thereby avoiding inappropriate referrals.	Thank you for your comment. Following consultation the committee reconsidered the evidence from the economic model along with evidence on the distribution of total cholesterol in different age/sex groups within the general population and decided to recommend primary care case finding in people aged 16-29 with a TC>7.5 mmol/l and in people aged 30+ with a TC>9.0 mmol/l. It was felt that these recommendations struck the best balance between the strength of the evidence, equitable representation among different age groups and the practicalities of implementation. A full discussion of these deliberations can be found in the evidence review document. The use of FH screening tools was not within the scope of this guideline update, and therefore it was not possible to make recommendations on this topic. However, should robust evidence become available, then this could be included within future updates of the guideline.

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				We are also aware of independently developed primary care screening/identification tools and would encourage NICE to consider the incorporation of these tools into the current guideline to allow for efficient identification of FH patients, which would in turn allow for appropriate cascade screening of family members.	
AMGEN	Short	4	4 - 5	We are concerned that '*Think about*' is a rather nebulous statement and would suggest some stronger wording here such as: 'The following are strongly predictive of FH and should be considered as a possible diagnosis of FH in adults:'	Thank you for your comment. The Committee has considered the wording around this awareness making recommendation, and agreed that it is appropriate to make it more active by using the phrase "suspect FH as a possible diagnosis …"
AMGEN	Short	7	21 - 23	It is highly unlikely that there will be an outcomes trial in FH patients so an evidence-based target will never be available. There is though overwhelming evidence from statins, ezetimibe, and now with the evolocumab GLAGOV and FOURIER trials, supporting a 'lower is better' approach for LDL-C reduction in non-FH cohorts. We firmly believe that an aggressive absolute target to aim for is most logical in FH patients, as a proportional 50% reduction will have varying absolute benefit depending on starting LDL-C levels. Patients with very high starting LDL-C may therefore miss out on having fully optimised treatment and thus remain at high risk of preventable cardiovascular events whilst still meeting the 50% reduction target. Given available evidence, we believe that an absolute target should align with the ESC/EAS guidance (of	Thank you for your comment. The Committee noted that the recommendation is to aim for "at least" a 50% reduction in LDL-C concentration from baseline (with initial statin treatment), and that this is a minimum and does not preclude clinicians from setting absolute targets (for larger reductions) if these are felt to be clinically appropriate.

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				1.8/2.6mmol/L) which will result in better care and more optimised therapy for all FH patients.	
AMGEN	Short	8	1	We firmly believe that full details of TA393 and TA394 need to be added here indicating PCSK9 inhibitors as NICE approved treatment options for FH patients. This is a particularly imperative for FH patients who are unable to tolerate statins as currently there are no other treatment options that can achieve desired LDL-C reductions, and thus CV events are almost inevitable in these patients. In support of this argument, although the full addendum states: - …*a decision was made only to address the efficacy of statin vs placebo* (p51) - *Evidence on Ezetimibe is not included in this review as a TA (TA385) was recently published (February 2016) and incorporated into CG71. Evidence on Alirocumab (TA393) and Evolocumab (TA394) is also not included in this review as Technology Appraisals were published in June 2016* (p82) we noted that other pharmacological treatment options beyond statins (i.e. ezetimibe, bile acid sequestrants, fibrates and nicotinic acid) are referred to in the guideline. This seems at odds with the statement in the full addendum that treatments including bile acid sequestrants, fibrates and nicotinic acid are now infrequently used, as they have been superseded by	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.

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				newer pharmacological treatments such as ezetimibe, alirocumab and evolocumab (p51). We therefore strongly believe PCSK9 inhibitors must also be included as an approved treatment option to ensure this guideline is up-to-date and relevant. We would also refer NICE to their manual for developing NICE guidelines: https://www.nice.org.uk/process/pmg20/chapter/linking-to-other-guidance which states that when developing a guideline and technology appraisal guidance concurrently, if the technology appraisal recommendations have not been finalised at the time of the guideline consultation, the guideline consultation draft should cross refer to the appraisal consultation document or final appraisal determination and that in general, recommendations from technology appraisal guidance are incorporated verbatim into the guideline that is being developed. Please note that this section should be reviewed in general and PCSK9 inhibitor guidance included throughout as appropriate in line with NICE TA393/TA394 (see below for examples)	
AMGEN	Short	9	3 - 7	Please refer to PCSK9 inhibitors as appropriate (see above)	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.

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AMGEN	Short	9	16 - 19	Please refer to PCSK9 inhibitors as appropriate (see above)	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.
AMGEN	Short	11	14 - 17	Please refer to PCSK9 inhibitors as appropriate (see above)	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.
AMGEN	Short	15	5 - 17	As evolocumab has been demonstrated to provide significant LDL-C lowering in the majority of HoFH patients, and is less invasive and cheaper than apheresis, we believe it should be offered as a preferred pharmacological treatment option in appropriate HoFH patients ahead of apheresis. Of note Repatha is the only PCSK9 inhibitor that is licensed to treat HoFH. Given the consistent and intensive LDL-C lowering seen with PCSK9 inhibitors in HeFH patients, they must be offered as a treatment option, in line with TA 393/394, before expensive and invasive apheresis is considered.	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.
AMGEN	Short	36	1 - 6	Please include details of TA393 and TA394	Thanks you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.
Bolton NHS Foundation Trust	Short	7	21 - 23	The advice on treatment targets (to aim for an LDL reduction of at least 50%) ignores the	Thank you for your comment. The guideline has now been amended to include cross-references to

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				recommendations in NICE TA 393/394, to add a PCSK9 inhibitor if the LDL cholesterol remains above 5 mmol/L in the absence of coronary heart disease (or 3.5 mmol/L in its presence), despite statin treatment.	the NICE technology appraisals on evolocumab and alirocumab. However, the committee agreed that the existence of these technology appraisals was not sufficient reason by itself for changes to be made to the treatment recommendations in this guideline.
Bolton NHS Foundation Trust	Short	7	16	This section ignores advice on the use of PCSK9 inhibitors (NICE TA393 and 394)	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.
Bolton NHS Foundation Trust	Short	9	16	Nicotinic acid is no longer licenced for use in the UK, following the findings of the HPS3-REVEAL trial.	Thank you for your comment. Whilst the scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy, references to nicotinic acid have been removed from the guideline due to it no longer being licensed.
Bolton NHS Foundation Trust	Short	32	General	The list of amended and deleted recommendations indicates that the diagnosis of FH is based on the presence or absence of an identifiable mutation/deletion/duplication. I would question whether it is possible to exclude FH by genetic testing, as this would assume that all causative genes and variants have been identified. While this may be possible in due course, I note the 100,000 Genome Project continues to accept patients with a clinical diagnosis of FH and relevant family history but without an identified mutation.	Thank you for your comment. The committee agreed that there may be a small group of people without a genetic diagnosis of FH in whom clinical suspicion remains sufficiently high that a clinical diagnosis of FH is nonetheless maintained. The view of the committee was that these people were likely to be treated in a similar way to those with a genetic diagnosis of FH, in particular because reducing cholesterol in these people would be equally important, whether or not a genetic diagnosis of FH is made.

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				The underlying assumption that those patients with "clinical FH" but without an identified mutation do not in fact have FH, leave open the question as to how these patients should be treated. This includes those patients found to have polygenic hypercholesterolaemia; should they be managed clinically in the same way as those with monogenic FH?	
Bolton NHS Foundation Trust	Short	33	General	Should phenotypic cascade screening remain an option for those families with a clinical diagnosis of FH but no identified mutation (e.g. those with a strong family history, eligible for referral to the 100,000 Genomes Project), or for those families where the proband declines genetic testing?	Thank you for your comment. The committee agreed that in the absence of any evidence that such testing would be cost-effective, it is only appropriate to undertake cascade testing based on people with a genetic diagnosis of FH.
British Heart Foundation	Addendum	General	General	We are concerned that the committee did not have representation from a lipidologist, who are the experts in this field.	Thank you for your comment. We agree that lipidologist provide an important perspective on this issue, and could have been part of the committee composition. However, we are confident that the composition of the committee was sufficiently broad that all relevant viewpoints will have been represented in the discussion. Additionally, the consultation process provides another opportunity for groups whose views are not directly represented on the committee to input them to the process.
British Heart Foundation	Addendum	General	General	The need for a systematic central database doesn't appear to have been covered.	Thank you for your comment. Recommendations for the setting up of a specific central database or registry would be outside the scope of this guideline update, but the committee did recognise the value such a database would provide.

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British Heart Foundation	Short	General	General	Comments are asked for on new recommendations and deleted recommendations only. Nevertheless, we noted that there is no reference to the importance of up-to-date data protection and Caldicott 2 compliance.	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
British Heart Foundation	Short	General	General	There is no mention of the importance of blood pressure management at all.	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
British Heart Foundation	Short	General	General	Life style interventions: there is no distinction between adult and children's diet. Previously, lipid management was separated by age – but here the language is – "advise people", or "People with FH should be" – this should be addressed. Clearly the growing child and their parents will need tailored advice by age. Should specialist dietary advice be offered?	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
British Heart Foundation	Short	General	General	The advice and guidelines on physical activity and alcohol have been revised since 2007. Physical Activity Guidelines 2011 Alcohol Guidelines 2016	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
British Heart Foundation	Short	General	General	The BHF note that there is no mention of importance of data audit and IT infrastructure. This is a key enabler to allow cascade testing to proceed. This includes consideration of software, licensing and staffing.	Thank you for your comment. Whilst this guideline makes recommendations that case finding and cascade testing should be carried out, it is outside of its scope to make specific recommendations about how these should be carried out in practice. NICE is working with external partners to best

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					consider ways to support implementation of the guidance.
British Heart Foundation	Short	General	1.2.5	Do you mean “offer a DNA test by the age of 10 years”, or “at the age of 10 years”. As currently worded the guideline suggests testing in infancy or the neonatal could be indicated.	Thank you for your comment; it is the first of your two options that is the correct interpretation. The Committee agreed that it is appropriate that DNA testing for children of people with FH be offered at the earliest opportunity, and the recommendation has been amended to make this clear (and this could include testing in infants or neonates). A reference to 10 years has also been retained to ensure people who initially decline testing are offered additional opportunities before people would become eligible for treatment.
British Heart Foundation	Short	4	10	The cut off point for primary care searches – Total Cholesterol greater than 9.3. This seems quite high although it’s acknowledged that further research is needed. There is potential to miss younger people with FH at this cut off point and wonder why LDLc measurement isn’t included in this recommendation.	Thank you for your comment. Following consultation the committee reconsidered the evidence from the economic model along with evidence on the distribution of total cholesterol in different age/sex groups within the general population and decided to recommend primary care case finding in people aged 16-29 with a TC>7.5 mmol/l and in people aged 30+ with a TC>9.0 mmol/l. It was felt that these recommendations struck the best balance between the strength of the evidence, equitable representation among different age groups and the practicalities of implementation. A full discussion of these deliberations can be found in the evidence review document.

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British Heart Foundation	Short	10	1.2.2	In order to facilitate search of primary care electronic patient records, there are currently available tools to do this, these should be referenced.	Thank you for your comment. Whilst this guideline makes recommendations that case finding and cascade testing should be carried out, it is outside of its scope to make specific recommendations about how these should be carried out in practice.
British Heart Foundation	Short	10	1.2.3	The BHF agree that people with a family history of premature coronary heart disease should be offered cholesterol testing. Should this recommendation also include other cardiovascular disease – stroke, peripheral vascular disease? The implication in section 1.2.2, is this is a job for primary care. However, there is an opportunity to suggest further investigation in secondary care – particularly following an admission with acute coronary syndrome, or new onset angina – at an early age as part of the routine pathway of care.	Thank you for your comment. This issue was not within the scope of this guideline update and therefore it was not possible to broaden this definition beyond coronary heart disease.
British Heart Foundation	Short	26	General	Is the population estimate right at 1 in 500?	Thank you for your comment – this has been updated to reflect the uncertainty in this estimate.
British Heart Foundation	Short	26	18	The prevalence is stated as 1:500 in the context section; however further evidence shows this is more likely to be nearer to 1:250. This is acknowledged later on in recommendations for further research (Page 27, line 21) but hasn't been made clear in the context.	Thank you for your comment – this has been updated to reflect the uncertainty in this estimate.
British Heart Foundation	Short	33	1.2.8	This statement has been deleted however the new recommendation (1.21) doesn't fully cover the need for a systematic countrywide comprehensive follow up system.	Thank you for your comment. Whilst this guideline makes recommendations that case finding and cascade testing should be carried out, it is outside of its scope to make specific recommendations about how these should be carried out in practice.
European Atherosclerosis Society (EAS)	Addendum	general	general	PCSK9s are not mentioned – should be addressed	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab.

