

# Health Supervision for Children With Fragile X Syndrome

Committee on Genetics; Pediatrics. 127 (5): 994 -1006

This article is of interest to SCATN pediatricians because of the frequency with which autism occurs in children with Fragile X Syndrome. According to the CDC, studies show that 5% of people with an ASD are affected by Fragile X and 10% to 15% of those with Fragile X show autistic traits. This article highlights what is important for pediatricians to know for their practice and also revisits the recommendation that all boys with a diagnosis of ASD have DNA testing for Fragile X.

Fragile X Syndrome (an *FMR1*-related disorder) is the most commonly inherited form of mental retardation. Early physical recognition is difficult, so boys with developmental delay should be strongly considered for molecular testing. The characteristic adult phenotype usually does not develop until the second decade of life. Girls can also be affected with developmental delay. Because multiple family members can be affected with mental retardation and other conditions (premature ovarian failure and tremor/ataxia), family history information is of critical importance for the diagnosis and management of affected patients and their families. This report summarizes issues for Fragile X Syndrome regarding clinical diagnosis, laboratory diagnosis, genetic counseling, related health problems, behavior management, and age-related health supervision guidelines. The diagnosis of Fragile X Syndrome not only involves the affected children but also potentially has significant health consequences for multiple generations in each family.

## Important points of the article

- Fragile X Syndrome should be suspected in a boy with developmental delay and hypotonia in early childhood
  - The clinical phenotype in males with Fragile X Syndrome can be subtle and difficult to detect, especially in prepubertal boys
- Cognitive deficits range from moderate to severe mental retardation
  - Language delay is common and a child with Fragile X Syndrome may not begin to speak until 2 or 3 years of age
  - Cognitive impairment can also be seen in females who carry the full mutation
- Behavioral problems occur in more than 50% of individuals with Fragile X Syndrome
  - ADHD features are seen in 80% of Fragile X Syndrome patients
  - Autism is present in 30% of people with the full Fragile X mutation, and PDD-NOD in an additional 20% (Conversely, Fragile X Syndrome is found in between 2 and 6% of people with autism)

This article is an excellent review of Fragile X Syndrome including its molecular basis, clinical phenotype, patient management, and guidance genetic counseling. The second half of the article provides detailed guidelines for health supervision of patients with Fragile X Syndrome from prenatal issues through adulthood.

Take home message: Because young children with fragile X syndrome may not have distinguishing physical features, any child with developmental delay, borderline intellectual abilities, mental retardation, or **autism of unknown etiology** should have DNA testing for Fragile X syndrome.

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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## Health Supervision for Children With Fragile X Syndrome

Committee on Genetics

*Pediatrics* 2011;127;994-1006; originally published online Apr 25, 2011;

DOI: 10.1542/peds.2010-3500

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/127/5/994>

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# Clinical Report—Health Supervision for Children With Fragile X Syndrome

## abstract

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Fragile X syndrome (an *FMR1*-related disorder) is the most commonly inherited form of mental retardation. Early physical recognition is difficult, so boys with developmental delay should be strongly considered for molecular testing. The characteristic adult phenotype usually does not develop until the second decade of life. Girls can also be affected with developmental delay. Because multiple family members can be affected with mental retardation and other conditions (premature ovarian failure and tremor/ataxia), family history information is of critical importance for the diagnosis and management of affected patients and their families. This report summarizes issues for fragile X syndrome regarding clinical diagnosis, laboratory diagnosis, genetic counseling, related health problems, behavior management, and age-related health supervision guidelines. The diagnosis of fragile X syndrome not only involves the affected children but also potentially has significant health consequences for multiple generations in each family. *Pediatrics* 2011;127:994–1006

## INTRODUCTION

This set of guidelines was designed to assist pediatricians in caring for children with fragile X syndrome after a diagnosis has been confirmed by DNA analysis. Fragile X syndrome (secondary to an abnormality in the fragile X mental retardation 1 [*FMR1*] gene) is the most commonly inherited form of mental retardation. The disorder affects the child and potentially the mother and other family members. These guidelines, therefore, discuss issues pertinent to the clinical manifestations of this disorder in younger and older people. The multiple manifestations in different age groups have led to fragile X syndrome being designated as one in the spectrum of *FMR1*-related disorders.<sup>1</sup>

Awareness that mental retardation has a sex-linked component, with an excess of males affected, has existed for more than a century.<sup>2</sup> This observation led to the suggestion that genes affecting cognition were located on the X chromosome. In 1943, Martin and Bell<sup>3</sup> reported that mental retardation segregated as an X-linked gene in a family in which both males and females were affected. Twenty-six years later, in 1969, Lubs<sup>4</sup> reported a distinctive fragile site on the X chromosome, which required culture media deficient in folic acid to be induced on a chromosome analysis, that segregated with mental retardation in 3 generations of a family. This is now known as the fragile X chromosome. In 1977, the relationship of this fragile site at band q27.3 on the long arm of the X chromosome (Xq27.3) to X-linked mental retardation was confirmed, and fragile X syndrome, as a clinical entity, was defined. Since

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### KEY WORDS

fragile X syndrome, *FMR1*-related conditions, mental retardation, health guidelines

### ABBREVIATIONS

*FMR1*—fragile X mental retardation 1 gene  
CGG—cytosine-guanine-guanine  
FMRP—fragile X mental retardation 1 protein  
mGluR—metabotropic glutamate receptor  
POI—primary ovarian insufficiency  
FXTAS—fragile X-associated tremor/ataxia syndrome

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

[www.pediatrics.org/cgi/doi/10.1542/peds.2010-3500](http://www.pediatrics.org/cgi/doi/10.1542/peds.2010-3500)

doi:10.1542/peds.2010-3500

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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that time, the clinical and molecular features of the condition have been more clearly delineated. Several literature sources are available for additional information.<sup>1,5-7</sup> New information regarding the role of the protein product in synaptic plasticity in the brain is under investigation.<sup>8</sup>

The clinical phenotype of fragile X syndrome, including cognitive abilities, is variable, and physical features often are nonspecific in nature, especially in young children. The disorder has been described in every ethnic group and has an estimated prevalence of 1 in 3700 white males and 1 in 2500 black males.<sup>1</sup> Clinical manifestations of fragile X syndrome also may occur in heterozygous females, in whom the prevalence is estimated to be 1 in 7000.

