UK National Screening Committee

Screening for familial hypercholesterolaemia in children

Review of evidence submission against criteria appraised in the 2015 external evidence review for the UK National Screening Committee (UK NSC)

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

Background

The UK NSC assesses evidence for screening programmes against select criteria for appraising the viability, effectiveness and appropriateness of screening. A decision is then made whether or not to recommend screening for that condition. When the decision is made not to recommend a screening programme, the evidence is standardly re-assessed every 3 years to see if the recommendation should be updated. However, if significant evidence is published in between reviews, stakeholders can submit a suggestion to the UK NSC for an early topic update.

Following the 2015 UK NSC external evidence review, the decision was made not to recommend screening for familial hypercholesterolaemia (FH) in childhood.

The review assessed the evidence against four main criteria and found that each of these criteria was not met:

4. there should be a simple, safe precise and valid screening test
11. there should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity
12. there should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public
14. the opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money)

The central piece of evidence relevant to universal child screening for FH in the UK was the Wald et al 2007 systematic review and meta-analysis of case-control studies. [1] The Wald et al review aimed to develop a population screening strategy for FH and identify the age at which cholesterol levels gave the best discrimination between those with and without FH. The review found best performance data in the 1 to 9 age category, with a total cholesterol (TC) cut-off threshold of ≥1.53 multiples of the median (MoM) estimated to identify 88% of children with FH at a low false positive rate (FPR). Within this age category, 2 case-control studies provided data that peak performance was at age 1 to 2 years.

Wald et al therefore proposed that screening could be performed by blood spot collection at the time of routine immunisation at 15 months. The proposed strategy would encompass screening parents of test positives (child-parent screening). Wald et al performed a 2011 pilot study[2] to assess acceptability and feasibility in 200 children at a single immunisation clinic. This study used a higher TC cut-off (≥2.0 MoM) and found that parents and practitioners almost universally accepted the screen test; however, no screen positives had been identified.

Therefore, despite identifying the potential of this strategy, at the time of the 2015 UK NSC review there was insufficient evidence on screen test performance, acceptability, cost effectiveness or effect on treatment outcomes and morbidity.

The 2015 external evidence review noted that a UK prospective cohort of child-parent screening at the time of routine child immunisation was currently underway, and that this would provide valuable evidence for the next UK NSC evidence review update in 2018.

Evidence submission from HEART UK

In January 2017 the UK NSC received a submission request from HEART UK to review the decision not to recommend screening for FH in children. This followed publication of the Wald et al prospective cohort in October 2016[3] which assesses the child-parent FH screening strategy.

This document covers the early appraisal of the Wald et al[3] cohort. It considers its potential impact across criteria and whether the FH screening programme should be re-assessed as a matter of priority ahead of the planned 2018 update.

Study appraisal

The Wald et al 2016[3] cohort (Table 1) screened 10,095 children by capillary heel prick blood sample at the time of 12 month immunisation at 92 general practices across the UK.

The study used the total cholesterol cut-off ≥1.53 MoM, as informed by the Wald et al 2007[1] systematic review. However, the full screen test was more in-depth than cholesterol measurement alone as it also used the same blood sample to analyse a panel of 48 common FH mutations (FH48).

Screen positives by cholesterol measure, who were not found to have an FH48 mutation, also received full DNA sequencing. If this found no mutation, they then had a repeat blood sample.

Therefore screen/test positives were considered as:

- those with TC ≥1.53 MoM plus FH48 or other mutation found on DNA sequencing; or
- those two separate samples with TC ≥1.53 MoM

If one-off cholesterol ≥1.53 MoM was considered the screen test – and diagnostic confirmation considered to be any mutation or positive repeat cholesterol – then there would be very few false positives (FPR 0.6%). However, sensitivity is low at 62%. Of 30 children in this cohort who had an FH48 mutation, 17 had TC below the cut-off. This means a very high false negative rate (FNR) of 57%.

However, that is when considering FH48 mutations only. In this study, screen negatives (TC <1.53) all received FH48 mutation analysis but did not receive full DNA sequencing. This is a significant limitation of this study as it means the number of true and false negatives cannot be known with certainty, preventing a reliable estimation of screen test performance. Wald et al[3] allow that there may be other non-FH48 mutations among screen negatives. On this basis they estimate that one-off cholesterol measure could have even lower sensitivity for FH of 55%.

Overall this suggests that a screening programme based on one-off cholesterol measure would not be a reliable enough screen test to detect children with FH. On this basis criterion 4 could not be met.

