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SPECIAL ISSUE

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A holistic approach to fragile X syndrome integrated guidance for person-centred care

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Abstract

Background: The Fragile X community has expressed a desire for centralised, national guidelines in the form of integrated guidance for Fragile X Syndrome (FXS).

Methods: This article draws on existing literature reviews, primary research and clinical trials on FXS, a Fragile X Society conference workshop and first-hand experience of clinicians who have worked with those living with FXS over many years.

Results: The article scopes proposed integrated guidance over the life course, including appendices of symptoms, comorbidities and referral options for FXS and Fragile X Premutation Associated Conditions.

Conclusion: Integrated guidance would provide an authoritative source for doctors, health professionals, therapists, care workers, social workers, educators, employers, families and those living with FXS, so that a holistic, person-centred approach can be taken across the United Kingdom to garner the best outcomes for those with FXS.

KEYWORDS
autism, fragile X syndrome, FXPAC (fragile X premutation associated conditions), integrated guidance, intellectual disability, newborn screening

1 | INTRODUCTION

One baby born every 3 days in the United Kingdom has fragile x syndrome (FXS). Despite this, there is currently no integrated guidance available for UK practitioners specifically for FXS. The lack of integrated guidance for FXS can leave those affected and their families to navigate multiple complex care systems. This risks them falling through the cracks between these systems, leading to inadequate care and support. Feedback from families is that integrated guidance for FXS would lighten the burden of being the experts in their child's treatment and support. Published integrated guidance can help professionals deliver care for this not-so-rare condition, making sure that no one is left behind through lack of knowledge or protocols.

This review article is based on the extensive body of research that exists on FXS, including previous reviews of the literature (Hardiman & McGill, 2017; Hunter et al., 2014; Jalnapurkar et al., 2019; Protic et al., 2022; Schneider et al., 2013), supplemented by research in related, usually broader, conditions (such as autism and intellectual disability). This research has been brought to life by the authors' experience in supporting families, research, and clinical practice, as well as the relevant first-hand experience of members of the Fragile X Society (UK syndrome support group) via workshops and conferences. Particularly, this paper is informed by the workshop discussions which took place at The Fragile X Society conference in Birmingham, 22 September 2022. The authors thank participants for their candour and insight.

In setting out the need for integrated guidance, an overview will first be given of the benefits of early diagnosis, including the fragile X community's desire for newborn screening as this may enable the earliest possible adaptations and interventions to support fragile X families. As FXS is caused by alteration in a gene on the X chromosome, each cell of the body is potentially affected, although mosaicism, the characteristics of the sex chromosomes and the usual variability of gene expression will affect each individual's presentation; therefore, a person-centred approach is necessary for the best approach to managing and supporting each affected individual to help them achieve the best outcome for a happy and fulfilled life. It should be noted that, although associated with the X chromosome, FXS does not follow the usual pattern of sex-linked inheritance because of its molecular basis as an unstable triplet repeat. This means that the condition can pass through an unaffected male to affect their grandchildren in a way that would not be possible in, for example, haemophilia or most other sex-linked conditions.

In this paper, FXS through the life-course is set out, with general guidelines on what issues are key for the person at each stage. While a clinician may oversee diagnosis and medical care, early support from non-medical services is also recommended. How these supports are realised will differ from country to country. The United Kingdom is used as a prototype to show how an integrated approach to health, social and educational care would benefit those living with FXS.

2 | FXS, OVERVIEW OF SYMPTOMS AND CO-MORBIDITIES

While FXS has typically been described as a condition whose primary characteristic is intellectual disability, any guideline requires a much broader view, incorporating an understanding of how FXS affects the entire body, with physical, psychological, social, and educational challenges explored. FXS (ICD-11, LD55) is defined as a sex chromosome anomaly within the broader category of developmental anomalies (WHO, 2023). With onset from conception, common physical health concerns include muscle laxity, mitral valve prolapse, epilepsy, gastrointestinal problems, and otitis media (Table 1) (Dunphy, 2020; Knott, 2021). Cognitive and behavioural concerns include sleeping issues, sensory processing differences, self-injurious behaviour, atypical speech development, intellectual disability, social and emotional difficulties, and autism. In parallel, commonly co-occurring psychiatric conditions include autism, ADHD, depression, and anxiety. It is important to stress that not all of these characteristics and co-morbidities will affect every person with FXS: some will experience many symptoms and others fewer (Crawford, Abbeduto, et al., 2020).