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European Atherosclerosis Society (EAS)	Addendum	general	general	The only mention about therapy is statins to reduce LDL by 50%. But only half of the subjects on a maximum tolerated dose of a statin will achieve this goal unless combination therapy is instituted, a place for PCSK9 inhibition should also be considered	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab.
European Atherosclerosis Society (EAS)	Addendum	general	general	Ezetimibe guidance unclear. When it is added to statins i.e., what % reduction or LDL target are we aiming for?	Thank you for your comment. The recommendations on ezetimibe in this guideline come from a NICE technology appraisal (TA385) and updating these recommendations was not within the scope of this guideline update. Therefore, it is not possible to make any changes to these recommendations as part of this update.
European Atherosclerosis Society (EAS)	Addendum	general	general	All FH patients need to be referred to a specialist service and not managed initially in primary care.	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
European Atherosclerosis Society (EAS)	Addendum	10	2	*Systematically search primary care records for people with a total cholesterol concentration greater than 9.3 mmol/l, as these are the people who are at highest risk of FH.* [2017] This is way too high, a LDL >4.9 and Total cholesterol >7.5	Thank you for your comment. Following consultation the committee reconsidered the evidence from the economic model along with evidence on the distribution of total cholesterol in different age/sex groups within the general population and decided to recommend primary care case finding in people aged 16-29 with a TC>7.5 mmol/l and in people aged 30+ with a TC>9.0 mmol/l. It was felt that these recommendations struck the best balance between the strength of the evidence, equitable representation among different age groups and the practicalities of implementation. A full discussion of

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					these deliberations can be found in the evidence review document.
European Atherosclerosis Society (EAS)	Addendum	10	9	Reduction of LDL by 50% is mentioned. No treatment goal value is given (does not agree with current European Guidelines by European Society of Cardiology & EAS) see http://eurheartj.oxfordjournals.org/content/ehj/early/2016/08/26/eurheartj.ehw272.full.pdf	Thank you for your comment. The Committee noted that the recommendation is to aim for "at least" a 50% reduction in LDL-C concentration from baseline, and that this is a minimum does not preclude clinicians from setting absolute targets (for larger reductions) if these are felt to be clinically appropriate.
HEART UK- The Cholesterol Charity	Addendum	General	General	The HEART UK Patient and Supporter Committee welcome all attempt to help identify more cases of FH and offer support and treatment. We welcome greater emphasis on DNA testing but remain concerned at the use of Simon Broome criteria that may miss too many patients with FH, especially without a full lipid profile. A measurement of total cholesterol will potentially exclude many patients and the gender and age difference needs further consideration, especially that of women of menopausal age. We are seriously concerned at the apparent omission of the latest treatments available for FH and would urge the explicit inclusion of PCSK9s, which have are highly effective at lowering LDL-C. We would urge support for a national FH registry, similar to that supported by HEART UK as an effective means of identifying families and individuals to cascade test.	Thank you for your comment. The Committee agreed that if only the definite criteria on the Simon Broome were to be used, this would result in a large number of people potentially being missed. However, the evidence identified for this update suggests that using both the possible and definite categories on the Simon Broome has a sensitivity for detecting FH similar to that of the DLCN, and therefore it was agreed to be appropriate to recommend its use. With regard to PCSK9s, the guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab. The committee agreed that a national FH registry would provide useful data; however, it was not in the scope of this update to provide recommendations on this topic.

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				Below are a few responses received from the consultation that give true and accurate reflections of living with FH and the potential impact of these NICE Guidelines.	
HEART UK- The Cholesterol Charity	Addendum	General	General	One other thing I wanted to mention regarding the guidelines which is quite an important one for me is the availability of new drugs. The new wave of super PCSK9 etc are not generally available if you are tolerating statins. I understand the cost of these new drugs is going to be high until patents expire etc but it is very frustrating knowing that my son and I could reduce our cholesterol dramatically without the possible side effects of statin use. I worry all the time if I'm doing right by my 10 yr old son in having him take statins at such a young age, but I don't have any alternative.	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.
HEART UK- The Cholesterol Charity	Addendum	General	General	GPs are best placed to detect FH within the healthy population but the likelihood of it happening is low. There is a great need for education about FH in Primary Care. I find it very annoying when I am just bombarded with lifestyle advice when I have spent all my adult life adhering to it. From my personal experience even though GPs knew of my elevated TC levels of 7-8mmol/L for years, they used the normal population risk calculator and as I was asymptomatic and a non-smoker, it always came out low. When a family member was genetically confirmed FH, I took the cascade letter to the GP and asked to be referred. They did not feel it was necessary and I had to provide evidence from NICE guidelines and Simon	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update. Following consultation the committee reconsidered the evidence from the economic model along with evidence on the distribution of total cholesterol in different age/sex groups within the general population and decided to recommend primary care case finding in people aged 16-29 with a TC>7.5 mmol/l and in people aged 30+ with a TC>9.0 mmol/l. It was felt that these

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				Brooke criteria before they agreed. They then referred me to a Genetics clinic and so an appointment with Lipid Clinic took 8 months. I am not confident that database screening in Primary Care will be effective. TC level of above 9.3mmol/L is too high and will not detect many people until they are much older and so reducing risk of early CVD is not actioned. I certainly would not have been identified. Raised TC levels are not investigated in Primary Care, they are just routinely placed on statins so level then reduces. Screening would have to be based on highest TC reading before treatment started and should also include LDL. When is the question about an early family history of CVD raised with patients? I was never asked as I was asymptomatic. It is not listed on my significant history with Reed Coding and so would not be identified. When is a cholesterol test first offered to patients? I don't think it is routinely tested until patients are offered 50 year old health checks unless they have early symptoms of CVD? Some people may be tested earlier through an Occupational Health Assessment and are then are advised to consult with their GP. The * criteria did help to identify myself as possible FH as there was no evident clinical criteria except borderline TC levels. This then enabled Lipid Clinic to authorise genetic testing which gave me a confirmed	recommendations struck the best balance between the strength of the evidence, equitable representation among different age groups and the practicalities of implementation. A full discussion of these deliberations can be found in the evidence review document. The guideline has now been amended to include cross-references to the NICE technology appraisals on PCSK9 inhibitors (evolocumab and alirocumab), which give guidance on when the use of these drugs is appropriate. The committee agreed that it is important to consider the potential long-term harms of statin therapy in children, and made a specific research recommendation to study the long-term effects of statin use in children.

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				diagnosis. This then activated the cascade process for my twin daughters to be tested and they are now genetically FH confirmed as well. Is there something more that should be considered when contacting family members for testing? This should be actioned as soon as possible to promote reassurance and compliance. I contacted all my relatives as requested and to gain their verbal consent for an information letter to be sent to them from a FH specialist nurse to continue cascade testing. Due to backlog of work, they are still waiting after 8 months! My big issue about treatment is the prescription charges that are due for lifelong treatment that is due to a genetic cause and not lifestyle issues. This is so unjust and unfair as other conditions qualify for exemption of prescription costs e.g. Diabetes, thyroid treatments, Addisons disease Will they be including the usage of the newer NICE approved PCSK9 inhibitors? I have just starting using them as I have been intolerant to high doses of statins and ezetimibe. The reduction in LDL levels has been very fast and well tolerated. The use of Co Q10 enzymes with statins has not been mentioned when there is growing evidence base for its helpful action. I did have more reservations about agreeing for my children to start on statins. There is lack of evidence on	

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				adverse effects in longterm statin use. They are the trial generation where statins are started early in life as a preventative measure. I feel from an ethical point of view there should be longitudinal studies conducted to monitor their progress. How else can we be sure we are doing no harm? Yes I believe the particular gender risks should be highlighted as males are more likely to experience clinical signs at an earlier age than females. I think the difference in myocardial infarction symptoms in women should also be explained as part of the education process as age advances. My GPs did not consider alternatives to oral contraceptives due to a diagnosis of FH for myself or for my daughters. Secondary care did explain and emphasise the importance of preventing unplanned pregnancies when taking statins and advised stopping statins at least 3 months before planning for a baby. My personal reflections of FH and use of guidelines The guidelines were essential in my case in order to educate my GP what course of action was required. The cost of education within Primary Care has not been mentioned or acknowledged. This is essential if the proposed plans for screening are to become a reality. I believe all suspected cases of FH should be referred to secondary care in order to instigate management and to implement the guidelines. Primary Care tends to	

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				treat all cases of hypercholesterolaemia the same due to lack of education. When I was eventually seen at Lipid Clinic in Bristol the specialist care was excellent and the guidelines were fully implemented. The first appointment included a medical consultation, ECG baseline and dietary review with a Dietician. Genetics tests were arranged and sub clinical CVD tests were booked, CT Calcium score and Carotid artery ultrasound due to family history. There is insufficient capacity at the clinic though and my review appointments are often squeezed in. My relatives are still waiting for the cascade letter and advice about requesting blood tests from their own GPs. My daughters were seen at a joint Lipid/Endocrinology Clinic at Bristol Children's Hospital. At age 17 years they are now being transitioned to adult Lipid Clinic. This is an area Heart UK could be involved in, producing teen related media information to help prepare them for this. The most shocking aspect for my daughter was the thought of having to remove her top for the ECG electrode placements! They were keen to see a Dietitian as this was not available at Paediatric clinic and making healthy food choices in the young persons fast food world, is very challenging. The use of a National Database is really useful as it will help to co-ordinate care and annual reviews when they move around the country to attend university. The issue of free prescriptions for their treatment is also another	

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				area of concern due to financial difficulties and will help compliance.	
HEART UK- The Cholesterol Charity	Addendum	General	General	I have been very lucky as a sufferer with FH. When I was diagnosed with FH following a heart attack and triple bypass way back in the 1980's, I was under a proactive consultant who referred me towards the LDL Apheresis route. I was not responding to the drugs available at that time and a trial was being set up in Llandough Hospital, Penarth in 1991. I received this treatment for over 26 years until a trial for PCSK9 was undertaken last year at Llandough. I responded well to this and as NICE approved the drug for use in June 2016, I have been on these injections since October 2016. During the 26 years of apheresis, I have had five stents and another bypass and aortic valve replacement and in that time I have not been aware of any other patient in my Health region being recommended for Apheresis, nor being involved in a drugs trial for PCSK9. All through my years of dealing with FH and my heart disease I feel fortunate that I have been under the care of very proactive specialists in Wales for my FH. I cannot say the same for my local area as there does not seem to be any screening for FH. During my spells in hospital locally with my heart problems, no patient, nurse and many doctors have ever heard of Apheresis.	The guideline has now been amended to include cross-references to the NICE technology appraisals on PCSK9 inhibitors (evolocumab and alirocumab), which give guidance on when the use of these drugs is appropriate. Whilst this guideline makes recommendations that case finding and cascade testing should be carried out, it is outside of its scope to make specific recommendations about how these should be carried out in practice.

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				My son and his two children have been confirmed with FH following DNA testing and all are being treated on statins. He has been under the care of another lipid specialist based in London. My daughter is in a different position. She also has FH and was originally advised by my original consultant in Wales. Unfortunately that consultant has retired, but did advise my daughter as much as possible. She has little help from her GP, other than prescribing statins and checking her levels when she reminds them. When she was pregnant with her son, she reminded everyone at every check up that his cord blood needed testing at birth and was stressing this even in labour. Needless to say, this was not done and even after querying what the next step is, no one has mentioned DNA testing. The cascade system in Cardiff was the way in which my genetic default was picked up and recognised in my children and two older grandchildren. My first concern with the NICE guidelines is the absence of any mention of PCSK9. This treatment has reduced my total cholesterol from 5.9/6 on statins and apheresis to 2.7. Screening could be undertaken by practice nurses. In Wales they have a dedicated nurse to run a cascade screening programme. Is this something that could be set up in England or if in existence, extended, as there does not seem to be anything like that in this area.	

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				Also, to make this system work, the lipid consultants have to take the situation more seriously. To be told that I was the only person in the Salisbury/Southampton/Bournemouth area that needed this treatment is astonishing. I think that cardioligists also need to be reminded that FH is a major factor in CHD and need to liaise with lipidoligists.	
HEART UK- The Cholesterol Charity	Addendum	General	General	Our comments are as follows: 1. The guidelines state they will systematically search primary care records, but what if you are not in the system how will they know your cholesterol is high. 2. Where a person has been identified as having FH their children should be tested asap. In our case our daughter was 11 when she died so testing at age 10 is still far too late. 3. Where a person has been identified as having FH, they should be given information about passing on the gene. They should also be told about the added risk if their partner also has FH. The partner should then be tested in advance of having children. If both parents are identified as having FH then they are aware of the added risk of one passing on the gene and two having a child with homozygous FH. If both have FH then the child should be tested immediately.	Thank you for your comment. As well as recommendations for case finding based on total cholesterol concentration, the guideline also recommends that total cholesterol be tested in people at higher risk of FH, to reduce the risk of people being missed through not have measurements on the system. The Committee also noted that this primary care record search would be conducted in addition to, rather than instead of, any other systems where people with FH are currently identified, and therefore should lead to a larger proportion of people overall being appropriately identified. The Committee agreed that it is appropriate that DNA testing for children of people with FH be offered at the earliest opportunity, and the recommendation (1.1.15 in the short guideline) has been amended to make this clear. A reference to 10 years has also been retained to ensure people who initially decline testing are offered additional opportunities before people would become eligible for statin treatment.

