UK National Screening Committee

Antenatal and Newborn Screening for Fragile X Syndrome

An evidence map 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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About the UK National Screening Committee (UK NSC)

The UK National Screening Committee (UK NSC) advises ministers and the NHS in the 4 UK countries about all aspects of population and targeted 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 the evidence map on antenatal and newborn screening for fragile X syndrome (FXS).

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Antenatal screening for FXS is a topic currently due for an update external review. The previous review of antenatal screening for FXS was undertaken by the UK NSC in 2019, concluding that antenatal screening for FXS was not recommended due to insufficient evidence.

A proposal for newborn screening for FXS was also submitted to the UK NSC during the 2022 annual call for topics. The proposal suggests introducing newborn screening for FXS to the newborn blood spot screening programme. The UK NSC agreed that work should be undertaken to revisit the evidence for antenatal screening alongside assessing the potential for newborn screening. To reflect both developments, a consolidated evidence map was developed which covers both populations to support an up-to-date overview of the available literature.

The database and supplementary searches found minimal relevant evidence supporting antenatal screening for FXS, as confirmed by the evidence found in this 2025 review as well as the previous 2019 review conducted by UK NSC. Therefore, the UK NSC will archive the topic of antenatal screening for FXS until new evidence becomes available that is likely to have a significant effect on the recommendation for antenatal screening.

Based on the findings of this evidence map, the recommendation is that further work on antenatal and newborn screening for FXS should not be commissioned at the present time.

Future requests to review the evidence for antenatal and newborn screening for FXS should be submitted through the UK NSC's open call (previously, annual call for topics).

Introduction and approach

Background and objectives

The UK NSC external 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 previous review of antenatal screening for FXS was undertaken by the UK NSC in 2019, concluding that antenatal screening for FXS was not recommended due to insufficient evidence.

A proposal for newborn screening for FXS was submitted to the UK NSC during the 2022 annual call for topics. The proposal suggests introducing newborn screening for FXS to the newborn blood spot screening programme. The UK NSC agreed that work should be undertaken to revisit the evidence for antenatal screening alongside assessing the potential for newborn screening. To reflect both developments, a consolidated evidence map was developed which covers both populations to support an up-to-date overview of the available literature.

Description of the condition

FXS is the most common inherited cause of intellectual disability and a leading monogenic cause of autism spectrum disorder (ASD).[1] It results from a mutation in the FMR1 gene on the X chromosome, where an unstable expansion of the CGG trinucleotide repeat leads to gene silencing and deficiency of the fragile X mental retardation protein (FMRP), which is critical for normal synaptic function and brain development.[2] The precise number of individuals with FXS is not known, but a 2014 meta-analysis suggested that approximately 1 in 7,000 males and 1 in 11,000 females have been diagnosed with the condition.[3] A recent UK study determined that the point prevalence of FXS was 1.15 per 10,000 people, equating to approximately 7,682 individuals across the UK (based on 1,520 diagnosed cases) applied to 2021 Office for National Statistics UK population statistics. The study also reported a higher prevalence in males than females (1.49 vs 0.82 per 10,000).[4]

While FXS is most commonly associated with moderate to severe intellectual disability in males, its clinical presentation spans a broad spectrum and includes developmental, physical, behavioural, and psychiatric features. Physical signs may include hypotonia, joint hypermobility, mitral valve prolapse, macroorchidism in post-pubertal males, epilepsy, recurrent otitis media, and gastrointestinal issues. Behavioural and neurodevelopmental features often include language delay, poor eye contact, social anxiety, sensory hypersensitivities, repetitive behaviours, self-injurious actions, and hyperactivity.[5, 6]

Around 60 to 75% of males and 20 to 41% of females with FXS also meet diagnostic criteria for ASD, making it one of the most common co-occurring conditions. Attention deficit hyperactivity disorder (ADHD) is also frequently reported in individuals with FXS, though prevalence estimates vary and are less consistently quantified in the literature.[7] Psychiatric co-morbidities such as generalised anxiety disorder, depression, and mood instability are also common, especially in adolescence and adulthood.[8] The clinical presentation varies widely between individuals, with females generally exhibiting milder cognitive and behavioural phenotypes due to X-inactivation patterns, and not all individuals displaying every characteristic.[8]

Diagnosis and management of FXS

Diagnosis of FXS is typically confirmed by molecular testing that identifies the number of CGG repeats and the methylation status of the FMR1 gene. Full mutation required for a diagnosis of FXS is defined as more than 200 CGG repeats and is associated with hypermethylation and silencing of the gene. Premutation alleles (55 to 200 repeats) do not typically cause FXS but are associated with other conditions such as fragile X-associated tremor/ataxia syndrome (FXTAS) and fragile X-associated primary ovarian insufficiency (FXPOI), posing important reproductive and familial implications.[9]

The gold standard remains Southern blot analysis, often combined with triplet-repeat polymerase chain reaction (PCR) , methylation-specific PCR, or methylation-specific multiplex ligation-dependent probe amplification (MLPA) to provide a full characterisation of repeat size and methylation status.[10] Emerging technologies, including long-read sequencing (for example, PacBio, Oxford Nanopore) and optical genome mapping, are showing some promise for more comprehensive assessment of FMR1 repeat expansions in a single assay, though they are not yet in routine use.[10] In the UK, whole genome sequencing (WGS) now includes FMR1 repeat analysis in NHS diagnostic pathways, helping streamline testing for patients presenting with intellectual disability or autism.[11] For reproductive risk counselling, analysis of AGG interruptions within the CGG repeat tract can help estimate the risk of a premutation expanding to a full mutation in offspring.[12]

Recent advances have further strengthened the scientific rationale for exploring methylation-based approaches in earlier detection of FXS. Studies have demonstrated that DNA methylation at the FMR1 FREE2 region provides a biologically proximal, highly specific marker that complements CGG-repeat sizing in identifying affected individuals.[13] In a U.S. referral cohort, a methylation-first workflow using methylation-specific quantitative melt analysis (MS-QMA) identified abnormal *FMR1* methylation and mosaic cases missed by standard CGG sizing, with sensitivity/specificity for full-mutation cases approaching 100% in that setting.[14] A large population-scale newborn programme is now underway applying MS-QMA to dried blood spots, demonstrating technical feasibility; diagnostic-accuracy readouts in newborns are not yet reported.[15] Collectively, these studies provide strong biological and technical support for a methylation-first screening strategy, while underscoring the need for prospective population-based validation, ethical evaluation and health-economic assessment before implementation in routine antenatal or newborn programmes.

