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Research Gaps in Fragile X Syndrome: An Updated Literature Review to Inform Clinical and Public Health Practice

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ABSTRACT: ***Objective:*** **The phenotypic impact of fragile X syndrome (FXS) has been well-documented since the discovery of the fragile X messenger ribonucleoprotein 1 gene 30 years ago. However, gaps remain in clinical and public health research. The purpose of this literature review was to determine the extent to which these gaps have been addressed and identify targeted areas of future research.** ***Methods:*** **We conducted an electronic search of several scientific databases using a variety of key words. The search focused on 5 areas identified as research gaps by an earlier review: (1) diagnosis, (2) phenotypic presentation, (3) familial impact, (4) interventions and treatments, and (5) life span perspectives. Inclusion criteria included publication between 2014 and 2020, focus on human subjects, and publication in English. A total of 480 articles were identified, 365 were reviewed, and 112 are summarized in this review.** ***Results:*** **Results are organized into the following categories: (1) FXS phenotype and subtypes (FXS subtypes, medical profile, cognitive/developmental profile, social and behavioral profile); (2) needs of adults; (3) public health needs (clinical diagnosis and newborn screening, health care needs, and access); (4) treatment (treatment priorities, pharmacological treatments, and behavioral and educational interventions); and (5) families (economic burden and mother-child relationship).** ***Conclusion:*** **Despite the progress in many areas of FXS research, work remains to address gaps in clinical and public health knowledge. We pose 3 main areas of focused research, including early detection and diagnosis, determinants of health, and development and implementation of targeted interventions.**

(*J Dev Behav Pediatr* 44:e56–e65, 2023) **Index terms:** fragile X syndrome, clinical phenotype, public health needs, treatment, family needs.

Fragile X syndrome (FXS) is the leading known single-gene cause of intellectual and developmental disabilities. Expansions of trinucleotide repeats cystosine-guanine-guanine (CGG) on the 5′untranslated region of the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene, located on the X chromosome, affect the production of fragile X messenger ribonucleoprotein (FMRP), which is crucial for brain development. Individuals with more than 200 CGG repeats have the full mutation, or FXS, whereas those with 55 to 200 repeats are carriers of FXS, also referred to as having the *FMR1* premutation. Typically, male patients are more severely affected given the protective factor of a second X chromosome in female patients.

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The phenotypic impact of FXS has been well-documented since the discovery of the *FMR1* gene 30 years ago, including our own public health literature review that summarized research between 1991 and 2014.[1] The goal of the previous review was to identify what was known about FXS in the areas of development, social-emotional well-being, medical needs, treatment options, and the impact on the family. Five gaps were identified as areas in need of further research: (1) identification of FXS subtypes; (2) needs of adults with FXS; (3) public health needs, such as access to health care services; (4) efficacy of educational, behavioral, and pharmacological treatments; and (5) impact on families of individuals with FXS.

The purpose of this updated literature review was to examine the progress made in addressing these gaps and to summarize recent research. These updated findings can be used to inform both future research initiatives and clinical and behavioral health services for individuals with FXS and their families.

METHODS

A list of search terms are provided in Table 1. We limited our search to articles published since our earlier review (2014–2021) with samples of human subjects. Language was limited to English. The following databases were searched: PubMed, CINAHL, EBSCOhost, PsycINFO, and Web of Science.

Table 1. Search Terms and Inclusion/Exclusion Criteria by Topic Area

Topic Area	Search Terms
Diagnosis	(Fragile X syndrome) or (fragile X) or (FMR1) or (carrier) AND (Diagnosis) or (PCR) or (Southern blot) or (genetic testing) or (cascade testing) or (screening)
Phenotype	(Fragile X syndrome) or (fragile X) or (FMR1) AND (Phenotype) or (clinical presentation) or (clinical description) or (neurocognitive) or (cognitive) or (behavior) or (social-emotional) or (language) or (communication)
Familial impact	(Fragile X syndrome) or (fragile X) or (FMR1) AND (Family adaptation) or (family impact) or (family outcomes) or (burden) or (cost of care)
Interventions and treatments	(Fragile X syndrome) or (fragile X) or (FMR1) AND (Treatment) or (intervention) or (pharmacological) or (educational) or (behavioral) or (medication) or (clinical trial)
Life span	(Fragile X syndrome) or (fragile X) or (FMR1) AND (Life span) or (adolescent) or (adult) or (services) or (transition to adulthood)

Articles were reviewed using Covidence,[2] a systematic review management program designed to organize complex literature reviews. The results were uploaded into Covidence and screened by the study team to remove articles that were not applicable (e.g., animal models, individuals with *FMR1* premutation) or were covered in the previous literature review. The remaining studies were double-coded for inclusion based on relevance. Any discrepancies between reviewers were discussed and resolved. A total of 112 articles were included in the current review. Figure 1 depicts the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[3] flow diagram for this review.

RESULTS

The results from the systemic review are organized based on the research gaps identified in the previous literature review.

Fragile X Syndrome Phenotype and Subtypes

Medical Profile

Classic clinical features of fragile X syndrome (FXS) include an elongated face, broad forehead, prominent ears, and flat feet. Hyperflexibility of joints and connective tissue problems are also common. New evidence suggests that as adults, individuals with FXS may be at increased risk for a number of other medical problems, such as obesity, hypertension, and gastrointestinal disorders. In addition, seizures are a common comorbid feature. Female patients with FXS have a less severe presentation given the presence of a second unaffected X chromosome.[4] A review of neuroanatomical studies of individuals with FXS has shown dendritic spine abnormalities and changes in brain structure, and electroencephalogram (EEG) studies show alterations in gamma waves which correlate with clinical symptomology.[5]

Cognitive/Developmental Profile

Our earlier article[1] provides a detailed overview of the cognitive development of individuals with FXS. A recent review furthers this work by summarizing what is known about executive function in FXS.[6] Verbal and nonverbal working memory is impaired in individuals with FXS across the life span, although performance on tasks was dependent on cognitive load. Challenges with inhibitory control, cognitive flexibility, and processing speed emerge early in childhood and persist into adulthood.

