

Recommendations from Multi-disciplinary Focus Groups on Cascade Testing and Genetic Counseling for Fragile X-associated Disorders

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Abstract The purpose of this paper is to report the outcome of a collaborative project between the Fragile X Research and Treatment Center at the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute at the University of California at Davis, the National Fragile X Foundation (NFXF), and the Centers for Disease Control and Prevention (CDC). The objective of this collaboration was to develop and disseminate protocols for genetic counseling and cascade testing for the multiple disorders

associated with the fragile X mental retardation 1 (*FMRI*) mutation. Over the last several years, there has been increasing insight into the phenotypic range associated with both the premutation and the full mutation of the *FMRI* gene. To help develop recommendations related to screening for fragile X-associated disorders, four, two day advisory focus group meetings were conducted, each with a different theme. The four themes were: (1) fragile X-associated tremor/ataxia syndrome (FXTAS); (2) premature

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ovarian failure (POF) and reproductive endocrinology; (3) psychiatric, behavioral and psychological issues; and (4) population screening and related ethical issues.

Keywords Fragile X syndrome · Fragile X-associated tremor/ataxia syndrome · Premature ovarian failure · Newborn screening · Population screening · Autism spectrum disorders · Genetic counseling · *FMRI*

Introduction

The purpose of this paper is to report the outcome of a collaborative project between the Fragile X Research and Treatment Center at the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute at the University of California at Davis, the National Fragile X Foundation, and the Centers for Disease Control and Prevention. The objective of this collaboration was to develop and disseminate protocols for genetic counseling and cascade testing for the multiple disorders associated with the fragile X mental retardation 1 (*FMRI*) mutation. Although the National Society of Genetic Counselors practice recommendations discussing fragile X testing and genetic counseling were recently updated (McConkie-Rosell *et al.* 2005); additional recommendations were needed to further address underdeveloped or controversial issues, including the variable phenotype found in some of the premutation carriers. This paper focuses on fragile X-associated tremor ataxia syndrome (FXTAS), fragile X-associated premature ovarian failure (POF), psychiatric disease, and population and newborn screening surrounding fragile X-associated disorders; provides recommendations for offering *FMRI* testing in specific populations; and identifies areas for future research.

Fragile X syndrome is the most common inherited cause of mental retardation and the most common single gene mutation associated with autism. It is caused by an expanded CGG trinucleotide repeat in the promoter region of the *FMRI* gene. Normal alleles have approximately 12–44 CGG repeats in this region. Full mutation alleles associated with fragile X syndrome have more than 200 CGG repeats and are partially or fully hypermethylated, resulting in the inactivation of the *FMRI* gene and reduction or absence of the *FMRI* gene product, fragile X mental retardation protein (FMRP). Premutation alleles have between 55 and 200 CGG repeats, are typically unmethylated, and usually do not result in gene inactivation. Premutations are potentially unstable when transmitted from one generation to the next. Intermediate or gray zone alleles, with approximately 45–54 repeats, (Maddalena *et al.* 2001), might or might not be unstable upon transmission (Nolin *et al.* 2003). The incidence of the full mutation is approximately 1 in 4,000

males and 1 in 6,000 females (Turner *et al.* 1996; Morton *et al.* 1997; Crawford *et al.* 2002). The prevalence of the premutation in North America is approximately 1 in 250 for females and 1 in 800 for males (Rousseau *et al.* 1995; Dombrowski *et al.* 2002). The prevalence of intermediate alleles (range 45–54) was reported to be approximately 1 in 72 to 1 in 145 (Murray *et al.* 1997).

Over the last several years, there has been increasing insight into the spectrum of the phenotype associated with both the premutation and the full mutation (Hagerman and Hagerman 2004a, b). This includes both the newly discovered fragile X-associated tremor/ataxia syndrome (FXTAS) and the occurrence of premature ovarian failure (POF) found in some carriers of the *FMRI* premutation. Additionally, there are reports of some children with *FMRI* premutations presenting with autism spectrum disorders (Aziz *et al.* 2003; Goodlin-Jones *et al.* 2004; Farzin *et al.* 2006). This last association is still under investigation to determine if these cases represent the population incidence of autism or are truly related to a specific effect of the premutation. Increasing awareness of these expanded phenotypes has led to the development of new terminology to describe fragile X-associated disorders and broader recommendations for testing for *FMRI* mutations.

Materials and Methods

We conducted four, two day advisory focus group meetings, each with a different theme. The four themes were: (1) fragile X-associated tremor/ataxia syndrome (FXTAS) associated with the premutation; (2) premature ovarian failure (POF) and reproductive endocrinology associated with the *FMRI* premutation; (3) psychiatric, behavioral and psychological issues; and, (4) population screening and related ethical issues.