Management of FXS is multidisciplinary and supportive, aimed at alleviating symptoms and maximising developmental, behavioural, and educational outcomes. Although early diagnosis can enable timely access to speech therapy, occupational therapy, and behavioural interventions, there is currently no curative treatment for FXS.[9, 16] As such, care typically involves coordinated input from paediatricians, clinical geneticists, psychologists, and educators, with pharmacological support used to manage co-occurring conditions such as ADHD, anxiety, sleep disorders, and epilepsy. Research into targeted therapies that address the underlying neurobiology of FXS is ongoing, although clinical trials to date have not shown consistent benefits of improving core cognitive or behavioural outcomes.[17] The potential benefits of early identification continue to be explored and may play an important role in shaping future screening policy.

Previous review on screening for FXS

The UK NSC currently recommends against antenatal screening for FXS [see recommendation online]. The Committee based this recommendation on the evidence provided by the 2019 review carried out by Evidence Team, UK NSC Secretariat.[18] The 2019 review also considered newborn screening for FXS, which is not included in the list of UK NSC's recommendations. This was included in the 2019 review because the topic had been raised by stakeholders during the consultation on the 2014 review.

The findings from the 2019 review revealed that neither antenatal nor newborn screening for FXS had enough evidence to justify a full review. For antenatal screening, there was lack of a high-throughput, validated test; in particular, PCR-based tests had not been evaluated in large unselected pregnant populations. Additionally, there were concerns regarding diagnostic accuracy (especially for females and those with premutation alleles), rendering screening unsuitable. Similarly, evidence supporting newborn screening was sparse: only preliminary PCR methods existed, with limited evaluation in large cohorts, and there was no clear evidence that early detection improved outcomes compared to standard clinical diagnosis. Furthermore, no national or international guidelines supported such population screening, and significant ethical concerns were identified around detecting premutation carriers and informing cascade screening. As a result, the UK NSC recommended against commissioning evidence reviews for both contexts.[18]

Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

This evidence map has been developed to assess whether a more sustained review on antenatal and newborn screening for FXS should be commissioned and to evaluate the volume and type of evidence on key issues related to antenatal and newborn screening for FXS.

The aim was to address the following questions:

1. Are there any guidelines and/or recommendations for antenatal or newborn screening for FXS?
2. What is the volume and type of evidence on the accuracy of screening tests for FXS in the pregnant population?
3. What is the volume and type of evidence on the accuracy of newborn screening tests for FXS using dried blood spots (DBS)?
4. What is the volume and type of evidence available on the benefits/harms of early interventions in infants and children with FXS identified through screening?
    a. Sub-question: Does early initiation of treatment following screening provide better outcomes for FXS compared to initiation of treatment following clinical detection?

Overall, the objective was to assess the volume and type of evidence relevant to screening for FXS, with a focus on accuracy of screening tests in pregnant women and newborns, as well as any formal guidelines and/or recommendations for antenatal and newborn screening. Lastly, evidence related to the benefits/harms of early interventions in infants and children with FXS identified through screening was also assessed.

The findings of this evidence map will provide the basis for discussion to support UK NSC decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on antenatal and newborn screening for FXS.

The aim of this document is to present the information necessary to inform UK NSC decision-making processes.

Search methods and results

The searches were conducted on 2 July 2025 in the following databases:

- MEDLINE®, including MEDLINE® In-Process, MEDLINE® Daily and Epub Ahead of Print
- Embase®
- Cochrane Library, including:
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Cochrane Database of Systematic Reviews (CDSR)

MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print, Embase, CDSR and CENTRAL were searched simultaneously. Automatic de-duplication was conducted using the Ovid SP platform. The search period was restricted to January 2018 to July 2025. The detailed search strategies, including exclusion and inclusion criteria are available in Appendix 1.

In addition to the database searches outlined above, additional supplementary searches of the following websites were also conducted to identify any additional, relevant clinical guidelines and recommendations:

- Dimensions
- Trip Medical Database
- Advanced Google Search

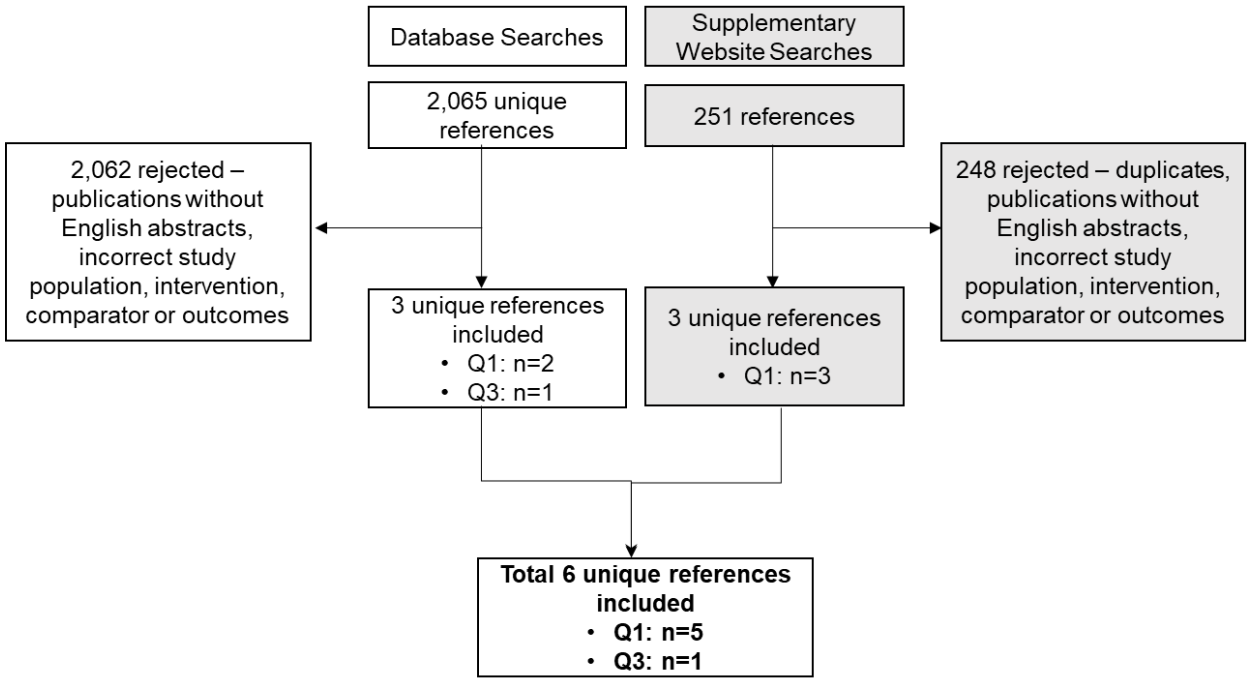
One reviewer assessed all titles and abstracts. All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

Abstract reporting tables are available in Appendix 2.

The database searches returned 3,381 results. After automatic and manual de-duplication, 2,065 unique references were reviewed for relevance to the questions and 3 references were included. An additional 251 results were identified via the supplementary searches of relevant websites. Of these, 3 references were included. In total, 6 references were included in the final evidence map.

A flow diagram summarising the number of studies included and excluded is presented in **Figure 1**.

Figure 1. Summary of included and excluded publications



Summary of findings

Question 1: Are there any guidelines and/or recommendations for antenatal or newborn screening for FXS?

Of the 2,065 unique references reviewed for relevance, 2 were included for this question.[19, 20] An additional 3 references were also included via the supplementary searches of relevant websites.[21-23] In total, 5 references were included in the final evidence map for Question 1.

Three studies were Australasian guidelines that recommend that information about reproductive genetic carrier screening (RGCS) for FXS be offered to all individuals planning a pregnancy or in early pregnancy, ideally pre-conception.[21-23] Screening is optional, non-directive, and generally follows a sequential model, testing the female partner first and offering male partner testing only if indicated. Positive results should lead to genetic counselling and discussion of reproductive options, including prenatal diagnosis (chorionic villus or amniocentesis), pre-implantation genetic testing, use of donor gametes, or continuing the pregnancy without further testing. These guidelines emphasise that RGCS complements, but does not replace, newborn screening; FXS is not part of standard newborn bloodspot screening programmes.

In contrast, the American College of Medical Genetics and Genomics (ACMG) technical standard states that both population carrier screening and newborn screening for FXS remain controversial and are not recommended at this time, restricting testing to diagnostic contexts or when there is a known family risk.[20] Similarly, Indian paediatric consensus guidance focuses on postnatal diagnostic testing in children with developmental delay, intellectual disability, or ASD, without supporting universal newborn screening.[19]

Taken together, some international guidance supports offering access to antenatal carrier screening for FXS, primarily as part of a broader RGCS panel, in jurisdictions such as Australia, but there is no recommendation anywhere for routine newborn screening. In most other settings, including the US, FXS testing is reserved for individuals or families with a known or suspected risk, or for diagnostic evaluation of symptomatic children.

In summary, at present there is limited evidence from published guidelines/recommendations to support antenatal and newborn screening for FXS. The type of evidence identified is unlikely to lead to a change in the UK NSC's current position.

Additional information:

The Johnson 2024 scoping review (not included in the evidence map due to lack of novel, relevant data; hand-searched instead) calls for UK-specific, integrated guidelines for FXS that address health, social, educational, and family support across the life course, with a strong emphasis on earlier identification.[24] While noting that FXS is not currently part of UK newborn bloodspot screening except where there is a known family history, the authors highlight significant diagnostic delays, especially for females, and the resulting missed opportunities for timely intervention. The UK fragile X community has expressed a clear desire for inclusion of FXS in newborn screening programmes, which the review suggests could enable earlier adaptations and supports, citing evidence of technical feasibility and potential benefit. Although it stops short of a formal recommendation, the paper positions newborn screening as a desirable option to be considered within a coordinated, person-centred national framework that also encompasses antenatal risk assessment and universal testing of children with unexplained developmental delay.[24]

Furthermore, two US payer documents provide further insight into how coverage decisions shape practice. Both limit screening to individuals with defined risk factors and explicitly do not recommend inclusion of FXS in newborn screening programmes.[25, 26]

Question 2: What is the volume and type of evidence on the accuracy of screening tests for FXS in the pregnant population?

No studies reporting on the accuracy of available screening tests to detect FXS in pregnant women were identified. The most common reasons that studies were deemed irrelevant were that they investigated an irrelevant population (that is, studies focused solely on general population or carrier screening outside the context of pregnancy), were an irrelevant study type (that is, narrative reviews, editorials, et cetera) or did not report any relevant outcomes of interest.

In summary, accuracy of available screening tests to detect FXS in pregnant women has not been extensively evaluated. At present there is no evidence in this area to justify commissioning an evidence summary.

Question 3: What is the volume and type of evidence on the accuracy of newborn screening tests for FXS using dried blood spots (DBS)?