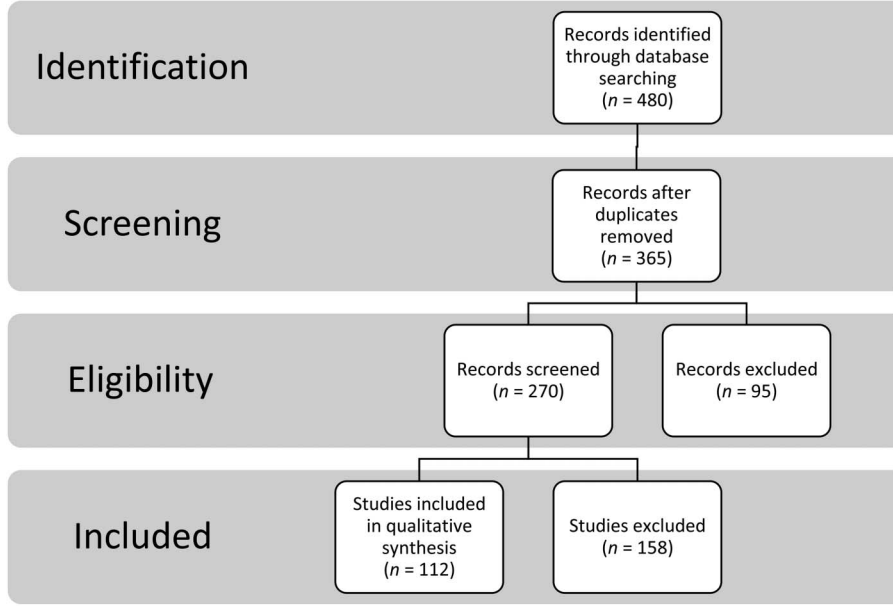

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram.

Attention is one of the core deficits in FXS, with impairments in both auditory and visual sustained attention when compared with chronologically age-matched and mental age–matched peers. In a study of infants with FXS, delays in overall development were seen as early as 6 months when compared with typically developing peers.[7]

Language development in FXS is well studied. Recent work adds to the knowledge base in receptive, expressive, and pragmatic development. Children with FXS show signs of receptive and expressive language delays as early as 12 months.[8] Early use of consonants during babbling and intentional communication, including the use of gestures, is predictive of later expressive language.[9] By the time of preschool, though, children with FXS have the ability to repair a breakdown in communication (i.e., when there is a miscommunication with a conversational partner), indicating well-developed language and social skills. In addition, maternal language plays a role in language development. Maternal commenting is associated with receptive, but not expressive, vocabulary from early childhood into adolescence.[10] Maternal pragmatic language is associated with receptive and expressive vocabulary in adolescents and young adults.[11] Although receptive language ability is lower in children and adolescents with FXS than those who are typically developing, it is a relative strength when compared with ability levels of those with autism spectrum disorder (ASD) or Down syndrome.[12,13]

Children with FXS continue to make improvements in their functional skills into middle childhood, at which point cognitive development begins to slow. However, those with lower nonverbal developmental scores or more ASD symptoms had different growth patterns and less overall skill attainment when examining raw scores.[14] Over time, male patients with higher adaptive behavior age-equivalent scores in early childhood had fewer aberrant behaviors at age 10 years.[15] When compared with typically developing children, those with FXS show plateaus or declines in their adaptive behavior over time, suggesting that those with FXS overall have a lower rate of skill attainment.[16] Cross-sectional studies have found similar patterns when comparing young children with FXS with their same-aged peers.[17] Another study, though, showed that adaptive skills, in particular standard scores for communication and social ability, improved over time.[18]

Social and Behavioral Profile

In a recent review of behavioral concerns, prevalence estimates across studies for individuals with FXS were 48.8% for self-injury, 35.8% for aggression, and 24.5% for destruction, with male patients significantly more likely than female patients to engage in any type of challenging behavior.[19] When compared with male patients with mixed-etiology intellectual disability, male patients with FXS had higher rates of self-injury and specific forms of aggression, such as scratching or biting others.[20,21] Functional analysis of these behaviors has shown that social or environmental factors, including gaining attention or access to preferred objects or escaping from social demands, reinforce and maintain these challenging behaviors.[22]

Other behavior problems include restrictive and repetitive behaviors and sensory issues. Cross-sectional studies across the life span show peaks in sensory-motor behaviors between ages 2 and 12 years and in restricted and repetitive behaviors between ages 7 and 12 years.[23] Restricted interests, such as being strongly attached to one specific object and fascination with one subject or activity, were rated as moderate to severe.[24] Studies differ, however, on whether restrictive and repetitive behaviors are related to an individual's intelligence quotient (IQ).[23,24] Recent studies exploring sensory processing indicate that hypersensitivity to visual, auditory, or tactile stimuli may be the underlying issue in behavioral challenges in individuals with FXS.[25,26]

Social avoidance is a key characteristic that emerges in male patients as early as infancy, with increases into middle childhood but steadying in later years.[27] During observational assessments, eye contact avoidance, in particular, was evident in adolescent and young adult male patients, especially in those with more ASD symptoms. Alternate measurement techniques of social avoidance have been developed, including caregiver-completed assessment scales,[28] other observational rating scales,[29] and eye-tracking techniques.[30]

Fragile X Syndrome Subtypes

One of the gaps we identified in our earlier article was lack of information regarding subtypes of the FXS phenotype. Since then, our understanding of the FXS phenotype has continued to grow, with increased focus on genotype-phenotype associations and neuroanatomical correlates of clinical features. Mosaicism (i.e., variation in CGG repeats across different cell types) and methylation status (i.e., variation in FMRP levels across different cell types) are now well-known molecular indicators of phenotypic impact.[31,32] Research uncovering novel mutations and mosaic genetic presentations on the *FMR1* gene have helped to identify disruptions on specific exons and untranslated regional variations, which have implications for the function of FMRP and the variable phenotypic expression seen in FXS.[33,34] Studies have explored how FMRP acts as a regulator and affects clinical features in individuals with FXS.[35,36] In 1 study, as FMRP levels decreased below 70% of the mean for unaffected individuals, individuals with FXS had declining IQ scores. An average FMRP level of 35% below the mean was needed for individuals with FXS to reach an IQ of 85 or 1 SD below average.[37] Given the role FMRP plays in cognitive functioning, studies have suggested it as a therapeutic target.[38] However, challenges remain in accurately measuring FMRP in different sample types (e.g., blood versus buccal cells).[35]

Work on identifying phenotypic subgroups in FXS has continued to emerge. One study examined how best to diagnose ASD in individuals with FXS using FX-specific

versions of the Social Communication Questionnaire and the Social Responsiveness Scale.[39] Additional studies have examined behavioral differences in those with FXS only compared with those with FXS and ASD. In keeping with earlier work, individuals with FXS and ASD show more severe behavioral problems, challenges with receptive and expressive language and social interaction, and greater cognitive impairment.[40–42] A second subgroup, those with both the FXS and the Prader-Willi phenotype, is marked by obesity, hyperphagia, and delayed puberty, with about half also diagnosed with ASD.[43]

Needs of Adults with Fragile X Syndrome

A second gap in the literature we identified in our earlier review was a lack of understanding of the needs of young adults, middle-aged adults, and seniors living with FXS. Individuals with FXS live, on average, to age 87 years,[44] underscoring the importance of understanding the trajectory of adult needs in this population.

