Premature Ovarian Failure (POF) and Related Disorders

POF Panel Gene List: *BMP15, CYP17A1, CYP19A1, ESR1, FGFR1, FIGLA, FSHR, GDF9, KISS1, KISS1R, LHB, LHCGR, NOBOX, NR5A1, POR, PROK2, PROKR2, PSMC3IP, SEMA3A, TAC3, TACR3, WDR11*

Clinical Features:

Premature ovarian failure (POF) is defined as amenorrhea in women under the age of 40, elevated gonadotrophin levels and reduced estrogen levels. POF is a common condition, affecting about 1% of women. POF may present as an absence of menarche (primary amenorrhea) or as premature postpubertal amenorrhea (secondary amenorrhea).[1,2] Loss of ovarian function may be the result of an absence of follicles, an increased rate of follicular atresia, or follicular unresponsiveness to hormone stimulation. Although approximately 5-10% of women are still able to conceive after a diagnosis of POF, most women with POF have a permanent loss of fertility. Additionally, due to prematurely low levels of estrogen, women with POF may experience menopausal symptoms and may be at an increased risk for osteoporosis and cardiovascular disease. Management can include hormone replacement therapy and infertility treatment. Additionally, early intervention for women with a family history of POF provides the opportunity for early family planning and/or storage of oocytes.[3]

The POF panel may clarify a clinical diagnosis or identify a genetic diagnosis for POF or a POF-related disorder. If a genetic diagnosis is found, genetic testing and recurrence risk information would be available for at-risk family members. In addition, having an identified genetic diagnosis may or may not impact medical management or treatment of the condition.

Genetics:

POF can be caused by genetic disorders, X-chromosome abnormalities, autoimmune disease, and environmental factors, although a cause remains unknown in many cases. Overall, a genetic etiology underlies POF in approximately 20-30% of individuals. Underlying chromosome abnormalities are reported in 10-13% of individuals with POF.[26] Several genes associated with POF have been identified. Variants in some of these genes cause syndromes that involve POF and/or primary amenorrhea, whereas variants in other genes result in non-syndromic POF. The most common genetic cause of POF is due to premutations in the *FMR1* gene. Individuals with *FMR1* premutations have 55 to 200 CGG repeats in the *FMR1* gene. While expansions of greater than 200 CGG repeats are associated with fragile X syndrome, premutations are associated with POF in 21% of carrier females and may also cause symptoms of fragile X-associated tremor/ataxia syndrome (FXTAS).[4.5.6] NOTE: testing for the *FMR1* gene is performed separately, this POF and Related Disorders Panel does not include testing of the *FMR1* gene.

In addition, aromatase deficiency due to variants in the *CYP19A1* gene is associated with POF, as 46,XX females exhibit primary amenorrhea at puberty.[7,8] Variants in the *NR5A1* gene can be associated with 46,XY primary amenorrhea or 46,XX POF. Although 46,XX females with *NR5A1* variants often have no symptoms, some do develop POF due to primary ovarian insufficiency.[9] *NR5A1* variants in 46,XY individuals result in a disorder of sex development (DSD), and patients may present at puberty with primary amenorrhea. Abnormal sex development can also be caused by abnormalities in steroidogenesis due to variants in the *CYP17A1* and *POR* genes. In addition to the syndromes associated with POF, many nonsyndromic causes of POF have been described, including variants in genes that are responsible for different stages of folliculogenesis. These genes include

BMP15, FIGLA, FSHR, GDF9, LHCGR, NOBOX, and *PSMC3IP*. Additional genes that have been associated with POF or primary amenorrhea include *ESR1, FGFR1, KISS1, KISS1R, LHB, PROK2, PROKR2, SEMA3A, TAC3, TACR3, WDR11*.

Test Methods:

The *FMR1* CGG repeat analysis is a separate test which can be ordered prior to or concurrent with the sequencing panel.

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: *KISS1R* gene, no copy number testing. For the *KISS1*, *LHB*, *NR5A1*, and *PROK2* genes only whole gene deletion/duplications can be detected.

Test Sensitivity:

Variants in the genes *BMP15* and *NOBOX* are among the more common as well with a prevalence of 1.5-12% and 1-6%, respectively.[12-15] In a study of 25 Europeans, variants in the *NR5A1* gene account for 8% of individuals with POF.[9] Variants in the *FIGLA* gene were identified in 2% of Chinese women with POF.[16] Variants in the genes *CYP17A1, CYP19A1, ESR1, FGFR1, FSHR, GDF9, KISS1, KISS1R, LHB, LHCGR, POR, PROK2, PROKR2, PSMC3IP, SEMA3A, TAC3, TACR3, WDR11* are rare making up <1% of individuals with POF, as they have only been reported in a small subset of families. [17-25] The *FMR1* gene has been reported in 3-15% of individuals with POF, making it likely the most common single gene cause of POF currently known.[11,25,26] *NOTE: testing of the FMR1 gene is not included in this panel.

