

Newborn, Carrier, and Early Childhood Screening Recommendations for Fragile X

abstract

Fragile X syndrome, diagnosed by Fragile X Mental Retardation 1 (FMR1) DNA testing, is the most common single-gene cause of inherited intellectual disability. The expanded CGG mutation in the *FMR1* gene, once thought to have clinical significance limited to fragile X syndrome, is now well established as the cause for other fragile X-associated disorders including fragile X-associated primary ovarian insufficiency and fragile X-associated tremor ataxia syndrome in individuals with the premutation (carriers). The importance of early diagnostic and management issues, in conjunction with the identification of family members at risk for or affected by *FMR1* mutations, has led to intense discussion about the appropriate timing for early identification of *FMR1* mutations. This review includes an overview of the fragile X-associated disorders and screening efforts to date, and discussion of the advantages and barriers to *FMR1* screening in newborns, during childhood, and in women of reproductive age. Comparison with screening programs for other common genetic conditions is discussed to arrive at action steps to increase the identification of families affected by *FMR1* mutations. *Pediatrics* 2012;130:1126–1135

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KEY WORDS

fragile X syndrome, fragile X-associated disorders, *FMR1* mutations, genetic screening, genetic testing recommendations, newborn screening

ABBREVIATIONS

ACMG—American College of Medical Genetics
ACOG—American Academy of Obstetrics and Gynecology
CF—cystic fibrosis
FMR1—Fragile X Mental Retardation 1
FMRP—fragile X mental retardation protein
FXCRC—Fragile X Clinical and Research Consortium
FXD—fragile X-associated disorder
FXPOI—fragile X-associated primary ovarian insufficiency
FXS—fragile X syndrome
FXTAS—fragile X-associated tremor ataxia syndrome
ID—intellectual disability
NFXF—National Fragile X Foundation
NBS—newborn screening
PCR—polymerase chain reaction

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Fragile X syndrome (FXS) is the most common single-gene cause of inherited intellectual disability (ID) and autism.¹ Caused by a trinucleotide repeat expansion in the 5' untranslated region of the Fragile X Mental Retardation 1 (*FMR1*) gene, accurate DNA testing is widely available for the diagnosis of FXS and identification of individuals with *FMR1* mutations.

Present screening recommendations primarily focus on individuals affected with a developmental disorder or clinical features of the fragile X–associated disorders (FXDs). This strategy fails to detect many *FMR1* mutation carriers without symptoms and those with mild or subtle effects. Furthermore, efficacy of available (eg, intensive early intervention) and promising (eg, neurobiologically targeted drug treatments) therapies would be enhanced by their earliest initiation. The importance of early diagnosis and intervention, in conjunction with the identification of other family members affected by or at risk for *FMR1* mutations, has prompted an intense discussion about the appropriate timing for identification of FXS and screening for *FMR1* carriers. With widespread general population screening, earlier identification of affected individuals and at-risk carriers can be accomplished.

BACKGROUND

In 1943, Martin and Bell⁹¹ reported the first family with the FXS phenotype. In 1985, Sherman and colleagues^{2,3} reported unusual patterns for an X-linked disorder in fragile X families which included a greater risk for FXS in subsequent generations (anticipation), affected females and identification of unaffected male carriers. In 1991, the *FMR1* gene and the expanded CGG trinucleotide repeat, which is responsible for FXS, were identified.⁴ Importantly, all individuals studied with the full mutation have inherited the full

mutation from a female carrier of an *FMR1* expansion; there are no “de novo” *FMR1* full mutations.⁵

The length of the CGG repeat region is highly polymorphic in the general population, ranging from 6 to 44 CGGs.^{6–8} The *FMR1* full mutation, seen in males and females with fragile X syndrome, contains >199 CGG repeats, and is usually hypermethylated. This leads to transcriptional silencing of the *FMR1* gene and absence or reduction of fragile X mental retardation protein (FMRP), an important protein for neural development and plasticity.^{9–11} The premutation allele, present in carriers, contains ~55 to 199 repeats and does not typically exhibit methylation.¹² Intermediate alleles range from 45 to 54 CGG repeats, and are not thought to have clinical implications other than the potential to expand to a premutation in future generations.¹³