Over the past several years, there have been a handful of studies describing the phenotype of adults, although mostly in young to middle adulthood. Receptive language skills continued to be a relative strength in adults when compared with expressive ability.[45] In a large-scale survey study, young adults aged 18 to 21 years had more ASD symptoms than middle-aged adults. Eye contact continues to be a deficit for adults with FXS.[46] Despite these challenges, adolescents and adults with FXS were more likely to engage in hobbies, spend time with friends or neighbors, and have a mutual friend when compared with those with ASD.[47]

Positive findings also emerge when functional and behavioral skills are examined into adulthood. Although some studies have found plateaus or even declines in functional skills, a longitudinal study of adolescents and adults showed some growth in adaptive behavior over time. Behavior and internalizing problems were inversely related to age. Maternal criticism was a significant predictor of behavior problems and externalizing problems.[48] IQ[48–50] and executive function[50] have been shown to be strongly associated with functional skills.

Public Health Needs

Another major gap in knowledge previously identified was the public health needs of individuals with FXS. These needs were categorized into (1) clinical diagnosis and newborn screening and (2) health care needs and access.

Clinical Diagnosis and Newborn Screening

Traditionally, diagnosis of FXS is performed clinically after the onset of symptoms.[51] However, this process can be long and arduous for families, with a mean age of diagnosis around 32 months and fewer than 20% of children receiving a diagnosis within the first year of seeking medical attention.[52] There have been efforts to decrease the diagnostic odyssey and improve the process for receiving a clinical diagnosis, including carrier screening of women before or during pregnancy,[53–55] preimplantation genetic testing,[56,57] and newborn screening.

Newborn screening for FXS in both male patients and female patients is supported by most developmental and behavioral pediatricians. However, voluntary screening is preferred over mandatory.[58] Voluntary screening in hospitals shortly after birth is possible, but challenging. In a multisite US study of 28,000 newborns, two-thirds of parents were willing to have their child screened, but educational materials were essential in supporting informed decision-making.[59] A smaller-scale study in Australia found higher rates of consent, with 94% agreeing to screening.[60] More recently, a statewide, voluntary newborn screening study conducted in North Carolina was implemented as a partnership between public health staff and researchers. One of the main considerations was how to best recruit families.[61–63] Barriers to full-scale newborn screening for FXS include public health burden to conduct the screening; the need for inexpensive, high-throughput screening methodologies; lack of demonstrated treatment for asymptomatic children; and insufficient capacity for long-term follow-up.[64,65]

Health Care Needs and Access

Indirect and direct health care costs are sizable for individuals with FXS. Using Medicare/Medicaid administrative claims data, annual all-cause health care costs ranged from $2222 to $9702, with higher costs in the Medicaid cohort. Main cost drivers included medical procedures, both routine (e.g., office visits, immunizations) and nonroutine (e.g., laboratory tests, therapies, anesthesia), followed by hospitalizations in a subset of individuals, and finally medications.[66] Studies in Europe have also found high health care and caregiver burden costs, with non–health care costs (e.g., informal care) being the main contributor.[67,68] Direct and indirect health care costs are higher for those with FXS and their families than those without FXS.[69,70]

In a survey study of over 600 caregivers of individuals with FXS, 20% reported having difficulty accessing specialty services, and nearly 40% indicated that their child's primary care provider was not knowledgeable about FXS.[71] Parent-reported data of preventive care services have shown that 92% of individuals with FXS met immunization guidelines and 75% met dental care guidelines, but only 55% met influenza vaccination guidelines, and just 24% met physical activity guidelines.[72]

Treatments for Fragile X Syndrome

At the time of our 2017 literature review, a noted gap was lack of research to explore the impact of symptom-based pharmaceuticals and behavior-based interventions. In the intervening years, however, there have been extensive studies focused on identifying treatment priorities, pharmacological treatments, clinical trial, and educational and behavioral interventions.

Treatment Priorities

Stakeholder involvement from the beginning of treatment development is considered best practice.[73] As such, understanding the perspectives of parents and individuals with FXS has been a key goal over the past few years. In a study of treatment targets, 439 family members of at least 1 individual with FXS indicated that medications to address anxiety, learning, and behaviors such as tantrums and aggression were their top priorities.[74] Similarly, Cross et al. [75] found behavior and self-care to be the most important targets for treatment for caregivers across age groups. Parents are generally supportive of pharmacological clinical trials, yet there may be concerns about safety and long-term implications for their child in the decision process.[76] Concerns about side effects, swallowing tablets, blood tests, financial costs, and travel can be barriers to participation in clinical trials,[77] as are misunderstanding of the objectives of pharmacological clinical trials[76] and the likelihood that their child will experience a direct benefit.[78]

Pharmacological Treatment

Psychotropic medications are used by more than two-thirds of adolescents and adults with FXS, whereas a quarter are likely to use nonpsychotropic medications.[79] Once on a medication, individuals with FXS were more likely to stay on medication over a 3-year period. Those with more autism symptoms, behavioral challenges, and greater family incomes were more likely to use psychotropic medications. In a review of psychopharmacological management in FXS, Eckert et al. [80] analyzed the use of medications to address irritability, aggression, agitation, and self-injury in 415 individuals with FXS. The most commonly used medications identified were the antipsychotics aripiprazole and risperidone (used by 37% and 27%, respectively), with most users experiencing no side effects from these medications. Psychopharmacological management tended to be accessed more often by older male patients who had more significant impairments. A retrospective analysis of the use of risperidone in conjunction with other nonantipsychotic medications to target irritability in 32 male patients with FXS found a 33% responder rate,[81] leading to a conclusion that monoantipsychotic treatment with risperidone is limited in FXS.

Clinical Trials

Clinical trials of gamma-aminobutyric acid (GABA) modulators, including ganaxolone (a $GABA_A$ receptor agonist) and arbaclofen (a $GABA_B$ receptor agonist), and amino-terminal tripeptide of insulin-like growth factor 1 (i.e., trofinetide), have been used to target the core pathophysiology of FXS. A randomized, double-blind, placebo-controlled trial of ganaxolone[82] in children with FXS did not meet primary (i.e., Clinical Global Impression-Improvement scale) or secondary (e.g., Pediatric Anxiety Rating Scale–Revised) study end points. However, post hoc analyses showed a trend in reducing anxiety, hyperactivity, and social avoidance for a subset of participants who entered the study with higher anxiety or lower IQ scores. A phase 3 trial of arbaclofen[83] demonstrated positive change in children who were on the highest dose (10 mg TID), with lower irritability and parenting stress scores; scores for social avoidance and hyperactivity trended toward statistical significance. More recently, a phase 2 trial of trofinetide demonstrated benefit, with individuals in the treatment group having lower clinician-reported and parent-reported symptom scores on 3 core efficacy measures.[84]