The prevalence figures cited for FXS vary, with a 2014 United States systematic review finding 1 of 7000 males and 1 of 11000 females affected (Hunter et al., 2014). Using UK cited figures, 1 of 4000 males and 1 of 6000 females are affected (Genomics England, 2023), which would equate to around 125 babies born each year in the United Kingdom and around 14,000 people in the entire population.

3 | THE NEED FOR GUIDELINES

There are currently no specific national pathways or guidelines for FXS that are tailored to the United Kingdom. Other countries have excellent FXS guideline documents (Centro di Coordinamento, 2018; De fragiele X vereniging Nederland et al., 2023; de Santé, 2021; Forster-Gibson & Berg, 2011; Hunter et al., 2019; Sachdeva et al., 2019; VSOP et al., 2014, 2015), however, not all are applicable to the UK's health, education, and social care systems which differ from those internationally. Clear guidelines would set out what other commonly co-occurring conditions should be considered once FXS is confirmed, and what carrier issues might need attention in the case of fragile X premutation associated conditions (FXPAC) (Johnson et al., 2020). This is a gap in our service provision, and one that is currently being filled by patients and clinicians seeking advice from other countries' websites (Fragile X Research Foundation of Canada, 2023; FRAXA, 2023; National Fragile X Foundation, 2023).[1]

The UK fragile X community has expressed an overwhelming desire for clear clinical and social guidance for FXS tailored for the United Kingdom (Crawford et al., 2022). Services have been perceived by families as slow to respond, poorly co-ordinated, and communicating badly with each other. Families report having to fight for services and feeling that their worries were ignored or disbelieved unless their specific concerns were observed by the clinician (Tumiene et al., 2022). Families also report being discharged very quickly from specialists, with a sense that there is little that can be done to help the child with FXS, that is, their difficulties are seen as an inevitable 'part of the fragile X diagnosis'. There is a perception that more is offered in early childhood, but once the child is of school age, much of the care defaults to the educational system, while FXS adults are offered even less (Crawford et al., 2022). A person-centred, integrated approach should work in tandem with educational and social provision and would alleviate the tension sometimes felt between families and professionals. With protocols, interventions, and procedures put in place to enable the best outcomes, people living with FXS could be supported by the best healthcare, social care, and educational provision available, adapted to their needs, difficulties, and strengths.

4 | DIAGNOSIS

Typically, FXS is tested for when developmental milestones are missed and there is concern about developmental delay. All children with an undiagnosed, suspected developmental delay should be tested for FXS, not dependent on family history. Early physical features of FXS may include muscle laxity, hypermobility, prominent ears,

[1]There are NICE guidelines for learning disability (NICE, 2018a,b) and autism (NICE, 2017, 2021a,b), ADHD (NICE, 2019), but there is a need for syndrome-specific guidelines given the unique characteristics of FXS. The NHS offers public-facing, condition-specific information for other genetic neurodevelopmental conditions, which are of much greater rarity than FXS, for example, Angelman Syndrome, DiGeorge Syndrome, Edward Syndrome, Patau Syndrome, Prader-Willi Syndrome (NHS, 2021), Rett Syndrome and Tuberous Sclerosis. It is noted that regional genetics services have some information on FXS which could be built upon to create a national resource (Yorkshire Regional Genetics Service, 2023).

TABLE 1 Fragile X Syndrome: symptoms, management and support; regular review recommended by physician and social care coordinator.