Of the 2,065 unique references reviewed for relevance, only 1 reference was included in the final evidence map for Question 3.[27]

The included study evaluated a new high-throughput method for newborn screening of FXS using DBS. The assay was designed to detect normal results, premutation (PM), and full-mutation (FM) gene changes in both males and females in a single test.[27]

Laboratory validation showed strong performance. When tested on 38 blinded reference samples, results matched the standard clinical test in every case (100% categorical concordance), with gene sizing accurate to within three repeats (and usually within one repeat for smaller alleles). The test was highly consistent across operators, days, and machines, with very low variation (less than 2%) and no false positives, showing high specificity. Sensitivity experiments showed that very small amounts of DNA were enough for reliable detection: FM changes were reliably detected from as little as 0.5 ng input DNA in males and 0.125 ng in females, with PM changes detectable at 0.125 ng. Artificially mixed samples also showed the method could detect FM alleles present in as little as ~1% and PM at ~2.5% of total DNA.[27]

A pilot population screen was then carried out on 963 anonymised newborn DBS samples. The assay achieved a 98.6% first-pass callable rate (that is, 98.6% of samples gave a clear result on the first attempt, without needing a repeat test), with the few that initially failed resolved with repeat testing. Six PM carriers (0.6% of the cohort) were identified, consistent with expected prevalence. No FM cases were detected in this cohort, meaning the study could not directly confirm real-world performance for identifying FM cases. Importantly, the overall distribution of normal results matched patterns seen in previous newborn screening studies, reinforcing the validity of the approach.

Overall, the study demonstrated that this assay is analytically accurate, precise, and practical for large-scale newborn screening for FXS. However, the authors noted that larger, prospective studies are needed to confirm real-world diagnostic performance and to assess the benefits, harms, and ethical implications of identifying PM carriers at birth.[27]

No other studies reporting on the accuracy of newborn screening tests for FXS using DBS were identified. The most common reasons that studies were deemed irrelevant were that they investigated an irrelevant population (that is, studies focused solely on general population, children or carrier screening outside the context of a newborn population), were an irrelevant study type (that is, narrative reviews, editorials, et cetera) or did not report any relevant outcomes of interest.

In summary, accuracy of available screening tests to detect FXS in newborns has not been extensively evaluated. At present there is very limited evidence in this area to justify commissioning an evidence summary.

Additional information:

It is worth noting that another Australian pilot study screened 2,000 newborns for FXS using a modified chimeric CGG-primer PCR assay alongside a standard Fu PCR (a conventional, long-range PCR method that amplifies the CGG repeat region of the FMR1 gene to identify normal

and some premutation alleles, using two primers (“Fu-c” and “Fu-f”) designed to flank the repeat region), showing 100% concordance and identifying 10 premutation carriers (1/124 females, 1/506 males); no full mutations were detected.[28] The study reports detection rates for PM alleles and confirms technical feasibility and assay agreement, but does not provide numerical sensitivity/specificity estimates. Findings are limited by the absence of FM cases in the cohort, small sample size for performance evaluation, and focus on feasibility rather than definitive diagnostic accuracy outcomes.

Question 4: What is the volume and type of evidence available on the benefits/harms of early interventions in infants and children with FXS identified through screening? Sub-question: Does early initiation of treatment following screening provide better outcomes for FXS compared to initiation of treatment following clinical detection?

No studies reporting on the benefits/harms of early interventions in infants and children with FXS identified through screening were identified. The most common reasons that studies were deemed irrelevant were that they investigated an irrelevant population (that is, studies focused solely on general population, infants/children outside the context of identification via screening or clinical diagnosis) or were an irrelevant study type (that is, narrative reviews, case report, editorials, et cetera).

In summary, the benefits and harms of early interventions in infants and children with FXS identified through screening has not been extensively evaluated. At present there is not sufficient evidence in this area to justify commissioning an evidence summary.

Additional information:

The Johnson 2024 scoping review (not included in the evidence map due to lack of novel, relevant data; hand-searched instead) supports the potential benefits of early intervention for infants and children with FXS, noting that earlier diagnosis, whether through newborn screening or prompt postnatal testing, can enable timely access to targeted therapies and supports before more severe behavioural, sensory, or developmental difficulties emerge.[24] It cites evidence from related conditions such as autism, as well as preliminary FXS-specific studies, indicating that early initiation of interventions (for example, speech and language therapy, occupational therapy, behavioural support) may reduce the intensity of later needs, improve cognitive and behavioural functioning, and enhance long-term developmental trajectories. While direct comparative data on outcomes following screening-led versus clinically triggered diagnosis are limited, the review argues that screening could prevent the prolonged diagnostic delays currently common in the UK, thereby maximising the window for effective early support and potentially yielding better outcomes than waiting until symptoms prompt clinical detection.

Furthermore, another case report detailing two young children with FXS who received early combined treatment (both targeted pharmacological therapy and intensive educational interventions) showed significant improvements in cognitive and behavioural outcomes.[29]

Conclusions

The findings of this evidence map are unlikely to impact the current recommendation on antenatal screening for FXS as sufficient new evidence was not identified that would change this conclusion. Therefore, the UK NSC will archive the topic of antenatal screening for FXS until new evidence becomes available that is likely to have a significant effect on the recommendation for antenatal screening.

Similarly, the evidence base in relation to newborn screening for FXS was also not sufficient to commission a more sustained analysis on this topic.

Recommendations

On the basis of this evidence map, the volume and type of evidence related to antenatal and newborn screening for FXS is currently insufficient to justify an update review at this stage.

The recommendation is that further work on antenatal and newborn screening for FXS should not be commissioned at the present time.

Future requests to review the evidence for antenatal and newborn screening for FXS should be submitted through the UK NSC's open call (previously, annual call for topics).