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					The guideline does contain a section on information needs of people with FH, but this section was not included in the scope for this guideline update, and therefore it is not possible to make any changes to these recommendations.
HEART UK- The Cholesterol Charity	Addendum	General	General	The current documentation suggests that for women, the coronary event has to have occurred at age 65 years or less in an index individual or first degree relative. If this had been lowered to <60 years, it is unlikely I would have been able to be tested for FH. As my Mum was 66 when she died of a heart attack she would have been well outside the new bracket considering it as being 'hereditary'. I feel lowering the age to <60 years could be detrimental for a number of people. I only got diagnosed due to my Mum having a heart attack. I had asked for years to be tested as my Dad had high cholesterol. However, most GPs told me that as I was female and in my twenties at the time, my oestrogen levels would protect me, and I didn't need to worry about such things until I was over fifty. I think lowering the age to 60 would mean less people are likely to be found, not more. I do believe that regardless of there being premature CHD in the family, if the individual concerned is young, fit, and healthy yet has high LDL they should be tested for FH. I finally had my cholesterol levels tested in the	Thank you for your comment. The Committee emphasised that the age categories mentioned here are only advisory, and the individual circumstance of each person need to be considered. There may well be circumstances where it is appropriate to test people for FH who do not meet the specific criteria stated. In particular, the committee noted that it would be entirely appropriate to test for FH solely on the basis of a cholesterol level, even without a known family history, if clinical suspicion were high enough.

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				UK age 33 (when my mother passed away from CHD). I am 5ft6, weigh 7 1/2 stone, exercise 5+ hours a week and follow a healthy diet. On paper I would not be recognised as having FH by your average GP. I know a number of people that refuse to go for an FH test (even though they have been advised to) due to their fear of statins - either the side effects or the general bad press statins receive. Also they have concerns around the diagnosis increasing life insurance/health insurance/mortgage premiums. I certainly think that reducing the age for index individual or first degree female relatives to >60 years for hereditary CHD is inadvisable as many young women may go undiagnosed as their e.g. Mother wasn't regarded as being high risk CHD in their mid-sixties.	
HEART UK- The Cholesterol Charity	Addendum	General	General	1) The document appears to refer to a change in the way FH is diagnosed from looking at blood cholesterol levels to looking at specific genetic tests. That is fine if your specific genetic mutation is one of the ones that is known to science to cause raised cholesterol. However, what if your specific mutation is not currently known to science and is not on "the list"? Does that mean you can have raised cholesterol due to a genetic mutation but not get a diagnosis (and therefore appropriate treatment) because that specific mutation is not on "the list"? It seems there should be a "backstop" suggestion for patients who have a raised blood cholesterol level that can't be explained by lifestyle to be assumed to	Thank you for your comment. The Committee agreed that there may well be circumstances that, even if a DNA test is negative, clinical suspicion of FH will remain sufficiently high that FH treatment would be continued nonetheless. This issue was not one considered in this update of the guideline and therefore it was not possible to make specific recommendations on this point. However, the Committee agreed that by the point someone has a DNA test, they will be in specialist secondary care and therefore appropriate care would be offered to manage a person's cholesterol, even if a genetic diagnosis of FH cannot be made.

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				have FH and to receive the appropriate treatment (perhaps while other genetic investigations are carried out in the background). 2) the document refers to multiple drug treatments such as Statins, Ezitemibe, bile acid sequestrant (resin), nicotinic acid, and fibrates. But there is no mention of PCSK9 inhibitors? We feel this is an oversight. We know that several HoFH patients at our FH clinic are already being treated with PCSK9 inhibitors, and we feel that NICE recommendations should be in synch with existing clinical practice. If the problem is that the final clinical trial results are not yet finalized, then NICE should either put the document update on hold until they can include PCSK9 inhibitor recommendations, or guarantee to revisit this document when the trial results are finalized.	The guideline has now been amended to include cross-references to the NICE technology appraisals on PCSK9 inhibitors (evolocumab and alirocumab), which give guidance on when the use of these drugs is appropriate.
HEART UK- The Cholesterol Charity	Addendum	General	1.1.1	This submission from HEART UK is in two parts. The initial section is a more detailed analysis of the guidance by the HEART UK Medical, Scientific and Research Committee and latterly a response from our Patients and Supporter Committee, which includes individuals affected by FH. HEART UK circulated notice of the NICE consultation to over 10,000 individuals, in addition to including in social media feeds and convened a special meeting of the FH Intelligence Network; a Medical, Scientific and Research Committee, Patient and Supporter Committee and a dial-in for patients. We also posted	Thank you for your comment. The Committee has considered the wording around this awareness making recommendation, and agreed that it is appropriate to make it more active by using the phrase “suspect FH as a possible diagnosis …”

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				notice on the front page of our website and invited comments via email. **Medical, Scientific and Research Committee** 1.1.1 The words 'think about' is too passive and should be amended to encourage further action.	
HEART UK- The Cholesterol Charity	Addendum	General	1.2	1.2 Identifying people with FH using cascade testing The health economic case for FH screening and cascade testing are very convincing using the model chosen. However one long-standing criticism of all health economic work done in FH has been the lack of a dedicated epidemiological mathematical relationship relating cardiovascular disease risk factors to event rates. All analyses to date tend to multiply Framingham-based CVD risk by a factor ranging from 3-13 fold to obtain the CVD risk in FH. A sensitivity analysis should be performed on the model using the equation derived from the SafeHeart Spanish FH cohort study to validate the conclusions using a specific risk calculation system and published (by example) in table 3 in the paper. Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study)	Thank you for your comment and for highlighting this important paper. A sensitivity analysis has been performed calibrating the model outcomes to those reported in the SAFEHEART study (Perez de Isla et al 2017) as far as was possible given the data reported. This analysis is presented in section O.4.6 of the addendum. The results were qualitatively similar to the original results in that cascade testing and primary care case finding remain cost effective, although the Simon Broome criteria appear somewhat less cost-effective when compared to the DLCN. This latter finding was not robust to realistic sensitivity analyses, however, so the overall recommendations have remained the same.

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				Pérez de Isla L, Alonso R, Mata N, Fernández-Pérez C, Muñiz O, Díaz-Díaz JL, Saltijeral A, Fuentes-Jiménez F, de Andrés R, Zambón D, Piedecausa M, Cepeda JM, Mauri M, Galiana J, Brea Á, Sanchez Muñoz-Torrero JF, Padró T, Argueso R, Miramontes-González JP, Badimón L, Santos RD, Watts GF, Mata P. www.ncbi.nlm.nih.gov/pubmed/28275165 Circulation. 2017 May 30;135(22):2133-2144	
HEART UK- The Cholesterol Charity	Addendum	General	1.1.15	1.1.15 Children at risk of FH because of one affected parent should be offered a DNA test at the earliest opportunity, with no mention to age. Treatment of children should be individualised.	Thank you for your comment. The Committee agreed that it is appropriate that DNA testing for children of people with FH be offered at the earliest opportunity, and the recommendation has been amended to make this clear. A reference to 10 years has also been retained to ensure people who initially decline testing are offered additional opportunities before people would become eligible for treatment.
HEART UK- The Cholesterol Charity	Addendum	General	1.1.16	1.1.16 Children with homozygous FH are at risk of death at a very early age and it is an oversight not to offer a DNA test to confirm diagnosis.	Thank you for your comment. This recommendation was not included in the scope of this guideline update, and therefore it is not possible to make any changes.
HEART UK- The Cholesterol Charity	Addendum	General	1.1.2	1.2 This needs to coordinate with CG181 which is the lead lipids guideline for the UK. CG181 suggest all patients with TC> 9mmol/L need to be considered for FH. The draft FH update suggests >9.3mmol/L The analytical variation in total choelsterol is at best 2.5% and the total variation in daily	Thank you for your comment. Following consultation the committee reconsidered the evidence from the economic model along with evidence on the distribution of total cholesterol in different age/sex groups within the general population and decided to recommend primary care case finding in people aged 16-29 with a

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				cholesterol can approach 15-20%. The number should be rounded down and made consistent with CG181. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. Ockene IS, Matthews CE, Rifai N, Ridker PM, Reed G, Stanek E. https://www.ncbi.nlm.nih.gov/pubmed/11238295 Simvastatin 80mg is not used and is not recommended in CG181. It is less efficacious (more expensive) and has significantly more side-effects than Atorvastatin 80mg. Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. https://www.ncbi.nlm.nih.gov/pubmed/23838105 Circ Cardiovasc Qual Outcomes. 2013 Jul;6(4):390-9 Additionally it needs to be noted that family history is often poorly documented in primary care and cannot be solely relied upon.	TC>7.5 mmol/l and in people aged 30+ with a TC>9.0 mmol/l. It was felt that these recommendations struck the best balance between the strength of the evidence, equitable representation among different age groups and the practicalities of implementation. A full discussion of these deliberations can be found in the evidence review document. This guideline update did not consider the differential effectiveness of different statins. However, the recommendation does state that the initial treatment should use the statin with the lowest acquisition cost, which is likely to exclude simvastatin from being used. The committee agreed that family history may not always be well document in primary care, and noted that the awareness raising recommendation for FH is specifically written as an and/or, meaning FH can be suspected solely based on cholesterol levels if family history data are not available or not reliable.

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HEART UK- The Cholesterol Charity	Addendum	General	1.1.3	1.1.3 We consider only measuring a total cholesterol as a retrograde step and would recommend a full lipid profile to give greater insight and should be amended	Thank you for your comment. The recommendation to measure total cholesterol relates to the case finding element of the guideline, as total cholesterol is the measurement that triggers a referral when primary care records are searched. This recommendation does not preclude additional measurements being taken if felt to be clinically appropriate.
HEART UK- The Cholesterol Charity	Addendum	General	1.3.1	1.3.1 Drug treatment We strongly believe a 50% LDL-C reduction target will dis-advantage patients with very high baseline LDL-C. This group of patients are those with more severe phenotype of the disease and carry a higher risk of premature CHD. There is considerable evidence for a lower-is-better approach and targets more in-line with the European Atherosclerosis Society ought to seriously be considered. The guidelines omit options for patients whose treatment fails to lower LDL-C below 50%. Ezetimibe monotherapy for patients intolerant to statins is insufficient to lower LDL-C to acceptable levels. It is a serious omission not to include PCSK9 inhibitors as treatment options with reference to TA394 and TA 393.	Thank you for your comment. The Committee noted that the recommendation is to aim for "at least" a 50% reduction in LDL-C concentration from baseline, and that this is a minimum does not preclude clinicians from setting absolute targets (for larger reductions) if these are felt to be clinically appropriate. The guideline has now been amended to include cross-references to the NICE technology appraisals on PCSK9 inhibitors (evolocumab and alirocumab), which give guidance on when the use of these drugs is appropriate.
HEART UK- The Cholesterol Charity	Addendum	General	1.3.2	1.3.2 Alcohol consumption need to be updated in line with other guidance as for the general population, men and women are advised not to regularly drink more	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin

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				than 14 units per week. Binge drinking should be avoided. Men and women should be advised to have several drink free days each week. More information can be found at Live Well	therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
HEART UK- The Cholesterol Charity	Addendum	General	1.3.1.13	1.3.1.13 Nicotinic acid and fibrates are rarely offered as a treatment option and should only be recommended in exceptional circumstances under specialist supervision for both adults and children. Gemfibozil is very rarely offered as a treatment and similarly should only be recommended in exceptional circumstances under specialist supervision.	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
HEART UK- The Cholesterol Charity	Addendum	General	1.1.5	1.1.5 Clarification is needed	Thank you for your comment. The Committee noted that recommendation 1.1.5 is concerned with ensuring that the person undertaking the assessment is suitably qualified to do so. Thresholds for referral are given in recommendation 1.1.6.
HEART UK- The Cholesterol Charity	Addendum	General	1.3.3	1.3.3 Specialist treatment Reference to PCSK9 inhibitors is a serious omission and ought to be included as a treatment option before apheresis and in line with TA 394 and TA393.	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.
HEART UK- The Cholesterol Charity	Addendum	General	1.4.1.1	1.4.1.1 Age appropriate materials should be offered to children and young people.	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.

