UK National Screening Committee

Screening for Fragile X Syndrome in Pregnancy

18 June 2015

Aim

1. This document provides background on the item addressing antenatal screening for Fragile X syndrome.

Current policy

2. The current UKNSC screening policy is to not screening for Fragile X syndrome in pregnancy. This recommendation and the supporting evidence review were published in 2011.

Current Review

3. The key conclusions from the 2011 UKNSC review and a summary of the evidence published since (addressing each) are listed below:

    - While the natural history and prognosis of full mutations in males is well understood, it is not possible to predict whether a female fetus carrying the full mutation will be affected by learning difficulties or to what extent.
      In the 2014 update, no new evidence (published since 2011) was identified and therefore no further comment can be made on the 2011 evidence review conclusion.
    - The clinical impact of carrying an FMR1 pre-mutation (55 to 200 repeats) mutation and the association FXPOI and FXTAS is unclear.
      In the 2014 update, no prospective cohort studies were identified related to this key question; this type of study is required to adequately describe the likelihood of developing one or more of the associated FXS conditions in people with a pre-mutation. However a number of papers addressing this issue were identified. These suggest that the precise mechanisms by which a pre-mutation status could increase the risk for FXPOI and FXTAS, and the factors that may contribute to this remain unclear. Evidence regarding the association between FMR1 intermediate allele status and Autism Spectrum Disorder (ASD) was inconclusive.

- The current approach to testing, southern blotting is labour intensive and not a practical use of resource in a universal screening programme requiring a high volume of tests. Alternative screening tests, for example PCR kits, are required. In the 2014 update, no studies were identified that assessed the performance of PCR kits in large, unselected, pregnant populations. However 6 exploratory studies assessing analytical validity were included. Those studies reported test sensitivity ranging from 88.6% to 100%, and specificity from 42.9% to 100%. PCR followed by selective Southern blot remains the only acceptable method for diagnosing FXS; further research is required on the accuracy of PCR tests in the pregnant population.
- There were no curative or preventive treatments for FXS, FXTAS, or FXPOI that could be offered to those identified as having these conditions or of being at risk of the conditions.

  In the 2014 update, no new randomised controlled trials were identified for the two prioritised treatments, folic acid and L-acetylcarnitine. Although research exploring alternative treatments for decreased levels of Fragile X mental retardation protein is ongoing, no studies met the inclusion criteria concerning these agents. The next update should consider advances made in this area, specifically in infants identified through antenatal screening.

Consultation

4. Comments were received from the RCOG, the Fragile X society and the Genetic Alliance. All three stakeholders agreed that screening should not be recommended. Their comments are listed below

The full consultation responses can be found below

FMCH March 2015 Meeting

5. The FMCH discussed the consultation comments at the meeting held on 4 June and recommended that NSC retain the current recommendation to not screen for Fragile X syndrome in pregnancy. The FMCH noted that a separate review on newborn screening for Fragile X syndrome could be feasible, but it would need to be approved through a formal topic selection process.

Action

The UK NSC is asked to

- Approve the above recommendation to not screen for Fragile X Syndrome in pregnancy.

UK National Screening Committee

Screening for fragile X syndrome in pregnancy- an evidence review

Consultation comments pro-forma

Name:	Dr Manish Gupta MRCOG and Dr Andrew Thomson MRCOG	**Email address:**	**XXXX XXXX**
Organisation (if appropriate):	Royal College of Obstetricians and Gynaecologists		
Role:	Co-Chairs, Guidelines Committee		
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.*
		We support the recommendation not to introduce antenatal screening for fragile X syndrome at this time.

Please return to David Bevan (Senior Evidence Review & Policy Development Manager) david.bevan@phe.gov.uk **by 5th May 2015**

UK National Screening Committee

Screening for fragile X syndrome in pregnancy- an evidence review

Consultation comments pro-forma

Name:	Becky Hardiman	**Email address:**	**XXXX XXXX**
Organisation (if appropriate):	Fragile X Society		
Role:	**CEO**		

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

Yes ☒ **No** ☐

Section and / or page	Text or issue to which comments relate	Comment

number		*Please use a new row for each comment and add extra rows as required.*
		We at the Fragile X Society agree with the recommendations of the UKNSC review that routine screening is not currently required for Fragile X Syndrome, due to the variation in outcomes and due to the lack of requirement for immediate intervention. Our priority is that there is greater awareness and understanding of Fragile X Syndrome so that those experiencing characteristics which may be associated with fragile X, such as learning disabilities or autism, may be appropriately tested. In this way, these individuals will be able to have their needs more accurately understood and the individual's family will be able to seek genetic counselling.

