UK National Screening Committee

Screening for familial hypercholesterolaemia in children

26 February 2020

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not screening for familial hypercholesterolaemia (FH) in children meets the UK NSC criteria for a systematic population screening programme.

Current recommendation

2. The UK National Screening Committee (NSC) does not currently recommend universal child screening for FH. This policy was informed by the last external evidence review on this topic, which was published in 2016. The Committee agreed that screening for FH in children should not be implemented nationally because:

    - no studies were identified that examined how well a population-wide screening test for children performed in practice
    - no studies were identified that assessed whether child screening reduces morbidity and mortality from FH
    - the review found little relevant evidence on the ethical issues and acceptability of universal child screening, including the management of the condition in screen-detected children.

Evidence Summary

1. The 2019 review was undertaken by Bazian in accordance to the UK NSC evidence review process https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process

2. The 2019 evidence summary addresses questions relating to screening test performance, the mortality and morbidity effects of screening and potential harms from universally screening children for FH.

3. The conclusion of the 2019 evidence summary is that the current recommendation, that whole population screening for FH in children (aged <10 years) should not be introduced in the UK, should be retained. This is for the following reasons:

    - There is remaining uncertainty over the optimal screening age (1–2 years or 9–10 years), test (TC and/or LDL-C) and test thresholds that would be used in a universal FH screening programme in children. Two UK studies met inclusion criteria for this question. One large prospective screening pilot of children aged 1–2 years and one smaller retrospective study evaluating the test performance of the TC and LDL-C thresholds in children 9 years of age.

      The prospective study found that half of children with FH variants had a TC level below the cut-off. Meanwhile almost a third did not have FH gene variants and were defined as having FH based on having 2 sequential cholesterol samples above the threshold (multifactorial/polygenic FH). There is some uncertainty over the natural history of this condition and whether it is distinct from FH. Therefore, there is need to understand how FH would be diagnosed in the context of a universal screening programme, whether by the carriage of gene variants and/or positive family history indicative of FH (as current diagnostic criteria), or by raised cholesterol alone, given this is the mediator of cardiovascular risk.

      The retrospective study found the best combination of sensitivity and specificity when using the LDL-C cut-off (1.84 MoM) at 9 years. Screening at age 9–10 years could potentially give a better indication of whether FH variants are going to raise cholesterol/cardiovascular risk. This could also have the benefit of placing diagnosis at the time when treatment could start. However, this is a retrospective analysis of a smaller sample with only 6 cases, this study alone provides insufficient evidence to be sure that LDL-C measurement would be the preferable screening test. **Criterion 5 is not met**

    - No evidence was found to inform whether universal screening affects FH-related morbidity or mortality compared with no screening. There is adequate evidence that statin treatment reduces LDL-C and TC levels at up to one year in children meeting diagnostic criteria for FH from age 9 – 10 years. Even given the lack of direct evidence that this reduces FH-related morbidity in the longer term, treatment is

expected to be beneficial for this group. However, there is no evidence to inform whether starting lifelong statins is beneficial for children with multifactorial/polygenic FH identified by screening. **Criterion 11 not met**

- There is no evidence to inform whether a universal screening programme may be associated with harms. There is evidence that statins for children meeting diagnostic criteria for FH are safe in the short to medium term, up to 2.5 years. Even given the lack of longer term safety data, treatment is considered to be beneficial for this group. However, there is no evidence to inform whether the risk-benefit balance may differ in children with multifactorial/polygenic FH. **Criterion 13 not met**

Consultation

4. A three-month consultation was hosted on the UK NSC website. Direct emails were sent to 27 stakeholders. **Annex A**

   Comments were received from the following four stakeholders (See **Annex B** for comments):

   - HEART UK
   - Royal College of General Practitioners
   - Royal College of Paediatrics and Child Health
   - Professor David Wald, Wolfson Institute of Preventive Medicine, QMUL

5. The public consultation closed on27 October 2019.

6. Two stakeholders, the Royal College of Paediatrics and Child Health and the Royal College of General Practitioners, agreed with the conclusions of the evidence review (see **Annex B**). However, two stakeholders HEART UK and Professor David Wald, Wolfson Institute of Preventive Medicine disagreed with the review's conclusions (see **Annex B**). Common issues were raised by these stakeholders and are summarised below.

   - The stakeholders disagree with the evidence review conclusions that '*There is a remaining uncertainty in the evidence regarding consensus on the diagnostic criteria that should be used to definitively diagnose FH in children identified through universal screening*'. They suggest that cut-offs and screening policy are based on evidence, such as the Wald et al prospective screening cohort study, would identify children with the higher cholesterol levels who would be at risk of future

cardiovascular disease, and therefore, would benefit from statin treatment. Such children would be eligible for treatment in accordance to the NICE clinical guideline (CG) 71 on the identification and management of FH.

Response: The update review identified two UK cohort studies that assessed the test performance of the TC and/or LDL-C cut-off values to be used in a screening programme. One was a large prospective pilot study assessing the TC cut-off (1.53 multiples of the median [MoM]) for screening children aged 1–2 years. The second was a small retrospective study evaluating the same TC cut-off, in addition to the LDL-C cut-off (1.84 MoM) in children aged 9 years. Both studies found that this TC cut-off had poor sensitivity for identifying children with FH as defined by carriage of an FH gene variant (NICE CG71 currently states that '*all people who have an identified mutation diagnostic of FH have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet the diagnostic criteria'*). In the prospective study half of children with FH variants had a TC below the cut-off. These would be expected to be false negatives using current diagnostic criteria for FH. Meanwhile almost a third of children detected in the study by having two sequential cholesterol samples above the threshold did not have FH gene variants (multifactorial/polygenic FH). The study proposed lowering the TC cut-off to 1.35 MoM, which would improve sensitivity for detecting those with variants. However, this may need to be evaluated in practice.

The retrospective study indicated that raising the screening age and/or using LCL-C rather than TC as the test may improve sensitivity for identifying those with variants. The advantage of this strategy is that the screening is performed at an age when treatment could also start. However, as this was a retrospective analysis based on few cases, more evidence would be needed to explore the reliability of LDL-C as the appropriate screening target in the 9–10 years age group.

- The consultation responses give considerable emphasis to the fact that high cholesterol increases risk of atherosclerosis. Therefore, screening would identify children with the highest cholesterol levels who would be at future cardiovascular risk and would benefit from statin treatment, which have been demonstrated to be an effective and safe treatment.

Response: The association between FH and raised LDL-C with increased risk of atherosclerosis is not disputed by this review. Neither does the review dispute that children with a diagnosis of FH should be managed in accordance to the NICE CG71 on the identification and management of FH. However, the aim of this review was to look at screening for FH in children and the implication of such a screening programme. As such the review looked primarily to current diagnostic criteria as providing the reference standard for this condition. Questions remain over the optimal screening age, test and cut-offs. Moreover, the management of a significant proportion of cases identified by some screening strategies is not addressed in current treatment guidance. This includes multifactorial FH and infants aged 12 months.

- Another frequent comment made was in relation to the lack of direct evidence on the effectiveness of a screening programme for FH in children reduce FH-related morbidity and mortality, and that statins are safe in the long-term beyond around 2 years of use. The comments assert that RCTs would be unethical and that statins are known to reduce LDL-C and atherosclerosis risk.

Response: The evidence in relation to the 2 key questions assessing these issues was limited and of low quality. However, the review states that, even without direct long-term evidence, it is expected that reduced future morbidity/mortality could be inferred from sustained reduced cholesterol, and that the benefits of statins are expected to outweigh the risks for children with an unequivocal diagnosis of FH. The review accepts that long-term RCTs of treatment vs no treatment in diagnosed FH would not be ethical. However, this may not rule out all RCTs. For example, evidence might be obtained by RCTs of screening (and treatment) vs no screening (and treatment). It also did not seem unreasonable to consider that follow-up of non-randomised comparative populations (for example in the FH register) might continue in the longer term.

- The stakeholders disagree with the evidence review statement that *'Future studies are needed to directly assess the views of the UK public and healthcare professionals towards universal screening for FH in young children; for example, whether there are any reservations towards early and lifelong treatment'*.

Response: All included studies in the review were searched for the views of the public and healthcare professionals in relation to universal screening for FH in young children. Only two studies provided sufficient information for inclusion. These studies were small, gave inconclusive results particularly because the views on the care and potential treatment of their child were not explored, and it was unclear whether these views relate to child screening or parents' carriers screening.

The stakeholders also highlighted a missed publication looking at perceptions and preferences of the general population concerning universal screening of FH in children. This was not included in the current review because it was published outside the search dates. Although the conclusion of this publication appears to support screening, it is not expected that its inclusion in the review would have changed it conclusion in relation to criterion 13. The paper will be considered for inclusion in the next review.

- Some consultees raised issues relating to the phraseology and content of the review, eligibility criteria for inclusion in the review and overall analysis.

Response: These suggestions were considered by the reviewer and alterations were made to the evidence review where appropriate. In relation to comments made on the eligibility criteria for inclusion in the review, the protocol of the evidence summary was developed *a priori* following discussion with experts in the field. Information on the inclusion and exclusion criteria are stated in the 'Methods' section of the evidence summary.

Recommendation

7. The Committee is asked to approve the following recommendation:
   A systematic population screening for familial hypercholesterolaemia in children is not recommended in the UK.

Criteria (only include criteria included in the review)	Met/Not Met
Section 1 - Criteria for appraising the viability, effectiveness and appropriateness of a screening programme	
The Test	
5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed	**Not Met**
The Screening Programme	
11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	**Not Met**
13. The benefit gained by individuals from the screening programme should outweigh any harms for example from over-diagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications	**Not Met**

UK National Screening Committee

List of organisations and individual contacted

Annex A

1. AntiCoagulation Europe
2. British Cardiac Patients' Association
3. British Cardiovascular Society
4. British Heart Foundation
5. British Inherited Metabolic Disease Group
6. Cardiac Risk in The Young
7. Cardio & Vascular Coalition
8. Cardiomyopathy UK
9. Children's Heart Federation
10. Circulation Foundation
11. David Wald
12. Faculty of Public Health
13. Genetic Alliance UK
14. HEART UK
15. Institute of Child Health
16. Metabolic Support UK
17. MetBio
18. Royal College of General Practitioners
19. Royal College of Nursing
20. Royal College of Paediatrics and Child Health
21. Royal College of Physicians
22. Royal College of Physicians and Surgeons of Glasgow
23. Royal College of Physicians of Edinburgh
24. Royal Society for Public Health
25. Scottish Lipid Forum
26. UK Genetic Testing Network
27. Wolfson Institute of Preventive Medicine

UK National Screening Committee

Annex B

Royal College of General Practitioners

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September 2019

RCGP Response to UK NSC consultation on Familial Hypercholesterolaemia in children

The Royal College of General Practitioners (RCGP) supports the position of the UK NSC to not recommend population-based screening for familial hypercholesterolaemia in children in view of the lack of evidence on its long term benefits and harms.