Wald et al[3] therefore propose an alternative screen test where all children with cholesterol above a much lower cut-off of ≥1.35 would receive full DNA sequencing. Those with no mutation identified but with cholesterol ≥1.50 would have repeat cholesterol several months later. If this was again ≥1.50 they would also be considered to have FH. This strategy would aim to identify those at highest cardiovascular risk – excluding those with a one-off high cholesterol measure but without FH, while identifying those with FH and unknown mutations. It would also aim to limit over-detection and unnecessary treatment for those who may carry FH mutations but with low cholesterol, so would theoretically be at low cardiovascular risk.

Wald et al[3] modelled this alternative strategy and estimated it would detect 40 children and 40 parents per 10,000: a case rate of 8 per 1000. However, this alternative screening strategy has not yet been assessed in practice and remains hypothetical. It cannot be known whether this would give optimal screen test performance and identify all those with FH who are at risk of cardiovascular morbidity.

Other questions remain related to acceptability, treatment and cost effectiveness.

Even if the screen test performance were optimised it would identify children who by current NICE guidelines[4] would not be considered for treatment until around age 10 years. In the immediate term it would identify the affected parent(s). In the Wald et al[3] cohort most parents of screen-detected children (32/37) participated in cholesterol/mutation testing. Of the 28 parents diagnosed with FH, none were currently taking statins and 25 started treatment.

The study states that no parents reported negative effects of screening and said that it was worthwhile. However, it is difficult to know what these views relate to. As a heel prick sample taken at the time of routine immunisation, this is a minimally invasive procedure and one that doesn't require an additional clinic visit. Follow-up DNA analysis was also performed on the same sample. Therefore in this regard it seems plausible that child participation in such a screening programme could be acceptable to parents.

However, parents may have also considered the programme as worthwhile and acceptable in terms of identifying if they were a mutation carrier themselves, and allowing them to make the decision whether or not to start statin treatment.

It is difficult to know at this early stage what effect identifying young children with FH would have. It is not known whether the child (and their parents) would find it acceptable for them to start lifelong treatment from age 10 (or younger), and whether this could have any negative effects.

Based on this early and limited information, it is not possible to say that the complete screening programme (test, diagnostic procedures, treatment/ intervention) would be clinically, socially and ethically acceptable according to criterion 12.

Cost effectiveness is another uncertainty, particularly when considering how the child-parent screening strategy would complement or compare with the current NICE[4] strategy of cascade testing. Of note a recently published cost effectiveness analysis[5] found that UK cascade testing is highly cost effective. The overall incremental cost effectiveness ratio (across all ages) was £5806 with a net lifetime cost per relative tested of £2781. This is well below the NHS cost effectiveness threshold of £20,000 to £30,000.

Wald et al[3] estimate a direct cost of $2900 per person identified to have FH (conversion £2244 at time of authoring), with no additional service delivery cost as screening is combined with immunisation. However, the cost effectiveness of child-parent screening and lifetime treatment is not known. Therefore criterion 14 could not be met currently.

Conclusion

This prospective UK cohort assesses a child-parent screening strategy for FH, based on one-off cholesterol testing of young children (aged 1 to 2 years) with follow-up mutation analysis. Cholesterol testing using the threshold identified as optimal by previous systematic review (1.53 MoM) had poor sensitivity for identifying children carrying FH mutations. However, full DNA

sequencing was not performed for screen negatives so screen test performance cannot be known with certainty.

The study authors proposed an alternative screening strategy using a lower TC cut-off (1.35 MoM) with full DNA sequencing for all those above this threshold. This would aim to identify all those with FH mutations at highest risk of cardiovascular morbidity. This alternative strategy has not yet been studied in practice so test performance remains uncertain.

Parents in the study reported screening to be acceptable and worthwhile. However, given that children would not be eligible for treatment until around age 10 years, acceptability and potential adverse outcomes cannot be known with certainty.

The study estimates direct screening costs, but cost effectiveness of child-parent screening and lifetime treatment is not known, particularly how this compares with the current strategy of cascade testing.

Overall on this basis the 4 criteria assessed by the 2015 UK NSC external evidence review could not be met at the current time. This does not suggest that this topic should be re-reviewed as a matter of priority ahead of its scheduled 2018 update.

