

# Screening for familial hypercholesterolaemia in children

## An Appraisal Report

## 1. Background

The UK National Screening Committee (UK NSC) evidence review process includes the opportunity for individuals or organisations to submit an early update proposal. This can be used to alert the UK NSC to new evidence published between the scheduled updates of evidence reviews which takes place on a 3-year cycle. The purpose is to identify published evidence which may alter a screening recommendation and which may prompt an early update of a UK NSC evidence review.

The UK NSC received a submission from HEART UK – the Cholesterol Charity in January 2017 through the annual call for new topics. This related to screening for hypercholesterolaemia in children aged 1 to 2 years old. This submission referenced the publication of a new study on child-parent screening for familial hypercholesterolaemia screening in primary care by Wald et al (2016)<sup>1</sup>.

This submission was considered by a UK NSC evaluation group who noted that FH in children is on the UK NSC's database of recommendations and is part of the Committee's regular review cycle. The last UK NSC evidence review was completed in March 2015<sup>2</sup> and the policy recommendation not to introduce a national screening programme for FH in children was published in March 2016 (UK NSC 2016)<sup>3</sup>. The next scheduled review for this topic is due in 2018/19.

### The 2015 UK NSC evidence review

Familial hypercholesterolaemia (FH) is a condition where high cholesterol is caused by an inherited genetic mutation<sup>2</sup>. Cholesterol is elevated from birth and is associated with the early development of atherosclerosis and coronary heart disease<sup>2</sup>. The National Institute for Health and Care Excellence (NICE) recommend that the Simon Broome criteria should be used to diagnose FH<sup>4</sup>. These criteria state that a child (as an index affected individual) should be diagnosed with definitive FH if they have a total cholesterol level of >6.7mmol/l and low-density lipoprotein (LDL) cholesterol level of >4.0 mmol/l, or DNA-based evidence of an LDL-receptor mutation, familial defective apo-B-100 or a PCSK9 mutation.

The 2015 UK NSC review of screening for FH in childhood considered evidence published between January 2004 and January 2015 and addressed key questions against 4 UK NSC criteria<sup>2</sup>. The criteria, key questions and main findings are summarised below.

#### **Criteria 5: There should be a simple, safe, precise and validated screening test**

- key question 1: What are the test characteristics of a universal screening programme for FH in children?
  - a) how does the sensitivity, specificity, positive predictive value and negative predictive value of universal screening for FH in children compare to cascade testing of relatives of clinically detected cases?
  - b) how many additional cases of FH will be found from universal screening over cascade testing?
  - c) has the timing of the screening test for FH in children been defined in the literature?

The 2015 UK NSC review concluded that it was “not possible to accurately determine the test performance of universal screening for FH in children due to the lack of published prospective studies”. The review did identify a systematic review of case-control studies that considered the age

and the cholesterol cut-off level that would give the best discrimination between people with and without FH and suggested 1-9 years as the optimal age category.

The 2015 UK NSC review identified that the Wald et al study was in progress with the aim of evaluating universal child-parent FH screening at the time of routine child immunisation at 1-2 years. It was felt that the results of this study were needed to inform the accuracy of the proposed strategy and its performance compared to cascade testing, which was suggested to identify less than a third of people (not limited to children) with FH in the general population.

**Criteria 13: There should be evidence from high quality randomised controlled trials (RCT) that the screening programme is effective in reducing mortality or morbidity.**

- key question 2: Is there any evidence from RCTs / trials that universal screening is more effective than cascade testing at reducing mortality and morbidity?

The 2015 UK NSC review did not identify any studies that assessed whether child screening (either universal or cascade testing) reduces morbidity or mortality from FH. The review stated that there would likely be feasibility issues due to the long follow-up required to examine cardiovascular outcomes and no clearly established thresholds to indicate the presence or progression of atherosclerosis in children.

**Criteria 14: 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**

- key question 3: Is there evidence that screening children for FH would be clinically, socially and ethically acceptable to health professionals and the public?
  - a) is there evidence that treating children with FH with statins would be clinically, socially and ethically acceptable?