The core group for the project was comprised of four genetic counselors certified by the American Board of Genetic Counseling/American Board of Medical Genetics, personnel from the M.I.N.D. institute (principal investigator, project coordinator, genetics associate), personnel from the Centers for Disease Control and Prevention, and the Executive Director of the National Fragile X Foundation. Each meeting was supplemented with healthcare professionals from medical fields related to the topic including: primary care, neurology, psychiatry, obstetrics, gynecology, reproductive endocrinology, medical genetics and genetic counseling, pediatrics, psychology, developmental pediatrics, medical ethics, and nursing. Researchers in molecular biology, epidemiology, patients with POF or FXTAS, and parents of children with fragile X syndrome also participated in the meetings. (See Acknowledgment section for a list of participants)

The core group facilitated the discussions in each advisory focus group. Parents of affected children, and individuals with FXTAS and fragile X-associated premature ovarian failure were included to give guidance about relevant issues. Through review of current research and practice, and discussion of key questions, each group sought to expand the *FMR1* cascade testing and genetic counseling recommendations, particularly in underdeveloped and controversial areas, for each theme. Cascade testing refers to the identification and the offering of genetic testing to family members of a proband. The following key questions were addressed:

- Who should be offered testing?
- What are the current standards of care or practice guidelines that could be affected by our protocols?
- What are the next steps after testing?
- What are the referral and treatment recommendations after testing positive?
- How can these recommendations be implemented into the current standard of care or practice guidelines for disciplines impacted by the protocols?
- How can the focus group recommendations best be disseminated to the disciplines involved?

A general meeting was held following the series of advisory meetings, in which key representatives of the medical, scientific and health professionals; parents; and parent foundations met to further review the proposed cascade testing and genetic counseling protocols. The final phase of the project included developing and implementing a plan to disseminate protocols to the healthcare professional community. Dissemination involved a number of mechanisms including website postings, presentations at professional conferences, professional journal publications, organizational newsletters, and direct mailings of informational postcards to clinicians.

Relevant background information and the major conclusions and recommendations of each advisory focus group follow are presented below. Genetic counseling recommendations are summarized at the end of each section. The recommendations were developed following each advisory group and were agreed upon by the authors. Representatives of the National Fragile X Foundation, the Canadian Fragile X Research Foundation, and Conquer Fragile X Foundation have reviewed and provided commentary on the study findings. Publication in this journal and the professional journals of other medical specialties including pediatrics, family practice, neurology, psychiatry and obstetrics and gynecology will allow appropriate feedback and revisions with the objective of establishing and fostering collaborations among disciplines and organizations that serve families with fragile X syndrome and associated disorders.

Results

Family History and Genetic Counseling General Recommendations

All focus groups highlighted the importance of health care providers obtaining and interpreting a targeted family history. All groups also made the recommendation that family history tools need to be developed. One resource available to health care providers and families in the development of a family history of sufficient quality for genetic purposes is a website developed by the Office of the Surgeon General (<http://familyhistory.hhs.gov/>). Information on targeted family history questions can be found in the NSGC practice care guidelines (McConkie-Rosell *et al.* 2005) and a guide to a medical genetics family history developed by the National Society of Genetic Counselors at <http://www.nsgc.org/>.

All groups also recommended that families diagnosed with fragile X-associated disorders be referred for genetic counseling. Families should be encouraged to include relevant family members in genetic counseling sessions or communicate the importance of genetic counseling for at-risk family members. The previously developed practice care guidelines for genetic counseling should also be followed as part of cascade testing (McConkie-Rosell *et al.* 2005).

Interdisciplinary Advisory Focus Group on Fragile X-associated Tremor/Ataxia Syndrome

Background

FXTAS is a progressive neurological condition that has emerged as a significant clinical issue for some adult carriers of the *FMR1* premutation. First described by Hagerman *et al.* 2001, common findings of this condition include an adult onset (>50 years of age) non-resting tremor, ataxia, autonomic dysfunction, executive function deficits, short term memory loss, irritability, neuropathy, and for some, dementia (Hagerman *et al.* 2001; Hagerman and Hagerman 2004a, b; Bacalman *et al.* 2006). Magnetic resonance imaging (MRI) findings include brain atrophy and white matter disease seen on T2 and FLAIR imaging (Brunberg *et al.* 2002; Jacquemont *et al.* 2003). The radiological features of FXTAS were first reported by Brunberg *et al.* (2002) and included brain atrophy and white matter disease, particularly involving the middle cerebellar peduncles (MCP). Neuropathological findings include eosinophilic intranuclear inclusions in neurons and astrocytes throughout the central nervous system. Psychiatric features include anxiety, depression, agitation and dementia.

Though most common in premutation carrier males older than 50 years of age, FXTAS has been reported in a small number (less than 50) of female premutation carriers (also older than 50 years of age). In females there are often fewer MRI findings including fewer inclusions and less white matter disease and atrophy. Likewise, symptoms in females are often milder including less dementia, fewer cognitive findings and less severe neurological findings (Hagerman *et al.* 2004; Zuhlke *et al.* 2004; Berry-Kravis *et al.* 2005).

