### Stage I: Rule-Out Dashboard

**Incidental Findings in Adults**

<table>
<thead>
<tr>
<th>GENE/GENE PANEL: SCNSA</th>
<th>CONDITION: Brugada syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC ID: 10593</td>
<td>OMIM ID: 601144</td>
</tr>
</tbody>
</table>

#### ACTIONABILITY

1. Is there a practice guideline or systematic review for the genetic condition?
   - YES
   - NO (STOP)

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 (STOP)

3. Is the result actionable in an undiagnosed adult with the genetic condition?
   - YES
   - NO (STOP)

#### 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 (STOP)

#### SIGNIFICANCE/BURDEN OF DISEASE

5. Is this condition an important health problem?
   - YES
   - NO (STOP)

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
### Stage II: Summary Report
#### Incidental Findings in Adults
Non-diagnostic, excludes newborn screening & prenatal testing/screening

<table>
<thead>
<tr>
<th>GENE/GENE PANEL: SNC5A</th>
<th>CONDITION: Brugada syndrome</th>
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<tbody>
<tr>
<td><strong>Topic</strong></td>
<td><strong>Narrative Description of Evidence</strong></td>
</tr>
<tr>
<td>1. What is the nature of the threat to health for an individual carrying a deleterious allele?</td>
<td>The prevalence of Brugada syndrome is difficult to estimate due to the recent identification of the disorder and the difficulty in diagnosis. Available prevalence estimates vary around the world, from 1/700-1/800 in certain endemic areas of Asia to 1/3,300-1/10,000 in Europe and the United States.</td>
</tr>
<tr>
<td><strong>Prevalence of the genetic disorder</strong></td>
<td>Brugada syndrome is characterized by a distinctive ECG pattern of sinus tachycardia (ST) segment elevation in the V1-V3 leads (termed “type 1 abnormality”) in the absence of gross structural abnormalities. Patients have a high risk for ventricular arrhythmias, which can result in syncope or sudden cardiac death. Clinical presentations may also include sudden infant death syndrome (SIDS) and the sudden unexpected nocturnal death syndrome (SUNDS). Other conduction defects can include first-degree AV block, intraventricular conduction delay, right bundle branch block, and sick sinus syndrome. Electrical storms, multiple episodes of ventricular arrhythmias over a short period of time, are malignant but rare in patients.</td>
</tr>
<tr>
<td><strong>Clinical Features</strong> (Signs/symptoms)</td>
<td>Brugada syndrome presents primarily during adulthood, with syncope as the most common presenting feature. Age at diagnosis ranges from 2 days to 85 years. The mean age of sudden death is approximately 40 years. Both sexes are at a high risk for ventricular arrhythmias and sudden death, though the vast majority of those affected are male. Patients who have easily induced sustained ventricular arrhythmias, a spontaneous type 1 ECG pattern (compared to pharmacologically-induced), and a history of syncope have a worse prognosis.</td>
</tr>
<tr>
<td><strong>Signif/Burden of Condition</strong> (Important subgroups &amp; survival/recovery)</td>
<td></td>
</tr>
<tr>
<td><strong>Natural History</strong></td>
<td></td>
</tr>
<tr>
<td>2. How effective are interventions for preventing the harm?</td>
<td>An implantable cardioverter defibrillator (ICD) is reasonable for patients with Brugada syndrome, though some guidelines only recommend ICD implantation for those with certain risk factors such as a history of syncope and/or documented ventricular tachycardia that has not resulted in cardiac arrest. ICD should also be considered in patients with a spontaneous type 1 ECG pattern. In the absence of a spontaneous type 1 ECG pattern, an implantable loop recorder (ILR) should be considered. A cohort study of 220 patients with Brugada and a history of syncope reported an appropriate ICD shock rate of 10% over 3 years. (Tier 2) Two additional cohort studies reported appropriate shock rates of 19%, 16%, and 12% for patients with a history of syncope, patients with a type 1 ECG pattern, and asymptomatic patients, respectively. (Tier 5)</td>
</tr>
<tr>
<td>Patient Management</td>
<td>Treatment of asymptomatic individuals is controversial and recommendations vary, but include observation until the first symptom develops and placement of an ICD in individuals with a family history of sudden cardiac death or when electrophysiological study indicates a likelihood of arrhythmias. (Tier 3) Quinidine is recommended to prevent primary symptoms, and has been shown to restore ST-segment elevation and decrease the incidence of arrhythmias. In one study, of 19 patients treated for 6 to 219 months and followed 0.5 to 22 years, none had an arrhythmic event. In another study, syncope occurred in 2 of 21 patients treated an average of 17 months. (Tier 3) Women experiencing arrhythmic events due to hormone changes during pregnancy can be treated with quinidine to normalize the ECG pattern. In a case study of a young pregnant woman, oral quinidine inhibited the recurrence of ventricular tachyarrhythmia. (Tier 3) Because perioperative pharmacological and physiological changes may precipitate malignant arrhythmias, specific management is required for patients under anesthesia. (Tier 3)</td>
</tr>
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</table>
## Stage II: Summary Report
### Incidental Findings in Adults
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| Surveillance | To establish extent of disease and individual needs after initial diagnosis, patients are recommended to undergo an ECG, induction with sodium channel blockers among those with a type 2 or type 3 pattern on ECG, electrophysiological study, and medical genetics consultation. *(Tier 4)*
| At-risk patients with a family history or a known pathogenic variant should undergo ECG monitoring every one to two years. *(Tier 3)* |

