



## Topic Brief: Management of Vestibular Schwannomas

**Date:** 7/8/2021

**Nomination Number:** 0954

**Purpose:** This document summarizes the information addressing a nomination submitted on June 11, 2021 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

**Issue:** The current guidelines for the management of vestibular schwannomas (VS) are based on evidence published through 2014. Clinical management of the condition is variable and a new systematic review based on current evidence would inform an updated guideline to be used for decision-making by providers and patients.

### Program Decision:

The scope of this topic met all EHC Program selection criteria and was considered for a systematic review. However, it was not selected.

### Key Findings

- We found only one study addressing diagnosis with imaging (Key Question 1).
- We found enough studies for an estimated medium-sized review addressing the effectiveness of radiation (KQ2), surgical (KQ3), and pharmacological (KQ4) interventions for VS.
- The original scope of this nomination focused solely on comparative effectiveness of interventions. However, the criteria was expanded to additionally include studies focused on questions of effectiveness after a preliminary review of the search output indicated that studies predominantly focused the on effectiveness of interventions.

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### Background

Vestibular schwannomas (VS), also known as acoustic neuromas, are benign tumors resulting from the overproduction of Schwann cells in the vestibular portion of the vestibulocochlear nerve, which is involved in balance and hearing.<sup>1</sup> The majority of VS are sporadic, or isolated, although few are part of a genetic syndrome called neurofibromatosis type 2 (NF2).<sup>2</sup> The development of these tumors can be associated with progressive hearing loss and tinnitus, facial paresthesia, and facial nerve palsy.<sup>3</sup> Treatment of VS includes observation, microsurgical resection, stereotactic radiotherapy, or a combination of these interventions.<sup>4</sup>

While the incidence of VS is not high, at approximately 1 per 100,000 person years in the U.S.,<sup>1</sup> clinical management is controversial and highly variable, and the costs of care are significant. In 2014, the average total cost of three years of surgical treatment for VS was \$80,074.<sup>5</sup>

The Congress of Neurological Surgeons (CNS) guidelines for care of patients with VS were published in 2017, and are based on evidence published through 2014.<sup>6</sup> An updated systematic review would inform an update to the CNS clinical practice guidelines.

## **Nomination Summary**

The nomination included 41 questions on audiologic screening, strategies for hearing preservation, intraoperative cranial nerve monitoring during surgery, diagnostic imaging, the association between pathologic features and prognosis, surgical treatment, and other emerging treatments. After consultation about the areas of greater interest and uncertainty, the focus was narrowed to diagnostic imaging, radiation treatment, surgical treatment, and pharmacologic treatment. Research questions on radiation and surgical interventions for VS originally focused on comparative effectiveness. However, once we found that the studies from our search focused almost exclusively on effectiveness, we communicated with the nominators, who confirmed their interest in studies of intervention effectiveness in addition to studies of comparative effectiveness. We then updated all key questions to include effectiveness, and incorporated these newly eligible studies in our assessment.

Additionally, while research question specifications for the radiation and pharmacological interventions include follow-up times of 1, 2, 5, and 10 years, the nominator conveyed a preference for 2-, 5-, and 10-year end points.

## **Scope**

1. What are the effectiveness, comparative effectiveness, and harms of magnetic resonance imaging (MRI) in diagnosis of vestibular schwannomas (VS)?
  - a. How does the accuracy of diagnosis vary based on the presenting symptoms of asymmetric sensorineural hearing loss (different definitions), unilateral or bilateral tinnitus with subjective asymmetry, or sudden sensorineural hearing loss?
  - b. How does the accuracy of diagnosis vary based on MRI sequence (e.g., T1, T2, fluid-attenuation inversion recovery, diffusion-weighted imaging)?
2. What is the effectiveness and comparative effectiveness of radiation therapy to the tumor margin on outcomes (hearing and tumor size) in patients with VS?
  - a. How do outcomes vary based on patient characteristics (age; underlying conditions; tumor size; location; and hearing ability before treatment, e.g. American Academy of Otolaryngology-Head and Neck Surgery class A or Gardner-Robertson grade I hearing)?
3. What are the effectiveness, comparative effectiveness, and harms of various surgical techniques for the treatment of sporadic VS?
  - a. How do outcomes vary by patient and tumor characteristics?
  - b. How are outcomes influenced by the surgical team's range of expertise?
  - c. How do perioperative treatments influence outcomes?
4. What are the effectiveness, comparative effectiveness, harms, and comparative harms of various pharmacologic agents for the treatment of patients with sporadic VS?
  - a. How do outcomes vary by patient and tumor characteristics?