The RCGP supports further research in this area and the reconsideration of this recommendation by the UK NSC once long term randomised controlled trial data is available.

The RCGP supports continuation of current practice in this area of identifying those with familial hyperecholesterolaemia through cascade screening as recommended by the National Institute for Health and Care Excellence (NICE).

UK National Screening Committee

UK National Screening Committee
Screening for familial hypercholesterolaemia in children
Executive Summary of HEART UK's consultation response

HEART UK welcomes the opportunity to comment on the review of evidence on screening for familial hypercholesterolaemia (FH) in children produced by Bazian for the UK National Screening Committee.

HEART UK strongly supports the implementation of a universal child screening programme and believes it is highly complementary of the NHS and Public Health England ambition to identify 25% of people with FH by 2024.

Through our consultation response, we hope to highlight several inaccuracies in Bazian's evidence review and identify where its conclusions are not supported by facts.

1. *There is a remaining uncertainty in the evidence regarding consensus on the diagnostic criteria that should be used to definitively diagnose FH in children identified through universal screening*

The proposed cut-offs and screening policy are based on the evidence from observed data and are reasonable given current knowledge. The approach identifies only a very high-risk group, either those with high cholesterol and an FH mutation or those with serial measurements of very high cholesterol. This approach also identifies all children with homozygous FH. Homozygous FH may cause very premature atheromatous arterial disease and death. Consensus *does* exist on the diagnostic criteria that should be used to definitively diagnose FH in children and has been recently published in the journal *Atherosclerosis*. Again, the criteria ensure that only very high-risk patients are diagnosed and clinically managed.

2. *It may be helpful to better understand the genotype-phenotype relationship to see whether certain FH gene variants carry higher risk of a child developing phenotypic FH and early atherosclerosis*

The clinically important phenotype in FH is the development of atherosclerosis and coronary heart disease caused by untreated LDL-C. Therefore, the exact molecular cause of FH in an individual is not relevant over and above their untreated LDL-C.

3. *Further study may help to understand whether the polygenic/multifactorial condition carries the same risk as monogenic FH or whether it should be considered a distinct condition*

As with almost all genetic conditions, not all FH mutations are known. Individuals with extremely high serum cholesterol (> 99th centile) on serial measurements are likely to have one or a collection of mutations that increase LDL cholesterol. Such individuals are at very high risk of premature ischaemic heart disease because cholesterol is the causal factor. Only those with persistently high serum cholesterol would be treated. Individuals with multifactorial hyperlipidaemia where no mutation is found who have lower mean levels of LDL-C and therefore lower risk of a cardiac event, are by definition not screen-positive in the proposed method. To the extent that such individuals may be identified in other ways, NICE CG71 (2017) states that these individuals with the clinical diagnosis of FH, who are found not to carry an FH-causing mutation, but may have polygenic hypercholesterolaemia, should be managed by GPs using QRISK charts to estimate coronary heart disease risk and offered lipid lowering therapy and other risk reducing therapies as appropriate.

4. *Understanding aspects of the natural history of FH may help to inform the appropriate screening test when considering that a number of young children who carry FH variants may have lower cholesterol, while others may have raised cholesterol despite have no identified gene variant*

There is no greater understanding of aspects of the natural history of FH that would help inform appropriate screening tests, because all individuals identified through universal screening for high cholesterol are, by definition, at high risk of coronary heart disease. All individuals identified will benefit from a lowering of their risk.

5. *Long-term RCTs assessing whether universal screening (or treatment) of children with FH affects long-term cardiovascular morbidity and mortality may be neither ethical nor feasible. However, comparative studies would be useful to understand whether screening (or treatment) improves intermediate markers of atherosclerosis in the medium term, such as carotid intima-media thickness or endothelial function*

Long-term RCTs are neither ethical nor feasible and will therefore never be carried out. However, there is overwhelming evidence that children with FH have elevated levels of the suggested intermediate markers of atherosclerosis, have a markedly elevated risk of future morbidity and mortality from coronary heart disease because of their elevated LDL-C, and that early identification and treatment to lower their LDL-C will concomitantly reduce this risk. This has been clearly demonstrated in a recent study by Luirink, Wiegman et al published in The New England Journal of Medicine, 20-Year Follow-up of Statins in Children with Familial Hypercholesterolaemia, which found that initiation of statin therapy during childhood in patients with FH, slowed the progression of carotid intima-media thickness and reduced the risk of cardiovascular disease in adulthood. In addition, children with untreated Homozygous FH are at risk of developing coronary heart disease in childhood, universal screening will prevent cardiovascular morbidity and mortality for these individuals in the short to medium term. We note that other newborn screening programmes have been introduced in the UK without RCT evidence, especially when such trials would be ethically unacceptable.

6. *It would also be beneficial to see whether [response] could differ by diagnostic criteria used for FH, age at treatment initiation, the statin or dose given*

There is always a variable response to treatment, as there is with all treatments, but the directional effect will be to *lower risk in all*, because cholesterol is high to start in all and high cholesterol is a causal risk factor for coronary heart disease.

7. *Follow-up of universally screened populations would be helpful to see that the full screening programme is not associated with any harm, such as from over-diagnosis (e.g. detection of multifactorial/polygenic or mildly elevated cholesterol), misclassification or missed diagnoses (e.g. monogenic FH without raised cholesterol in young childhood) or psychological or quality of life effects*

There is published evidence of no significant harm in children identified as having FH through cascade testing programmes, either from a physical, treatment or psychological perspective. There is similarly no evidence of physical harm to the child from universal screening and it is perverse to infer that there is any material difference between identifying a child through universal screening and cascade testing in terms of treatment and psychological impact of an FH diagnosis, even though universal screening will tend to identify the child at an earlier age. Furthermore, there cannot be any overdiagnosis, misclassification, or missed diagnoses, as the approach identifies only a high-risk group that all have a high cholesterol and it is the high cholesterol that causes premature cardiovascular disease.

8. *Further follow-up of treated children with FH would be beneficial to see whether statins or other management approaches are safe in the longer term and do not have adverse effects on quality of life, liver and muscle function, neurological and cognitive development, diabetes, or growth and reproduction. Again, it would helpful to see whether this may differ by diagnostic criteria used for FH, age at treatment, statin or dose given*

Statins and other management approaches recommended by NICE are safe in the longer term. NICE is an impartial, national regulator that provides evidenced-based clinical guidance to the NHS. Bazian are in effect undermining the decision of NICE CG71 (2017) to recommend the use of statins in children and HEART UK does not believe that this is within Bazian's scope.
With specific reference to the long-term safety of statins, 20-year follow up of statin therapy in children with FH has been carried out by Luirink, Wiegman et al and published recently in The New England Journal of Medicine. There were no serious adverse events reported, including no cases of rhabdomyolysis, and no significant differences in liver function were observed between patients with FH and their unaffected siblings. No further follow up is required.

9. *Studies are needed to directly assess the views of the UK public and healthcare professionals towards universal screening for FH in young children; for example, whether there are any reservations towards early and lifelong treatment*

Universal child screening has been found to be acceptable by the UK and Australian public and UK healthcare professionals. Early and lifelong treatment for those with FH is recommended by NICE CV71, and is already in practice in the NHS. Allowing any reservations to early and lifelong treatment with statins held by the general public or healthcare professionals to influence this review is in fact perpetuating the misinformation that surrounds statins and further undermining NICE guidance and NHS policy.
In Summary: HEART UK believes that there is overwhelming evidence that universally screening children for FH at the age of 1-2 years during routine immunisation visits to their GP is feasible and acceptable in the UK. The approach would enable all children at greatly increased risk of cardiovascular disease because of elevated cholesterol to mitigate that risk through the appropriate intervention at the appropriate earliest possible age.
In light of our consultation submission, HEART UK urges the UK National Screening Committee to review the conclusions of Bazian's evidence review in detail, with the support of relevant clinical expertise, and overturn its flawed conclusion that there is insufficient evidence to recommend a child screening programme for FH in the UK.

UK National Screening Committee

Name:	Jules Payne	**Email address:**	xxxx xxxx
Organisation (if appropriate):	HEART UK		
Role:	**Chief Executive**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
11	The assertion that there is a remaining uncertainty in the evidence regarding consensus on the diagnostic criteria that should be used to definitively diagnose FH in children identified through universal screening	*<u>Summary</u>* *The proposed cut-offs and screening policy are based on the evidence from observed data and are reasonable given current knowledge. The approach identifies only a very high-risk group, either those with high cholesterol and an FH mutation or those with serial measurements of very high cholesterol. This approach also identifies all children with homozygous FH. Homozygous FH may cause very premature atheromatous arterial disease and death.* *<u>Benefit to the child of this approach</u>* *All children with a high risk of premature cardiovascular disease are identified with no overdiagnosis or misclassification* This is not correct. The optimum age to screen for FH, in the general population, is in childhood between ages 1 and 2. At this age, the discrimination of a Total cholesterol (TC) measurement (or LDL-C) for identifying individuals with FH (defined clinically or genetically or using a combination) is strongest. Discrimination is worse in neonates or in older children/adults. Based on this the following policy is proposed: • Measure TC between age and 1 and 2 years • FH positive if TC ≥1.35 multiples of the median (MoM) + FH mutation