It is estimated that at least one third of male carriers develop symptoms of FXTAS in their lifetime with increased penetrance in each decade of life after 50 years of age (Jacquemont *et al.* 2004). Often individuals with FXTAS are misdiagnosed with Parkinson's, other ataxias, stroke, Alzheimer's, multiple sclerosis and other conditions (Zuhlke *et al.* 2004; Hall *et al.* 2005). A number of screening studies have been carried out among individuals, both male and female, with neurological diagnoses, including ataxia and multiple system atrophy (MSA), with a significant yield of the premutation frequency varying from 2.2 to 5.1% (Kamm *et al.* 2005; Van Esch *et al.* 2005; Hall *et al.* 2006; Jacquemont *et al.* 2006).

Conclusions of the Focus Group

I. Diagnostic criteria

The focus group reviewed and clarified diagnostic guidelines for FXTAS in patients with *known FMRI* premutations and neurological and/or psychiatric findings. The diagnostic criteria included major and minor findings on MRI and clinical exam (Jacquemont *et al.* 2003). Previously considered categories of definite, probable, and possible FXTAS (Jacquemont *et al.* 2003; Hagerman and Hagerman 2004a, b) were reviewed and are outlined in Table I.

II. Testing recommendations

Testing recommendations were developed for individuals without prior *FMRI* testing and are based on clinical information including neurological symptoms and signs, neuroimaging findings, and family and personal history

data. The recommendations developed are shown in Table II.

III. Tailored genetic counseling issues

(A) Assess family history for:

1. Children, grandchildren, or siblings with mental retardation, autism, and social/ behavioral, or learning disorders;
2. Daughters or female relatives with infertility, premature menopause, or both; and
3. Family members with tremor, ataxia or other neurological (neuropathy, multiple sclerosis), and/or psychiatric problems (anxiety disorders, depression, dementia, cognitive decline).

(B) Issues to consider when FXTAS diagnosis arises:

1. Genetic counseling is indicated and should include pedigree and risk assessment for carrier status in extended family members. Genetic counseling should include natural history and clinical issues of FXTAS, multigenerational nature and possible expansion of *FMRI* mutations, variable phenotype in premutation carriers, and phenotype of fragile X syndrome.
2. All female offspring (and many other female relatives) of male carriers of the premutation or full mutation are at-risk for POF, infertility, having children affected with fragile X syndrome. Some of these women may be undergoing expensive, invasive, diagnostic, or fertilization procedures.
3. There might be other family members with neurological or psychiatric symptoms who also have FXTAS. When a FXTAS diagnosis is made, patients might suspect this diagnosis in their relatives and genetic counselors can help facilitate the appropriate and sensitive work-up or genetic counseling for at-risk relatives

IV. Recommendations for further research and education

- ##### (A) As most clinical and research studies have been focused on FXTAS in males, further research needs to be focused on the prevalence and clinical

Table I Clinical Criterion for Definite, Probable, and Possible FXTAS in Those with Known *FMRI* Premutations

Molecular	55–200 CGG repeats
Clinical	
Major	Intention tremor, cerebellar gait ataxia
Minor	Parkinsonism, moderate to severe short term memory deficit, executive function deficit
Radiological	
Major	MRI white matter lesions involving middle cerebellar peduncles
Minor	MRI lesions involving cerebral white matter, moderate to severe generalized brain atrophy
Diagnostic Categories	
Definite	One major clinical and one major radiological, or presence of FXTAS inclusions
Probable	Two major clinical, or one minor clinical and one major radiological
Possible	One major clinical and one minor radiological

Adapted from Jacquemont *et al.* 2003 and Hagerman and Hagerman 2004a, b

- phenotype in carrier females as this could be an under diagnosed and overlooked at-risk population.
- (B) As many males with FXTAS initially have mild symptoms, further delineation of symptoms at onset of the disease would be helpful in identifying and providing services to those in the early stages of the disease.
- (C) To ascertain accurate family histories, clinicians unaccustomed to taking detailed pedigrees will need tools and resources to determine both at-risk family members and their own patients' risk factors.
- (D) Publication in neurology, neuroradiology, and movement disorders journals are necessary to disseminate this information to clinicians caring for this population of at-risk individuals.

Interdisciplinary Advisory Focus Group on Fragile X-associated Premature Ovarian Failure

Background

Premature ovarian failure (POF) associated with the *FMRI* premutation is clinically distinct from fragile X syndrome and affects approximately 15–22% of females who carry the *FMRI* premutation (Sullivan *et al.* 2005). In screening individuals with POF, an *FMRI* mutation occurs in 0.8 to 7.5% of women with idiopathic sporadic POF and in up to 13% of women with a family history of POF and no known history of fragile X syndrome (Wittenberger *et al.* 2007). Genotype–phenotype correlations have shown a non-linear trend, with the frequency of POF increasing gradually among women with CGG repeat numbers in the lower premutation range. The risk then rises significantly in women with >80–100 CGG repeats, and then plateaus or drops in women with >100–200 CGG repeats (Sullivan *et al.* 2005). In addition to an increased prevalence of POF, women carrying the *FMRI* premutation might also have experienced menopause at a

younger age with or without characteristics consistent with a premature decline in ovarian function (decreased inhibin B and elevated follicle stimulating hormone (FSH) levels) when compared with non-carriers of the same age (Murray *et al.* 1999; Hundscheid *et al.* 2001; Welt *et al.* 2004; Sullivan *et al.* 2005).