Please return to David Bevan (Senior Evidence Review & Policy Development Manager) david.bevan@phe.gov.uk

UK National Screening Committee

Screening for fragile X syndrome in pregnancy- an evidence review

Consultation comments pro-forma

Name:	Alastair Kent	**Email address:**	**XXXX XXXX**
Organisation (if appropriate):	Genetic Alliance UK		
Role:	Director		
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.*
Page 4	The 2014 review suggests that the body of evidence identified by the literature search is an insufficient basis on which to change the current screening policy.	We would like to reiterate comments from our previous responses that alongside evidence gathered from peer reviewed sources other types of evidence, such as that which could be offered by patients and patient groups, should be sought out and collated. This would ensure that the most relevant and up to date information is always captured; a particularly pertinent issue for the vast majority of rare conditions where the available published literature is either limited or out of date. We look forward to working with the UKNSC in future to devise practical solutions for better engagement with patient communities and the wider public in order to develop a comprehensive evidence base that the UKNSC can use to inform their recommendations. For Fragile X, we support the views expressed by our patient group member the Fragile X Society that the introduction of a screening programme for this condition is not desirable at the present time. We acknowledge that Fragile X is an example of where relatively recent published literature is available on the condition, despite its rarity, as attested to the fact that nearly 95% of the

		literature referenced in the review used to help inform the screening decision are five years old or less.
Page 4	There is no sufficiently well researched test which could be used for antenatal screening purposes.	Where current technology is unable to offer a sufficiently robust and accurate method of testing, we recognise that a screening programme is not feasible. We hope that improvements in testing for this condition are forthcoming so that screening can be considered in future. To this end, we note the value of genetic testing and next generation sequencing (NGS) technology. Many children that are suspected to have Fragile X syndrome will have this diagnosis confirmed by a genetic test, which have been evaluated and recommended for use on the NHS by the UK Genetic Testing Network (http://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/test-service/fragile-x-mental-retardation-syndrome-513/). Further investigation into the potential to apply learning from these diagnostic genetic tests and NGS to screening for Fragile X and other rare genetic conditions should be considered.
Page 4	There are no interventions to reduce the risk of developing FXS or the adverse outcomes associated with it.	Genetic Alliance UK know from working with the rare disease and undiagnosed patient community that gaining speedier access to treatment is not the only benefit that can be gained from early diagnosis: • It provides families with time to come to terms with their child's condition and can empower them to make better decisions about where they live, what school they choose,

		or personal choices about the future of their family. We would welcome the UKNSC gathering more evidence from patients and families affected by Fragile X about the value that they would have placed on having had an earlier diagnosis for their child. • Early diagnosis can enable couples to choose to avoid the birth of another affected child, if they so wish. It has been shown that the average time it takes for a child to be diagnosed with Fragile X is approximately three years. Within that time frame, between 25 and 39% of affected families will have had a second child also affected by the condition (Bailey et al., 2009: http://www.ncbi.nlm.nih.gov/pubmed/19581269). It is clear from this evidence that delays in diagnosis means that couples are not given the opportunity to exercise reproductive choice. We would like to see the UKNSC take these additional considerations into account when they consider additional conditions for their screening programmes, including Fragile X. As the UK NSC recognises, it can take multiple years to implement a recommended screening programme. It would therefore also be valuable to implement a horizon scanning approach to identify and initiate screening programmes if a treatment is likely to be available in the near future so that the absence of a screening programme does not stand in the way of enabling timely access to an effective treatment.

Page 4	The natural history of premutations and intermediate alleles remains insufficiently understood. As such the information from screening and diagnosis would not be adequate to support reproductive decision making.	We welcome the recognition in the evidence summary of the potential value that early diagnosis could have for reproductive choice (see above). Although a clear understanding of the 'natural history' of a condition would be ideal before introducing a screening programme, many rare conditions are characterised by having a range of symptoms of variable severity with unpredictable progression or penetrance. Uncertainty over natural history is compounded by a paucity of data, due to the small number of patients and a general lack of research interest in many rare conditions. Given the importance to the UKNSC's decisions on screening for Fragile X of the genotype-phenotype relationship and how that may be perceived by those undergoing population-wide screening, would we welcome the UKNSC taking a role in flagging the lack of research in this area to the relevant research bodies for them to action.
General		We would welcome further information and clarity on why Fragile X is only being considered for antenatal screening and not for the newborn screening programme.