Appendix 1 — Search strategy for the evidence map

Databases and platforms searched

- MEDLINE®, including MEDLINE® In-Process, MEDLINE® Daily and Epub Ahead of Print
- Embase®
- Cochrane Library, including:
    - CENTRAL
    - CDSR
- Relevant websites (to search clinical guidelines and recommendations):
    - Dimensions
    - Trip Medical Database
    - Advanced Google Search

Search dates

- MEDLINE®, including MEDLINE® In-Process, MEDLINE® Daily and Epub Ahead of Print (1946 to July 01, 2025)
- Embase® (1974 to 2025 July 01)
- Cochrane Library, including:
    - CENTRAL: Issue 5 of 12, May 2025
    - CDSR: Issue 6 of 12, June 2025
- Relevant websites: All searched on 1 July 2025

The hits from all databases/websites were date limited to 2018 to identify evidence published since the last review.

Search strategies

Lists of search terms used in MEDLINE, Embase, CDSR, and CENTRAL (searched simultaneously via the Ovid SP platform), along with number of hits:

1. *Fragile X Syndrome/ – 11,100
2. (fragile x syndrome$1 or (martin bell adj1 syndrome) or marker x syndrome or FXS).ti,ab,kf,kw. – 14,319
3. 1 or 2 – 16,958
4. Animals/ – 9,427,234

5. Humans/ – 52,229,253
6. 4 not 5 – 6,579,693
7. (conferenc$ or comment or editorial or case reports or historical article or preprint).pt. – 12,036,508
8. editorial/ or case report/ – 4,669,829
9. (case stud$ or case report$).ti. – 988,460
10. or/6-9 – 21,407,741
11. 3 not 10 – 12,776
12. limit 11 to yr=2018-current – 3,381
13. remove duplicates from 12 – 2,141

Search strategy used to search the relevant websites:

- Dimensions: Log in to the database by creating an account. Go to search and explore homepage and enter the search terms in the search box. Search for the following terms in title/abstract one by one: Fragile X newborn screening, Fragile X antenatal screening, Fragile X guideline, Fragile X recommendation. Limit publication year to since 2018. Select "Article" under publication type. First screen the titles for relevance and then proceed to screen the abstract/full text.
- Trip Medical Database: Search for "fragile x syndrome" in the search bar. Limit year to 2018 to 2025. Screen articles under "Guidelines" for relevance.
- Advanced Google Search: Search for any of these terms in the search bar: fragile x syndrome or martin bell syndrome or marker x syndrome or FXS. Screen first 5 pages for relevance.

Numbers of results for each database and platform

Database searches:

- MEDLINE®: 1,492
- Embase®: 1,821
- Cochrane Library, including:
  - CENTRAL: 68
  - CDSR: 0
- Total: 3,381
- **Total unique results after de-duplication: 2,065**

Relevant website searches:

- Dimensions: 152

- Trip Medical Database: 49
- Advanced Google Search: 50
- **Total: 251**

Inclusions and exclusions

Inclusion criteria for Question 1: Are there any guidelines and/or recommendations for antenatal or newborn screening for FXS?

- **Population**: Pregnant individuals, newborns
- **Concept:** Antenatal or newborn screening for FXS
- **Context:**
    - Any national or international guidelines/recommendations on antenatal or newborn screening, diagnosis, or clinical management for FXS
    - Recommendations that address ad hoc diagnosis or management may also be included, but should be differentiated from systematic screening guidance
- **Study design**: Guidelines, consensus statements, position papers, or policy documents from professional bodies or authoritative health organisations
- **Other considerations:** Abstract or full-text available in English, published since 2018 (or earlier if updated/reaffirmed post-2018)

Inclusion criteria for Question 2: What is the volume and type of evidence on the accuracy of screening tests for FXS in the pregnant population?

- **Population**: Pregnant individuals
- **Intervention**: Any test used to screen for FXS (for example, PCR, Southern blot)
- **Reference standard**: Genetic confirmatory testing (for example, PCR, Southern blot, or other study-defined gold standard)
- **Comparator**: Any or none
- **Outcomes**: Sensitivity, specificity, positive and negative predictive values, likelihood ratios, area under the curve (AUC), incidental findings (for example, FXPOI or FXTAS)
- **Study design**:
    - Tier 1: Systematic literature reviews (SLRs), randomised controlled trials (RCTs), cohort studies, case-control studies
    - Tier 2: Any other primary study design that reports diagnostic accuracy outcomes
- **Other considerations**: Abstract or full-text in English, published since 2018

Inclusion criteria for Question 3: What is the volume and type of evidence on the accuracy of screening tests for FXS in newborns using dried blood spots (DBS)?

- **Population**: Newborns
- **Intervention**: Any test performed using DBS to screen for FXS (for example, PCR, Southern blot)
- **Reference standard**: Genetic confirmatory testing (for example, PCR, Southern blot, or other study-defined gold standard)
- **Comparator**: Any or none
- **Outcomes**: Sensitivity, specificity, positive and negative predictive values, likelihood ratios, AUC, incidental findings (for example, FXPOI or FXTAS)
- **Study design**:
    - Tier 1: SLRs, RCTs, cohort studies, case-control studies
    - Tier 2: Any other primary study design that reports diagnostic accuracy outcomes
- **Other considerations**: Abstract or full-text in English, published since 2018

Inclusion criteria for Question 4: What is the volume and type of evidence available on the benefits/harms of early interventions in infants and children with FXS identified through screening?

- **Population**: Presymptomatic or asymptomatic infants or children with FXS identified through screening
- **Intervention**: Screening followed by management strategies identified in the studies, including:
    - Non-pharmacological (for example, physical therapy, occupational therapy, speech-language therapy)
    - Pharmacological (for example, symptom-based or targeted treatments)
    - Combined approaches
- **Comparator**: Standard of care or any comparator treatment provided to infants/children diagnosed through non-screening methods. No comparator also acceptable
- **Outcomes**:
    - Delay in symptom presentation or reduction in symptoms
    - Improvement in quality of life
    - Harms of interventions
    - Any study-reported developmental or clinical outcome
- **Study design**: SLRs, RCTs, cohort studies, or case-control studies
- **Other considerations**: Abstract or full-text in English, published since 2018

Appendix 2 – Abstract reporting

Question 1

Citation 1

Sachdeva, A., Jain, P., Gunasekaran, V. et al. Consensus Statement of the Indian Academy of Pediatrics on Diagnosis and Management of Fragile X Syndrome in India. Indian Pediatr 56, 221–228 (2019).[19]

Study type

National consensus guideline developed by the Indian Academy of Pediatrics (IAP).