Possible issues	Treatment/support
Heart: mitral valve prolapse; aortic root dilation; hypertension (may be related to anxiety)	Cardiology
Gastroenterology: reflux; indigestion, constipation	Treat using standard techniques; consider referral to gastroenterology if persistent
Epileptic seizures: usually childhood, often lessen by adulthood	Neurology
Sleep Issues: disturbed sleep, sleep apnea	Sleep hygiene measures; refer to sleep specialist if concerns of apnea
Muscle hypotonia: swallowing; sucking; crawling/walking; sitting (poor core strength)	Physical therapy, breast-feeding support, other specialist services as appropriate
Hypermobility: hyperflexibility; flat feet; scoliosis; inguinal hernias	Podiatry, physiotherapy, other specialist services as appropriate
Incontinence; Urinary Tract Infections; Urinary reflux	Treat using standard techniques; consider referral to urology if persistent
Ear infections (usually early childhood)	Treat using standard techniques; Consider referral to ENT if persistent
Eyes: strabismus; ptosis; eye-tracking; nystagmus; Astigmatism; myopia/hyperopia	Optometry
Sexual Health: males, macroorchidism, particularly after puberty	
Diet: needs to be balanced; being overweight can be an issue in older children/adults	Dietician, nutritionist
Speech: can be non-verbal; making sounds; forming words; speech perseveration; echolalia pragmatic speech, communication skills	Speech and language therapy
Coordination issues: Fine motor (eating, writing); Gross motor (uneven gate in walking/running, difficulties in throwing/catching, proprioception)	Physiotherapy; occupational therapy
Behavioural Issues: outbursts; impulsivity; aggression towards self and others; feeding issues; lower tolerance of unexpected changes/ transitions	Consider referral to Child and Adolescent Mental Health Services (CAMHS), management is multidisciplinary and dependent on specific problem to be addressed. Specialist OT/BT can provide aids and interventions, e.g., visual schedules.
Sensory processing difficulties; tactile defensiveness; sensory overload	Referral to specialist OT
Psychiatric Issues and neurodevelopmental diagnoses: ADHD; autism; anxiety; depression; phobias; other anxiety-related issues	Referral to mental health services
Relational issues: difficulty relating to others; extreme shyness; oversensitivity to perceived rejection or criticism; making and sustaining friendships; vulnerability to exploitation	Social care support, consider referral for psychological therapy if individual work is appropriate.
Life issues: difficulties with transitions; managing independent living skills (e.g., travel, using money)	Educational and/or Social Care Support
Intellectual Disability and cognitive skills: including poor attention; executive function; sequencing; working memory; verbal comprehension; and so forth.	If appropriate, referral to Neuropsychology for tests to determine strengths and difficulties, with follow-up at 3-yearly intervals as necessary in childhood

high-palate, and elongated face (McKechanie et al., 2020). Typically, a GP will refer a child to a paediatrician for checks, and then a FXS test may be ordered. However, FXS is not always tested for and there are many stories in the fragile X community of diagnostic delay. The diagnostic odyssey can last years (Bailey et al., 2009), with a US study finding, on average, a 2-year delay in boys between first concerns noticed and diagnosis. A regional study in the United Kingdom found the time from birth to diagnosis in boys to be 2.83 years and girls 5.92 years (Smith et al., 2013). A protracted diagnosis is costly, with children being unnecessarily moved around the system, with symptomatic treatment, expert intervention, and access to support and services delayed. Early intervention is likely to prove more effective than delayed provision. For example, less speech therapy may be needed in the longer term if started earlier. An early diagnosis means behavioural and sensory integration therapies can be put in place before onset of severe behavioural or sensory symptoms. There is a body of evidence for related conditions, such as autism, which shows the efficacy of early intervention (Landa, 2018); and material, for example, from the American Journal of Occupational Therapy, proving the benefits of early occupational therapy support from birth (Clark & Kingsley, 2020). While there is a paucity of research on the benefits of early intervention in FXS specifically, preliminary evidence suggests that early intervention and treatment can have significant improvements on cognitive and behavioural functioning for young children with FXS (Winarni et al., 2012).

Despite the potential effectiveness of early intervention, babies are currently not screened at birth for FXS unless there is a family history of fragile X (Lee et al., 2020). The inclusion of FXS in newborn blood spot screening is desired by the fragile X community (Boardman, 2021) and the efficacy of newborn blood spot testing has

been demonstrated. Relevant authorities should consider the potential inclusion of FXS in newborn screening programmes.

Diagnostic methods have evolved over the years and reports of cytogenetic testing or Southern blotting may still be found in some patients' notes. However, diagnosis is now usually achieved with initial use of a simple PCR-based test. In the absence of one allele, a modified PCR and/or methylation studies of the *FMR1* gene promoter may be used to demonstrate expansion of the CGG repeat. As methods of DNA sequencing improve, especially long-read sequencing, this approach may be used instead. FXS is included in the NHS Genomics Test Directory, with referral by paediatrician, geneticist, psychiatrist, or neurologist (NHS England, 2023). Those with FXS typically have an expanded CGG repeat of over 200 in the 5′ untranslated region of the *FMR1* (fragile x messenger ribonucleoprotein 1) gene at Xq27.3 (Fu et al., 1991). Set against an average of 30 CGG repeats in the general population, those who have between 55 and 200 repeats are described as having the fragile X premutation. It should be noted that modern testing can also identify mosaicism, meaning that only some cells have an expanded repeat. Adults with FXS and a higher IQ, who may have had a diagnostic test many years ago should be offered another test to determine whether they are actually mosaic (Biancalana et al., 2015).

