



Complete Summary

GUIDELINE TITLE

Genetic counseling for fragile X syndrome: updated recommendations of the National Society of Genetic Counselors.

BIBLIOGRAPHIC SOURCE(S)

McConkie-Rosell A, Finucane B, Cronister A, Abrams L, Bennett RL, Pettersen BJ. Genetic counseling for fragile X syndrome: updated recommendations of the National Society of Genetic Counselors. J Genet Counsel 2005 Aug;14(4):249-70. [141 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: McIntosh N, Gane LW, McConkie-Rosell A, Bennett RL. Genetic counseling for fragile X syndrome: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2000;9(4):303-25.

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SCOPE

DISEASE/CONDITION(S)

Fragile X syndrome

GUIDELINE CATEGORY

Counseling
Risk Assessment
Screening

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Medical Genetics
Obstetrics and Gynecology
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

GUIDELINE OBJECTIVE(S)

To present practice recommendations for genetic counselors and other health care professionals who provide genetic counseling and risk assessment for patients with suspected or confirmed fragile X syndrome and their families

TARGET POPULATION

Patients with suspected or confirmed fragile X syndrome and their families

INTERVENTIONS AND PRACTICES CONSIDERED

1. Assessment, including family history, medical history of proband, pregnancy history of at-risk carriers, and psychosocial history of the consultand
2. Prenatal testing (amniocentesis, chorionic villus sampling) and risk assessment
3. Genetic counseling
4. Education/health promotion
5. Fragile X Mental Retardation-1 (FMR1) gene testing
6. Risk assessment by analysis of the pedigree and FMR1 deoxyribonucleic acid (DNA) test results
7. Genetics management, including informing family members and FMR1 testing of additional relatives
8. Psychological support and referral
9. Address ethical issues including testing on healthy unaffected minors and family members
10. Follow-up with genetic test results, other support resources, referrals

MAJOR OUTCOMES CONSIDERED

Not stated

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The authors searched the MEDLINE and PsycINFO databases for relevant English language medical and psychosocial literature between 1999 and 2004, including seminal articles from earlier dates. Key words included: fragile X syndrome, genetic counseling, psychosocial assessment gene testing, premature ovarian failure, prenatal diagnosis, carrier testing, and preimplantation diagnosis. Guidelines and policy statements published by the American College of Medical Genetics and genetic counseling guidelines developed by genetic counselors in the state of Washington were also reviewed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The literature was reviewed and evaluated for quality according to the categories outlined by the U.S. Preventive Services Task Force (1995):

- I.** Evidence obtained from at least one properly designed randomized controlled trial
- II-1.** Evidence obtained from well-designed controlled trials without randomization
- II-2.** Evidence obtained from well-designed cohort or case-control-analytic studies, preferably from more than one center or research group
- II-3.** Evidence obtained from multiple time series with or without the intervention
- III.** Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

A draft document was made available to the 2,072 members of National Society of Genetic Counselors (NSGC) for comment. The NSGC membership includes genetic counselors, physicians, nurses, attorneys, doctors of philosophy, and students. The revised document was reviewed by the NSGC attorney and the NSGC Ethics Subcommittee and no conflicts with the NSGC Code of Ethics or issues regarding legal liability were identified in the final document. The NSGC Board of Directors reviewed and approved the final document in March, 2005.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Testing and Screening Recommendations

Testing Guidelines

The American College of Medical Genetics' Policy Statement on fragile X syndrome recommends fragile X testing for:

1. Individuals of either sex with mental retardation, developmental delay, or autism, especially when associated with other physical and behavioral characteristics of fragile X syndrome, a family history of fragile X syndrome, or a relative with undiagnosed mental retardation
2. Individuals with a family history of fragile X syndrome or a family history of undiagnosed mental retardation who are seeking reproductive counseling. When there is no established diagnosis of fragile X syndrome, testing the affected proband is preferable to screening an unaffected relative. However, this is not always feasible, especially in the prenatal setting.
3. Prenatal testing offered to individuals who are known Fragile X Mental Retardation-1 (FMR1) mutation carriers
4. Individuals tested previously by cytogenetics who have results inconsistent with phenotype
5. Women with reproductive or fertility problems associated with elevated follicle stimulating hormone (FSH) levels, especially if there is a family history of premature ovarian failure, fragile X syndrome, or undiagnosed mental retardation
6. Individuals with late onset tremor or cerebellar ataxia of unknown origin, particularly when there is a family history of movement disorders, fragile X syndrome, or undiagnosed mental retardation