As *FMRI*-mRNA toxicity appears to lead to FXTAS in both human and animal studies (Hagerman *et al.* 2004; Van Dam *et al.* 2005), a similar etiology for POF in *FMRI* premutation carriers is under investigation. This condition has only recently been characterized; thus, the clinical phenotype, appropriate treatment, and interventions for women at risk are still being investigated (Wittenberger *et al.* 2007).

Conclusions of the Focus Group

I. Terminology

The advisory focus group recommended that this disorder is more appropriately termed “fragile X-associated primary ovarian insufficiency” rather than premature ovarian failure because the clinical spectrum in females with the *FMRI* premutation can include women with unexplained infertility, irregular menses, or women who are concerned about their infertility, are normal cyclers, but are found to have elevated FSH levels. Recognizing that the term “POF” is well embedded in the literature, the advisory focus group acknowledged that further discussion is needed to fully evaluate the impact on all stakeholders to reach final consensus.

II. Testing recommendations for the obstetrician, gynecologist, reproductive endocrinologist, and general practitioner.

- (A) *FMRI* testing should be offered to:
1. Infertile women, particularly those with increased FSH levels
 2. Egg and sperm donors
 3. Patients presenting with a personal or family history of mental retardation, developmental disability, or autism

Table II Testing Guidelines for Fragile X-associated Tremor/Ataxia Syndrome

Clinician should offer testing for *FMRI* mutation if the patient has any of the following:

Onset of cerebellar ataxia of unknown cause in an individual over 50 years of age
Onset of action tremor of unknown cause in individual over 50 years of age with Parkinsonism or cognitive decline
Prior diagnosis of multiple system atrophy, cerebellar subtype
MCP sign on T2/FLAIR images of MRI with signs consistent with FXTAS
Positive family history of <i>FMRI</i> mutation in an individual who could be a carrier based on position in pedigree if signs consistent with FXTAS are present
Family or patient history of infertility/premature menopause in a patient with signs consistent with FXTAS.
Presence of an MCP sign (increased T2 signal intensity in the middle cerebellar peduncles), family history of <i>FMRI</i> mutation and possible carrier status, and patient history of POF (premature ovarian failure), even without clinical signs of FXTAS would be appropriate criteria for screening for an <i>FMRI</i> mutation

4. Additionally, for those patients who have fertility concerns but are normal in their cycles, take a family history to identify those at increased risk
 - (a) Include all phenotypes of the fragile X-associated disorders in the medical and family history
 - (b) Consider FSH studies
 - (B) For pregnant women or those with a positive test:
 1. Some pregnant women at increased risk to be *FMRI* carriers will be having a prenatal diagnosis such as amniocentesis or chorionic villus sampling (CVS) for another indication. In instances when the prenatal diagnostic procedure is being done concurrently with carrier testing, it is important to alert the laboratory to set aside fetal cells for prenatal fragile X testing in the event the patient is found to be a carrier.
 2. Refer all patients with positive test results for genetic counseling to review *FMRI* genetics as well as reproductive issues, options, and technologies.
- III. Tailored genetic counseling issues
- (A) The following reproductive issues for carriers of the *FMRI* mutation need to be discussed:
 1. Family planning in view of the potentially reduced reproductive timeline in women carriers;
 2. The risk of having a child with fragile X syndrome;
 3. Child-free living, adoption, use of egg donors, and embryo adoption;
 4. The reduced success of preimplantation genetic diagnosis related to a decrease in the number of harvested eggs; and
 5. prenatal diagnosis for those women who achieve pregnancy.
 - (B) The genetic counseling issues for patients ascertained in the infertility setting might be different from those ascertained due to a positive family history of mental retardation. The information shared during pretest and post-test genetic counseling for individuals without a personal experience with fragile X might need to be adjusted to account for an unexpected fragile X diagnosis, the emotional issues that arise with such a diagnosis, and the implications for family members (McConkie-Rosell *et al.* 1997; McConkie-Rosell *et al.* 2000; McConkie-Rosell *et al.* 2002).
 - (C) Because intermediate or 'gray zone' alleles (alleles in the 45–54 CGG repeat range) will be identified as part of any *FMRI* testing program, clinicians providing this service need to be prepared to provide information and genetic counseling referrals to individuals and their families found to have alleles in this range (Nolin *et al.* 2003).
 - (D) Patients with a positive result, including an intermediate result, should be referred for genetic counseling to review the genetics of *FMRI* including the effect of CGG repeat size on chances of having a child with fragile X syndrome, and discuss recurrence risks and available options. (McConkie-Rosell *et al.* 2005)
- IV. Recommendations for future research and education
- (A) The following areas require further research:
 1. Effects of *FMRI* CGG repeats on ovarian function at the molecular level;
 2. Premutation frequency among women with occult or biochemical primary ovarian insufficiency, especially among those planning pregnancies;
 3. Better risk estimates of the likelihood of primary ovarian insufficiency based on family history of the disorder and the number of CGG repeats;
 4. Validated measures that predict the onset of primary ovarian insufficiency; and
 5. Genetic counseling issues, including:
 - (a) How and when should girls and young women who are premutation carriers be informed about their risk for primary ovarian insufficiency?
 - (b) What are the informational needs of individuals being screened because of a history of primary ovarian insufficiency?
 - (B) Educational materials need to be developed:
 1. To educate obstetricians, family practitioners, and reproductive endocrinologists about *FMRI* mutations and fragile X associated conditions.
 2. To facilitate family history taking and assist physicians with identifying high-risk individuals such as:
 - (a) Family members with mental retardation, autism, behavioral, or learning disorders,
 - (b) Female relatives with infertility or primary ovarian insufficiency, and
 - (c) Adult relatives with ataxia, psychiatric and neurological problems.

