Summary of recommendations from multi-disciplinary focused-advisory groups on cascade testing and genetic counseling for fragile X-associated disorders.

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Introduction

- Fragile X syndrome (FXS) is the most common inherited cause of mental impairment.
- Increasing insight into *FMR1* premutation and full mutation phenotypes has highlighted the need for broader recommendations for *FMR1* mutation testing.
- This poster summarizes recommendations for cascade testing and genetic counseling developed through several focused-advisory group meetings of experts in fragile X-associated disorders.

Methods

- In 2006, four focused-advisory group meetings were held to address:
  1) Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)
  2) Fragile X-associated Premature Ovarian Failure (FXPOF)
  3) Psychiatric, behavioral and psychological issues in fragile X
  4) *FMR1* population screening and related ethical issues
- Each advisory group was led by a core group composed of board certified genetic counselors and staff from the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute at the University of California at Davis, the Centers for Disease Control and Prevention (CDC), and the National Fragile X Foundation (NFXF).
- Each group also included healthcare professionals and researchers from medical fields related to the focus group topic. Stakeholders such as family members also provided input.
- Each group reviewed current research and practice and discussed key questions.
- Final protocols were vetted through healthcare professionals, researchers, and fragile X advocacy groups.
- A plan for dissemination of the protocols to the healthcare community was established.

Results

General Recommendations

General recommendations common to all four focused-advisory groups included the importance of:

1) Healthcare providers obtaining and interpreting a targeted family history
2) The development and use of family history tools by non-genetic healthcare providers
3) Referring all families diagnosed with fragile x-associated disorders for genetic counseling
4) Using the recommendations in conjunction with the previously developed 2005 guidelines (McConkie-Rosell, Finucane et al. 2005)

Pedigree analysis:
When a diagnosis of FXS, POF, or FXTAS is made, assess family history for:

- Family members with mental retardation, autism, and social/behavioral, or learning disorders
- Female relatives with infertility, premature menopause, or both
- Family members with tremor, ataxia or other neurological and/or psychiatric problems

Topic Specific Recommendations

Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)

FXTAS testing recommendations for neurology patients
Offer *FMR1* testing in patients with:

- Cerebellar ataxia of unknown cause in an individual over 50
- Action tremor of unknown cause in individual over 50 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

Results (continued)

Genetic counseling for FXTAS should include:

- Natural history and clinical issues of FXTAS
- Multigenerational nature and possible expansion of *FMR1* mutations
- Variable phenotype in premutation carriers
- Phenotype of fragile X syndrome

Fragile X-associated Primary Ovarian Insufficiency (FXPOI)

Premature ovarian failure (POF) is commonly used in the literature to describe the infertility experienced by some *FMR1* premutation carriers. As fragile X-associated primary ovarian insufficiency (FXPOI) more accurately describes the infertility issues, the advisory group recommended that FXPOI be substituted for POF.

Carrier testing recommendations for reproductive medicine patients
FMR1 testing should be offered to:

- Infertile women, especially with increased FSH and/or POF/POI
- Egg and sperm donors
- Patients with a personal or family history of mental retardation, developmental disability, or autism
- Patients with family history of fragile X
- Any woman can be offered *FMR1* testing

In addition:

- For pregnant patients found to be carriers
  - Set aside fetal cells for *FMR1* testing when amnio or CVS is being performed
  - Refer to genetic counseling to review *FMR1* genetics as well as reproductive issues and options

Genetic counseling issues for POF: Issues will likely differ between patients assessed because of a family history and those assessed for infertility. Genetic counseling should be adjusted accordingly, but generally include:

- Review of the genetics of *FMR1* and the effect of repeat size on the risk for children with FXS
- Family planning in view of the potentially reduced reproductive timeline
- Child-free living, adoption, use of egg donors, and embryo adoption
- Reduced success of preimplantation genetic diagnosis
- Option of prenatal diagnosis for women who achieve pregnancy

Psychiatric, behavior, and psychological issues

Testing guidelines for psychiatrists and behaviorists
FMR1 testing should be offered to:

- Children or adults with mental retardation or autism spectrum disorders
- Individuals with behavioral problems typical of fragile X with normal or borderline intellectual abilities, particularly with physical features or family history of fragile X
- Individuals with a fronto-subcortical dementia or cognitive decline when accompanied by neurological features of FXTAS

Genetic counseling issues:

- Counseling should include a discussion regarding the distinction between genetic and psychiatric diagnoses.
- Severe cognitive and/or psychiatric impairment can impact the counselee's understanding and ability to make informed decisions.
- Clarify legal guardianship issues for counselees with significant cognitive and/or psychiatric impairment.

Population screening and related ethical issues

- The advisory group discussed issues pertaining to carrier screening of women of reproductive age and newborns.
- Population carrier screening and/or newborn or infant screening may be desirable, but well-designed pilot testing needs to be carried out before population screening for FX is recommended.
- 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.
- Any screening program should plan for resources such as genetic counseling and follow up needs.

Dissemination

- "Recommendations from multi-disciplinary focus groups on cascade testing and genetic counseling for fragile X-associated disorders" was published in the October 2007 issue of the Journal of Genetic Counseling.
- Publications in neurology, reproductive medicine, and psychiatry journals
- Presentations at various professional society meetings
- Postcards summarizing recommendations to healthcare providers

Future Research and Education

- Future research should focus on further elucidating the national history, prevalence, and effects of repeat sizes on the various phenotypes of the premutation and full mutation.
- In considering screening for newborns or women of reproductive age, it will be important to weigh benefits and limitations of screening, develop pre- and post-counseling materials for effective informed consent, and establish procedures and procure resources for follow up.
- Early childhood developmental intervention strategies must be developed and resources available to children who are diagnosed with *FMR1* mutations.
- Materials will need to be developed to educate healthcare providers and their patients on fragile X- associated disorders and implications of testing.

Conclusions

- The multigenerational mutation process and the variable phenotype associated with the *FMR1* mutation presents the clinician with many challenges.
- It is important for clinicians to be familiar with the variable clinical presentations from classic fragile X syndrome, to FXTAS, to FXPOI.
- The variable phenotype must be considered when taking family histories and offering testing to a patient.
- Anyone identified with an *FMR1* mutation or premutation should be referred for genetic counseling, regardless of ascertainment.

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