The 2015 UK NSC review concluded that there remain unanswered questions related to the ethics and acceptability of universal screening at 1-2 years, including the management of screen-detected cases.

**Criteria 16: 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 (i.e. value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.**

- Key question 4: Would a universal screening programme for FH in children be more cost-effective than cascade testing in relatives of clinically detected cases?
  - a) What are the modelled costs of childhood universal FH screening vs the modelled costs of cascade testing and what are their dependencies (e.g. participation rates for universal child/ cascade testing)?

The 2015 UK NSC review did not identify any new studies which assessed the cost-effectiveness of universal screening at 1-2 years or of child screening at any age. The review also noted that a

previous Health Technology Assessment had concluded that universal screening at 16 years would be cost effective.

Solutions for Public Health (SPH) were commissioned by the UK NSC to conduct a critical appraisal of the Wald et al (2016) paper and to provide a commentary on the impact of this paper on the relevant UK NSC criteria and overall conclusions of the 2015 UK NSC evidence review.

One SPH researcher conducted the critical appraisal and commentary. This was then quality assured by a second SPH researcher.

## 2. The submission

The submission from HEART UK proposed child-parent screening for FH in primary care to identify persons at high risk of inherited premature cardiovascular disease. The submission stated their view that, since the publication of the Wald et al (2016) paper on child-parent FH screening in primary care “there is now a suitable screening strategy for general population screening, which addresses the ethics and acceptability of universal screening at 1-2 years”. The submission also states that “it is accepted that statins reduce the risk of myocardial infarction and death in people with FH at a low cost per case detected and child-parent screening is low cost and affordable when linked to routine immunisation”.

The submission includes a flow chart using information from the Wald et al (2016) study. In this flow chart screen positive children have either a total cholesterol level of  $\geq 1.35$  multiples of the median (MoM) and a FH mutation or an initial and repeat total cholesterol level of  $\geq 1.50$  MoM. The submission suggests that 40 screen positive children and 40 screen positive parents would be detected from 10,000 children screened. The cost is estimated at £1,500 per new FH positive individual identified.

## 3. Critical appraisal of Wald et al (2016)<sup>1</sup>

Wald et al (2016)<sup>1</sup> assessed the feasibility and efficacy of child-parent FH screening in UK primary care practices. In this method the child provides the screening entry point and the parents of screen positive children are subsequently tested<sup>1</sup>. Between March 2012 and March 2015 the parents of children aged approximately 13 months old were invited to participate in FH screening to take place at the same time as the child’s immunisation. The key elements of the study are presented and discussed in Table 1.

**Table 1: Key elements of Wald et al (2016)**

	Details	Comments
<b>Population and participation</b>	<p>The parents of 13,097 children were invited to participate in FH screening</p> <ul style="list-style-type: none"> <li>• 11,010 agreed to participate (84%)</li> <li>• 10,118 satisfactory samples obtained (92% of samples taken)</li> <li>• 10,095 children included in analysis (92% of samples taken)</li> </ul>	<p>No inclusion or exclusion criteria are stated for inviting parents to participate in FH screening in the published paper. The study protocol, provided as an online appendix, states that there were no exclusion criteria. There is the potential for introducing bias into a study population if inappropriate exclusion</p>