There is inequality between genders, with many girls with FXS going undiagnosed and hence being unsupported throughout their entire lives, unless they are tested for FXS following a (typically male) diagnosis in their family (Bartholomay et al., 2019). Girls are affected, some severely and others in less obvious ways (Lightbody et al., 2022). A review of the health data from 3.8 million people showed the underdiagnosis and health inequalities evident in FXS: 'The estimated rate of underdiagnosis in women was considerably higher than in men (86.75% vs. 61.06% in Marshfield Clinic; 71.88% vs. 58.04% in UW Health)' (Movaghar et al., 2021). Several families reported receiving little or no support from paediatricians for their daughters with FXS, with FXS females, or those with the premutation generally thought to be 'unaffected' by professionals (Crawford et al., 2022).

Once there is a diagnosis, the family should be seen by a geneticist and/or genetic counsellor, who will map inheritance and then offer further testing to other family members who may be either affected or carriers of a full or pre-mutation. Reproductive options should be discussed if appropriate, including preimplantation genetic testing (PGT) for future pregnancies.

5 | MANAGEMENT

The nature of FXS is such that there is not a one-size-fits-all treatment. There is no cure, but symptoms can be alleviated by a wide range of interventions which are well-documented and evidenced: 'Early non-drug interventions in combination with symptom-based and core-symptoms targeted treatments pharmacotherapy is the main management in individuals with FXS' (Protic et al., 2022). Another overview of pharmacological and non-medical treatment options is in Jalnapurkar et al. (2019). A recent report highlights the importance of coordinated care in rare diseases, with benefits including the effective management of complex medical care; aiding the transition from child to adult services; and 'bridging the gap between healthcare and other services' (Genetic Alliance UK, 2023). The next section will look at FXS through the life course and set out management options as appropriate. A chart of symptoms and referral guidance is found in Table 1.

6 | FRAGILE X SYNDROME THROUGH THE LIFE COURSE

Specific research on FXS is limited, but the following is a first step towards integrating existing guidance from related conditions with relevant research specific to FXS, incorporating family perspectives. These are not intended to be comprehensive guidelines for FXS, but rather to cover some of the main areas of difficulty that may be experienced. While it is important to have guidelines for the person with FXS, families also ask that a holistic approach is taken with support and guidance for the entire family (e.g., parents, siblings, and the wider family). Offering guidance at the family level is particularly important given that parents of children with FXS often report clinically significant levels of mental health difficulties and stress which can negatively affect how parents view their relationship with their partner and children, finances, employment opportunities and coping abilities (Iriarte-Redín et al., 2020; Ouyang et al., 2014; Potter et al., 2022). This whole-family dynamic will be paramount for each stage of FXS through the life-course.

6.1 | Infancy

Infants with FXS may experience delays in muscular development which may affect them in a variety of ways: sucking (therefore feeding issues); holding their head up; crawling; first steps; and so forth. Connective tissue abnormalities may be seen with hyperextensibility and joint laxity apparent (Wheeler et al., 2021). Early referral for physical therapy should be considered (Lieb-Lundell, 2016). There may be gastro-intestinal issues, for example, reflux, and otitis media is also common. Both are easily treatable and should be considered in an upset infant. Related to the connective tissue abnormalities, mitral valve insufficiency may be noted on physical examination, although clinical manifestations are often not apparent in early life (Lozano et al., 2016). FXS infants may have heightened sensory awareness (Lachiewicz et al., 2023) and may therefore benefit from OT assessment and support (Jalnapurkar et al., 2019; Protic et al., 2022). There may be sleep issues (Budimirovic, 2022), in which case it is important that support is offered as would be the case for other developmental conditions (NICE, 2021a). Poor sleep has been linked to negative health outcomes for mothers of children with FXS (Dembo et al., 2023).

