UK National Screening Committee

UK National Screening Committee (UK NSC)

Antenatal and newborn screening for fragile X syndrome

Date: 26 March 2026

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Aim

To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, on whether antenatal and newborn screening for fragile X syndrome (FXS) meets the UK NSC criteria for a population screening programme.

Current Recommendation

The 2019 review of antenatal screening for FXS concluded that systematic population screening is not recommended. This was because:

- the test is not accurate; some babies with a positive result will never have symptoms
- some mothers may have to make difficult decisions on their pregnancy without knowing if their baby will develop symptoms
- the test is labour intensive and not suitable for use in a screening programme
- there is a lack of evidence that screening would improve outcomes in children compared to usual health care

The 2019 review also considered newborn screening for FXS because the topic had been raised by stakeholders during the consultation on the 2014 review. The recommendation based on the 2019 review was that an evidence summary should not be commissioned and that future requests to review the evidence for newborn

screening should be submitted through the UK NSC's annual call for topics (now the open call for topics).

UK NSC 2025 Evidence Map

Antenatal screening for FXS is a topic currently due for an update external review. A proposal for newborn screening for FXS was submitted to the UK NSC during the 2022 annual call for topics. An evidence map was subsequently commissioned to consider both antenatal and newborn screening for FXS.

The aim of the 2025 evidence map was to gauge the volume and type of evidence related to antenatal and newborn screening for FXS to support whether the evidence was sufficient to justify commissioning further evidence synthesis work. The following questions were addressed:

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?

The 2025 evidence map found:

- limited evidence from published guidelines and/or recommendations to support antenatal or newborn screening for FXS
- no studies reporting on the accuracy of available screening tests to detect FXS in pregnant women, so it is unclear whether antenatal screening would reliably identify FXS
- limited evidence on the accuracy of newborn screening tests using DBS, meaning some babies identified through screening may not have FXS, while others could be missed
- no studies reporting on the benefits/harms of early intervention in infants and children identified through screening with FXS, so it is unknown whether screening would improve outcomes

Consultation

A three-month consultation was hosted on the UK NSC website from 24 November 2025 to 16 February 2026. Direct emails were sent to 14 stakeholder organisations and 25 individual subscribers. Annex A contains a list of the 14 stakeholder organisations contacted.

Comments were received from the following stakeholders (see Annex B for comments):

- 4 members of the public
- University Hospitals of Leicester
- The Fragile X Society
- MRC Holland Foundation
- Patrick Wild Centre, University of Edinburgh
- Genetic Alliance UK

Key points raised in the consultation:

Members of the public

I. The UK NSC received four responses from parents of children diagnosed with FXS, all of whom supported screening in pregnancy or the newborn period. Their comments reflected a strong desire for earlier diagnosis, emphasising that delays had caused prolonged uncertainty, missed opportunities for early support, and considerable emotional strain. Respondents felt that earlier identification could inform reproductive decision-making, prevent unknowingly passing on the condition, and allow families to access appropriate care sooner. Several also highlighted low awareness of FXS among health professionals as an important issue in its own right.

Response: The UK NSC is incredibly grateful to the parents who shared their personal stories and perspectives. FXS is a complex neurodevelopmental condition with wide ranging cognitive, behavioural and physical effects, and we recognise the impact that delayed diagnosis can have on families.

As with all screening programmes, the UK NSC will only recommend screening where there is strong evidence that it does more good than harm and can be delivered safely and effectively at scale. This means considering not just the potential benefits of earlier diagnosis, but also test accuracy, clinical pathways, and possible unintended harms.

However, the current evidence base is limited. The evidence map did not identify any studies evaluating the accuracy of screening tests in pregnancy, and only early

feasibility data is available for newborn dried blood spot testing, with no robust real-world evidence on test performance. There is also no evidence that diagnosing children through screening leads to better developmental outcomes compared with diagnosis following clinical concerns.

Other stakeholders

II. Most stakeholders supported or were positively disposed to targeted newborn screening for boys with a full FMR1 mutation. Several referenced antenatal carrier screening internationally, but none explicitly called for the UK to implement population antenatal screening now. Most stakeholders discussed DNA-based newborn screening approaches. One (a technology manufacturer) described a specific assay designed for use on DBS. The others discussed genetics conceptually without specifying the testing methodology, although genomic screening approaches for FXS such as whole genome sequencing were often referenced.

III. Stakeholders expressed conditional support for DNA-based newborn screening for FXS primarily targeted at identifying boys with a full FMR1 mutation, often in reference to genomic screening, with one stakeholder specifically referencing the Genomics England Generation Study. This support was closely linked to the availability of an integrated early intervention and family support pathway, delivered through appropriately resourced specialist services.

Response: We are grateful to stakeholders for their views on the potential role of DNA-based newborn screening for FXS, and that screening can only be effective as part of an integrated and well-supported pathway.

The UK NSC's review focused specifically on the accuracy of DBS testing for FXS, reflecting previous reviews, the open call submission, and the technology currently used within the UK newborn screening programme. It is important to note that the evidence map did not assess the accuracy of genomic screening approaches for FXS. Evidence from genomic studies is still developing, and the UK NSC welcomes evidence from these studies. Proposals relating to genomic screening for FXS should be submitted through the UK NSC's open call for topics. It should be noted that FXS is not one of the conditions tested for in the Genomics England Generation Study.

Stakeholder comments emphasising the importance of integrated early intervention and family support pathways are noted and will inform future consideration as new evidence becomes available. It is important to note that the UK NSC always evaluates screening as part of an end-to-end programme rather than as a standalone test, considering how testing links to diagnosis, treatment and care, and longer-term outcomes. Current research has not yet shown whether children with FXS identified through screening have better outcomes than those diagnosed later in clinical care. No studies directly comparing these groups were found, and many publications focused on unrelated populations or study designs.

IV. Some stakeholders supporting newborn screening suggested that the evidence map may underestimate the potential benefits of earlier diagnosis of FXS by focusing only on FXS-specific outcomes. They highlighted that indirect evidence from related neurodevelopmental conditions, such as intellectual disability and autism, indicates that earlier diagnosis can be beneficial. One stakeholder noted that the lack of FXS-specific evidence on the benefits and harms of early intervention may reflect limitations in evidence generation, as without newborn screening it is difficult to identify infants early enough to support early intervention trials. They also raised concerns that the review may apply evidence thresholds that are difficult to meet in the absence of an established screening programme and referenced emerging approaches, such as EquipoISE, to address evidence gaps. Additionally, it was suggested that the revised review cycle could delay reconsideration of FXS despite emerging evidence.

Response: We appreciate stakeholders' reflections on the potential benefits of earlier diagnosis for families affected by FXS and recognise both the seriousness of the condition and the challenges of generating condition-specific evidence. While insights from related neurodevelopmental conditions may help contextualise possible benefits, the UK NSC must base its recommendations on robust evidence across the screening pathway that demonstrates clear improvements in outcomes for babies identified through screening compared with clinical presentation.

However, for FXS specifically, fundamental gaps remain around real-world test effectiveness for newborn DBS screening. At present, evidence on the accuracy of newborn screening tests for FXS using DBS is extremely limited, consisting only of small feasibility studies with no real-world data confirming detection of full mutations. These gaps make it difficult to meaningfully integrate indirect or related early intervention data or progress to further evaluation.

We recognise the particular challenges of generating evidence for rare conditions, which is part of the motivation for approaches such as EquipoISE. The UK NSC welcomes and actively encourages the submission of substantial new evidence through the open call process, allowing stakeholders to bring forward important data outside the scheduled review cycle.

V. Stakeholders highlighted screening initiatives and research in other countries, including newborn screening pilots in the USA and Australia, and antenatal carrier screening programmes in Israel. One stakeholder suggested that the evidence map may not have fully reflected this work and recommended engagement with programme leads in countries where screening programmes are in place. This stakeholder listed 6 specific publications with a request to clarify whether they were considered for the review and, if excluded, the rationale for their exclusion.

Response: We appreciate stakeholders drawing attention to international research and screening initiatives, including newborn screening pilots in the USA and Australia and longstanding antenatal carrier screening programmes in Israel. These programmes represent important developments in the global evidence landscape.