### Molecular Basis of Fragile X Syndrome

Cytogenetic assay for fragile X syndrome is no longer regarded to be sufficiently precise for clinical diagnostic use. In 1991, the *FMR1* gene was mapped to the fragile site at Xq27.3.<sup>5,9</sup> *FMR1* harbors a novel, unstable CGG (cytosine-guanine-guanine) trinucleotide repeat within the 5'-untranslated region of the gene, which accounts both for the fragile site and the genetic peculiarities associated with the region. The CGG repeat is highly polymorphic in the general population. The normal range is from 5 to 40, and 30 CGG repeats represents the most common number found within the gene. Full mutations, which cause fragile X syndrome, are the consequence of unstable expansion of the repeats, which results in a CGG number that exceeds 200. A full mutation results in hypermethylation of *FMR1*, which leads to gene-silencing and a decrease in the production of the fragile X mental retardation 1 protein (FMRP). The most important factor that determines the clinical severity of fragile X syndrome

is the degree of *FMR1* methylation and gene-silencing rather than the length of expansion reflected by the number of CGG repeats, which explains why 2 people with the same number of expanded CGG repeats but different FMRP levels will have different clinical presentations, because methylation may differ. Classically, in a person with a full mutation, the repeat number is massively expanded. Premutations, which have a CGG repeat number that ranges from 55 to 200, are meiotically unstable in the female. Premutations are unmethylated, are transcriptionally active, and produce FMRP, although possibly in lower amounts than normal alleles. Repeats in the range of 45 to 54 are considered to be intermediate or "gray-zone" alleles and are not considered to be predisposed to meiotic instability.<sup>1</sup> Molecular clinical correlations have demonstrated that variation in the clinical phenotype of affected people is related to the presence of mosaicism of methylation status, which results in preservation of some gene function and partial expression of FMRP. Although most instances of fragile X syndrome result from CGG expansion into the full mutation range, a rare point mutation within the *FMR1* gene or deletion in *FMR1* can produce the typical phenotype of fragile X syndrome as well.

### Clinical Phenotype

The clinical phenotype in males with fragile X syndrome can be subtle, and its detection in the prepubertal period can be difficult. In fact, it was reported from a parent survey that 24% of families with a child in whom fragile X syndrome was diagnosed had seen a health care provider more than 10 times before fragile X testing was performed.<sup>10</sup> Often, it is the presence of development delay, mental retardation, or specific behavioral patterns that leads to suspicion of fragile X syn-

drome; mean age at diagnosis is 32 months. The classical facial appearance that includes a prominent forehead, a long, narrow face, a prominent jaw, and protuberant ears becomes more evident late in childhood or in early adolescence. The palate frequently is highly arched, and cleft palate has been reported. Dental crowding and malocclusion are common. Strabismus may be present, and refractive errors, including hyperopia and astigmatism, are present in 23% to 50% of cases. Nystagmus and ptosis also are occasional ocular findings. Macro-orchidism is observed in more than 80% of adolescent and adult males with fragile X syndrome; mean testicular volume is approximately 50 mL (normal mean testicular volume: <25 mL). Macro-orchidism is less common in prepubertal boys. Fragile X syndrome also has a connective tissue dysplasia, and findings may include soft velvet-like skin; joint hypermobility, especially in the fingers; pes planus; congenital hip dislocation; scoliosis and clubfoot; and, in adults, occasionally mitral valve prolapse.<sup>6</sup> Feeding problems are common, and gastroesophageal reflux has been reported for one-third of affected infants. Chronic otitis media, seen in 60% to 80% of cases, has its onset early in life, and recurrent otitis media is present in 23% of males with fragile X syndrome. Seizures have been reported in approximately 13% to 18% of affected males and 5% of females with a full mutation, and there may be relative macrocephaly. Birth weight in affected people typically is normal. Accelerated linear growth with tall stature is common throughout childhood; however, growth velocity tends to slow in adolescence, and 26% of adult men with fragile X syndrome have a height that is equal to or less than the 5th percentile.<sup>6</sup>(p27-28)

A subgroup of males with the full mutation has been described in which the clinical phenotype is reminiscent of Prader-Willi syndrome.<sup>11</sup> Affected males have extreme obesity, short stature, stubby hands and feet, and diffuse hyperpigmentation.

### Cognitive Profile

Fragile X syndrome should be suspected in a boy with developmental delay and hypotonia in early childhood. Cognitive deficits frequently result in moderate-to-severe mental retardation; the average IQ is approximately 40 in an adult man with a completely methylated full mutation. Males who are less severely affected can have incomplete methylation resulting in some gene product and present with only mild intellectual deficits or learning problems. In addition, slowing in the acquisition of cognitive skills can occur with age.

Language delay also is evident in early childhood. A child with fragile X syndrome may not begin to speak until 2 to 3 years of age. Although vocabulary and syntax may be less involved, deficits in conversational speech are frequent.

In females with a full mutation, the cognitive profile is similar to that of males, but there is wider phenotypic variability, especially in relation to IQ scores. Intellectual abilities range from normal to significant mental retardation, and the majority of females with a full mutation have a normal or borderline IQ. The milder phenotype in affected females correlates with the degree of X inactivation of the X chromosome that contains the CGG expansion during lyonization. A more severe phenotype would be anticipated when there is skewed X inactivation (eg, when the majority of X chromosomes randomly inactivated are those with a normal CGG repeat number), thus preferentially activating the X chromosome with an expanded CGG repeat number.

### Neurobiology

Gross abnormalities have not been observed in the brains of people with fragile X syndrome on autopsy. Although diffuse brain atrophy and white matter abnormalities have been noted on MRI, routine neuroimaging of the brain is not indicated. At the cellular level, longer and thinner dendritic spines on which most of the synapses occur have been detected, which suggests a possible misregulation in their development and maturation. FMRP has an important role in the regulation of protein synthesis at a local level in the dendrites of neurons. Protein synthesis in dendritic spines is important for synaptic transmission, synaptic plasticity, learning, and memory. A proposed role for FMRP at the synapse is that it is a negative regulator of protein synthesis stimulated by group 1 metabotropic glutamate receptor (mGluR) activation.<sup>8</sup> Therefore, fragile X syndrome is at least partially a result of exaggerated responses to mGluR stimulation.