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HEART UK- The Cholesterol Charity	Addendum	General	1.3.3.3	1.3.3.3 The recommendation for arterio-venous fistulae is contrary to usual best practice. Vein-to-vein access is the first choice whenever feasible. Arterio-venous fistulae is the second choice.	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
HEART UK- The Cholesterol Charity	Addendum	General	1.5.1.3	1.5.1.3 HEART UK supports a national FH Registry and would further support a recommendation in the guidance to include patients with heterozygous FH. We would further encourage consideration for a register of patients with homozygous FH	Thank you for your comment. Recommendations for the setting up of a specific central database or registry would be outside the scope of this guideline update, but the committee did recognise the value such a database would provide.
HEART UK- The Cholesterol Charity	Addendum	General	1.5.1.5	1.5.1.5 Needs to be in line with CG181 Additional research required 1. Additional information is needed on the benefits of Simon Broome, the Dutch Lipid Clinic Network and the Welsh Scoring Criteria in clinical practice 2. Further research is required into any adversary effects of statins on the development of children. 3. Further research is required into the cost benefits of liver transplants for people with homozygous FH	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update. Research recommendations have been made on the comparative accuracy of different FH criteria, and the long-term effects of statins in children. Issues around liver transplantation are outside the scope of this guideline update, and therefore it was not possible to make recommendations for additional research in this area.
HEART UK- The Cholesterol Charity	Addendum	General	1.4.3.6	1.4.3.6 Serum cholesterol concentrations should be measured routinely during pregnancy, especially in pregnant women with homozygous FH in whom it will indicate the need for and frequency of apheresis.	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.

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HEART UK- The Cholesterol Charity	General	General	General	Thank you for the opportunity to comment on the draft guidance. HEART UK- the cholesterol charity includes a broad network of health care professionals, patients and those affected by high cholesterol. Our patient education materials offer information and support as well as our helpline, which is run by cardiac nurses and dietitians. The HEART UK board of trustees includes health care professionals and patients with familial hypercholesterolaemia and we also host a number of expert committees that include leading lipidologists and other relevant health care professionals. An FH Intelligence Network teleconference is held monthly for providers and commissioners of FH services and includes a range of representation from CCGs, FH nurses, GPs and others. Our Medical, Scientific and Research Committee includes expertise from mostly lipidologists across the UK and our Annual Scientific Conference attracts worldwide delegation.	Thank you for taking the time to comment on this guideline.
Merck Sharp & Dohme Limited	Addendum	General	General	MSD Welcome the opportunity to comment on this addendum of Clinical Guideline 71, familial hypercholesterolaemia. • MSD has noted there is no update on the targets and in light of extra benefit with lower levels of LDL-C achieved with combination therapy (statin +non-statin) studies; we feel this should be updated. • We would also welcome a clear treatment flow as a practical guide for health care professionals.	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update. However, we have passed your comments about the potential need to update the parts of the guideline on combination treatment to the NICE surveillance team, who make decisions about which parts of guidelines need to be updated in the future.

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				We would welcome a case finding flow as a practical guide for the primary care setting.	
Merck Sharp & Dohme Limited	Addendum	51	8	The guideline refers to ezetimibe as a 'newer' therapy which may suggest that the therapy is a recent addition to treating high cholesterol when in fact it has been available for 14 years.	Thank you for your comment. This statement merely refers to ezetimibe as being a newer treatment than bile acid sequestrants, fibrates and nicotinic acid, which we believe to be an accurate statement.
Merck Sharp & Dohme Limited	Addendum	51	12	It would be helpful to provide clear guidance on the use of ezetimibe, alirocumab and evolucumab in the full guideline rather than refer readers to the technology appraisals. As it has been made clear in the short version but not the full version we feels that for consistency this should be included in the full version as well.	Thank you for your comment. The technology appraisal recommendations included in the short version of the guideline have now also been included in the evidence review (full version).
Merck Sharp & Dohme Limited	Addendum	58	3	We suggest that a 50% reduction in LDL-C in FH patients would not be enough for this high risk group, and would suggest a greater % reduction and/or an absolute LDL- C target. For example Reiner et al advocate for adults, 2.5 mmol/L (100 mg/dL), and for adults with CHD or diabetes, 1.8 mmol/L (70 mg/dL) (Reiner Z, e t al. (ESC/EAS) Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769–1818).	Thank you for your comment. The Committee noted that the recommendation is to aim for "at least" a 50% reduction in LDL-C concentration from baseline, and that this is a minimum does not preclude clinicians from setting absolute targets (for larger reductions) if these are felt to be clinically appropriate.
Merck Sharp & Dohme Limited	Addendum	58	4	We believe that in practice, a % reduction vs. baseline would be impractical especially if patients were already on an established lipid lowering therapy. We believe that an absolute target LDL-C value would offer greater clarity for non-FH specialists.	Thank you for your comment. The Committee noted that the recommendation is to aim for "at least" a 50% reduction in LDL-C concentration from baseline (with initial statin treatment), and that this is a minimum does not preclude clinicians from

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					setting absolute targets (for larger reductions) if these are felt to be clinically appropriate.
MPT	Short	General	General	Should TAs 393 and 394 on alirocumab and evolocumab be incorporated as they include recommendations on familial hypercholersterolaemia? Ezetimibe is included	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.
MPT	Short	7	22-23	'aim for at least a 50% reduction in LDL-C concentration from the baseline measurement' This is repeated in similar wording in the next recommendation 1.3.1.3. Just wondered if this was necessary, although I can see there may be reasons for including twice	Thank you for your comment. Since one of these recommendation refers to the setting of initial targets, and the second to dose adjustment if those targets are not met, the Committee agreed it was useful to retain both of these recommendations.
NHS England	General	General	General	• I welcome this guidance and congratulate NICE on a helpful contribution towards improving the detection and management of people with FH • Various obvious challenges arise in implementing this guidance (such as ensuring adequate genetic education of healthcare professionals outside genetic centres, interrogating disparate GP data systems, the capacity of specialist lipid clinics, ensuring FH services can offer children-friendly environments etc.), but this guidance does overall provide a useful blueprint for these (and other) service delivery discussions. • It would be very helpful if this guidance were supported by the development of a commissioner toolkit.	Thank you for your comment. NICE will be producing a resource impact tool that will be published alongside this guideline. Recommendations for the setting up of a specific central database or registry would be outside the scope of this guideline update, but the committee did recognise the value such a database would provide. The guideline has now been amended to include cross-references to the NICE technology appraisals on PCSK9 inhibitors (evolocumab and alirocumab), which give guidance on when the use of these drugs is appropriate.

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				• It is probably outside the scope of the guidance but a national source of data (national database) of those with FH would be invaluable and if NICE were to support this it would be helpful. I couldn't find reference to PCSK-9 Inhibitors and their place in the management of FH (see TA394). I understand this may be because the TA was published after the evidence review was completed, but does it not warrant reference as an additional means of treating more resistant cases of hypercholesterolaemia?	
NHS England	Short	4	4	The recommendation to "think about" seems vague and has been queried by a GP colleague in NHSE as to what action is recommended or intended on the part of GPs. If patients meet the two criteria in the bullet points, then they have possible FH and should they not be referred for investigation?	Thank you for your comment. The Committee has considered the wording around this awareness making recommendation, and agreed that it is appropriate to make it more active by using the phrase "suspect FH as a possible diagnosis …"
NHS England	Short	4	4	I realise that systematic searching for young heart attack patients was found not to be cost effective and that the evidence for systematic searching of pathology databases was poor, but it would seem that some additional cases of particularly high cholesterol could very simply be identified from, for instance, pathology databases even if this were opportunistic. Does NICE feel able to include a comment to the effect that '**all clinicians should consider'** rather than '**think about'** so that pathologists, cardiologists and other clinicians could be encouraged to consider FH and use their locally available data (clinical records, pathology	Thank you for your comment. The Committee has considered the wording around this awareness making recommendation, and agreed that it is appropriate to make it more active by using the phrase "suspect FH as a possible diagnosis …"

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				databases etc.) opportunistically to identify additional cases?	
NHS England	Short	4	7	We welcome clarification regarding the definition of a positive family history of premature CHD, which was not previously clear.	Thank you for your comment.
NHS England	Short	4	10	We welcome the recommendation that primary care records should be systematically searched for people with a cholesterol above 9.3mmol/l but wonder if it should be greater than or equal to 9.3 mmol/l since the number 9.3 will become more widely established as the threshold by those undertaking the interrogation. At present we would be searching for those with a TC of 9.4 or above. If it is so cost-effective to identify people above a cholesterol of 9.3mmol/l might it not still be highly cost effective at, for instance, 8.5mmol/l? Is the 9.3mmol/l threshold set simply because that's a threshold for which published evidence exists? I assume that NICE did sensitivity analyses for cost-effectiveness at lower thresholds (and I apologise if I missed this in the main document) I realise that systematic searching for young heart attack patients was found not to be cost effective and that the evidence for systematic searching of pathology databases was poor, but it would seem that some additional cases of particularly high cholesterol could very simply be identified from pathology databases even if this were opportunistic. Does NICE feel able to include a comment to the effect that pathologists,	Thank you for your comment. Following consultation the committee reconsidered the evidence from the economic model along with evidence on the distribution of total cholesterol in different age/sex groups within the general population and decided to recommend primary care case finding in people aged 16-29 with a TC>7.5 mmol/l and in people aged 30+ with a TC>9.0 mmol/l. It was felt that these recommendations struck the best balance between the strength of the evidence, equitable representation among different age groups and the practicalities of implementation. A full discussion of these deliberations can be found in the evidence review document. The committee agreed that, because it is highly cost-effective at a threshold of 9.0mmol/l, it is also likely to be cost-effective (compared to no case finding) at cholesterol thresholds lower than 9.0mmol/l. However, having made a positive recommendation at 9.0mmol/l, they noted that it was now necessary not only to show case finding at lower thresholds would be cost-effective compared to no case finding, but also that it would be cost-effective compared to case finding at

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				cardiologists and other clinicians should be aware of FH and use their locally available data opportunistically to identify additional cases? E	9.0mmol/l. In the absence of any evidence to address this question, the committee agreed it could not make recommendations for a lower threshold than 9.0mmol/l. The committee agreed that, in the absence of any robust evidence of effectiveness, it was not appropriate to make any recommendations about opportunistic case finding from pathology databases.
NHS England	Short	5	1.1.1	This section needs some clarification. 'think about' is very vague and it is not clear what action is to be prompted. If patients meet the two criteria in the bullet points, then they have possible FH according to SB criteria and should be referred for investigation. It would also be worth adding that if TC >7.6, clinicians should be excluding sec causes and applying the SB or DLCN criteria. If positive refer, if negative, manage as per CG181.	Thank you for your comment. The Committee has considered the wording around this awareness making recommendation, and agreed that it is appropriate to make it more active by using the phrase "suspect FH as a possible diagnosis …". They also agreed it would be appropriate to exclude other causes before referring for FH diagnostic testing, and this should form part of standard clinical practice. The committee noted that the guideline already contains a reference to CG181 for managing people who are found not to have FH.
NHS England	Short	5	1.1.5	The draft guidance states "refer to an FH specialist for DNA testing if they meet the Simon Broome criteria for possible or definite FH, or they have a DCLN score of greater than 5". Please could NICE comment on whether the possibility of referring patients from primary care for DNA testing	Thank you for your comment. Direct GP referral for DNA testing was not considered in the pre-consultation version of the economic model as the committee believed that the infrastructure is not in place nationally for them to recommend such a strategy.

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				was explored in terms of feasibility and cost effectiveness	An exploratory analysis was conducted that showed that direct referral, relying purely on the TC values rather than clinical assessment with the SB/DLCN criteria may be slightly more cost-effective than the recommended strategies without being less effective. Nevertheless, the committee's reservations about the practicalities of implementation remained so no further action was taken.
NHS England	Short	5	8	Referral to a 'specialist' has long been a barrier to referral by GPs (because of perceived cost). Was it intended by NICE that referral by a GP directly for genetic testing should not be encouraged? Could the term 'specialist FH service' be clarified? Is this a lipidologist, geneticist, either, or something different. It would help if GPs and the service knew exactly what was intended by the recommendation in terms of establishing referral pathways.	Thank you for your comment. The committee agreed that there were many different models of specialist FH service around the country, and there was no evidence that enabled them to recommend one as being preferable to the others. The committee agreed that direct referral from a GP for genetic testing may be a plausible alternative in the future, but that at the moment it was rare for the necessary systems to be in place (for example, the availability of genetic counselling) to enable this to be possible.
NHS England	Short	6	5	We welcome the avoidance of CVD risk algorithms because those with FH are at high risk whatever their algorithmic score. However, the 10-year QRISK score, the one most widely used in GP will rarely suggest a high 10 year risk in those who are under the age of 50, whatever their level of cholesterol or presence of other risk factors. I wonder whether it could be made more explicit that use of 10-year risk scoring is inappropriate (reinforcing the recommendation). I realise it would not be possible to recommend a lifetime risk assessment, since this was not part of the guidance, but it would be	Thank you for your comment. This recommendation has been amended to also specify that tools such as QRISK2 should not be used in people with FH.