In line with the UK NSC's established evidence review process, however, the evidence map relied on systematically identified and published studies that met predefined inclusion criteria, including date limits (2018 to 2025), study design requirements, and a focus on diagnostic performance or screening outcomes. Much of the broader international literature highlighted by stakeholders focused on feasibility, acceptability, or programme implementation in specific contexts, and did not report the types of outcomes, particularly robust diagnostic-accuracy data, required to assess a potential UK population screening programme. As a result, some of the 6 publications identified by the stakeholder did not meet the inclusion criteria for this evidence map. Specifically, the evidence map reviewers confirmed that 3 of the 6 publications (Bailey 2019; Corbo 2024; Okoniewski 2019) were retrieved by the search strategy for the 2025 review but were excluded because they did not meet the inclusion criteria. Earlier international newborn screening publications cited by the stakeholder (Bailey 2017; Riley 2017) informed the 2019 UK NSC evidence review, which remains publicly available. Another reference (Bailey 2015) was outside the search years for this review.

The evidence map reviewers also conducted a quick scoping exercise and found 4 studies relevant to the antenatal screening programme in Israel. However, as above, these publications fell outside the types of evidence eligible for inclusion.

In line with established evidence review criteria, the UK NSC bases its assessments on systematically identified and published evidence. Relevant published data from international screening programmes would be considered where available. Engagement with individual international programme leads may be considered where such published evidence exists.

Where stakeholders believe that new or emerging international evidence is likely to materially affect the case for screening, they are encouraged to submit this evidence through the UK NSC open call.

VI. A stakeholder expressed concern that combining antenatal screening and newborn screening within a single evidence map reduced the visibility and clarity of evidence specific to newborn screening for FXS.

Response: The Committee notes the concerns raised regarding the combined presentation of antenatal and newborn screening within a single evidence map. However, the conclusions, and recommendations were assessed independently for antenatal and newborn screening.

VII. A stakeholder raised concerns with the timing of the evidence map, noting that it was conducted at a point when evidence is expected to emerge shortly.

Response: The Committee recognises that new evidence may emerge after a review has been concluded. Stakeholders who consider that newly published evidence is likely to have a significant impact on a recommendation can submit a request for an early review through the UK NSC open call process.

VIII. A stakeholder suggested that ethical considerations associated with antenatal screening for FXS should not be used to justify caution on inaction for newborn screening for FXS and that the UK NSC should clarify how this risk will be managed at the March UK NSC meeting.

Response: The Committee acknowledges the stakeholder's comment regarding ethical considerations and the distinction between antenatal and newborn screening for FXS. While one study identified through the 2025 evidence map noted potential ethical implications associated with identifying premutation carriers at birth, ethical considerations did not determine the Committee's position. These issues were referenced only as contextual background and were outside the formal scope of this evidence map. Consequently, there will be no discussion at this stage on the management of ethical risks.

IX. A stakeholder drew attention to the development of an assay that could be used to identify boys with FXS and indicated a willingness to engage further, including sharing additional information about the assay or exploring potential collaboration.

Response: Should newborn screening for FXS be introduced in the future, the assessment and selection of screening technologies would be considered by the National Health Service (NHS).

Recommendation

The UK NSC is asked to:

1. Consider the comments received during the consultation and confirm that they are happy with the responses provided.

2. Agree with the recommendation that no further evidence synthesis work should be undertaken on antenatal screening for FXS.

3. Agree that antenatal screening for FXS should be archived and any future requests to examine this topic should be submitted through the UK NSC's open call for topics.

4. Agree with the recommendation that no further evidence synthesis work should be undertaken on newborn screening for FXS.

5. Agree that any future requests to examine newborn screening for FXS should be submitted through the UK NSC's open call for topics.

Annex A: List of Organisations Contacted

1. British Institute of Learning Disabilities
2. The British Society for Human Genetics
3. Contact
4. The Fragile X Society
5. Genetic Alliance UK
6. MENCAP
7. NHS England Genomics Unit
8. Royal College of General Practitioners
9. Royal College of Midwives
10. Royal College of Obstetricians and Gynaecologists
11. Royal College of Paediatrics and Child Health
12. Royal College of Physicians
13. Royal College of Physicians and Surgeons of Glasgow
14. Royal College of Physicians of Edinburgh

Annex B: Consultation Responses

1. **From: UK National Screening Committee**
   Sent: Thursday, November 27, 2025 12:21
   To: UK NSC Inbox
   Subject: [Fragile X] Comment from member of the public

   Name: XXXX XXXX
   Email: XXXX XXXX
   Notify: True
   Condition: Fragile X

   Affected Comment:

   This condition has affected my wider family, until my son was diagnosed we then had answers to associated issues with wider family members.
   We didn't receive diagnosis of my son until age 8, he could have had more support and help earlier. My Dad would have had a earlier diagnosis of FXTAS and treatment.

   Evidence Comment:

   Yes no diagnosis until son aged 8, sisters and myself would have known they were carriers

2. **From: UK National Screening Committee**
   Sent: Friday, November 28, 2025 09:30
   To: UK NSC Inbox
   Subject: [Fragile X] Comment from a stakeholder

   Name: Sabrina Kinsella
   Email: XXXX XXXX
   Organisation: XXXX XXXX
   Role: Nurse
   Publish submitter's name: True
   Publish Organisation name: False

   Condition: Fragile X

   As a nurse within the NHS, and a mother of a child with full mutation fragile X syndrome I have recognised the lack of awareness of the condition across both health care providers, educational settings and the general public. I feel genetic screening should be routinely checked just as much as other conditions to help provide essential early interventions and expectations for both the affected families, as well as the health care providers. By doing so will ensure that the crucial support is put in place in order for all those affected to have a fair and fundamental opportunity in reaching their full potential.

3. **From:** UK National Screening Committee
   Sent: Friday, November 28, 2025 09:30
   To: UK NSC Inbox
   Subject: [Fragile X] Comment from member of the public

   Name: XXXX XXXX
   Email: XXXX XXXX
   Notify: False
   Condition: Fragile X

   Affected Comment:

   Having 2 daughters with Fragilex has been very difficult as a mother. Having children who require support, schools etc to support their needs has been a constant battle. It shouldnt be this difficult. the government don’t fund for parents to continue to work if you have a disabled child. This condition is genetic and continues to ruin families lives. I have grieved for my kids loss of a ‘normal life’. I dint get to retire and do the things I enjoy as my kids need me. However if I could have been tested prior to pregnancy I would have taken the test and stopped this gene for future generations.

   Evidence Comment:

   None

   Discussion comment:

   None

   Recommendation comment:

   Definitely screening should take place

   Alternatives comment:

   Screening is a priority to stop the condition altogether in families.

4. **From:** UK National Screening Committee
   Sent: Saturday, January 24, 2026 16:56
   To: UK NSC Inbox
   Subject: [Fragile X] Comment from a stakeholder

   Name: Julian Barwell
   Email: XXXX XXXX
   Organisation: University Hospitals of Leicester
   Role: Chair of the Holistic Fragile X Syndrome hub
   Publish submitter's name: True
   Publish Organisation name: True

   Condition: Fragile X

   Summary recommendations

   1. We would recommend supporting the introduction of newborn screening for boys with a full expansion in the FMR1 gene if DNA-based newborn screening is introduced, in the light of findings from the Generation study.
   2. This DNA-based screening will require discussion with relevant stakeholders such as DNA molecular laboratories, clinical genetics, allied professionals and community paediatrics.
   3. This type of newborn screening would require consent and information for families in a different format to current assent used for biochemical newborn screening methods.
   4. For this to be in keeping with national recommendations for the introduction of a newborn screening programme, we recommend that any introduction of national screening should be best supported by an integrated early intervention package which is not universally available. This is something the national hub being developed in Leicester would like to help to discuss with national leaders and contribute to. We have outlined what this support might look like.
   5. Where pre-mutations or females with a full expansion are detected, we would recommend the ability for clinicians and/or families to be aware that further analysis of genetic data be carried out to reveal the genotype if significant medical or cognitive concerns are raised during the first few critical years of life, especially during the period of neuroplasticity. A debate can occur as to whether these results should be released at the age of 16 for family planning reasons. All of these points would need additional educational support for healthcare professionals involved in the diagnosis and support of individuals with learning disabilities.

Background of family challenges

Fragile X Syndrome does have an unique set of challenges that need consideration when considering newborn screening. There are other conditions where more than one child can be affected, which is the case in 20-25% of families with Fragile X Syndrome, but is rare for the mother to have a specific mental health, premature menopause and potentially cognitive challenges and even rarer for a grandparent to have an ataxia type disorder or other affected grandchildren to look after.

