Stage I: Rule-Out Dashboard
Secondary Findings in Adults

GENE/GENE PANEL: MET
HGNC ID: 7029

DISORDER: Familial papillary renal cell carcinoma 1
OMIM ID: 605074

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 ☐ UNKNOWN

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: Summary Report

**Secondary Findings in Adults**

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

<table>
<thead>
<tr>
<th>GENE/GENE PANEL: MET</th>
<th>DISORDER: Familial papillary renal cell carcinoma 1</th>
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<tbody>
<tr>
<td><strong>Topic</strong></td>
<td><strong>Narrative Description of Evidence</strong></td>
</tr>
<tr>
<td><strong>Prevalence of the genetic disorder</strong></td>
<td>The incidence of familial papillary renal cell carcinoma (FPRCC) is unknown. However, the annual incidence of all familial renal cell carcinoma (RCC) syndromes is less than 1 in 1,500,000.</td>
</tr>
<tr>
<td><strong>Clinical Features</strong> (Signs/symptoms)</td>
<td>FPRCC is characterized by a predisposition for developing multiple bilateral papillary RCCs. Patients may develop 1100-3400 microscopic tumors in a single kidney. The types of papillary tumors range from microscopic lesions to clinically symptomatic carcinomas. However, tumors are always type 1 papillary RCC with low nuclear grade. However, some tumors do metastasize.</td>
</tr>
<tr>
<td><strong>Natural History</strong> (Important subgroups &amp; survival/recovery)</td>
<td>FPRCC has late onset, typically between ages 50 and 70 years. A study of 10 families with FPRCC reported that the average age of diagnosis of affected individuals in these families was 45, with an estimated mean survival of 7 years following diagnosis. Although 5-year survival rates for patients with RCC have improved in recent years, the outcome for patients with advanced stage disease remains poor.</td>
</tr>
</tbody>
</table>

### 1. What is the nature of the threat to health for an individual carrying a deleterious allele?

**Patient Management**

Treatment aims at controlling the risk of advanced disease, including metastasis, while at the same time preserving renal function due to the high likelihood of future de novo RCC. Sporadic and certain types of hereditary RCC usually acquire metastatic potential when their size reaches >3-7 cm. For some forms of hereditary RCC (such as FPRCC, von Hippel-Lindau syndrome, and Birt-Hogg Dube syndrome), the standard recommendation is the removal of all lesions in the same kidney once a single solid lesion or the largest solid is >3cm (the “3cm rule”), while other hereditary forms (such as hereditary leiomyomatosis and renal cell cancer and SDH-associated tumors) require more aggressive surgery due to a more aggressive nature with metastatic potential at smaller tumor size. (Tier 5) Partial nephrectomy (PN), also known as nephron-sparing surgery is now the standard method of hereditary RCC treatment. Bilateral nephrectomy eliminates the risk of metastasis from RCC but requires renal replacement therapy, including dialysis and kidney transplantation. However, the significant morbidity, mortality, and effects on quality of life, associated with dialysis makes this form of renal replacement therapy a last resort. In addition, options for kidney transplantation in hereditary patients may be limited due to the presence of RCC or other co-morbidities. Evidence for effectiveness of PN compared to bilateral nephrectomy among patients with FPRCC specifically was not available. However, available evidence suggest promising overall survival outcome for the PN intervention in hereditary RCC cases. One study assessed a cohort of 58 patients with hereditary RCC treated with PN for solid tumors greater than 4cm. The cohort which included 41 (71%) patients with von Hippel-Lindau, 10 (17%) patients with Birt-Hogg-Dube, and 7 (11%) with FPRCC. The mean age was 43.7 (range 18–63) and the mean largest tumor size was 5.3 cm (range 4–13). The mean number of resected kidney tumors was 6.4 (range 1–44). Overall survival of the cohort was 93% and metastasis-free survival was 96.5% at the median follow up of 45 months (range 2–163), rates similar to those reported in the literature series for patients undergoing PN for tumors in the sporadic population. (Tier 3) | (4) |

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

**Information on the effectiveness of the recommendations below was not provided unless otherwise stated.**

**Surveillance**

Imaging is often difficult due to the small size of lesions and their hypovascularity. In this context, CT is the imaging modality of choice for FPRCC patient screening. Surveillance should be started at age 30-35 and/or 10 years before the earlier age or onset of an RCC in the family. The frequency of surveillance can range from every 3-6 months to every 2-3 years depending on the size of the lesions. (Tier 3) | (2) |

**Family**

Once a specific gene anomaly has been demonstrated in a proband, genetic testing may be
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<th>Management</th>
<th>offered to at-risk relatives, and clinical follow-up has to be initiated for carriers of the familial germline mutation. (Tier 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumstances to Avoid</td>
<td>Information on circumstances to avoid was not available.</td>
</tr>
</tbody>
</table>

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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<td>Topic</td>
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<tr>
<td>3. What is the chance that this threat will materialize?</td>
<td></td>
</tr>
<tr>
<td>Mode of Inheritance</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Prevalence of Genetic Mutations</td>
<td>Information on the prevalence of MET mutations was not available.</td>
</tr>
<tr>
<td>Penetrance OR Relative Risk (include high risk racial or ethnic subgroups)</td>
<td>FPRCC is associated with high penetrance with a 90% likelihood of developing RCC by age 80. (Tier 3)</td>
</tr>
<tr>
<td>Information on relative risk was not available.</td>
<td></td>
</tr>
<tr>
<td>Expressivity</td>
<td>Information on expressivity was not available.</td>
</tr>
<tr>
<td>4. What is the nature of the intervention?</td>
<td></td>
</tr>
<tr>
<td>Nature of Intervention</td>
<td>Interventions identified in this report include surveillance with CT scans and treatment with nephron-sparing surgery. Surgical mortality of partial nephrectomy is less than 1% at experienced centers. A study of 50 patients with hereditary RCC who underwent 65 partial nephrectomies indicated the most common complications were pneumothorax (4.2%), renal atrophy (4.6%), prolonged urinal drainage (4.6%), and perinephric abscess (1.5%).</td>
</tr>
<tr>
<td>5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?</td>
<td></td>
</tr>
<tr>
<td>Chance to Escape Clinical Detection</td>
<td>In a study of 10 families with FPRCC reported that RCC was often detected incidentally in asymptomatic individuals or during screening of asymptomatic members of RCC families. (Tier 3)</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>MET</td>
<td>Morbidity/mortality associated with papillary renal cell carcinoma / Periodic surveillance via renal CT imaging</td>
<td>2</td>
<td>3C</td>
<td>3E</td>
<td>2</td>
<td>10CE</td>
</tr>
</tbody>
</table>

To see the scoring key, please go to: [https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/](https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/)
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Date of Search (MM.DD.YYYY): 10.17.2016

References