Prenatal Diagnosis

Amniocentesis and Chorionic Villus Sampling

Prenatal diagnostic options for fragile X syndrome include amniocentesis and chorionic villus sampling (CVS). Amniocentesis is both accurate and reliable using the combined standard deoxyribonucleic acid (DNA) diagnostic methods of Southern Blot and polymerase chain reaction (PCR). The methylation status of the FMR1 region and the number of CGG repeats in the fetus can be accurately determined in amniocytes. Prenatal detection of the CGG repeat number for fragile X syndrome using CVS is accurate and reliable; however, there are special considerations that should be taken into account regarding the degree of methylation of the placental tissue. The methylation pattern observed in placental (CVS) tissue at 10-12 weeks gestation is incomplete and does not always reflect that observed in the liveborn. Because the clinical phenotype is influenced by both the number of CGG repeats and the degree of methylation, it can be difficult to distinguish large unmethylated premutations and small methylated full mutations. The possibility of follow up amniocentesis to clarify the status of the fetus, if the CVS result is indeterminate, should be discussed as part of the pretest counseling. For both amniocentesis and CVS, it may be helpful to determine both maternal and paternal allele number either prior to or concurrent with the prenatal testing. PCR analysis of fetal and parental DNA can be useful in assessing the fetal genotype prior to completion of the Southern analysis.

Genetic Counseling Issues

Comprehensive genetic counseling for individuals and families in whom the diagnosis of fragile X syndrome is suspected or has been made may require several sessions and may involve a long-term commitment on the part of the genetic counselor to follow these families. If this commitment cannot be made,

referring the family to a genetic counselor or center experienced with fragile X syndrome should be considered.

The general assessment (medical, family, and psychosocial histories; risk assessment), genetic counseling, management, and follow-up processes pertinent to fragile X syndrome are similar to those outlined in previous National Society of Genetic Counselors (NSGC) practice guidelines. Genetic counseling for fragile X syndrome should follow the recommendations in these guidelines with special attention given to genetic counseling methods and issues associated with X-linked disorders.

Diagnostic Evaluation

When obtaining family, medical, and psychosocial histories from patients and families, follow standard genetic counseling practice recommendations (refer to www.guideline.gov). Targeted medical family history questions specific to fragile X syndrome are included in the table below titled "Suggested Targeted Family History Questions for Fragile X Syndrome" and are appropriate for use in cases of suspected fragile X syndrome, families with a confirmed diagnosis, and at-risk or known carriers.

Suggested Targeted Family History Questions for Fragile X Syndrome

Note for each relative, any history, and the age of onset of:
<ul style="list-style-type: none">• Cognitive effects: Mental retardation, developmental delay, learning disabilities, specific problems with math• Speech delay or unusual speech pattern• Autistic spectrum disorders or autistic-like behaviors (gaze avoidance, repetitive behaviors, hand-flapping, hand biting, touch avoidance, etc.)• Attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD)• Dysmorphic features--macrocephaly, large ears, long face, broad forehead, prominent jaw, strabismus• Features of loose connective tissue: hyperextensible joints, flat feet, hypotonia, mitral valve prolapse, large testicles, hernias, recurrent ear infections• Neurologic symptoms: seizures, late-onset progressive tremor, ataxia, difficulty walking, balance problems, short-term memory loss, loss of sensation in limbs• Mental illness/personality disorders: depression, schizophrenia, bipolar disorder, obsessive-compulsive disorder, schizoaffective disorder, schizoid personality, etc.• Behavioral problems: impulsiveness, anger outbursts, violent behavior, solitary behavior, counseling or medication for behavioral difficulties• Shyness, social anxiety, excessive worrying, counseling or medication for emotional difficulties• Premature menopause, fertility problems

