**Stage I: Rule-Out Dashboard**
*Secondary Findings in Adults*

**GENE/GENE PANEL:** MEFV  
**HGNC ID:** 6998  
**DISORDER:** Familial Mediterranean Fever (AD)  
**OMIM ID:** 134610

### ACTIONABILITY

1. Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?  
   - [ ] YES  
   - [x] NO

2. Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?  
   - Patient Management
   - Surveillance or Screening
   - Family Management
   - Circumstances to Avoid
   - [ ] YES (≥ 1 of above)  
   - [ ] NO

3. Is the result actionable in an undiagnosed adult with the genetic condition?  
   - [ ] YES  
   - [x] NO

### PENETRANCE

4. Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?  
   - [x] YES  
   - [ ] NO  
   - [x] UNKNOWN

### SIGNIFICANCE/BURDEN OF DISEASE

5. Is this condition an important health problem?  
   - [x] YES  
   - [ ] NO

### NEXT STEPS

6. Are Actionability (Q2-3), Penetrance (Q4), and Significance (Q5) all “YES”?  
   - [x] YES *(Proceed to Stage II)*  
   - [ ] NO *(Consult Actionability Working Group)*

   - [ ] Exception granted, proceed to Stage II  
   - [ ] Exception not granted, STOP
Stage II: Summary Report
Secondary Findings in Adults
Non-diagnostic, excludes newborn screening & prenatal testing/screening

<table>
<thead>
<tr>
<th>Topic</th>
<th>Narrative Description of Evidence</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the nature of the threat to health for an individual carrying a deleterious allele?</td>
<td>Familial Mediterranean Fever (FMF) predominantly affects populations living in the southeastern Mediterranean region. Populations having a high prevalence (1/200-1/1000) include non-Ashkenazi Jews, Armenians, Turks, and Arabs. FMF is also seen in many other countries, although in much lower numbers. However, the proportion of cases attributed to a single MEFV pathogenic variant is unknown.</td>
<td>(1-4)</td>
</tr>
<tr>
<td>Prevalence of the genetic disorder</td>
<td>FMF is an autoinflammatory fever syndrome characterized by recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis and meningitis. Attacks can vary in frequency (as often as once a week or every few years), typically last 1-4 days, and resolve spontaneously. Mild symptoms (myalgia, headache, nausea, dyspnea, arthralgia, low back pain, asthenia and anxiety) precede attacks and last about 17 hours in approximately 50% of patients. Attacks manifest as fever, diffuse or localized abdominal pain, constipation or diarrhea, arthralgias (in large joints), arthritis (in upper/lower limb/knee joints) chest pain caused by pleuritis and/or pericarditis, and skin eruption. Joint attacks can result in severe damage to the joint and permanent deformity may require joint replacement. The main long-term complication is amyloid A (AA) amyloidosis, which is common in untreated individuals, can lead to renal failure, and has a poor prognosis. Untreated individuals with FMF, especially those with multiple attacks and/or amyloidosis, are at higher risk for infertility.</td>
<td>(1, 3, 4)</td>
</tr>
<tr>
<td>Clinical Features (Signs/symptoms)</td>
<td>Heterozygotes are typically asymptomatic, though some manifest a spectrum of findings from classic to mild FMF. Clinical features in individuals with a single pathogenic MEFV mutation are typically milder and the attacks shorter and less frequent than patients with two MEFV mutations. Most patients have an incomplete abdominal attack as the major criterion of the disease. Patients manifest mainly fever and abdominal symptoms.</td>
<td>(4)</td>
</tr>
<tr>
<td>Natural History (Important subgroups &amp; survival/recovery)</td>
<td>Younger children with a single pathogenic variant and symptoms of recurrent autoinflammatory disorder have a milder disease course compared to individuals with biallelic pathogenic variations, with no major differences in presenting signs. However, clinical signs have been reported to completely disappear at puberty in some cases, indicating that a single pathogenic variant may not necessarily predict lifelong illness.</td>
<td>(4)</td>
</tr>
</tbody>
</table>

2. How effective are interventions for preventing the harm?
Information on the effectiveness of the recommendations below was not provided unless otherwise stated.

| Patient Management | To establish the extent of disease and needs in an individual diagnosed with FMF, the following evaluations are recommended (Tier 4):
|                   | • Physical examination to assess joint problems
|                   | • Urinalysis for the presence of protein. If proteinuria is found, further evaluation is required, including 24-hour urinary protein assay and renal function tests, and also, if indicated, rectal biopsy for the presence of amyloid.
|                   | • Medical genetics consultation.
|                   | The presence of a single MEFV pathogenic variant together with clinical symptoms is sufficient to warrant the initiation of a trial of colchicine. Therefore, manifesting heterozygotes should be treated. However, since the natural history and outcome for persons with FMF who are heterozygous for a single MEFV pathogenic variant are unknown, there is no recommendation of lifelong treatment with colchicine for this group. A report of clinical diagnosed FMF patients with a single MEFV variation indicated that 21 of 25 (84%) either completely or partially responded to colchicine therapy. A second report of 94 heterozygous patients with recurrent fever indicated that 82% required colchicine treatment, which was effective in over 90%. (Tier 3) | (4) |
| Surveillance | No recommendations specific to surveillance in heterozygous patients were identified. | |
### Stage II: Summary Report