This set of challenges is compounded by the fact that a significant proportion of children with Fragile X Syndrome not only commonly have autistic traits and cognitive challenges but also extreme agitation and aggression. This combination of pressures on family units is immense and should not be underestimated.

1. 25% have more than one affected child and it can be difficult to make a diagnosis in the first few years of life
2. 70% would consider reproductive choices for future pregnancies if had the opportunity. This has enormous health and social care economic considerations.
3. Families often struggle not just because of the diagnosis but cognitive and mental health challenges in the mother alongside a premature menopause. Any additional support to families in crisis that require early interventions to keep family units together has a massive and well-proven impact from a societal and economic perspective.
4. There is less wider family support due to ataxia in grandparent and other affected grandchildren to support
5. It can take over a year to access additional assessments for ADHD and autism
6. There is evidence that an early intervention in autism can improve outcome.
7. Accessing additional holistic support such and SALT, occupational therapy and educational psychology can be challenging
8. We are setting up a national hub and the aim is to support families and improve access to holistic care for the entire family. This will include counselling which we are providing as well as provide a framework for new interventions through coordinated research opportunities and commercial partnerships.

Evidence for supporting family units

Research confirms that relationship and family counselling significantly stabilize young families raising children with additional needs by improving communication, reducing parental conflict, and preventing children from entering the care system.

Key Evidence and Impact
• Preventing Family Separation and Care Entry: Evidence-based family therapy has been shown to keep more children safely out of care, with outcomes-based models delivering 25% better results in family stability compared to standard approaches. For some programs, this has translated to keeping children with their families for the equivalent of over 1,000 years collectively since 2019.
• Strengthening the Couple Bond: Targeted counselling helps couples navigate the “intense pressure” of parenting children with complex needs, such as those with Undiagnosed Genetic Conditions (SWAN). It fosters emotional attunement and mutual support, which are critical for maintaining a resilient, connected environment.
• Buffering Chronic Stress: Interventions focusing on dyadic coping (how partners support each other during stress) are directly associated with higher relationship stability and better overall family functioning.
• Reducing “Spillover” Effects: Relationship education for parents has been found to improve constructive conflict behaviours, which in turn reduces children’s emotional insecurity and behavioural issues.
• Cost-Effectiveness: Successfully completing these interventions saves local authorities between £39,000 and £88,000 per family by avoiding the costs associated with a child entering care.
Specialized Therapeutic Benefits
• Systemic Family Therapy: Helps families adapt their roles and interactions to accommodate a child’s disability, ensuring every member feels heard and understood.
• Gottman & EFCT Methods: New programs in 2026 are increasingly using the Gottman Method and Emotionally Focused Therapy (EFCT) to prioritize the romantic relationship as the primary driver for family stability.
• Parent-to-Parent Support: While professional counselling is vital, research also highlights that perceived peer support increases a parent’s quality of life and strengthens the parent-child relationship.

When should newborn screening be introduced using DNA based approaches?
Newborn screening based on DNA testing focus on detecting serious, treatable conditions with clear natural histories and actionable interventions, using established principles (Wilson-Jungner) for selection, requiring robust evidence for gene-disease links, ensuring equitable treatment access, and involving parents for informed consent, all while managing the vast data from genome sequencing. Key criteria include
conditions presenting in infancy, significant health impact if untreated, reliable tests, available treatments, and cost-effectiveness
.
Key Principles for Selecting Conditions (Wilson-Jungner Criteria Adapted)
• Important Health Problem: The condition must be a significant health issue with severe consequences if untreated, like some rare genetic disorders, hemoglobinopathies (sickle cell), or metabolic disorders (PKU).

• Treatable & Actionable: There must be a known, effective treatment or intervention available, and the condition should have a recognizable early stage where treatment is most effective (e.g., before symptoms).
• Adequate Understanding: The disease's natural history, from latent to symptomatic, must be well understood, and a suitable test must exist.
• Equitable Access: Interventions must be accessible to all, with no treatment for conditions where care isn't available on the NHS (in the UK).
• Informed Consent: Parents must provide informed consent, understanding the significant genetic information being analysed, including potential for uncertain findings.
DNA-Specific Criteria for Genome Screening
• Robust Gene-Variant Evidence: Only gene variants with strong evidence linking them to disease in newborns or young children are included, focusing on highly probable disease-causing variants.
• Management of Variants: Differentiating disease-causing variants from benign ones is crucial, acknowledging uncertainty.
• Data Handling: Managing the huge amount of data generated from whole-genome sequencing, including incidental findings, requires clear protocols.
Practical/Logistical Criteria
• Timing: Samples (heel prick blood spots) are taken early (e.g., 5-10 days old) to allow for timely intervention.
• Sample Quality: Adequate sample quality is required for accurate lab processing.
• Follow-Up: A clear pathway for diagnosis and treatment after a positive screen is essential.
In essence, DNA screening criteria aim to balance the potential benefits of early detection with the practical, ethical, and clinical realities, focusing on conditions where early action saves lives or significantly improves outcomes.

Reflection and assumption:
Newborn screening would require DNA testing logistic support and a consent discussion with families with access to relevant information for families. This requires a healthcare professional education programme for consent and also information to healthcare professionals involved in the diagnosis and care of individuals with learning disabilities. This would need consideration as part of a reflection in the light of the findings of the Generation Study. A precedent has been established for Spinal Muscular Atrophy in the United States and Scotland.

1. As previously noted, we support the introduction of newborn screening for boys with a full FMR1 expansion, conditional on access to post-diagnostic support.

2. This DNA-based screening with require discussion with relevant stakeholders such as DNA molecular laboratories, clinical genetics, allied professionals and community paediatrics.

3. This type of newborn screening would require consent and information for families in a different format to current assent used for biochemical newborn screening methods.
   Evidence of summary:

Early intervention in fragile X syndrome (FXS) is increasingly supported by converging pharmacological, clinical, and neurodevelopmental evidence that the greatest gains are achievable when treatment targets brain and behaviour while circuits are still forming. The systematic review by Watkins et al. (2024) underscores that, although no single pharmacological agent yet has definitive evidence, emerging precision approaches (for example cannabinoids, PDE4D inhibitors, and gene directed therapies) are explicitly built on the rationale of intervening early on FMR1-related molecular pathways rather than treating only downstream symptoms. Winarni et al. (2012) provide striking case level support for this principle, showing that two young children with FXS who received combined targeted pharmacological treatment and intensive educational intervention in early childhood demonstrated marked cognitive and behavioural improvements, with both ultimately scoring in the normal IQ range, suggesting that aggressive early treatment can partially normalise developmental trajectories in at least a subset of children. Complementing these human data, Svalina et al. (2022) demonstrate in FXS mouse models that there is a sensitive period in basolateral amygdala development during which early pharmacological modulation of hyperexcitable fear circuits can ameliorate precocious fear learning, implying that timely intervention may prevent progression to entrenched anxiety phenotypes frequently observed in FXS. Developmental and functional evidence further indicates that the early years represent a critical window to alter the natural history of communication, sensory regulation, and behaviour in FXS. Prospective studies show that a high proportion of infants and toddlers with FXS (for example, around two thirds) exhibit significant delays in early communication before 24 months, highlighting an opportunity for very early speech language and social communication intervention to mitigate later expressive and pragmatic language deficits that are otherwise difficult to remediate. In parallel, clinical and practice based evidence emphasises that individuals with FXS function best when environments and programmes are matched early to characteristic hyperarousal, sensory processing difficulties, and anxiety, with multidisciplinary plans that combine behavioural, occupational, and sensory integration approaches outperforming generic social skills training in reducing distress and improving participation. Together, these findings support a shift from reactive, school age onset support to proactive, infancy and toddler focused intervention that is tightly aligned with the neurocognitive profile of FXS rather than generic developmental disability models. A final pillar of the argument for early intervention comes from current and emerging research programmes that are explicitly designed around early brain monitoring and early stage disease modification. Phase 3 EXPERIENCE trials of the PDE4D inhibitor zatolmilast in adolescents and adults with FXS build on preclinical work showing that pharmacological targeting of core synaptic and signalling abnormalities can rescue aspects of synaptic maturation,