Interdisciplinary Advisory Focus Group on Psychiatric and Behavioral Issues in Individuals with *FMRI* Mutations

Background

FMRI gene expansions are associated with a wide range of developmental, behavioral, and psychiatric symptoms in both males and females. Among the most commonly noted behavioral symptoms in individuals with fragile X full mutations are autism spectrum disorders, attention deficit/hyperactivity disorder, and anxiety (Freund *et al.* 1993;

Lachiewicz 1995; Mazzocco *et al.* 1997; Kaufmann *et al.* 2004; Hatton *et al.* 2006). Less commonly, individuals can present with selective mutism, obsessive-compulsive features, and psychosis (Hagerman *et al.* 1999; Chiu *et al.* 2007). The psychiatric aspects of FXTAS, including depression, anxiety and dysinhibition, are common and may eventually evolve into fronto-subcortical dementia (Bacalman *et al.* 2006). Approximately 70% of girls with the full mutation do not have mental retardation, but may present with psychiatric problems including anxiety and mood instability that typically requires treatment (Freund *et al.* 1992; Lachiewicz 1992; de Vries *et al.* 1996; Sobesky *et al.* 1996; Franke *et al.* 1998; Hagerman *et al.* 1999; Hagerman 2002).

Although the psychiatric problems of individuals with the full mutation and mental retardation have been well describe, concerns about possible psychiatric problems of individuals with the premutation remains controversial. Some studies have found an increased frequency of anxiety, obsessive-compulsive symptoms, depression, and/or social deficits in small series or in minority subgroups of premutation carriers (Sobesky *et al.* 1996; Franke *et al.* 1998; Johnston *et al.* 2001; Cornish *et al.* 2005; Hessel *et al.* 2005), whereas other studies have not (Reiss *et al.* 1993). Some studies have found an increased frequency of attention deficit hyperactivity disorder and autism spectrum disorders, social deficits, or a combination thereof, among boys and some girls with the premutation (Tassone *et al.* 2000; Aziz *et al.* 2003; Goodlin-Jones *et al.* 2004; Farzin *et al.* 2006). In addition, there is some evidence that a higher repeat number in the premutation range may be associated with emotional difficulties (Johnston *et al.* 2001) and lowered FMRP levels (Tassone *et al.* 1999a, b). Currently existing studies addressing psychiatric, emotional, and social functioning in carriers may be subject to referral bias and additional population-based epidemiologic research is needed to better understand these preliminary studies.

Psychiatrists and psychologists, particularly those working with clients who have cognitive disabilities, potentially play an important role in fragile X identification, family referral, and symptom management. Special education professionals, including teachers and school psychologists, also represent an important target group for fragile X cascade testing initiatives. Identified barriers to awareness about fragile X among these professionals include an historical lack of collaboration and cross training between behaviorists and genetic professionals. In addition, psychiatrists, school systems, and adult mental health agencies continue to rely heavily on the behaviorally defined Diagnostic & Statistical Manual for Mental Disorders diagnostic system, which does not include a focus on medical etiology.

Currently, the American College of Medical Genetics recommends testing for *FMRI* mutations in individuals

with mental retardation of unknown etiology and autism, as well as in family members of people known to have *FMRI* mutations (Sherman *et al.* 2005). Outside of these well-defined groups, there are no set standards for *FMRI* testing in children and adults who present with behavioral symptoms or psychiatric diagnoses. There was little support among the advisory focus group members for testing all patients with common psychiatric disorders, such as anxiety, attention deficit/hyperactively disorder, and dementia. Even though these symptoms are commonly found in people with *FMRI* mutations, the converse is not true and the yield of fragile X diagnoses is likely to be very low among people with these common conditions in the general population. However, the presence of co-morbid conditions and behaviors, such as learning disabilities and gaze aversion in a woman who presents with anxiety disorder, or a movement disorder in a man with cognitive decline and depression, should warrant consideration of *FMRI* testing. In addition, the advisory focus group acknowledged the importance of the family history in determining whether testing is warranted in patients with psychiatric symptoms. Specific elements of the family pedigree, including mental retardation, learning disabilities, autism, movement disorders, and primary ovarian insufficiency, should heighten suspicion about the presence of *FMRI* mutations in a family.