The risk for expansion from the premutation to the full mutation depends on the gender of the carrier parent and the repeat size. Premutation alleles transmitted by carrier fathers to all their daughters remain relatively stable and no report has confirmed an expansion to a full mutation. Thus, daughters of male carriers are not thought to be at risk for FXS. All offspring of women with a premutation or full mutation inherit the *FMR1* mutation 50% of the time; however, the risk of the premutation to expand to the full mutation increases linearly by maternal repeat size ranging from ~4% to 5% in women with 55 to 69 CGG repeats and gradually increasing to nearly 100% for repeat alleles of >99.¹⁴ A positive family history of FXS appears to influence risk for expansion.¹⁵ In addition, the role of interspersed AGG triplets within the CGG repeat is being investigated, as long tracts of CGG repeats without interspersed AGG anchors appear to be at greater risk of expansion than those

alleles where AGG anchors have been preserved.¹⁶

The development of the *Fmr1* knockout mouse in 1994¹⁷ led to the identification of a role for FMRP in dendritic spine maturation and synaptic plasticity and its regulation by metabotropic glutamate receptor signaling.^{18,19} Bear and colleagues developed the mGluR theory of fragile X in 2002,²⁰ based on the finding of exaggerated group 1 mGluR-dependent depression in the *FMR1* knockout mouse. This proposed mechanism opened the way for potential targeted treatments, specifically mGluR5 antagonists^{21,22} and γ -aminobutyric acid-B agonists currently in clinical trials for FXS.²³

It is now appreciated that the premutation leads to a significant medical burden that has been well described in premutation carriers. Fragile X–associated primary ovarian insufficiency (FXPOI), seen in ~20% of premutation female carriers, is the most common known single-gene cause of ovarian insufficiency.²⁴ Clinical involvement in premutation carriers also includes fragile X–associated tremor ataxia syndrome (FXTAS), which affects older adults.^{25,26} Together, FXS, FXPOI, and FXTAS are known as FXDs.

FXDS: CLINICAL PHENOTYPES

FXS

FXS is characterized by a variable pattern of physical, behavioral, and cognitive features in male and female patients. Hallmark physical characteristics of FXS include postpubertal macroorchidism, a long face, hyperextensible joints, and prominent ears.^{27–29} Physical findings are often subtle in infants and young children with FXS, particularly girls, and even at older ages, the physical phenotype may not be readily apparent. Therefore, the presence of key developmental and behavioral features, such as poor eye contact, hand flapping, hand biting, attention

deficits, anxiety, and social avoidance, should alert clinicians to the need for fragile X DNA testing, even in children without obvious physical findings.

Many infants with FXS present with hypotonia and mild to moderate motor delays that are usually noticeable by 9 to 12 months.^{30–33} Expressive language delays are common and often the primary reason for referral to early intervention services. Autism is present in up to 30% of boys^{32,34,35} and 20% of girls with FXS.³⁶ An additional 30% are diagnosed with an autism spectrum disorder.^{35,37}

Generally, all male patients with FXS have some degree of ID, ranging from mild to severe.^{38–40} Up to 5% of male patients have IQs >70, typically attributable to mosaicism (a mixture of methylated and unmethylated alleles), which results in production of FMRP in a fraction of cells.²⁹ Approximately 30% of females with the *FMR1* full mutation have ID, and another 40% have significant learning and behavioral difficulties.^{41,42} Approximately 25% of female patients with the full mutation have IQs in the normal range (>85), but may have difficulty with executive function and mental health issues.^{38,43} Women with mild or no apparent features of FXS have been identified with a full mutation after the birth of an affected child. Therefore, one cannot assume that all unaffected mothers of affected children have a premutation.