Other trials targeting cognition and/or behavior have found moderate success. A small study of individuals with FXS who received between 2.5 and 10.0 mg of donepezil, an acetylcholinesterase inhibitor, did not demonstrate change on cognitive or behavioral outcomes.[85] However, after 12 weeks of treatment, improvements were seen on direct versus averted gaze as measured by functional magnetic resonance imaging. In a randomized, double-blind, placebo-controlled trial of sertraline,[86] a selective serotonin reuptake inhibiter, children with FXS showed improvements in secondary end points, including improved motor and visual perception skills and social participation. Two case series of individuals with FXS examined the use of metformin, typically used to treat type 2 diabetes, obesity, or glucose intolerance.[87,88] The results showed improvements in behavior and language development. Finally, cannabinoids have been used to reduce anxiety and aberrant behavior and improve language skills and overall quality of life.[89,90]

Behavioral and Educational Interventions

In 2015, Moskowitz and Jones[91] published a systematic review of 31 behavioral intervention studies. The findings suggest that behavioral approaches are promising for addressing a variety of disruptive behaviors or functional outcomes in individuals with FXS. In a 12-week trial of a telehealth-delivered function-based behavior analytic intervention, rates of problem behavior decreased significantly in 8 of 10 children with FXS (ages 2 to 10 years).[92] In another intervention study, 20 boys with FXS, ages 8 to 18 years, were randomized to receive discrete trial instruction plus relaxation training administered at 1 of 2 prescribed doses over a 2-day period.[93] Levels of social gaze behavior increased significantly across blocks of training trials for 6 boys (60%) who received the high-dose behavioral treatment and for 3 boys (30%) who received the low-dose behavioral treatment. Therapeutic physical exercise[94] and specific diet[95] have also been used to address behavioral or socioemotional challenges in FXS. Both of these studies suggest diet and exercise may be helpful for individuals with FXS, but each approach requires further study.

A series of studies evaluated the use of Cogmed, a validated computer-based training designed to improve working memory and executive functioning in children with FXS. The results from the first study demonstrated the feasibility of a 5-week Cogmed training.[96] A follow-up study indicated significant improvement in working memory, some domains of executive function, and

parent-reported and teacher-reported behaviors during the treatment period, with many changes maintained at follow-up after 3 months without training.[97] In a subsequent "deep dive" into the data, those with a higher IQ or mental age at baseline showed greater gains.[98]

Communication is a significant challenge for many individuals with FXS, and frustration with communication failures is likely a major contributor to problematic behaviors. In 2015, a multiple baseline study of a delayed video feedback intervention for a mother and her 31-month-old son showed that the behavior support strategies used increased appropriate requesting and reduced the frequency of the child's self-injurious behavior.[99] Two pilot studies of a parent-mediated language intervention found that mothers were able to increase their use of strategies to help focus their child's attention and communicative acts.[100,101] A follow-up randomized trial found that mothers in the treatment group used these strategies at posttreatment significantly more often than mothers of children in the comparison group. When compared with those in the control group, children in the treatment group were more likely to show increased duration of engagement, use more utterances that maintained the topic of the story, and use prompted inferential language.[102] Similar results were found in sample of younger boys and their mothers.[103] A combined pharmacological and language treatment study used a randomized, double-blind trial design and assigned families to the same parent-mediated language intervention plus lovastatin (10–40 mg/d) or an intervention group plus placebo.[104] Both groups demonstrated improvements in all primary outcome measures, including direct assessment and parent report measures, further supporting the efficacy of the language intervention but not providing evidence for the benefit of the addition of medication.

For a subsample of individuals with FXS, verbal expressive language does not develop with enough capacity for efficient communication. For these individuals, augmentative or alternative communication (AAC) techniques may be beneficial to provide an avenue for communicating their wants and needs. Schladant and Dowling recently conducted a qualitative study to explore parental acceptance, use, and engagement of AAC in 4 FXS affected mother-child dyads. The investigation exposed 3 main systemic gaps that may limit the successful integration of AAC in the home including (1) failure to consider unique aspects of the family context, (2) limitations of AAC technologies, and (3) inadequate knowledge of FXS and AAC among practitioners.[105]

Families

The initial public health literature review identified several gaps regarding the impact on families of individuals with FXS given the complex nature of the *FMR1* gene expansions. Families of individuals with FXS are unique; in most cases, there is more than 1 family member affected. Given the hereditary patterns of *FMR1* expansions, biological mothers of children with FXS nearly always have an *FMR1* premutation or may have a full mutation themselves. Given the high penetrance of symptoms among those with a premutation, mothers of children with FXS are at high risk for fragile X–associated physical or mental health issues.[106] In addition, many families have a second child with FXS before the first is diagnosed and/or choose to have additional children even after knowing the risk for FXS. Some families will have multiple members across generations with fragile X–associated disorders.

Mothers of children with FXS frequently reported behaviors such as defiance, tantrums, inattention, stereotypy, aggression, and social inappropriateness in their children and describe these as having a major negative impact on family life.[41] Relative to other neurogenetic conditions (e.g., Williams syndrome), parents of children with FXS were more likely to indicate restrictions on the family and a less positive perspective of parenting because of their child's behavioral or psychiatric conditions.[107] Challenging behaviors of children over time negatively affected maternal mental health, which in turn influenced the quality of the mother-child relationship.[108] Similar results were found in another study, with child challenging behavior serving as a predictor of changes in maternal depression over time.[109] Moreover, high levels of child challenging behavior were related to increased feelings of maternal closeness toward the child over time.

In a study exploring expressed emotion, mothers with FXS were described as having high levels of worry and emotional overinvolvement.[110] This increased anxiety may have a negative impact on the outcomes of the child; lower closeness in the mother-child relationship and higher maternal distress were found to be associated with higher levels of withdrawal. In female patients with FXS, the closeness of the mother-child relationship predicted greater fluid and crystallized intelligence.[36] Maternal responsivity, 1 factor in the mother-child relationship, has also been found to be an important predictor of outcomes for individuals with FXS. Sustained maternal responsivity has a significant positive impact on the trajectories of communication and, to a lesser extent, other adaptive behavior domains through middle childhood, with many effects remaining significant after controlling for autism symptoms and developmental level.[111,112]

Family resources and social supports are important predictors of quality of life, well-being, and overall impact of the diagnosis[113]; however, little research has explored strategies to improve access to these necessary supportive resources. How and when the diagnosis is obtained and shared with family members remains another important topic for future exploration.[114,115]

DISCUSSION

The primary goal of this updated review was to assess progress made in addressing identified research gaps in

the fragile X syndrome (FXS) literature. Although progress has been made in the past few years, there is still work to be performed to fill these gaps. In this study, we summarize the 3 main areas of that remain in need of more focused clinical and public health research.

Early Detection and Diagnosis

The American Academy of Pediatrics provides guidance to pediatricians for the evaluation and referral to genetic testing for children with intellectual disability with unknown etiology.[116] Similarly, for children diagnosed with ASD, there are recommendations for fragile X testing.[117] However, children with FXS are typically diagnosed around age 3 years, after clinical onset of symptoms.[118] Thus, early emergence of symptoms in infants and toddlers with FXS has not been well described. Without universal screening for FXS, it is likely that children with FXS are underdiagnosed. This makes it challenging to determine the timing and degree of symptom onset and delays access to early intervention or genetic services. Early detection and diagnosis of FXS is critical to ensuring optimal health and well-being. Additional work remains on determining how best to identify and diagnose young children with FXS, such as through newborn screening or routine developmental surveillance. Further work is needed to understand the early phenotype of infants and toddlers with FXS. Finally, research documenting the impact of early intervention services on child and family outcomes will provide evidence on best practices to supporting development.