**Table 1. PICOTs (population, intervention, comparator, outcome, and timing) for KQ1 and KQ2**

Questions	1. Diagnosis of VS	2. Radiation therapy for VS
<b>Population</b>	<p>Patients <math>\geq 18</math> years of age with VS presenting with asymmetric sensorineural hearing loss, unilateral or bilateral tinnitus with subjective asymmetry, or sudden onset sensorineural hearing loss not related to trauma</p> <p>Criteria for hearing loss: 1995 AAO-HNS or GR hearing classification system, or presented data using word recognition score WRS and PTA for defining hearing status, or having individual patient data presented such that the latter criteria can be applied and analyzed</p>	<p>Patients <math>\geq 18</math> years of age with sporadic VS (isolated lesion rather than as part of a genetic syndrome)</p> <p>Characteristics: age; comorbidities (e.g., history of cerebral vascular disease, hypertension, diabetes); patients with AAO-HNS class A or GR grade I hearing at baseline</p> <p>Tumor subgroups: tumor size, tumor location</p>
<b>Interventions</b>	MRI	<ul style="list-style-type: none"> <li>SFRT using <math>\leq 13</math> Gy to the tumor margin</li> <li>FSRT</li> </ul>
<b>Comparators</b>	<ul style="list-style-type: none"> <li>Other imaging</li> <li>Other MRI sequence (T1, T2, FLAIR, DWI)</li> <li>No imaging</li> </ul>	Other intervention (radiation only or surgical, pharmacotherapy); no intervention
<b>Outcomes</b>	Diagnostic yield	<ul style="list-style-type: none"> <li>Hearing outcomes: maintenance of or decline in serviceable hearing (defined as a PTA or speech reception threshold lower than 50 dB and speech discrimination score better than 50%) in the ipsilateral ear</li> <li>Tumor size</li> </ul>
<b>Timing</b>	NA	1, 2, 5, 10 years following treatment
<b>Study parameters</b>	Studies include at least 6 participants	Studies include at least 20 participants

Abbreviations: AAO-HNS= Academy of Otolaryngology-Head and Neck Surgery; dB=decibels; DWI= diffusion-weighted imaging; FLAIR=fluid-attenuation inversion recovery; FSRT= fractionated stereotactic radiotherapy; GR= Gardner–Robertson; Gy=gray (unit of measurement); KQ=key question; MRI=magnetic resonance imaging; NA=not applicable; PTA=pure-tone average; SFRT=single-fraction radiation therapy; VS=vestibular schwannomas; WRS=word recognition score.

**Table 2. PICOTs (population, intervention, comparator, outcome, and timing) for KQ3 and KQ4**

Questions	3. Surgery for VS	4. Pharmacotherapy for VS
<b>Population</b>	<p>Patients <math>\geq 18</math> years of age with VS</p> <p>1a. Characteristics of interest:</p> <ul style="list-style-type: none"> <li>Presence or absence of serviceable hearing prior to treatment</li> <li>Tumor size</li> <li>Intracanalicular location</li> <li>Presence of NF2</li> </ul>	<p>Patients <math>\geq 18</math> years of age with sporadic VS</p> <p>1a. Characteristics of interest:</p> <ul style="list-style-type: none"> <li>Tumor subgroups: Tumor size, tumor location</li> </ul>
<b>Interventions</b>	1a. Surgery (with or without visual guidance)	<ul style="list-style-type: none"> <li>Bevacizumab</li> <li>Lapatinib</li> </ul>