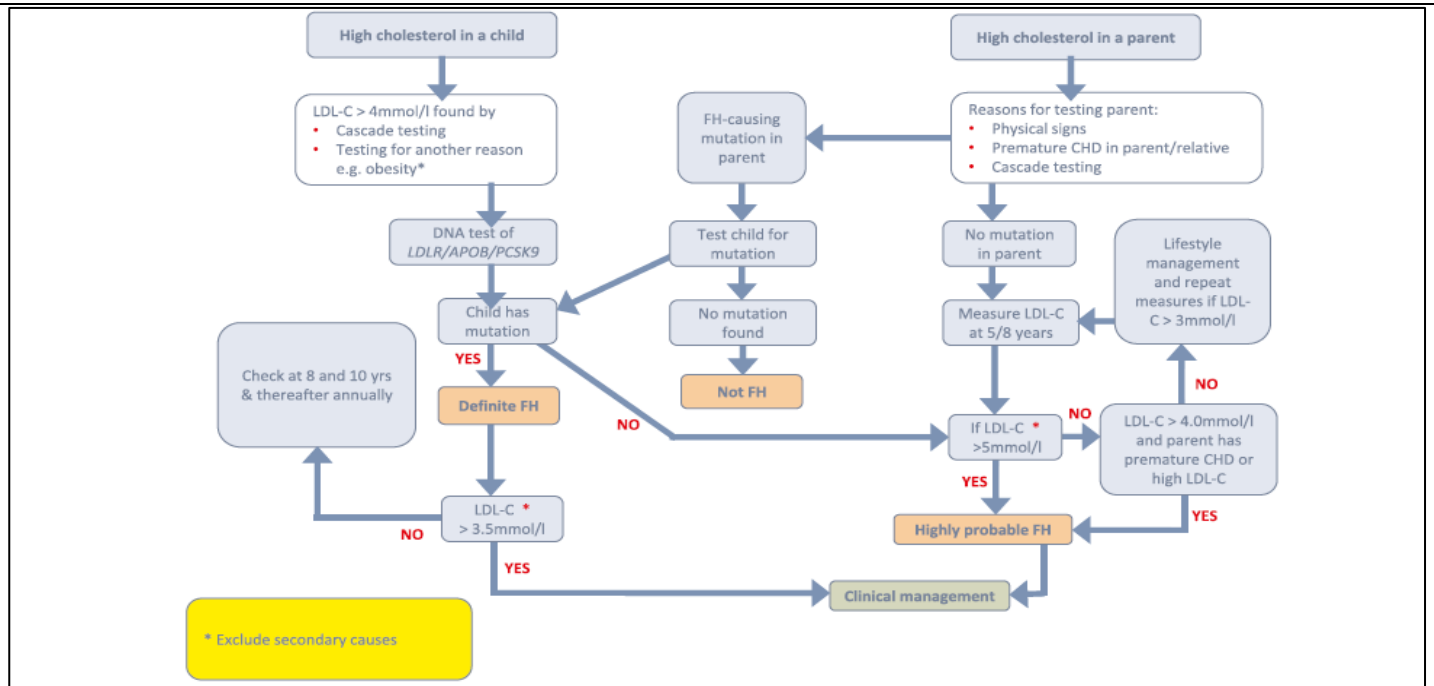
		• Or TC ≥1.50MoM on two measurements 3 months apart, without an FH mutation There is agreement that this approach identifies only a high-risk group because all have a high cholesterol and it is the high cholesterol that causes the disease (premature ischaemic heart disease). The Bazian report incorrectly states that some children are classified as screen positive with a low cholesterol. To screen positive requires a high cholesterol. There is no uncertainty that these criteria identify a very high risk group that need to be offered treatment to reduce their future risk of ischaemic heart disease – high cholesterol (>1.35MoM is equivalent to >95th centile plus an FH mutation and very high cholesterol (≥1.50MoM is equivalent to ≥99th centile) on serial measurements, which includes those with unidentified mutations or combinations of mutations. All physicians would accept that this defines a very high risk group for future ischaemic heart disease, given that cholesterol is the causal factor. Using screening performance (detection rates for a given false positive rate) to determine cholesterol cut-offs is invalid because the disorder (FH) is defined by its screening test (a tautological limitation). Much of the Bazian report focuses on this misconception instead of recognising that the key element of screening is identifying the cause of the disease Furthermore, this approach will identify all children with homozygous FH (HoFH) which may cause very premature atheromatous arterial disease and death, despite treatment with Lp apheresis combined with statin, ezetimibe and bile acid sequestrants. Consensus has been established for managing HoFH in the UK and published in the Atherosclerosis journal in 2016.[1] **Supporting Evidence:** • Comparing the distributions of cholesterol in children with and without FH indicates that discrimination (TC or LDL-C) in identifying children with FH (defined clinically or by an FH mutation or both) is greatest after the first year of life, between ages 1 and 9 years. [2] Within this age range, discrimination peaked between ages 1 and 2. Age 1-2 years is proposed as the optimal age and is when children are already attending their doctor for routine immunisation, so screening and immunisation can be undertaken together [3]. The tautological limitation is likely to have a minimal effect over when to test but a large effect on quantifying screening performance.

- Cholesterol is the cause of ischaemic heart disease in FH so a positive test needs to be based on a high cholesterol level supported by an FH mutation (identifies inherited high cholesterol securely) or two very high cholesterol levels measured 3 months apart (includes the highest risk children without a mutation since not all mutations are known).
- Observations from a demonstration project (10,095 children aged 13 months with paired TC and FH mutation test results) show that a cholesterol cut-off ≥1.35MoM plus an FH mutation or two cholesterol levels ≥1.50MoM measured 3 months apart identified 32 and 8 FH-positive children respectively (40 in total, prevalence of 1 in 250). The MoM values correspond to the 95th and 99th centiles, approximately 5.3mmol/L and 5.9mmol/L, respectively, based on the population median of 3.9mmol/L in 10,095 UK children aged 1-2 years. [4]
- The corresponding LDL-C values are 1.52MoM (95th centile, 3.3mmol/L) and 1.83MoM (99th centile, 4.0mmol/L, based on an LDL median of 2.4mmol/L aged 1-2 years, but TC is the preferred measurement because it is simpler and less expensive to measure.[4]
- As in all screening, cut-offs are a judgement based on balancing various considerations. Higher cholesterol cut-offs could be considered but this would miss a large proportion of high-risk individuals (eg. using a 1.50MoM cut-off instead of 1.35MoM misses 10 out of the 32 with an FH mutation). Lower cholesterol cut-offs could be used but this would identify few extra children with an FH mutation at the cost of considerably more FH mutation testing (eg. using a 1.30MoM cut-off (90th centile) doubles the number of FH mutation tests and identifies only 2 more children with an FH mutation, who are at lower risk of IHD because their cholesterol is lower. [4] The proposed cut-offs, critically identify a high-risk group without including low-risk individuals.

References

1. Michael France et al, HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. 2016. Atherosclerosis 255: 128-139.
2. Wald DS, Bestwick J, Wald NJ. Child-parent screening familial hypercholesterolaemia; a screening proposal based on a meta-analysis. 2007 BMJ 335:599-605.
3. Wald DS, Kasturiratne A, Godoy A et al. Child-Parent Screening for Familial Hypercholesterolaemia. J Pediat 2011;159(5):865-7
4. Wald DS, Bestwick JP, Morris JK et al.. Child-Parent Familial Hypercholesterolemia Screening in Primary Care. N Engl J Med 2016;375(17):1628-1637.

11	The assertion that there is a remaining uncertainty in the evidence regarding consensus on the diagnostic criteria that should be used to definitively diagnose FH in children identified through universal screening	*Summary* *Consensus does exist on the diagnostic criteria that should be used to definitively diagnose FH in children and has been recently published in the journal Atherosclerosis. Again, the criteria ensure that only very high-risk patients are diagnosed and clinically managed.* *Benefit to the child of this approach* *All children with a high risk of premature cardiovascular disease are identified with no overdiagnosis or misclassification* **Current management of children and young people with heterozygous familial hypercholesterolaemia - HEART UK statement of care.** Ramaswami U, Humphries SE, Priestley-Barnham L, Green P, Wald DS, Capps N, Anderson M, Dale P, Morris AA. Atherosclerosis. 2019 Sep 12;290:1-8. https://doi.org/10.1016/j.atherosclerosis.2019.09.005 There is consensus on the diagnostic criteria that should be used to diagnose FH in children and their management, including when to start statin treatment. Please see recently published consensus statement on the management of children and young people with heterozygous familial hypercholesterolaemia (FH) which addresses management of paediatric FH in the UK, identified by cascade testing when a parent is diagnosed with FH and for those diagnosed following incidental lipid tests. Atherosclerosis: **Further studies on this issue are not needed.** **Figure 4: Identification of childhood heterozygous FH**

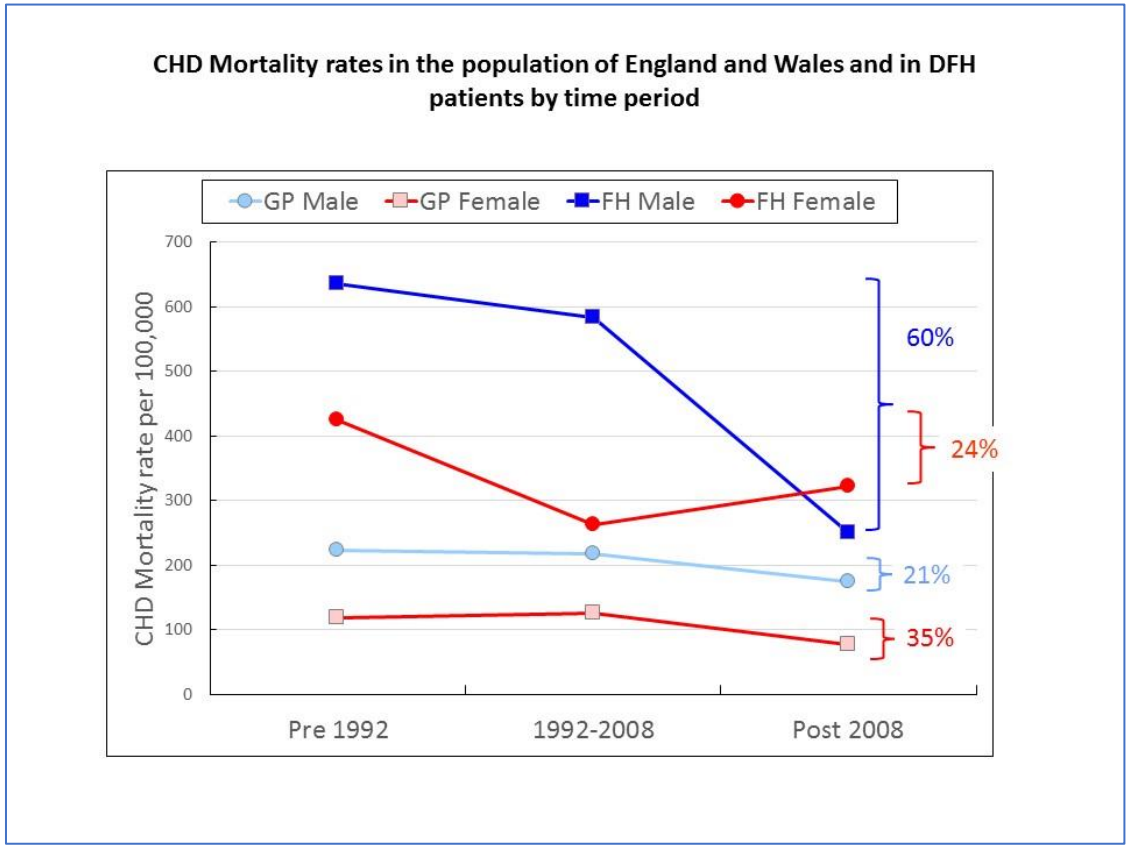
		 **Fig. 1.** Identification of childhood heterozygous FH. Exclude secondary causes of high cholesterol. For children and young people with definite FH, clinical follow up and management is detailed in Figs. 2 and 3.
11	It may be helpful to better understand the genotype-phenotype relationship to see whether certain FH gene variants carry higher risk of a child developing phenotypic FH and early atherosclerosis.	*<u>Summary</u>* *The clinically important phenotype in FH is the development of atherosclerosis and coronary heart disease caused by untreated LDL-C. Therefore, the exact molecular cause of FH in an individual is not relevant over and above their untreated LDL-C.* *<u>Benefit to the child of this approach</u>* *All at risk children are identified and can begin clinical management* This shows a lack of understanding of the considerable literature on this genotype-phenotype relationship. The clinically important phenotype in FH is the development of atherosclerosis and CHD. The data shows unequivocally that the single most important risk factor for future CHD in an individual with FH is their level of