Conclusions of the Focus Group

The following conclusions were developed from the advisory focus group's presentations and discussions:

- I. The psychiatric and behavioral manifestations of *FMRI* mutations are under-diagnosed. Psychiatric and behavioral issues are extremely common among males and females with full mutations and may be present among those with premutations. Psychiatrists and behaviorists represent a potentially important but untapped resource to assist in the diagnosis and treatment of individuals with fragile X mutations.
- II. Who should be offered testing?
 - (A) Children or adults with mental retardation or autism spectrum disorders should be tested for the *FMRI* mutation and this should be ordered by the psychiatrist if not done by the primary care physician. If a positive result is found, the psychiatrist should refer the patient for genetic counseling and cascade testing of potentially affected family members.
 - (B) *FMRI* testing is also important in individuals with behavioral problems typical of fragile X with normal or borderline intellectual abilities, particularly when physical features of fragile X or a

family history of intellectual impairment are present.

- (C) Although the yield of positive fragile X diagnoses among people with common psychiatric conditions such as attention deficit/hyperactivity disorder, anxiety, and depression is likely to be low, as it is among those diagnosed with obsessive–compulsive or psychotic disorders, fragile X testing should be considered by the clinician when such individuals have a family history and/or co-morbid psychiatric, and cognitive, physical, and medical symptoms suggestive of fragile X syndrome.
 - (D) Psychiatric aspects of FXTAS have been under appreciated. Individuals with a fronto-subcortical dementia or cognitive decline associated with disinhibition, when accompanied by tremor, ataxia, or other neurological features of FXTAS (see previous text), should be offered *FMRI* testing.
- III. Tailored genetic counseling issues
- (A) Family history should be assessed for relatives with mental retardation, autism spectrum disorders, learning and/or behavioral disorders.
 - (B) Genetic counseling should include a discussion regarding the distinction between genetic and psychiatric diagnoses.
 - (C) Genetic counselors should be aware that severe cognitive and/or psychiatric impairment can impact the counselee's understanding and ability to make informed decisions.
 - (D) Genetic counselors should clarify legal guardianship issues for counselees with significant cognitive and/or psychiatric impairment to determine who is able to give consent for genetic testing.
- IV. Recommendations for future research and education
- (A) To better understand the prevalence of the *FMRI* mutations among common psychiatric diagnoses, high-risk screening research is warranted, particularly among those with anxiety disorders, obsessive–compulsive disorder, selective mutism, and mood disorders.
 - (B) Large-scale research on the psychiatric and behavioral aspects of *FMRI* mutations is lacking, particularly with regard to interventions including psychopharmacology.
 - (C) Advances in our understanding of fragile X will hinge on transdisciplinary research, which brings together experts from the behavioral, medical, and laboratory sciences.
 - (D) Efforts are needed to increase awareness among clinicians involved in caring for people with behavioral disorders about the clinical spectrum of *FMRI* mutations among clinicians involved in caring for people with behavioral disorders. These

include primary care clinicians, psychiatrists, pediatricians, neurologists, psychologists, psychiatric nurses, special educators, and social workers.

Interdisciplinary Advisory Focus Group on Screening and Ethics

Background

Screening for *FMRI* mutations has been a topic of consideration since the *FMRI* gene was identified. Advances in understanding the molecular basis of fragile X syndrome and advances in genetic testing methods have elicited new prospects for identifying a greater number of individuals at risk for the disorder or transmitting the disorder. The topic of population screening, including newborn and preconception/prenatal screening was discussed at the final focus group advisory meeting. Because implications of a positive test and the concomitant genetic counseling vary depending on the population being screened, the group first focus on general population screening of low-risk groups (e.g. preconception screening of women of reproductive age) then, on the second day, newborn screening.

Conclusions of the Focus Group

Issues that Affect Both Low-Risk Population Screening in Women Of Reproductive Age and Newborn Screening. The challenge of low risk population screening will be to arrive at a broad consensus, educate individuals, parents and clinicians, and balance ethical concerns and available resources. It is imperative that anticipating and planning for future resources, particularly those that address genetic counseling and follow up needs, be included in and funded for any screening program.

It is important to provide individuals considering screening with accurate estimates of prevalence of *FMRI* mutations in the general population. Epidemiological studies are needed to better estimate fragile X allele frequencies for all racial and ethnic groups.

Knowledge is critically needed regarding the penetrance of *FMRI* associated disorders, FXTAS and fragile X-associated primary ovarian insufficiency, in order to provide anticipatory guidance and to assist with the development of genetic counseling protocols that address the complexity of all *FMRI* mutation allele sizes (premutation, full mutation, and intermediate).

