Familial Mediterranean Fever (**MEFV**)

**Indications for Ordering**
- To confirm a diagnosis of familial Mediterranean fever (FMF) in a symptomatic individual
- Diagnostic or carrier testing in individuals with a family history of FMF
- Carrier testing for the reproductive partner of an individual who is a carrier of, or affected with, FMF
- To guide appropriate drug therapy (response to colchicine therapy differs for some pathogenic variants)

**Test Description**
Bidirectional sequencing of the entire **MEFV** coding region and intron/exon boundaries

**Tests to Consider**

**Primary test**
**Familial Mediterranean Fever (**MEFV**) Sequencing 2002658**
- Preferred test for suspected FMF

**Related tests**
Initial testing for minor criteria
- **Sedimentation Rate, Westergren (ESR) 0040325**
- **Fibrinogen 0030130**
- **White Blood Cell Count 0040320**
**Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication 2007370**
- Includes **ELANE, LPIN2, MEFV, MVK, NLRP3, PSTPIP1, and TNFRSF1A** genes
- May be used as initial test to identify genetic cause of FMF, or as a second test after normal **MEFV** sequencing
- Sequencing and deletion/duplication also orderable as separate tests
**Familial Mutation, Targeted Sequencing 2001961**
- Useful when a pathogenic familial variant identifiable by sequencing is known

**Disease Overview**

**Incidence**
- Up to 1/1,000 in individuals of Armenian, Arab, and Turkish descent
- Carrier frequencies among commonly affected populations
  - North African Arabs – 1/100
  - North African Jews, Iraqi Jews, Armenians, and Turks – 1/3 to 1/7
  - Ashkenazi Jews – 1/5

**Age of onset** – generally childhood, rare onset after age 30

**Symptoms/diagnostic criteria**
Fever plus at least one major symptom AND one minor symptom
- Major symptoms
  - Abdominal pain
    - Sudden onset of diffuse pain
    - Occurs in 90-95% of FMF individuals
  - Chest pain
  - Joint pain
  - Skin eruption
  - Amyloidosis
    - Most severe complication
    - Leads to end-stage renal disease
- Minor symptoms
  - Increased ESR
  - Leukocytosis
  - Elevated serum fibrinogen

**Genetics**

**Gene** – **MEFV**

**Inheritance** – mostly autosomal recessive
- Most affected individuals have two **MEFV** pathogenic variants
- Some activating variants can cause FMF in a heterozygous individual, appearing autosomal dominant

**Variants**
- ~80 reported, most located in exon 10
  - Most common pathogenic variant is p.Met694Val
  - Some genotype/phenotype correlations exist
    - Homozygotes for p.Met694Val pathogenic variant have higher risk for amyloidosis
    - Individuals with certain pathogenic variants may respond differently to colchicine

**Test Interpretation**

**Sensitivity/specificity**
- Clinical sensitivity – ~80% (Aksentijevich, 1999; Shohat, 2014; Touitou, 2001)
- Analytical sensitivity/specificity – 99%
Results

- Two pathogenic MEFV variants detected
  - Individual is predicted to be affected with FMF
- One or no pathogenic MEFV variants detected in a clinically affected individual
  - May have FMF – medical management should rely on clinical findings
  - Some affected individuals may not have two detectable pathogenic variants
  - Carriers of some pathogenic variants may manifest symptoms
- One or no pathogenic MEFV variants detected in a clinically unaffected individual
  - Predicted to be at least a carrier
- No pathogenic MEFV variants detected in a clinically unaffected individual
  - Neither a carrier nor affected
- Inconclusive
  - MEFV variants of unknown clinical significance may be detected

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not detected
  - Regulatory region and intronic variants
  - Large deletions/duplications
  - Variants in genes other than MEFV

References