		untreated LDL-C**.** This determines the "LDL-C Burden" as demonstrated in Figure 3 above. While some classes of the genetic causes of FH are associated with lower LDL-C than others (eg *APOB* mutation carriers generally lower LDL-C than *LDLR* mutation carriers, LDLR defective mutation carriers generally have lower LDL-C than LDLR receptor negative carriers), the exact molecular cause of FH in an individual is not relevant, over and above their untreated LDL-C. **Further studies on this issue are not needed**
11	further study may help to understand whether the polygenic/multifactorial condition carries the same risk as monogenic FH or whether it should be considered a distinct condition	*<u>Summary</u>* *As with almost all genetic conditions, not all FH mutations are known. Individuals with extremely high serum cholesterol (> 99th centile) on serial measurements are likely to have one or a collection of mutations that increase LDL cholesterol. Such individuals are at very high risk of premature ischaemic heart disease because cholesterol is the causal factor. Only those with persistently high serum cholesterol would be treated. Individuals with multifactorial hyperlipidaemia where no mutation is found who have lower mean levels of LDL-C and therefore lower risk of a cardiac event, are by definition not screen-positive in the proposed method. To the extent that such individuals may be identified in other ways, NICE CG71 (2017) states that these individuals with the clinical diagnosis of FH, who are found not to carry an FH-causing mutation, but may have polygenic hypercholesterolaemia, should be managed by GPs using QRISK charts to estimate coronary heart disease risk and offered lipid lowering therapy and other risk reducing therapies as appropriate.* *<u>Benefit to the child of this approach</u>* *NICE guidelines already exist to ensure that all children are managed appropriately* This shows a lack of understanding of the considerable literature on this issue**.** The data from many studies has shown that FH patients where no mutation can be found have lower mean levels of LDL-C, (usually higher mean levels of triglycerides) and have lower risk of prevalent and incident CHD.* One such study is shown in Figure 2, where CHD risk was higher in mutation carriers vs non-carriers across the entire spectrum of LDL-C values. NICE CG71 states that "When DNA testing has excluded FH……. healthcare professionals should manage the person's coronary heart disease risk as in the general population." The management of polygenic hypercholesterolaemia was included in the NICE 2017 updated guideline. This states that individuals with the clinical diagnosis of FH but who are found not to carry an FH-causing mutation but who have polygenic hypercholesterolaemia, should be managed by GPs using QRISK charts to estimate CHD risk and offered lipid lowering therapy and other risk reducing therapies as appropriate.

		Further studies on this issue are not needed. *reference: *Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk.* ***Humphries SE**, Whittall RA, Hubbart CS, Maplebeck S, Cooper JA, Soutar AK, Naoumova R, Thompson GR, **Seed** M, Durrington PN, Miller JP, Betteridge DJ, **Neil** HA; Simon Broome Familial Hyperlipidaemia Register Group and Scientific Steering Committee.* *J Med Genet. 2006 Dec;43(12):943-9.*
11	Understanding these aspects of the natural history of FH may help to inform the appropriate screening test when considering that a number of young children who carry FH variants may have lower cholesterol, while others may have raised cholesterol despite have no identified gene variant.	*Summary* *There is no greater understanding of aspects of the natural history of FH that would help inform appropriate screening tests, because all individuals identified through universal screening for high cholesterol are, by definition, at high risk of coronary heart disease. All individuals identified will benefit from a lowering of their risk.* *Benefit to the child of this approach* *All individuals identified will benefit from a lowering of their coronary heart disease risk* This shows a lack of understanding of the literature on this subject**.** There is no uncertainty over the natural history of FH because all individuals identified through universal screening have a high cholesterol and cholesterol is the causal factor. Whilst some individuals may benefit more than others from lowering their cholesterol, all will benefit by experiencing a lowering of their CHD risk. This is no different from any other preventive measures, such as lowering cholesterol in the general population or lowering blood pressure for the prevention of IHD or stroke. **Further studies on this issue are not needed.**
11	Long-term RCTs assessing whether universal screening (or treatment) of children with FH affects long-term cardiovascular	*Summary* *Long-term RCTs are neither ethical nor feasible and will therefore never be carried out. However, there is overwhelming evidence that children with FH have elevated levels of the suggested intermediate markers of atherosclerosis, have a markedly elevated risk of future morbidity and mortality from coronary heart disease because of their elevated LDL-C, and that early identification and treatment to lower their LDL-C will concomitantly reduce this risk. This has been clearly demonstrated in a recent study by Luirink, Wiegman et al published in The New England Journal of Medicine, 20-Year Follow-up of Statins in Children with Familial Hypercholesterolaemia,*

	morbidity and mortality may be neither ethical nor feasible. However, comparative studies would be useful to understand whether screening (or treatment) improves intermediate markers of atherosclerosis in the medium term, such as carotid intima-media thickness or endothelial function	*which found that initiation of statin therapy during childhood in patients with FH slowed the progression of carotid intima-media thickness and reduced the risk of cardiovascular disease in adulthood. In addition, children with untreated Homozygous FH are at risk of developing coronary heart disease in childhood, universal screening will prevent cardiovascular morbidity and mortality for these individuals in the short to medium term. We note that other newborn screening programmes have been introduced in the UK without RCT evidence, especially when such trials would be ethically unacceptable.* *<u>Benefit to the child of this approach</u>* *Interventions to reduce risk of CHD can take place at the earliest possible opportunity, as recommended by NICE* *If atherosclerosis is prevented through early intervention and manage the child's risk can be reduced to that of a person who does not have FH* Identification of children with FH by whatever method used (ie universal screening for high cholesterol in infancy, or cascade testing from an affected parent) followed by appropriate lifestyle advice and lipid-lowering treatment will reduce mortality and morbidity. This is because screening identifies a group with inherited high-cholesterol (total or LDL), the cause of ischaemic heart disease, and it is known that lowering serum cholesterol will necessarily reduce the risk of the disorder. Individuals with heterozygous Familial Hypercholesterolaemia (FH) have a much higher risk of developing premature Coronary Heart Disease (CHD) than those in the general population and those with HoFH have a high risk of developing CHD in during childhood. In FH the cumulative risk of a coronary event by the age of 60 years without effective treatment is at least 50% in men and about 30% in women (1,2). Coronary disease occurs about ten years earlier in men than women, with a marked increase in women post-menopause (1,2). Before effective treatment with HMG-Co reductase inhibitors (statins) became available (from 1992 onwards), compared to the general population, mortality from coronary disease was nearly 100-fold higher in young adults aged 20 to 39 years, and about 4-fold for patients aged 40-59 years. As shown in the figure below this is equivalent to a CHD mortality rate per 100,000 population of 635 in Men and 425 in Women with Definite FH compared to the general population rates of 222 and 118 respectively.

Figure 1 Changes in CHD mortality 1992-2008

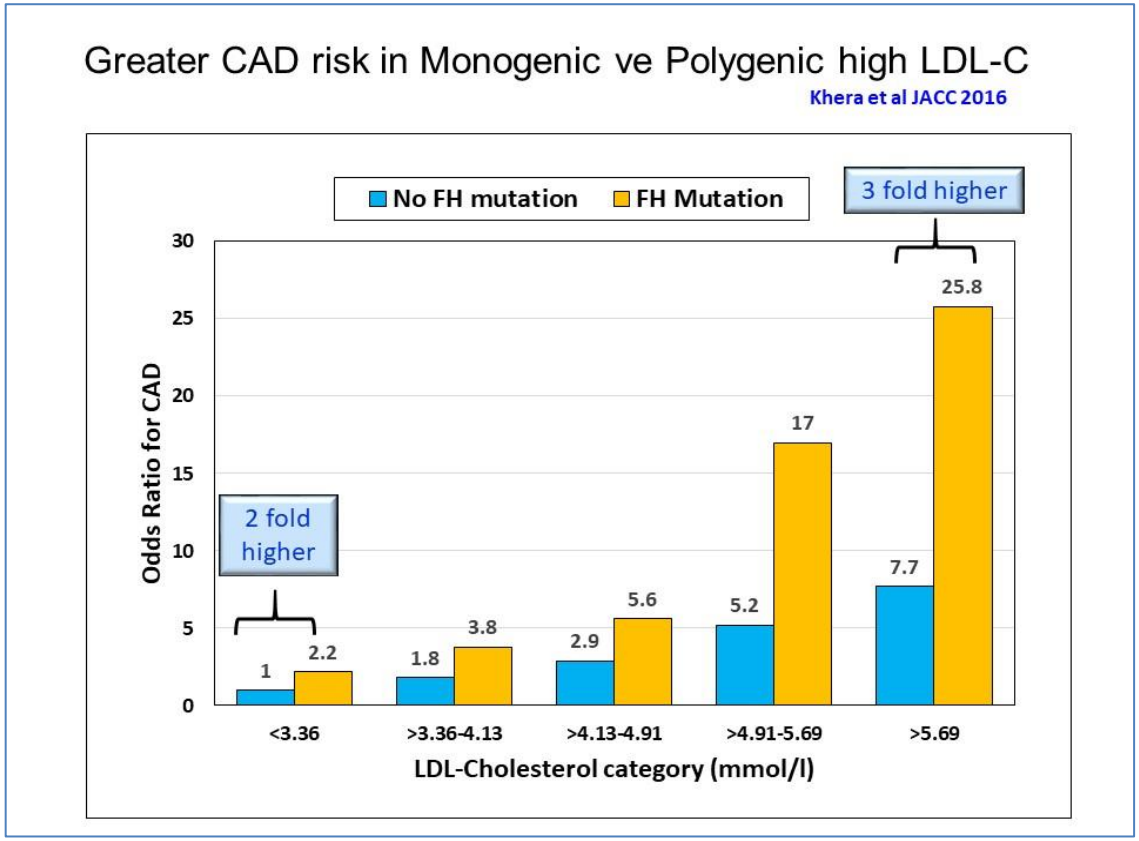


GP Male/GP Female (GP = General Practice). The CHD mortality data was obtained from the Health Survey of England and Wales website.
https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset

No randomised, placebo-controlled trials (RCTs) of statin use to reduce CHD have been carried out in adults with FH because their high risk makes a placebo arm unethical. However, observational studies, using for example the UK Simon Broome FH Register, have demonstrated that, when FH patients are treated with

		the high intensity lipid-lowering statin agents, the CHD Standardised Mortality Ratio (SMR) is reduced to that seen in the general population (3-5), and as presented in the Figure above. Universal Screening (US) for high cholesterol in childhood, followed by genetic testing to identify those with an FH-causing mutation, will therefore identify children who have a high future risk of premature CHD, and it is reasonable to extrapolate the available data to predict that the actual CHD risk of these children can be essentially completely removed by statin treatment. The combined use of US for high cholesterol followed by DNA testing to identify those with an FH-causing mutation is important since it identifies those with the highest future CHD risk. Several lines of evidence support this view. In a US study (6), among 20,485 CAD-free control and prospective cohort participants, 1,386 (6.7%) had LDL-cholesterol ≥ 5.0mmol/l and of these, 24 (1.7%) carried an FH mutation. As shown in the figure below, the Hazard Ratio (HR) for CHD rose as LDL-C levels rose, with the HR for CHD being 2-3 fold higher over the whole spectrum of LDL-C in those with a monogenic cause of their high LDL, compared to those with a similar level of LDL-C but who do not carry such a mutation (6).

Figure 2. CHD risk in monogenic and polygenic FH

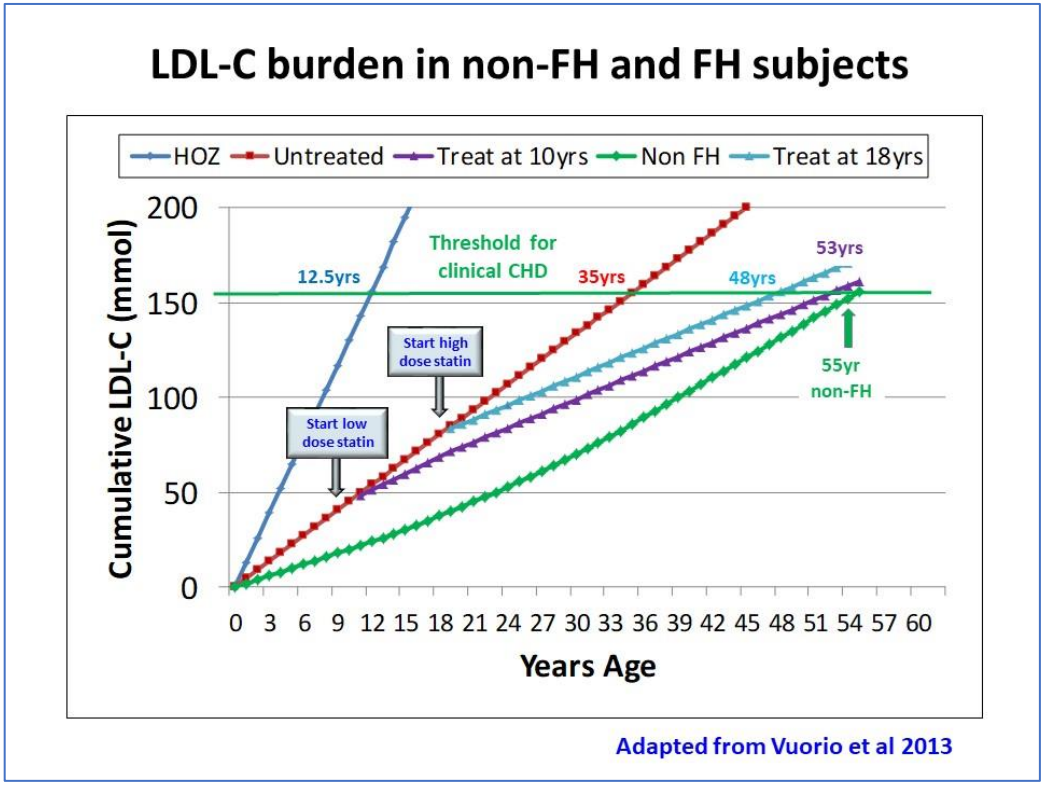


Direct relationship between LDL-C levels and future risk of CHD

Both RCTs in non-FH subjects (7) and genetic studies (8) have shown without doubt that elevated LDL-C is a direct cause of atherosclerosis and CHD and that there is a linear relationship between levels of LDL-C and CHD risk. In addition, using a 9-SNP LDL-C "gene score" Ference et al (9) have demonstrated that prolonged exposure to lower LDL-C beginning early in life is associated with a substantially greater reduction in the risk of CHD than the current practice of lowering LDL-C beginning later in adulthood. Children with FH have roughly twice the normal LDL-C levels from birth and thus their LDL-C burden (average level x years of age) increases at

twice the rate of their non-FH sibling (10). This higher accumulated LDL-C burden is illustrated in the figure below. The threshold for clinical CHD is shown as the burden achieved by a non-FH subject at the age of 55 years (total accumulated since birth of ~160mmol LDL-C). An untreated homozygous FH child reaches this level by the age of 12.5 years and a heterozygous FH adult by the age of 35 years. The cumulative LDL-C burden by the age of 18 years is 15% lower in FH patients treated with low dose statin from the age of 10 years onwards (ie accumulated burden of only 70mmol) than in untreated FH patients (accumulated burden of 80mmol), and the clinical threshold will be reached at 53 years. By contrast, delaying the start of treatment until 18 years means that the threshold will be reached by 48 years, suggesting this delay could reduce healthy life expectancy by 8 years.

Figure 3. LDL-C Burden



No randomised, placebo-controlled trials of statin use to reduce CHD have been carried out in children with FH because, as for adults, their high risk makes a placebo arm unethical. Since a child is only likely to develop CHD in their 3-4th decade, it is also impractical to fund an RCT of the benefit of statin therapy because of the time needed to observe such a benefit. **However, there can be no doubt that, as a group, children with FH have a markedly elevated risk of future CHD because of their elevated LDL-C, and that reducing their LDL-C will concomitantly reduce their future risk of CHD.** We note that in 2008 (and again in 2017) when the NICE Guideline committee reviewed the published evidence for the utility of lipid-lowering treatment for children with FH (CG71), they recommended (**even in the absence of RCT data**) that testing of at-risk children and identification of those with FH should occur before the age of 10 years, and that initiation of statin treatment should be considered by this age (10). The testing of the first degree relatives of an FH patient with an identified FH-causing mutation is known as DNA-based "Cascade Testing" (CT). Such CT is routinely being carried out in Scotland, Wales, Northern Ireland and in more than 10 centres throughout England (11). The approach is cost effective (12) and feasible and acceptable to parents and clinicians (13), and since 2015 more than 250 children aged under 10 years and more than 250 young people under the age of 20 years have been identified. These individuals are being referred to and managed in more than 60 paediatric centres around the UK (14).

Carotid IMT measures as a surrogate for atherosclerosis

Children with heterozygous FH seldom present with identifiable clinical features. However, there is progressive atherosclerosis through childhood, demonstrated by carotid intima media thickness (CIMT) studies (15). CIMT represents the combined intima and media thickness of the arterial wall and is widely accepted as marker of the presence of atherosclerosis in the arterial tree. Individuals in the top quintile of CIMT have a higher future risk of CHD (eg 16), and CIMT in childhood is therefore a useful predictor of CHD in later life. It can be accurately determined using a non-invasive procedure of ultrasound. Children with FH have roughly twice the normal LDL-C levels from birth and as a consequence of this they develop atherosclerosis that is detectable as significant CIMT as compared with their non-FH siblings by the age of 8-10 years (17). In a randomised placebo controlled trial of the use of pravastatin, further change in CIMT was prevented (18). Based on this data the NICE guidance (CG71) is that the use of statins should be considered in children with FH by the age of 10 years using clinical judgement, based on the child's LDL-C level, the age of onset of CHD in the parent or relatives, and the presence of other CHD risk factors. (10).

We therefore argue that, although no RCT of statin use in children has ever been carried out (and never will be carried out) to demonstrate unequivocally a reduction in morbidity or mortality of identification at 12 months, there is overwhelming epidemiological, observational and genetic data that children with FH have a markedly elevated risk of future morbidity and mortality from CHD because of their elevated LDL-C, and that early identification and

		treatment to lower their LDL-C will concomitantly reduce this risk. We note that other new born screening programmes have been introduced in the UK without RCT evidence, especially when such trials would be ethically unacceptable. We therefore argue that, although no RCT of statin use in children has ever been carried out (and never will be carried out) to demonstrate unequivocally a reduction in morbidity or mortality of identification at 12 months, there is overwhelming epidemiological, observational and genetic data that children with FH have a markedly elevated risk of future morbidity and mortality from CHD because of their elevated LDL-C, and that early identification and treatment to lower their LDL-C will concomitantly reduce this risk. We note that other new born screening programmes have been introduced in the UK without RCT evidence, especially when such trials would be ethically unacceptable. References for this section are provided at the end of the document.
11	Long-term RCTs assessing whether universal screening (or treatment) of children with FH affects long-term cardiovascular morbidity and mortality may be neither ethical nor feasible. However, comparative studies would be useful to understand whether screening (or treatment) improves intermediate markers of atherosclerosis in	Please also consider the most recent published evidence summarised here: **20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia** Ilse K. Luirink, M.D., Albert Wiegman, M.D., Ph.D., D. Meeike Kusters, M.D., Ph.D., Michel H. Hof, Ph.D., Jaap W. Groothoff, M.D., Ph.D., Eric de Groot, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., and Barbara A. Hutten, Ph.D. October 17, 2019 N Engl J Med 2019; 381:1547-1556 DOI: 10.1056/NEJMoa1816454 Familial hypercholesterolemia is characterized by severely elevated low-density lipoprotein (LDL) cholesterol levels and premature cardiovascular disease. The short-term efficacy of statin therapy in children is well established, but longer follow-up studies evaluating changes in the risk of cardiovascular disease are scarce. This paper is a 20-year follow-up study of statin therapy in children. A total of 214 patients with familial hypercholesterolemia (genetically confirmed in 98% of the patients), who were previously participants in a placebo-controlled trial evaluating the 2-year efficacy and safety of pravastatin, were invited for follow-up, together with their 95 unaffected siblings. Participants completed a questionnaire, provided blood samples, and underwent measurements of carotid intima–media thickness. The incidence of cardiovascular disease among the patients with familial hypercholesterolemia was compared with that among their 156 affected parents.