There are no prognostic tests for the severity of expression among females and males carrying the premutation and females carrying the full mutation except for limited correlations with the activation ratio, FMRP studies, and

FMRI mRNA (Tassone *et al.* 1999a, b; Reiss and Dant 2003; Loesch *et al.* 2004; Hessel *et al.* 2005). These studies are research based and not used clinically. Population and family based genotype/phenotype studies are needed to help address this need.

The overlap of normal and premutation alleles in the intermediate range makes it difficult to interpret the significance of the intermediate size alleles when they are found in the general population. Current recommendations are to interpret an intermediate allele within the context of the family and clinical history (McConkie-Rosell *et al.* 2005).

A defined network of genetic service providers should be established to develop standards of care, acknowledge qualified providers outside of medical centers and to convene a work group to meet annually. The evolution of education and recommendations for *FMRI* screening must include point-of-care education targeted to the roles of providers.

Approaches to genetic counseling for the different genotypes and phenotypes associated with the *FMRI* gene and its complex inheritance pattern need to be well developed and tailored to adult low-risk and newborn screening.

Issues Specific to Low Risk Screening in Women of Reproductive Age.

I. Who should be offered screening?

Population-based screening for *FMRI* mutations may be clinically desirable in the pre-pregnant or pregnant population. Pilot studies exploring women's understandings and attitude toward low risk screening for *FMRI* mutations have found a generally favorable endorsement (Fanos *et al.* 2006; Anido *et al.* 2005; Anido *et al.* 2007).

II. Suggested time points for preconception *FMRI* screening that offer an opportunity to reach a significant number of women in the general population include routine gynecologic visits, infertility visits, and primary care visits.

III. Advantages and disadvantages to screening females of reproductive age identified were:

(A) Advantages:

1. Options for family planning would be available to a female identified with an *FMRI* mutation.
2. A positive test result could have implications for relatives.
3. Screening prior to conception allows for increased awareness of the implications of an *FMRI* mutation. This includes risk for and management of fragile X-associated primary ovarian insufficiency, FXTAS, and counseling regarding the risk for offspring with *FMRI* mutations.
4. Increased awareness of risk for having an affected child might lead to early diagnosis and intervention for children affected by fragile X syndrome.
5. Relief related to a negative test result.

(B) Disadvantages:

1. Increased anxiety about reproductive and health implications.
2. Loss or changes to expected future of parenthood.
3. Potential stress in present or future personal relationships.
4. Potential for negative emotions related to the implications of a positive carrier status.

V. Increased community awareness and education will be critical to a successful program.

Because of the implications of and difficulty in interpreting positive test results, it is imperative that women offered screening understand the risks and benefits before screening occurs. Along with written materials such as brochures and fact sheets, other forms of media and appropriate informational methods will need to be developed and tested to try to achieve optimal understanding of screening.

VI. Tailored Genetic Counseling Issues

The pretest and post-test genetic counseling that should accompany low risk screening of women in the general population is critically important. Findings from focus groups conducted with women who underwent such screening as well as women with a family history of fragile X syndrome found that even with written materials regarding *FMRI* screening, women from the general population who tested negative were unprepared for the possibility of a positive result (Anido *et al.* 2005). The investigators also confirmed that there were differences in women who had a positive family history from those in the general population. These were: (1) mothers of children with fragile X syndrome have difficulty formulating their opinions on population screening because of their unique experiences surrounding their own carrier diagnosis and their relationship with their affected children, (2) the motivation for carrier testing and need for information differed for those with or and those without a family history of fragile X syndrome and parental status, and (3) the timing of carrier testing with respect to a woman's life stage influences how carrier information will be viewed (beneficial or detrimental). Additionally, follow-up interviews of women who screened positive found that these women were unprepared for a positive result and had difficulty in applying the genetic risk information to their own lives (Anido *et al.* 2007). Investigators recommended that genetic counselors consider the women's reproductive life stage to help her personalize the information. Similarly, Fanos and colleagues (2006), found in a small pilot study that low risk women had very limited pre and post test knowledge about fragile X syndrome.

Issues Specific to Newborn Screening. Although newborn screening for *FMRI* mutations could potentially fit into the established public health infrastructure for existing

newborn screening programs, the focus group recommended that newborn screening should only be done, at this time, as part of a well designed research study. Because the potential risks and benefits of newborn screening will vary based on the objectives of screening and the technology used (i.e.: screening for all allele sizes will result in diagnosing both premutations and full mutations while testing for only the full mutation will result in not identifying individuals and families with premutation size alleles) the goals of *FMRI* screening must be carefully considered. Multiple models should be investigated in a research setting and the ethical concerns related to the potential risks and benefits of presymptomatic testing of minors as well as carrier testing in minors should be addressed as part of the process.