Examining Determinants of Health

There are many factors that affect health outcomes for all individuals, including personal, genetic, and environmental/social factors. Although the literature to date has provided a wealth of knowledge about the FXS phenotype, there is still much to learn. Given the wide variation in individuals with FXS, it is important to better understand personal or individual determinants of health. Studies are needed to document individual differences in FXS, such as phenotypic variation within male patients and female patients, and identify subgroups of FXS beyond simply classifying those with FXS only or those with FXS and comorbid ASD. Moreover, longitudinal studies into adulthood are needed to determine the lifelong impact of FXS on individuals. For example, little is known about the physical and mental health needs of adults with FXS. This information is helpful not only for further understanding the wide variation in functioning in individuals with FXS but, importantly, for determining inclusion/exclusion criteria for clinical trials and the potential impact of therapeutics.

Despite being a single-gene disorder, there is much to learn about the genetics of FXS. Genotype-phenotype association studies, in particular, are needed to understand how molecular and biochemical functioning has differential impact on individuals with FXS. For example, recent work has shed light on the relationship between FMRP and cognitive and behavioral functioning. However, more studies are needed to understand how the transcription of the *FMR1* gene and downstream regulation affect the daily life of individuals with FXS. Additional research is needed on the extent to which cell or methylation mosaicism contributes to development and functioning and how behavioral characteristics cluster together and are related to molecular indicators.

There is a significant lack of knowledge regarding the environmental and social determinants of health in individuals with FXS. Only a handful of studies have examined the access to health care services and the educational needs of individuals with FXS. Critically, there remains a lack of information about the potential differential needs and access to health care for those from minority backgrounds. Racial inequalities for individuals with intellectual and developmental disabilities have been described for other conditions but are lacking in FXS. More information is needed to understand the community and social factors and their impact on individuals with FXS. These could include studies on access to leisure activities and the quality of friendships for individuals of all ages with FXS. Finally, research on employment and housing of adults with FXS would provide additional insights into the impact of aging.

Developing and Implementing Pharmacological and Other Interventions

It is clear that a large focus over the past 6 years has been on the development of targeted therapeutics and identification of appropriate outcome measures for use in clinical trials. Advances in understanding molecular pathways have paved the way for promising new treatments. However, there is more work to do in understanding the molecular biology and systemic function of FMRP.[119,120] A deeper understanding of the expression of *FMR1* and the role FMRP plays in regulation of cellular activity will provide new insights into potential pharmacological treatment targets. Moreover, many outcome measures still require additional evaluation to determine their sensitivity to change, a quality necessary for being able to assess the efficacy of a given treatment.

Research into effective educational and behavioral interventions is also needed. The handful of studies conducted to date provide a foundation on acceptable, feasible, and efficacious approaches. However, many are focused on small samples and target very specific skills or behaviors. Next steps should include large-scale replication studies to build the evidence base and demonstrate scale-up of implementation. In addition, continued development and testing of new interventions that address broad areas of development are needed to complement targeted interventions. Ideally, the field will create a variety of intervention approaches to support individuals with FXS and their families.

CONCLUSION

Despite significant progress made in addressing clinical and public health research gaps identified in our earlier review, much work remains for the FXS field. Early diagnosis and understanding of the FXS phenotype, from infancy through adulthood, will provide insights in variation in individuals with *FMR1* mutations. Detailing the impact of personal, genetic, family, social, and environmental factors on individuals with FXS will not only advance our understanding but also enable more targeted treatment approaches. With additional research, clinicians and other professionals will be well poised to meet the needs of individuals with FXS and their families.

