FRAGILE X SYNDROME/FRAGILE X-ASSOCIATED TREMOR ATAXIA SYNDROME (FXTAS)/*FMR1*-RELATED PREMATURE OVARIAN FAILURE (POF) - *FMR1* GENE

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Background Information:

- Fragile X syndrome is an X-linked disorder associated with an expansion of a CGG repeat in the 5' end of the *FMR1* gene. It is estimated that 99% of cases are due to this expansion. The remaining 1% of cases are thought to be caused by deletions or point mutations within the gene. Normal individuals have between 5 and 44 repeats. Some individuals have a repeat size of 45 to 54 repeats and these 'grey zone' alleles do not confer a clinical phenotype. Individuals, with a premutation, have between 55 and 200 repeats and are at risk for developing fragile X-associated tremor/ataxia syndrome (FXTAS). Approximately 20% of females with a premutation will develop premature ovarian failure (POF). Above 200 repeats is considered a full mutation and is consistent with a diagnosis of fragile X syndrome in males and in 50% of females.

Change in or New Test Procedure:

- Southern blot analysis for the *FMR1* gene has been discontinued.
- A new PCR/RP-PCR based assay is now being used clinically in place of the Southern blot assay. This assay is based on the Asuragen AmplideX *FMR1* PCR kit and has been validated in-house with a sensitivity of 100% (95% CI 82-100%) and a specificity of 100% (95% CI 77-100%).
- To summarize, all patients are tested using a laboratory developed PCR test that is able to accurately size all normal, grey-zone, and premutation sized alleles up to ~120 CGG repeats. Where appropriate, the second PCR assay is performed. This is a proprietary commercial kit (AmplideX *FMR1* PCR kit) that combines repeat-primed PCR (RP-PCR) with PCR that detects expanded CGG repeats beyond the capabilities of conventional PCR including alleles >200 CGG repeats. However, sizing of the *FMR1* CGG expansion becomes less accurate beyond 200 repeats and can only be reported as a full mutation allele (i.e. greater than 200 CGG repeats).
- Reports remain unchanged except when reporting full mutations. Here, the report will simply state that the patient has greater than 200 CGG repeats in the *FMR1* gene. (i.e. This patient has greater than 200 CGG repeats in the FMR1 gene.)
- AGG sequences that may be interspersed within the CGG repeats are now detected. For individuals with premutations between 55 and 90 repeats, the AGG interruption analysis may be useful in refining their risk of passing on a fully expanded allele to their offspring. Such analysis may not always be conclusive and may require the analysis of AGG interruption patterns in selected family members.

Patient Impact:

- Improved turnaround times.

System Improvements:

- The benefits of eliminating the Southern blot include faster turnaround times, improved laboratory safety, and reduced costs, with little to no impact on the interpretation of patient results.

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