**Secondary Findings in Adults**

**Non-diagnostic, excludes newborn screening & prenatal testing/screening**

| Family Management | Routine genetic testing for MEFV mutations is not recommended in siblings of an index case. However, parents or siblings should be made aware of clinical signs of FMF in order to give them the possibility of seeking advice from a physician in case of suspected symptoms. In cases where the parents of a patient are very concerned about their other children, screening for acute phase reactants can be done. In case of elevated inflammatory markers on two successive blood tests in totally asymptomatic individuals, genetic testing should be considered, as elevated acute phase reactants may unveil a hidden disease. **(Tier 2)** |
|---|
| Circumstances to Avoid | A single report has suggested that cisplatin worsens symptoms of FMF. **(Tier 3)** Cyclosporin appears to adversely affect renal transplant graft survival in individuals with FMF. It has also been reported to trigger FMF attacks, which responded well to colchicine in a previously asymptomatic individual with myelodysplastic syndrome who was heterozygous for the MEFV pathogenic variant M694I. **(Tier 3)** |

### Description of sources of evidence:

**Tier 1:** Evidence from a systematic review, or a meta-analysis or clinical practice guideline clearly based on a systematic review

**Tier 2:** Evidence from clinical practice guidelines or broad-based expert consensus with non-systematic evidence review

**Tier 3:** Evidence from another source with non-systematic review of evidence with primary literature cited

**Tier 4:** Evidence from another source with non-systematic review of evidence with no citations to primary data sources

**Tier 5:** Evidence from a non-systematically identified source
<table>
<thead>
<tr>
<th>GENE/GENE PANEL:</th>
<th>MEFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISORDER:</td>
<td>Familial Mediterranean Fever (AD)</td>
</tr>
</tbody>
</table>

### 3. What is the chance that this threat will materialize?

<table>
<thead>
<tr>
<th>Mode of Inheritance</th>
<th>FMF is usually inherited in an autosomal recessive manner, although recent studies have suggested that some heterozygotes manifest a spectrum of findings from classic to mild FMF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of Genetic Mutations</td>
<td>No information on the frequency of MEFV mutations in the general population was identified. The pathogenic variant A2080G is found in more than 90% of affected Jewish persons of North African origin. (Tier 4) About 85% of patients of Mediterranean origin that meet clinical criteria have a mutation in both copies of the MEFV gene, with only one mutation identified in about 20% of affected cases. (Tier 3)</td>
</tr>
<tr>
<td>Penetration OR Relative Risk (include high risk racial or ethnic subgroups)</td>
<td>Information on the penetrance among patients who have a single pathogenic MEFV variant was not identified. Information on relative risk was not identified.</td>
</tr>
<tr>
<td>Expressivity</td>
<td>Symptoms and severity vary among affected individuals, even among members of the same family suggesting that manifestations are also influenced by other genes and/or environmental factors. (Tier 4)</td>
</tr>
</tbody>
</table>

### 4. What is the nature of the intervention?

| Nature of Intervention | Colchicine toxicity is a serious complication that should be given adequate consideration and be prevented. Colchicine is an alkaloid with a narrow therapeutic range. High concentrations may cause serious toxicity that can be life threatening. Complications of colchicine use occasionally include myopathy and toxic epidermal necrolysis-like reaction. Colchicine treatment may induce oligospermia/azoospermia. Other identified interventions include blood and urine tests, associated with low burden and risk. |

### 5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?

| Chance to Escape Clinical Detection | Symptoms associated with FMF (e.g., fever, pain) are not specific and may not direct the correct diagnosis. |

### Final Consensus Scores

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Outcome/intervention pair</th>
<th>Severity</th>
<th>Likelihood</th>
<th>Effectiveness</th>
<th>Nature of the Intervention</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEFV-AD</td>
<td>Recurrent serositis + Colchicine</td>
<td>1</td>
<td>0D</td>
<td>3C</td>
<td>2</td>
<td>6DC</td>
</tr>
<tr>
<td></td>
<td>Amyloidosis + Colchicine</td>
<td>1</td>
<td>0D</td>
<td>3C</td>
<td>2</td>
<td>6DC</td>
</tr>
<tr>
<td></td>
<td>Joint problems + Colchicine</td>
<td>1</td>
<td>0D</td>
<td>3C</td>
<td>2</td>
<td>6DC</td>
</tr>
</tbody>
</table>

To see the scoring key, please go to: [https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-basedsummaries/](https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-basedsummaries/).
Stage II: Summary Report
Secondary Findings in Adults
Non-diagnostic, excludes newborn screening & prenatal testing/screening

Date of Search (MM.DD.YYYY): 05.23.2016

References