	<p>The median age of children was 12.7 months (Interquartile range (IQR) 12.4 to 13.3).</p> <p>Data were available on 10,094 mothers and 10,087 fathers. The median age of mothers was 31 years (IQR 27 to 35). The median age of fathers was 34 (IQR 30 to 38).</p> <p>1,094 (11%) had a family history of premature myocardial infarction ie in a first or second degree relative &lt; 50 years old.</p>	<p>criteria are applied. The study appears to have recruited a consecutive sample of participants and therefore to be at low risk of bias with regards to the study population.</p> <p>8% of children were not included in the analysis. Reasons for exclusion included slow collection of capillary blood resulting in clotting or an insufficient sample and 23 results were excluded due to transcription errors in the initial estimation of low-density lipoprotein cholesterol levels. The authors noted that staff who collected at least 200 blood samples had lower rates of unsatisfactory samples. As not all participants were included in the analysis this introduces some potential for bias as people with FH may have been missed.</p> <p>No information was provided on parents who declined to participate in FH screening.</p>
<p><b>Tests performed</b></p>	<p>All children had a heel-stick capillary blood sample taken to test for:</p> <ul style="list-style-type: none"> <li>• total cholesterol level</li> <li>• high-density lipoprotein cholesterol levels</li> <li>• triglyceride levels</li> <li>• 48 FH mutations (FH 48)</li> </ul> <p>Children who had a total cholesterol of <math>\geq 1.53</math> MoM but did not have one of the 48 FH mutations had DNA sequencing (Sanger sequencing and Multiplex ligation-dependent probe amplification) to search for additional FH mutations.</p> <p>Children with a total cholesterol of <math>\geq 1.53</math> MoM who did not have a mutation identified by initial mutation or further DNA sequencing had a repeat total cholesterol measurement at least 3 months later.</p>	<p>The authors state that FH can be identified by a mutation, but that not all mutations are known. The authors also state that some people with an FH mutation do not have high total cholesterol levels. Data on both total cholesterol level and FH mutation were therefore analysed in this study.</p> <p>All children had an initial test for total cholesterol level and were tested for 48 FH mutations. However only a sub-set of children had further DNA sequencing to identify further mutations or a repeat total cholesterol test. It is possible that people with FH could be missed using this approach.</p> <p>It is also not clear if there could be any false negatives amongst children who had an initial total cholesterol level of <math>&lt; 1.53</math> MoM but did have an FH 48 mutation. A repeat total cholesterol test was not performed for this group.</p>
<p><b>Test interpretation</b></p>	<p><b>Children</b> The total cholesterol cut-off levels</p>	<p>A pre-specified cut-off threshold (99<sup>th</sup> percentile) was used, taken from a</p>

	<p>used to determine a screen positive result in children are described below.</p> <ul style="list-style-type: none"> <li>• a pre-specified cut-off level of 1.53 MoM (corresponding to a percentile of 99.2) in combination with a mutation or at initial and repeat testing</li> </ul> <p>Children were considered to have a positive screening result if:</p> <ul style="list-style-type: none"> <li>• their total cholesterol level was <math>\geq 1.53</math> MoM and they had an FH mutation, or</li> <li>• their initial total cholesterol level was <math>\geq 1.53</math> MoM and they had a repeat elevated total cholesterol level of <math>\geq 1.53</math> MoM at repeat testing at least 3 months later</li> </ul> <p><b>Parents</b></p> <p>A parent of a child with a positive screening result was considered themselves to have a positive screening result if:</p> <ul style="list-style-type: none"> <li>• he or she had the same mutation as the child</li> <li>• he or she had the higher cholesterol level of the 2 parents (on the assumption that the parent had a non-detectable mutation)</li> </ul>	<p>previous meta-analysis which estimated that a total cholesterol cut-off level of 1.53 MoM would identify 88% of children aged 1 to 9 years who had FH.</p>
<p><b>Results</b></p>	<p><b>Children</b></p> <p><b>Analysis using the pre-specified cut-off level (<math>\geq 1.53</math> MoM):</b></p> <ul style="list-style-type: none"> <li>• 92 children (0.9%) had an elevated total cholesterol level (<math>\geq 1.53</math> MoM) on initial testing</li> <li>• 37 children (0.4%) had an FH mutation<sup>1</sup></li> <li>• 72 of 92 children (78%) called for repeat total cholesterol testing</li> </ul> <p>Of these, 28 children (0.3%) were screen positive. This included:</p> <ul style="list-style-type: none"> <li>• 20 with elevated total cholesterol</li> </ul>	<p>A decision about whether the child was screen positive or screen negative was made from the initial total cholesterol level and FH mutation (FH 48) test for 99% of children (10,003 with a total cholesterol level <math>&lt; 1.53</math> and 13 with a total cholesterol level of <math>\geq 1.53</math> MoM and an FH 48 mutation). DNA sequencing to identify further FH mutations was conducted for 79 children. 72 children were called for repeat total cholesterol testing.</p> <p>The detection rate and false positive rate (specificity 100%-FPR) were calculated for the analysis using the pre-specified cut-off</p>