Objectives

To contribute to the dissemination of knowledge on FXS among health professionals, and thus improve the diagnosis and management of these patients.

Components of the study

- **Population**: Children with intellectual disability, developmental delay, or ASD; female relatives of affected individuals; pregnant carrier women
- **Concept**: This guideline includes national-level recommendations for prenatal diagnosis of FXS in foetuses of carrier mothers. It also advises that at-risk female relatives of affected individuals be offered carrier testing and genetic counselling. These recommendations are directly tied to antenatal decision-making in the context of known family history
- **Context:** The document is a formal national recommendation from a professional body (IAP)

[The full text was consulted to identify relevant information.]

Outcomes reported

- The consensus committee recommends that the FMR1 molecular tests can be used for diagnosis of a fragile X mutation in the foetus of pregnant carrier mother on chorionic villus or amniotic fluid sampling
- Diagnosing FXS would help at-risk families to decide on their appropriate management of family planning and future pregnancies. They could benefit from options of prenatal diagnosis if appropriate for them
- The consensus committee recommends to perform molecular genetic tests in following conditions:
    - Family history suggestive of FXS – with consult and at risk of intellectual disability in self or offspring

    - Family history suggestive of intellectual disability of undiagnosed nature –for accurate reproductive counselling
- Genetic counselling is recommended for all family members who are affected or at risk of having a pre-mutation (PM) or an offspring with a full-mutation (FM)

[The full text was consulted to identify relevant information.]

Conclusions

The consensus committee recommends that all children presenting with intellectual disability and/or developmental delay and/or ASD with no known diagnosis should have FMR1 DNA testing. The same molecular tests should be used for diagnosis of a fragile X mutation in the foetus of pregnant carrier mother on chorionic villus or amniotic fluid sampling. It is recommended that in all children with developmental delay and intellectual disability having phenotype not strongly suspicious of FXS, chromosomal microarray is recommended as first tier test (screening test) followed by fragile X DNA test (if microarray remains inconclusive). Early use of supportive strategies including speech therapy, occupational therapy, special educational services and behavioural interventions are key measures to manage children with FXS. Medications should be used judiciously for control of symptoms under the care of a specialist health care provider. The panel recommends genetic counselling for all family members who are affected or at risk of having a pre-mutation or an offspring with a full mutation.

Citation 2

Spector E, Behlmann A, Kronquist K, et al. Laboratory testing for fragile X, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(5):799–812.[20]

Study type

Technical standard/guideline developed by the ACMG Laboratory Quality Assurance Committee.

Objectives

To revise and provide updated technical standards for FMR1 genetic testing, including guidance on:

- Methodological approaches for Southern blot and PCR-based assays
- Definitions and nomenclature for FMR1 alleles
- Reporting recommendations
- Use in diagnostic, prenatal, and carrier screening contexts
- Interpretation of results including implications for clinical diagnosis and reproductive risk

Components of the study

- **Population:** Individuals undergoing genetic testing for FMR1-related conditions, including:

    - Pregnant individuals (prenatal testing via amniocentesis or chorionic villus)
    - Newborns (screening studies)
    - Individuals with a family history of intellectual disability, premature ovarian insufficiency, or tremor/ataxia syndromes
    - Patients with clinical features suggestive of FXS or related disorders (for example, ASD, developmental delay)
- **Concept:** Laboratory testing and interpretation of FMR1 variants to support:
    - Diagnosis of FXS and related disorders
    - Antenatal/preconception carrier screening and reproductive counselling
    - Prenatal diagnosis using molecular testing
    - Evaluation of variant pathogenicity and transmission risk (including CGG repeat size, AGG interruptions, methylation status, and mosaicism)
- **Context:** Clinical and laboratory settings in which FMR1 testing is offered; guidance from professional organisations (ACMG, American College of Obstetricians and Gynecologists (ACOG), National Society of Genetic Counselors (NSGC) regarding indications, methods, and reporting of FMR1 testing

[The full text was consulted to identify relevant information.]

Outcomes reported

- **Prenatal testing guidance:**
    - Amniocentesis and chorionic villus are acceptable for prenatal testing
    - It is acceptable to omit methylation analysis entirely when testing chorionic villus specimens
    - Follow-up amniocentesis may be needed in some ambiguous cases
- **Newborn and population screening:**
    - Population carrier screening and newborn screening for FXS are somewhat controversial and not recommended at this time
- **Diagnosis/clinical management:**
    - Identification of full mutation in males is considered diagnostic due to near-complete penetrance
    - Diagnosis in females is less certain (less than 50% exhibit intellectual disability)
    - Mosaicism and methylation status influence phenotypic expression and diagnostic interpretation
    - Guidelines include interpretations and reporting language for clinical use

[The full text was consulted to identify relevant information]

Conclusions

This updated ACMG technical standard provides comprehensive, evidence-based guidance for the molecular testing of the FMR1 gene, supporting accurate diagnosis, prenatal and carrier screening, and clinical management of Fragile X-associated disorders. It emphasises the importance of using validated methodologies (for example, triplet repeat–primed PCR, Southern blot, methylation analysis) to detect full mutations, premutations, and mosaic patterns, while also clarifying the clinical implications of each allele category. Although the standard supports the use of FMR1 testing in diagnostic and prenatal contexts, particularly in individuals with suggestive family histories or clinical features, it explicitly states that routine population-based carrier or newborn screening for FXS is not currently recommended. The document also stresses the need for genetic counselling and careful result interpretation, particularly in reproductive settings, to ensure informed decision-making and appropriate follow-up.

