The Familial Hypercholesterolemia (FH) Panel is a comprehensive next-generation sequencing (NGS) panel that can be used to confirm a clinical diagnosis of FH or identify at-risk individuals.

Familial hypercholesterolemia is characterized by severely elevated levels of LDL cholesterol, which lead to plaque formations in major blood vessels starting at a young age, contributing to an increased risk for cardiovascular disease. Patients experience coronary artery disease and increased risk for severe cardiovascular events, like heart attacks. Some patients may also experience the formation of xanthomas (fatty deposits) around their eyelids and the tendons of the extremities.

**PREVALENCE**
Familial hypercholesterolemia affects approximately 1 in 250 individuals (de Ferranti SD et al, 2016).

**INCLUDED DISORDERS**
This panel includes genes associated with familial hypercholesterolemia.

**CLINICAL SENSITIVITY**
Individuals with a definite diagnosis of familial hypercholesterolemia will be identified to have a mutation in one of the genes on this panel in 60-80% of cases (Marduel et al, 2010). The yield of genetic testing in patients with a “possible” diagnosis of familial hypercholesterolemia is reduced (Graham et al, 2005).

**METHODOLOGY AND ANALYTICAL SENSITIVITY**
Next-generation sequencing technology is used to test clinically relevant portions of each gene, including coding exons, adjacent intron/exon boundaries, and selected introns/noncoding variants. Pathogenic and likely pathogenic variants are confirmed by orthogonal methods. Copy number variants, including intragenic deletions and duplications are detected to a resolution of single exon. To request analysis of a specific single exon copy number variant, please contact our Client Services team prior to ordering. Analytical sensitivity of the assay is >99%.

**INHERITANCE AND PENETRANCE**
The majority of familial hypercholesterolemia (FH) is inherited in an autosomal dominant fashion, with the exception of mutations in the LDLRAP1 gene, which are inherited in an autosomal recessive manner. However, individuals with multiple mutations in an autosomal dominant FH gene, such as LDLR and APOB have a more severe presentation than individuals with a single mutation.

Penetrance in autosomal dominant familial hypercholesterolemia is incomplete, with an estimated 73-90% of individuals with a mutation in LDLR or PCSK9 developing disease (Khera et al, 2016; Naoumova et al, 2005), with reduced penetrance also being reported in APOB (Fahed and Nemer, 2011).

**INDICATIONS FOR TESTING**
- Personal or family history of elevated LDL cholesterol; >190 mg/dL in individuals older than 20 years and >160 mg/dL in individuals younger than 20 years
- Physical findings of familial hypercholesterolemia including xanthomas and corneal arc
- Family history of familial hypercholesterolemia
**INCLUDED GENES (4):**

| APOB | LDLR | LDLRAP1 | PCSK9 |

**REFERENCES**