<sup>1</sup> 30 had one of the 48 FH mutations initially tested for and 7 had another FH mutation identified in children for which further DNA sequencing was performed

	<p>levels (<math>\geq 1.53</math> MoM) and an FH mutation</p> <ul style="list-style-type: none"> <li>• 8 with elevated total cholesterol levels (<math>\geq 1.53</math> MoM) at first testing and on repeat testing 3 months later</li> </ul> <p>17 of 37 children (46%) had an FH mutation but a total cholesterol level <math>&lt; 1.53</math> MoM.</p> <p>64 of 92 children (70%) had an elevated total cholesterol level on initial testing but did not have an FH mutation and had a repeat cholesterol level of <math>&lt; 1.53</math> MoM.</p> <p>Detection rate (DR), false positive rate (FPR) and odds of being affected given a positive result (OAPR) were presented in an online appendix that accompanies the published study. For the 28 screen positive children:</p> <ul style="list-style-type: none"> <li>• DR 62% (95%CI 47% to 76%)</li> <li>• FPR 0.6% (95%CI 0.5% to 0.8%)</li> <li>• OAPR 1:2 (95% CI 1:1 to 1:4)</li> </ul> <p>The prevalence for a positive screening result was 0.3% (95%CI 0.2 to 0.4). The overall mutation prevalence was 1 in 273 children (95%CI 1 in 198 to 1 in 388).</p> <p>All the children who tested as screen positive were heterozygous for FH.</p> <p><b>Additional analysis of results using revised cut-off levels</b></p> <p>In this analysis screen positive cases had a total cholesterol level of <math>\geq 1.35</math> MoM plus an FH mutation or an initial and repeat cholesterol level of <math>\geq 1.50</math> MoM.</p> <p>When the cut-off level was lowered and applied to the results 40 children were screen positive. This included:</p> <ul style="list-style-type: none"> <li>• 32 with elevated cholesterol levels (<math>\geq 1.35</math> MoM) and an FH mutation</li> <li>• 8 with elevated cholesterol levels</li> </ul>	<p>level of <math>\geq 1.53</math> MoM. The detection rate was 62% although the confidence intervals are fairly wide reducing confidence in the result. The false positive rate was less than 1%. The odds of being affected given a positive result (1:2) is the positive predictive value expressed as odds. This is equivalent to 66.7%</p> <p>A modelled analysis was performed with an initial lower cut-off level of <math>\geq 1.35</math> MoM (95<sup>th</sup> percentile) applied to the test results.</p> <p>Twelve children were reassigned to the screen positive group when the initial cut-off was lowered to <math>\geq 1.35</math> MoM. No test performance data (eg detection rate) was provided for the analysis using the lower cut-off levels.</p>
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	<p>(<math>\geq 1.50</math> MoM) at first testing and on repeat testing 3 months later</p> <p><b>Parents</b></p> <p><b>Analysis using the pre-specified cut-off level (<math>\geq 1.53</math> MoM):</b> Cholesterol levels in the parents were available for 32 of the 37 children who had an FH mutation (for 5 children a parent either declined or was unavailable for testing).</p> <p>In 27 of the 32 parents (84%) the parent with the higher cholesterol level had the FH mutation.</p> <p>28 parents had a positive screening result and were not previously receiving statins. Of these 25 subsequently started taking statins (2 were pregnant and planned to start taking statins later and 1 could not be contacted).</p> <p><b>Additional analysis of results using the revised cut-off levels</b> In this analysis 40 parents were considered screen positive (corresponding to the 40 children testing as screen positive).</p>	
<p><b>Acceptability of screening</b></p>	<p>Parents who had a positive screening result completed a questionnaire that assessed whether the screening was worthwhile. All indicated that they thought screening was worthwhile and non-reported negative effects.</p> <p>The effect of screening on immunisation was assessed by comparing rates in the year before screening (76%) and after the second year of screening (85%) in a sample of 24 practices. The authors concluded that screening did not reduce immunisation rates.</p>	<p>The acceptability of screening was not tested amongst parents who did not have a positive screening test.</p> <p>The uptake of the offer of screening was fairly high at 84%. No information was provided on reasons for declining the offer of screening or on the demographics of parents who did or did not participate in screening.</p>
<p><b>Study Conclusions</b></p>	<p>The authors concluded that child-parent screening was feasible in 92 primary care immunisation clinics.</p> <p>The authors proposed that based on</p>	<p>The number of screen positive persons in the analysis using the lower cut-off levels was used to inform the numbers cited in the study conclusions. No rationale was given for using 1.35 MoM or 1.50 MoM in</p>