Parental support in the early days is key for the reasons listed above and also because the FXS infant may not bond in expected

ways (Roberts, Crawford, Will, et al., 2019), for example, eye contact and tactile defensiveness may be issues (Roberts, Crawford, Hogan, et al., 2019). Practitioners should help the parents support their infant in the best possible way, but also alleviate the feelings of helplessness of not knowing what to do with a baby who is not responding as expected. A person-centred approach is necessary, as infants will differ in how FXS affects them, and a holistic, family-inclusive plan helps to nurture the infant in the best way possible.

6.2 | Childhood

Parents report that many young children with FXS enjoy being in toddler groups, play groups, and early educational settings. A child with FXS can be a happy child, although self-injurious behaviour, aggression, and property destruction are reported in around 40% if individuals (Hardiman & McGill, 2017). Temper outbursts may be related to frustration and difficulties communicating, as well as sensory hypersensitivities. Appropriate support should be put in place to facilitate their inclusion in educational settings, as are suggested in guidelines for young people with autism (NICE, 2021b). These include consideration of the sensory environment and reasonable adjustments available to manage this, as well as support for effective communication. Input from occupational therapists and speech and language therapists may be required to support staff in developing and implementing recommendations. For those with persistent behavioural challenges which are not easily understood then input from a clinical psychologist is likely to be helpful to determine the triggers of undesirable behaviours and develop appropriate interventions (Crawford et al., 2019). Such professional advice would help mitigate outbursts and effect a more productive learning environment. Children with FXS often learn by mimicry; therefore, good modelling is beneficial to social and emotional development. They have strengths, such as great senses of humour, fantastic recall, honesty, an affinity to defined schedules, which should be identified and celebrated. School exclusions and being told off for undesirable behaviour is not helpful. Helping playgroup leaders and educators understand FXS is key to achieving best outcomes.

For both genders, evidence suggests that early speech therapy is key to developing effective communication strategies (Fielding-Gebhardt et al., 2020). Autism is frequently diagnosed in children with FXS, with around one-third of those with FXS also having an autism diagnosis (Doherty & Scerif, 2017; Kaufmann et al., 2017). Formal diagnostic assessment for autism should be considered (although may not be necessary) for all children with FXS.

ADHD is also prevalent (Doherty et al., 2020) and diagnostic assessment should be considered for those with significant impairment relating to in attention, hyperactivity, or impulsive behaviour. OT advice is especially useful to optimise the learning environment. One small study has reported potential benefits from stimulant use in FXS, but more evidence is needed before definitive recommendations can be made. Pragmatically, a trial of anti-ADHD medication is reasonable for those individuals with significant functional impairment who do not respond to non-medication interventions alone. Should stimulant medication not be tolerated then non-stimulant medication should be trialled (Eley et al., 2022; Hagerman et al., 2009).

Neuropsychiatric testing, specialist paediatric neuropsychologist and/or educational psychologist assessments can help determine strengths and difficulties (Huddleston et al., 2014). Ideally, these should be done at transitional milestones during childhood, so that schools are best placed to offer appropriate support. Testing can include assessments in language comprehension (receptive vocabulary, as this is often reported as a strength), expression (expressive vocabulary is often reported as more delayed than receptive language and characterised for some by repetitions) and pragmatics (i.e., social comprehension and use of language) (Finestack et al., 2009). Numerical skills should be captured early, as these are often reported as a weakness later in life (Rivera et al., 2002), so that early play-based approaches may be beneficial before difficulties are fully embedded. Attention (e.g., focus, avoiding distraction) and executive demands (e.g., planning, remembering goals, flexible thinking) can be a challenge (Guy et al., 2020), so they must be supported throughout early learning environments.

In terms of physical health, epilepsy develops in ~12% of children with FXS, and should trigger referral to neurology. The mean age of onset is 6.4 years old and over 80% have onset before the age of 10 years old. Seizures are variable in nature and severity but are often relatively mild and improve with age (Berry-Kravis et al., 2021). Ongoing issues with reflux and otitis media can also be seen. Connective tissue problems should be actively enquired about, including any symptoms of mitral valve disease. A small number of children may develop sleep apnea and referral to a sleep clinic may be required where there are concerns around the typical symptoms of this condition (Budimirovic et al., 2022). Sleep itself may be disrupted in FXS and may be helped by the promotion of a bedtime routine and good sleep hygiene. Melatonin has been suggested to be useful (Wirojanan et al., 2009) although it should be acknowledged that the effects of long-term melatonin use are not well described.