### Behavioral Phenotype

Behavioral problems occur in more than 50% of affected patients and are generally out of proportion with the affected child's cognitive level, compared with children with other developmental disorders who are functioning at similar intellectual levels.<sup>6,7</sup> In general, behavioral difficulties can be separated into a few symptom clusters. Features of attention-deficit/hyperactivity disorder, including hyperactivity, inattentiveness, distractibility, restlessness, and impulsivity, are present in 80% of patients with fragile X syndrome. Affected children also can exhibit anxiety-related symptoms including obsessive-compulsive-like and perseverative behaviors. Emotional lability is common. Aggressive and self-injurious behaviors can occur, related to a difficult temperament, with irritability and frequent temper tantrums.

Hypersensitivity to sensory stimuli can lead to heightened and prolonged arousal in situations in which there is excessive auditory, visual, or tactile stimuli. This behavior can lead to an increase in tantrums, hyperactivity, oppositionality, and restricted verbal output. On the other hand, affected males often have a good sense of humor, are persistent and hardworking, and have an endearing quality. Features of autism may be present in early childhood, including stereotypies such as hand-flapping, biting, perseverative speech, poor eye contact, and lack of interest in social interaction. Autism is present in 30% of people with a full mutation, and pervasive developmental disorder—not otherwise specified has been reported in another 20% to 30% of affected children. Fragile X syndrome also is found in approximately 2% to 6% of people with autism. Psychiatric comorbidity also is frequently observed in affected people and includes oppositional defiant disorder, separation anxiety, and obsessive-compulsive disorder. Females with a full mutation tend to have a higher risk of emotional problems compared with the general population. In fact, shyness, social avoidance, social anxiety, mood lability, and depression may be presenting features in a female with the full mutation.

### Premutation

Both females and males with a CGG repeat number that ranges from 55 to 200 are considered to carry a premutation. The prevalence of a premutation has been estimated to be approximately 1 in 259 in females and 1 in 813 in males. People carrying the premutation originally were believed to be clinically normal, because the *FMR1* gene is not methylated with a CGG repeat number below 200, which results in FMRP activity. However, it is now recognized that carriers of a premutation can present with 1 or more distinct

clinical disorders: mild cognitive and/or behavioral deficits; primary ovarian insufficiency (POI); and a neurodegenerative disorder in older adult premutation carriers, especially males, called fragile X-associated tremor/ataxia syndrome (FXTAS). In contrast to decreased messenger RNA (mRNA) in people with a full mutation and absence of FMRP, mRNA levels are elevated and FMRP is present in people with a premutation.

A minority of female carriers of a premutation have mild physical features of fragile X syndrome, which can include prominent ears or hypermobile finger joints. Emotional problems also may be present, including anxiety, obsessive thinking, schizotypy, and/or depression. It was observed recently that depression and interpersonal sensitivity were more likely to occur in females with a premutation with more than 100 CGG repeats than in those with fewer repeats.<sup>12</sup> These emotional findings are likely to represent a mild form of the anxiety and perseverative thinking that occurs in those with a full mutation and may be the result of a mild deficit in FMRP found in the upper half of the premutation range. Males with a premutation are prone to have attentional problems, executive dysfunctions, social deficits, and obsessive-compulsive behavior.<sup>13</sup>

A disorder unique to female carriers of a premutation is POI (previously referred to as premature ovarian failure [POF]), in which there is cessation of menses before 40 years of age.<sup>14–17</sup> This disorder is seen in approximately 20% of women who carry a premutation allele, in contrast to approximately 1% in the general population. Subclinical ovarian dysfunction that leads to elevated follicle-stimulating hormone levels is seen in another 25% of adult women younger than 40 years with a premutation. An increased risk

of twinning also exists for conceptions in a woman with a premutation.

Recently, a new phenotype that develops in the later years of the majority of adult men who carry a premutation (rarely reported in female premutation carriers) has emerged, designated FXTAS.<sup>18,19</sup> A progressive intention tremor develops after 50 years of age and is typically followed by ataxia. Associated features include a peripheral neuropathy; parkinsonian manifestations; autonomic dysfunction such as incontinence, impotence, and orthostatic hypotension; progressive cognitive impairments that involve loss of memory and deficits in executive function; and psychological features including disinhibition, anxiety, mood lability, irritability, outbursts, depression, and isolation. Some patients progress to having dementia. This neurodegenerative disorder seems pathogenetically distinct from fragile X syndrome and is probably related to *FMR1* messenger RNA levels that are elevated in premutation carriers. FXTAS has not been observed in males with a full mutation. Maternal grandfathers of affected males should be counseled and evaluated as appropriate for adult-onset movement disorders.

The expansion of the number of CGG repeats occurs during reproduction in a female with a premutation. This may be a small expansion to a slightly larger CGG repeat number in the premutation range, or it may result in a massive expansion into a full mutation. The risk of expansion to a full mutation is determined by the size of the mother's premutation. As the CGG repeat number increases, so does the risk of expansion to a full mutation (Table 1). Therefore, the larger the number of repeats, the more likely it will expand to a full mutation in an offspring. To date, no offspring with a full mutation has been described when the CGG repeat number is less than 59. Because the

**TABLE 1** Risk of Expansion to a Full Mutation in Male Offspring Based on the CGG Repeat Number in the Mother<sup>1,34</sup>