Confirmed Diagnosis of Fragile X Syndrome

Genetic counseling sessions for families with newly diagnosed fragile X syndrome offer opportunities for education, counseling, and guidance regarding the issues and concerns specific to fragile X syndrome. Particular challenges inherent in genetic counseling for fragile X syndrome include:

- The extremely variable expression of the disorder, especially in females with the full mutation
- The concepts of intermediate, premutation, and full mutation alleles and the mechanism of expansion including the multigenerational mutation process and complexity inherent in understanding the concept of carrier males in an X-linked disorder
- The variable recurrence risks based on size of the premutation in the female carrier
- The recent findings of fragile X-associated tremor/ataxia (FXTAS) and premature ovarian failure (POF) in carriers of the premutation

Genetic counselors should be cognizant of the fact that, in general, families are initially overwhelmed, both emotionally and intellectually, by the complexity of the disorder and its implications for other family members. Suggested components for genetic counseling sessions for families with a suspected or confirmed diagnosis of fragile X syndrome appear below.

Education/Health Promotion

1. Discuss the clinical presentation and natural history of fragile X syndrome in males and females.
2. Discuss the inheritance pattern and genetics of fragile X syndrome and the approach to testing the proband and other family members and interpretation of results.
 - a. FMR1 testing, including a discussion of the CGG repeat, methylation, sensitivity, and specificity
 - b. X-linked inheritance pattern, including examples of females and males with the premutation and full mutation, and the risk of expansion/reversion in such cases
 - c. Reproductive options and testing available to fragile X carriers (e.g., adoption, donor egg or sperm, prenatal diagnosis, preimplantation genetic diagnosis); include ethical concerns raised by such options, if appropriate
 - d. Costs of genetic testing and test limitations (e.g., limitations of CVS)
3. Be prepared to answer general questions relating to suggested treatment, therapy, and the function of the FMR1 protein.
4. Discuss follow-up recommendations (e.g., identification and testing of at-risk family members, scheduling follow-up visits).
5. Make appropriate referrals for medical, educational, and mental health interventions and discussions that are beyond the scope of genetic counseling practice.
6. Provide contact information for support groups and patient-appropriate resources, as requested (see Table III in the original guideline document).

Risk Assessment

Analyze the pedigree and FMR1 DNA results and provide genetic risk assessment for carrier status and chance of having affected or carrier offspring. Inheritance principles for fragile X syndrome include:

1. All daughters of a male with a permutation are obligate premutation carriers, whereas none of his sons will inherit the mutation.
2. Females with premutations and full mutations are at risk to have affected sons and daughters.
3. The risk for affected offspring in females carrying premutations varies with the length of the repeat number (see Table I of the original guideline document).
4. Women with full mutations have a 50% risk with each pregnancy to pass the full mutation to the fetus. Although rare, there are reports of women with full mutations having offspring with reversions (decreases in the number of the repeat) or premutation-sized alleles.
5. Males with a full or mosaic mutation will not pass it on to their sons and most likely will pass on a premutation to their daughters. Though it was previously thought that all males with full mutations have only permutations in their sperm, there are rare reports of daughters with full mutations born to males with full/mosaic mutations.

Informing Family Members

The diagnosis of fragile X syndrome can have far-reaching genetic and emotional implications for extended family members. Newly-identified mutation carriers as well as families who have been previously diagnosed usually benefit from discussion of strategies for disclosing information about fragile X syndrome to other relatives, some of whom may react with anger, guilt, blame, disbelief, or indifference. Difficult ethical situations arise when key family members refuse to relay information about fragile X syndrome to at-risk relatives.

