UK National Screening Committee

Evidence maps: antenatal and newborn screening for Fragile X Syndrome

A literature search to outline the volume and type of evidence related to antenatal and newborn screening for Fragile X Syndrome for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.
Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Summary

This document discusses the findings of two evidence maps on antenatal and newborn screening for Fragile X syndrome (FXS).

Evidence maps are a way of scanning published literature to look at the volume, type and direction of the evidence base in relation to a specific topic. They inform whether the evidence is enough to commission an external review on the topic under consideration.

Based on the findings of the evidence maps, rapid reviews on antenatal and newborn screening for FXS should not be commissioned at the present time.

The UK National Screening Committee (UK NSC) will return to antenatal screening for FXS in 3-years' time. Future requests to review the evidence for newborn screening should be submitted through the UK NSC's annual call for topics.

Introduction and approach

Background & Objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Antenatal screening for Fragile X Syndrome (FXS) is a topic currently due for an update external review.

The UK NSC currently recommends against antenatal screening for FXS. The Committee based this recommendation on the evidence provided by the 2014 review carried out by Bazian Ltd. The review highlighted that available approaches to testing were not suitable for high volume screening in a whole population. Preliminary work was undertaken to gauge whether this situation had changed. This took the form of an internally developed evidence map.

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.

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. However, it is worth noting the 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.

The aim of this document is to present the information necessary for the UK NSC to consider whether:

- an evidence summary on antenatal screening for FXS should be commissioned in 2018/19;
- an evidence summary on newborn screening for FXS should be commissioned.

Previous review on antenatal screening for FXS

The previous review focused exclusively on antenatal screening and was undertaken by Bazian Ltd in 2014[*]. The review did not recommend the introduction of an antenatal screening programme due to the following key points:

1. Natural history: While the natural history and prognosis of full mutations in males is well understood, 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.
2. Test: 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. As an alternative to this testing strategy, several PCR-based diagnostic strategies had been proposed for the identification of CGG repeat expansions on the FMR1 gene. However, in the 2014 review 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%).
3. Treatment: 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.

In summary, the 2014 review concluded that the body of evidence identified by the literature search was an insufficient basis on which to

[*] The 2014 external review on antenatal screening for FXS can be accessed online at: https://legacyscreening.phe.org.uk/fragilex

change the recommendation not to offer screening for FXS to pregnant women. A major requirement for considering this topic further was the need for additional research evaluating the performance of PCR-based tests for screening large, unselected prenatal cohorts.

Consultation responses agreed with the conclusions of the UK NSC external review that antenatal screening for FXS should not be recommended. However, one response suggested that the evidence relating to newborn screening should be considered.

Outcomes

On the basis of the evidence maps, it is recommended that evidence summaries on antenatal screening or newborn screening for FXS should not be commissioned at the present time.

The Committee will return to antenatal screening in 3-years' time. Future requests to review the evidence for newborn screening should be submitted through the UK NSC's annual call for topics.

Evidence maps

Two evidence maps have been developed as part of a process to assess whether an update review on antenatal screening for FXS should be commissioned in 2018/19 and to evaluate the volume and type of evidence on key issues related to newborn screening for FXS. The two evidence maps aim to address the following questions:

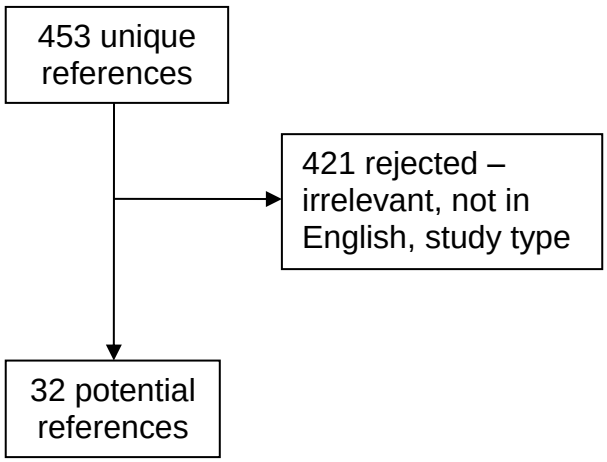
- First evidence map
    1. Has a test, which is suitable for whole population screening, been evaluated in the pregnant population?