| Family management | Serial ECGs and a pharmacological drug challenge can assist in risk stratification in individuals with a family history of Brugada syndrome. *(Tier 2)*
| If the pathogenic variant is known, relatives at risk should undergo genetic testing to identify those who should undertake preventive measures as well as rule out risk for those not carrying the pathogenic variant. *(Tier 3)* |

| Circumstances to Avoid | Patients should avoid certain antiarrhythmic, psychotropic, and anesthetic drugs that can induce cardiac arrhythmias. Other agents to avoid include acetylcholine, alcohol toxicity, cocaine, and ergonovine. *(Tier 2)*
| Patients should also avoid or quickly mitigate high fever and electrolyte disturbances. *(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
## Stage II: Summary Report

### Incidental Findings in Adults

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<td><strong>Topic</strong></td>
<td>Narratives Description of Evidence</td>
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<tr>
<td>3. <strong>What is the chance that this threat will materialize?</strong></td>
<td></td>
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<tr>
<td>Mode of Inheritance</td>
<td>Autosomal Dominant</td>
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<tr>
<td>Prevalence of Genetic Mutations</td>
<td>Pathogenic mutations in SCN5A account for 15-30% of Brugada syndrome cases. (Tier 3)</td>
</tr>
<tr>
<td>Penetrance OR Relative Risk (include any high risk racial or ethnic subgroups)</td>
<td>Among individuals with a pathogenic variant in SCN5A, approximately 20-30% have a type 1 ECG pattern and approximately 80% manifest the characteristic ECG change when challenged with a sodium channel blocker. (Tier 3)</td>
</tr>
<tr>
<td></td>
<td>The majority of patients remain asymptomatic, while 20-30% experience syncope and 8-12% experience at least one cardiac arrest (potentially leading to sudden death). (Tier 4)</td>
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<tr>
<td>Expressivity</td>
<td>Information on variable expressivity was not available.</td>
</tr>
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</table>

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

**Burden and/or Risk**
Identified interventions include the implantation of an ICD, which would involve invasive surgery.

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

**Chance to escape clinical detection in adults**
Brugada syndrome is typically diagnosed with ECG, a screening procedure not typically recommended for asymptomatic adults with apparently low risk of coronary heart disease. It is very likely this disorder could go unrecognized and present in a patient as ventricular arrhythmia and cardiac arrest, resulting in sudden death in 8-12% of affected individuals. (Tier 3)

<table>
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<th>Final Consensus Scores</th>
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<td>Gene(s)</td>
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<td>SCN5A</td>
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To see the scoring key, please go to: https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/

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Date of Search: 08.07.2014 (updated 04.10.2015)

**Reference List**


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