

## Genetic Testing ACT Sheet

# Fragile X [FraX] Syndrome

**Condition Description:** Abnormalities of the fragile X intellectual disability (*FMR-1*) gene cause three distinct conditions: Fragile X Syndrome (intellectual disability with or without autism/autism spectrum disorder); premature ovarian failure (POF); and Fragile X-associated Tremor Ataxia Syndrome (FXTAS).

**Major Indications for Ordering Fragile X Testing:** Fragile X testing may be considered in males and females with intellectual disability and autism or autism spectrum disorder, females with premature ovarian failure, and older males with progressive development of intention tremor and ataxia with or without dementia.

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### **YOU SHOULD TAKE THE FOLLOWING ACTIONS:**

- Inform individual/family of the test result.
  - Refer for genetic evaluation and counseling.
  - Obtain consultation for evaluation, early intervention, and management of intellectual disability, autism, developmental delay, neurological disorders or infertility, as appropriate.
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**Diagnostic Evaluation:** Intellectually disabled males with intermediate and premutation repeat sizes may require immunohistochemical staining of lymphocytes for FMR protein to establish causation. Mosaicism may also be found. There are rare forms associated with FMR gene deletions.

**Clinical Considerations:** Fragile X syndrome is the most common inherited form of intellectual disability. Approximately 1/3 of affected children have autism or autism spectrum disorders. As an X-linked disorder, it affects males more severely than females. It is caused by an increased number (>200 – full mutation) of DNA repeats (trinucleotide-CGG) sequences in the *FMR1* gene, normal alleles of which have ≈5 to ≈44 repeats. Severity of intellectual disability cannot be predicted based on repeat length. Females with premutations (≈55 to ≈200 repeats) are at high risk for POF. Males with a “full” mutation usually have intellectual disability in the mild to moderate range. Approximately 70% of females with the full mutation have an IQ of 85 or lower; and the majority present with learning disabilities, although intellectual disability occurs in about 25%. Young males with the premutation often have ADHD and occasionally social deficits. Older males (>50 yrs.) and some females with a premutation may develop the FXTAS, characterized by intention tremor, ataxia, neuropathy and cognitive decline. Premutations can expand to full mutations in the next generation, particularly in carrier females, that is a premutation carrier can have a child with a full mutation. Individuals with repeat numbers of “intermediate” size (≈45 to ≈54 repeats) may expand to full mutations over more than one generation, meaning that children of individuals with an intermediate repeat could inherit a gene that has undergone expansion to premutation size with the attendant risks.

### **Additional Information:**

[Gene Tests/Gene Clinics](#)

[American College of Medical Genetics—Practice Guideline](#)

[American College of Medical Genetics—Laboratory Guideline](#)

[American Academy of Pediatrics](#)

### **Referral (local, state, regional and national):**

[Testing](#)

[Find Genetic Services](#)

Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care. It should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. Adherence to this guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians also are advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that become available after that date.

**LOCAL RESOURCES:** Insert State newborn screening program web site links

State Resource site (insert state newborn screening program website information)

Name	<input type="text"/>
URL	<input type="text"/>
Comments	<input type="text"/>

Local Resource Site (insert local and regional newborn screening website information)

Name	<input type="text"/>
URL	<input type="text"/>
Comments	<input type="text"/>

APPENDIX: Resources with Full URL Addresses

**Additional Information:**

**Gene Tests/Gene Clinics**

<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=fragileX>

**Genetics Home Reference**

<http://ghr.nlm.nih.gov/condition=fragilexsyndrome>

**American College of Medical Genetics -Practice Guideline**

<https://www.acmg.net/PDFLibrary/Autism-Spectrum-Genetics-Evaluation.pdf>

**American College of Medical Genetics - Laboratory Guideline**

<https://www.acmg.net/PDFLibrary/Fragile-X-Testing.pdf>

**Referral (local, state, regional and national):**

**Testing**

<https://www.ncbi.nlm.nih.gov/gtr/all/labs/?term=C0016667%5BDISCU1%5D>

**Find Genetic Services**

[https://www.acmg.net/ACMG/Genetic\\_Services\\_Directory\\_Search.aspx](https://www.acmg.net/ACMG/Genetic_Services_Directory_Search.aspx)

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