- Second evidence map
    1. Has a test, which is suitable for whole population screening, been evaluated in the newborn population?
    2. Are any treatments/early interventions available for people with FXS and how effective are they?
    3. Are there any guidelines and/or recommendations for antenatal or newborn screening for FXS?

These evidence maps will provide the basis for discussion on whether evidence summaries in these areas are justified.

Summary of the first evidence map findings

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. A detailed search strategy including exclusion and inclusion criteria is available in appendix 1. The search returned 680 references. After automatic and manual de-duplication, 453 unique references were sifted for relevance to the key question and 32 references were included in the final evidence map. All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information.



First Evidence Map, Question 1: Has a test, which is suitable for whole population screening, been evaluated in the pregnant population?

Of these 32 references, only 3 studies were carried out in pregnant women. However, none of these assessed the accuracy and the clinical performance of the test. One study aimed to determine the prevalence of FXS pre-mutation and asymptomatic full mutation carriers in a Chinese pregnant population (see ref 1). The other 2 were pilot studies of FXS screening carried out in the Balearic Islands. The studies mainly focused on collecting epidemiological information about the incidence of the disease in that specific population rather that assessing the accuracy of the testing strategy (see ref 2–3).

Sixteen out of 32 studies were carried out in non-pregnant populations. Therefore these were of limited relevance. Three studies focused on markers which might be used for optimisation of preimplantation genetic diagnosis of FXS (see ref 4, 11–12). Eleven studies aimed to assess the analytical validity of a PCR-based test in which the test's performance was in most cases evaluated on archived clinical specimens derived from a cohort of affected patients (see ref 5–10, 13, 15–16, 18–19). Two studies were also included in the findings of the second evidence map where they will be discussed in more detail (see ref 14, 17[†]).

Finally, a further 13 out of the 32 studies were also carried out in non-pregnant populations. However, upon checking the abstracts for relevance, these were not strictly relevant to the key question on test accuracy because:

- Two studies described an assay to detect specific AGG interruptions in FXS pre-mutation carriers to determine expansion risk (see ref 20–21)
- One reference was a technical update focusing on preimplantation genetic diagnosis (see ref 28)
- One study aimed at determining the prevalence of FXS among children with developmental disability in Malaysia (see ref 22)
- Seven studies described a number of options for molecular diagnosis of FXS, suggesting the possibility in the future of

[†] Also labelled as 34 and 35 in the second evidence map

minimising the need to reflex patient samples for Southern Blot analysis (see ref 23, 25–27, 29–31)

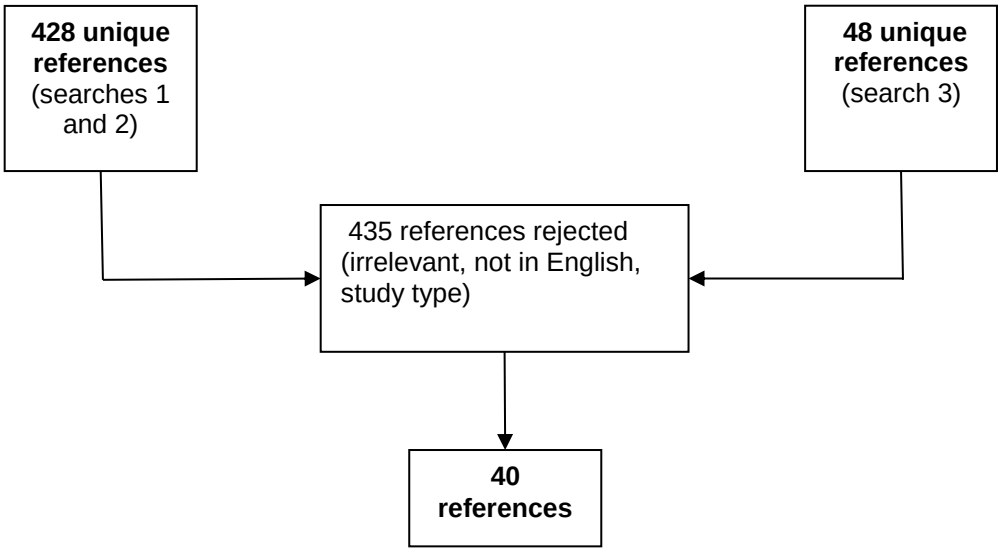
- Two references were also included in the second evidence map and will be discussed in more detail later as they are more relevant to the second set of key questions (see ref 24, 32[‡])