	the medium term, such as carotid intima-media thickness or endothelial function	Of the original cohort, 184 of 214 patients with familial hypercholesterolemia (86%) and 77 of 95 siblings (81%) were seen in follow-up; among the 214 patients, data on cardiovascular events and on death from cardiovascular causes were available for 203 (95%) and 214 (100%), respectively. The mean LDL cholesterol level in the patients had decreased from 237.3 to 160.7 mg per decilitre (from 6.13 to 4.16 mmol per litre) — a decrease of 32% from the baseline level; treatment goals (LDL cholesterol <100 mg per decilitre [2.59 mmol per litre]) were achieved in 37 patients (20%). Mean progression of carotid intima–media thickness over the entire follow-up period was 0.0056 mm per year in patients with familial hypercholesterolemia and 0.0057 mm per year in siblings (mean difference adjusted for sex, −0.0001 mm per year; 95% confidence interval, −0.0010 to 0.0008). The cumulative incidence of cardiovascular events and of death from cardiovascular causes at 39 years of age was lower among the patients with familial hypercholesterolemia than among their affected parents (1% vs. 26% and 0% vs. 7%, respectively) In this study, initiation of statin therapy during childhood in patients with familial hypercholesterolemia slowed the progression of carotid intima–media thickness and reduced the risk of cardiovascular disease in adulthood.
11	It would also be beneficial to see whether this could differ by diagnostic criteria used for FH, age at treatment initiation, the statin or dose given	There is always a variable response to treatment, as there is with all treatments, but the directional effect will be to lower risk in all, because cholesterol is high to start in all and cholesterol is the cause of heart attack.
11	Follow-up of universally screened populations would be helpful to see that the full screening programme is not associated with any harm, such as from over-diagnosis (e.g.	<u>*Summary*</u> *There is published evidence of no significant harm in children identified as having FH through cascade testing programmes, either from a physical, treatment or psychological perspective. There is similarly no evidence of physical harm to the child from universal screening and it is perverse to infer that there is any material difference between identifying a child through universal screening and cascade testing in terms of treatment and psychological impact of an FH diagnosis, even though universal screening will tend to identify the child at an earlier age. Furthermore, there cannot be any overdiagnosis, misclassification, or missed diagnoses, as the approach identifies only a high-risk group that all have a high cholesterol and it is the high cholesterol that causes premature cardiovascular disease.*

	detection of multifactorial/polygenic or mildly elevated cholesterol), misclassification or missed diagnoses (e.g. monogenic FH without raised cholesterol in young childhood) or psychological or quality of life effects.	*<u>Benefit to the child of this approach</u>* *They do not suffer any of the potential harms cited by Bazian* **Overdiagnosis** There should be no concern for over-diagnosis as all positive children identified, by definition, have high (plus mutation) or repeat very high cholesterol readings, which is the cause of heart attacks. **Misclassification or missed diagnoses** There is agreement that this approach identifies only a high-risk group because all have a high cholesterol and it is the high cholesterol that causes the disease (premature ischaemic heart disease). The Bazian report incorrectly states that some children are classified as screen positive with a low cholesterol. To screen positive requires a high cholesterol. **Potential physical harm from screening procedure** There is a potential harm to the child from the heel prick test to collect a capillary blood sample at the time of the child's immunisation. However, In the CPSS study, 10,095 children were tested for cholesterol and FH mutations at the time of immunisation at 1-2 years, using a heel prick blood test at the time the immunisation was administered. There were no reports of adverse effects on children from the procedure. (27) In a pilot phase of the study, 200 parents were sent questionnaires after the screening procedure and asked "if you had a second child would you want him/her screened in this way for FH if screening were made available?" 94% said they would screen a second child, (28) indicating overwhelming parental acceptability and no indication of harm to their child. **Potential harms of early treatment with statins** One potential harm of US and identification and treatment of children with FH, would be if statin use at an early age (eg. age 10 years) were associated with any long term safety issues. Statins have been used in adults (with FH and in those in the general population) since the late 1980s, and in the ensuing 40 years no major long term safety issue have been identified (7). Studies in children have also found no long term safety concerns (29). The 2017 Cochrane review update on the safety of statins in children (30) included 26 potentially eligible studies, which included nine randomized placebo-controlled studies (1177 participants). The magnitude of LDL cholesterol

		lowering varied from study to study, most likely due to different statins and doses and possibly due to different definitions about true monogenic heterozygous FH. The review did not identify any clinically significant side effects with statins. Abnormal liver transaminase was defined as a 3-fold increase and Creatine Kinase values over a 10-fold increase from normal ranges, and neither were found as reported side effects. Sexual maturation was not dissimilar to normal population groups. The review concluded that statin use in childhood was safe in the medium term. This finding is fully supported by the UK FH Children's Register which found no instances of safety issues and an equal growth rate in statin treated and non-treated children (21). However, longitudinal studies are lacking and will be helpful to confirm the long term safety of statins started in children. Although statin use in the general population has been associated with an increased risk of developing type 2 diabetes (T2D), this risk seems not to be high in patients with FH. Many studies have reported that the prevalence of T2D is low in adults with FH, and in a study of over 63,000 subjects from Holland (31), even in treated adults with FH the prevalence of T2D was significantly lower than in their unaffected relatives (1.75% vs 2.93%). Also, the benefits of statin treatment in FH for preventing CHD outweighs the modest potential risk of Type 2 diabetes. However it is important to mitigate this risk with the dietary and lifestyle advice for the prevention of T2D/metabolic syndrome, as is used in the general population. A study in 2014, reported on a 10-year follow-up of 194 statin-treated children (mean age at baseline 13 years) and identified one new case of Type 2 Diabetes with a similar incidence in their 83 non-FH siblings (32). Furthermore, the long-term safety of statins, 20-year follow up of statin therapy in children with FH has been carried out by Luirink, Wiegman et al and published recently in The New England Journal of Medicine. There were no serious adverse events reported. **Psychological or quality of life effects** One potential harmful effect of a diagnosis of FH would be if there were any evidence of a detrimental psychological impact, and several (mostly small) studies have examined this. The psychological effects of any screening or testing process include how a person thinks (risk perception and understanding of diagnosis), feels (levels of anxiety, depression, reassurance) and behaves (coming for repeat screening, taking medication, changing lifestyle). It is possible that relatives may become anxious, or angry, when they receive news that they are at risk of having an inherited disorder like FH. However, studies suggest that

		relatives usually believe that genetic information is beneficial (33). Reports on the impact of receiving a diagnosis of FH show that the proportion of individuals experiencing anxiety is no higher than would be expected in the general population, approximately 10% (34). There are fewer data on the additional psychological impact of DNA testing (over and above cholesterol testing) in FH patients. A randomised trial study of 241 previously diagnosed FH patients demonstrated that a DNA diagnosis was not associated with significantly increased adverse psychological effects in patients or their relatives over and above that seen in the cholesterol-only arm (35). Interestingly, the DNA diagnosis was perceived to be more accurate and was recalled later with greater accuracy and appeared to reinforce the need for medication. Whether this translated into higher compliance with statin use was not examined. There are few data examining this issue in children. An early study of 152 boys and girls aged 7-16 years from Norway (36) concluded that the prevalence of psychosocial dysfunction was not greater than expected in children treated for FH. Psychosocial function within the group was associated with the usual demographic characteristics and with the loss or disease of a parent, beyond the period of bereavement or immediately after the event. A study from Holland which included children with other inherited cardiac conditions as well as FH (35) reported that children were overall quite articulate about the disease they were tested for, including its mode of inheritance. They expressed positive future health perceptions, but feelings of controllability varied. Adherence and side-effects were significant themes with regard to medication-use. Refraining from activities and maintaining a non-fat diet were themes concerning lifestyle modifications. Some children spontaneously reported worries about the possibility of dying and frustration about being different from peers. Children coped with these worries by expressing faith in the effectiveness of medication, trying to be similar to peers or, in contrast, emphasizing their "being different." Children generally appeared effective in the way they coped with their carrier status and its implications. Neonatal screening for rare disorders has reasonably been introduced without knowledge of the long-term psychological effects of the disorder (e.g. cystic fibrosis) on the child, on the basis that the benefits of an early diagnosis outweigh any potential psychological harm. The same reasonable approach applies to FH. One of the clear additional benefits to the child with FH identified at an early age through US is that this will usually (excluding adoptees, or IVF egg donor children) result in the identification of one of their biologically related parents as also having FH. This parent is at high risk of early CHD (for example having a debilitating heart attack or even a fatal myocardial infarction) and this could be prevented by offering them appropriate intensive lipid lowering therapy as recommended by NICE guidelines (10). Prevention of morbidity and mortality in the parent of a child with FH is of *direct benefit* to the child. Several studies have reported that parentally bereaved children are at increased risk for mental health problems, as they grow up, including depression, anxiety, and behaviour problems (22, 23). Children in single parent families may also show poorer educational achievement

		(24, 25). In a study from three Nordic countries (26), parental death before the child was 18 years old was associated with a 50% increased all-cause mortality (MRR = 1.50, 95% CI 1.43–1.58) over ~30 years of follow up, an effect that was independent of age of bereavement. Please find list of references at the end of this document.
11	further follow-up of treated children with FH would be beneficial to see whether statins or other management approaches are safe in the longer term and do not have adverse effects on quality of life, liver and muscle function, neurological and cognitive development, diabetes, or growth and reproduction. Again, it would helpful to see whether this may differ by diagnostic criteria used for FH, age at treatment, statin or dose given.	*<u>Summary</u>* *Statins and other management approaches recommended by NICE are safe in the longer term. NICE is an impartial, national regulator that provides evidenced-based clinical guidance to the NHS. Bazian are in effect undermining the decision of NICE CG71 (2017) to recommend the use of statins in children and HEART UK does not believe that this is within Bazian's scope.* *With specific reference to the long-term safety of statins, 20-year follow up of statin therapy in children with FH has been carried out by Luirink, Wiegman et al and published recently in The New England Journal of Medicine. There were no serious adverse events reported, including no cases of rhabdomyolysis, and no significant differences in liver function were observed between patients with FH and their unaffected siblings. No further follow up is required.* *<u>Benefit to the child of this approach</u>* *They are able to receive the appropriate intervention as recommended by NICE at the earliest possible opportunity* There is an ever-increasing number of studies demonstrating that early identification and appropriate treatment is of benefit for the child and safe in the long term. A 20-year follow-up study of statin therapy in children has recently been published. A total of 214 patients with familial hypercholesterolemia (genetically confirmed in 98% of the patients), who were previously participants in a placebo-controlled trial evaluating the 2-year efficacy and safety of pravastatin, were invited for follow-up, together with their 95 unaffected siblings. In this study, initiation of statin therapy during childhood in patients with familial hypercholesterolemia slowed the progression of carotid intima–media thickness and reduced the risk of cardiovascular disease in adulthood. Crucially, there were no serious adverse events reported, including no cases of rhabdomyolysis, and no significant differences in liver function were observed between patients with FH and their unaffected siblings (38).