REFERENCES

1. Raspa M, Wheeler AC, Riley C. Public health literature review of fragile X syndrome. *Pediatrics*. 2017;139:S153–S171.
2. *Covidence Systematic Review Software [Computer Program]*. Melbourne VIC, Australia: Veritas Health Innovation; 2020.
3. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Plos Med.* 2009;6:e1000097.
4. Salcedo-Arellano MJ, Dufour B, McLennan Y, et al. Fragile X syndrome and associated disorders: clinical aspects and pathology. *Neurobiol Dis.* 2020;136:104740.
5. Razak KA, Dominick KC, Erickson CA. Developmental studies in fragile X syndrome. *J Neurodev Disord.* 2020;12:13.
6. Schmitt LM, Shaffer RC, Hessl D, Erickson C. Executive function in fragile X syndrome: a systematic review. *Brain Sci.* 2019;9:E15.
7. Roberts JE, McCary LM, Shinkareva SV, Bailey DB Jr. Infant development in fragile X syndrome: cross-syndrome comparisons. *J Autism Dev Disord.* 2016;46:2088–2099.
8. Kover ST, McCary LM, Ingram AM, et al. Language development in infants and toddlers with fragile X syndrome: change over time and the role of attention. *Am J Intellect Dev Disabil.* 2015;120:125–144.
9. Fielding-Gebhardt H, Warren SF. Early predictors of later expressive language in boys with fragile X syndrome. *Am J Intellect Dev Disabil.* 2019;124:11–24.
10. Brady NC, Fleming K, Bredin-Oja SL, et al. Language development from early childhood to adolescence in youths with fragile X syndrome. *J Speech Lang Hear Res.* 2020;63:3727–3742.
11. Klusek J, McGrath SE, Abbeduto L, Roberts JE. Pragmatic language features of mothers with the FMR1 premutation are associated with the language outcomes of adolescents and young adults with fragile X syndrome. *J Speech, Lang Hear Res.* 2016;59:49–61.
12. Oakes A, Kover ST, Abbeduto L. Language comprehension profiles of young adolescents with fragile X syndrome. *Am J Speech Lang Pathol.* 2013;22:615–626.
13. Thurman AJ, Hoyos Alvarez C. Language performance in preschool-aged boys with nonsyndromic autism spectrum disorder or fragile X syndrome. *J Autism Dev Disord.* 2020;50:1621–1638.
14. Hahn LJ, Brady NC, Warren SF, Fleming KK. Do children with fragile X syndrome show declines or plateaus in adaptive behavior? *Am J Intellect Dev Disabil.* 2015;120:412–432.
15. Hustyi KM, Hall SS, Jo B, et al. Longitudinal trajectories of aberrant behavior in fragile X syndrome. *Res Dev Disabil.* 2014;35:2691–2701.
16. Klaiman C, Quintin EM, Jo B, et al. Longitudinal profiles of adaptive behavior in fragile X syndrome. *Pediatrics*. 2014;134:315–324.
17. McCary LM, Machlin L, Roberts JE. The development of adaptive behavior in toddlers and preschoolers with fragile X versus autism. *Int J Dev Disabil.* 2013;59:67–79.
18. Frolli A, Piscopo S, Conson M. Developmental changes in cognitive and behavioural functioning of adolescents with fragile-X syndrome. *J Intellect Disabil Res.* 2015;59:613–621.
19. Hardiman RL, McGill P. How common are challenging behaviours amongst individuals with fragile X syndrome? A systematic review. *Res Dev Disabil.* 2018;76:99–109.
20. Britton TC, Wilkinson EH, Hall SS. Examining the specificity of forms and functions of aggressive behavior in boys with fragile X syndrome. *Am J Intellect Dev Disabil.* 2020;125:247–259.
21. Hall SS, Barnett RP, Hustyi KM. Problem behaviour in adolescent boys with fragile X syndrome: relative prevalence, frequency and severity. *J Intellect Disabil Res.* 2016;60:1189–1199.
22. Hall SS, Hustyi KM, Barnett RP. Examining the influence of social-environmental variables on self-injurious behaviour in adolescent boys with fragile X syndrome. *J Intellect Disabil Res.* 2018;62:1072–1085.
23. Reisinger DL, Shaffer RC, Tartaglia N, et al. Delineating repetitive behavior profiles across the lifespan in fragile X syndrome. *Brain Sci.* 2020;10:E239.
24. Moskowitz LJ, Will EA, Black CJ, Roberts JE. Restricted and repetitive behaviors in males and females with fragile X syndrome: developmental trajectories in toddlers through young adults. *J Autism Dev Disord.* 2020;50:3957–3966.
25. Rais M, Binder DK, Razak KA, Ethell IM. Sensory processing phenotypes in fragile X syndrome. *ASN Neuro.* 2018;10:1759091418801092.
26. Rotschafer SE, Razak KA. Auditory processing in fragile X syndrome. *Front Cel Neurosci.* 2014;8:19.
27. Roberts J, Crawford H, Hogan AL, et al. Social avoidance emerges in infancy and persists into adulthood in fragile X syndrome. *J Autism Dev Disord.* 2019;49:3753–3766.
28. Hall SS, Venema KM. A screening tool to measure eye contact avoidance in boys with fragile X syndrome. *J Autism Dev Disord.* 2017;47:2254–2264.
29. Ellis K, Oliver C, Stefanidou C, et al. An observational study of social interaction skills and behaviors in Cornelia de Lange, fragile X and Rubinstein-Taybi syndromes. *J Autism Dev Disord.* 2020;50:4001–4010.
30. Hong MP, Eckert EM, Pedapati EV, et al. Differentiating social preference and social anxiety phenotypes in fragile X syndrome using an eye gaze analysis: a pilot study. *J Neurodev Disord.* 2019;11:1.
31. Baker EK, Arpone M, Vera SA, et al. Intellectual functioning and behavioural features associated with mosaicism in fragile X syndrome. *J Neurodev Disord.* 2019;11:41.
32. Jiraanont P, Kumar M, Tang H-T, et al. Size and methylation mosaicism in males with fragile X syndrome. *Expert Rev Mol Diagn.* 2017;17:1023–1032.
33. Handt M, Epplen A, Hoffjan S, et al. Point mutation frequency in the FMR1 gene as revealed by fragile X syndrome screening. *Mol Cel Probes.* 2014;28:279–283.
34. Sitzmann AF, Hagelstrom RT, Tassone F, et al. Rare FMR1 gene mutations causing fragile X syndrome: a review. *Am J Med Genet A.* 2018;176:11–18.
35. Budimirovic DB, Schlageter A, Filipovic-Sadic S, et al. A genotype-phenotype study of high-resolution FMR1 nucleic acid and protein analyses in fragile X patients with neurobehavioral assessments. *Brain Sci.* 2020;10:E694.
36. Del Hoyo Soriano L, Thurman AJ, Harvey DJ, et al. Genetic and maternal predictors of cognitive and behavioral trajectories in females with fragile X syndrome. *J Neurodev Disord.* 2018;10:22.
37. Kim K, Hessl D, Randol JL, et al. Association between IQ and FMR1 protein (FMRP) across the spectrum of CGG repeat expansions. *PLoS One*. 2019;14:e0226811.
38. Lozano R, Rosero CA, Hagerman RJ. Fragile X spectrum disorders. *Intractable Rare Dis Res.* 2014;3:134–146.
39. Kidd SA, Berry-Kravis E, Choo TH, et al. Improving the diagnosis of autism spectrum disorder in fragile X syndrome by adapting the