The UK NSC's current position is that a test which is suitable for population screening is not available. In summary, at present there is an insufficient volume of evidence in this key area to justify commissioning an evidence summary. The type of evidence identified is unlikely to lead to a change in the UK NSC's current position.

[‡] Also labelled as 33 and 36 in the second evidence map

Summary of the second evidence map findings

The searches for the second evidence map were conducted on 12 and 14 June 2018 on three databases: Medline, Embase and the Cochrane Library. Since the previous review did not cover newborn screening, the dates of the searches were extended to cover a period of 10 years from 2008 to 2018. The detailed search strategies including exclusion and inclusion criteria are available in appendix 2. The searches returned 626 references. After automatic and manual de-duplication, 476 unique references were sifted for relevance to the key questions and 40 references were included in the final evidence map. All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information.



Specifically, out of these 40 references there were:

- Twelve test accuracy/validation studies
- Six reviews of treatments/interventions (4 of these systematic)
- Seven randomised clinical trials: 6 for pharmacological interventions, one for behavioural therapy (3 trials currently ongoing)
- One prospective cohort study on behavioural interventions
- Six guidelines/recommendations
- Eight references on newborn screening, including for example a systematic review on population-based screening for FXS and 5 pilot studies on newborn screening

Second Evidence Map, Question 1: Has a test, which is suitable for whole population screening, been evaluated in the newborn population?

The evidence map identified one systematic review regarding population-based screening for FXS in newborns and women of reproductive age, either before or during pregnancy (see ref 66). This review was published in 2010 and it found only one population-based study that addressed offering newborn screening. In this prospective study carried out in 2 hospitals in the US, parents were only offered the option of testing their child when the newborn was male (see ref 72). A total of 1,844 newborns were included in the study which reported a test uptake of 79%.

This evidence map found a further 3 pilot studies. Of these, 2 were conducted in the US (see ref 68–69) and one in Northwest Spain (see ref 70). Sample size ranged from 3,042 (see ref 68) to 14,207 (see ref 69) screened newborns. All 3 studies focused on exploring the technical feasibility of newborn screening and on establishing mutation frequency in newborn populations.

The evidence map retrieved a further 12 articles published between 2008 and 2016 which were relevant to this question. These studies did not have a prospective design, were not carried out in large newborn populations and 5 out of 12 studies did not use dried blood spots (DBS) as the primary specimen for testing[§]. However, they focused on the possible application of various testing strategies to newborn screening. The tests under consideration varied: some studies used immunoassay-based techniques to quantify the fragile X mental retardation protein in DBS (see ref 36–37); others employed PCR and capillary electrophoresis (see ref 39–40) or PCR and melt peak analysis (see ref 34–35) or PCR and mass spectrometry (see ref 42) or a two-stage PCR with 2 sets of different primers (see ref 44). One study focused mainly on providing a more accurate estimate of FXS incidence and used quantitative methylation-sensitive PCR to assess FMR1 methylation in DNA isolated from DBS of newborn males only,