		Previously, the 214 Dutch children with FH, aged 8-18 years were followed up for over ten years (18). Comparisons were made on CIMT in patients with FH and unaffected siblings (adjusted for sex, age, blood pressure, and body mass index [BMI]); and the association between carotid IMT and age at statin initiation (adjusted for sex, BMI, baseline carotid IMT, and duration of follow-up) was also evaluated. This cohort had previously participated in a randomised double blind placebo controlled study of pravastatin. At completion of the two-year study in 1999, all participants were commenced on pravastatin and followed up for ten years. Ten-year follow-up was achieved in 91% of FH patients with FH and 87% of siblings, all aged 18 to 30 years. After 10 years of statin therapy, whilst children who started on statins in early childhood had a significant reduction in CIMT from baseline, these children continued to have significantly high CIMT compared to their unaffected siblings. The authors conclude that more robust lipid-lowering therapy or earlier initiation of statins may be required to completely restore arterial wall morphology and prevent early onset CHD. However, in this (relatively short) follow up period, none of the children had experienced a CHD event, but in several families the children were already older than their (untreated) FH parent who had had an early heart attack (19). NICE guidelines (CG71) recommend that children identified with FH are to receive clear healthy lifestyle advice (10), which should of course be also adopted by the whole family. This includes healthy diet choices as well as exercise and non-smoking information. In the light of the epidemic of childhood obesity currently seen in the UK, with over 21% of 11-15 year olds having a BMI in the "obese" range (>95th percentile for age and gender) (20), this lifestyle information is particularly important. Data from the UK Children's FH register has shown that the prevalence of obesity is around 50% lower than in the UK general population (21). **This is most likely to be a direct result of the lifestyle advice given to these children by their managing paediatrician, and this constitutes a direct benefit to the child of an early diagnosis**.
11	Future studies are needed to directly assess the views of the UK public and healthcare professionals towards universal screening for FH in young children; for example, whether there are any reservations towards	<u>*Summary*</u> *Universal child screening has been found to be acceptable by the UK and Australian public and UK healthcare professionals. Early and lifelong treatment for those with FH is recommended by NICE CV71, and is already in practice in the NHS. Allowing any reservations to early and lifelong treatment with statins held by the general public or healthcare professionals to influence this review is in fact perpetuating the misinformation that surrounds statins and further undermining NICE guidance and NHS policy.* <u>*Benefit to the child of this approach*</u> *They can receive early and lifelong treatment, as is recommended by NICE, to reduce their risk of premature cardiovascular disease*

	early and lifelong treatment.	Studies on views of the public: **Identifying Perceptions and Preferences of the General Public Concerning Universal Screening of Children for Familial Hypercholesterolaemia** Public Health Genomics - DOI: 10.1159/000501463 – Published online: July 22, 2019 **Abstract** ***Background/Aims:*** Familial hypercholesterolaemia (FH) is a common genetic disorder that, if untreated, predisposes individuals to premature coronary heart disease. As most individuals with FH remain undiagnosed, new approaches to detection are needed and should be considered a priority in public health genomics. Universal screening of children for FH has been proposed, and this study explores public perspectives on the acceptability of this approach. ***Methods:*** A one-day deliberative public forum was held in Perth, WA, Australia. Thirty randomly selected individuals were recruited, with self-reported sociodemographic characteristics used to obtain discursive representation. Participants were presented with information from a variety of perspectives and asked to discuss the information provided to identify points of consensus and disagreement. The data collected were analysed using thematic analysis. ***Results:*** Of the 17 participants at the forum, 16 deemed universal screening of children for FH to be acceptable. Fifteen of these 16 believed this was best performed at the time of an immunisation. Participants proposed a number of conditions that should be met to reduce the likelihood of unintended harm resulting from the screening process. ***Discussion/Conclusion:*** The outcomes of the forum suggest that establishing a universal screening programme for FH in childhood is acceptable to the general public in WA. Studies recording views of healthcare professionals:

		Child-Parent Screening for Familial Hypercholesterolemia - *David S. Wald, MD, Anuradhani Kasturiratne, MD, Angela Godoy, BSc, Louise Ma, MD, Jonathan P. Bestwick, MSc, Nick Brewer, MD, and Nicholas J. Wald, FRS. J Pediatr 2011;159:865-7* **Background** Familial hypercholesterolemia (FH) results in raised serum cholesterol levels and about a 100-fold higher risk of coronary heart disease before age 40 years. Cholesterol-lowering medications reduce risk, so screening would be worthwhile if an effective method of distinguishing people with and without FH were available. Child-parent FH screening is a means of achieving this. It involves measuring total cholesterol in children aged 1 to 2 years. A meta-analysis indicated that at this age cholesterol measurement discriminates best between individuals with and without FH, identifying about 88% of affected children and 0.1% of unaffected children. **Methods** Children aged 1 to 2 years requiring routine immunization were identified from the register of a London general practice. Parents were asked whether their child could be screened for FH. To avoid distressing children twice, once from the immunization and again from the blood sampling, the immunization (left thigh) and blood spot (left heel, with 2-mm Tenderfoot lancet; ITC, Edison, New Jersey) were performed simultaneously by two clinical staff members. Parents were telephoned several days after immunization with the result and to assess the acceptability of screening. **Results** Of 214 parents asked, 200 (94%) agreed to FH screening. Concurrent heel prick and immunization was successful in all children. Of the 200 parents of screened children, 184 were subsequently reached via phone (92%), and 181 (98%) said the screening was acceptable; 173 parents (94%) said they would have a second child screened if they had one and if screening were offered. **All 7 practice staff members said screening was acceptable and would adopt child-parent screening into immunization practice if screening were routinely offered.** The cost of screening was £14 per child, including the analyser and consumables. The average staff time required was 14 minutes per child.

		Discussion The results show that child-parent screening for FH is feasible and acceptable in clinical practice. Screening can be done at the same time as childhood immunization and requires no new clinical facilities; immunization clinics and arrangements for systematically seeing children aged 1 to 2 years already exist. There was no indication that screening adversely affected immunization rates, which were, for Haemophilus Influenza B/Meningitis-C, 71% in the year preceding the study and 84% during the study. **Full paper available:** https://www.gmul.ac.uk/wolfson/media/wolfson/current-projects/Child-Parent_Screening__for_familial_Hypercholesterolaemia.pdf

UK National Screening Committee

Name:	Comments received on behalf of Dr Eugene Strehle	**Email address:**	XXXX XXXX
Organisation (if appropriate):	Royal College of Paediatrics and Child Health		
Role:			

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
General	General	The reviewer agrees with the recommendations made in the document.

UK National Screening Committee

Name:	David Wald	**Email address:**	XXXX XXXX
Organisation (if appropriate):	Wolfson Institute of Preventive Medicine, QMUL		
Role:	Professor of Cardiology		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Whole document	Scope of review and accuracy of Bazian report	Criticisms relating to the Bazian review (hereafter referred to as B) arise from (a) the National Screening Committee (NSC) unfortunately limiting the scope of the review to the child when the available method of screening identifies two generations (child and parent) in one go and (b) B reaching seriously flawed conclusions. B overlook the benefits of screening. Child-parent Screening (CPS) is inexpensive, effective, safe and has been shown to be easily administered within the context of NHS primary care. The method would prevent about 4000 fatal or non-fatal heart attacks under the age of 50 due to FH each year in the UK at a cost of about £5 per child-screened with no expectation of serious harm. The method is justified based on the benefits conferred to the child alone, but identification of an affected child leads to the affected relatives within a family through cascade testing, further extending the benefits. B fails to understand the concept of CPS and their incorrect decision against recommending FH screening is based on factual error and incorrect judgements.
Page 5 Page17 Pages 34-35	B believes that that some children are classified as screen positive with a low cholesterol.	This is incorrect. All screen-positives require a high cholesterol.
Page 5 Page 8 Pages 34-35	B states that screening may lead to over-diagnosis (a lowrisk group).	This is incorrect. The screening method only identifies a high-risk group by virtue of having a high serum cholesterol (>95th centile or >1.35MoM)) plus an FH mutation or a very high cholesterol (>99th centile or >1.50MoM)) on at least two occasions several months apart.
Page5 Page Pages 34-35	B states that the CPS study did not test these cut-offs	This is incorrect. By measuring cholesterol and FH mutations in all 10,095 children, the study was designed to test all levels of cholesterol as possible screening cut-offs in practice, and did so.

	(1.35MoM or 1.5MoM) in practice.	
Page 5 Page 8 Pages 27-29 Pages 34-35	B fails to recognise that standard assessments of screening performance (calculating detection rates for specified false positive rates) are not appropriate when the disorder is defined by its screening test.	Much of the B review focuses on this misconception instead of recognising that a critical element of the screening test is identifying a factor in the causal pathway that leads to premature ischaemic heart disease (IHD) – the disorder that screening and treatment prevents.
Page 5 Page 8 Pages 36-42	B fails to realise that lowering serum (Total or LDL) cholesterol will necessarily reduce or avoid the excess risk of heart attacks because cholesterol is itself the main cause of the disorder.	B provides no evidence to counter the evidence that Total (LDL cholesterol) is a cause of IHD. B adopts the puzzling position that this won't apply in people with FH, and that extra evidence in this group is needed. This is particularly surprising because individuals with FH have some of the highest serum cholesterol levels in thepopulation, and consequently the highest risk of early onset heart attack (eg a 100-fold excess risk of fatal IHD between ages 20 and 39) and therefore stand to benefit most from lowering cholesterol. The screening method that is proposed simply identifies this high-risk group before the onset of clinical IHD allowing preventive treatment to be offered.
Page 5 Page 8 Pages 36-42	B makes the extraordinary assertion that further evidence is needed that lowering serum cholesterol reduces the risk of heart attack.	B ignores three decades of research that have established serum cholesterol as a cause of IHD; evidence that and has been translated into accepted practice throughout the world. Further evidence in populations with FH, where serum cholesterol levels are even higher, is not needed.
Page 5 Page 8 Page 54	B fails to acknowledge the substantial evidence that long-term statin use is safe and that starting statins, after age 10 is established medical practice in sporadically identified children with FH. B fails to see the importance of screening at age 1-2 years.	The reason for not screening at age 10 and for screening at age 1 is because the most accurate age to screen is 1-2 years ie discriminates between FH and not FH, most effectively at this age. Screening at age 1- 2 years has two additional advantages – it allows screening to be combined with routine immunisation at low cost. It also identifies the affected parent, whose treatment needs to be implemented immediately, not 9 or more years later. We understand that the NSC wanted to limit its assessment of screening to the child (ie not the parent) but identifying the affected parent and preventing their premature death is a benefit to the child. The NSC were wrong to limit the scope of the consultation in this way. A substantial advantage of the screening approach is that both child and parent benefit and the child benefits directly and indirectly through avoiding the premature death of one of their parents.