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				helpful to make explicit to those who use 10-year QRISK routinely that it will often misleadingly suggest a 'low risk' when lifetime risk is high – particularly an issue for those with FH.	
NHS England	Short	7	1.2.1	In the draft guidance it states "Carry out cascade testing using DNA testing to identify affected first- and second- and, when possible, third-degree biological relatives of people with a diagnosis of FH". In our view, it would be helpful for the guidance to be explicit in the fact that cascade testing only applies to those who have a received a positive DNA test. As currently drafted, it could be interpreted that everyone will require DNA testing. In addition, it would be helpful to clarify where responsibility for ensuring cascade testing is performed on biological relatives is carried out.	Thank you for your comment. This recommendation has been clarified to specify that cascade testing should be carried out when someone has a genetic diagnosis of FH. Whilst this guideline makes recommendations that case finding and cascade testing should be carried out, it is outside of its scope to make specific recommendations about how these should be carried out in practice, which are implementation decisions to be made at a local level.
NHS England	Short	7	4	Is it clear to non-expert readers that 'cascade testing' implies that the proband has been positively identified by genetic testing, as opposed to being suspected on clinical criteria? Might it be better to say "Carry out……..relatives of people with a genetic diagnosis of FH' Also, does NICE have a view about who should be responsible for ensuring cascade testing taking place? At present some occurs as a result of contact between family members, some by contact between FH services, and some from work of FH nurses, specialist clinics, as well as GPs. Is NICE in a position to	Thank you for your comment. This recommendation has been clarified to specify that cascade testing should be carried out when someone has a genetic diagnosis of FH. Whilst this guideline makes recommendations that case finding and cascade testing should be carried out, it is outside of its scope to make specific recommendations about how these should be carried out in practice, which are implementation decisions to be made at a local level..

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				recommend where principal responsibility lies for contacting family members – is it in the genetics services that identify the proband, or others? I realise that this is a service delivery challenge but if the GDG has a view this could be helpful as we try to overcome various barriers and improve the pathway of care for those with FH or suspected as having it.	
NHS England	Short	14	1.3.2.13	The alcohol recommendation needs amending to reflect updated recommendations.	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
NHS England	Short	14	17	Has advice on alcohol intake for men changed since 2008, i.e. been lowered?	Thank you for your comment. These recommendations were not part of the scope for this update of the guideline, and therefore these recommendations have not been altered from those in the 2008 guideline.
Public Health England	Addendum	Chapter 2	General	NHS Health Check. The NHS Health Check programme has become a systematic means of measuring and recording cholesterol and positive family history of coronary heart disease across the adult population in England. We would therefore recommend that the role that this programme could have on the identification of FH in adults aged 40 plus is recognised in this guidance. The Queen Mary University national evaluation of the programme (Robson BMJ Open) found that over 90% of the population who had a NHS Health Check had a total cholesterol recorded in their records compared to 43% in those who had not had a Health Check.	Thank you for your comment. The Committee agreed that measurements taken as a result of health checks would provide a useful source of information to use as part of the FH primary care case finding. A comment to this effect has been added to the addendum.

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Public Health England	Addendum	39	General	The implications of the potential doubling of prevalence estimates are not fully explained - that such a common carrier state means that primary care will have a key role to play and genetic centres role in supporting primary care capacity and expertise (such as has happened with the British Heart Foundation (BHF) funded pilots which have funded primary care nurses to help areas to develop a consistent scalable approach). A similar approach was adopted by the NHS Sickle Cell programme to scaling up capacity for detection of carrier states and providing training to nurses including health visitors dealing with notifying parents of new-born carrier results, and for which special training was established and operated effectively for a decade. Additionally the increased prevalence, whilst having little impact on cost effectiveness, will increase the cost to commissioners due to larger numbers and it will increase clinical benefit at a population level. It would be helpful if NICE could supplement this with a commissioner toolkit. The existing costing template is very out of date.	Thank you for your comment. The estimates of prevalence drawn from the literature were key in determining the case finding threshold used in the economic model, which was configured to produce short and long term resource impact arising from the various strategies. NICE will produce a resource impact tool that will aid commissioners with the implementation of the recommendations in this guideline update.
Public Health England	Addendum /Short	general	General	Polygenic FH – it should be made very clear that cascade testing is only recommended for monogenic cases and not for polygenic cases. This is an important change from 2008.	Thank you for your comment. This recommendation has been clarified to specify that cascade testing should only be carried out when someone has a genetic diagnosis of FH.
Public Health England	Addendum /Short	general	general	We welcome this guidance and congratulate NICE on a helpful contribution towards improving the detection and management of people with Familial Hypercholesterolaemia (FH).	Thank you for your comment.

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Public Health England	Addendum /Short	general	general	Various challenges arise in implementing this guidance, such as ensuring adequate genetic education of healthcare professionals outside genetic centres, interrogating disparate general practitioner (GP) data systems, the capacity of specialist lipid clinics, and ensuring FH services can offer children-friendly environments; but overall this guidance does provide a useful blueprint for these (and other) service delivery discussions. Therefore, it would be very helpful if it were supported by the development of a commissioner toolkit. The costing toolkit from 2009 is now very out of date and a costing template could be supplemented by advice to commissioners.	Thank you for your comment. NICE will be producing a resource impact tool that will be published alongside this guideline.
Public Health England	Addendum /Short	general	general	To support implementation there is a need for a consistent national data-set as well as, ideally, a national database and a system of national audits of services to determine how effectively they are performing, to ensure that the cascade element of the programme is working. It would be helpful if these were emphasised as key elements of such a programme.	Thank you for your comment. Recommendations for the setting up of a specific central database or registry would be outside the scope of this guideline update, but the committee did recognise the value such a database would provide. NICE is working with external partners to best consider ways to support implementation of the guidance.
Public Health England	Addendum /Short	general	general	PCSK-9 Inhibitors and their place in the management of FH are not mentioned (see TA394). Whilst the Technical Appraisal was published after the evidence review was completed, there should be a reference to cross link to this report on this drug, as it provides another treatment for the specific cases of hypercholesterolaemia with this gene variant and a specific reason for genetic testing.	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.
Public Health England	Addendum /Short	general	General	Case finding: It would be helpful if it is emphasised that primary care records should be systematically searched for people already found to have a	Thank you for your comment. Following consultation the committee reconsidered the evidence from the economic model along with

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				cholesterol above 9.3mmol/l to ensure that advice on the importance of testing family members such as children, and nieces and nephews, who are therefore at risk can also have their risk identified. We note that this is highly cost-effective threshold (£1572/QALY). It would be helpful if the reason for this threshold being selected e.g. c.f. 8.5 was clear and justified.	evidence on the distribution of total cholesterol in different age/sex groups within the general population and decided to recommend primary care case finding in people aged 16-29 with a TC>7.5 mmol/l and in people aged 30+ with a TC>9.0 mmol/l. It was felt that these recommendations struck the best balance between the strength of the evidence, equitable representation among different age groups and the practicalities of implementation. A full discussion of these deliberations can be found in the evidence review document.
Public Health England	Addendum /Short	general	General	It is also helpful having clear outlines of the meaning of first, second and third-degree relatives in the document. This is an aspect of genetic literacy required for the taking of family history and the recording of family trees, which primary care professionals in general are now required to understand and use (which will be of increasing importance as genetic tests and genomics in general scale up and are used much more routinely). It may be helpful to consider how these aspects of genetic literacy can be highlighted more generally across the guidance	Thank you for your comment. We have now added in definitions of these terms to both the short and full versions of the documentation.
Public Health England	Addendum /Short	general	General	It is not clear how much of the pathway can be managed in primary care. It is also not clear what is meant by “healthcare professional competent in using the [Simon Broome or Dutch Lipid Clinic criteria] – it would be helpful both of these points could be spelled out more clearly”. In general it is important to note, due to the frequency	Thank you for your comment. The committee discussed the issue of who should undertake clinical diagnosis of FH in primary care, and agreed it was not possible to make more specific recommendations about this, other than that they should be competent in using the relevant criteria.

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				of the gene, genetic centres will not be able to deliver all the counselling for this condition. Models of service delivery that work with, for example, primary care nurses trained to support the programme are needed, such as the BHF nurses scheme currently in place, or the training programmes established for the NHS Sickle Cell and Thalassaemia Screening Programme which has counselled over 100,000 pregnant women carriers in the past decade. Potentially 19000 children aged 10-17 are carriers in England (estimated on 1:250 carrier prevalence and 600,000 children in each age cohort) if they were all detected. Given the size of this population and the likely adult population it should be clear that alternative service delivery models to one where genetic counsellors do all the counselling will be needed.	The committee agreed on the importance of genetic counselling, but noted that it was not within the scope of this update to make recommendations on where and how this should be carried out.
Public Health England	Addendum /Short	general	General	It would be helpful if it could be more clearly highlighted that CVD risk algorithms are not appropriate in the consideration of risk for FH, as those with FH are at high risk whatever their algorithmic score (e.g. the 10-year QRISK score, the one most widely used in Primary care will rarely identify a high 10-year risk in those who are under the age of 50, whatever their level of cholesterol or presence of other risk factors). This is particularly important in relation to the 7.5 threshold – where a risk score such as QRISK will often misleadingly suggest 'low risk' over a ten year period, when lifetime risk is high, due to Familial hypercholesterolemia where raised cholesterol exists from birth.	Thank you for your comment. This recommendation has been amended to also specify that tools such as QRISK2 should not be used in people with FH.

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Public Health England	Addendum /Short	general	General	Is NICE able to recommend where principal responsibility lies for contacting family members – whilst this is a service delivery challenge it would be helpful if the Guideline Development Group has a view. This could be helpful as we try to overcome various barriers and improve the pathway of care for those with FH or suspected as having it.	Thank you for your comment. The Committee agreed that the evidence presented did not enable it to distinguish between the effectiveness of different approaches to cascade testing, based on who should have responsibility for contacting relevant family members. Therefore, they agreed it was not possible to make recommendations on this topic.
Public Health England	Addendum /Short	general	General	Case finding: Whilst it is helpful to understand that case finding is not cost-effective in secondary care it would be useful to know if the detection/cost-effectiveness through lipid clinics has been considered. Or to be clear about this. This is not specifically secondary care and has been found to be a useful way to detect cases in practice. It is unclear if analysis has been performed using information from lipid clinics.	Thank you for your comment. The model only examined case finding in early MI rather than case finding in secondary care in general (due to a lack of evidence). We have altered the wording throughout the document to make this clearer.
Public Health England	Addendum /Short	general	general	Mutation detection: A key question for commissioners to consider is the cost-effective mutation identification rate for genetic testing.	Thank you for your comment. The committee determined that the sensitivity and specificity of DNA testing for index cases and their relatives would be assumed to be 100% in the economic model, although acknowledged that it might be slightly less than this in new index cases. The economic model assumed that only 2.04 relatives per index case would be able to be invited and that their take up rate was ~60%. These values were varied in deterministic (including high and low values) and probabilistic sensitivity analysis and found not to affect the results of the model. Due to the extremely high cost effectiveness of treating FH once identified it is reasonable to assume that

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					realistic reductions in the 100% accuracy of DNA testing would not alter the conclusions of this model.
Public Health England	General	General	General	Thank you for the action you took in 2015 in deciding to review this guideline and the opportunity to respond to this consultation. We are grateful that most of the main points raised in our previous letter have been considered and outline below a few further suggestions: **The previous underestimation of prevalence** This is mentioned on page 39 of the long document but the implications are not fully explained. This makes familial hypercholesterolaemia (FH) a relatively common condition (1:250-1:500) rather than a rare condition which can be dealt with within the confines of specialist services. This frequency also means that primary care services need to be able to respond to this condition, and that clear guidance on how to manage FH is available to practitioners. This increase in prevalence will have negligible impact on cost effectiveness, but will increase the cost to commissioners and the benefit at a population level.	Thank you for your comments. The committee noted that increases in the estimated prevalence of FH would have cost implications, but did not feel this change in prevalence impacted on any of the recommendations made as part of this update.
Public Health England	General	General	General	**Polygenic FH** We suggest that there should be an explicit recommendation that cascade testing on Total Cholesterol should not be done if a mutation is not identified, a substantial change from 2008 guideline.	Thank you for your comment. This recommendation has been clarified to specify that cascade testing should only be carried out when someone has a genetic diagnosis of FH.
Public Health England	General	General	General	**NHS Health Check** The NHS Health Check programme has become a systematic means of measuring and	The Committee agreed that measurement taken as a result of health checks would provide a useful source of information to use as part of the FH

