Recommendations for Von Hippel–Lindau Disease Tumor Surveillance in Childhood and Adolescence

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Objectives

• Review the scope of pediatric tumor risks in VHL
• Compare and contrast existing paradigms for tumor surveillance in VHL
• Advocate for new surveillance guidelines applicable for children and adolescents with VHL

VHL Related Tumor Risks

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Lifetime Risk</th>
<th>Average Age</th>
<th>Cumulative Risk &gt; 5%</th>
<th>Youngest Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal hemangioblastoma</td>
<td>≤ 60%</td>
<td>25 years</td>
<td>First 10 years</td>
<td>0 years</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>≤ 25%</td>
<td>27 years</td>
<td>First 10 years</td>
<td>2 years</td>
</tr>
<tr>
<td>Endolymphatic sac tumor</td>
<td>≤ 25%</td>
<td>22 years</td>
<td>Teens</td>
<td>6 years</td>
</tr>
<tr>
<td>CNS hemangioblastoma</td>
<td>≤ 80%</td>
<td>30 years</td>
<td>Teens</td>
<td>8 years</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>≤ 72%</td>
<td>33 years</td>
<td></td>
<td>9 years</td>
</tr>
<tr>
<td>Brainstem</td>
<td>≤ 25%</td>
<td>32 years</td>
<td></td>
<td>12 years</td>
</tr>
<tr>
<td>Spinal</td>
<td>≤ 50%</td>
<td>33 years</td>
<td></td>
<td>8 years</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td>≤ 70%</td>
<td>44 years</td>
<td>20s</td>
<td>13 years</td>
</tr>
<tr>
<td>Pancreatic NET</td>
<td>≤ 17%</td>
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Multiple screening paradigms have been implemented in VHL

• VHL Alliance, Netherlands, Denmark, etc.

• Evidence based
  • Registry, database, historical series
  • Broadly target all VHL tumor types
  • Account for variations in tumor risks by age
  • Improved life expectancy
  • Variable adherence

The screening regimens have some similarities and some differences

• The methodologies recommended are fairly consistent:
  • Ophthalmology exam
  • Audiology evaluations
  • Neuro-imaging and abdominal imaging
  • Biochemical testing

• Some significant differences are apparent:
  • The ages at which to initiate different screening components
  • The frequency of performing the evaluations
  • Whether to include abdominal ultrasounds

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In 2016, AACR sponsored a workshop focused on childhood cancer predisposition

- Experts in Genetics, Pediatric/Medical Oncology, Endocrinology, and Radiology participated
- Reaffirm, revise, or create cancer screening guidelines for children with hereditary cancer predisposition syndromes
  - Based on review of literature and personal experience
  - Recognition that recommendations would evolve as new data emerges and further discussion occurs
- Consensus position papers were published in Clinical Cancer Research on optimal cancer screening for high risk children

### Recommendations

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Surveillance</th>
<th>Starting</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal hemangioblastoma</td>
<td>Eye exam</td>
<td>Birth</td>
<td>Annual</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>BP at all visits</td>
<td>2 years</td>
<td>Annual</td>
</tr>
<tr>
<td></td>
<td>Metanephrines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endolymphatic sac tumor</td>
<td>Audiogram</td>
<td>5 years</td>
<td>Biennial</td>
</tr>
<tr>
<td>CNS hemangioblastoma</td>
<td>MRI brain</td>
<td>8 years</td>
<td>Biennial</td>
</tr>
<tr>
<td></td>
<td>MRI spine</td>
<td></td>
<td></td>
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<tr>
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<td>MRI abdomen</td>
<td>10 years</td>
<td>Annual</td>
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### Screening for Retinal Hemangioblastoma

- Annual eye exams
- Starting at birth

**Rationale**
- Risk is significant
- May present very early in life
- Pre-symptomatic detection is possible
- Early intervention may prevent permanent vision loss

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Screening for Retinal Hemangioblastoma

- Additional Considerations
  - Consistent with most current screening paradigms
  - Growth of lesions is variable, but mostly slow
  - Degree of threat to vision varies by lesion location

- Risks
  - May contribute to anxiety and/or screening fatigue

Screening for Pheochromocytoma

- Blood pressure at all medical visits
- Annual fractionated plasma metanephrines
  - May substitute with 24 urine metanephrines
- Starting at 2 years of age

- Rationale
  - Risk is significant
  - May present early in life
  - Pre-symptomatic detection is possible
  - May prevent severe hypertension and sequelae
  - May facilitate partial adrenalectomy
  - May reduce risk of metastases

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Screening for Endolymphatic Sac Tumors

- Biennial audiology evaluation
- Starting at 5 years of age

- Rationale
  - Risk is significant
  - May present early in life
  - Pre-symptomatic detection is possible
  - May prevent permanent hearing loss

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Screening for Endolymphatic Sac Tumors

- Additional Considerations
  - Consistent with most current screening paradigms
  - Tumor growth is variable, but mostly slow

- Risks
  - May contribute to anxiety and/or screening fatigue
  - False positives may trigger further imaging studies

Screening for CNS Hemangioblastoma

- Biennial MRI brain/spine
- Starting at 8 years of age
- Consider advancing to annual frequency in mid-teens
- Consider delaying MRIs until sedation not required

- Rationale
  - Risk is significant
  - Most new lesions appear in first 2 decades of life
  - Pre-symptomatic detection is possible
  - May prevent severe, possibly irreversible neurologic symptoms
  - Significant risk (~7%) of developing symptomatic lesions in interval between biennial scans

Lifetime Risk

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Screening for Renal Cell Carcinoma/PNET

- Annual MRI abdomen
- Starting at 10 years of age
- Consider delaying MRIs until sedation not required

- Rationale
  - Risk is significant
  - May present in 2nd decade of life
  - Preferable to screen with single primary modality (MRI)
  - Early detection is possible: prior to functional impact and/or metastases
  - May prevent morbidity/mortality
Screening for Renal Cell Carcinoma/PNET

- Additional Considerations
  - Age of initiation is earlier than most other paradigms
  - Annual MRIs are more frequent
  - RCC/PNET are still quite uncommon in childhood
  - Tumor growth is variable, but mostly slow
  - Surgery is usually reserved until lesions near ~3 cm
- Risks
  - May contribute to anxiety and/or screening fatigue
  - Younger patients are more likely to need anesthesia for MRI

Final thoughts

- Overall, these guidelines advance the age of initiating of screening evaluations and increase the frequency of MRI scans
  - Is this excessive for patients and families?
  - Do the potential benefits of earlier MRIs outweigh anesthesia risk concerns? Gadolinium risk concerns?
  - They are pediatric focused, but have adult implications
  - Experts disagree on screening recommendations, particularly when faced with limited evidence, as in rare conditions
    - Differences in how the benefits and risks are weighed
  - Guidelines standardize practice and drive insurance coverage
  - Critical to identify optimal screening practices to ensure best patient outcomes

Thank you

- Our patients and their families
- Symposium organizers
- Co-authors on the VHL screening recommendations paper