raising the possibility that deploying such agents even earlier in development could yield larger and more durable cognitive benefits. In parallel, translational pipelines in antisense oligonucleotide approaches, gene reactivation, and gene editing aim to restore or upregulate FMRP during early brain development, directly addressing the root molecular deficit and conceptually moving FXS toward a condition where pathophysiology is modified rather than accommodated. Finally, longitudinal studies such as EEG based early brain activity monitoring programmes (for example, BRIDGE style cohorts in preschool children) are working to identify biomarkers that can predict which children are at highest risk for specific cognitive and behavioural outcomes, enabling personalised, pre emptive intervention rather than delayed, symptom driven care. Current evidence suggests that early, integrated intervention in fragile X syndrome (FXS) can meaningfully shift developmental trajectories rather than merely compensating for established deficits. When targeted pharmacological treatments are combined with intensive educational and behavioural programmes in early childhood, some children show marked gains in cognition and behaviour, with rare cases even reaching the normal IQ range. This supports the view that neurodevelopment in FXS is more malleable than previously assumed when treatment begins during periods of high brain plasticity and is delivered in a coordinated, multidisciplinary way across health, social, and educational systems. A second key conclusion is that there appears to be a sensitive window for shaping brain circuits and behaviour in FXS, particularly those related to anxiety, communication, and sensory regulation. Preclinical work on maladaptive fear learning, alongside clinical observations of early communication delay and hyperarousal in infants and toddlers, implies that anxiety and language circuits can be redirected if intervention starts before maladaptive patterns consolidate. This argues against a “wait and see” approach and instead supports pre symptomatic or very early intervention guided by early developmental signs and emerging biomarkers, rather than waiting for full behavioural and cognitive symptoms to manifest. From these findings, several aims emerge for both clinical practice and research. Clinically, services should aim for much earlier identification, ideally in infancy, so that children access speech language, behavioural, sensory, and family focused support before the age of two, with the goal of improving communication, adaptive functioning, anxiety, and sensory regulation compared with historical cohorts. Research and service design should aim to test timing explicitly (for example, starting targeted agents and structured programmes earlier), develop reliable biomarkers that predict who will benefit from which interventions, and move gene reactivation or antisense approaches into early development protocols. The overarching ambition is to intervene early enough that many of the classic cognitive, language, and anxiety outcomes of FXS are softened, delayed, or, in some cases, substantially prevented

Early Intervention:

Although there are no specific pharmaceutical treatments for Fragile X Syndrome, there is evidence that treating sleep disturbances, anxiety and agitation

can be helpful. Reducing anxiety may also help the acquisition of speech. There is also considerable interest and hope in gene specific therapy and cognition enhancing trials. There have been many treatments and support available and approved for children for autism, ADHD, learning disabilities and agitation.

Due to neuroplasticity, early interventions have been shown to be beneficial and these are currently difficult to assess through standard educational, social and NHS routes. An earlier diagnosis is highly likely to improve access to additional and crucially earlier and impactful support due to neuroplasticity in the first five years. We have authored a review of all of the evidence of intervention in Fragile X Syndrome

https://pubmed.ncbi.nlm.nih.gov/38393835/

Although earlier interventions in speech and language, physiotherapy, educational psychology and occupational therapy can be helpful, especially at a time of maximum neuroplasticity, there are considerable concerns about access to this support, particularly after a diagnosis is made. We recommend that any introduction of national screening would be best supported by an integrated early intervention package which is something the national hub being developed in Leicester would like to be involved in and contribute.

We appreciate there are challenges with predicting the phenotype in girls and pre-mutation carriers, which can make counselling and planning interventions difficult. These results can be critical to families when considering future reproductive decisions. We understand it has been decided that family planning is not to be a main reason for newborn screening, which is NHS treatment focused. We appreciate the screening programme is not designed to detect carrier or pre-mutation carrier status for family planning reasons where there is an unclear phenotype.

We would recommend the ability for clinicians and/or families to be aware that further analysis of genetic data be carried out to reveal the genotype if significant medical or cognitive concerns are raised during the first few critical years of life, especially during the period of neuroplasticity.

AI review of early intervention evidence:

Clinical and Behavioural Evidence

- Winarni et al. (2012): This landmark study reported on young children with FXS who received a combination of targeted pharmacological treatment and intensive educational interventions. The findings showed significant improvements in cognition and behavior, with some children achieving a normal IQ.

- Johnson et al. (2024): A recent systematic review highlights that while research specific to FXS is still growing, preliminary evidence confirms

that early integrated support from health, social, and educational services benefits children as their brains are still forming.

- Journal of Neuroscience (2022): A study by Svalina et al. identified a critical window in early brain development where pharmacological intervention could effectively reduce “maladaptive” fear-learning in FXS models, suggesting that early treatment can prevent the progression of anxiety disorders.

Developmental Evidence

- Communication & Language: Research indicates that 68.2% of infants and toddlers with FXS show significant delays in early communication before 24 months, providing a clear window for early language intervention to mitigate long-term speech deficits.

- Sensory and Behavioural Support: Evidence shows that individuals with FXS function better when environment and supportive programming are matched to their needs early on. Highly individualized plans addressing hyperarousal and sensory processing are more effective than standard social skills training.

Ongoing 2025/2026 Research Streams

- EXPERIENCE Phase 3 Trials (2025): Recent clinical trials for Zatolmilast (a PDE4D inhibitor) are evaluating safety and efficacy in adolescents and adults to address cognitive deficits, building on evidence that targeting underlying molecular pathways early can rescue synaptic maturation.

- Gene Reactivation & ASO Therapy (2025-2026): Groundbreaking research into Antisense Oligonucleotide (ASO) therapy and gene editing is currently moving into commercialization stages, aiming to reactivate the silenced FMR1 gene during early development.

- Early Brain Activity Monitoring: The BRIDGE Study (2022–2026) at Boston Children’s Hospital is actively recruiting children ages 2–7 to use EEG markers to predict and treat cognitive and behavioural difficulties earlier than previously possible.

Concern over the first year of life:
Sleeping (and preferred position), breast feeding and bonding can all be affected by Fragile X and having a diagnosis may help mothers and families understand differences that emerge in the first few months of life, which may reduce any concerns about guilt about potential ability as parents or carers and improve access to support.

Family representative view:

‘On the face of the proposal the response would be a supportive yes, we should screen for full mutation FXS at birth. However, with a diagnosis should come a responsibility to support and treat if available. As no specific evidence supported pharmacological treatment is currently available for FXS and because allied services currently routinely discharge all patients with an intellectual disability diagnosis, such as FXS, it is our overwhelming concern that families with a new born FXS child would find themselves in a position of zero support and alienation from our national health service at a very vulnerable and damaging time as new parents struggle to find their feet and how to care for a new born with additional and sensory needs beyond a “typical” new born, with then a future prospect roadmap of continued fights and lack of support.

At its core this current lack of support is why we have form the FXS hub in Leicester, but we are limited by budget and access to allied services to offering an individual care assessment rather than our ultimate goal of hands on, holistic care, treatment and support for the whole family unit.
So with diagnosis we really must also consider investment into care, support and allied services to ensure we are progressive both is discovery but also in early intervention being key for life and situation improvement for patient outcomes and their family with semi independence later in life being the goal.

We would also like to note that deeper considerations should be made into diagnosis of female full mutation children, as females have two X chromosomes, it isn’t uncommon for the “good X” to work over the FX – X and for the individual to show little or no symptoms. This has led to FX being called, incorrectly, “a boy’s condition” which has led to further imbalance and struggles for females with FXS. However, with boys we know FXS will have pronounced impact, while females need time to establish what impact there is. It wouldn’t be questionable to not screen females, but the current genomic stance is to not inform of a result unless it has immediate or definite impact. Therefore this scenario falls into a conflict position or an ethical in balance from current practice.’

Holistic care framework steps:

1. A timely referral to clinical genetics to understand the inheritance pattern of the condition, the natural history of the condition, reproductive advice and signposting to additional support. This includes cascade testing to the mother and referral and on-going support to a holistic hub as appropriate
2. A timely referral to a community paediatrician for consideration for steps 3-7
3. A referral to physiotherapy
4. A referral to the portage early years’ service
5. A referral to SALT

6. A referral to educational psychology
7. A referral to occupational health
8. A referral to a family counselling service such as The Relationship Centre
9. An opportunity to seek advice from a national holistic care specialist centre with access to clinical research trials on request, as appropriate
10. An opportunity to seek information and advice from the Fragile X Society

In summary:
We would recommend supporting the introduction of newborn screening for boys with a full expansion as this could assist earlier interventions with the aim of improving independence, as well as potentially support the wider family. This advice needs to be supported by a clear package of support for identified children.