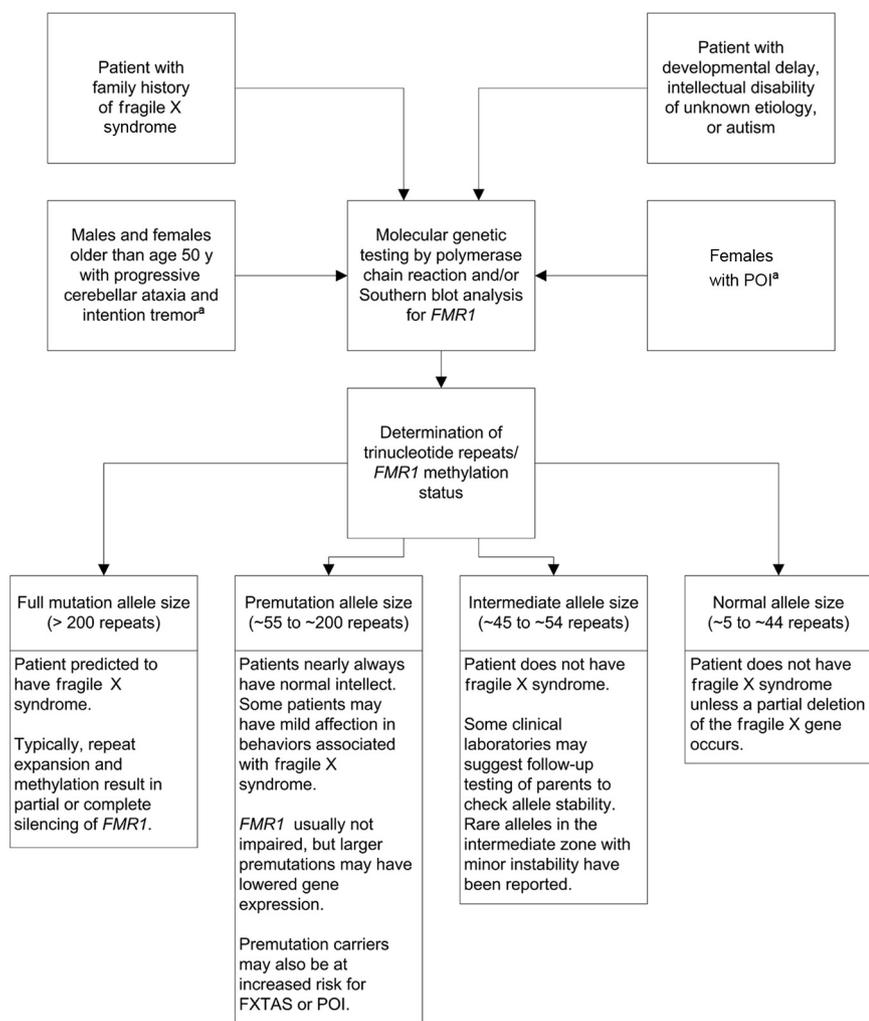
CGG Repeat Number	Risk for Expansion to a Full Mutation, %
59–69	37
70–79	65
80–89	70
90–99	95
≥100	100

number of CGG repeats in a female with a premutation has the potential to increase through several generations of a family, the risk of expansion to a full mutation also increases.

A premutation will be transmitted to all female offspring of a male with a premutation. In these females, the CGG repeat number is similar to their fathers' repeat number or may expand slightly. However, the CGG repeat number may undergo expansion when a female with a premutation reproduces, which could result in an offspring with a full mutation and fragile X syndrome. A premutation in a male will not be transmitted to his male offspring, because the son inherits his father's Y chromosome.

### Who Should Be Tested for Fragile X Syndrome

Because children with fragile X syndrome may not have apparent physical features, any child who presents with developmental delay, borderline intellectual abilities, or mental retardation or has a diagnosis of autism without a specific etiology should undergo molecular testing for fragile X syndrome to determine the number of CGG repeats (Fig 1). Approximately 2% to 6% of these patient populations will be found to have an *FMR1* mutation. The family should be made aware of the implications of the testing for other family members and given the option of genetic counseling before testing. Array comparative genomic hybridization (or array



**FIGURE 1** Testing algorithm for fragile X syndrome and *FMR1*-related disorders. <sup>a</sup> Adults to be considered for *FMR1* molecular testing. (Adapted with permission from Saul RA, Tarleton JC. *FMR1*-related disorders. *GeneReviews* [online]. October 28, 2010. Available at: [www.ncbi.nlm.nih.gov/books/NBK1384](http://www.ncbi.nlm.nih.gov/books/NBK1384). Copyright, University of Washington, Seattle, 1997–2010.)

testing) should also be considered. Phenotypic checklists have also been created for use in males with developmental delay of undetermined etiology to help identify candidates for fragile X molecular testing. These checklists slightly increase the diagnostic yield, especially when used in concert with targeted family fragile X history questionnaires. Fragile X testing should also be considered in patients in whom there is suspected, but not molecularly proven, Sotos syndrome or Prader-Willi syndrome. On the other hand, fragile X testing, is not routinely warranted for chil-

dren with isolated attention-deficit/hyperactivity disorder.

When evaluating a family with fragile X syndrome, questions also should address whether there are people with mild emotional and/or learning problems, POI, and/or features of FXTAS. Because people with a premutation are at risk of having these conditions, molecular testing is suggested for asymptomatic siblings of a child with fragile X syndrome and for other family members at risk of carrying the mutation. In family members found to have a premuta-

tion allele (55–200 CGG repeats), developmental testing may be indicated, and in older people, monitoring is warranted for POI and FXTAS.

### Management of a Child With Fragile X Syndrome

Diagnosing fragile X syndrome is beneficial to the family, because it establishes the reason why a child has cognitive deficits and/or behavioral problems. Establishing a diagnosis of fragile X syndrome also will allow parents and/or caregivers to gain an understanding of the disorder and how it affects the child's development and behavior. Diagnosis also will allow the family to focus on appropriate management strategies that will maximize their child's potential. Formal assessment tools are available to assist with a behavior-management plan. Current approaches to therapy are supportive and symptom based. Psychopharmacologic intervention to modify behavioral problems in a child with fragile X syndrome may represent an important adjunctive therapy when combined with other supportive strategies including speech therapy, occupational therapy, special educational services, and behavioral interventions. Medication management may be indicated to modify attentional deficits, problems with impulse control, and hyperactivity. Anxiety-related symptoms, including obsessive-compulsive tendencies with perseverative behaviors, also may be present and require medical intervention. Emotional lability and episodes of aggression and self-injury may be a danger to the child and others around him or her; therefore, the use of medication(s) to modify these symptoms also may significantly improve an affected child's ability to participate more successfully in activities in home and school settings.

