UK National Screening Committee

Evidence maps: antenatal and newborn screening for Fragile X Syndrome

27 February 2019

Aim

1. To ask the UK National Screening Committee (UK NSC) whether or not, based on the evidence presented in this document, any further action is required to make a recommendation on antenatal and newborn screening for Fragile X Syndrome (FXS).

Current recommendation

2. The 2014 review on antenatal screening for FXS concluded that systematic population screening should not be recommended.

3. This recommendation was made for the following reasons:

    - While the natural history and prognosis of full mutations in males was well understood, other elements of the natural history were not. For example, it is still not possible to predict whether a female fetus carrying the full mutation will be affected by learning difficulties or to what extent. Furthermore, in males and females, the clinical impact of carrying a fragile X mental retardation 1 gene (FMR1) pre-mutation (55 to 200 repeats) remained unclear. Similarly, in females alone, the association between a pre-mutation and Fragile X associated primary ovarian insufficiency (FXPOI) remained unclear. In addition, evidence on the association between FMR1 intermediate allele status (between 41–54 or 45–54 repeats) and Autism Spectrum Disorder (ASD) in males and females remained inconclusive.

    - Polymerase chain reaction (PCR) followed by selective Southern blot remained the only acceptable method for diagnosing FXS. Southern blot is, however, labour and time intensive, and therefore was not considered suitable for the rapid high-throughput testing required in a population-based screening programme. Several PCR-based diagnostic strategies had been

proposed as an alternative. However, no studies were identified that assessed the performance of PCR kits in large, unselected, pregnant populations. Only 6 exploratory studies assessing analytical validity were included and they reported various degrees of sensitivity (ranging from 88.6% to 100%), and specificity (ranging from 42.9% to 100%).

- There are currently no interventions/treatments that could be offered to reduce the risk of developing FXS or the adverse outcomes associated with the condition.

4. Newborn screening for FXS has not been previously reviewed by the UK NSC. This topic had been raised by stakeholders during the consultation on the previous review on antenatal screening for FXS.

Evidence Maps

5. This document discusses the findings of two evidence maps. One was conducted on antenatal screening for FXS and one was conducted on newborn screening for the condition.

6. Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic. This approach has been used for this topic to support decision making on whether or not the evidence is sufficient to justify commissioning a more sustained external review of the evidence.

7. The two evidence maps addressed the following questions:

   - First evidence map
     a) Has a test, which is suitable for whole population screening, been evaluated in the pregnant population?

   - Second evidence map
     a) Has a test, which is suitable for whole population screening, been evaluated in the newborn population?
     b) Are any treatments/early interventions available for people with FXS and how effective are they?

c) Are there any guidelines and/or recommendations for antenatal or newborn screening for FXS?

8. The evidence maps recommend that:

- An update review on antenatal screening for FXS should not be commissioned at this stage and the topic should be re-considered in 3-years' time.

- An evidence summary on newborn screening for FXS should not be commissioned. As newborn screening for FXS has not been previously reviewed by the UK NSC, future consideration of newborn screening for FXS would need to be approved through the annual call for new screening topics.

9. These recommendations were made for the following reasons:

- No new evidence that evaluated a suitable test in a large, unselected, pregnant population was identified. As such the volume and type of evidence related to antenatal screening for FXS is insufficient to justify an update review.

- The evidence indicates that newborn screening using PCR-based methods could be feasible but this would need to be explored in larger studies. At present the evidence base is limited, particularly with regard to prospective studies in large, unselected newborn populations.

- At present, there is insufficient evidence to compare the benefits of early treatment/interventions for FXS to late treatment after clinical presentation of symptoms.

- No national or international guidelines identified by the evidence maps recommend population screening for FXS either antenatally or in newborns. There is no precedent for newborn screening for FXS.

- Multiple discussion papers have highlighted that newborn screening for FXS raises a number of ethical, policy, and social concerns, particularly the detection of infant pre-mutation carriers and cascade screening of extended family members.

Consultation

10. A three month consultation was hosted on the UK NSC website. Direct emails were sent to 12 stakeholder organisations. **Annex A**

11. Only one set of comments was submitted by:

    i. Genetic Alliance UK

    (See **Annex B** for comments)

12. The following points were made:

- The consultee noted that relying solely on peer reviewed literature excludes the direct contribution of the patient voice to the process. Other agencies accept qualitative evidence from patient communities and the UK NSC should follow the same approach.