We understand that many females could benefit but as the impact of pre-expansions and full expansions in females is unclear, we recommend that these results are not declared at present and that this information is available on request if concerns are raised in the first five years or at the age of sixteen. This advice can be reviewed based on the introduction of the newborn screening programme.

About us:
Our team at the Leicester Fragile X Syndrome hub includes clinical genetics, research collaborations, community paediatrics, family counselling, the Rutland Rotoract Family Support Centre (winner of Queen's Award-community charity MBE), the Fragile X Society and parental co-creation expertise. We would offer ourselves available for further consultation and input into this important consideration.

The Fragile X Centre of Excellence
The Fragile X Centre of Excellence aims to provide a holistic needs assessment for children diagnosed with Fragile X as well as enabling access to research opportunities. With endorsements from the Fragile X Society as well as Harmony Biosciences and Shionogi pharmaceutical companies, the University Hospitals of Leicester aims to open a Fragile X Centre of excellence providing a national holistic care centre for the whole family underpinned by access to research. The service will continue to build on strong stakeholder collaborations and co-creation between clinical services and patient champions. Core team members would include clinical genetics, occupational therapy and educational psychology and access to research studies. Additional support would be offered by Community Paediatrics, the Relationship Centre, Gynaecology, Paediatric, Neurology, Speech and Language Therapy, General Practice and The Fragile X Society.

This service will develop a national repository of expertise to support children diagnosed with Fragile X, their parents, siblings and wider family as well as developing a research base for pharmaceutical intervention, starting with assessing the applicability of the NIHR toolkit for British families affected by Fragile X Syndrome. In addition, to providing an invaluable resource for children and their parents the expert centre will also actively improve medical and public awareness of the condition. Funding for a genetic counsellor and family counselling is already in place.

Appendix 1
The importance of early intervention on neural plasticity

Scientific research confirms that early intervention leverages the peak of neural plasticity in the first few years of life to significantly improve outcomes for children with learning and neurodevelopmental disabilities.

Key papers and reviews highlight that experience-dependent interventions during “critical periods” can restructure neural circuits, often leading to gains in cognitive, motor, and social functions.

Key Scientific Papers & Reviews

- Nelson et al. (2024), “Early intervention viewed through the lens of developmental neuroscience”: This comprehensive review in the Journal of Child Psychology and Psychiatry discusses how early intervention capitalizes on postnatal neuroplasticity, turning periods of vulnerability into opportunities for neural reorganization.

- Guralnick (2017), “Early Intervention for Children with Developmental Delays”: A seminal study demonstrating that early intervention significantly improves developmental trajectories, with the most pronounced gains observed in cognitive functioning.

- Perdue et al. (2023), “Reading intervention and neuroplasticity”: A systematic review and meta-analysis published in NeuroImage showing that specific reading interventions lead to measurable neuroplastic changes in the brain regions associated with reading abilities in children with reading disabilities.

- Dawson (2008/2025 update), “Early behavioral intervention, brain plasticity, and the prevention of ASD”: This research provides evidence that intensive behavioral interventions (such as the Early Start Denver Model) can successfully connect synaptic activities and enhance social behavior outcomes by engaging experience-expectant neural mechanisms.

- Sarkar (2025), “Early Childhood Education and Brain Development”: This study examines how structured early learning experiences enhance neural connections and executive functions during critical periods of brain plasticity.

- Environmental Enrichment: Recent studies, such as the GAME trial (2023/2026), have shown that combining motor training with environmental enrichment can induce neuroplasticity that maximizes the potential of an injured or delayed brain.

Appendix 2:
Early intervention for children with learning disabilities whose behaviours challenge
The Challenging Behaviour Foundation November 2014

https://share.google/GQuf0xhD5ft5PqoQs

Knowledge drawn from behavioural research clearly indicates the potential benefits of providing evidence-based behavioural interventions and of doing so early. There is robust evidence that early behavioural interventions can have positive effects on both parent and child outcomes and NICE recommends parental training.

The Government has acted on this evidence through the roll out of CAN-PARENT parenting classes. Systematic reviews of evidence-based parenting programmes (in particular the Triple P and Incredible Years interventions) have shown the effects to be improved parenting skills, improved parental well-being and reduced behavioural problems among children. 1

The Triple P Parenting Programme is a well-used example with a specific programme called “Stepping Stones” designed for parents of children aged 2-8 with LD. RCTs have found strong evidence that Stepping Stones improves child and parent outcomes. 2

Triple P is a multilevel system of family intervention that aims to prevent severe emotional and behavioural disturbances in
children by promoting positive and nurturing relationships between parents and children. It is also designed to address parental problems such as stress and/or depression. 3

1 Hastings, R. P., Allen, D., Baker, P., Gore, N. J., Hughes, J. C., McGill, P.,... & Toogood, S. (2013). A conceptual framework for understanding why challenging behaviours occur in people with
developmental disabilities. International Journal of Positive Behavioural Support, 3(2), 5-13.

NICE (2013). Antisocial behaviour and Conduct Disorder in Children and Young people: The NICE guidance on recognition, intervention and management

[Online]. Available at: http://www.nice.org.uk/guidance/cg158.

2 Plant, K. M., & Sanders, M. R. (2007). Reducing problem behavior during care-giving in families of preschool-aged children with developmental disabilities. Research in Developmental Disabilities, 28, 362-385.
3 Sanders, M. R., Turner, M. K., & Markie-Dadds, C. (2002). The Development and Dissemination of the Triple P-Positive Parenting Program: A Multilevel, Evidence-Based System of Parenting and Family Support. Prevention Science, 3(3), 173-189.

Nowak, C. & Heinrichs, N. (2008). A comprehensive meta-analysis of Triple P – Positive Parenting Program using hierarchical linear modelling: Effectiveness and moderating variable. Clinical children and Family Psychology, Review, 11, 44-144. 13 Early Intervention Project: Briefing Paper
Appendix 5:
Scientific research indicates that early intervention in Fragile X Syndrome (FXS) leverages critical periods of postnatal neuroplasticity to improve cognitive and behavioural outcomes.

Key papers and findings include:

- Human Case Studies and Reviews:
- Winarni et al. (2012) reported that early environmental enrichment combined with targeted pharmacological treatment led to significant cognitive improvements and even normal IQ in young children with FXS.
- Greiss Hess L., Fitzpatrick S.E., Nguyen D.V., Chen Y., Gaul K.N., Schneider A., Lemons Chitwood K., Eldeeb M.A., Polussa J., Hessl D., et al. A randomized, double-blind, placebo-controlled trial of low-dose sertraline in young children with fragile X syndrome. J. Dev. Behav. Pediatr. 2016;37:619–628. doi: 10.1097/DBP.0000000000000334. [DOI] [PMC free article] [PubMed] [Google Scholar]
- Nelson, Sullivan, and Engelstad (2023) highlighted how early interventions capitalize on the brain's heightened plasticity during the first years of life, converting periods of neurobiological vulnerability into opportunities for functional improvement.
- Johnson et al. (2024) provided integrated guidance emphasizing that early diagnosis and holistic intervention services (social skills, life skills, and mental health) significantly improve long-term functional abilities.
- Animal and Preclinical Research:

- Rais et al. (2022) demonstrated that re-expressing the FMRP protein in cortical cells during early postnatal development can ameliorate structural and behavioral abnormalities in mouse models, specifically targeting synaptogenesis.
- He et al. showed that early inhibition of the chloride co-transporter (NKCC1) normalizes the development of thalamocortical synapses, having lasting impacts on adult brain function.
- Sustained correction study (2019) found that brief, early treatment in rat models could permanently correct associative learning deficits.
- Recent Clinical Developments (2025-2026):
- Spinogenix SPG601 (2025 trial): Phase 2 results showed that this small molecule therapy could normalize gamma band activity—a key biomarker for learning and memory—further supporting the role of synaptic correction in treating FXS.
- Alpha Auditory Entrainment Study (Ongoing 2026): Research is investigating if normalizing brain activity through auditory stimulation can enhance early intervention efficacy by altering the trajectory of intellectual development.