[§] Of these 5 studies: one was conducted on DNA from cell lines only (see ref 33), 2 used whole blood samples (see ref 34, 41) and 2 spotted whole blood from previously genotyped samples onto blood cards for subsequent feasibility studies (see ref 39–40). Out of the total 12 studies, a further 2 studies used DBS but it is unclear whether these were collected from adult controls (see ref 42, 44)

whilst also detecting males with Klinefelter syndrome (47, XXY)** (see ref 43). Two further methylation tests to identify FXS-related epigenetic elements were found that have potential to be used to differentiate FXS males and females from controls, as well as to be used along with a test for sex-determining region Y (SRY) to provide the option of combined FXS and sex chromosome aneuploidy newborn screening (see ref 38, 41).

All 12 studies had limitations: specifically, they were all relatively small scale feasibility studies and not all of them used DBS as primary specimen for testing. Crucially, these studies focused on the analytical validation of the test and in most cases, they evaluated assay technical performance using archived samples. Key performance measures such as positive and negative predictive values, sensitivity and specificity, which are essential to determine if a test is amenable for use in a population-based screening programme, were not adequately addressed as the study designs did not allow for assessment of clinical validity of these tests.

In summary, the evidence retrieved suggests that there is interest in newborn screening. However, the limited number of prospective studies in newborn populations restricts what conclusions could be drawn and what could be expected from an evidence summary. Overall, this represents a limited volume of studies whose design does not enable to fully assess the performance and to establish the clinical validity and utility of these testing strategies for screening large, unselected newborn populations.

** Amelogenin PCR amplification used for gender verification to detect the presence of a Y chromosome

Second Evidence Map, Question 2: Are any treatments/early interventions available for people with FXS and how effective are they?

The evidence map returned 6 reviews of treatments/interventions, of which 4 were systematic. To date, there has not been a successful clinical trial for a drug treating FXS in terms of key outcomes such as verbal and non-verbal intellectual functioning. The systematic reviews assessing the effectiveness of folic acid, L-acetylcarnitine and amphetamine among other drugs found that the evidence base is not sufficient to support recommendations on pharmacological treatments in patients with FXS (see ref 46, 48–50). Another review suggested that although some forms of behavioural and parent training interventions appear to have some benefit at reducing the behavioural problems in children with developmental disabilities, there is currently a paucity of large-scale effectiveness studies in clinical or applied settings (see ref 47).

The 2010 systematic review on population-based screening for FXS noted that there is contention around the topic of newborn screening, particularly around the issue of whether it meets established criteria for guiding screening implementation, as the benefits of early interventions for FXS have not been established (see ref 66). A similar point is made by a further review published in 2017, which noted that at present there is insufficient evidence on the efficacy of earlier treatment compared to late treatment, after the presentation of symptoms (see ref 45). This review also noted that some pharmacological treatments for symptoms have been reported to be beneficial for reducing some of the core features of FXS, such as impulsivity, hyperactivity, anxiety, and irritability (see ref 45, 55–57). However, the number of randomised controlled trials that have been conducted to prove efficacy of these medications in the FXS population is limited.

The evidence map retrieved 6 such randomised clinical trials specifically for pharmacological interventions. A further trial focused on behavioural therapy. Of these trials, 3 are currently ongoing with estimated study completion date ranging between end of 2017 and 2020:

- One is assessing the safety and efficacy of vitamin C and vitamin E (n=40) (see ref 53)
- One is investigating whether AFQ056, an mGluR5 negative modulator[††], can enhance neural plasticity in the form of language learning during an intensive language intervention in very young children with FXS (n=100) (see ref 54)
- One is assessing the effectiveness of administering a standardised function-based behavioural treatment for FXS and evaluating it via telemedicine (n=80) (see ref 51)

In terms of the 4 completed trials, despite some potential benefits, these studies did not specifically explore the benefits of early intervention; they had limitations in their study designs and indicated that further longer trials are needed to assess benefits, side effects, and factors associated with the clinical responses observed (see ref 52, 55–57).

