The Female Infertility Panel is a comprehensive next-generation sequencing (NGS) panel that analyzes genes associated with increased risks for female infertility, including primary ovarian insufficiency, polycystic ovary syndrome, sex chromosome aneuploidy, ovarian hyperstimulation syndrome, and thrombophilia related pregnancy loss.

**INDICATIONS FOR TESTING**

- Molecular confirmation of a clinical diagnosis
- Personal history of premature ovarian insufficiency, polycystic ovary syndrome, ovarian hyperstimulation syndrome, recurrent pregnancy loss, or other infertility causes
- A family history suggestive of a hereditary infertility syndrome
- Risk assessment for asymptomatic family members of proband with a molecular diagnosis

**Primary Ovarian Insufficiency/Ovarian Dysfunction**

Primary ovarian insufficiency (POI) occurs when the ovaries cease to function appropriately prior to the age of 40 years. POI is a common condition, affecting approximately 1% of women, and typically includes depletion of ovarian follicles and a cessation of normal menstruation. Approximately 5–10% of women with primary ovarian insufficiency experience spontaneous conception and delivery indicating varying and unpredictable ovarian function (Nelson et al, 2009; Persani et al, 2010). Treatment for this condition may include hormone or fertility treatment, or early intervention, including oocyte storage, to preserve fertility (Woad et al, 2006).

**INCLUDED DISORDERS:**

- Aromatase Deficiency
- Primary Ovarian Insufficiency
- Pseudohypoparathyroidism
- Hypogonadotropic hypogonadism
- FMRT-Related Disorders
- Leydig Cell Hypoplasia
- Galactosemia
- Oocyte Maturation Defect

**INHERITANCE:**

Disorders that cause primary ovarian insufficiency and ovarian dysfunction are inherited in autosomal dominant, autosomal recessive, and X-linked fashions.

**INCLUDED GENE(S) (17):**

- BMP15
- CYP19A1
- FOXL2
- FSHR
- GDF9
- GNRHR
- LHCGR
- NR5A1
- ZP1
- CYP17A1
- FMR1
- FSHB
- GALT
- GNAS
- KISS1R
- NOBOX
- STAG3

**EMERGING EVIDENCE GENE(S) (8):**

Emerging evidence genes can also be included. These genes do not have a clear association with primary ovarian insufficiency, but emerging evidence suggests that they may play a role in disease pathogenesis.

- EIF2B2
- EIF2B3
- FIGLA
- LHB
- POF1B
- POLG
- PSMC3IP
- WT1

**REFERENCES:**

Polycystic ovary syndrome (PCOS) is characterized by high androgen levels, lack of ovulation, and ovarian cysts. Women may have irregular or absent menstrual periods, excess body and facial hair, acne, obesity, and decreased fertility, including anovulation. PCOS is a common disorder, affecting 5%-10% of women between the ages of 15-44 (Trivax and Azziz, 2007). The symptoms of PCOS are highly variable, and increase a woman’s risk for a variety of other health conditions, including diabetes, high blood pressure, high cholesterol, and sleep apnea (Mccartney and Marshall, 2016). Although PCOS does not have a cure, it is frequently treatable. Treatments may include lifestyle modification including weight loss, medications for regulating menstrual cycles, inducing ovulation and reducing excessive hair growth, as well as surgery.

**INCLUDED DISORDERS:**
This panel includes genes associated with:

- Polycystic Ovary Syndrome (PCOS)

**INHERITANCE:**
Polycystic ovary syndrome is typically inherited in a multifactorial manner, meaning that both genetic and environmental factors play a role in the development of this disease. The genes included in this panel are associated with increased risks for developing polycystic ovary syndrome.

**INCLUDED GENE(S) (7):**

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<tr>
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**EMERGING EVIDENCE GENE(S) (8):**
Emerging evidence genes can also be included. These genes do not have a clear association with polycystic ovary syndrome, but emerging evidence suggests that they may play a role in disease pathogenesis.

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<td>IRS2</td>
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**REFERENCES:**

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Ovarian hyperstimulation syndrome (OHSS) typically occurs as a side effect in 3-6% of women who are taking follicle stimulating drugs during the course of IVF treatment (Kumar et al, 2011). OHSS can cause abdominal discomfort, nausea, vomiting, and diarrhea due to enlarged polycystic ovaries, and in severe cases can lead to rupture and hemorrhaging of ovarian cysts, which can lead to organ failure and death. In some cases, OHSS can occur spontaneously during pregnancy in women who are not undergoing fertility treatment. Genetic factors can influence the severity of symptoms in women who develop OHSS during IVF treatment (Smits et al, 2003).

**INCLUDED DISORDERS:**
This panel includes genes associated with:

- Ovarian Hyperstimulation Syndrome (OHSS)

**INHERITANCE:**
Spontaneous ovarian hyperstimulation syndrome is inherited in an autosomal dominant manner. Ovarian hyperstimulation syndrome typically occurs as an iatrogenic complication related to in vitro fertilization and is influenced by genetic and environmental factors.

**INCLUDED GENE(S) (7):**

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**REFERENCES:**
Sex chromosome aneuploidy is the presence of an abnormal number of sex chromosomes. Male individuals typically have 46 chromosomes, including one X chromosome and one Y chromosome, while females typically have 46 chromosomes, including two X chromosomes. The most common sex chromosome abnormality in females leading to infertility is Turner syndrome, which occurs in 1 in 2,500 females (Culen et al, 2017). Turner syndrome results when one normal X chromosome is present in a female's cells and the other sex chromosome is missing or structurally altered. Females with Turner syndrome typically have short stature, cardiac abnormalities, and ovarian insufficiency. Approximately 2-5% of individuals with Turner syndrome may become pregnant spontaneously, although many women may become pregnant through the use of assisted reproductive technologies (ART) (Karnis et al, 2012).

**References:**

Inherited thrombophilia is a genetic predisposition to blood clotting that is caused by abnormalities in the blood clotting cascade. The most common manifestation of inherited thrombophilia is venous thromboembolism (VTE). Risks for VTE is increased by smoking, obesity, age, oral contraceptive and hormone replacement therapy, air travel, pregnancy, and surgery. The specific risk for VTE depends on the gene involved and environment factors e.g., individuals who are heterozygous for F5 Leiden allele have a 3 to 8 fold increased risk for VTE in their lifetime, and individuals who are heterozygous for the F2 c.20210G>A allele have a 2 to 5 fold increased risk (Rosendaal and Reitsma, 2009).

In addition to increased risks for blood clotting, individuals with hereditary thrombophilia may be at increased risk for recurrent pregnancy loss, which is the highest during the second and third trimester (Lissalde-lavigne et al, 2005). Individuals with an inherited thrombophilia have been shown to have a 2 to 3 fold increased risk for a late miscarriage versus unaffected individuals (Martinelli et al, 2000). Also, individuals who have experienced recurrent pregnancy loss are more likely to have an inherited thrombophilia than those who have not (Martinelli et al, 2000).
EMERGING EVIDENCE GENE(S) (33):
Emerging evidence genes can also be included. These genes do not have a clear association with thrombophilia related recurrent pregnancy, but emerging evidence suggests that they may play a role in disease pathogenesis.

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