Appendix 3:
Watkins LV, Moon S, Burrows L, Tromans S, Barwell J, Shankar R. Pharmacological management of fragile X syndrome: a systematic review and narrative summary of the current evidence. Expert Opin Pharmacother. 2024 Feb;25(3):301-313. doi: 10.1080/14656566.2024.2323605. Epub 2024 Mar 18. PMID: 38393835.

5. **From:** UK National Screening Committee
   Sent: Wednesday, February 11, 2026 19:30
   To: UK NSC Inbox
   Subject: [Fragile X] Comment from member of the public

   Name: XXXX XXXX
   Email: XXXX XXXX
   Notify: True
   Condition: Fragile X

   Affected Comment:

   My son XXXX XXXX was diagnosed with Fragile X Syndrome in XXXX XXXX, just shy of his 2nd birthday. This is an extremely early age for a diagnosis I hear often, we were very lucky to have a paediatrician who knew lots about FXS and saw the characteristics in XXXX XXXX.
   I was 16 weeks pregnant with our second child at the time of XXXX XXXX's diagnosis. We hadn't even heard of the condition before, and I was tested myself and told I carried the pre mutation of the gene, a gene that had been passed down through each generation of my family. We were then referred to genetic counselling and decided to test umbilical cord DNA at the time of delivery, we found out when our daughter XXXX XXXX was 6 weeks old, that she did not have the gene, nor did she carry the pre mutation.

   I am thankful this testing was available to XXXX XXXX at such a young age, it left the wondering and guessing to if she had the condition or not, and had she inherited the gene, it meant we could move forwards with getting the right care, treatment and therapies in place as we all know early intervention is key.

   I spent the first two years of XXXX XXXX's life in a very difficult place mentally. I couldn't understand why my baby wasn't meeting milestones, had health problems, didn't sleep and had issues feeding, mixed with family, friends and health professionals telling me he was just a boy and was taking his time. I knew in my heart there was something deeper going on, and it would've saved a lot of personal heart ache had we known earlier in XXXX XXXX's life, From newborn screening.

   It takes time to come to terms with a diagnosis for your child, there is a grieving process and a lot of questions. These children deserve the best possible chance and the sooner parents know and can get them on the right path the better chance they will have.

   Recommendation comment:

   I absolutely believe screening should be recommended.
   It gives parents the opportunity to access therapy, treatment care and intervention as early as possible. We know that is key in giving children the absolute best that they deserve.

Alternatives comment:

I think the condition should be recognised more at least. It is very unusual to even speak to a health professional who has heard of fragile X syndrome.

6. **From:** UK National Screening Committee
Sent: Thursday, February 12, 2026 13:55
To: UK NSC Inbox <UKNSC@dhsc.gov.uk>
Subject: [Fragile X] Comment from a stakeholder

Name: Peter Richardson
Email: XXXX XXXX
Organisation: The Fragile X Society
Role: Managing Director
Publish submitter's name: True
Publish Organisation name: True

Condition: Fragile X

This submission represents the official feedback of The Fragile X Society, the only UK-wide organisation solely dedicated to supporting individuals and families affected by Fragile X syndrome. We work across England, Scotland, Wales and Northern Ireland, providing information, emotional support, peer networks, advocacy, and professional education.
Our response reflects the lived experience of real families within the Fragile X community. Many parents tell us that the greatest challenge is not simply the diagnosis itself, but the long delay in recognition, the struggle to access appropriate support, and the lifelong impact this can have on children and family wellbeing.
Fragile X syndrome (FXS) is one of the most common identifiable inherited causes of intellectual disability and the most common genetic cause of autism. Around 125 babies are born with FXS in the UK each year.
We welcome the opportunity to contribute to the UK NSC's updated review of antenatal and newborn screening. We recognise the challenges involved, including current limitations in available services and the absence of a definitive cure. However, we believe that earlier identification has the potential to significantly improve access to supportive interventions at the most critical stage of development.
We therefore recommend that the UK NSC explores newborn screening for boys with a full mutation in the FMR1 gene, alongside an integrated pathway of early intervention and family support.

Unique pressures on Fragile X families
Fragile X creates a particularly complex family burden. In around one quarter of families, more than one child is affected, creating compounding caregiving demands. This is partly because Fragile X is often not diagnosed until around 18 months to 2 years of age, when developmental differences become clearer. By this stage, some parents may already be pregnant again or have welcomed another baby, before they have had the opportunity to receive answers or appropriate genetic counselling. Earlier identification through newborn screening could help families access timely information and support sooner, in a way that

is respectful of all children and focused on reducing avoidable uncertainty for parents.
Many children with Fragile X also experience severe anxiety, sensory distress, hyperarousal and, in some cases, significant agitation or aggression. Families repeatedly tell us that these early years can be overwhelming without timely understanding and support.
Fragile X also places unique pressures on mothers in particular. Mothers are almost always carriers of Fragile X, and carrier status can be associated with Fragile X-related premature ovarian insufficiency (FXPOI), alongside increased vulnerability to anxiety and other mental health challenges. This means families may be managing multiple layers of need at the same time, often with limited wider support.

The importance of early identification
Evidence shows that developmental delay often becomes apparent within the first two years of life, suggesting that earlier identification is needed to enable timely support during the period of greatest neuroplasticity.
Although there is no Fragile X-specific cure, many evidence-based interventions already exist for associated needs such as autism, ADHD, anxiety, sleep disturbance and communication delay. Early access to speech and language therapy, occupational therapy, behavioural support and symptom-based care can improve long-term outcomes.
Families also report major delays in accessing assessments and therapies. It can take over a year to secure autism or ADHD assessments, and access to holistic support services is inconsistent across the UK.
We also recognise that laboratories and clinical services are already under significant pressure. Any move toward DNA-based national screening would require careful planning and appropriate resourcing to ensure it is deliverable and sustainable.

Screening must come with support
Families are clear that screening should never be introduced without responsibility to provide meaningful follow-up care. A diagnosis without support risks leaving parents isolated at an extremely vulnerable time.
Any newborn screening programme must therefore be accompanied by an integrated early intervention package, including counselling, developmental monitoring, access to therapies, and coordinated specialist pathways.

The Leicester Fragile X Hub model
We highlight the development of the Leicester Fragile X Hub as an emerging national model bringing together genetics, paediatrics, psychology, family counsel-

ling and parental co-creation expertise. This hub aims to improve access to holistic care and create a framework for research readiness and future therapeutic developments.

The voice of families and the Fragile X community

Most importantly, this consultation is not simply about genetics or screening criteria. It is about real children, real parents, and lifelong outcomes. Earlier identification has the potential to reduce suffering, improve independence, strengthen family wellbeing, and ensure that children with Fragile X are supported from the very start of life.

Furthermore, while newborn screening is primarily treatment-focused, families also emphasise the importance of reproductive information. Around 70% of families indicate they would consider future reproductive choices if given earlier knowledge.

We believe it is important that progress is made now, as delays could mean many more years before this issue is reviewed again. A proportionate, targeted approach could allow the UK to move forward while building the evidence and service pathways needed.

Conclusion

The Fragile X Society urges the UK NSC to revisit its 2019 recommendation and consider:

• Targeted newborn screening for boys with full FMR1 mutation
• Screening linked directly to an early intervention and family support pathway
• Evaluation through integrated specialist hubs with appropriate resourcing

We would welcome continued engagement with the UK NSC and stand ready to support further consultation or pilot development on behalf of the UK Fragile X community.

7. **From:** XXXX XXXX
   Sent: Monday, February 16, 2026 12:31
   To: UK NSC Inbox <UKNSC@dhsc.gov.uk>
   Subject: Consultation Fragile X newborn screening

Dear all,

Hereby my comments for the consultation on the inclusion of Fragile X syndrome testing in the newborn screening programme. If you have any questions or would like to collaborate on this topic, please be in touch.

