Stage I: Binning Dashboard

Incidental Findings in Adults

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

**GENE/GENE PANEL:** PMP22, MPZ, LITAF, EGR2, NEFL

**DISORDER:** Charcot-Marie-Tooth Disease, Type 1

### 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

### 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

### SIGNIFICANCE/BURDEN OF DISEASE

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

### 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
## Stage II: Binning Summary

**Incidental Findings in Adults**

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<table>
<thead>
<tr>
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### 1. What is the nature of the threat to health for an individual carrying a deleterious allele?

<table>
<thead>
<tr>
<th>Topic</th>
<th>Narrative Description of Evidence</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of the genetic disorder</td>
<td>The overall prevalence of hereditary neuropathies is estimated at approximately 30:100,000 population. The prevalence of CMT1 is 15:100,000-20:100,000.</td>
<td>[1]</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>The CMT1 subtypes, identified solely by molecular findings, are often clinically indistinguishable. CMT1A (70%-80% of CMT1) is associated with PMP22. CMT1B (6%-10% of CMT1) is associated with MPZ. CMT1C (1%-2% of CMT1) is associated with LITAF, and CMT1D (&lt;2% of CMT1) is associated with EGR2. CMT1E (&lt;5% of CMT1) is associated with PMP22. CMT2E/1F (&lt;5% of CMT1) is associated with NEFL. The classic phenotype of CMT1 is a demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity. It is usually slowly progressive and often associated with pes cavus foot deformity and bilateral foot drop. Musculoskeletal or neuropathic pain is reported in some cases. Small studies have reported sleep apnea in CMT1 patients. Other findings in CMT1 individuals include impotence, hip dysplasia, pulmonary insufficiency, deafness or early hearing loss, and lower-limb muscle atrophy and fatty infiltration.</td>
<td>[1;3]</td>
</tr>
<tr>
<td>Natural History</td>
<td>The average age of onset of clinical symptoms among CMT1A patients is five to 25 years. Men and women are equally disabled by CMT1. The disease does not decrease life span.</td>
<td>[1;4]</td>
</tr>
</tbody>
</table>

### 2. How effective are interventions for preventing the harm?

| Patient Management | No treatment reverses or slows the natural progression of CMT. At diagnosis the following evaluations are recommended: physical examination, nerve conduction velocity (NCV), family history, and medical genetic consultation. (Tier 4) Daily heel cord stretching exercises to prevent Achilles’ tendon shortening are desirable. (Tier 4) Preoperative assessment for co-morbidities and autonomic denervation is recommended. During surgical positioning, transport and mobilization, cautious positioning and protection of pressure points is recommended to avoid nerve compression. Neuromuscular block monitoring during surgery is also recommended. (Tier 4) | [1] |
| Surveillance | Information on the effectiveness of the surveillance recommendation(s) below was not provided. Individuals should be evaluated regularly by a team comprising physiatrists, neurologists, and physical and occupational therapists to determine neurologic status and functional disability. (Tier 4) | [1] |
| Family Management | Asymptomatic adults at risk of inheriting CMT1-causing mutation may wish to pursue further evaluation, either through genetic testing or through clinical evaluation and NCV testing. (Tier 4) | [1] |
| Circumstances to Avoid | Obesity should be avoided because it makes walking more difficult. (Tier 4) Vincristine, a chemotherapy agent, should be avoided by all persons with CMT, including those who are asymptomatic. Other medications may pose moderate to significant risk. (Tier 4) Avoiding succinylcholine, a muscle relaxant used for anesthesia, is recommended. (Tier 4) | [1;4] [3] |
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### 3. What is the chance that this threat will materialize?

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<th>Mode of Inheritance</th>
<th>Description of Evidence</th>
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<tr>
<td>Autosomal dominant</td>
<td>The prevalence of mutations associated with CMT1 was unavailable.</td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence of Genetic Mutations</strong></td>
<td>Penetration of CMT1 is usually nearly 100%, but the wide range in age onset and severity may result in under-recognition of individuals with mild or late-onset disease. (Tier 4)</td>
<td>[1]</td>
</tr>
<tr>
<td><strong>Penetrance OR Relative Risk</strong></td>
<td>Information regarding relative risk was unavailable.</td>
<td></td>
</tr>
<tr>
<td><strong>Expressivity</strong></td>
<td>Inter- and intra-familial phenotypic variability is common. Cases of mosaicism have been identified. (Tier 3)</td>
<td>[1;2;4]</td>
</tr>
</tbody>
</table>

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

| Nature of Intervention | Examinations (physical exam, NCV, family history, genetics consultation) and interventions (heel cord stretching) are non-invasive. |     |

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

| Chance to Escape Clinical Detection | Mild disease may go unrecognized by the affected individual and physician. (Tier 4) | [1] |

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
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Date of Search (MM.DD.YYYY): 05.28.2014

References

   Ref Type: Online Source

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