	<p>the modelled analysis using the lower cut-off level children would be considered to have a positive screening result if:</p> <ul style="list-style-type: none"> <li>• their total cholesterol level was <math>\geq 1.35</math> MoM and they had an FH mutation, or</li> <li>• their initial total cholesterol level was <math>\geq 1.50</math> MoM and they had a repeat elevated total cholesterol level of <math>\geq 1.50</math> MoM at repeat testing</li> </ul> <p>The authors concluded that using this approach for every 1,000 children screened, 8 persons (4 children and 4 parents) would be screen positive for FH.</p>	<p>the proposed screening strategy.</p>
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### Commentary

Wald et al (2016) do not suggest that the primary screening strategy used in their study as described in Table 1 is applied in practice. In the study total cholesterol levels and testing for 48 FH mutations was performed in all children. This strategy resulted in some children being identified who had an FH mutation but did not have an elevated total cholesterol level. These children were not considered to be screen positive using the pre-defined cut-off level of  $\geq 1.53$  MoM.

A total cholesterol level of 1.53 MoM is equivalent to 5.95mmol/l. This is lower than the value of 6.7mmol/l used for the diagnosis of FH in the Simon Broome criteria recommended by NICE. The study authors suggest a different approach in an application of their findings to a typical population of 10,000 children using a lower initial cut-off level of 1.35 MoM. This represented the 95<sup>th</sup> percentile but it is not clear what the rationale for using this particular initial cut-off was. Reducing the total cholesterol cut-off level may detect more screen positive cases but it will also increase the number of false positive screening tests.

The strategy suggested by the study authors involves testing total cholesterol levels in all children but only testing for FH mutations in children whose total cholesterol level is elevated ('reflex' DNA testing). This approach would avoid a situation where screening would identify children who had an FH mutation but did not have elevated total cholesterol levels. Having a FH mutation does not always lead to high cholesterol and a cardiovascular event and the authors consider the presence of the mutation a risk factor rather than leading inevitably to disease. However it is not clear if this approach could potentially miss people with FH.

The strategy the authors recommend for identifying screen positive cases with raised cholesterol and no detected mutation uses a cut off of  $\geq 1.50$  MoM in two consecutive tests taken several months apart. The assumption is that these children will have FH as a result of an as yet unknown mutation. There is no rationale presented for the use of the cut off  $\geq 1.50$  MoM and this strategy would identify a group of children with a total cholesterol level between 1.35 MoM and 1.50 MoM but no detectable FH mutations who would be considered screen negative.

The study included a questionnaire for parents who had a positive screening result to assess whether they felt that screening was worthwhile. However, the acceptability of screening was not tested amongst parents who did not have a positive screening test.

The authors also suggest that advances in DNA sequencing have lowered costs and that the approach used in their study (eg testing for 48 FH mutations followed by further DNA sequencing) is redundant. The authors state that mutation testing could be based on sequencing alone. Some illustrative costs are provided. For example, if cholesterol testing costs \$7 (US) and DNA sequencing costs \$300 per sample the cost of screening would be \$2,900 per person identified as having a positive screening result (£2,233<sup>2</sup>). The authors state that additional service delivery costs would be avoided if screening was combined with immunisation.

Longer term follow-up of these children and their parents would be needed to assess the outcomes of child-parent screening. For example, the follow-up and management of children identified as screen positive at age 1-2 years and their subsequent use of statins; and the prevalence of cardiovascular disease in screened children and parents compared to non-screened populations. There may be issues around the feasibility of such longer term follow-up studies.

The authors suggest that FH is better regarded as a marker that indicates an increased risk of premature cardiovascular disease rather than a separate medical disorder.