6.3 | Adolescence

Puberty can lead to macroorchidism in males. Females may become upset with the onset of menses and need sensitive support in coming to terms with the changes in their bodies. In both genders, there is an increased vulnerability to being taken advantage of. This will differ from person to person, but oversight should be given to sexual education, including what it is appropriate to discuss or do in public, as boundaries will need to be explained in a caring and affirming way.

Relationship education is also important. This would include how to make and maintain friendships, and also issues around having a partner. Conversations around their desires are important, and these could be had with, for example, a psychologist or counsellor skilled in supporting someone with an intellectual impairment. Pragmatic speech therapy is also useful, as learning skills in communication will help with relationships and developing independent living skills.

While both young men and women are likely to experience clinically significant anxiety during adolescence, anxiety, specifically social

and generalised anxiety, is of particular concern for girls and young women with FXS (Cordeiro et al., 2011; Crawford, Moss, et al., 2020; Lightbody et al., 2022). Targeted therapeutic and behavioural interventions may be appropriate avenues of support to ameliorate anxiety for both males and females; however, a clinical psychologist can design an individualised treatment plan that best supports the adolescent with FXS. When medication is being considered then (in the United Kingdom) referral to psychiatry is required. There is no FXS specific evidence for the use of medications to manage anxiety. One study of sertraline, an SSRI often used for anxiety, was found possibly to be helpful in 2–6-year-olds with FXS, although the study did not consider anxiety per se (Hess et al., 2016). Cannabidiol is also a potentially promising treatment for anxiety (Berry-Kravis et al., 2022), although at the present time Phase III trial results are awaited. Broadly speaking though, treatment choices for anxiety are based on evidence from the general population and other populations with intellectual disability/autism. General principles of starting at a low dose and escalating slowly should be observed as side effects may be more common. When an SSRI is required, it would seem sensible to prescribe sertraline given Hess et al. (2016).

Behavioural difficulties, such as self-harm and aggression, may become more apparent or problematic during adolescence. A multidisciplinary approach is recommended, incorporating the aforementioned approaches and following the NICE guideline for Challenging Behaviour in Learning Disabilities (NICE, 2015). When medication is used for behavioural difficulties, especially in the absence of a mental health diagnosis or ADHD, then clear goals for treatment should be decided beforehand and the use of medication should be monitored regularly and consideration given as to whether it remains necessary, as per NICE guidance (NICE, 2015).

Secondary education may lead to vocational education, but may also, particularly in the case of some girls with FXS, lead to university. There is every reason to put supports in place and to continue to evaluate what best helps the young person learn as they move through education. An adolescent with FXS may take longer to learn but can learn. Some subjects, such as maths, may prove extremely difficult and need a lot of support, but other subjects may be more accessible and achievable. Again, a person-centred approach is necessary, with no limitations put in place but instead a lot of positive support and encouragement. The focus should be on playing to the strengths of the person with FXS.

Ongoing monitoring of physical issues is required, including specific enquiry for the common conditions described in earlier sections. In general, connective tissue abnormalities are likely to increase with age so the emergence of new symptoms must always be considered (Lozano et al., 2016).

6.4 | Transition to adulthood

In England, Education, Health and Care Plans, and in Wales, Additional Learning Needs provision, can last until the age of 25 and provide scope for the person with FXS to continue supported learning into young adulthood. Families have identified that more support is needed for the young person's transition to adulthood. Much service provision (e.g., CAMHS) ends at the age of 18, and then it is a sudden jump to adult services, for which provision varies substantially across the country. Clear guidance on what is helpful for that transition will unify the approach to helping someone with FXS successfully transition into adult life, in particular adopting the 'whole life' approach recommended by NICE (2019). Independent living skills continue to be acquired through adolescence and into adulthood (Bailey et al., 2009), and efforts should be made to enhance their development. A recent report (Cambridge Rare Disease Network, 2022) into the challenges of transition in the context of rare diseases included suggestions such as starting the transition early, having a designated transition coordinator, and holding regular multidisciplinary team meetings.