I. Focus group recommendations:

- (A) Protocols for newborn screening for *FMRI* mutations should require active informed consent rather than dissention from routine testing.
- (B) Offering testing beyond the newborn period as part of routine, well baby check-ups should be evaluated. This option is currently being considered for Duchene Muscular dystrophy (Ross 2006)
- (C) The field of newborn screening is a rapidly changing landscape. Advocacy groups are becoming more vocal, perceived benefits are being reframed and expanded, technology is advancing, and private market forces are offering screening outside the public health system. Care needs to be taken to avoid developing a two-tiered system where only those with advanced knowledge or financial means can access testing.

II. Recommendations for areas of research or education

- (A) Early childhood developmental intervention strategies must be developed and resources available to children who are diagnosed with *FMRI* mutations.
- (B) As newborn screening for *FMRI* is being considered for children, it is important to assess the current state of existing developmental services and to build an infrastructure to ensure that appropriate services can be provided. There were many concerns regarding access to quality care for infants diagnosed with fragile X syndrome. Some of those identified were:
 1. Private insurance may not cover developmental therapies;
 2. Early intervention services may not be intensive or accessible; and
 3. Early intervention specialists may not be familiar with fragile X syndrome.
- (C) As stated previously, if newborn screening identifies all allele sizes, both premutations and full

mutations of the *FMRI* gene will be diagnosed. Thus, research is needed to identify the informational needs as well as coping strategies of families who would then be managing genetic risk information of their minor children.

- (D) Most states have centralized newborn screening coordinators, often nurses or genetic counselors who report results to primary care providers and clinics, and coordinate services for those with positive newborn screening results. While state newborn screening programs do not take responsibility for genetic counseling for families and patients, they do ensure that confirmatory testing is made available. These centralized programs and staff are essential to the effectiveness and equal distribution of services to state wide populations and are overseen by state public health services and genetic disease branches. Therefore, statewide genetic disease branches and public health divisions will require additional training and budgeting for program administration and staff.

III. Tailored Genetic Counseling Issues

- (A) Caution needs to be taken when considering the genetic counseling needs of families diagnosed with an *FMRI* mutation as part of newborn screening. As has been shown with women who were screened as part of a low risk screening research study, the response to the outcome of the test of a newborn might be quite different from those found in families with concerns about an already affected child. To date, no research has been published regarding the psychosocial implications for a family without previous knowledge of this disorder whose newborn infant has been diagnosed with an *FMRI* mutation.
- (B) As mentioned previously, all families identified through newborn screening will require genetic counseling and cascade testing for other family members. The genetic counseling would encompass the existing Practice Recommendations of the NSGC for families diagnosed with *FMRI* mutations (McConkie Rosell *et al.* 2005). There might also be additional areas that will need to be addressed that have not yet been clearly delineated.
- (C) Genetic counselors will need to partner with families and other health and educational professionals to help advocate for the needed support and developmental interventions.
- (D) There are significant ethical concerns regarding pre-symptomatic and carrier testing in minors that have yet to be adequately addressed. There are both risks and benefits to pursuing newborn screening. Dis-

discussion of all potential consequences should occur prior to screening.

Limitations

There are several limitations to the focus group format used in this project that need to be considered. Although attendees and group facilitators were encouraged to openly express their opinions, the focus group format might have been uncomfortable for those who did not wish to express their opinion in a public forum. In order to create a working discussion and comply with budgetary constraints, advisory focus groups were each limited to 10 to 15 attendees, in addition to the core group. Attendees offered their individual expert opinions that did not necessarily reflect the opinions of their professional association, affiliation, or institution. Efforts were made to invite clinicians, researchers, and individuals themselves or their families who have been affected by mutations in the *FMR1* gene. The recommendations presented here are the opinions of the participants and were compiled by the authors. However, the multidisciplinary professionals taking part in the advisory focus meetings are considered experts in their respective areas regarding *FMR1* mutations and represent a multitude of views and opinions. Thus, the consensus findings of the focus group reflect the diversity, experiences, and knowledge of the participants. The recommendations are also limited by the current state of the science and future discoveries regarding *FMR1* mutations might necessitate changes in these recommendations.

Conclusion

The multigenerational mutation process, as well as the variable phenotype associated with the *FMR1* mutation presents the clinician with many challenges. It is important for clinicians, regardless of how a patient is ascertained, to be familiar with the variable clinical presentations from classic fragile X syndrome, to FXTAS, to fragile X-associated primary ovarian insufficiency. When taking family histories and offering testing to a patient, the variable phenotype must be considered. Because the diagnosis of an *FMR1* mutation has significant implications beyond the immediate concerns for the proband, anyone identified with an *FMR1* mutation or premutation should be referred for genetic counseling, regardless of ascertainment. The advisory focus groups were one important step towards better defining cascade testing and genetic counseling recommendations for clinicians. By fostering collaborations among disciplines and organizations that serve families

with fragile X syndrome and *FMR1*-related disorders, families will receive the information they need and the services to address the clinical issues they face.

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Conflicts of Interest Amy Cronister is an employee and stock holder of Genzyme Genetics, a for profit company that performs molecular diagnostic testing for fragile X syndrome.

Focus Group Participants

Interdisciplinary advisory focus group on fragile X-associated tremor/ataxia syndrome

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