Gene	Protein	Inheritance	Related Disease Associations
BMP15	Bone morphogentic protein 15	XL	POF, ovarian dysgenesis
CYP17A1	Cytochrome P450, family 17, subfamily A, polypeptide 1	AR	Disordered steroidogenesis
CYP19A1	Cytochrome P450, family 19, subfamily A, polypeptide 1	AR	Aromatase deficiency
ESR1	Estrogen receptor 1	AR	Estrogen resistance

FGFR1	Fibroblast growth factor 1	AD	Primary amenorrhea, hypogonadotropic hypogonadism
FIGLA	Folliculogenesis	AD	POF
FSHR	Follicle-stimulating hormone receptor	AD and AR	Ovarian dystgenesis
GDF9	Growth differentiation factor 9	AD	POF
KISS1	Kisspeptin	AR	Hypothalamic amenorrhea, hypogonadotropic hypogonadism
KISS1R	KISS1 receptor, G protein-coupled receptor 54	AR	Primary menorrhea, hypogonadotropic hypogonadism
LHB	Luteinizing hormone, beta polypeptide	AR	Secondary amenorrhea, hypogonadotropic hypogonadism
LHCGR	Luteinizing hormone, choriogonadotropin receptor	AR	Primary amenorrhea, hypogonadotropic hypogonadism
NOBOX	NOBOX oogenesis homeobox	AD	POF
NR5A1	Nuclear receptor subfamily 5, group A, member 1	AD and AR	POF, sex reversal
POR	Cytochrome P450 reductase	AR	Disordered steroidogenesis
PROK2	Prokinectin 2	AD and AR	Primary amenorrhea, hypogonadotropic hypogonadism
PROKR2	Prokinectin receptor 2	AD and AR	Primary amenorrhea, hypogonadotropic hypogonadism
PSMC3IP	PSMC3 interacting protein	AR	Ovarian dysgenesis
SEMA3A	Sprouty, drosophila, homolog 4	AD	Primary amenorrhea, hypogonadotropic hypogonadism
TAC3	Tachykinin 3	AR	Primary amenorrhea, hypogonadotropic hypogonadism
TACR3	Tachykinin receptor 3	AR	Primary amenorrhea, hypogonadotropic hypogonadism
WDR11	WD repeat domain 11	AD	Primary amenorrhea, hypogonadotropic hypogonadism

References:

1. Persani et al., (2010) J Mol Endocrinol 45:257-279 (PMID: 20668067).
2. Shelling (2010) Reproduction 140(5):633-641 (PMID: 20716613).
3. Woad et al., (2006) Aust N Z J Obstet Gynaecol 46(3):242-244 (PMID: 16704481).
4. Pirozzi et al., (2011) Am J Med Genet A 155:1803-1816 (PMID: 21739597).
5. Willemsen et al., (2011) Clin Genet 80(3):214-225 (PMID: 21651511).
6. ACOG Committee Opinion Number 469 (2010) Obstet Gynecol 116:1008-1010 (PMID: 20859177).
7. Conte et al., (1994) J Clin Endocrinol Metab 78(6):1287-1292 (PMID: 8200927).
8. Jones et al., (2006) Trends Endocrinol Metab 17(2):53-62 (PMID: 16480891).
9. Lourenco et al., (2009) N Engl J Med 360:1-11 (PMID: 19246354).
10. Bennett (2004) Pharmacogenomics 5(4):433-438 (PMID: 15165179).
11. McConkie-Rosell et al., (2005) J Genet Couns14:249-270 (PMID: 16047089).
12. Bouilly et al., (2011) Hum Mutat 32(10):1108-1113 (PMID: 21837770).
13. Qin et al., (2007) Am J Hum Genet 81(3):576-581 (PMID: 17701902).
14. Tiotiu et al., (2010) Hum Reprod 25(6):1581-1587 (PMID: 20364024)
15. Laissue et al., (2006) Eur J Endocrinol 154(5):739-744 (PMID: 16645022).
16. Zhao et al., (2008) Am J Hum Genet 82(6):1342-1348 (PMID: 18499083).

17. Quaynor et al., (2013) N Engl J Med 368(2): 164-171 (PMID: 23841731).
18. Bernard et al., (2017) J Clin Endocrinol Metab 102(1): 93-99 (PMID: 27754803).
19. Caronia et al., (2011) N Engl J Med 364(3): 215-225 (PMID: 21247312).
20. Topaloglu et al., N Engl J Med (2012) 366: 629-635 (PMID: 22335740).
21. Valdez-Socin et al., (2014) Front Endocrinol 9;5: 109 (PMID: 25071724).
22. Gianetti et al., (2010) J Clin Endocrinol Metab 96(6): 2857-2856 (PMID: 20332248).
23. Hanchate et al., (2012) PLoS Genet 8(8): e1002896 (PMID: 22927827).
24. Kim et al., (2010) Am J Hum Genet 87(4): 465-476 (PMID: 20887964).
25. Fortuno and Labarta (2014) J Assist Reprod Genet 31(12): 1575-1585 (PMID: 25227694).
26. Qin et al., (2015) Hum Reprod 21(6): 787-808 (PMID: 26243799).