8th November 2017

John Marshall
Evidence Lead
UK National Screening Committee

Dear Mr Marshall

The submission on Child-Parent Screening for FH by HEART UK was sent on Jan 9th 2017 to the National Screening Committee (NSC) together with a paper published in the New England Journal of Medicine (NEJM) describing a demonstration project of child-parent screening in over 10,000 children across England. HEART UK received a negative response on Sept 4th 2017 together with 2 external assessments by unnamed authors.

The method identified in our submission identifies all children in the population at greatest risk of a premature heart attack due to inherited high cholesterol; that is one child in every 250 screened (the expected prevalence of FH). No other method provides a universal screening strategy.

For every child with FH, the method identifies an extra person at high risk – the affected parent – effectively screening two generations simultaneously. In this way for every 1,000 children screened eight FH positive individuals are identified before the onset of heart disease, allowing preventive treatment (adopting a healthier lifestyle and medication) to be offered to avoid a heart attack at a young age.

HEART UK has considered the objections raised by NSC and I detail below our response each one and appreciate your consideration:

1. The NSC states that “the submission focused on a “universal child-parent screening strategy as an alternative to the cascade testing approach recommended by NICE”

The starting point for this assessment is incorrect. Child-parent screening and cascade testing are not alternative strategies and should not be assessed against each other; child-parent screening is a population screening strategy, capable of identifying all families with FH, while cascade testing is a method of testing relatives, within a family, once an affected person in that family has been identified. Cascade testing is self-limiting because it stops once all relatives in a family have been tested. It is not, nor has it ever been, regarded as a population screening method. Moreover, cascade testing can only be sustained if there is a completely separate method of identifying new unrelated index cases. Child-parent screening provides such a method. The two methods are therefore complementary, not competitive.
2. The NSC states “although the child-parent screening strategy is intrinsically interesting....there is:

(i) an absence of information on the management of children with FH identified by screening”.

This is incorrect. Dietary advice is given and, according to NICE Guidelines CG71 “1.2.1.18 Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of 10 years” and 1.2.1.20 “Offer statins to children with FH by the age of 10 years or at the earliest opportunity thereafter.”

ii) “the acceptability of the strategy was only evaluated in those with positive results”

This is incorrect. The acceptability of screening was assessed by questionnaire in a pilot study and found to be 94% among all parents of children screened (whether found to be positive or negative for FH); specifically, 94% of parents whose children were screened, said that they would have another child screened by the same method if they had a second child and if screening were routinely offered. (Results in Wald et al. Journal of Pediatrics 2009 cited in the NEJM paper)

iii) “clinical and cost effectiveness compared with current practice is not addressed”

This is incorrect. The cost-effectiveness of cascade testing for FH is accepted (NICE guideline CG71). The question to address, for child-parent screening, is how much it costs to identify a new FH positive person (the starting point for cascade testing) in the general population and whether this is affordable. This was addressed in the NEJM paper - about £2,000. If cholesterol testing costs were about £1 (as used in NICE estimates) rather than £5 (the actual cost in the study), the cost per case identified would reduce significantly to about £1,000 per person identified.

The cost of child-parent screening is low relative to accepted medical screening for other conditions, in part because the screening is linked to routine child immunisation at 1 year of age (the most accurate age to screen). No new clinical infrastructure is needed as children are already passing through primary care; screening and immunization are efficiently combined in a single procedure.

3. “The assessments point out that the study authors considered the observed strategy to be insufficiently reliable in terms of the detection of FH”.

This is incorrect. On page 1631 of the NEJM paper it states that calculation of detection and false positive rates are misleading when the screening test (cholesterol and/or an FH mutation) also defines the disorder (FH), because a tautology is created that makes such calculations unreliable. This does not mean screening is not worthwhile, it simply means calculation of detection and false positive rates can not be used to assess this. Both external assessors focus heavily on these calculations, ignoring the tautological problem referred to above and explained in the NEJM paper.
Child-parent screening identifies children with cholesterol levels in the highest 5% of the population who also have an FH mutation, together with children in the highest 1% without an FH mutation (confirmed on repeat cholesterol measurement 3 months later). This is a practical approach that identifies the group in the population at greatest risk of a future premature heart attack due to inherited high cholesterol. Preventive treatment can and would be offered, so screening is worthwhile.

4. “The proposed strategy is based on modelling using a lower total cholesterol threshold to prompt further testing for FH mutations”.