Several classes of medications alone or in combination have proven to be beneficial in managing behavior problems in fragile X syndrome.<sup>7,20</sup> Stimulants target hyperactivity, inattention, and impulsivity, and two-thirds to three-quarters of symptomatic children with fragile X syndrome benefit from the use of methylphenidate. However, in some affected people, stimulants may exacerbate anxiety, mood lability, or aggressive tendencies. The  $\alpha$ -2-adrenergic agonists clonidine and guanfacine have been effective in treating hyperactivity, hyperarousal to sensory stimuli, impulsivity, and aggressive behaviors in approximately 70% of young boys with fragile X syndrome. These agents may be especially helpful in a child who is younger than 5 years and does not tolerate or respond to stimulants. Clonidine also is effective for the management of sleep disturbances,<sup>21</sup> and melatonin may be beneficial for regulating sleep patterns.<sup>22</sup>

Selective serotonin-reuptake inhibitors can be useful in the management of mood disorders, anxiety, obsessive-compulsive behaviors, tantrums, and aggression in people with fragile X syndrome. Atypical antipsychotics generally are reserved for people with fragile X syndrome who exhibit more extreme behaviors, particularly aggression, marked mood lability, self-injury, and other undesired behaviors. Parent reports of improvement in mood stabilization, attention, and academic performance have been described with aripiprazole, which should be used at low doses to avoid agitation induced by higher doses.<sup>23</sup> However, adverse effects can include excessive weight gain, sedation, nausea, constipation, diabetes, and tardive dyskinesia.<sup>24</sup>

Current psychopharmacologic therapy for fragile X syndrome is supportive or symptom-based, and no therapy

exists that is specifically directed at improving cognitive ability in patients with fragile X syndrome. However, because excessive mGluR signaling plays a role in the fragile X syndrome phenotype, drugs that target mGluR may be an effective treatment in this disorder. As more information regarding specific dendritic functions of FMRP are elucidated, pharmacologic investigations will likely be designed to address specific neurochemical and synaptic deficits generated by the absence of FMRP, targeting cognitive deficits and also leading to improvements in behavior.<sup>7,25</sup>

Factors in the environment also may influence adaptive behaviors, cognitive abilities, and behavioral symptoms of patients with fragile X syndrome. For instance, in 1 study, behavioral symptoms in children with fragile X syndrome who resided in a nurturing home environment displayed few autistic behaviors, better adaptive behavior, and higher IQ.<sup>26</sup>

### Genetic Counseling

Fragile X syndrome and *FMR1*-related disorders (ie, POI and FXTAS) are inherited in an X-linked dominant manner with often complex expression. Genetic counseling is recommended for all family members who are affected or at risk of having a premutation or an offspring with a full mutation. Genetic counseling is critical to provide information regarding the inheritance pattern and variability of the clinical phenotype in people being affected with both a full mutation and premutation and to offer the option of pursuing molecular testing. Options for reproductive planning can be discussed in anticipation of family planning for adults at risk of having an affected child. In addition to seeking help from professionals who are knowledgeable of the condition, information to assist families also can be obtained from support orga-

nizations and through contact with parents who have a similarly affected child.

The mother of a child with an *FMR1* mutation is almost always a carrier of a premutation or full mutation. Females who are premutation carriers may have inherited the premutation from their father or from their mother who also carries a premutation. Women with a premutation are at risk of premature ovarian insufficiency and at small risk of FXTAS. They carry a 50% risk of transmitting an abnormal gene, which either contains a premutation copy number (55–200) or a full mutation (>200) in each pregnancy. Rarely, a decrease in the number of CGG repeats has been reported when the abnormal allele is transmitted from a woman with a premutation to her daughter. The risk of expansion of a premutation in a mother to a full mutation in her offspring correlates with the number of CGG repeats in her mutation. Therefore, the higher the number of repeats in the mother, the greater the likelihood of expansion to a full mutation in her offspring (Table 1).

Males who are premutation carriers are referred to as transmitting males. During reproduction, all of their daughters will inherit a premutation, but their sons will not inherit the premutation, because they inherit a Y chromosome. All daughters of transmitting males are unaffected premutation carriers. Transmitting males also need to be aware of the risk of developing FXTAS after the fifth decade of life.

Males with a full mutation, in most instances, have mental retardation and decreased fertility. The FMRP plays a role in spermatogenesis, and in 1 study it was found that in later stages of spermatogenesis, men with fragile X syndrome had significantly malformed spermatids and a reduction in normally differentiated spermatids, which may cause reduced fertility. A full

mutation cannot be maintained during spermatogenesis; therefore, the sperm contains only expanded *FMR1* gene CGG repeat sizes in the premutation range.

Both males and females can have mosaicism as a result of either full mutation/premutation mosaicism or methylation/unmethylation mosaicism. In men, only a premutation will be transmitted to their female offspring.<sup>27</sup> Women with a full mutation are at 50% risk of having male or female offspring with a full mutation.

Genetic counseling is more problematic when CGG repeats are in the range of 41 to 58 in the *FMR1* allele. This is viewed as a “gray zone,” because unstable alleles of this size have been reported, but expansion is unlikely. To date, the smallest repeat number to expand to a full mutation in a single generation was 59 CGG repeats.

Because fragile X syndrome can be difficult to diagnose in a child, various studies have documented that 50% of families with males with fragile X syndrome may have their second child before the diagnosis is established in the first child.<sup>3,28–30</sup> Families with an affected male have indicated that early diagnosis would have influenced their reproductive decision-making. After a diagnosis was made, 73% of families reported that the diagnosis of fragile X syndrome affected their decision to have another child, and 43% of the families surveyed had a second child with a full mutation. Therefore, detection of fragile X syndrome not only would enable at-risk families to receive accurate reproductive counseling for the immediate and extended family but also could allow for appropriate intervention beginning in infancy. Recently, a pilot study in South Carolina on newborn filter-paper blood screens to perform testing for fragile X syndrome was completed

and established the potential feasibility of such a screening process.<sup>31</sup> Various policy issues still need to be considered.<sup>32</sup>

### THE PRENATAL VISIT

In some instances, pediatricians may be called on to counsel an expectant couple whose fetus has been determined to have fragile X syndrome or when there is a family history of the condition. In some settings, the pediatrician may be the primary resource for counseling parents and family members. The pediatrician should:

1. Review the diagnostic studies that led to establishment of the diagnosis.
2. Explain the cause of fragile X syndrome in the fetus and the potential for a recurrence risk.
3. Review the clinical manifestations, the variability seen in fragile X syndrome, and the long-term prognosis.
4. Review currently available treatments and interventions. This discussion should include the efficacy, potential complications and adverse effects, and costs or other burdens of these treatments.
5. Explore, using a nondirective approach, the options available to the family for treatment and rearing of the child. In cases of prenatal diagnosis, this approach may include discussion of pregnancy continuation or termination, rearing the child at home, foster care placement, or adoption.