Social Communication Questionnaire and the Social Responsiveness Scale-2. *J Autism Dev Disord.* 2020;50:3276–3295.
40. Niu M, Han Y, Dy ABC, et al. Autism symptoms in fragile X syndrome. *J Child Neurol.* 2017;32:903–909.
41. Muller K, Brady NC, Warren SF, Fleming KK. Mothers' perspectives on challenging behaviours in their children with fragile X syndrome. *J Intellect Dev Disabil.* 2019;44:481–491.
42. Thurman AJ, McDuffie A, Hagerman RJ, et al. Language skills of males with fragile X syndrome or nonsyndromic autism spectrum disorder. *J Autism Dev Disord.* 2017;47:728–743.
43. Muzar Z, Lozano R, Kolevzon A, Hagerman RJ. The neurobiology of the Prader-Willi phenotype of fragile X syndrome. *Intractable Rare Dis Res.* 2016;5:255–261.
44. Coppus AMW. People with intellectual disability: what do we know about adulthood and life expectancy? *Dev Disabil Res Rev.* 2013;18:6–16.
45. Hoffmann A, Krause SE, Wuu J, et al. Vocabulary comprehension in adults with fragile X syndrome (FXS). *J Neurodev Disord.* 2019;11:25.
46. Hartley SL, Wheeler AC, Mailick MR, et al. Autism symptoms across adulthood in men with fragile X syndrome: a cross-sectional analysis. *J Autism Dev Disord.* 2015;45:3668–3679.
47. DaWalt LS, Usher LV, Greenberg JS, Mailick MR. Friendships and social participation as markers of quality of life of adolescents and adults with fragile X syndrome and autism. *Autism*. 2019;23:383–393.
48. Smith LE, Hong J, Greenberg JS, Mailick MR. Change in the behavioral phenotype of adolescents and adults with FXS: role of the family environment. *J Autism Dev Disord.* 2016;46:1824–1833.
49. Maenner MJ, Smith LE, Hong J, et al. Evaluation of an activities of daily living scale for adolescents and adults with developmental disabilities. *Disabil Health J.* 2013;6:8–17.
50. Martin A, Quintin EM, Hall SS, Reiss AL. The role of executive function in independent living skills in female adolescents and young adults with fragile X syndrome. *Am J Intellect Dev Disabil.* 2016;121:448–460.
51. Macpherson JN, Murray A. Development of genetic testing for fragile X syndrome and associated disorders, and estimates of the prevalence of FMR1 expansion mutations. *Genes (Basel)*. 2016;7:E110.
52. Gabis LV, Hochberg O, Leon Attia O, et al. Prolonged time lag to final diagnosis of fragile X syndrome. *J Pediatr.* 2018;193:217–221.e1. e211.
53. Archibald AD, Hickerton CL, Wake SA, et al. It gives them more options: preferences for preconception genetic carrier screening for fragile X syndrome in primary healthcare. *J Community Genet.* 2016;7:159–171.
54. Johansen Taber K, Lim-Harashima J, Naemi H, Goldberg J. Fragile X syndrome carrier screening accompanied by genetic consultation has clinical utility in populations beyond those recommended by guidelines. *Mol Genet Genomic Med.* 2019;7:e1024.
55. Metcalfe SA, Martyn M, Ames A, et al. Informed decision making and psychosocial outcomes in pregnant and nonpregnant women offered population fragile X carrier screening. *Genet Med.* 2017;19:1346–1355.
56. Haham LM, Avrahami I, Domniz N, et al. Preimplantation genetic diagnosis versus prenatal diagnosis-decision-making among pregnant FMR1 premutation carriers. *J Assist Reprod Genet.* 2018;35:2071–2075.
57. Kieffer E, Nicod JC, Gardes N, et al. Improving preimplantation genetic diagnosis for fragile X syndrome: two new powerful single-round multiplex indirect and direct tests. *Eur J Hum Genet.* 2016;24:221–227.
58. Acharya K, Schindler A. Developmental and behavioral pediatricians' attitudes toward screening for fragile X. *Am J Intellect Dev Disabil.* 2013;118:284–293.
59. Bailey DB Jr, Berry-Kravis E, Gane LW, et al. Fragile X newborn screening: lessons learned from a multisite screening study. *Pediatrics*. 2017;139:S216–S225.
60. Christie L, Wotton T, Bennetts B, et al. Maternal attitudes to newborn screening for fragile X syndrome. *Am J Med Genet A.* 2013;161A:301–311.
61. Okoniewski KC, Wheeler AC, Lee S, et al. Early identification of fragile X syndrome through expanded newborn screening. *Brain Sci.* 2019;9:E4.
62. Paquin RS, Lewis MA, Harper BA, et al. Outreach to new mothers through direct mail and email: recruitment in the Early Check research study. *Clin Transl Sci.* 2021;14:880–889.
63. Guillory J, Jordan A, Paquin R, et al. Using social media to conduct outreach and recruitment for expanded newborn screening. *Front Commun.* 2020;5:21.
64. Riley C, Wheeler A. Assessing the fragile X syndrome newborn screening landscape. *Pediatrics*. 2017;139:S207–s215.
65. Tassone F. Newborn screening for fragile X syndrome. *JAMA Neurol.* 2014;71:355–359.
66. Sacco P, Capkun-Niggli G, Zhang X, Jose R. The economic burden of fragile X syndrome: healthcare resource utilization in the United States. *Am Health Drug Benefits.* 2013;6:73–83.
67. Chevreul K, Berg Brigham K, Brunn M, et al. Fragile X syndrome: economic burden and health-related quality of life of patients and caregivers in France. *J Intellect Disabil Res.* 2015;59:1108–1120.
68. Chevreul K, Gandré C, Brigham KB, et al; BURQOL-RD Research Network. Social/economic costs and health-related quality of life in patients with fragile X syndrome in Europe. *Eur J Health Econ.* 2016;17:43–52.
69. Vekeman F, Gauthier-Loiselle M, Faust E, et al. Patient and caregiver burden associated with fragile X syndrome in the United States. *Am J Intellect Dev Disabil.* 2015;120:444–459.
70. Vekeman F, Gauthier-Loiselle M, Faust E, et al. Health care resource use and direct costs associated with fragile X syndrome (FXS) in the United States. 2013;16(7):A621.
71. Wheeler AC, Wylie A, Villagomez A, et al. Health care for individuals with fragile X syndrome: understanding access and quality. *Disabil Health J.* 2019;12:269–277.
72. Gilbertson KE, Jackson HL, Dziuban EJ, et al. Preventive care services and health behaviors in children with fragile X syndrome. *Disabil Health J.* 2019;12:564–573.
73. Erickson CA, Kaufmann WE, Budimirovic DB, et al. Best practices in fragile X syndrome treatment development. *Brain Sci.* 2018;8:224.
74. Weber JD, Smith E, Berry-Kravis E, et al. Voice of people with fragile X syndrome and their families: reports from a survey on treatment priorities. *Brain Sci.* 2019;9:18.
75. Cross J, Yang JC, Johnson FR, et al. Caregiver preferences for the treatment of males with fragile X syndrome. *J Dev Behav Pediatr.* 2016;37:71–79.
76. Reines V, Charen K, Rosser T, et al. Parental perspectives on pharmacological clinical trials: a qualitative study in Down syndrome and fragile X syndrome. *J Genet Couns.* 2017;26:1333–1340.
77. Eley SEA, McKechanie AG, Campbell S, Stanfield AC. Facilitating individuals and families affected by fragile X syndrome to participate in medication trials. *J Intellect Disabil Res.* 2020;64(11):864–874.
78. D'Amanda CS, Peay HL, Wheeler AC, et al. Fragile X syndrome clinical trials: exploring parental decision-making. *J Intellect Disabil Res.* 2019;63:926–935.
79. Laxman DJ, Greenberg JS, DaWalt LS, et al. Medication use by adolescents and adults with fragile X syndrome. *J Intellect Disabil Res.* 2018;62:94–105.
80. Eckert EM, Dominick KC, Pedapati EV, et al. Pharmacologic interventions for irritability, aggression, agitation and self-injurious behavior in fragile X syndrome: an initial cross-sectional analysis. *J Autism Dev Disord.* 2019;49:4595–4602.