Citation 3

Queensland Clinical Guidelines. Preconception and prenatal genetic screening. Queensland Health 2024[21]

Study type

Clinical practice guideline developed by Queensland Health, based on evidence review and expert consensus

Objectives

To provide evidence-based guidance on prenatal screening and diagnostic testing in pregnancy, including the use of reproductive genetic carrier screening (RGCS). The guideline supports healthcare professionals in offering appropriate testing and information to pregnant women and those planning a pregnancy

Components of the study

- **Population:** Pregnant individuals and those planning pregnancy in Queensland, Australia
- **Concept:** Reproductive genetic carrier screening and prenatal testing, including conditions such as FXS
- **Context:** Antenatal care in Queensland; guidance intended for statewide clinical practice in both public and private maternity settings

[The full text was consulted to identify relevant information]

Outcomes reported

Relevant guidance for antenatal screening and clinical diagnosis of FXS includes:

- **RGCS recommendations**:
    - FXS is explicitly included in recommended three-gene screening panels (alongside CF and SMA) for carrier screening

    - Screening is recommended pre-pregnancy or in the first trimester (preferably prior to 10 weeks gestation)
    - When a woman is identified as a carrier for FXS, testing of the partner is not routinely required due to the X-linked inheritance pattern
    - Counselling should cover the limitations, implications of carrier status, and potential options for reproductive decision-making
- **Testing, interpretation, and follow-up**:
    - If FXS carrier status is identified, the guideline advises referral for genetic counselling to discuss reproductive options
    - Couples at high risk (for example, female carriers) should be offered invasive prenatal diagnostic testing (for example, chorionic villus or amniocentesis)
    - Referral for preimplantation genetic testing (PGT) can also be considered
- **Male screening:**
    - Male testing for FXS is not routinely indicated unless female partner is identified as a carrier
    - Testing of sperm or egg donors may be indicated in some contexts
- **Medicare-funded screening:**
    - Australia's Medicare Benefits Schedule (MBS) funds a panel including FXS, CF and SMA once per lifetime
    - MBS-funded testing is only available to females; male partners can be tested if a relevant carrier status is identified
- **Newborn screening**: FXS is not included in standard newborn screening in Queensland. Screening is confined to preconception or antenatal carrier identification

[The full text was consulted to identify relevant information]

Conclusions

The guideline recommends that all individuals planning a pregnancy or in early pregnancy be offered carrier screening for FXS, along with CF and SMA. This approach supports informed reproductive choices and enables access to options such as prenatal diagnosis or preimplantation testing. The focus is on carrier detection in females prior to or early in pregnancy, with no recommendation for newborn screening. Clear pathways are outlined for counselling, follow-up, and referral when carrier status is identified, reinforcing FXS as a key condition in antenatal reproductive screening practice.

Citation 4

Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) Guidelines. Genetic carrier screening. First endorsed March 2019; interim update July 2024.[22]

Study type

Clinical guidance statement / consensus guideline

Objectives

To advise health professionals on offering and delivering genetic carrier screening to women and couples before and during early pregnancy, including for FXS, cystic fibrosis (CF), and spinal muscular atrophy (SMA). The guideline aims to support informed reproductive decision-making and equitable access to carrier screening.

Components of the study

- **Population:** Women and couples planning pregnancy or in early pregnancy in Australia and New Zealand
- **Concept:** Reproductive genetic carrier screening (RGCS) for autosomal and X-linked conditions, including FXS
- **Context:** Antenatal/preconception care in general practice, obstetrics, and genetic counselling services; updated in context of Medicare-funded screening in Australia

[The full text was consulted to identify relevant information]

Outcomes reported

Guidance relevant to antenatal screening and clinical management of FXS includes:

- **Recommendation 3**: Information on carrier screening should be offered to all women planning a pregnancy or in the first trimester of pregnancy. Options include screening with a panel for a limited selection of the most frequent conditions (for example, cystic fibrosis, spinal muscular atrophy and FXS
  (Consensus-based recommendation)
- **Recommendation 7**: All couples with a high chance of having a child with one of the conditions screened for should be referred for genetic counselling to be informed of available reproductive options and to assist with prenatal testing if the woman found to have a high chance is pregnant when the result becomes known
  (Consensus-based recommendation)
- **Risk and screening logic:**
  - FXS is described as the most common X-linked recessive condition. Female carriers have a 1 in 4 chance of having an affected son
  - Carrier screening is most effective prior to conception but should still be offered during early pregnancy
  - Couples found to be at high risk should be offered genetic counselling and prenatal diagnostic testing (for example, amniocentesis, chorionic villus)
  - Preimplantation genetic diagnosis (PGD) is listed as an option for those identified pre-conception

- **Testing methodology and limitations**:
    - FXS carrier screening is generally only performed in females (due to the X-linked nature)
    - Sequential testing models prioritise screening the woman first
    - Variants of uncertain significance (VUS) should not be reported
- **Medicare rebate update (Australia only):**
    - Testing is only reimbursed once per lifetime, and male partners are only tested if the female is found to be a carrier
- **No newborn screening recommended for FXS:** Although newborns are screened for other conditions via the heel prick test, FXS is not included in standard newborn screening in Australia or NZ. However, antenatal carrier screening for FXS is explicitly recommended

[The full text was consulted to identify relevant information]

Conclusions

RANZCOG recommends offering reproductive carrier screening for FXS to all women in preconception and early pregnancy stages, regardless of family history. The guidelines emphasise the role of informed consent, genetic counselling, and access to prenatal diagnosis or PGD when a female is found to be a carrier. Testing is most impactful when offered preconception but remains relevant in early pregnancy. The guidance supports a public health model of screening, now partially subsidised in Australia, and seeks to ensure ethical delivery and equitable access.