In England (NHS, 2022) anyone aged 14 and over who is on their GP's disability register can have an Annual Health Check. In Wales (National Centre for Mental Health, 2023), a Welsh Health Check is available from age 14 for those with a learning disability (NHS Wales, 2023); and in Scotland, Annual Health Checks for those with learning disability are now available from the age of 16 (Scottish Government, 2022). Families have reported that these annual checks are not broad enough and do not pick up on some of the health concerns families may have. Mental health issues are flagged by families as not being considered, and the lack of physical appointments since COVID has led to limited annual checks, sometimes conducted virtually or via telephone. Given the difficulties in eliciting symptoms and engaging through virtual methods, it is recommended that someone with FXS should always be seen in person for annual checks, assessments, mental health concerns, or therapies. The Royal College of General Practitioners previously published guidance around annual checks for people with a learning disability, including specific guidance on health checks for individuals with FXS (Hoghton, 2010). Cerebra's *Be Well Checklist* has been highlighted as a positive step forward, helping to create a dialogue for families and clinicians around the annual health check (Cerebra, 2023).

6.5 | Adulthood

Annual health checks continue into adulthood, either through a GP or a specialist learning disability team. It is recommended that annual checks should consider both physical and mental health needs.

In some cases, those with FXS may lack mental capacity to make some decisions. Each of the UK legislatures has in place systems for the appointment of proxy decision-makers and families/carers should be encouraged to explore this. However, where a person with FXS has capacity to make their own decisions, this must of course be respected. Some adults will wish to live independently; some will need to be in supported living; others may wish to remain in the family home. Social care services should work with those with FXS and their families to explain the options available. Social services should also offer advice on benefits available and support in accessing those

funds. The person with FXS may need support in managing their finances and help in being as independent as possible. Having a job and being integrated into community life is important for wellbeing and should be facilitated as much as possible.

It is important that adults do not become isolated. Many with FXS find social interaction difficult, experience social anxiety, or have communication difficulties. Putting in place a range of activities to maintain fitness and social interaction is important. Being overweight can become an issue, so healthy eating and good exercise habits should be set out and encouraged.

6.6 | Older adults

All the above issues may still be relevant. Further, older adults may not have family support as parents die and extended families move on; they may need to be cared for in small group care homes. It may be helpful to produce documents to advise those caring for older adults on their individual preferences and wishes. If an older person with FXS has capacity to do so, they may wish to make an advanced decision regarding what medical treatment they would want and/or a document setting out their wishes if they become seriously ill.

Less is known about the physical effects of FXS in the older adult, with more research needed in this demographic. Analysis in 2010 of data held of persons with FXS over 40 years old showed that the most common medical issues were 'neurological problems (38.7%), gastrointestinal problems (30.6%), obesity (28.8%), hypertension (24.2%) and heart problems (24.2%)' (Utari et al., 2010). A 20-year follow up of males with FXS identified that characteristics evident in childhood (e.g. poor eye contact, hyperactivity, tactile defensiveness, perseverative speech) persisted into older adulthood (Arvio, 2016). There is some evidence that people with FXS may be more prone to earlier cognitive decline than the general population (Sauna-aho et al., 2020), though larger studies will be needed to confirm this. Some people with FXS may be at risk of developing a condition called FXTAS (Fragile X Associated Tremor Ataxia Syndrome) which is usually found in premutation carriers (see below) and has a different pathophysiological mechanism than FXS. However, many people with FXS are actually mosaic (up to 40%) for both the full mutation and the premutation, and so there is the possibility they will develop some of these symptoms (Schneider et al., 2013). Premature cognitive decline or the emergence of neurological symptoms should precipitate a referral to neurology for review.

7 | FRAGILE X PREMUTATION ASSOCIATED CONDITIONS

The remit of this article is guidance for FXS; however, the wider family may be affected by carrier issues, and it is important that professionals treating the person with FXS are aware of these, including that ovarian dysfunction may arise in younger women and a pattern of neurodegeneration in late middle age, in either sex (McKechanie et al., 2019). If 1 in 200 people carry the premutation, then there are potentially 340,000 people in the United Kingdom who may experience FXPAC. There is ongoing research on how carriers may be affected, which is complicated by what symptoms are naturally occurring in the population and those which might be directly linked to being a *FMR1* carrier (Allen et al., 2020). One population study in Wisconsin determined that there was a higher prevalence of certain conditions within the FMR1 carrier population (Movaghar et al., 2019). Table 2 contains an overview of how premutation carriers may be affected, listing possible symptoms and issues.

Research in FXPAC is burgeoning, as evidenced in the comprehensive review and papers published in summary of the 5th International Conference on the FMR1 Premutation (Tassone et al., 2023).

