Stage I: Rule-Out Dashboard  
Incidental Findings in Adults

**GENE/GENE PANEL:** VHL  
**HGNC ID:**  12687  
**DISORDER:** von Hippel-Lindau Syndrome (VHL)  
**OMIM ID:**  193300

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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?
   - ✔️ 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: VHL</th>
<th>DISORDER: von Hippel-Lindau Syndrome (VHL)</th>
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<table>
<thead>
<tr>
<th>Topic</th>
<th>Narrative Description of Evidence</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>VHL has a prevalence of 1/39,000-1/53,000 and is estimated to account for approximately a third of patients with a CNS hemangioblastoma, &gt;50% of patients with a retinal angioma, 1% of patients with renal cell carcinoma, 50% of patients with apparently isolated familial pheochromocytoma, and 11% of patients with an apparently sporadic pheochromocytoma. (1)</td>
</tr>
<tr>
<td>Prevalence of the genetic disorder</td>
<td>VHL is characterized by hemangioblastomas of the brain, spinal cord, and retina; renal cysts and clear cell renal carcinoma; pheochromocytomas; pancreatic tumors including simple cysts, serous cystadenomas, and neuroendocrine tumors; endolymphatic sac tumors; and epididymal and broad ligament cysts. (1-5)</td>
</tr>
<tr>
<td>Clinical Features (Signs/symptoms)</td>
<td>Retinal angiomas are the most common presenting feature of VHL, have an average age of diagnosis of 25, and are multiple and bilateral in ~50% of cases with 35% experiencing visual loss. CNS hemangioblastomas are the prototypic lesions of VHL, are the presenting feature in ~40% of cases, and have an average age of diagnosis of 29-34 years. Multiple renal cysts are common and lead to renal cell carcinoma in 70% of cases by age 60. Renal cell carcinoma has an average age of diagnosis of 40-45 years and is a leading cause of mortality. Pancreatic lesions are found in ~60% of patients with 5-10% developing pancreatic tumors. Overall, the median age of tumor diagnosis is 22-26 years, significantly younger than sporadic cases of the associated tumors, and the median life expectancy is ~50 years. There is no sex or ethnicity bias. (1-5)</td>
</tr>
<tr>
<td>Natural History (Important subgroups &amp; survival/recovery)</td>
<td>Retinal angiomas are the most common presenting feature of VHL, have an average age of diagnosis of 25, and are multiple and bilateral in ~50% of cases with 35% experiencing visual loss. CNS hemangioblastomas are the prototypic lesions of VHL, are the presenting feature in ~40% of cases, and have an average age of diagnosis of 29-34 years. Multiple renal cysts are common and lead to renal cell carcinoma in 70% of cases by age 60. Renal cell carcinoma has an average age of diagnosis of 40-45 years and is a leading cause of mortality. Pancreatic lesions are found in ~60% of patients with 5-10% developing pancreatic tumors. Overall, the median age of tumor diagnosis is 22-26 years, significantly younger than sporadic cases of the associated tumors, and the median life expectancy is ~50 years. There is no sex or ethnicity bias. (1-5)</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.**

<table>
<thead>
<tr>
<th>Patient Management</th>
<th>No patient management recommendations were available.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>Patients should undergo screening for pheochromocytomas. (Tier 2) (6)</td>
</tr>
<tr>
<td></td>
<td>Patients should undergo annual neurologic, vision, ophthalmology, and hearing evaluation; annual blood pressure monitoring; annual blood or urinary normetanephrine levels; thin-slice MRI with contrast of the internal auditory canal in those with repeated ear infections; annual abdominal ultrasound and every other year MRI scan of the abdomen; and MRI of the brain and total spine every 1-3 years. (Tier 4) (1;2;5)</td>
</tr>
<tr>
<td></td>
<td>Women should undergo intensified surveillance for cerebellar hemangioblastoma and pheochromocytoma during preconception and pregnancy, including MRI without contrast of the cerebellum at four months’ gestation. (Tier 4) (2)</td>
</tr>
<tr>
<td>Family Management</td>
<td>If the mutation in a family is known, genetic testing can be used to clarify the genetic status of at-risk family members to eliminate the need for surveillance of those who have not inherited the mutation. (Tier 3) (2)</td>
</tr>
<tr>
<td></td>
<td>At-risk relatives with unknown genetic status should undergo the same surveillance as individuals with VHL. (Tier 4) (1;2;4;5)</td>
</tr>
<tr>
<td>Circumstances to Avoid</td>
<td>Tobacco products should be avoided since they are considered a risk factor for kidney cancer; chemicals and industrial toxins known to affect VHL-involved organs should be avoided; and contact sports should be avoided if adrenal or pancreatic lesions are present. (Tier 4) (2)</td>
</tr>
<tr>
<td></td>
<td>Computed tomography should only be applied in particular situations given the high cumulative radiation load. (Tier 4) (1;5)</td>
</tr>
</tbody>
</table>

Description of sources of evidence:
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**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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**DISORDER:** von Hippel-Lindau Syndrome (VHL)

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<th>Topic</th>
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<th>Ref</th>
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<tbody>
<tr>
<td><strong>3. What is the chance that this threat will materialize?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of Inheritance</td>
<td>Autosomal dominant</td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence of Genetic Mutations</strong></td>
<td>VHL mutations have the same prevalence as VHL, which is estimated as 1/39,000-1/53,000. (Tier 3)</td>
<td>(1)</td>
</tr>
<tr>
<td>Penetration</td>
<td>VHL mutations are highly penetrant, with almost all individuals expressing a disease-related symptom by age 65. The frequencies of specific features among cases are: CNS hemangioblastomas=60-80%, retinal angiomas=70%, renal cell carcinoma=70%, epididymal cystadenomas in males=60%, endolymphatic sac tumors=10-11%, and head and neck paragangliomas=0.5%. (Tier 3)</td>
<td>(1;2)</td>
</tr>
<tr>
<td>OR Relative Risk (include high risk racial or ethnic subgroups)</td>
<td>60% of cases have pancreatic lesions. Neuroendocrine tumors are found in 15% of patients with 2% found to be malignant. (Tier 1)</td>
<td>(3)</td>
</tr>
<tr>
<td>Expressivity</td>
<td>VHL manifestations and their severity are highly variable both within and between families, even among those with the same mutation. (Tier 4)</td>
<td>(1;2;4)</td>
</tr>
</tbody>
</table>

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

| Nature of Intervention | The interventions identified in this report involve extensive clinical surveillance. |

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

| Chance to Escape Clinical Detection | The clinical management of VHL is highly complex, extends beyond routine clinical surveillance, and involves referral to medical specialists and centers. The majority of patients are diagnosed after the discovery of CNS tumors. Thus tumor development and progression is likely to escape detection in the setting of general clinical care. (Tier 4) | (1;3) |

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**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>VHL</td>
<td>Pheochromocytoma/Surveillance</td>
<td>2</td>
<td>3C</td>
<td>2B</td>
<td>3</td>
<td>10CB</td>
</tr>
<tr>
<td></td>
<td>Renal cell carcinoma/Surveillance</td>
<td>2</td>
<td>3C</td>
<td>3C</td>
<td>3</td>
<td>11CC</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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Reference List


Ref Type: Online Source


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