It is strongly encouraged that this counseling be done in conjunction with genetic counseling or referral to a genetic counselor or clinical geneticist to provide a more in-depth discussion of fragile X syndrome, including the associated medical conditions, prognosis, management strategies, recurrence risk, future reproductive options, and

recommendations for evaluating at-risk family members.

Health care providers should ensure that children with fragile X syndrome are afforded the standard care for all children as outlined in the American Academy of Pediatrics “Recommendations for Preventive Pediatric Health Care”<sup>33</sup> and specific fragile X syndrome health supervision guidelines according to their age (Table 2).

### HEALTH SUPERVISION FROM BIRTH TO 1 MONTH: NEWBORNS (TABLE 2)

#### Examination

1. Examine the neonate for any orthopedic abnormalities, especially congenital hip dysplasia and clubfoot.
2. Review the molecular testing results with the family. In this age group, the diagnosis will only have been made if there was a confirmed family history or if it was previously established in utero. Although the typical phenotype of fragile X syndrome generally will not be present in the neonate, review the clinical manifestations and characteristic patterns of growth and development and problems associated with this condition, which may become more apparent with time. Evaluate the neonate’s occipitofrontal circumference, which may be increased, and begin to monitor head-growth velocity.
3. Monitor for feeding difficulties and symptoms of gastroesophageal reflux.

#### Anticipatory Guidance

1. Review the support groups and services that are available to the child and family. Supply written materials on fragile X syndrome and provide the address and telephone number of organizations involved in fragile X syndrome (eg, National Fragile X Foundation [www.

**TABLE 2** Fragile X Syndrome: Guidelines for Health Supervision

	Infancy to 1 y			Early Childhood, 1–5 y	Late Childhood, 5–12 y	Adolescence to Early Adulthood, ≥13 y
	Newborn	1–6 mo	6–12 mo			
<b>Examination</b>						
Ocular	● <sup>a</sup>	● <sup>a</sup>	● <sup>a</sup>	● <sup>a</sup>	●	●
Ear, nose, throat	—	● <sup>b</sup>	● <sup>b</sup>	● <sup>b</sup>	●	●
Skeleton	● <sup>c</sup>	—	—	—	●	● <sup>d</sup>
Cardiac	—	—	—	—	● <sup>d</sup>	● <sup>d</sup>
Measure testes	—	—	—	●	●	●
Development	●	●	● <sup>e</sup>	●	●	●
Neurologic	—	—	● <sup>f</sup>	●	● <sup>g</sup>	●
Behavior	● <sup>h</sup>	● <sup>h</sup>	● <sup>h</sup>	● <sup>h</sup>	● <sup>i</sup>	● <sup>i</sup>
<b>Anticipatory guidance</b>						
Genetics	● <sup>j</sup>	●	●	●	● <sup>k</sup>	● <sup>k</sup>
Psychosocial	● <sup>l</sup>	● <sup>l</sup>	● <sup>l</sup>	● <sup>l</sup>	● <sup>l</sup>	—
Support groups	●	●	●	●	●	●
Early intervention, physical and other therapies	—	●	●	●	●	●
Behavior	●	●	●	●	● <sup>m,n</sup>	● <sup>m,n</sup>
Education	—	—	—	● <sup>o</sup>	● <sup>p</sup>	● <sup>p</sup>

Health care providers should ensure that, in addition to the specific guidelines provided here, patients with fragile X syndrome are afforded the standard care for all children as outlined in the American Academy of Pediatrics "Recommendations for Preventive Pediatric Health Care."<sup>33</sup> ● indicates to be performed; —, not applicable.

<sup>a</sup> Strabismus may occur anytime between birth and 4 years of age.

<sup>b</sup> Serous otitis can occur throughout childhood, and the resulting hearing loss can further impair speech development. Pressure-equalizing tubes may be needed.

<sup>c</sup> Joint laxity, hip dislocation, or clubfoot may be seen.

<sup>d</sup> Mitral valve prolapse is possible.

<sup>e</sup> Irritability, hypotonia, and tantrums may begin to be seen.

<sup>f</sup> Seizures more commonly occur in this age group.

<sup>g</sup> Assess for atypical seizures, especially when any neurologic symptoms exist or if intellectual function decreases.

<sup>h</sup> Infants with fragile X syndrome are often described as stiff and irritable and may feed poorly.

<sup>i</sup> Violent outbursts may appear in this age group.

<sup>j</sup> Review molecular testing and discuss risks within the family; genetic counseling is strongly encouraged.

<sup>k</sup> Review risk to offspring of the affected person.

<sup>l</sup> Family support and issues of what to tell others are important at the time of diagnosis regardless of the child's age.

<sup>m</sup> Address sexual issues.

<sup>n</sup> Ask parents about violent outbursts.

<sup>o</sup> Review the preschool program with regard to special educational needs and future placement.

<sup>p</sup> Discuss the need for planning for vocational training.

FragileX.org], FRAXA Research Foundation [www.FRAXA.org]).

- Discuss resources available for support, such as family clergy, mental health professionals, families who have an affected child residing in the area, and friends.
- Discuss how and what to tell family members and friends about the neonate's condition.
- Review the recurrence risk for subsequent pregnancies; discuss options for family planning, including prenatal and preimplantation genetic diagnosis; or refer for formal genetic counseling to address these issues.
- Review the family history regarding evaluation of other family members at risk of having a premutation or

full mutation, or refer for formal genetic counseling to address these issues.

### HEALTH SUPERVISION FROM 1 MONTH TO 1 YEAR: INFANCY (TABLE 2)

#### Examination

Early growth and development may be normal, although neurologic abnormalities and delayed development may be present. Monitor the infant for the following problems:

- Hypotonia that frequently results in mild motor delay.
- Irritability, which is usually secondary to sensory problems, including tactile hypersensitivity.

- Feeding problems, which are common in infancy, and the presence of vomiting secondary to gastroesophageal reflux.