Best wishes,

XXXX XXXX

XXXX XXXX

MRC Holland

MRC Holland

Phone: **+31 (0) 6 15884961**

Technical Support: **info@mrcholland.com**

Orders: **order@mrcholland.com**

Website: **www.mrcholland.com**

More info on the **MRC Holland Foundation** can be found here

UK National Screening Committee

Name:	XXXX XXXX	**Email address:**	XXXX XXXX
Organisation (if appropriate):	MRC Holland bv		
Role:	**COO**		
Do you consent to your name being published on the UK NSC website alongside your response?		**Yes**	**No X**

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.*
14	**Question 3: What is the volume and type of evidence on the ac-curacy of newborn screening tests for FXS using dried blood spots (DBS)?**	We'd like to bring under your attention that our methylation-specific digitalMLPA technology might offer an affordable opportunity to include methylation analysis of the FMR1 gene in newborn screening. The main advantage is that digitalMLPA allows for simultaneous testing of FMR1 and 25 other DNA based disorders that can be of interest for newborn screening. This includes testing for SMA, SCID, DMD, CMV and confirmation of biochemical testing for disorders like HBA/HBB and CFTR. The selection of disorders can be adjusted for every country. The assay that we're currently developing contains 15 copy number probes for the FMR1 gene and 5 methylation-specific probes, making it possible to identify boys with the Fragile X syndrome. No results will be reported for girls (as symptoms are usually less severe) and carriers. The test depends on methylation changes that are only present in full mutation individuals. The assay uses only a single 3 mm DBS punch and does not require DNA purification. As a targeted, probe-based technique, digitalMLPA lacks the privacy concerns that come with newborn sequencing and is at least ten times more affordable. Moreover, methylation analysis

		is not possible with short read whole genome sequencing and long-read sequencing is still too expensive for routine use. Our ambition is that this assay will make it possible to expand the newborn screening with multiple severe and often treatable diseases that are until now out of reach because of the complexity or the cost, including methylation and imprinting disorders. Fabella T. et al (manuscript under review, *European Journal of Human Genetics),* describe results of testing DBS samples from 2,069 newborns using this digitalMLPA assay. Validation of the test was done on cell line derived DNA samples with variable repeat lengths and Fragile X patient samples. Results showed absence of methylation in all newborn male samples. All female samples showed the presence of a methylated FMR1 copy. One female outlier had a methylation level 50% higher than all other female samples. This proved to be an XXX individual. Please get in touch if you like to know more about digitalMLPA in newborn screening or if you are interested in collaborating on this topic. MRC Holland is a genetic testing company from The Netherlands, well known for developing MLPA, the gold standard for copy number detection and for MS-MLPA, widely used in methylation analysis. Moreover we are an experienced provider for newborn screening programmes for SMA – our IVDR certified MC002 assay is used as a first tier test in Poland and Serbia among others.

8. **From:** UK National Screening Committee
   Sent: Monday, February 16, 2026 15:31
   To: UK NSC Inbox
   Subject: [Fragile X] Comment from a stakeholder

   Name: Andrew Stanfield
   Email: XXXX XXXX
   Organisation: Patrick Wild Centre, University of Edinburgh
   Role: Director of Clinical Research and Honorary Consultant Psychiatrist
   Publish submitter's name: True
   Publish Organisation name: True

   Condition: Fragile X

   This response is submitted on behalf of The Patrick Wild Centre, a translational research centre based at the University of Edinburgh. The focus of The Patrick Wild Centre is on the development and testing of interventions for genetic neurodevelopmental disorders, with fragile X syndrome (FXS) being primary among these.

   We recognise the committee's conclusion that current evidence is insufficient to recommend population screening. However, we believe that the appraisal may underestimate several domains of potential benefit that are well supported in adjacent areas of neurodevelopmental and genomic research. Although direct outcome trials for FXS are limited, substantial evidence from intellectual disability, autism, and genomic research indicates that earlier diagnosis can meaningfully influence developmental trajectories, family wellbeing, and long-term service utilisation. We therefore suggest that indirect but highly relevant evidence should inform policy considerations.

   In particular, we highlight three interrelated considerations: 1) the developmental impact of early identification enabling early intervention; 2) the reproductive and familial implications of earlier genetic diagnosis; 3) the economic and service-use implications of reducing diagnostic delay.

   1. Early intervention
      FXS is the most common inherited cause of intellectual disability and a leading monogenic cause of autism and ADHD. Its phenotype frequently includes speech-language delay, executive dysfunction, sensory processing differences, anxiety, and adaptive functioning challenges [1]. Children with FXS are often diagnosed several years after developmental concerns first arise, with the mean age of diagnosis being approximately 3 years old for boys and 6 years old for girls [2]. This delay restricts access to intervention during early childhood, when neural plasticity is greatest and developmental trajectories are most modifiable [3, 4].

Given its relatively late diagnosis, there is little FXS specific research around the benefits of early intervention. However, across neurodevelopmental conditions, early therapeutic engagement is consistently associated with improved outcomes, with evidence coming from both the autism literature [5, 6] and reviews of developmental disorders more broadly [7]. There is no reason to suspect that FXS should be any different as the mechanisms underlying these benefits (e.g. sensitive periods of learning, prevention of secondary behavioural difficulties, and enhanced caregiver scaffolding) are directly relevant to FXS. There is no developmental rationale to assume children with FXS would benefit less from early intervention than those with other neurodevelopmental disorders with comparable clinical profiles.

1. Reproductive implications and cascade testing
   Informed decision making around reproductive choices was not included in the evidence summary, missing the significant value that early postnatal diagnosis brings in these regards. FXS differs from many screened conditions in that diagnosis frequently reveals carrier status within families, with implications extending beyond the affected child. Evidence demonstrates that families value genetic diagnosis partly because it enables informed reproductive decision-making and planning of future pregnancies [8], with preimplantation genetic testing now widely available in the UK. At present, with diagnosis delayed until 3- 6 years old, many parents opt to have more children without being aware of the potential for future offspring to be affected.

The beneficial effects of early diagnosis multiply when the wider family is considered. Cascade testing following diagnosis of a child with FXS often identifies previously unrecognised carriers among extended relatives, supporting informed reproductive choices across multiple related family groups.

1. Service utilisation and the impact of diagnostic delay
   Diagnostic delay in FXS frequently involves multiple referrals across primary care, paediatrics, therapy services, and education without a unifying diagnosis guiding care. Research on rare genetic developmental disorders shows that this “diagnostic odyssey” increases cumulative healthcare costs due to repeated investigations, fragmented care pathways, and delayed intervention [9]. Earlier genetic diagnosis of FXS would reduce unnecessary testing and specialist referrals, improve coordination of developmental and educational services and shorten time to appropriate family support.

While direct cost-effectiveness analyses of FXS screening are limited, economic literature from autism and intellectual disability demonstrates that initial investments in diagnosis and early intervention programmes may be offset by later reductions in educational and support costs [10, 11].

Beyond direct service costs, the societal cost of intellectual disability and autism includes long-term impacts on employment, caregiver wellbeing, and informal support networks [12]. Even modest improvements in adaptive functioning may therefore produce substantial cumulative economic effects.

References

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8. Boardman, F.K., Attitudes toward population screening among people living with fragile X syndrome in the UK: ‘I wouldn’t wish him away, I’d just wish his fragile X syndrome away’. J Genet Couns, 2021. 30(1): p. 85-97.
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11. Schofield, D., et al., Long-term economic impacts of exome sequencing for suspected monogenic disorders: diagnosis, management, and reproductive outcomes. Genet Med, 2019. 21(11): p. 2586-2593.
12. Buescher, A.V., et al., Costs of autism spectrum disorders in the United Kingdom and the United States. JAMA Pediatr, 2014. 168(8): p. 721-8.

9. **From:** Dani Bancroft
   Sent: Monday, February 16, 2026 19:24
   To: UK NSC Inbox
   Subject: Consultation response - FXS

Dear UK NSC team,

Please find attached Genetic Alliance UK's response to the consultation on antenatal and newborn screening for Fragile X syndrome.

Many thanks,

Dani Bancroft

Senior Policy & Research Officer

GENETIC ALLIANCE UK

geneticalliance.org.uk | linkedin | instagram | twitter | facebook

Genetic Alliance UK is the largest alliance of organisations supporting people with genetic, rare and undiagnosed conditions in the UK. Our members and the people they support are at the heart of everything we do.

We advocate for fast and accurate diagnosis, good quality care and access to the best treatments. We actively support progress in research and engage with decision makers and the public about the challenges faced by our community.

We run two long standing projects:

– Rare Disease UK, a campaign focused on making sure the UK Rare Diseases Framework is as successful as possible, and to ensure that people and families living with rare conditions have access to a final diagnosis, coordinated care and specialist care and treatment.

– SWAN UK supports families affected by a syndrome without a name - a genetic condition so rare it often remains undiagnosed. We are the only dedicated support network for these families in the UK.