Because of the difficulty frequently encountered when informing relatives of genetic risk, genetic counselors should work with clients to develop a strategy to inform relatives as part of initial as well as follow-up genetic counseling sessions. Genetic counselors can assist families by identifying at-risk relatives in the pedigree and reviewing strategies for broaching the subject of diagnostic or carrier testing. Utilization of a family network approach, which allows relatives to initially be informed by a family member known to them with follow-up by a genetic counselor, may be helpful in facilitating informing relatives about their genetic risks. Families should be reassured that it is not their responsibility to provide in-depth genetic counseling or ensure that other family members pursue testing. Families with fragile X syndrome often find it helpful to have an objective document, such as a succinct summary letter with the genetic counselor's contact information, to give to other relatives at the time of disclosure. As always, genetic counselors dealing with different branches within a family should be careful to maintain confidentiality and avoid revealing clinical and diagnostic information without the consent of those involved.

Special Issues Regarding FMR1 Carrier Testing

Family History of Mental Retardation of Unknown Etiology

Individuals with family history of mental retardation of unknown etiology (e.g., an affected proband is not available for testing) should be offered fragile X carrier testing after counseling and education about fragile X syndrome. Implications of results of carrier testing, including available methods of prenatal diagnosis and possible results and their meaning should also be discussed.

Women With a Positive Family History

All women with a family history of fragile X syndrome who have been determined by pedigree analysis to be at risk to be carriers should be offered genetic counseling, including an informed consent process, prior to carrier testing. The carrier testing process in fragile X syndrome has been studied from the perspectives of at-risk women, obligate carriers, and parents of children with fragile X syndrome. Findings from this research can be used to develop genetic counseling interventions.

Findings suggest that pretest genetic counseling interventions should include assessment of the coping behaviors used to manage feelings related to "being at risk" and facilitation of positive coping skills to manage carrier test results. Coping resources include physical resources (e.g., family finances, job skills, education), social and family support networks, and psychological resources such as beliefs, cognitive skills, problem solving abilities, and self-concept. The adaptive coping behaviors identified in response to genetic testing in adults include: pursuing hope, constructing meaning, acquiring new knowledge and coping methods, minimization, and perceived control.

Daughters of Males With Premutations

Test results for daughters of a male with a permutation should not be inferred from their father's results. There is a possibility of misattributed paternity or of gene reversion. Additionally, testing obligate carriers may help them to better understand their own genetic status.

Males With a Positive Family History

FMR1 testing in males has become more complicated with the discovery of fragile X-associated tremor/ataxia syndrome (FXTAS). The newly described clinical complication in premutation carriers means that carrier testing may uncover a risk of unknown magnitude for FXTAS later in life. Therefore, presymptomatic testing concerns may apply. Additional epidemiological data are needed in order to determine the age-related risk for FXTAS. Carrier testing in males occurs under several different circumstances: testing of maternal grandfathers; concerns regarding reproductive risk; and parental request for testing secondary to educational or behavioral concerns in a son. Carrier males may also be diagnosed through prenatal testing. Each of these different circumstances has unique implications that affect the risks and benefits of testing which should be considered in genetic counseling.

Once the diagnosis of fragile X syndrome is made in the family, testing of the maternal grandparents is often recommended in order to determine which side of the family is at risk. The grandfathers of an affected child are often close to the age of onset of FXTAS or they may already be symptomatic. For these men, DNA

carrier testing may become diagnostic testing, and referral for neurological evaluation may be appropriate.

Male relatives of an affected child may request FMR1 testing for reproductive purposes because males with premutations are at risk to have daughters who are premutation carriers. Therefore, genetic counseling should include a discussion regarding the issues of informing a daughter about her genetic risk (see the section on "Minors," below) and the potential clinical implications.

Testing may also be requested by parents because of an educational or behavioral concern in their minor son. Careful consideration and discussion of the risks and benefits of carrier testing to the male in question should be the focus of the genetic counseling session (as noted below). For carrier males identified through prenatal screening genetic counseling should focus on helping the family to determine when and how to inform about the genetic risk.

Minors

Fragile X carrier testing for children less than 18 years of age must be approached carefully, with medical and emotional benefits to the child weighed against potential harms (see table IV of the original guideline document and "Potential Benefits/Harms" field of this summary).