This is incorrect. There is no modelling. In the study, cholesterol levels and FH mutations were tested in all children. The results provide a direct assessment of the number of children and parents identified as positive and therefore at high risk of inherited heart disease.

In the study, a pre-specified cholesterol cut-off at the 99th centile was used to define a positive screening result but, given the study results, a cut-off at the 95th centile is justified (1/3rd of children with FH mutations had cholesterol levels between the 99th and 95th centile levels of cholesterol). This is a direct, not inferred or modelled result.

5. “A different approach to genetic testing and a different approach to those with negative genetic test results was assumed in the model”.

This is incorrect. As stated above, there is no model. The screening proposal is based on the study results.

There may be some confusion, on the part of the report authors, because in the study (stated on page 1630 of the NEJM paper), all children were tested for the 48 most common FH mutations regardless of cholesterol. This was inexpensive and was expected to pick up most mutations. DNA Sequencing to identify all known mutations is expensive and was reserved for children with extremely high cholesterol levels (top 1%) in whom none of the common 48 mutations were found. Had sequencing been used in children in the top 5% of cholesterol (rather than only the top 1%) it would have identified 32, rather than 29 children with FH mutations (based on the proportion of mutations found on sequencing the top 1%). The difference between 32 and 29 is minor (not a major limitation as one of the assessors states) and it is wrong to claim the child-parent screening proposal is a model or based on assumptions.

In practice, different approaches to genetic testing could be used. In the NEJM paper, a new method (Next Generation Sequencing) was suggested going forward because this has the potential to identify more mutations at lower cost.

5. “Rather than providing a basis for policy making, it may be that the modelled results provide a hypothesis for a further study”.

This is incorrect. The original child-parent screening proposal was made in 2007 (published in the BMJ), first tested in a pilot study in 2009 (published in the Journal of Paediatrics) and then expanded into a demonstration project in over 10,000 children across England in 2013.
There is no need for further research but do recognise that review and audit is necessary to improve quality.

6. “For example the assessments point out that the number of false positives would increase in the modelled strategy compared to the observed strategy. The parents of a large number of very young children are likely to be informed that, although their child does not have FH, he or she has a total cholesterol level sufficiently high to justify further testing. It is unclear what information would be fed back to parents at different points in the pathway but the potential for anxiety seems very real here. Similarly the arrangements for post test management in this group, should it be required, were not described in the paper”.

This is incorrect. The programme does not yield a large number of false positives. It identifies 80/10,000 children with very high cholesterol levels (top 1%) and no FH mutation, who require repeat cholesterol testing before a final result is given. This two-step process, is needed because not all mutations are known and was understood and accepted by parents.

7. “This kind of issue, as well as those raised in the first bullet point, would need to be studied before it could be said that the strategy, as proposed, was acceptable”.

This is incorrect. Child-parent screening was acceptable in the 92 general practices that participated in the study across England. Key results which have been published and so were available for the NSC to review include:

- 84% of parents who were offered child screening accepted the invitation. The uptake may be higher outside a research setting if screening were simply bolted onto immunization as routine practice.

- 94% of parents said they would have a 2nd child screened if screening were offered.

- 90% of parents identified as FH positive started statin treatment.

- No parent of a positive child reported negative effects of screening (in questionnaires conducted afterwards). Comments by parents indicated that this was a widely appreciated screening opportunity, with a clear understanding of what was involved and the benefits.

- Immunisation rates increased from 76% to 85% over the period of screening.

7. “In addition, this the strategy raises some interesting ethical issues which have been touched on above. The UK NSC is in the process of convening an ethics task group and we will ask the group to consider some of the issues arising from the reflex testing strategy as part of its work”.

We do not consider that there should be an ethical barrier to child-parent FH screening. Individuals identified as positive are at the highest risk of a future premature heart attack in the population. This high risk can be largely abolished by preventive medication, so it would be unethical not to implement such screening. There is no need for a ‘task group’.
In summary, Child-parent screening could be implemented at little cost to existing services – about £10 per child screened – a similar amount to that a GP receives for immunising a child. Heart disease and infection prevention would be combined in a single encounter when parents are focused on prevention and the future health of their child. Both child and parent benefit, but the child benefits twice, once by reducing their own risk of premature heart disease but also by avoiding the premature death of a parent.

HEART UK urges the NSC to again examine the clear benefit of child-parent FH screening and re-examine the two assessments that contain incorrect and poor advice.

I would welcome the opportunity to meet with you and explore opportunities for the NSC to reconsider HEART UK’s submission to screen children for FH.

Yours sincerely

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