With regard to behavioural interventions, only one study met the inclusion criteria, though the sample size was relatively small (n=55). This examined the relationship between maternal responsivity and child vocabulary development through middle childhood in children between 2 and 10 years of age. The study suggested that children with FXS who experience consistent sustained responsivity have better vocabulary outcomes in middle childhood. However, the authors acknowledged that the long-lasting effects of these interventions remain to be demonstrated given that the study focused exclusively on vocabulary as opposed to more comprehensive measures of language and cognitive development (see ref 58). During the sifting stage, a further 3 titles appeared relevant as they examined the potential benefits of technology as an interactive medium to help delivering behavioural therapy. However, they were excluded as the number of participants was less than 10.

In summary, the benefits of early treatment/interventions for FXS compared to late treatment after the presentation of symptoms have not been explored. The limited amount of studies currently available are often restricted by sample size and other study design biases, making the quality of the evidence unsuitable for drawing conclusions on the effectiveness of the interventions.

[††] This is a compound that acts on proteins called receptors, responding specifically to the neurotransmitter L-glutamate

Second Evidence Map, Question 3: Are there any guidelines and/or recommendations for antenatal or newborn screening for FXS?

Six guidelines/recommendations for FXS were retrieved. However, none of these recommend general population screening either antenatally or in newborns.

In March 2017, the American College of Obstetricians and Gynecologists made the following recommendations in relation to carrier screening for FXS:

- FXS pre-mutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability and who are considering pregnancy or are currently pregnant
- FXS pre-mutation carrier screening is recommended for women with unexplained ovarian insufficiency or an elevated follicle-stimulating hormone level before 40 years of age
- Prenatal diagnostic testing for FXS should be offered to known carriers of the fragile X pre-mutation or full mutation (see ref 59)

Similar recommendations were made by the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the Canadian College of Medical Geneticists (CCMG) who also advised that population carrier screening for FXS in all women of reproductive age cannot be recommended at this time (see ref 60). A further guideline emphasised the important role of genetic counsellors in providing pre-test information and post-test advice to affected individuals and their families (see ref 63). In addition, the evidence map retrieved a technical recommendation by the American College of Medical Genetics and Genomics (ACMG) providing updated methodological considerations for Southern blot analysis and PCR amplification of the FMR1 gene only (see ref 62). The search also returned a further document describing best practice guidelines for genetic analysis, quality assurance and reporting in FXS, FXPOI, and FXTAS, including carrier and prenatal testing (see ref 61).

In summary, no national or international guidelines identified by the search recommended population screening for FXS either antenatally or in newborns.

Feasibility of newborn screening for FXS

The evidence map retrieved 2 additional references whose main focus was newborn screening and its feasibility. One was a study in which voluntary newborn screening for FXS was offered to approximately 28,000 families in 3 US hospitals, with an uptake of 62% and just over 17,000 infants screened. The aim was to assess screening acceptance, evaluate the consent process and determine whether identification of babies resulted in any measurable harms or adverse events. The study outlined a number of challenges, particularly relating to the consent process, the detection of carriers, family follow-up, and adequate genetic counselling and psychosocial support for screen-positive infants and their families (see ref 67).
The other document published in 2017 assesses the FXS newborn screening landscape and, similarly to the study aforementioned and to the 2010 systematic review, it identifies a series of challenges:

- Limited data currently available on the prognosis of females with the FMR1 full mutation and the prevalence of FMR1 intermediate alleles and pre-mutations;
- Lack of treatment and crucially, insufficient evidence that interventions are more effective if administered early i.e. prior to clinical presentation;
- Screening/testing methodology i.e. consideration will need to be given to the type of test used and its suitability for large scale screening, as well as to the laboratory equipment requirements. Depending on the type of screening method used, the screen may or may not identify girls with full mutation and currently, it is not possible to determine how impacted a girl with FXS would be based on molecular information;
- Adequate capacity for follow-up i.e. difficulty in relaying potential risks associated with pre-mutation, given the broad range of phenotypic presentations and the fact that screening could lead to cascade testing of extended family members and identification of a large number of carriers (see ref 65)

In summary, some studies suggest that newborn screening using PCR-based methods could be feasible but this would need to be explored in larger studies, as the volume of evidence is currently limited, particularly with regard to prospective studies in large, unselected newborn populations.

A number of challenges have been outlined by researchers, which limit the feasibility of a population-based screening programme:

specifically, the insufficient evidence that early interventions are more effective compared to those administered after clinical presentation and more broadly, the lack of an effective treatment for FXS.

Multiple studies have also highlighted that newborn screening for FXS raises a number of ethical, policy, and social concerns, one of the most controversial of which is the detection of infant pre-mutation carriers and cascade screening of extended family members.

Conclusions

The findings of the evidence maps are unlikely to impact on current guideline recommendations on antenatal screening for FXS as no new evidence was identified that would change those conclusions. Similarly, the evidence base in relation to newborn screening for FXS has outlined a number of gaps, barriers and challenges that will need to be addressed before a population screening programme in newborns can be considered outside of a research protocol setting.

Recommendations

- The volume and type of evidence related to antenatal screening for FXS is currently insufficient to justify an update review at this stage and it should be re-considered in 3-years' time.
- The volume, type and direction of the evidence related to newborn screening is currently insufficient to justify an evidence summary in this area. It is worth noting the 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 when, at a minimum, significant evidence relating to the test and benefit of early intervention has been published.

Appendix 1 — Search strategy for the first evidence map

SOURCES SEARCHED: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to April 11 2018, Embase 1996 to 2018 Week 16, and the Cochrane Library.

DATES OF SEARCH: 2014 – April 2018

SEARCH STRATEGIES:

Medline	**Embase**
1. Fragile X Syndrome/ (4638) 2. Fragile X Mental Retardation Protein/ (2481) 3. fragile X.tw. (6200) 4. fra X.tw. (443) 5. (xlmr or fraxa or fraxd or fraxf or fmr1).tw. (2800) 6. x linked mental retard$.tw. (960) 7. FXS.tw. (1278) 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (8083) 9. Prenatal Diagnosis/ (34672) 10. (pregnan$ or antenatal$ or prenatal$).tw. (516589) 11. Pregnancy/ (814976) 12. (screen$3 or detect$3 or test or tests or testing or identif$).tw. (5911105) 13. 10 or 11 (946474) 14. 12 and 13 (211801) 15. 9 or 14 (230924) 16. 8 and 15 (500) 17. limit 16 to yr="2014 -Current" (52) 18. Polymerase Chain Reaction/ (233577) 19. (polymerase chain reaction or PCR$).tw. (551771) 20. Trinucleotide Repeats/ (3812) 21. ((CGG or triple or trinucleotide) adj repeat$).tw. (3709) 22. (high throughput adj3 (strategy or assay)).tw. (3751)	1. fragile X syndrome/ (6140) 2. fragile X mental retardation protein/ (2915) 3. fragile X.tw. (5913) 4. fra X.tw. (55) 5. (xlmr or fraxa or fraxd or fraxf or fmr1).tw. (3211) 6. x linked mental retard$.tw. (827) 7. FXS.tw. (1570) 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (9432) 9. prenatal diagnosis/ (35818) 10. (pregnan$ or antenatal$ or prenatal$).tw. (475516) 11. pregnancy/ (318707) 12. (screen$3 or detect$3 or test or tests or testing or identif$).tw. (6436095) 13. 10 or 11 (566933) 14. 12 and 13 (203989) 15. 9 or 14 (223145) 16. 8 and 15 (535) 17. limit 16 to yr="2014 -Current" (125) 18. polymerase chain reaction/ (322528) 19. (polymerase chain reaction or PCR$).tw. (711147) 20. trinucleotide repeat/ (4954) 21. ((CGG or triple or trinucleotide) adj repeat$).tw. (3958) 22. (high throughput adj3 (strategy or assay)).tw. (4751)