The genetic counseling should focus on the adjustment to genetic risk status throughout the life cycle. How this information is managed when a child is young is critical and will influence how the child adjusts to his/her genetic risk and copes with that information as an adult.

Genetic counseling interventions should be tailored to the developmental stage of the child, and consideration made to use a family approach in order to facilitate problem solving and open discussion. Genetic counselors need to be prepared to work with the parents to develop a plan for how to approach talking with children about genetic risk and carrier testing, and also be able to facilitate the discussions between parents and their children. Topic areas to discuss in the development of a plan include:

- How, when, and why parents want to talk with their children about the genetic risk.
- Parents should be encouraged to think about what "message" they are trying to convey to their children about fragile X syndrome, how it is inherited, and what "being a carrier" means.
- Parents should be encouraged to take their time in considering what they want to say and be able to discuss genetic risk without overwhelming the child with facts or emotion.
- Parents should also be aware that their children's needs and understanding may change over time and discussions may need to be repeated to address misunderstandings or changes in their child(ren)'s needs. Genetic counselors are encouraged to plan with the parents potential times for follow-up counseling sessions to address new issues.

Once a plan has been developed, genetic counselors can facilitate discussions between parents and their children. Using age and developmentally appropriate words, counseling with children should include:

- What have they been told and what do they understand about fragile X syndrome, in general?
- What do they understand about how fragile X syndrome is inherited?
- What do they understand about their risk for being a carrier? (If their status is known, e.g., a daughter of a carrier male, what does "being a carrier" mean to them?)
- Are they interested in being tested?
- Do they understand what the test results might mean?

In summary, there are both risks and benefits to pursuing carrier testing in minors. Discussion of all potential consequences should occur prior to decisions about testing. It is important to adapt the above genetic counseling approaches for minors identified as premutation carriers through prenatal diagnosis and for minor daughters who are assumed to be obligate carriers because of paternal transmission of an FMR1 premutation.

Counseling Issues for Carriers

Premature Ovarian Failure

Although the incidence of POF in females who are carriers of the premutation has been found to be about 20% for women under the age of 40 years, the specific incidence in young women between the ages of 20 and 35, who may be actively making reproductive plans or who are not yet ready to consider their reproduction, has not yet been established. Carriers of the premutation who are in this latter category may be faced with altering their life plans related to child bearing. Female carriers of the premutation should be informed about the potential for reduced fertility. However, similar to counseling young girls with Turner syndrome, care should be taken to present a balanced picture of the potential for reduced fertility in the context of life decisions and timing for reproduction. Although surveillance for the clinical onset of POF is difficult, it may also be helpful to recommend close medical follow-up for early signs of POF.

Family Planning Issues and Options

In addition to providing factual information regarding reproductive options, genetic counseling for families managing the genetic risk for fragile X syndrome may also require helping the client reframe the parental role. Fundamental concepts of the parental role, including how it is defined and fulfilled may need to be reevaluated due to the potential barrier to reproduction inherent in the genetic risk. In this regard, the genetic counseling should include discussion of different ways to fulfill the parental role (e.g., adoption, foster care, remaining childless or no further children, parenting a child with fragile X syndrome, and prenatal testing options), exploration of the couple's/family's personal definition of what being a parent means and how important this role is to them.

Females With Full Mutations

Carrier testing may reveal that a female has either a premutation or a full mutation allele. It is important to be aware that some cognitively normal females with a family history of fragile X syndrome may have the full mutation. The possibility of either the pre- or full mutation and the implications of each should be addressed prior to carrier testing.

Psychiatric and intellectual disabilities related to fragile X mutations can also adversely affect the genetic counseling process. Mental retardation, concreteness, inconsistent attitudes, and tangential thinking in some women may limit the success of traditional genetic counseling approaches. Women with cognitive and psychological impairments may benefit more from exploration of feelings and attitudes rather than an education-based model of genetic counseling.