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				recording cholesterol in adults aged 40-65 in England and could also support identifying FH more proactively with a cardiovascular disease (CVD) family history event review, aligned to National Institute for Health and Care Excellence (NICE) guidance. A national evaluation of the programme found that a cholesterol measurement was recorded in the general practice record for over 90% of those who had an NHS Health Check compared to 43% who had not (Robson J, et al. BMJ Open 2016;6:e008840. doi:10.1 136). We would suggest that the contribution of the Health Check in identifying FH through raised cholesterol could be strengthened within the clinical guidelines with a clear family history enquiry.	primary care case finding. A comment to this effect has been added to the addendum.
Public Health England	General	General	General	The guidance does not address the issue of how much of the pathway can be managed in general practice. This is a key point that does need clarification noting the frequency of the gene,	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
Public Health England	General	General	General	Given the increased frequency of the gene and the importance of giving clarity to the role of primary care, we repeat our earlier suggestion that the guidance is supported by the development of a commissioner toolkit. The current National Institute for Health and Care Excellence (NICE) costing template from 2009 is now very out of date and a new costing template could be supplemented by advice to commissioners.	Thank you for your comment. NICE will be producing a resource impact tool that will be published alongside this guideline.
Public Health England	General	General	General	We would also like to request that the guidance be revisited again in four to five years. At that	Thank you for your comment. We have passed the reference to this study on to our surveillance team,

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				time, the Health Technology Assessment study findings [HTA — 15/134/02 Chief Investigator Quereshi NJ on cost-effectiveness of different existing models of cascade testing will be available.	who will use it as part of the evidence when deciding on the appropriate timescales for the guideline to be updated.
Public Health England	General	General	General	Public Health England (PHE) is working with NHS England, the British Heart Foundation, Heart UK and others on this topic. PHE continues to emphasise the important contribution that the NHS can make to improving the prevention of CVD; action on FH is an element of this. As you will be aware, through the work of PHE and NEtS commissioners, an increasing proportion of the population are now covered by testing arrangements such as in the West Midlands	Thank you for your comment.
Public Health England	Short	4	4	The phrase “think about FH as a possible diagnosis in adults with a total cholesterol level “greater than 7.5 mmol/l” is too vague. We suggest that it is made clear that for those found to have such an elevated level of total cholesterol (TC) (e.g. via being found to be at higher risk of cardiovascular disease (CVD))**,** a specific enquiry into family history (as specified both in coronary event before the age of 60 in families) is made as part of the process before a referral was made. Therefore, it would be helpful if NICE brought together its third recommendation with the first one in a more consistent manner which would do this.	Thank you for your comment. The Committee has considered the wording around this awareness making recommendation, and agreed that it is appropriate to make it more active by using the phrase “suspect FH as a possible diagnosis …”
Public Health England	Short	4	7	It is helpful, especially for primary care, to have a clear definition of what it means to have a positive family history of premature coronary heart disease (CHD), which was not previously clear (events under age 60).	Thank you for your comment. Issues around the appropriate ways to standardise terminology and practice were not within the scope of this update,

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				This is a meaningful term which will help primary care understand the importance of this condition and help with enquiries into family history. It may be helpful to recommend the need for consistency in both "CVD event" and "family history" including suggesting that information (IT) systems could support accurate family history taking with clear definitions to assist consistent recording of positive family history for this condition and a focus on those families where this is most important.	and therefore it was not possible to make any recommendations on this topic.
Royal College of General Practitioners	Short	General	General	Thank you for asking us to comment at this stage. The guidelines may help us to identify high risk FH affected individuals. However as the criteria used for diagnosis are based on secondary care data, the likelihood is that there is the potential for over diagnosis. We recognise that the lipid clinics will have a major input, particularly around cascade testing and DNA testing. We are concerned about the difficulty primary care might have in terms of workload in identifying patients with FH , through search of their databases. We are also concerned about how to manage children in terms of dosing around the use of statins and invariably will lead to a spike in referrals to paediatrics or the lipid clinics.	Thank you for your comments, which have been responded to individually where they appear Over-diagnosis and the associated costs were specifically included within the economic model used to evaluate case finding, which found it to be a highly cost-effective intervention. The committee were aware of the workload necessary in primary care to carry out the case finding, but felt with such clear evidence of benefits and value for money that it was appropriate for a strong recommendation to be made. The committee were aware of the particularly difficulties around the use of statins in children. However, they noted the current recommendations around statins in children are not substantially different to those in the old guideline, and therefore there should not be a substantial change in workload or costs.
Royal College of General Practitioners	Short	4	10	1.1.2: Is this a total cholesterol test greater than 9.3 mmol/l ever i.e not necessarily the latest?	Thank you for your comment. Your interpretation is correct; this would be any test greater than

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					9.3mmol/l. In particular, the committee noted that if people were now on treatment values would be lower, but an old test result above the threshold would still be a reason for action.
Royal College of General Practitioners	Short	4	13	1.1.3: Can NICE provide the search read codes and the snomed Ct codes to ensure the practices can do complete searches	Thank you for your comment. Implementation issues like this are not within the remit of a NICE clinical guideline. However, NICE is working with external partners to best consider ways to support implementation of the guidance.
Royal College of General Practitioners	Short	5	5	1.1.5: How does someone become competent in using these criteria and what are the costs? If a practice does not have someone competent in a practice what do they do? Will the genetics secondary care service decline referrals?	Thank you for your comment. The committee agreed that there were no specific requirements that could be specified for being competent in their use, and it was reasonable for local services to develop their own policies on this. The main issue the committee wished to address was that because both criteria had similar diagnostic accuracy, it a healthcare professional was competent in using one set of criteria, it would be reasonable for them to go on using that set, rather than needing to gain additional experience with an alternative criteria. The committee agreed that because the Simon Broome were simple to use, it would be highly unlikely for a practice not to have someone who could become competent in the use of the criteria.
Royal College of General Practitioners	Short	5	5	1.1.5: Simon Broome criteria uses total cholesterol greater than 7.5mmol and includes secondary degree relatives with ischaemic heart disease under 50 years. The Dutch Lipid clinic network uses LDL-C rather than Total cholesterol. They appear not to be entirely consistent with NICE guidelines? Have these been	Thank you for your comment. Recommendation 1.1.5 only references the tests that should be used for clinical diagnosis of FH. Where thresholds for those tests are mentioned in recommendation 1.1.6, these are based on the best cut-offs for

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				validated in primary care? Have any the clinical GP clinical IT systems tried providing a scoring tool like Qrisk? What was the response by Nice GP reference group? Has NICE considered using FAMCAT tool? This paper may help for a GP population. https://www.nottingham.ac.uk/research/groups/primarycarestratifiedmedicine/documents/weng-atherosclerosis-2015-new.pdf	sensitivity and specificity from the identified evidence. The criteria mentioned in recommendation 1.1.1 are not designed to match either of the criteria, but simply to raise awareness of the possibility of FH in a population of people who may be at high risk and therefore appropriate to assess using one of the criteria. No criteria such as QRISK are available for people with FH, and the committee was keen to discourage the use of such scoring systems as the ones currently available all underestimate the risks in people with FH. The committee were aware of the FAMCAT tool, and while the scope of this guideline update was not such that it could be considered as part of it, they agreed that it had promise as a potential way of implementing the recommendations made in the future.
Royal College of General Practitioners	Short	6 7	16 4	1.1.15 and 1.2.1: Most Primary care cannot access genetic testing at present.	Thank you for your comment. The committee were aware that primary care cannot routinely access genetic testing in many areas, and therefore did not consider making a recommendation that this testing should be carried out in primary care. However, they agreed that referral to a specialist service for genetic testing should be feasible for the relevant people.

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Royal College of General Practitioners	Short	7	21	1.3.1.2: The starting dose of statin should be explicit and how long after introducing statin or changing dose to recheck. I assume it is 4 weeks	Thank you for your comment. The committee agreed that the evidence available did now allow them to make specific recommendations on monitoring after starting statins or changing doses.
Royal College of General Practitioners	Short	10	21	1.3.1.20: The dose of statin needs to clear. Is there any monitoring of the child's cholesterol pre or post treatment?	Thank you for your comment. The committee agreed that the evidence available did now allow them to make specific recommendations on dosage or monitoring of statins in children.
Royal College of General Practitioners	Short	10	23	1.3.1.21: The statins that are licenced at present should be explicitly stated	Thank you for your comment. Because the statins that are licensed may change in the future, it was agreed to be more appropriate not to list these details here, particularly when there are sources for this information that are likely to be updated more regularly than a clinical guideline.
Royal College of Pathologists	General	General	General	The terminology used to refer to FH diagnosed using clinical and DNA testing is confusing. The use of the term FH without qualification, as is frequent throughout the document, should be avoided. The categories of clinical diagnosis should be clarified e.g. Uncertain Familial Hypercholesterolaemia (when DLCN score is 3 - 5 points, Simon Broome Possible criteria not fulfilled) Possible Familial Hypercholesterolaemia (when DLCN score is 3 - 5 points, Simon Broome Possible criteria fulfilled) Probable Familial Hypercholesterolaemia (when DLCN score is 6 - 8 points, Simon Broome Possible or Definite criteria fulfilled Definite Familial Hypercholesterolaemia (when DLCN score is > 8 points or LDL-C > 8.5 mmol/L, Simon Broome criteria fulfilled)	Thanks you for your comment. The committee discussed the terminology used to describe FH throughout the documentation, and agreed that it was sufficiently clear as to be highly unlikely to cause confusion for healthcare professionals or individuals with FH. In particular, they agreed that in discussions with patients, the term FH was likely to be regularly used without further qualification, and therefore it was appropriate for it to appear in this form in the recommendations and guideline. The term genetic diagnosis is used where necessary to make clear that DNA testing is the subject of the recommendation.

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				Only when a DNA test (comprehensive genetic analysis) has been done and patients are proven to have a pathogenic FH causing mutation should they be referred to as “Heterozygous Familial Hypercholesterolaemia or HeFH”. ” If they have two different pathogenic mutations they are “Compound Heterozygous FH” or “Homozygous Familial Hypercholesterolaemia or HoFH”. Patients in whom no mutation is found should be reclassified as Polygenic Hypercholesterolaemia if the LDL-SNP analysis is analysed and found to be consistent with this. If the latter is not available they should retain their clinical diagnosis to which “no mutation detected” (NMD) should be added.	
Royal College of Pathologists	General	General	General	The cost effectiveness of DNA testing is dependent on not only the cost of the test, but the mutation detection rate (% of patients tested who are found to have a pathogenic mutation) and the number of at risk relatives who are tested. The latter will depend on the co-operation of individual relatives but the number of eligible first and second degree relatives will give an indication of the number of additional cases which are likely to be diagnosed of a pathogenic mutation is found and all the relatives are tested. If the mutation detection rate and number of relatives tested are low DNA testing is unlikely to be cost-effective. A sensitivity analysis should be undertaken to determine the minimum acceptable mutation detection rate and number of relatives per family required to make DNA testing cost-effective at current prices. The system of identification of cases for DNA testing (e.g. DLCN or	Thank you for your comment. The committee determined that the sensitivity and specificity of DNA testing for index cases and their relatives would be assumed to be 100% in the economic model, although acknowledged that it might be slightly less than this in new index cases. The economic model assumed that only 2.04 relatives per index case would be able to be invited and that their take up rate was ~60%. These values were varied in deterministic (including high and low values) and probabilistic sensitivity analysis and found not to affect the results of the model.

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				Wales score) can then be judged according to whether it can deliver the required detection rate, and DNA testing discourage if there are insufficient relatives eligible for cascade testing.	
Royal College of Pathologists	General	General	General	The document fails to discuss the uncertainty regarding the cardiovascular risk multiplier applied to patients with a diagnosis of FH for cost-effectiveness analysis, typically set at 7 fold (as in TA393 and TA394). This may be significantly lower (the Spanish Safeheart Study suggests this is closer to 3) however this may be modified by co-existence of other measureable genetic risk factors such a Lipoprotein(a). A sensitivity analysis of the cost-effectiveness should be done on the risk multiplier.	Thank you for your comment. The relative risks were drawn from the Simon Broome register and were acknowledged to be uncertain, but were agreed to be the best source available to provide data, and not radically dissimilar from other values. Values of ~4.2 and 1.9 were used for younger and older patients respectively in the base case. These values were the subject of extreme sensitivity analysis, halving and doubling relative to unity, and these analyses were found not to lead to meaningfully different results. The inputs are discussed in section O.3.3 and the outputs in the "Detailed Scenario Analysis: Alternative Relative Risks" sub-heading in O.4.5. A sensitivity analysis calibrated to SAFEHEART data has also been added in section O.4.6.
Royal College of Pathologists	General	General	General	Lipoprotein(a) is an autosomal dominant risk trait which may underlie the clinical phenotype of FH, but this has not been mentioned. Measurement of Lipoprotein(a) is recommended by European societies in patients with a personal or family history of premature CHD, and would be particularly appropriate in patients with a clinical diagnosis of Possible FH below the threshold for DNA testing, being much (20 fold) cheaper than a DNA analysis.	Thank you for your comment. These issues are not within the scope of this guideline update (having not been identify as a high priority area for recommendations to be updated), and therefore it is not possible to make any recommendations in this area.