#### Anticipatory Guidance

- Monitor growth parameters closely.
- If feeding problems are severe, pursue diagnostic evaluations to determine if they are the result of oral motor problems and/or gastroesophageal reflux. If gastroesophageal reflux is identified, initiate appropriate management strategies or refer the infant for further evaluation by a pediatric gastroenterologist. If oral motor problems exist, refer the infant to an appropriate

interventionist to initiate feeding therapy.

3. Review the available resources to provide the infant with early-intervention services and assist the individualized family service plan team in providing the most appropriate services to maximize the infant's developmental potential. Parents should consider applying for Supplemental Security Income (SSI) through the Social Security Administration.

## **HEALTH SUPERVISION FROM 1 TO 5 YEARS: EARLY CHILDHOOD (TABLE 2)**

### **Examination**

1. Perform an ophthalmologic evaluation or arrange for ophthalmologic referral to check for strabismus and refractive errors, especially hyperopia and astigmatism, which are seen in 25% to 50% of affected children. Also monitor for ptosis and nystagmus, which are seen occasionally.
2. Evaluate the child for orthopedic problems related to connective tissue dysplasia, such as pes planus (80% of affected children), hypermobile joints, and scoliosis. Pronated feet require treatment with orthotics if a gait disturbance exists or there is uneven wearing of shoes.
3. Examine the child for inguinal hernias, especially at 1 to 3 years of age.
4. Assess the child's history for seizures or staring episodes and obtain an electroencephalogram if clinically indicated.
5. Monitor the child for recurrent otitis media (60%–80% of affected children), which could be associated with conductive hearing loss, and also for recurrent sinusitis (23% of affected children). Monitor the child's audiologic status yearly.
6. Receptive and expressive communication should be monitored closely, because language delay is usually evident by 2 years of age. An occupational therapy evaluation also may be indicated and should include an assessment of sensory integration abilities. A complete psychological evaluation that includes IQ testing is an important part of the developmental evaluation of the preschool-aged child with fragile X syndrome. Affected children require early developmental services to facilitate language, motor, and cognitive skills. These services are mandated by federal law and should be followed by enrollment in a developmental preschool and supplemented with special education services. Occupational and speech-language therapy should be incorporated into the program and should include continued attention to language, motor, and cognitive skills up to and including kindergarten. Computer technology with software programs that enhance language skills and early academic abilities, including reading and mathematics, can be incorporated into special education programming. Inclusion in a preschool setting is achievable with appropriate supports.
7. Monitor the child's emotional and behavioral status closely. Tantrums and hyperactivity frequently develop in the second year of life, especially related to transitioning and excessive sensory stimuli. Evidence of anxiety and depression as well as the presence of aggression and obsessive-compulsive behaviors may develop during this time period. Manifestations of autism, such as hand-flapping, self-injury, poor eye contact, lack of social engagement, and absent joint attention may be present before 3 years of age and necessitate further evaluation. Excessive sensory stimulation should be avoided when possible, including exposure to large crowds and loud noises; earphones can be used in such settings to allow the child to listen to a favorite tape or calming music to avoid behavioral outbursts. Significant behavior problems, such as tantrums, oppositional behavior, or severe hyperactivity, usually benefit from intervention by a psychologist or other behavioral specialist. Behavioral intervention techniques that emphasize the importance of decreasing excessive sensory stimuli and using positive behavioral reinforcement and the use of behavioral charting are beneficial.
8. Psychopharmacologic interventions can be helpful. The use of stimulant medication to treat hyperactivity, short attention span, and impulsivity decreases symptoms in approximately 60% to 70% of affected children but may be more effective for a child who is of school age than of preschool age. At a younger age, antihypertensive medications, such as clonidine or guanfacine, may have a better calming effect and improve hyperactivity and hyperarousal. For treatment of anxiety, social phobia, obsessive-compulsive tendencies, depression, and aggression, use of a selective serotonin-reuptake inhibitor is safe and can be effective. Monitoring for the development of akathisia (motor restlessness) is important. In addition, in the presence of severe mood instability and/or aggression that are unresponsive to a selective serotonin-reuptake inhibitor or stimulant medication, use of an atypical antipsychotic agent to provide mood stabilization may be indi-

cated. Approximately 10% of people with fragile X syndrome develop psychotic symptoms often associated with severe paranoia, which also may lead to aggressive behavior.

9. Linear growth during this period should be monitored closely, and linear growth velocity should be similar to that of unaffected children.
10. Structural changes of the face may start to become evident in preschool years and include a long face, high forehead, high arched palate, and prominent ears. Facial changes can result in dental crowding and malocclusion, and regular dental evaluation is recommended.
11. Occasionally, in affected children, obstructive sleep apnea occurs, which may be related, in part, to facial changes but also can be the result of the connective tissue dysplasia and hypotonia of facial and pharyngeal muscles. Excessive snoring, restless sleep, or fatigue during the day should signal the need for further evaluation of the child's sleep problem with evaluation of adenoidal size and the child's sleep pattern by using polysomnography.
12. Delayed toilet-training is common during this age range and is likely to reflect the child's cognitive status.

### Anticipatory Guidance

The pediatrician should review the child's preschool placement and ancillary services that complement the program. Inclusion with typically developing children should be considered when appropriate and may require supervision in that setting. Consider a formal developmental evaluation and discuss the role of behavior/psychological intervention when indicated.

1. Determine if behaviors such as hyperactivity, aggression, self-injury, and tantrums warrant medication management.
2. Seizures are an important clinical manifestation that occurs in approximately 20% of people with fragile X syndrome and usually have their onset in early childhood. Appropriate evaluation and treatment is indicated when suspicion of seizures is present.
3. Auscultation of the heart should be performed and blood pressure should be obtained at all clinic visits. The presence of a murmur or click should indicate the need for further evaluation by a pediatric cardiologist, and elevated blood pressure will require monitoring and a determination of whether medical treatment is indicated.
4. Delays in toilet-training can be helped by behavioral interventions including the use of a music video to facilitate toilet-training for people with developmental disabilities.<sup>6</sup>(p291)
5. Review the future reproductive plans of the parents and discuss recurrence risk and family-planning options when indicated.

### HEALTH SUPERVISION FROM 5 TO 12 YEARS: LATE CHILDHOOD (TABLE 2)

1. Macro-orchidism usually begins to develop at approximately 9 years of age, and the testes will increase in size throughout puberty (mean testicular volume in adulthood: ~50 mL). Testicular volume should be measured with an orchidometer, and boys should be assessed for the presence of a hernia, which occurs in approximately 15% of males with a full mutation. Assure the parents that macro-orchidism has no relation to sexual function and that it is not a sign of precocious puberty.

