



Association for Molecular Pathology
Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology

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Cynthia Fletcher
Deputy Project Manager/Conference Services Manager
Education Services, Inc.
4350 East West Highway, Suite 1100
Bethesda, MD 20814

RE: Response to The *FMRI* Premutation and Premature Ovarian Failure: Worldwide Community Guideline Development

Dear Ms. Fletcher:

AMP is an international not-for-profit educational society representing over 1,400 physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on nucleic acid technology. AMP members practice their specialty in widely diverse settings: academic medical centers, independent medical laboratories, community hospitals, federal and state health laboratories, and the *in vitro* diagnostic industry. In this capacity, AMP members are involved in every aspect of molecular diagnostic testing: administration and interpretation of molecular diagnostic tests, research and development, and education. For the last several years AMP has provided national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing in the health care industry.

AMP's Mission Statement identifies the Society as "dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics." Our goal is to represent all members regardless of the setting in which they practice because they are united in the end intent to provide high quality, relevant information for the purpose of directing individual and patient community health management. We acknowledge, however, that different perspectives may emerge from those widely diverse settings. In those instances, our primary responsibility is to comment from the standpoint of molecular testing laboratories and the patients they serve.

Overall AMP applauds the mission and goal of developing guidelines regarding detection of *FMRI* premutations and the association with premature ovarian failure. Mutations in the *FMRI* gene lead to a variety of clinical entities and understanding the similarities and differences in coordinating care for these conditions is critical. We suggest the following specific ideas for consideration:

Section: *FMRI* Testing: Reproductive Indications
Line 2, *FMRI* should be italicized.

Section: *FMRI* Testing: Reporting Results

There are already existing Clinical Practice Guidelines for Fragile X testing and reporting (http://www.acmg.net/resources/policies/FragileX_GIM_2005.pdf) and Technical Standards and Guidelines for Fragile X Molecular Testing (http://www.acmg.net/Pages/ACMG_Activities/stds-2002/fx.htm). As with any medical test, informed consent is important, but to emphasize that

requirement for *FMRI* testing for POF seems excessive. Perhaps this is due to the predictive nature of the findings. Also as with any medical test, it is important to discuss the limitations of the assay with the patient prior to and following testing. These functions should be the responsibility of the ordering physician, because clinical laboratories typically do not have the opportunity to interact directly with the patient.

We agree that for premutation alleles the number of triplet repeats should be included in the laboratory report. It should be noted that the reported $(CGG)_n$ may differ among laboratories, but for most cases the clinical interpretation of slight variations in reported repeat number is not impacted. Genetic testing for *FMRI* repeats is technically challenging and performance on proficiency testing (PT) as administered by the College of American Pathologists (CAP) demonstrates some disparity among laboratories, due, in part, to the lack of *FMRI* reference materials available for routine quality control and test development. The variation in allele sizing increases as the $(CGG)_n$ number increases, with more consistent data in the lower repeat range for males and somewhat greater variability for females and for expanded alleles in the expected range for making a diagnosis of POF. Therefore, it should be noted that the reported $(CGG)_n$ may differ among laboratories, though the clinical risk of POF should not be impacted.

The POF guideline suggests that all abnormal results should be given face to face by providers aware of psychological defenses to abnormal results. Are the authors suggesting that psychological support is needed? As with any abnormal medical test results, abnormal *FMRI* results should be provided by current practice standards including recommendation for genetic counseling. As summarized in the Technical Standards and Guidelines (FX 3.3.1.4), all positive results should state that genetic counseling is indicated and testing is appropriate for at-risk family members (http://www.acmg.net/Pages/ACMG_Activities/stds-2002/fx.htm).

Thank you for the opportunity to comment on this important document. AMP, many of whose members provide molecular testing of the triplet repeat size within the *FMRI* gene, appreciates the opportunity to provide information regarding genetic testing and its implications. Please do not hesitate to contact V.M. Pratt, PhD, AMP Clinical Practice Committee Chair at victoria.m.pratt@questdiagnostics.com if we can provide further assistance or clarification.

Sincerely,



Andrea Ferreira-Gonzalez, PhD
President