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

**GENE/GENE PANEL:** RYR1, CACNA1S  
**HGNC ID:** 10483, 1397  
**DISORDER:** Malignant Hyperthermia Susceptibility  
**OMIM ID:** 145600, 601887

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**ACTIONABILITY**

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

2. Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?  
   - **Yes**  
   - **No**
     - 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**  
   - **NO**

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**PENETRANCE**

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

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**SIGNIFICANCE/BURDEN OF DISEASE**

5. Is this condition an important health problem?  
   - **YES**  
   - **NO**

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**NEXT STEPS**

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

   - Exception granted, proceed to Stage II  
   - Exception not granted, STOP

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### Stage II: Summary Report

**Incidental Findings in Adults**

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

<table>
<thead>
<tr>
<th>GENE/GENE PANEL: RYR1, CACNA1S</th>
<th>DISORDER: Malignant Hyperthermia Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topic</strong></td>
<td><strong>Narrative Description of Evidence</strong></td>
</tr>
<tr>
<td><strong>1. What is the nature of the threat to health for an individual carrying a deleterious allele?</strong></td>
<td>Malignant hyperthermia (MH) has an estimated prevalence of 1/60,000-1/100,000. However, as many individuals undergoing surgery who experience marked hyperthermia may be coded as being MH susceptible, the exact prevalence has been difficult to clarify. It seems certain that there are more than 1,000 cases of MH in the US each year. It is unclear whether all MH cases are due to a mutation in RYR1 or CACNA1S.</td>
</tr>
<tr>
<td><strong>Prevalence of the genetic disorder</strong></td>
<td>MH susceptibility (MHS) is a pharmacogenetic skeletal muscle disorder where exposure to certain volatile anesthetics, either alone or with a depolarizing muscle relaxant, may trigger uncontrolled skeletal muscle hypermetabolism. In rare cases, similar episodes may also be triggered by heat and exercise. An MH episode may begin with hypercapnia and tachycardia followed by hyperthermia. Additional symptoms may include increased CO\textsubscript{2} production, increased O\textsubscript{2} consumption, acidosis, muscle rigidity, compartment syndrome, rhabdomyolysis and subsequent increased creatine kinase, and hyperkalemia with a risk for cardiac arrhythmia or even arrest, and myoglobinuria with a risk for renal failure.</td>
</tr>
<tr>
<td><strong>Clinical Features</strong> (Signs/symptoms)</td>
<td>In nearly all cases, the first manifestations of MH occur during anesthetization in the operating room, though manifestations may also occur within an hour or so of anesthesia termination. MH presentation can vary depending on the triggering agents and environmental factors, such as metabolic state and body temperature, at the beginning of anesthesia. Without proper and prompt treatment, mortality is extremely high. Even with treatment and survival, the individual is at risk for life-threatening consequences and recurrence of the syndrome within the first 24-36 hours following an episode. A significant male preponderance has been reported.</td>
</tr>
<tr>
<td><strong>Signif/Burden of Condition</strong></td>
<td><strong>Natural History</strong> (Important subgroups &amp; survival/recovery)</td>
</tr>
<tr>
<td><strong>2. How effective are interventions for preventing the harm?</strong></td>
<td>If a pregnant woman with MHS requires non-emergent surgery, a non-triggering anesthetic (local, nerve block, epidural, spinal anesthesia or a total intravenous general anesthetic) should be administered. Continuous epidural analgesia is highly recommended for labor and delivery. If a Cesarean delivery is indicated in a woman who does not have an epidural catheter in place, neuraxial (spinal, epidural, or combined spinalepidural) anesthesia is recommended, if not otherwise contraindicated. If a general anesthetic is indicated, a total intravenous anesthetic technique should be administered, with an anesthesia machine that has been prepared for an MH-susceptible individual. (Tier 4)</td>
</tr>
<tr>
<td><strong>Patient Management</strong></td>
<td>MHS patients should carry identification of their susceptibility and inform those responsible for their care of their MH status. (Tier 2)</td>
</tr>
<tr>
<td></td>
<td><strong>Surveillance</strong></td>
</tr>
<tr>
<td><strong>Family Management</strong></td>
<td>If the disease-causing mutation has been identified in the family, molecular genetic testing of at-risk relatives is warranted to identify those who have the mutation and will benefit from avoiding anesthetic agents that increase the risk for a MH episode. (Tier 4)</td>
</tr>
<tr>
<td><strong>Circumstances to Avoid</strong></td>
<td>When suspicion of MHS exists, family members should not be given trigger anesthetic agents. (Tier 4)</td>
</tr>
<tr>
<td><strong>Do not use the following MH triggering drugs for MHS patients: inhaled general anesthetics (Desflurane, Enflurane, Halothane, Isoflurane, Sevoflurane) and depolarizing muscle relaxants (Succinylcholine). (Tier 2)</strong></td>
<td></td>
</tr>
<tr>
<td>MHS patients who have not experienced adverse effects of heat and exercise should not restrict their activity, and those who have experienced adverse effects of heat or exercise should restrict their activity based on their own experience. (Tier 2)</td>
<td></td>
</tr>
</tbody>
</table>
**Stage II: Summary Report**

**Incidental Findings in Adults**

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<table>
<thead>
<tr>
<th>Description of sources of evidence:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tier 1</strong>: Evidence from a systematic review, or a meta-analysis or clinical practice guideline clearly based on a systematic review</td>
<td></td>
</tr>
<tr>
<td><strong>Tier 2</strong>: Evidence from clinical practice guidelines or broad-based expert consensus with non-systematic evidence review</td>
<td></td>
</tr>
<tr>
<td><strong>Tier 3</strong>: Evidence from another source with non-systematic review of evidence with primary literature cited</td>
<td></td>
</tr>
<tr>
<td><strong>Tier 4</strong>: Evidence from another source with non-systematic review of evidence with no citations to primary data sources</td>
<td></td>
</tr>
<tr>
<td><strong>Tier 5</strong>: Evidence from a non-systematically identified source</td>
<td></td>
</tr>
</tbody>
</table>

**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>RYR1, CACNA1S</td>
<td>MH event/Avoidance of triggering anesthetics</td>
<td>2</td>
<td>2D</td>
<td>3B</td>
<td>3</td>
<td>10DB</td>
</tr>
</tbody>
</table>
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Date of Search (MM.DD.YYYY): 02.13.2015 (updated 06.15.2015)

Reference List