		There is extensive published literature on the harmful effects to a child of losing one of their parents at an early age. These events would be avoided by recommending Child-parent Screening. Unfortunately none of the harms to the child of not implementing Child Parent screening were considered in this review.
Page 8 Page 17	B suggests uncertainty over the natural history of FH. B states Universal screening may identify a large proportion of children with moderate or low cholesterol, where natural history and rationale for statins remains unclear	There is no uncertainty directionally because all screen-positives have high cholesterol and any reduction in cholesterol will reduce risk, recognising that some will benefit considerably and others to a lesser extent. The situation is no different from other areas of prevention such as the use of BP-lowering drugs in adults, where variability in individual response is accepted because everyone will experience some benefit even though this can vary from person to person. This is incorrect. Screening does not identify children with moderate or low cholesterol level- It only identifies children with high levels. Neither natural history nor statin therapy in children with low/moderate cholesterol levels are relevant because they will not be identified as screen positive.
Page 8	B says there is "no evidence" to "inform the risk-benefit balance" of starting statins in children with cholesterol in the top 1% of the population (confirmed on repeat testing).	This is incorrect. Lowering LDL cholesterol from any starting level confers benefit and the benefit is greater in absolute terms if the starting level is higher. This has been shown in prospective studies and randomised trials in many different patient groups (eg. primary prevention, secondary prevention, with diabetes, without diabetes, men, women etc). All results show a continuous proportional reduction in heart attack risk for a given change in Total or LDL cholesterol. B's implication that children with serum cholesterol levels in the top 1% of the population should somehow be an exception to this observation is absurd. Such children, if left untreated, will be amongst the highest risk for early onset ischaemic heart disease, because cholesterol is the causal factor. Direct evidence for his in FH would require at least a 50 year-long cohort study following up such children, who would not be allowed treatment. This would be unethical.
Page 5, 11, 20, 36	B suggests that randomised trials of cholesterol lowering or screening in children are needed.	Such studies would be unethical because it would be unacceptable to knowingly withhold treatment to any individual with high cholesterol and an FH mutation or two very high cholesterol levels measured months apart. There are no RCTs to show that the avoidance of smoking prevents lung cancer. The evidence is based on avoiding the main cause. The same applies to the reduction of cholesterol in FH for the prevention of heart attack. B's judgement on RCTs is perverse and at some points in their review even contradictory.
		In answer to the three specific questions that the NSC set:
Page 5 Page 55	1. B say: "It is still not clear which is the best screening test	This is incorrect. While any screening test may be improved with time, the proposed CPS method is the best available population method and good enough to use in practice.

	to find out who will benefit from a treatment"	The CPS method identifies (i) children with inherited high cholesterol securely and (ii) excludes children with a chance high cholesterol and an as yet undiscovered mutation (not surprisingly, not all mutations are known). Critically this approach only identifies children with high or extremely high cholesterol so there is no "over-diagnosis". It unambiguously identifies the group in the population at the highest risk of a future premature heart attack due to inherited high cholesterol (based on information from both cholesterol and FH mutations).
Page 5 Page 55	2. B say: "There was no evidence to tell us whether screening children for FH would reduce their risk of developing heart disease".	This is an astonishing assertion that calls into question whether lowering serum cholesterol (Total or LDL) reduces the risk of heart attacks. Prospective studies in the general population show a constant proportional relationship between Total (LDL) cholesterol and heart attacks and randomised trials have shown that lowering cholesterol from any starting level reduces the risk of heart attack by an amount predicted by these prospective studies. This is the basis for using cholesterol-lowering treatment in people at high risk of a heart attack and individuals with FH are amongst the highest risk group for heart attack. To reject cholesterol as a cause of heart attack would be to reject the basis for the prevention of heart attacks throughout the world.
Page 5 Page 45 Page 55	3. B say: "There was no evidence to tell us whether screening children for FH could cause any harm or side effects. We also need to know that screening would not cause any extra problems like causing excessive worry among children or parents or affect the child's quality of life". B seeks to undermine the evidence on acceptability from the 2016 NEJM paper that demonstrated acceptability	This is incorrect. There is extensive evidence that statins are safe in children. All screening causes anxiety, but evidence shows that this is not excessive and acceptable given the life-saving benefit. In the Child-parent Screening pilot (2011) study 94% of 200 parents, whose children had undergone screening said they would screen a second child if screening were routinely offered. None of the screened children in this pilot were identified as FH positive. In the Child-parent Screening study (2016) on 10,095 children, all of the parents whose children were identified as FH positive (37) confirmed they would screen a second child if screening were offered. B misrepresents the results of the CPS study (NEJM 2016). B states that whilst "all parents indicated that they thought screening was worthwhile and none reported negative effects" that the NEJM paper was still unclear whether this high level of acceptability related to the parent or the parents' views about their child. If B were confused over whether the high level of acceptability related to parent, child or both, they could have contacted the corresponding author of the study (as is normal practice in performing academic reviews) but they did not. The authors of the study confirm that parents were asked about the impact of screening, on both themselves and their child and their view that screening was worthwhile with no negative effects related to both parent and child. On page 45, B misses the point that the study of 10,095 children in 92 general practices across England provided the evidence of acceptability that was needed. This was a highly appreciated screening initiative. Both parents and staff confirmed this, partly because the screening was simple to administer when combined with an existing service (immunisation) and partly because all recognised they were identifying a high risk condition that could be simply treated.

		B adopts an imbalanced approach to the NEJM paper, focusing for example on the 5 parents of screen-positive children who were unavailable for testing or declined (in almost all cases those untested were unavailable eg. in Nigeria) instead of focusing on the 32 parents who tested positive and who reported that screening was worthwhile and that they would screen a second child if they had one. The B review misrepresents the evidence on acceptability, claiming uncertainties when there were none.
Page 10-11		**B recommends further studies to address "remaining uncertainties" that are in fact either not uncertain or not sufficiently uncertain to delay implementing CPS.**
	Uncertainties claimed by B	
Page 11 Page 13-17	Need for consensus on criteria used to definitively diagnose FH in children identified through universal screening	Not needed. High cholesterol (top 95th centile, 1.35MoM) plus an FH mutation or very high cholesterol (top 1st centile, 1.50MoM) on serial measurements identifies an extremely high risk group that needs treatment to reduce risk of heart attack. No physician would defend not offering such individuals treatment. B confuse cascade testing with population (universal) screening. The former is not the latter and the latter requires both high cholesterol and an FH mutation or two very high cholesterol levels several months apart as stated above.
Page 11	Long-term RCTs may be needed.	RCTs are not needed and would be unethical.
Page 11	Comparative studies needed to understand whether screening (or treatment) improves intermediate markers of atherosclerosis	Studies already exist. Statin use in children lowers cholesterol levels (the causal factor for heart attack). Short term studies on surrogates for atherosclerosis (eg. carotid intima thickness) show benefit.
Page 11	It would be beneficial to see whether treatment effect differs by diagnostic criteria used for FH, age at treatment initiation, the statin or dose.	Not needed. There is always a variable response to treatment, as there is with all treatments, but the directional effect will be to lower risk in all, because cholesterol is high to start in all and cholesterol is the cause of heart attack.
Page 11	Follow-up of universally screened populations would be helpful to see that the full screening programme is not	There is no concern of harm from over-diagnosis because all positive children, by definition, have high (plus mutation) or repeat very high cholesterol, which is the cause of heart attacks.

	associated with any harm such as from over-diagnosis	
Page 11	Need for follow-up of treated children with FH to see whether statins are safe in the longer term and do not have adverse effects on quality of life, liver and muscle function, neurological and cognitive development, diabetes, or growth and reproduction.	Not needed. Evidence of statin safety is established with millions of person-years of use. Statins are licensed from age 8 and used throughout the world. No cases of liver failure or rhabdomyolysis reported. No evidence from trials or registries of cognitive delay, diabetes or growth impairment reported that outweigh the observed benefits.
Page 11	Future studies are needed to directly assess the views of the UK public and healthcare professionals towards universal screening for FH in young children.	Not needed. Studies have been done and show >90% acceptance of screening and treatment
	Whole document	**Summary** The B report reveals a concerning lack of knowledge of the subject matter. The B report (102 pages with 40 references) gives the impression of being thorough but is seriously flawed and falls well short of what the public deserve. It substantially fails in determining the value of screening children for FH, which it was commissioned to do. Dismissing FH screening in children and simply suggesting that more research is needed is a mistake that the National Screening Committee need not and should not make
	Relevant paper not considered in review	An important paper on FH has just been published in the NEJM (Luirink IK et al.NEJM 2019;381:1547-56). In a 20 year follow up of 214 FH-positive children, who were enrolled in a Randomised trial of pravastatin (median age 13 years), there was, from age 10 to 39 only 1 non-fatal cardiovascular disease event and no cardiovascular deaths compared with 26% and 7% respectively among their FH-positive parents who were identified with FH and started treatment as adults. The 1 CVD event in the FH-positive child group happened at age 28 years in one of the few children who decided to stop statin treatment at about age 15.

		After about 20-years of statin treatment the LDL-cholesterol levels in FH-positive children were lowered to the same levels as their unaffected siblings – effectively abolishing the excess CVD risk because cholesterol is the causal factor for CVD. Long-term treatment was well-accepted (about 80% remained on treatment for 20 years), safe and effective. Had the FH-positive parents of the FH-positive children been identified earlier, then most, if not all of the nonfatal CVD events and premature deaths could have been avoided. This study provides compelling evidence in support of Child-parent Screening, a population screening method which identifies children at age 1-2 years (the most accurate age for population screening) and allows their affected parents to be identified and treated immediately - importantly at an age when there is still time for treatment to prevent most CVD events and premature deaths that would otherwise occur.