  Response: The literature search process for a UK NSC evidence summary follows a systematic approach, as outlined in the UK NSC evidence review process. The evidence review process used by the UK NSC reviews is published on the GOV.UK webpage and is available to the public: https://www.gov.uk/government/publications/uk-nsc-evidence-review-process

- The stakeholder expressed concerns about the methodology of the evidence maps in regard to the fact that all references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information. The stakeholder noted that whilst understanding the UK NSC's reasoning behind the rapid review methodology, a "review needs to involve

reading the full text of each reference in order to adequately and accurately grasp their conclusions".

Response: The document that the stakeholder commented on is not a rapid review but an internally developed evidence map. Evidence maps aim to gauge the volume and type of evidence relating to a specific topic. An analysis and quality appraisal of the references at full-text level is outside the scope of an evidence map. This evidence map has been used for this topic to support decision making on whether or not the evidence is sufficient to justify commissioning a more sustained external review.

The evidence team is exploring the use of this approach for selected topics as an additional step in the overall UK NSC evidence review process.

Recommendation

13. The Committee is asked to approve the following recommendations:
    - *An update review on antenatal screening for FXS should not be commissioned in 2018/19 and the topic should be re-considered in 3-years' time.*
    - *An evidence summary on newborn screening for FXS should not be commissioned as the volume and type of the evidence related to newborn screening is currently insufficient to justify further work in this area. Since newborn screening for FXS has not been previously reviewed by the UK NSC, future consideration of this topic would need to be approved through the annual call for new screening topics when, at a minimum, significant evidence relating to the test and benefit of early intervention has been published.*

Annex A

List of organisations contacted

1. British Institute of Learning Disabilities
2. The British Society for Human Genetics
3. Faculty of Public Health
4. The Fragile X Society
5. Genetic Alliance UK
6. MENCAP
7. Royal College of General Practitioners
8. Royal College of Obstetricians and Gynaecologists
9. Royal College of Physicians
10. Royal College of Physicians and Surgeons of Glasgow
11. Royal College of Physicians of Edinburgh
12. UK Genetic Testing Network

Annex B

Evidence maps: antenatal and newborn screening for Fragile X Syndrome

Consultation comments

1. Genetic Alliance UK

Name:	Dr Jayne Spink	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 200 patient organisations. Our aim is to ensure that high quality services, information and support are provided to all who need them. We actively support research and innovation across the field of genetic medicine. Rare Disease UK is a multi-stakeholder campaign run by Genetic Alliance UK, working towards the delivery and implementation of a national strategy for rare diseases in the UK. The UK Strategy for Rare Diseases was published in November 2013. Pertinent to this consultation, the Strategy includes a commitment from all four Governments of the UK to: "Continue to work with the UK National Screening Committee to ensure that the potential role of screening in achieving earlier diagnosis is appropriately considered in the assessment of all potential new national screening programmes and proposed extensions to existing programmes." Commitment 9, The UK Strategy for Rare Diseases, November 2013. This commitment recognises the value that the rare disease community places on early diagnosis, not only for the benefits it can bring to an affected individual but because of the impact it can have on improving the quality of life for their whole family.		
Role:	Chief Executive		

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

Yes ☒ **No** ☐

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.*
p9 p12	'The search for the first evidence map was conducted on 17 April 2018 on three databases: Medline, Embase and the Cochrane Library. The time period was restricted to 2014 – April 2018.' 'The searches for the second evidence map were conducted on 12 and 14 June 2018 on three databases: Medline, Embase and the Cochrane Library'	Relying solely on peer reviewed literature excludes the direct contribution of the patient voice to the process. While information from clinicians and patients may not be published, it represents the most recent and relevant information on a condition coming from those that either directly manage or are affected by the condition today. NHS England, the National Institute for Health and Care Excellence and the European Medicines Agency all have facility to consider evidence from patients and clinicians that is not sourced from peer reviewed literature. These agencies have accepted that evidence will always be scarce in the area of rare disease, and is likely to be of weaker statistical significance than that expected from more common conditions. They have resolved to fill this gap by accepting qualitative evidence from the patient community. We believe the UK NSC should take steps to do the same.
p9 and p12	'All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information.'	We do not consider that reading only the abstracts of selected references is likely to have provided sufficient information about the level of evidence available for each of these questions being considered. While we understand the UK NSC's reasoning behind the rapid review methodology, we believe that such a review needs to involve reading the full text of each reference in order to adequately and accurately grasp their conclusions.