#### 4. Assessment of impact on the UK NSC criteria

The impact of the findings of the Wald et al (2016) study against the UK NSC criteria considered in the 2015 UK NSC evidence review is provided below.

##### **Criteria 5: There should be a simple, safe, precise and validated screening test**

The 2015 UK NSC review concluded that it was not possible to accurately determine the test performance of universal screening for FH in children due to the lack of published prospective studies. Detection rates (DR) for different cut-off levels were provided in the 2015 UK NSC study, taken from a systematic review and meta-analysis investigating the age at which cholesterol levels give the best discrimination between those with and without FH. In this review results for the 1 to 9 years age group were:

- at a total cholesterol cut-off of 1.53 MoM and FPR of 0.1% DR = 88 (95% CI 84 to 92)
- at a total cholesterol cut-off of 1.42 MoM and FPR of 0.5% DR = 94 (95% CI 91 to 97)
- at a total cholesterol cut-off of 1.37 MoM and FPR of 1.0% DR = 96 (95% CI 93 to 98)

The Wald et al (2016) study found a DR of 62 (95%CI 47 to 76) and an FPR of 0.6% at a total cholesterol cut-off of 1.53 MoM which is lower than the rates cited in the 2015 review.

No information on detection rate and false positive rate was provided for the lower initial cut-off level of  $\geq 1.35$  MoM suggested by Wald et al. However, the modelling using the lower initial cut-off

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<sup>2</sup> Using the exchange rate on 30.06.2017

level estimated that 40 children and parents would be screen positive compared to the 28 children and parents detected using the cut-off level of 1.53 MoM.

The Wald et al (2016) study does provide an example of universal screening for FH in practice which was not available to the 2015 UK NSC review. However, the detail of the testing process used in conducting the Wald et al study differs from that proposed in the HEART UK submission which is based on the modelled cut-off levels proposed by Wald et al.

**Criteria 13: There should be evidence from high quality randomised controlled trials (RCT) that the screening programme is effective in reducing mortality or morbidity.**

The 2015 UK NSC review did not identify any studies that assessed whether child screening (either universal or cascade testing) reduces morbidity or mortality from FH. The Wald et al (2016) study does not provide any further information relating to this criterion.

**Criteria 14: 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**

The 2015 UK NSC review concluded that there remain unanswered questions related to the ethics and acceptability of universal screening at 1-2 years, including the management of screen-detected cases.

The Wald et al (2016) study provides some information about the feasibility and acceptability of the testing and diagnostic aspects of child-parent screening in primary care. The uptake of the offer of screening was 84%. No information was provided on reasons for declining the offer of screening or on the demographics of parents who did or did not participate in screening. Linking the screening programme to immunisations did not appear to have a negative impact on immunisation rates in a sample of 24 practices.

In the Wald et al study parents who had a positive screening result completed a questionnaire and indicated that they thought screening was worthwhile. No negative effects were reported. The views of parents who did not have a positive screening result, or who were recalled for further testing was not sought. The views of these groups are also important in understanding the acceptability of a screening programme.

Wald et al also provide some information on the acceptability of treatment/ intervention in parents. Almost all parents with a positive screening result who were not previously receiving statins started taking or planned to start taking statins. The study did not discuss the future management of children who were identified as screen positive or the information provided to parents.

**Criteria 16: 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 (i.e. value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.**

The 2015 UK NSC review did not identify any new studies which assessed the cost-effectiveness of universal screening at 1-2 years or of child screening at any age. The Wald et al (2016) study included an estimate of the cost of screening per positive screening result and assessed the feasibility of child-parent screening linked to routine immunisation. The study did not include a cost effectiveness analysis. The Wald et al (2016) study provides some additional information relating to this criterion that could potentially be used in an assessment of the opportunity cost of a child parent screening programme.

## Conclusions

The Wald et al (2016) study adds to the evidence base for screening for FH in children and provides an example about the feasibility of a universal screening programme for children that was not available to the 2015 UK NSC review. However, it is unlikely that this study alone would change the conclusions of the 2015 review for the specified criteria. The modelled screening strategy developed by the study authors would benefit from being tested in practice to better inform future screening policy decisions.

## References

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