Table 1

Publication	Wald et al. Child-parent familial hypercholesterolaemia screening in primary care. New England Journal of Medicine. 2016; 375(17):1628-1637.
Study design and setting	Prospective screening cohort in the setting of the child immunisation programme; 92 UK general practices, March 2012 to 2015.
Population	N=10,095 children (median 12.7 months, 52% male) N=13,097 invited to participate; n=11,010 (84%) agreed participation; satisfactory sample obtained for n=10,118 (8% sampling failure rate); with n=23 incorrect transcription results (<0.3% failure rate).
Test	Total cholesterol (TC), low density lipoprotein (LDL) cholesterol, triglyceride measurement and analysis of 48 FH mutations (FH48) in heel prick capillary sample. Screen positive cut-off: • TC ≥1.53 multiples of the median (MoM, corresponding to ≥99.2 centile) Confirmed screen positive: • TC ≥1.53 MoM plus an FH48 mutation; or • TC ≥1.53 MoM on a repeat test DNA sequencing was also performed for those with TC ≥1.53 and no FH48 mutation. Parents of screen positives were tested and considered positive if: • they had the same FH mutation as the child; or

	• whichever parent had the higher cholesterol level
Reference standard	Confirmation as index test NB. Isolated cholesterol was not considered the screen test in practice as mutation analysis was performed, though the below test performance data compared with a scenario of cholesterol testing only

Outcomes	**Child screening**
	92 screen positive (TC ≥1.53 MoM):
	• 13 with an FH48 mutation
	• 79 with no FH48 mutation: 7 with mutation found on DNA sequencing
	• 72 with no mutation on DNA sequencing:
	  o 8 with repeat TC ≥1.53 MoM
	  o 64 with repeat TC <1.53 MoM
	
	10,003 screen negative (TC <1.53 MoM)
	• 9986 with no FH48 mutation
	• 17 with an FH48 mutation
	
	<u>Performance of TC ≥1.53 MoM for a specified outcome</u>
	• Presence of FH48 mutation:
	  o sensitivity 43% (13/30)
	  o FPR 0.8% (79/10,065)
	• Presence of FH48 or other mutation found on DNA sequencing:
	  o sensitivity 54% (20/37)
	  o FPR 0.7% (72/10,058)
	• Presence of any mutation or two TC measures ≥1.53 MoM:
	  o sensitivity 62% (28/45)
	  o FPR 0.6% (64/10,050)
	• FH48 or other mutation given that DNA sequencing was not performed for those with TC<1.53 (assuming a further 6 FH mutations expected):
	  o sensitivity 47% (20/43)
	  o FPR 0.7% (72/10,052)
	• Presence of any mutation or two TC measures ≥1.53 MoM given that DNA sequencing was not performed for those with TC<1.53:
	  o sensitivity 55% (28/51)
	  o FPR 0.6% (64/10,044)
	
	Parent screening
	• 32/37 parents of children with any FH mutation participated in testing (5 declined/were unavailable)
	• 27/32 cases the parent with higher cholesterol had the FH mutation (rate 84%, 95% CI 67 to 95)

	• 25/28 parents with positive screen results (assumed from reporting to be presence of mutation or high cholesterol) subsequently started taking statins (none on prior treatment)
	• No parents reported negative effects and said screening was worthwhile
	
	Hypothetical application of results to a screening population using lower cut-off TC ≥1.35 MoM
	• 10,000 children screened
	• 500 have TC ≥1.35 (95th centile)
	• 32 children have FH mutation (based on full sequencing)
	  ○ 32/64 parents have the same mutation
	• 468 children with no FH mutation
	  ○ 80 with TC ≥1.50 MoM have repeat cholesterol 2 to 3 months later
	  ▪ 8 have repeat TC ≥1.50 MoM
	  ▪ 8/16 parents identified on the basis of having the higher cholesterol of the two
	• 40 children and 40 parents identified per 10,000: case rate of 8 per 1000
	
	Cost estimates
	Cholesterol testing reported to cost $7 and DNA sequencing $300 per sample, resulting in $2,900 per person identified as having positive screening results for familial hypercholesterolemia (with no additional service delivery cost when screening is combined with immunisation).

References

1. Wald et al. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ. 2007; 335:599.
2. Wald et al. Child-parent screening for familial hypercholesterolaemia. Journal of Pediatrics. 2011; 159:865-7.
3. Wald et al. Child-parent familial hypercholesterolaemia screening in primary care. New England Journal of Medicine. 2016; 375(17):1628-1637.
4. NICE. Identification and management of familial hypercholesterolaemia (CG71). National Institute for Health and Care Excellence, 2008.
5. Kerr et al. Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK. European Heart Journal. 2017