2. Girls with the full mutation should be monitored for the development of precocious puberty, which has been reported occasionally. Although the cause in most instances is unknown, hypothalamic dysfunction has been described with fragile X syndrome and may be the cause of precocious puberty.
3. Continuing to monitor the child's developmental status is critical for making certain that cognitive, speech and language, and motor needs are being addressed. Being provided with reports of interval progress in school is useful in determining the effectiveness of the child's programming and whether modifications or further evaluation are indicated.
4. Hyperactivity frequently will persist throughout childhood and is present in approximately 70% to 80% of affected boys and 30% to 50% of girls with a full mutation. Addressing this problem behaviorally and/or in combination with medication management may be indicated.
5. Monitor the child for obsessive-compulsive behaviors, especially because they may blend in with perseverative or repetitive behaviors and not be recognized. Anxiety—especially social anxiety—frequently is present, particularly in children who do not have hyperactivity or impulsivity. Pursuing appropriate management strategies to address the child's emotional needs is important for effective adaptation in the home and school settings.
6. Cognitive impairments result in mental retardation in most boys who have a full mutation that is fully methylated (average IQ: ~40). Occasionally, males with a full mutation are higher functioning because of incomplete methylation of FMRP as a result of mosaicism. Approximately 50% of females with a full

mutation have cognitive deficits (IQ range: 70–84). Recognition of cognitive impairments and adaptive functioning deficits should signal the need for pursuing appropriate support services in the school setting to meet the child's needs.

- In addition to delayed toilet-training, enuresis is common in both boys and girls with fragile X syndrome. Although affected children are not considered to be at increased risk of recurrent urinary tract infections, the connective tissue dysplasia may predispose to dilatation of the ureters and vesicoureteral reflux.<sup>6</sup>(p27) Further evaluation of the urinary tract through radiographic and ultrasonographic studies is indicated in the presence of a urinary tract infection, and referral to a nephrologist or urologist is indicated if urinary tract infections are recurrent in nature or a structural abnormality or reflux is identified. Behavioral strategies should be implemented in the presence of nighttime enuresis. In addition, treatment of enuresis may also require the use of behavior-modification techniques and an alarm system. If unsuccessful, medication management with agents such as imipramine, oxybutynin (an anticholinergic agent), or desmopressin acetate (an analog antidiuretic hormone) should be considered. Only occasionally will children require medication for this problem. Macro-orchidism will be maintained throughout adult life and does not require intervention.
- Because of the connective tissue dysplasia, children should be monitored for scoliosis, which occurs in approximately 20% of affected children. However, when present, it is usually mild and does not require treatment.

### **HEALTH SUPERVISION FROM 13 TO 21 YEARS OR OLDER: ADOLESCENCE TO EARLY ADULTHOOD (TABLE 2)**

- Hyperactivity may decrease during adolescence, but attentional problems and impulsivity frequently persist and may continue to need to be addressed behaviorally and medically.
- Assess adolescents for seizures, especially atypical seizures, particularly if intellectual performance is decreasing, although seizures tend to decrease during this time period.
- Reassure parents that macroorchidism will persist. Males (especially with a premutation or mosaicism) and females with fragile X syndrome can reproduce. Only a premutation will be present in the sperm of a male who has a full mutation, in contrast to other tissues, because a full mutation cannot be maintained in spermatogenesis; therefore, fertility is decreased in males.
- The adolescent growth spurt may be slightly less compared with unaffected children, although the timing is normal. Psychosocial development, physical sexual development,<sup>35</sup> and fertility should be discussed, as well as the need for appropriate supervision and birth control. Counseling should be tailored appropriately to cognitive level.
- Genetic mechanisms responsible for fragile X syndrome should be discussed with people with full mutations and premutations, and the risk of having an affected offspring should be reviewed. Males who are of reproductive age and have nonmosaic full mutations are infertile. Females with full mutations are fertile. Females with premutations are at increased risk of premature ovarian insufficiency, whereas females with full mutations are not. Males who are premutation carriers have no known fertility problems.

- Determine if behavioral problems continue to represent a concern, and pursue behavioral/psychological intervention if indicated.
- Discuss the availability and need for vocational training and group home placement if appropriate.
- Monitor for a cardiac murmur or click; if either is heard, pursue a cardiology evaluation (see recommendation 1 in "Health Supervision in Adulthood").
- Facilitate transition to adult medical care as appropriate or desired.
- Agencies that serve people with developmental disabilities are present in most states and may provide respite for parents, adult day care programs, and personal assistance and nursing services as needed.

### **HEALTH SUPERVISION IN ADULTHOOD (TABLE 2)**

During the transition from pediatric to adult medical care, the pediatrician can be a valuable source of information to the affected person's new primary care physician and/or obstetrician/gynecologist. The following information about fragile X syndrome can be communicated to facilitate the care of an affected adult:

- Mitral valve prolapse occurs in approximately 50% of affected adults. Mild aortic root dilatation also has been reported, although it has not been documented to enlarge. In addition, hypertension is common in adulthood.
- Up to 20% of women with a premutation will develop premature menopause before 40 years of age.
- There is a greater risk of emotional problems in affected females, espe-

cially at times of hormonal changes or estrogen deficiency, such as menopause, the postpartum period, and during menstrual periods.

4. Genetic counseling should be provided to review the risk for having an offspring with either a premutation or full mutation and options available for family planning. An increased risk of twinning also should be discussed with females who have a premutation.
5. Men and, to a lesser degree, women with a premutation are at increased risk of developing FXTAS after 50 years of age. Awareness of this risk, particularly in a man

with a premutation, warrants close monitoring for symptoms, especially when approaching 50 years of age.

People with fragile X syndrome and *FMR1*-related disorders face challenges throughout their entire lives. Therefore, coordinating medical, developmental, and behavioral services with available community resources can maximize the potential for affected people and minimize the stressors faced by other family members.

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## Health Supervision for Children With Fragile X Syndrome

Committee on Genetics

*Pediatrics* 2011;127;994-1006; originally published online Apr 25, 2011;

DOI: 10.1542/peds.2010-3500

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