CLINICAL PHENOTYPES ASSOCIATED WITH THE *FMR1* PREMUTATION

FXTAS

Characterized by progressive neurologic, cognitive, and psychiatric features, FXTAS is a neurodegenerative condition associated with the *FMR1* premutation.^{44,45} Male patients are more commonly affected than female patients, with typical onset after age 50.^{25,46} Neurologically, the disorder is

characterized by intention tremor, cerebellar ataxia, autonomic dysfunction, peripheral neuropathy, parkinsonism, and cognitive decline.⁴⁷ Psychiatric symptoms are common, such as anxiety, depression, increased irritability, and impulsive behavior.⁴⁸ The diagnosis of FXTAS is based on the presence of key clinical and/or radiologic findings in adults with a premutation.⁴⁹ Approximately 46% of male patients and 8% of female patients with the *FMR1* premutation develop FXTAS symptoms after age 50,^{50,51} although some individuals may experience symptoms that do not meet full clinical criteria for the diagnosis of FXTAS.

FXPOI

At least 20% of women with an *FMR1* premutation experience FXPOI,²⁴ a constellation of symptoms characterized by diminished ovarian reserve leading to irregular menses, elevated follicle-stimulating hormone levels, reduced fertility, and at the more severe end of the spectrum, premature ovarian failure (cessation of menses before age 40). The severity and age of onset of FXPOI are correlated nonlinearly with premutation size, with the risk increasing linearly in women with 60 to 100 CGG repeats and then decreasing at premutation sizes from 100 to 200 CGG repeats.⁵² In women with ovarian insufficiency, the prevalence of the *FMR1* premutation ranges from 2% to 15%, depending on family history.²⁴ *FMR1* testing is recommended for women with infertility or ovarian insufficiency.⁵⁵

MOLECULAR DIAGNOSIS OF *FMR1* MUTATIONS

Molecular diagnostic testing of the *FMR1* mutation has historically been conducted with genomic DNA, by using both Southern blot analysis and polymerase chain reaction (PCR). Recent developments have led to improvements

in the molecular testing for fragile X. Tassone et al⁵⁴ developed a PCR-based methodology that uses a CGG repeat primer able to detect expanded alleles throughout the premutation and full mutation ranges in both genders, and several other groups have reported on the use of this approach.^{15,55–58} A number of laboratories now offer PCR-only testing for general screening of low-risk populations, and it is likely that a PCR-based technology will be the primary testing method for *FMR1* expansion mutations in the near future. It is important to note that whole exome sequencing, comparative genomic hybridization (CGH), and chromosome microarrays do not identify *FMR1* mutations.

PREVALENCE OF *FMR1* FULL MUTATIONS

FXS has been identified in every ethnic group studied, although no definitive study has been completed to assess mutation frequencies in the pan-ethnic population of the United States. General population-based studies suggest a full mutation prevalence of ~1/4000 in white males.⁵⁹ Seven newborn screening (NBS) studies have been carried out, including a recent study among a racially diverse group of 36 124 newborns from Georgia that identified 1 in 5161 male newborns with the full mutation (95% confidence interval of 1/2500–1/10 653). There was no significant difference in prevalence estimates among the 3 major ethnic/racial groups in the United States (white, African American, and Hispanic), although once stratification was done, numbers were small. NBS studies completed in other countries include a study of 5267 male newborns in northwest Spain, which found a prevalence of 1 of 2633 with a full mutation, although confidence limits were wide,⁶⁰ and a study in Taiwan of 10 046 male newborns that identified only 1

newborn with the full mutation. This lower frequency may reflect true population differences or it may be a function of sample size.

In South Carolina,⁶¹ families of 1459 newborns were offered screening for FXS. Two full mutations and 2 pre-mutations were identified (1:730), a rather high frequency, suggesting a statistical fluctuation owing to a small sample size.

PREVALENCE OF *FMR1* PREMUTATION AND INTERMEDIATE ALLELES

Broad-based general population study prevalence figures for intermediate and premutation alleles vary significantly because of study design (eg, repeat range definition, small sample size, various exclusion criteria, and race/ethnicity). In unselected populations, a large Canadian study reported a premutation (defined as 55–199 repeats) frequency of 1 in 259 in female individuals.⁶² Cronister et al⁶³ found a similar prevalence among women of reproductive age with no family history suggestive of FXS (1 in 257). This compares to 1 in 158 reported in a large Israeli study of women with no relevant family history,⁶⁴ and suggests variation among different ethnic/racial groups.