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Royal College of Pathologists	Short	General	General	We welcome the publication of this update but are disappointed that the opportunity has been missed to address the major shortcomings of the 2008 guideline. Implementation of the 2008 guideline was hampered by the recommendation of the Simon Broome criteria with a single total and LDL-cholesterol cut-off for all adults over 16 regardless of age and gender. The perception in primary was that total cholesterol greater than 7.5 mmol/L was extremely common and assessment of all such patients for potential referral for DNA testing was impractical and unachievable. A more selective approach has been widely adopted, using the DLCN and other scoring systems which assign a variable score depending on the LDL-cholesterol concentration, but none take account of the age and gender dependency of the distribution of LDL-cholesterol in the general population. In the Netherlands, the age and gender specific 95th LDL-cholesterol centile for the general is used to select patients for genetic testing and this approach would be feasible using UK general population data from the Health Survey for England.	Thank you for your comment. The recommendations made for case finding, cascade testing and scoring criteria were based on the best available evidence for both clinical and cost effectiveness. Evidence was not identified for alternative approaches to these issues, and in particular not for approaches to referral for DNA testing stratified by age and sex.
Royal College of Pathologists	Short	4	4	1.1.1. We are concerned that the change in wording from “should consider” to “think about” makes this recommendation weaker and more easily ignored, with no requirement for specific action. We would suggest amendment to “think carefully about” to strengthen this recommendation.	Thank you for your comment. The Committee has considered the wording around this awareness making recommendation, and agreed that it is appropriate to make it more active by using the phrase “suspect FH as a possible diagnosis …”
Royal College of Pathologists	Short	4	6	1.1.1 The recommendation of a single cut-off for total cholesterol of 7.5 mmol/L for consideration of a diagnosis of Familial Hypercholesterolaemia in all adults over 16 years perpetuates the most serious	Thank you for your comment. The recommendations made for case finding, cascade testing and scoring criteria were based on the best available evidence for both clinical and cost

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				shortcoming of the 2008 guideline. Although enshrined in the Simon Broome criteria as first published in 1991, it is widely recognised that the optimum cut-off for identification of Familial Hypercholesterolaemia varies according to age and gender, and that in primary care, total cholesterol of greater than 7.5 mmol/L is seen too often in middle aged and older patients to allow consideration of a possible diagnosis of FH in every case, while discriminating against younger people who have the most to gain from early diagnosis. Indeed, according to the Health Survey for England, this cut-off represents the 80th to 90th centile for 45 to 55 year old men and the 75th to 80th centile for 55 to 65 year old women, so values in this range are found in 15-25% of people, very few of whom will have FH. Conversely, a total cholesterol of 7.5 mmol/L is found in less than 5% of females under 35 years, in less than 10% of males under 35 years and even fewer in younger age groups, despite uniform genetic risk. It would be much better to use an appropriate age and sex specific centile as the cut-off (e.g. 95th centile) to ensure that manageable numbers, including those at highest risk, are identified consistently in all age groups. UK general population data published by Health Survey for England could easily be adapted for this purpose.	effectiveness. Evidence was not identified for alternative approaches to these issues, and in particular not for approaches to referral for DNA testing stratified by age and sex. In particular, the committee agreed it would not be appropriate to use general population data on cholesterol distributions to set thresholds for considering a diagnosis of FH without any evidence on the practical effect such a change would have. In particular, the committee were concerned at the lack of data on how FH prevalence changes by cholesterol level at different ages.
Royal College of Pathologists	Short	4	8	1.1.1 Coronary event is an ambiguous term which is not defined here – a more appropriate alternative would be confirmed CHD (MI, CABG, PCI and/or definite coronary artery disease on coronary angiography)	Thank you for your comment. The committee agreed that it was appropriate to make with recommendation clearer, and it has been amended along the lines of your suggestion.
Royal College of Pathologists	Short	4	10	1.1.2 See comment 3. The age discrimination is even with this higher single cut-off for total cholesterol of 9.3	Thank you for your comment. Following consultation the committee reconsidered the

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				mmol/L. This is the 97.5th centile for men and women aged 55 but greater than the 99th centile in men under 35 years and greater 99.5th centile in women under 35 years. It would be better to build in appropriate centile cut-offs (e.g. 97.5th) into search strategies to eliminate the potential for age discrimination.	evidence from the economic model along with evidence on the distribution of total cholesterol in different age/sex groups within the general population and decided to recommend primary care case finding in people aged 16-29 with a TC>7.5 mmol/l and in people aged 30+ with a TC>9.0 mmol/l. It was felt that these recommendations struck the best balance between the strength of the evidence, equitable representation among different age groups and the practicalities of implementation. A full discussion of these deliberations can be found in the evidence review document.
Royal College of Pathologists	Short	4	11	1.1.2 The cut-off of 9.3 is close (within the margins of measurement uncertainty) to that specified in the CG181 guideline for specialist referral even in the absence of an adverse family history, if secondary causes have been excluded (Total cholesterol greater than 9.0 mmol/L and/or non-HDL-cholesterol greater than 7.5 mmol/L, equivalent to LDL-cholesterol greater than 6.5 mmol/L if triglycerides are less an 2.3). These should be harmonised to reduce unnecessary confusion.	Thank you for your comment. Following consultation the committee reconsidered the evidence from the economic model along with evidence on the distribution of total cholesterol in different age/sex groups within the general population and decided to recommend primary care case finding in people aged 16-29 with a TC>7.5 mmol/l and in people aged 30+ with a TC>9.0 mmol/l. It was felt that these recommendations struck the best balance between the strength of the evidence, equitable representation among different age groups and the practicalities of implementation. A full discussion of these deliberations can be found in the evidence review document.
Royal College of Pathologists	Short	5	1	1.1.3 This recommendation is contradictory to the CG181 guideline which recommends a non-fasting full lipid profile. Triglycerides must be measured in all	Thank you for your comment. This recommendation to measure total cholesterol relates to the case finding element of the guideline,

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				cases as severe hypertriglyceridaemia is frequently found in association with elevated total cholesterol and could otherwise be missed, with consequent risk of acute pancreatitis. In the absence of secondary causes, non-fasting triglycerides greater than 4.5 or fasting triglycerides greater than 2.3 mmol/L are against the diagnosis of FH. If total (or non-HDL-) cholesterol exceeds the cut-off chosen in 1.1.1 then a fasting lipid profile should be measured.	as total cholesterol is the measurement that triggers a referral when primary care records are searched. This recommendation does not preclude additional measurements being taken if felt to be clinically appropriate.
Royal College of Pathologists	Short	5	8	1.1.6 Both the Simon Broome criteria and Dutch Lipid Network Score (DLCN) yield several overlapping categories of clinical diagnosis. While patients with a DLNC score of greater than 5 have a higher probability of having a pathogenic FH causing mutation than those with lower scores, in the majority of patients with a clinical diagnosis of Possible FH the DLCN score may be only 3 to 5. A clinical diagnosis of Definite FH by Simon Broome criteria requires the finding of tendon xanthoma (ideally corroborated by 2 experienced observers) which is rarely identified in primary care, but such patients are quite likely to have a pathogenic FH causing mutation. We suggest this recommendation be amended to say “Refer ....for DNA testing if they meet the Simon Broome criteria for definite FH, or they have a DLCN score greater than 5.	Thank you for your comment. This recommendation was based on the available evidence for these clinical tools, which showed two alternatives: i) the Simon Broome possible and definite criteria ii) a DLCN score >5 had the best balance between sensitivity and specificity.
Royal College of Pathologists	Short	5	8	1.1.6 The recommendation to refer for DNA testing should surely take account of the number of eligible relatives (at least first and second degree, at 50% and 25% risk respectively) for cascade testing. If there are none, there is no benefit in DNA testing. Indeed there may be a minimum number of eligible relatives may be	Thank you for your comment. The economic model made conservative assumptions about the number of relatives able to be contacted and the proportion that took up cascade testing. Even if these assumptions were halved, strategies including cascade testing remained cost effective. The

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				required to ensure that the recommendation is cost-effective.	committee also believed that there would be benefits to definitively confirming or ruling out a diagnosis of FH over and above the effectiveness observed in trials of statin treatment in the non-FH specific population. In the rare case where a primary care practitioner knew that 0 relatives could be contacted, DNA testing may therefore still be cost-effective. In general, the committee believed the evidence to be robust regarding the general population suspected of having FH but these recommendations do not preclude individual clinicians from deviations that they believe beneficial in individual cases.
Royal College of Pathologists	Short	5	10	1.1.6 The purpose of using the DLCN score in this context is to identify those with a higher probability pathogenic FH causing mutation but the score has not been validated in the UK population. The DLCN score parameter weightings may not be calibrated correctly to give an acceptable mutation positive rate with a score of greater than 5. The cost-effectiveness of DNA testing will depend on the mutation positive rate achieved in those tested, and other scoring systems (e.g. Wales FH score) may perform better in the UK population.	Thank you for your comment. This recommendation was based on the available evidence for these clinical tools, which showed two alternatives: i) the Simon Broome possible and definite criteria ii) a DLCN score >5 had the best balance between sensitivity and specificity. The committee noted that the DLCN score has not been validated in the UK, but agreed the results were unlikely to be meaningfully different from those found in the available studies. The committee noted that a number of other scoring systems (including the Wales score) were available, but agreed that at the moment there was

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					not sufficient evidence to recommend any of them for routine use.
Royal College of Pathologists	Short	5	11	1.1.7 The clinical diagnosis of Homozygous FH should be referred to a specialist centre and the diagnosis confirmed by DNA testing.	Thank you for your comment. This recommendation is outside the scope of this guideline update, and therefore changes to this recommendation cannot be made.
Royal College of Pathologists	Short	5	17	1.1.8 We agree with this recommendation, which requires two fasting blood tests, in cases where the LDL-cholesterol is close to the threshold for diagnosis (within 10%) but this be difficult to achieve in all circumstances (e.g. following admission for a premature coronary event) and should not delay commencement of appropriate treatment. This recommendation should appear immediately below 1.1.5	Thank you for your comment. This recommendation is outside the scope of this guideline update, and therefore changes to this recommendation cannot be made. The committee agreed that, since this whole section of the guideline relates to the use of LFL-cholesterol for diagnosis of FH, the order of the recommendations was unlikely to make a meaningful different to how the guidance was interpreted, and therefore it was not necessary to change tis ordering.
Royal College of Pathologists	Short	5	20	1.1.9 We agree with this recommendation which should appear immediately below 1.1.6	Thank you for your comment. These recommendations have been reordered as suggested.
Royal College of Pathologists	Short	6	18	1.1.16 In children at genetic risk of Homozygous FH, genetic testing should be carried out as soon as possible after birth as they are at risk of cardiac death as early as 2 years of age, and should certainly not be delayed until 5 years. LDL-cholesterol measurement is subsequently required to assess the severity of the clinical phenotype and the modality of treatment.	Thank you for your comment. This recommendation is outside the scope of this guideline update, and therefore changes to this recommendation cannot be made.
Royal College of Pathologists	Short	7	4	This wording “people with a diagnosis of FH” is ambiguous. This should specify those in whom the clinical diagnosis has been confirmed with a genetic test – e.g. “genetically confirmed diagnosis of heterozygous (or homozygous) FH.”	Thank you for your comment. This recommendation has been clarified to specify that cascade testing should only be carried out when someone has a genetic diagnosis of FH.