23. 18 or 19 or 20 or 21 or 22 (651749) 24. 8 and 12 and 23 (985) 25. limit 24 to yr="2014 -Current" (202) 26. 17 or 25 (234)	23. 18 or 19 or 20 or 21 or 22 (828562) 24. 8 and 12 and 23 (1236) 25. limit 24 to yr="2014 -Current" (333) 26. 17 or 25 (403)

Cochrane
#1 MeSH descriptor: [Fragile X Syndrome] this term only (59) #2 MeSH descriptor: [Fragile X Mental Retardation Protein] this term only (10) #3 "fragile X":ti,ab,kw (99) #4 "fra X":ti,ab,kw (7) #5 (xlmr or fraxa or fraxd or fraxf or fmr1):ti,ab,kw (24) #6 ((x linked) near/3 (mental retard*)):ti,ab,kw (1) #7 FXS:ti,ab,kw (44) #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 Publication Year from 2014 to 2018 (43)

Results by database

Medline	**234**
Embase	**403**
Cochrane Library	**43**
Total	**680**

Inclusions and exclusions

Case reports, conference abstracts and publications not in English were excluded. Studies were included if the number of patients was 10 or more.

Appendix 2 — Search strategy for the second evidence map

DATABASES SEARCHED: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to June 06, 2018, Embase 1996 to 2018 Week 24 and the Cochrane Library.

DATES OF SEARCH: 2008-2018

SEARCH STRATEGIES:

1. Newborn screening (12 June 2018)	
Medline	**Embase**
1. Fragile X Syndrome/ (4670) **2.** Fragile X Mental Retardation Protein/ (2510) **3.** fragile X.tw. (6256) **4.** fra X.tw. (443) **5.** (xlmr or fraxa or fraxd or fraxf or fmr1).tw. (2826) **6.** x linked mental retard$.tw. (960) **7.** FXS.tw. (1309) **8.** 1 or 2 or 3 or 4 or 5 or 6 or 7 (8144) **9.** Neonatal Screening/ (9048) **10.** (screen$3 or detect$3 or test or tests or testing).tw. (4041504) **11.** (newborn$ or infant$ or neonat$ or baby or babies or postnatal$).tw. (710511) **12.** 10 and 11 (132698) **13.** 9 or 12 (134866) **14.** 8 and 13 (202) **15.** limit 14 to yr="2008 -Current" (108)	**1.** fragile X syndrome/ (6211) **2.** fragile X mental retardation protein/ (2949) **3.** fragile X.tw. (5989) **4.** fra X.tw. (55) **5.** (xlmr or fraxa or fraxd or fraxf or fmr1).tw. (3239) **6.** x linked mental retard$.tw. (827) **7.** FXS.tw. (1608) **8.** 1 or 2 or 3 or 4 or 5 or 6 or 7 (9534) **9.** newborn screening/ (14919) **10.** (screen$3 or detect$3 or test or tests or testing).tw. (4374004) **11.** (newborn$ or infant$ or neonat$ or baby or babies or postnatal$).tw. (595697) **12.** 10 and 11 (150752) **13.** 9 or 12 (154102) **14.** 8 and 13 (287) **15.** limit 14 to yr="2008 -Current" (211)

2. Early interventions/treatment (12 June 2018)	
Medline	**Embase**
1. Fragile X Syndrome/ (4670) **2.** Fragile X Mental Retardation Protein/ (2510)	**1.** fragile X syndrome/ (6211) **2.** fragile X mental retardation protein/ (2949)