81. Dominick KC, Wink LK, Pedapati EV, et al. Risperidone treatment for irritability in fragile X syndrome. *J Child Adolesc Psychopharmacol.* 2018;28:274–278.
82. Ligsay A, Van Dijck A, Nguyen DV, et al. A randomized double-blind, placebo-controlled trial of ganaxolone in children and adolescents with fragile X syndrome. *J Neurodev Disord.* 2017; 9(1):1–3.
83. Berry-Kravis E, Hagerman R, Visootsak J, et al. Arbaclofen in fragile X syndrome: results of phase 3 trials. *J Neurodev Disord.* 2017;9:3.
84. Berry-Kravis E, Horrigan JP, Tartaglia N, et al.; FXS-001 Investigators. A double-blind, randomized, placebo-controlled clinical study of trofinetide in the treatment of fragile X syndrome. *Pediatr Neurol.* 2020;110:30–41.
85. Bruno JL, Hosseini SH, Lightbody AA, et al. Brain circuitry, behavior, and cognition: a randomized placebo-controlled trial of donepezil in fragile X syndrome. *J Psychopharmacol.* 2019;33: 975–985.
86. Greiss Hess L, Fitzpatrick SE, Nguyen DV, 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.
87. Biag HMB, Potter LA, Wilkins V, et al. Metformin treatment in young children with fragile X syndrome. *Mol Genet Genomic Med.* 2019;7:e956.
88. Dy ABC, Tassone F, Eldeeb M, et al. Metformin as targeted treatment in fragile X syndrome. *Clin Genet.* 2018;93:216–222.
89. Tartaglia N, Bonn-Miller M, Hagerman R. Treatment of fragile X syndrome with cannabidiol: a case series study and brief review of the literature. *Cannabis Cannabinoid Res.* 2019;4:3–9.
90. Heussler H, Cohen J, Silove N, et al. A phase 1/2, open-label assessment of the safety, tolerability, and efficacy of transdermal cannabidiol (ZYN002) for the treatment of pediatric fragile X syndrome. *J Neurodev Disord.* 2019;11:16.
91. Moskowitz LJ, Jones EA. Uncovering the evidence for behavioral interventions with individuals with fragile X syndrome: a systematic review. *Res Dev Disabil.* 2015;38:223–241.
92. Monlux KD, Pollard JS, Bujanda Rodriguez AY, Hall SS. Telehealth delivery of function-based behavioral treatment for problem behaviors exhibited by boys with fragile X syndrome. *J Autism Dev Disord.* 2019;49:2461–2475.
93. Gannon CE, Britton TC, Wilkinson EH, Hall SS. Improving social gaze behavior in fragile X syndrome using a behavioral skills training approach: a proof of concept study. *J Neurodev Disord.* 2018;10:25.
94. Lee S, Won J, Park S, et al. Beneficial effect of interventional exercise on autistic fragile X syndrome. *J Phys Ther Sci.* 2017;29: 760–762.
95. Barnhill K, Devlin M, Moreno HT, et al. Brief report: implementation of a specific carbohydrate diet for a child with autism spectrum disorder and fragile X syndrome. *J Autism Dev Disord.* 2020;50:1800–1808.
96. Au J, Berkowitz-Sutherland L, Schneider A, et al. A feasibility trial of Cogmed working memory training in fragile X syndrome. *J Pediatr Genet.* 2014;3:147–156.
97. Hessl D, Schweitzer JB, Nguyen DV, et al. Cognitive training for children and adolescents with fragile X syndrome: a randomized controlled trial of Cogmed. *J Neurodev Disord.* 2019;11:4.
98. Scott H, Harvey DJ, Li Y, et al. Cognitive training deep dive: the impact of child, training behavior and environmental factors within a controlled trial of Cogmed for fragile X syndrome. *Brain Sci.* 2020;10:E671.
99. Oakes A, Ma M, McDuffie A, et al. Providing a parent-implemented language intervention to a young male with fragile X syndrome: brief report. *Dev Neurorehabil.* 2015;18:65–68.
100. McDuffie A, Machalicek W, Bullard L, et al. A spoken-language intervention for school-aged boys with fragile X syndrome. *Am J Intellect Dev Disabil.* 2016;121:236–265.
101. McDuffie A, Oakes A, Machalicek W, et al. Early language intervention using distance video-teleconferencing: a pilot study of young boys with fragile X syndrome and their mothers. *Am J Speech Lang Pathol.* 2016;25:46–66.
102. Nelson S, McDuffie A, Banasik A, et al. Inferential language use by school-aged boys with fragile X syndrome: effects of a parent-implemented spoken language intervention. *J Commun Disord.* 2018;72:64–76.
103. Bullard L, McDuffie A, Abbeduto L. Distance delivery of a parent-implemented language intervention for young boys with fragile X syndrome. *Autism Dev Lang Impair.* 2017;2:1–22.
104. Thurman AJ, Potter LA, Kim K, et al. Controlled trial of lovastatin combined with an open-label treatment of a parent-implemented language intervention in youth with fragile X syndrome. *J Neurodev Disord.* 2020;12:12.
105. Schladant M, Dowling M. Parent perspectives on augmentative and alternative communication integration for children with fragile X syndrome: it starts in the home. *Intellect Dev Disabil.* 2020;58:409–421.
106. McKechanie AG, Barnicoat A, Trender-Gerhard I, et al. Fragile X-associated conditions: implications for the whole family. *Br J Gen Pract.* 2019;69:460–461.
107. Reilly C, Murtagh L, Senior J. The impact on the family of four neurogenetic syndromes: a comparative study of parental views. *J Genet Couns.* 2015;24:851–861.
108. Fielding-Gebhardt H, Warren SF, Brady NC. Child challenging behavior influences maternal mental health and relationship quality over time in fragile X syndrome. *J Autism Dev Disord.* 2020;50:779–797.
109. Hauser CT, Kover ST, Abbeduto L. Maternal well-being and child behavior in families with fragile X syndrome. *Res Dev Disabil.* 2014;35:2477–2486.
110. Coleman J, Riley K. The expressed emotion of mothers of children with fragile X syndrome. *Life Span Disabil.* 2014;XVII:59–88.
111. Warren SF, Brady N, Fleming KK, Hahn LJ. The longitudinal effects of parenting on adaptive behavior in children with fragile X syndrome. *J Autism Dev Disord.* 2017;47:768–784.
112. Sterling A, Warren SF. Parenting of children with Down syndrome compared to fragile X syndrome. *Dev Neurorehabil.* 2018;21:64–67.
113. Raspa M, Bailey DB Jr, Bann C, Bishop E. Modeling family adaptation to fragile X syndrome. *Am J Intellect Dev Disabil.* 2014;119:33–48.
114. Bailey DB Jr, Wheeler A, Berry-Kravis E, et al. Maternal consequences of the detection of fragile X carriers in newborn screening. *Pediatrics.* 2015;136:e433–e440.
115. Raspa M, Edwards A, Wheeler AC, et al. Family communication and cascade testing for fragile X syndrome. *J Genet Couns.* 2016; 25:1075–1084.
116. Moeschler JB, Shevell M; American Academy of Pediatrics Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. *Pediatrics.* 2006;117:2304–2316.
117. Schaefer GB, Mendelsohn NJ. Genetics evaluation for the etiologic diagnosis of autism spectrum disorders. *Genet Med.* 2008;10:4–12.
118. Bailey DB Jr, Raspa M, Bishop E, Holiday D. No change in the age of diagnosis for fragile X syndrome: findings from a national parent survey. *Pediatrics.* 2009;124:527–533.
119. Dockendorff TC, Labrador M. The fragile X protein and genome function. *Mol Neurobiol.* 2019;56:711–721.
120. Richter JD, Zhao X. The molecular biology of FMRP: new insights into fragile X syndrome. *Nat Rev Neurosci.* 2021;22:209–222.