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Royal College of Pathologists	Short	7	7	1.2.2 This recommendation to offer "all people with FH a referral" is contradictory to 1.1.6 which recommends selective referral of those at greater risk of having a pathogenic FH causing mutation on DNA testing.	Thank you for your comment. The Committee does not believe these recommendations are contradictory, as they both mention the need to refer people who have a clinical diagnosis of FH to specialist services.
Royal College of Pathologists	Short	7	23	1.3.1.2 To be consistent with the CG181 guideline and to offer greater convenience for patients and healthcare teams, patients should not be required to fast in order to assess response to statin therapy which can be monitored quite satisfactorily with non-fasting non-HDL-cholesterol measurements. The wording should be changed to "50% reduction of non-HDL-cholesterol from the baseline measurement."	Thank you for your comment. The committee agreed that measuring of non-HDL-cholesterol rather than LDL cholesterol is often common in practice, but the evidence did not enable them to make specific recommendations on this point, as this was not an issue considered within the scope of this guideline update.
Royal College of Pathologists	Short	7	23	1.3.1.2 As baseline measurements (particularly of fasting LDL-cholesterol) are frequently unavailable in secondary prevention patients initiated on high intensity statins in hospital after ACS/MI, an alternative absolute target would be valuable for such patients e.g. non-HDL-cholesterol less than 2.5 mmol/L, as by definition, virtually all clinically diagnosed FH patients have pre-treatment non-HDL-cholesterol greater than 5.0 mmol/L.	Thank you for your comment. The committee agreed that measuring of non-HDL-cholesterol rather than LDL cholesterol is often common in practice, but the evidence did not enable them to make specific recommendations on this point, as this was not an issue considered within the scope of this guideline update.
Royal College of Pathologists	Short	7	26	1.3.1.3 Again non-fasting non-HDL-cholesterol reduction should be recommended for routine monitoring. Assessment of achieved LDL-cholesterol is only required those being considered for PCSK9 inhibitor therapy as currently recommended in TA393 and TA394	Thank you for your comment. The committee agreed that measuring of non-HDL-cholesterol rather than LDL cholesterol is often common in practice, but the evidence did not enable them to make specific recommendations on this point, as this was not an issue considered within the scope of this guideline update.
Royal College of Pathologists	Short	8	10	1.3.1.6 As in 1.3.1.2 and 1.3.1.3 , non-HDL-cholesterol should be recommended for assessment of response	Thank you for your comment. This recommendation is from a NICE technology

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				to statin therapy and there is no place for total cholesterol in assessment of response. Assessment of achieved LDL-cholesterol is only required those being considered for PCSK9 inhibitor therapy as currently recommended in TA393 and TA394	appraisal (TA385) that is not being updated as part of this guideline, and therefore it is not possible to make changes to these recommendations as part of this update.
Royal College of Pathologists	Short	8	20	1.3.1.8 This presumably refers back to the earlier paragraph 1.3.1.2, the "relevant population" being FH. this should be included for clarity.	Thank you for your comment. This recommendation is from a NICE technology appraisal (TA385) that is not being updated as part of this guideline, and therefore it is not possible to make changes to these recommendations as part of this update.
Royal College of Pathologists	Short	9	6	1.3.1.11 Again non-fasting non-HDL-cholesterol reduction should be recommended for routine monitoring. Assessment of achieved LDL-cholesterol is only required those being considered for PCSK9 inhibitor therapy as currently recommended in TA393 and TA394	Thank you for your comment. This recommendation is outside the scope of this guideline update, and therefore changes to this recommendation cannot be made.
Royal College of Pathologists	Short	9	6	As defined in paragraphs 1.3.1.6 and 1.3.1.8 and 1.3.1.11 if patients remain inadequately controlled on the maximum tolerated combination or statins and ezetimibe, they should be considered for PCSK9 inhibitor therapy and recommended by TA393 and TA 394. For FH patients this would require the addition of a statement cross -referencing this guidance, e.g. "In patients with FH being treated for primary prevention consider evolocumab or alirocumab if the reduction of non-HDL-cholesterol concentration is not greater than 50% or LDL-cholesterol remains persistently greater than 5.0 mmol/L. In patients with FH being treated for primary prevention consider evolocumab or alirocumab if the reduction of non-HDL-cholesterol concentration is	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.

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				not greater than 50% or LDL-cholesterol remains persistently greater than 5.0 mmol/L. In patients with FH being treated for secondary prevention consider evolocumab or alirocumab if the reduction of non-HDL-cholesterol concentration is not greater than 50% or LDL-cholesterol remains persistently greater than 3.5 mmol/L "	
Royal College of Pathologists	Short	9	16	1.3.1.13 Nicotinic acid is no longer available in the UK and has no place in the management of FH. Fibrates are not part of the drug flow in FH as they are rarely effective in FH are used only in rare exceptional cases in specialist care. Although they may be effective, alone or in combination with statins, in patients with inherited mixed lipid disorders (e.g. Familial combined Hyperlipidaemia and Familial Type III Hyperlipidaemia) to be consistent with CG181 they should be reserved for management of severe hypertriglyceridaemia and should be deleted from this statement.	Thank you for your comment. Whilst the scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy, references to nicotinic acid have been removed from the guideline due to it no longer being licensed. The same is not true of fibrates, and therefore reference to those has been left in the recommendation.
Royal College of Pathologists	Short	9	19	1.3.1.13 Again non-fasting non-HDL-cholesterol reduction should be recommended for routine monitoring. Assessment of achieved LDL-cholesterol is only required those being considered for PCSK9 inhibitor therapy as currently recommended in TA393 and TA394	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
Royal College of Pathologists	Short	9	20	1.3.1.14 Delete "nicotinic acid or a fibrate" – as already stated these should not be used	Thank you for your comment. Whilst the scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy, references to nicotinic acid have been removed from the guideline due to it no longer being licensed. The same is not true of

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					fibrates, and therefore reference to those has been left in the recommendation.
Royal College of Pathologists	Short	9	23	1.3.1.15 Delete the whole statement as nicotinic acid and fibrates should not be used	Thank you for your comment. Whilst the scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy, references to nicotinic acid have been removed from the guideline due to it no longer being licensed. The same is not true of fibrates, and therefore reference to those has been left in the recommendation.
Royal College of Pathologists	Short	9	27	1.3.1.16 Delete the whole statement as nicotinic acid should not be used	Thank you for your comment. Whilst the scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy, references to nicotinic acid have been removed from the guideline due to it no longer being licensed.
Royal College of Pathologists	Short	11	17	1.3.1.26 Delete “fibrates” – as already stated these should not be used	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.
Royal College of Pathologists	Short	19	18	1.5.1.5 There is no need for a fasting lipid profile as part of the routine annual structured annual review. For reasons already given, non-fasting non-fasting non-HDL-cholesterol reduction should be recommended for routine monitoring. Assessment of achieved LDL-cholesterol is only required those being considered for PCSK9 inhibitor therapy as currently recommended in TA393 and TA394	Thank you for your comment. The scope of this update only included specific questions on case finding, scoring criteria for diagnosis and statin therapy. Therefore, it is not possible to make changes to the guideline in any other areas as part of this update.

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Royal College of Pathologists	Short	21	8	DLCN criteria/score assigns a numerical value (the maximum possible score being 18) but also a diagnostic sub-classification into possible (score 3-5), probable (score 6-8) and Certain/Definite (score 9 or greater). These should be stated here.	Thank you for your comment. We have added more detail to this effect in the glossary section of the evidence review.
Royal College of Pathologists	Short	21	22	Simvastatin 80 mg is no longer recommended due to unacceptable risk of muscle toxicity and should be deleted. The high intensity doses of atorvastatin (20-80 mg) and rosuvastatin (20-40 mg) are tabulated in CG181 which should be cross-referenced	Thank you for your comment. The differential effectiveness of different statins was not within the scope of this guideline update. However, the recommendation does state that the initial treatment should use the statin with the lowest acquisition cost, which is likely to exclude simvastatin from being used.
Royal College of Pathologists	Short	22	13	Non-HDL-cholesterol should be included here, mentioning that fasting is not required. The Friedewald equation assumes that the sample is a fasting one with triglyceride concentration less than 4.5 mmol/L, otherwise the calculation is not valid.	Thank you for your comment. This recommendation comes from a NICE technology appraisal which is not being updated at this time, and therefore it is not possible to make changes to this recommendations.
Sanofi	Addendum	General	General	**Addendum to Clinical Guideline CG71, Familial hypercholesterolaemia** **Consultation comments** Sanofi welcomes the updated recommendations made for the identification of people with Familial Hypercholesterolaemia and appreciate the opportunity to provide comment. We note the reference to the Technology Appraisal Guidance's for PCSK9i inhibitors (TA393[1] and TA394[2]) on page 51, line 9 in the context that the role of these medicines, for people with FH, will not be discussed as part of CG71.	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.

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				Sanofi feel there is an opportunity to include information on the place of PCSK9 inhibitors or to refer readers to the available Technology Appraisal Guidance in a way that communicates their role within the management options for relevant people, even if information about the medicines is not provided. Sanofi would suggest inclusion of information or referral to TA393[1] and TA394[2] on page 10, 1.2 Recommendations and page 5, 4.1 Introduction. Sanofi requests the inclusion of PCSK9 inhibitors as a treatment option in Clinical Guideline 71 (CG71) based on the following reasons: Alirocumab received a technical appraisal recommendation [TA393[1]] in June 2016. Alirocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if: • Low-density lipoprotein concentrations are persistently above the thresholds specified despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached or further titration is limited by intolerance (as defined in NICE's guideline on familial hypercholesterolaemia: identification and management). • Primary heterozygous-familial hypercholesterolaemia without cardiovascular disease treatment threshold LDL-c persistently above 5mmol/l and	

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				• Primary heterozygous-familial hypercholesterolaemia with cardiovascular disease treatment threshold LDL-c persistently above 3.5mmol/l The 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias[3] have included PCSK9i class as a treatment option *Table 16 Recommendations for the pharmacological treatment of hypercholesterolaemia* In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered. The ESC/EAS Guidelines 2016 highlight that all patients with FH are considered to be at high risk of CV events (SCORE classification not required). The recommendation for the very high-risk group: LDL-C <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL). *Supplementary Table A Percentage reduction of low-density lipoprotein cholesterol (LDL-C) requested to achieve goals as a function of the starting value.* The table indicates that people with an LDL-c >6.2mmols/l would require a 70% reduction from baseline to achieve an LDL-c of 1.8mmol/l or a 60%	

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				reduction from baseline to achieve an LDL-c of 2.6mmol/l. High intensity statins are proven through LDL-c lowering to improve cardiovascular outcomes for patients. There is also considerable inter individual variation in LDL-C reduction with the same dose of drug[4]. NICE Clinical Guidance 181[5] describes issues with adherence to statins Non-adherence to statin therapy is highlighted in the NICE clinical guideline CG181[5]. *11.10 Adherence to statin therapy. The development of statins has been heralded as an important advance in the primary and secondary prevention of CVD. Adherence to statin treatment has however been shown to decrease over time. Continuation rates in the West of Scotland Coronary Prevention Study (WOSCOPS) were 84.5% patients after 1 year and this fell to 70.4% at 5 years [6]. Adherence in the real world is substantially worse than that seen in clinical trials. Adherence with statins declines over time and a significant proportion of patients stop taking their statin within 2 years of initiation.* The studies showing safety and efficacy of statins have led to their recommendation for use in patients with FH. Odyssey FH I and II[7] has shown efficacy and safety of alirocumab in 490 patients with confirmed HeFH over a 24 weeks. The patients were treated with maximally	

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				tolerated lipid lowering therapy achieved a mean -48% reduction of LDL-c from baseline. **Sanofi welcomes the recommendations to increase the identification of patients with FH; the guidelines fall short by not fully sign posting the reader to the available medicines that could help achieve the 50% reduction in LDL-c from baseline.** **We would ask the committee to consider the treatment recommendations to include PCSK9i's NICE TAGs (TAG 393[1] and TAG 394[2]) or more robust referral to the TAG's**. *References.* 1. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia Technology appraisal guidance [TA393] Published date: 22 June 2016 2. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [TA394] Published date: 22 June 20162016 ESC/EAS Guidelines for the Management of Dyslipidaemias European Heart Journal (2016) 37, 2999–3058 3. Boekholdt SM, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol. 2014; 64:485–494. 4. Cardiovascular disease: risk assessment and reduction, including lipid modification	

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				5. Clinical guideline [CG181] Published date: July 2014 6. Shepherd J et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. New England Journal of Medicine. 1995; 333(20):1301-1307 7. John J.P. Kastelein et al. Odyssey FH I and II European Heart Journal doi:10.1093/eurheartj/ehv370	
Western Health & Social Care Trust	Addendum	10	General	Section 1.2 (2) Need to exclude secondary causes of dyslipidaemia and also mixed dyslipidaemia. The majority of subjects with cholesterol >9.3mmol/L will have a significant mixed dyslipidaemia and will have a low probability of having FH. Failure to exclude such patients, which could be easily undertaken by database search would greatly dilute the yield. (3) The guideline refers to measuring 'cholesterol'. In fact a full lipid profile should be measured as LDL and triglycerides are required for assigning a Dutch Lipid Clinic Network score to assess FH risk. (4) The Dutch Lipid Clinic Network or Simon Broome are used to assess likelihood [rather than diagnosis] of FH and therefore the need for genotyping	Thank you for your comments. (2) The committee agreed that it was important to exclude people with clear alternative causes of high total cholesterol when undertaking searches, but noted that there was no evidence on which they were able to make specific recommendations on this topic. (3) This recommendation to measure total cholesterol relates to the case finding element of the guideline, as total cholesterol is the measurement that triggers a referral when primary care records are searched. This recommendation does not preclude additional measurements being taken if felt to be clinically appropriate. (4) The committee agreed that DNA testing was the appropriate way to confirm a diagnosis of FH.

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Western Health & Social Care Trust	Short	General	General	The guideline [shortened form] appears not to make any mention of PCSK9 inhibitors despite the fact that they have been approved in the relevant NICE Technology Appraisals [evolocumab and arilocumab] for use in FH. This is an important omission.	Thank you for your comment. The guideline has now been amended to include cross-references to the NICE technology appraisals on evolocumab and alirocumab, which give guidance on when the use of these drugs is appropriate.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*