UK National Screening Committee

Name:	Dani Bancroft	**Email address:**	XXXX XXXX
Organisation (if appropriate):	Genetic Alliance UK		
Role:	Senior Policy & Research Officer		
Do you consent to your name being published on the UK NSC website alongside your response?	**Yes**		

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.*
N/A	Overall approach	Genetic Alliance UK welcomes the opportunity to comment on the 2025 evidence review for fragile X syndrome (FXS) screening. While we recognise the framework within which the UK NSC produces evidence maps, we have a number of concerns regarding the structure, timing and scope of this review. In particular, we are concerned that it may draw definitive conclusions at a point when key evidence is emerging as several peer-reviewed publications, internationally anticipated to make a significant contribution to this field, are expected imminently but will not be considered due to the timing of this review. These factors may therefore limit the review's ability to assess newborn blood spot screening (NBSS) specifically, and there is strong support across our community for newborn screening of FXS. We are also concerned that consulting on both antenatal carrier screening and NBSS within a single evidence map has reduced clarity, as these are fundamentally different interventions with distinct aims, ethical frameworks and outcome measures. Feedback from our community and wider stakeholder network indicates that this has made it more difficult to engage clearly with the consultation and may have reduced the visibility of relevant evidence relating to NBSS. We understand that this concern has previously been raised with the UK NSC by several stakeholders, including our member organisation, the Fragile X Society, and remains unresolved in the current review. Our specific comments are outlined below.

p. 11	'Limited evidence was identified on the feasibility of newborn screening for Fragile X syndrome.' 'The evidence base remains limited and uncertain'	On review, Genetic Alliance UK shares concerns raised about whether the evidence map reflects the full volume and maturity of relevant international evidence. To our knowledge, the review does not adequately account for major screening programmes and pilots that are directly relevant to newborn screening for FXS, including large-scale work underway in Australia, the Early Check Program in the US and longstanding antenatal screening programmes in Israel. These initiatives provide evidence on feasibility, acceptability and integration into public health systems and are relevant to the questions under consideration. It is unclear whether the references below were considered by the reviewers. If they were excluded, it would be helpful for the UK NSC to clarify the rationale for exclusion. • Bailey DB Jr, Berry-Kravis E, Gane LW, Guarda S, Hagerman R, Powell CM, Tassone F, Wheeler A. 2017. Fragile X newborn screening: lessons learned from a multisite screening study. Pediatrics 139(Suppl 3):S216-S225. https://doi.org/10.1542/peds.2016-1159H • Bailey DB Jr, et al. 2019. Early Check: translational science at the intersection of public health and newborn screening. BMC Pediatrics 19(1):238. https://doi.org/10.1186/s12887-019-1606-4 and the Clinical Trials record for this: https://clinicaltrials.gov/study/NCT03655223 • Bailey DB Jr, et al. 2015. Maternal consequences of the detection of fragile X carriers in newborn screening. Pediatrics 136(2):e433-e440. https://doi.org/10.1542/peds.2015-0164 • Corbo A, et al. 2024. Parent perspectives following newborn screening resulting in diagnoses of fragile X syndrome or fragile X premutation. Research in Developmental Disabilities 148:104719. https://doi.org/10.1016/j.ridd.2024.104719 • Riley C, Wheeler A. 2017. Assessing the fragile X syndrome newborn screening landscape. Pediatrics 139(Suppl 3):S207-S215. https://doi.org/10.1542/peds.2016-1159G • Okoniewski KC, Wheeler AC, Lee S, Boyea B, Raspa M, Taylor JL, Bailey DB Jr. 2019. Early identification of fragile X syndrome through expanded newborn screening. Brain Sciences 9(1):4. https://doi.org/10.3390/brainsci9010004

		Genetic Alliance UK agrees that evidence gaps may remain, as is the case for nearly all rare conditions. However, we note that several large studies expected to publish in 2026 aim to address the specific gaps identified by the UK NSC. For example, two key publications are expected imminently: • A major publication from the team running the large newborn screening study in Victoria, Australia (expected imminently) • A publication on the Early Check newborn screening programme in North Carolina, US, where identified babies were enrolled into a study and families were supported while babies were monitored in their first years of life (expected March 2026) Given this, we are concerned that a definitive recommendation now could limit the Committee's ability to consider evidence that will emerge shortly after the consultation closes. We also note that the UK NSC's move to a three-year cycle may mean these developments are not reviewed for several years, despite being expected within months.
p. 13	'Concerns remain regarding test performance and scalability.'	Genetic Alliance UK notes that this assessment does not fully reflect advances since the previous 2019 review. While we defer to the Fragile X Society and Fragile X International's response for the relevant condition-specific expertise, we understand that high-throughput PCR-based assays and methylation-sensitive methods suitable for routine NBSS are now being used at scale in international pilots. As noted in our July 2025 report, *Time to Decide: international approaches to newborn screening decision-making* (link below) advances in genetic screening technologies have significantly shifted feasibility across multiple conditions internationally, requiring decision frameworks to adapt to current technical capability. https://geneticalliance.org.uk/wp-content/uploads/2025/07/Time-to-decide-Learning-from-international-approaches-newborn-screening-decision-making_Highres-3.pdf
p. 16	'No studies were identified that assessed the benefits and harms of	Genetic Alliance UK is concerned that this conclusion reflects a structural challenge in evidence generation, rather than a clear indication that early intervention has no benefit. Without newborn screening, it is difficult to identify infants early enough to generate robust, Fragile X-specific early intervention trials. This challenge is widely recognised in neurodevelopmental research and we suggest it should be acknowledged in the interpretation of evidence gaps.

	early intervention following newborn identification…'	
P. 16	'There is insufficient evidence that early identification improves outcomes'	Genetic Alliance UK notes that a substantial proportion of individuals with FXS meet criteria for autism spectrum disorder, for which the benefits of early intervention are well established. While Fragile X-specific trials are limited, excluding relevant autism and wider neurodevelopmental evidence risks overlooking clinically meaningful and biologically plausible benefits of early identification. Further, in relation to p. 7, 'Screening should be limited to conditions with effective early treatments.' Genetic Alliance UK encourages a broader interpretation of actionability for neurodevelopmental conditions. For FXS, early detection can enable timely developmental support, reduce the diagnostic odyssey, support informed family planning and facilitate the participation in emerging clinical trials. For families, receiving this knowledge in a timely way has demonstrable value, including in qualitative research on the impacts of diagnosis timing.
p.18	'No evidence was identified on the benefits and harms of population antenatal screening for Fragile X syndrome.'	Genetic Alliance UK considers that as written, this statement may be potentially misleading. To our knowledge, there is substantial real-world evidence from countries with established antenatal FXS carrier screening programmes, particularly Israel, where screening has been offered nationally for over 10 years. Engagement with programme leads in these countries may provide the UK NSC with relevant data on uptake, acceptability, follow-up pathways and outcomes, even where formal comparative trials are limited. In addition, while we agree that antenatal screening raises distinct ethical considerations, we suggest these should not be used to justify caution or inaction in relation to NBBS, which involves different ethical principles and outcomes. We note that combining ethical discussions risks importing antenatal-specific concerns into newborn screening assessment and we suggest the UK NSC clarifies how this risk will be managed in its meeting in March. For example, in this paper by Felicity Boardman in 2020. https://onlinelibrary.wiley.com/doi/full/10.1002/jgc4.1355

p. 20	'FXS does not currently meet the criteria for inclusion in the newborn screening programme.'	As we outlined above and more broadly in our report, *Time to Decide*, Genetic Alliance UK is concerned that the current review underrepresents international newborn screening evidence, applies evidence thresholds that cannot realistically be met without screening in place, and the revised review cycle means that it will not be reconsidered for several years, despite imminent publication of new evidence. For these reasons, Genetic Alliance UK urges the Committee to consider alternatives to a definitive 'non-recommendation', including potentially positioning FXS as an active candidate for the proposed EQUIPOISE ISE, or explicitly deferring a decision in recognition of this. Learning from how other countries have approached this, such as the Australian Medical Services Advisory Committee (MSAC) or the Dutch system, allow more flexibility in how evidence is periodically reviewed rather than requiring conditions to only be re-considered after an extended exclusion period. This approach can promote a more agile decision-making process that also promotes more transparency and trust from the stakeholders involved. We therefore encourage the UK NSC to keep FXS under active consideration and to adopt a more flexible, proportionate approach to evidence gathering for rare conditions.