3. fragile X.tw. (6256) **4.** fra X.tw. (443) **5.** (xlmr or fraxa or fraxd or fraxf or fmr1).tw. (2826) **6.** x linked mental retard$.tw. (960) **7.** FXS.tw. (1309) **8.** 1 or 2 or 3 or 4 or 5 or 6 or 7 (8144) **9.** "Early Intervention (Education)"/ (2558) **10.** ((early or education$ or behaviour$ or behavior$ or development$ or medical or drug) adj3 (service$ or treat$ or therap$ or intervention$)).tw. (508350) **11.** 9 or 10 (509733) **12.** exp Child/ (1774964) **13.** exp Infant/ (1067518) **14.** (newborn$ or infant$ or neonat$ or baby or babies or child$).ti. (1002174) **15.** 12 or 13 or 14 (2487489) **16.** 8 and 11 and 15 (119) **17.** limit 16 to yr="2008 -Current" (73)	**3.** fragile X.tw. (5989) **4.** fra X.tw. (55) **5.** (xlmr or fraxa or fraxd or fraxf or fmr1).tw. (3239) **6.** x linked mental retard$.tw. (827) **7.** FXS.tw. (1608) **8.** 1 or 2 or 3 or 4 or 5 or 6 or 7 (9534) **9.** early intervention/ (19994) **10.** ((early or education$ or behaviour$ or behavior$ or development$ or medical or drug) adj3 (service$ or treat$ or therap$ or intervention$)).tw. (607531) **11.** 9 or 10 (615285) **12.** child/ (1089554) **13.** infant/ (364117) **14.** (newborn$ or infant$ or neonat$ or baby or babies or child$).ti. (757687) **15.** 12 or 13 or 14 (1522475) **16.** 8 and 11 and 15 (138)

1 & 2 (12 June 2018)
Cochrane
#1 MeSH descriptor: [Fragile X Syndrome] this term only (92) #2 MeSH descriptor: [Fragile X Mental Retardation Protein] this term only (10) #3 "fragile X":ti,ab,kw (133) #4 "fra X":ti,ab,kw (8) #5 (xlmr or fraxa or fraxd or fraxf or fmr1):ti,ab,kw (25) #6 ((x linked) near/3 (mental retard*)):ti,ab,kw (2) #7 FXS:ti,ab,kw (60) #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 (105) Publication Year from 2008 to 2018

Guidelines (14 June 2018)
Medline
1. Fragile X Syndrome/ (4676) **2.** Fragile X Mental Retardation Protein/ (2512)

3. fragile X.tw. (6266)
4. fra X.tw. (443)
5. (xlmr or fraxa or fraxd or fraxf or fmr1).tw. (2829)
6. x linked mental retard$.tw. (960)
7. FXS.tw. (1313)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (8154)
9. 8 + CADTH filter for guidelines (107)
10. limit 9 to yr="2008 -Current" (48)

Results by database

	1.	2.	3.
Medline	**108**	**73**	**48**
Embase	**211**	**138**	**-**
Cochrane Library		**48**	**-**
Total		**578**	**48**

Inclusions and exclusions

Case reports, conference abstracts, comments editorials and publications not in English were excluded. Studies were included if the number of patients was 10 or more.

References

First evidence map

The test in pregnancy (3)

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Validation studies in other populations (16)

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for CGG repeat expansion at FMR1 locus: Implication of combined triplet repeat primed polymerase chain reaction and methylation-specific polymerase chain reaction analysis. Neurology India. 2016;64(6):1175-9
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Uncertain (13)

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Second evidence map

Test accuracy/validation studies (12)

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Early interventions/treatment

Reviews (6, of which 4 systematic)

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Randomised controlled trials (7)

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Behavioural interventions (1)

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Guidelines and recommendations (6)

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Newborn screening (8)

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