Studies of the premutation frequency in male individuals are limited. A Canadian study of 10 572 male individuals found 1 in 813 with the premutation.⁶⁵ A Spanish NBS study of 5267 male blood spots reported a premutation frequency of 1 in 251.⁶⁰ A recent study of a cohort of 6747 Wisconsin high school graduates from 1957, primarily white, found a premutation prevalence of 1 of 468 male individuals and 1 of 151 female individuals.^{13,66}

Studies of intermediate allele frequency are difficult to compare because of inclusion criteria. By using the current definition of intermediate alleles of 45 to 54 repeats,⁶⁷ Brown et al⁶⁸ identified

43 intermediate alleles (45–54) among 2500 controls (1 in 58). Among 9538 women with no family history of IDs, using the same allele range, Cronister et al⁶³ found 1 in 53 women were intermediate allele carriers.

A collaborative NBS pilot study designed, in part, to assess full, premutation, and intermediate allele prevalence in the general population in the United States is ongoing.⁶⁹

POTENTIAL FOR GENERAL POPULATION SCREENING FOR *FMR1* PREMUTATIONS AND FULL MUTATIONS

Widespread population screening programs for *FMR1* mutations could be established among 2 groups: preconception/pregnant women of reproductive age and newborns. Prenatal and preconception settings would primarily identify premutation carriers. Screening for carriers would alert families to the possibility of having a child with FXS, allowing them prenatal testing and family planning options. In addition, screening these groups would alert carriers to their risk for FXPOI and potential fertility problems.

SCREENING IN THE OBSTETRIC SETTING

Musci et al⁷⁰ concluded that a population-based *FMR1* carrier screening program is clinically desirable and cost-effective. Others have examined feasibility and decision-making by premutation carriers. Four studies reported that women made changes in reproductive decisions as a result of *FMR1* testing. One study that screened women with ovarian dysfunction found that most (15/20) reported it would have been important for them to have known sooner that they were premutation carriers.⁷¹ Furthermore, women in the general population have been

quite positive about prenatal *FMR1* testing and considered FXS a very serious condition with severe consequences for their children.⁷²

Based on successful prenatal screening clinical trials in Israel, a recommendation was made, from both a human and cost perspective, for consideration of full population screening. Currently, the American Academy of Obstetrics and Gynecology (ACOG) recommends screening for women with a positive family history of FXS or developmental disabilities, or elevated follicle-stimulating hormone levels of unknown cause, and considers general population screening an option for interested women.

SCREENING IN THE NEWBORN POPULATION

The average age of FXS diagnosis is still quite delayed, averaging about 35 to 37 months in boys and 41 months in girls, making the burden and the “diagnostic odyssey” encountered by the families, overwhelming. A survey of parents of children diagnosed with FXS found that 37.6% reported that they underwent more than 10 symptom-related visits to their health care professional before a diagnostic DNA test for FXS was ordered; additionally, 55.5% of the parents studied already had another child before the first child was diagnosed.⁷²

In 2005, the American College of Medical Genetics (ACMG) task force formed to evaluate and recommend conditions for inclusion in state newborn screening panels, considered and rejected FXS for universal NBS. This was primarily because of lack of medical treatment or data on the benefits of early intervention and absence of a cost-effective screening test. Since that decision, advances have been made in both pharmacological and nonpharmacological treatment, development of cost-effective molecular

tests for *FMR1* mutations, and identification of other benefits to screening for FXS. In addressing presumptive benefit, Bailey et al⁷³ concluded that existing evidence is sufficient to support NBS for conditions associated with ID.⁷³ Van der Schuit et al⁷⁴ found that children in an early intervention group showed greater progress than those in a control group on all measures related to language development. Importantly, in 2006, Alexander and Van Dyck⁹² challenged the dogma that NBS applies only to conditions with effective treatments and broadened the concept to include benefits for the family, including reproductive decision-making, potential to participate in research or innovative therapies, and avoiding the diagnostic odyssey.⁷⁵ Additionally, the substantial progress in PCR technology has raised the possibility of universal testing for FXS.