Premutations and Predisposition to Psychological Issues

Psychological issues such as denial, anxiety, anger, grief, survivor and parental guilt, shame, blame, depression, inability to cope, damage to self-esteem, changed relationship with family of origin, and change in sense of identity are potential reactions to any X linked disorder. Complicating the reactions to the diagnosis or carrier status itself can be one or more of the psychological components inherent to a proportion of premutation carriers (see the section on Clinical Presentation in the original guideline document). Risks for these conditions should be discussed and, if symptoms or signs present, appropriate referrals to mental health professionals should be made.

Prenatal Diagnosis and Genetic Counseling

Prenatal diagnosis should be offered to women identified as carriers of a pre- or full mutation. Males identified as premutation carriers, and therefore at risk to have premutation daughters, should also be presented with the benefits and limitations of an invasive procedure and the implications of prenatal results and be allowed to make the choice that is right for them. As with other genetic conditions, it is the role of the genetic counselor in the prenatal setting to fully explain the implications of different test results, including the range of possible outcomes for a female fetus with a full mutation. The variable phenotype among males and females with premutations should also be emphasized. This information, as well as information regarding the benefits and limitations of an invasive procedure, can facilitate patient decision making and help prepare patients who ultimately are faced with a positive result.

Carrier Testing for Reasons Other Than Fragile X Syndrome

Increasingly individuals are being referred for fragile X testing for reasons other than a positive family history of mental retardation. Such individuals may include women with POF and individuals with ataxia/tremor. Although there is currently no published literature on the impact of fragile X carrier testing for these individuals, genetic counselors should be aware that the issues and responses to this information may differ significantly from those that have been identified in individuals and families referred for family history of mental retardation.

Based on clinical experience, the guideline developers postulate that areas in which differences might be expected to occur include:

- Unexpected finding--For example: A woman with POF may have previously been very focused on achieving a pregnancy and may have been reassured that if she does become pregnant her risk is no different than any other woman her age. In this circumstance the finding of fragile X syndrome might result in a significant shift in this perception.
- Regret or anger--For example: If testing and the diagnosis of fragile X syndrome occurred after multiple expensive and/or invasive medical procedures or multiple tries at pregnancy, regret or anger may be expressed by the patient/family that testing was not considered sooner in the diagnostic process. For both FXTAS and POF different medical or life choices may have been made if the risk for fragile X syndrome had been known earlier in the evaluation process.
- Implications for family--As noted previously, once the diagnosis of fragile X syndrome has been made there are significant implications for the extended family. A positive test for fragile X syndrome would be expected to shift their focus from the individual as the "patient" to now include the extended family.

Population Screening

Pregnant and Nonpregnant Women

Although currently not standard of care, offering fragile X carrier screening to pregnant women or women considering pregnancy is becoming more prevalent. Genetic counselors need to be aware of the issues regarding carrier testing in women with no family history of fragile X syndrome and be able to counsel them prior to screening regarding the implications of all possible results. Women found to have expanded allele sizes need counseling and education regarding their particular results, the risks for expansion during pregnancy, reproductive options, and implications of their result for other family members. Genetic counselors are likely to receive referrals for women who have had general population screening with results showing premutation or intermediate allele sizes as well as full mutations. Comprehensive education and genetic counseling regarding the implications of these results in regard to family planning as well as risk to other family members is essential.

Women With Intermediate-Sized Alleles

Population carrier screening for fragile X syndrome is likely to detect many women with intermediate-sized alleles. Genetic counseling should emphasize the fact that individuals with intermediate size alleles are not generally considered to be at risk for clinical manifestations of either pre- or full mutations. Some alleles in this range have been shown to be unstable and to expand in subsequent generations, while others appear stable. The important issue to emphasize is that although guarantees cannot be given for any allele size, to date, no female with fewer than 59 repeats has had a child with a full mutation. Some women with intermediate allele sizes may still request prenatal diagnosis despite this information. Risks and benefits, including cost and potential complications of prenatal diagnosis compared to the negligible risk of having a fetus with a full mutation, need to be discussed at length with clients who are found to have intermediate-size alleles.