TABLE 2 Fragile X Premutation Associated Conditions: symptoms, management, and support.

Possible issues	Treatment/support
Females: FXPOI (Fragile X-associated Primary Ovarian Insufficiency: irregular menses; POF (premature ovarian failure); early menopause	POI clinic if available; Gynaecology; refer to local specialist clinic for early menopause. Further info: https://www.daisynetwork.org/ Daisy Network (2023)
Family planning/fertility issues	Geneticist; Fertility clinic (PGT possibly)
Females: osteoporosis (related to low-hormone levels/FXPOI/early menopause)	Identify and treat as appropriate
FXTAS: usually seen in carriers over 50: tremor; memory difficulties; balance problems; neuropathy; personality changes (mood instability; irritability); short-term memory issues; anxiety and depression	FXTAS clinic; Ataxia clinic; Neurology; PT and OT
Psychiatric issues: Anxiety, depression	Identification is key; treat using standard approaches; refer to mental health services when required
Thyroid issues: hypothyroidism	Screening; treat using thyroxine if required
Fibromyalgia: muscle pain, chronic pain	Identify and refer to specialist services when required.
Chronic fatigue syndrome	Identify and refer to specialist services when required.
Migraines	Identify and refer to specialist services when required.
Cardiovascular problems: likely increased risk for hypertension and potentially other cardiovascular conditions (Tassanakijpanich et al., 2020)	Identify and treat as appropriate, with referral to Cardiology as necessary.

Fragile X-associated Primary Ovarian Insufficiency (FXPOI) may affect around 20% of female carriers (Allen et al., 2018); and Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) may affect both genders over the age of 50 but is seen more commonly in male carriers (40%) and less in females (8%–16%) (Leehey et al., 2016). FXTAS is a degenerative neurological condition characterised by tremor, ataxia, and gradual cognitive decline. Those who are carriers may also wish to consider reproductive issues and make choices around future pregnancies. One option may be to access pre-implantation genetic testing (PGT). FXS is included on the list held by the Human Fertilisation and Embryology Authority of conditions for which a fertilised egg may be screened (HFEA, 2023). Fragile X Associated Neuropsychiatric Disorders (FXAND) was coined in 2018 (Hagerman et al., 2018) to draw attention to the more severe psychiatric symptoms which some with the FMR1 premutation may experience, though the patient community has expressed a preference for the term Fragile X Associated Neuropsychiatric Conditions (FXANC) (Johnson et al., 2020) as many with the FMR1 premutation experience milder forms of mental health issues which do not fit the diagnostic criteria for psychiatric disorders as outlined in DSM-5. Needless to say, the umbrella term FXPAC, accepted by both clinicians and patients, covers the full spectrum of how premutation carriers may be affected.

8 | CONCLUSION

A holistic approach to FXS is needed, one which includes health, social, emotional and educational aspects. Early diagnosis of FXS is key—with proper planning and supports, an infant with FXS will have the best chance possible to live a settled and happy life. This article has looked at the stages of FXS, though how this plays out in individuals can vary between genders and be affected by home environment and the levels of support put in place. Person-centred care is necessary, as the combination of symptoms in how FXS affects each person is unique to them. Needless to say, a child with FXS who is isolated, denigrated, seen as hopeless and therefore neglected, will have a completely different outcome from one who is loved, supported, integrated into family and community life, and enjoyed. The hope is that clear professional guidelines will enable structures and treatments to be put in place to give persons living with FXS the security and support they need to live fulfilled lives. These could take the form of online resource in traditional forms, or be a digital navigation guide for both clinicians, families, educators, therapists, and all those involved in the support of the person living with FXS to access. The development of integrated guidance would greatly help the 14,000 people and their families living with FXS in the United Kingdom.

AUTHOR CONTRIBUTIONS

Angus Clarke: Writing (supporting). **Hayley Crawford**: Writing (equal). **Jonathan Herring**: Conceptualization (lead); writing—original draft (lead); writing—review and editing (equal). **Kirsten Johnson**: Conceptualization (lead); writing—original draft (lead); writing—review and editing (equal). **Andrew McKechanie:** Writing—review and editing (equal). **Gaia Scerif:** Writing—review and editing (equal). **Kayla Smith:** Writing—(supporting). **Andrew C. Stanfield**: Writing—review and editing (equal).

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