The arguments in favor of an *FMR1* NBS program are based on the high prevalence in the general population, accurate, quick and specific DNA testing, the high risk for recurrence and risk in extended family members, the clinical significance of FXS, opportunities for earlier intervention and participation in research, and the emotional and economic burden of the diagnostic odyssey for families and, ultimately, society.

Concerns have been raised related to NBS and identification of premutations that are not fully expressed and are typically late onset and full mutations in female individuals that may be incompletely penetrant. There are also concerns related to the incidental detection of other genetic disorders, such as sex chromosome abnormalities.⁷⁶ Finally, in considering NBS for FXS, it is important to provide resources for genetic counseling and early intervention programs to the families that are identified.

The possibility of developing symptoms related to the premutation, particularly

FXTAS and FXPOI, must be explained to the family and is an ethical issue. Screening tests that would identify only the full mutation avoid this dilemma, but lose the potential to identify the vast majority of *FMR1* mutation carriers who define at-risk families.

Informing families of a positive *FMR1* screening result would likely fall on the child's pediatrician, genetic counselor, or other health professional. Access to essential information on FXS and FXDs must be available for informing pediatricians and genetic counselors. Additional education, use of the National Fragile X Foundation (NFXF) Web site, and consultation with Fragile X Clinical and Research Consortium (FXCRC) specialists can provide pediatricians and genetic counselors with appropriate education and support regarding FXDs. This has also proven feasible for many disorders currently screened using the ACTION (ACT) Sheets developed by the American College of Medical Genetics.

FXS SCREENING OUTSIDE OF THE HEALTH CARE SYSTEM

Special educators; behavior, speech, and occupational specialists; and other professionals have direct involvement with children with ID over extended periods of time, allowing them to potentially recognize cognitive and behavioral symptoms of FXS. Because of their frequent contact with families, they are in an excellent position to initiate and follow-up on referrals made for genetic evaluation. With involvement of educators and therapists, the universally implemented Part C, special education preschool program (age 3–5 years) could be an important setting to generate referrals for FXS screening.

IDENTIFIED POTENTIAL BARRIERS TO SCREENING

FXS challenges current criteria for NBS.⁷⁶ Social scientists and bioethicists

question whether identifying newborns as having an “untreatable” condition could negatively affect the parent-child bond, and increase parental anxiety. Because screening for FXS has the potential to raise issues that other NBS core conditions do not, including identifying individuals at risk for FXPOI and FXTAS, initially it could be conducted voluntarily with informed consent. All efforts would need to be made to ensure that a consent process would not tax hospital staff, overwhelm parents, or reduce participation in the standard NBS program. NBS for FXS would also increase the need for genetic counseling, early intervention, and family support programs. These and other issues are currently being explored in a pilot research study of NBS for FXS.⁷⁷

In a recent survey of genetic health care professionals' (medical geneticists and genetic counselors) attitudes regarding FXS screening, most the respondents were in favor of newborn and prenatal screening.⁷⁸ The most commonly endorsed time for screening was for women before pregnancy. An important component in *FMR1* population screening is the time required for genetic counseling because of the multigenerational mutational process and the variable phenotypes associated with each genotype.⁷⁹ A further issue is the relative frequency of, and limited knowledge regarding, the implications of an intermediate-size allele, that if reported as abnormal, may lead to increased anxiety in a significant number of individuals being screened. Genetic counseling strategies and educational information have been developed and are available for families and professionals (www.fragilex.org).⁸⁰

There are also socioeconomic barriers to population screening that need to be identified and addressed. Research is

limited on the interrelated role that cultural, racial, educational, and other socioeconomic factors play in the access and availability of genetic testing. However, some prior studies address factors that affect access to genetic services. In a study exploring access to genetic counseling services for children with IDs, including autism and Down syndrome, investigators found that the single most important variable determining referral was to have a consistent medical provider as well as having the child covered by either private or public insurance.⁸¹ Access was also influenced by how parents perceived the severity of the disorder. Access issues related to socioeconomic factors would be predicted to potentially delay the diagnosis of FXS even longer in medically underserved populations.