Patient And Professional Resources

All clients with a family history of possible or confirmed fragile X syndrome and individuals who are confirmed mutation carriers can be offered patient oriented resources. High quality resources appropriate for clients and families are listed in the original guideline document. Health professionals caring for individuals with fragile X syndrome or managing reproductive-related issues in fragile X carriers may benefit from available resources for health professionals (see table III in the original guideline document).

Summary

Genetic counseling for fragile X syndrome is challenging because of the complex multigenerational inheritance, variable phenotype, and the implications of these issues for families. Genetic counselors can provide support with an emphasis on anticipatory guidance for families throughout the life cycle—from newborn screening, pediatric evaluations, reproductive counseling, to evaluations of individuals for FXTAS and POF. This important area of genetic counseling will continue to evolve as new information is learned. Additionally, as experts in this area, genetic counselors have an important role in policy development and implementation regarding FMR1 testing.

CLINICAL ALGORITHM(S)

A suggested FMR1 gene-testing flowchart is provided in the guideline document.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

All supporting evidence is class III, opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. No supporting literature of categories I and II was identified.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate genetic counseling for fragile X syndrome

Potential benefits of testing a minor include:

- Resolution of the parent's (and possibly the child's) concerns about carrier status
- Allows child and family time to adjust to test outcome and to develop coping behaviors
- Genetic counseling can be tailored to the developmental stage of the child and anticipatory guidance provided for future concerns.
- Child and parents can be informed of genetic risk prior to the occurrence of an unintended pregnancy.
- Allows for long-term integration of information regarding genetic status for family planning issues

- Awareness of risk of premature ovarian failure allows decision-making regarding timing of future pregnancies.

POTENTIAL HARMS

Potential adverse consequences of testing a minor include:

- Damage to the minor's self-esteem
- Distortion of the family's perception of the child
- Siblings may be treated differently depending on genetic status.
- Loss of future adult autonomy and confidentiality for the tested child
- Adverse effects on the child's capacity to form future relationships
- Fear/guilt if person wants biological children
- Discrimination (insurance, employment, education, choice of mate)

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The genetic counseling recommendations of the National Society of Genetic Counselors (NSGC) are developed by members of the NSGC to assist practitioners and patients in making decisions about appropriate management of genetic concerns. Each practice recommendation focuses on a clinical or practice issue and is based on a review and analysis of the professional literature. The information and recommendations reflect scientific and clinical knowledge current as of the submission date and are subject to change as advances in diagnostics techniques, treatments, and psychosocial understanding emerge. In addition, variations in practice, taking into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments, or procedures alternative to the recommendations outlined in this document. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. Genetic counseling recommendations are never intended to displace a health care provider's best medical judgment based on the clinical circumstances of a particular patient.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

McConkie-Rosell A, Finucane B, Cronister A, Abrams L, Bennett RL, Pettersen BJ. Genetic counseling for fragile X syndrome: updated recommendations of the National Society of Genetic Counselors. *J Genet Counsel* 2005 Aug;14(4):249-70. [141 references] [PubMed](#)

ADAPTATION

This guideline was partially adapted from the American College of Medical Genetics Policy Statement: Sherman S, Pletcher BA, & Driscoll DA. (in press). Fragile X syndrome: diagnostic and carrier testing. *Genetics in Medicine*.

DATE RELEASED

2000 (revised 2005 Aug)

GUIDELINE DEVELOPER(S)

National Society of Genetic Counselors - Medical Specialty Society

SOURCE(S) OF FUNDING

National Society of Genetic Counselors

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: McIntosh N, Gane LW, McConkie-Rosell A, Bennett RL. Genetic counseling for fragile X syndrome: recommendations of the National Society of Genetic Counselors. *J Genet Counsel* 2000;9(4):303-25.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [National Society of Genetic Counselors Web site](#).

Print copies: Available from the National Society of Genetic Counselors, 401 N. Michigan Avenue, Chicago, IL 60611; Web site: www.nsgc.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 29, 2000. The information was verified by the guideline developer on October 27, 2000. This summary was updated by ECRI on March 23, 2006. The updated information was verified by the guideline developer on May 3, 2006.

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