Citation 5

Kirk E, Mundy L, Lee E, et al. Guidelines for reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome and spinal muscular atrophy. Pathology 2025;57:539-545.[23]

Study type

Guideline / Consensus statement developed by a multidisciplinary working group convened by the Royal College of Pathologists of Australasia (RCPA) and the Human Genetics Society of Australasia (HGSA)

Objectives

To provide practice guidelines for laboratories and clinical genetic services in Australia and New Zealand on implementing reproductive genetic carrier screening (RGCS) for cystic fibrosis (CF), spinal muscular atrophy (SMA), and FXS. The aim is to support high-quality, equitable RGCS, particularly in the context of Australian Medicare-funded testing, while informing reproductive decision-making

Components of the study

- **Population:** Reproductive-age individuals and couples, including those planning or already in early stages of pregnancy.

- **Concept:** RGCS for FXS (alongside CF and SMA); recommendations on test methodology, reporting, counselling, and implications for antenatal care
- **Context:** Australian and New Zealand healthcare settings; includes implementation in the context of publicly funded (Medicare) testing in Australia and guidance relevant regardless of funding

[The full text was consulted to identify relevant information]

Outcomes reported

The paper provides multiple guideline-level recommendations relevant to antenatal screening and clinical management of FXS, including:

- **Timing**: RGCS for FXS should ideally be offered pre-conception but may also be offered during early pregnancy (first trimester)
- **Reporting of Results:**
    - Premutation (PM) carriers (55 to 200 CGG repeats) in females have a risk of expansion to a full mutation (FM) in offspring
    - Risk of expansion depends on repeat size and AGG interrupt status
    - Laboratories may provide an “increased chance” or “low chance” classification rather than raw repeat numbers in some cases
- **Clinical implications of carrier status**:
    - Female PM carriers should be made aware of personal health implications, including increased risk for FXPOI and FXTAS
    - Male screening is not routinely recommended due to low utility in detecting transmission risk (PMs in males rarely expand to FM)
- **Management recommendations**:
    - Referral for genetic counselling is recommended when a PM or FM is identified
    - If a full mutation is detected in an apparently unaffected female during RGCS, the report should note the 50% chance of transmitting the FM and the potential clinical implications
- **Laboratory recommendations:**
    - Use of validated methodologies to detect CGG repeat expansions and AGG interruptions.
    - Avoid reporting variants of uncertain significance
    - Clear plain-language explanations recommended in reports, especially when clinical action is indicated

- **Newborn screening:** While FXS is not currently included in newborn screening, RGCS is presented as a complementary approach aimed at identifying reproductive risk prior to or during pregnancy

[The full text was consulted to identify relevant information]

Conclusions

The guideline supports offering RGCS for FXS to all individuals or couples planning a pregnancy or in early pregnancy. It outlines key considerations in testing, interpretation, and reporting of FMR1 results, and highlights the importance of genetic counselling in cases where carriers or affected individuals are identified. The document does not support population-wide newborn screening for FXS but reinforces RGCS as a proactive strategy to inform reproductive choices and reduce the risk of transmitting FXS to offspring. Clinical utility is maximised by focusing on pathogenic variants with established reproductive significance and by providing clear, accessible test interpretation.

Question 3

Citation 1

Lee S, Taylor JL, Redmond C, et al. Validation of Fragile X Screening in the Newborn Population Using a Fit-for-Purpose FMR1 PCR Assay System. *J Mol Diagn.* 2020;22(3):346–354.[27]

Study type

Analytical validation study with a prospective pilot component using deidentified newborn dried blood spot (DBS) samples

Objectives

To validate the analytical performance and workflow of a fit-for-purpose FMR1 PCR screening system for high-throughput newborn screening (NBS) of FXS. Specifically, the study aimed to assess the system's accuracy, sensitivity, specificity, precision, and feasibility for detecting FMR1 gene CGG repeat expansions using DBS specimens

Components of the study

- **Population:**
    - Deidentified residual DBS samples from 963 newborns collected through routine newborn screening in North Carolina, USA
    - Additional control samples (n = 38) with known FMR1 CGG repeat lengths, including normal alleles, premutation (PM) carriers, full mutation (FM) cases, mosaic samples
- **Intervention (Index Test)**
    - A customised, high-throughput FMR1 PCR and capillary electrophoresis (CE) screening system, developed using AmplideX technology (Asuragen Inc.)

    - Designed to detect CGG repeat expansions in the FMR1 gene from DBS samples without prior DNA quantification
    - Includes automated analysis software to classify results into: normal (less than 54 repeats), premutation (54 to 189 repeats), full mutation (more than 189 repeats)
- **Comparator (reference standard)**
    - Results compared against reference FMR1 genotypes from previously validated clinical testing laboratories
    - For 38 blinded samples, comparison was made to known CGG repeat sizes determined by clinical diagnostic PCR or Southern blot assays

[The full text was consulted to identify relevant information]

Outcomes reported

- **Accuracy:** 100% concordance with reference calls (Normal, PM, FM). CGG sizing accuracy within 3 repeats for all alleles
- **Precision:** High repeatability across runs, operators, and instruments, with less than 2% coefficient of variation
- **Sensitivity:** Detection of PM at 0.125 ng DNA input and FM at 0.5 ng (males) or 0.125 ng (females)
- **Specificity:** No false positives or carryover contamination observed
- **Prevalence:** 0.6% (6/963) of newborns identified as PM carriers
- **Operational feasibility:** 98.6% first-pass assay success, automation reduces manual analysis time

[The full text was consulted to identify relevant information]

Conclusions

The study demonstrated that the FMR1 PCR assay system is a robust, accurate, and scalable platform suitable for fragile X screening in a newborn screening setting. The system successfully identified normal and PM alleles using a streamlined, automated workflow and showed high concordance with reference genotypes. The approach is feasible for high-throughput laboratories and supports the potential implementation of routine NBS for FXS, subject to broader clinical and ethical considerations regarding carrier detection and follow-up.

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