Studies of other genetic disorders can help with identification of barriers to *FMR1* testing. Such studies have suggested that the level of genetics literacy, trust in medical providers, and tailored culturally sensitive recruitment strategies are major factors in African American and other racial/ethnic minorities' decisions to participate in genetics research and clinical testing.⁸² Additionally, Johnson et al⁸³ found that like-ancestry of the participant-researcher/recruiter is key to successful recruitment and retention of racial/ethnic minorities in genetics research. Genetic counseling educational materials that are culturally sensitive need to be developed, as these materials have been shown to reduce concerns about genetic testing (Barlow-Stewart, Yeo et al 2006; Baty, Dudley et al 2006; Charles, Kessler et al 2006).^{93–95} In line with many other human services organizations, the Centers for Disease Control and Prevention, March of Dimes, and NFXF have recognized this need and have initiated the process of incorporating culturally

sensitive photographs and other representations in their educational materials.

For population-based screening programs to be successful, it will be critically important to address potential barriers and to focus on developing, implementing, and assessing genetic counseling, educational, and therapeutic interventions. This research should partner with families and other stakeholders, such as the NFXF to help inform best practices.

COMPARISONS WITH OTHER NBS PROGRAMS OF GENETIC DISORDERS

Given the high carrier frequency of *FMR1* premutations, resulting FXDs are among the most common genetic conditions. Comparison with population-screening programs for other common genetic conditions is informative and can help initiate the discussion of widespread screening. Cystic fibrosis (CF), an autosomal recessive condition, with a carrier rate of 1 of 31 Caucasians, and a prevalence rate of 1 of 3000 births, has recently been included in newborn and prenatal screening. Years of debate preceded the introduction of routine CF carrier testing in prenatal care because of concerns regarding the complexity of CF mutations, the need for education of medical professionals, and the difficulty of defining the disease phenotype.⁸⁴ In 2001, however, both ACOG and ACMG recommended that all pregnant women be offered CF carrier screening, with subsequent carrier testing for partners on identification of a carrier. Additionally, CF is now included in the mandatory NBS panel in all 50 states.⁸⁵ The road to universal screening for CF followed a path that included strong advocacy by the CF Foundation, the advent of testing by inexpensive PCR-based DNA technologies, evidence of the benefit of early diagnosis, and

support for carrier screening from patients and the obstetrics community.⁸⁶

Similarities between FXS and CF include the delay of diagnosis, often after the birth of a second, affected child; variable phenotype in carriers (men with congenital absence of the vas deference are often CF carriers); accurate, available PCR-based DNA testing; and high carrier rate and genetic risks to extended family members.

SUGGESTIONS/PROPOSALS FOR ALLEVIATING BARRIERS TO EARLY IDENTIFICATION

Evaluation of screening for *FMR1* mutations at any level must weigh the costs and benefits of early identification of *FMR1* mutations. Some obvious benefits include the following: opportunities for enhancement of development and adaptive functioning through early intervention and intensive therapy programs, elimination of the “diagnostic odyssey” for the family searching for the cause of their child's difficulties, opportunities to participate or benefit from clinical trials of promising new treatments, ability to provide genetic counseling regarding risk for future pregnancies in the immediate and extended family, and identification of other family members with undiagnosed FXDs who could benefit from diagnosis-based management.

NEWBORN SCREENING ADVANTAGES

Parent studies indicate that most parents are in favor of NBS for “less-treatable” conditions, the category under which FXS would fall at this time. Although therapeutic interventions are not a “cure,” they do stimulate development and address delays and disabilities early on to maximize the potential of the therapy and the

individual. In a recent study of 2045 parents' decision to participate in a pilot newborn *FMR1* gene screening project, most parents accepted the screening for reasons including "wanting to know," "benefiting research/social responsibility," and "minimal risk."⁷⁷ If development efforts for new FXS targeted therapeutics, including mGluR5 antagonists, γ -aminobutyric acid agonists,⁸⁷ and other medications presently being investigated in clinical trials are successful, more effective treatment is potentially available. With the formation of the FXCRC, an infrastructure now exists to help coordinate clinical trials as well as medical treatment in the future. The recent development of rapid and inexpensive PCR technologies will further support the feasibility and implementation of mass NBS for FXS. Identified families will have the opportunity to take part in clinical trials, research studies, and genetic counseling, and will have the advantage of entering into early intervention before symptoms arise.

PRECONCEPTION/PRENATAL SCREENING ADVANTAGES

In a recent study of FXS caregivers, 83% agreed or strongly agreed that preconception and/or prenatal screening should be offered at all times.⁸⁸ Prenatal or preconception screening for *FMR1* mutations has been available through commercial laboratories servicing the obstetrics community and is offered on a voluntary basis to patients in select obstetrics practices that routinely offer it as part of genetic screening. Although the ACMG and ACOG do not have a policy statement regarding "low-risk" general population screening, this is occurring in various socioeconomic, educational, and geographic populations that investigate (and request) genetic testing. At this point, as more carriers are identified in large US metropolitan areas

with higher income and educated populations, this is creating a stratified class system of carrier testing for *FMR1* gene mutations. Offering all pregnant and pre-pregnant women *FMR1* screening would alleviate this imbalance. A further advantage to preconception or prenatal screening is to assist in the identification of women with possible ovarian insufficiency. The latter is of importance because expensive fertility treatments are often undertaken by unknowing premutation carriers.

ADVANTAGES OF EARLY CHILDHOOD SCREENING

In the absence of widespread prenatal screening or NBS, every attempt should be made to lower the age of diagnosis in affected children. In this regard, the well-child visits are a preferred setting to evaluate early development and screen for common etiologies of developmental, speech or behavioral disorders. Based on the American Academy of Pediatrics recommendations for developmental evaluations at 9, 18, and 30 months, a thorough screening should be done to include gross motor, fine motor, social, cognitive, and language development. Clinical models for genetic screening outside of the newborn period have been suggested, primarily in the context of informed consent, counseling, and well-child care.⁸⁹ At this time, however, mass screening for genetic conditions outside of the newborn or prenatal period does not exist, so we are forced to rely on clinical presentations of symptoms to initiate childhood testing.

In line with the American Academy of Pediatrics fragile X health supervision guidelines,⁹⁰ which recommend *FMR1* testing in any child with developmental delay, our recommendation would be that all children with delays be screened for *FMR1* mutations as soon as delays are identified. This would lower the age of identification of FXS

while the issues regarding universal screening (prenatal/preconception screening, and NBS) are being worked through. One should be aware that this method of screening is likely to miss many affected girls and some mildly affected boys. On the other hand, if *FMR1* screening was to be offered for all children, regardless of developmental status, the period for early intervention and/or family planning that is optimized by NBS may have passed by the time young children are identified.

CONCLUSION AND RECOMMENDATIONS

To more accurately quantify and begin to ameliorate the significant public health burden of *FMR1* mutations, we propose the goals of increasing the identification of families affected by *FMR1* mutations and of lowering the age of identification of children with FXS. Toward that end, we propose the following action steps:

1. Support and continue the pilot NBS studies that are under way with the goal of identifying the full range of costs and benefits of NBS for *FMR1* mutations.
2. Encourage the American Society of Reproductive Medicine and ACOG to address/endorse the offering of general population *FMR1* screening to all preconception or prenatal patients, regardless of family history.
3. Recommend that pediatricians order *FMR1* DNA testing for children with developmental delays at the office visit when the delays are identified. Pediatricians may choose to have consultation with a medical geneticist or clinical staff at 1 of the FXCRC fragile X clinics (www.fragilex.org) if they have questions.
4. Increase education and awareness of FXD in nonmedical professionals

through use of the Part C established networks providing services to children with developmental delays.

5. Increase education for health and education professionals serving underserved populations about FXDs,

by using publicly funded health and education agencies.

6. Use the existing FXCRC infrastructure to promote greater outreach to underserved populations within 100 miles of each clinic,

based on efforts that have demonstrated success in reaching historically underserved populations.

7. Support additional studies to determine/establish the true prevalence of *FMR1* mutations.

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