	<ul style="list-style-type: none"> <li>Complete microsurgical resection of sporadic VS with facial nerve preservation using retrosigmoid surgical approach for those with serviceable hearing</li> <li>Retrosigmoid surgical approach in those without serviceable hearing</li> </ul> <p>1b. Surgical team: multidisciplinary team, consisting of neurosurgery and neurotology professionals</p> <p>1c. Perioperative treatments: vestibular ablation, vestibular rehabilitation, treatment of vasospasm with nimodipine or hydroxyethyl starch</p>	<ul style="list-style-type: none"> <li>Erlotinib</li> <li>Everolimus</li> <li>Aspirin</li> </ul>
<b>Comparators</b>	<p>1a. Comparators</p> <ul style="list-style-type: none"> <li>Surgical techniques (with or without visual guidance) <ul style="list-style-type: none"> <li>Microsurgical middle fossa approach</li> <li>Translabyrinthine surgical approach</li> </ul> </li> <li>Stereotactic radiosurgery</li> <li>Subtotal resection followed by stereotactic radiosurgery</li> <li>Surgical resection following stereotactic radiosurgery</li> <li>No comparator</li> </ul> <p>1b. Surgical team: neurosurgeon/ neurotologist working alone, none, or any</p> <p>1c. Perioperative treatment: none, placebo or other treatment</p>	Other intervention (e.g., other radiation, surgery pharmacotherapy), no comparator
<b>Outcomes</b>	Serviceable hearing (proportion, prevalence, achievement, maintenance, decline); facial and vestibulocochlear nerve preservation/function; resection completeness; trigeminal neuralgia; balance problems (e.g., perceived dizziness, dizziness questionnaire score measured via DHI, disequilibrium-related symptom incidence rate, vertigo incidence rate); harms (CSF leaks, wound infection); mortality	<ul style="list-style-type: none"> <li>Hearing outcomes: maintenance of or decline in serviceable hearing in the ipsilateral ear</li> <li>Tumor size</li> <li>Adverse effects</li> </ul>
<b>Timing</b>	NA	1, 2, 5, 10 years following treatment
<b>Study parameters</b>	Studies include at least 6 participants	Studies include at least 6 participants

Abbreviations: CFS=cerebrospinal fluid; DHI= dizziness handicap index; KQ=key question; NA=not applicable; NF2= Neurofibromatosis type 2; VS=vestibular schwannoma.

## Assessment Methods

See Appendix A.

### Summary of Literature Findings

We identified a small number of studies that addressed diagnostic imaging (KQ1) and pharmacological interventions (KQ4), and a larger number of studies that addressed radiation therapy (KQ2) and surgical interventions (KQ3) for VS. We concluded that the identified body of literature would be appropriate for a mid-sized systematic review focusing primarily on effectiveness, rather than comparative effectiveness, of interventions. Retrospective or prospective studies largely measured outcomes for single groups at pre-intervention and follow-up time points.

We reviewed all studies from the search yield for diagnostic imaging (KQ1) and only one<sup>7</sup> met the key question specifications. The study examined the diagnostic performance of MRI in differentiating vestibular ganglion from small intracranial schwannomas.

We reviewed all studies from the search yield that addressed radiation therapy (KQ2), and found 66 studies<sup>8-73</sup> that met the key question specifications. Most of these studies addressed the effectiveness of radiation therapy, and only 10 addressed the comparative effectiveness of radiation therapy. In most studies, patients received radiation therapy alone; however, in five studies, the patients additionally received a surgical intervention.

We reviewed all studies from the search yield that addressed surgical interventions (KQ 3) and found 18 studies<sup>74-91</sup> that met the key question specifications. Again, most of these studies addressed effectiveness of surgical interventions, and only two addressed the comparative effectiveness of surgical interventions. Further, three of the studies were conducted in patients who had previously received failed radiation therapy.

Finally, we reviewed a sample of the search yield for pharmacological interventions (KQ4) and found six studies<sup>92-97</sup> that addressed the effectiveness of pharmacological interventions and met the key question specifications. None of these studies addressed the comparative effectiveness of pharmacological interventions. In four of the six studies, the pharmacological intervention was bevacizumab.

**Table 3.** Literature identified for each KQ

Question	Systematic reviews (7/2018-7/2021)	Primary studies (7/2016-7/2021)
Question 1: Diagnosis of VS	Total: 0	Total: 1 <ul style="list-style-type: none"><li>• Non-randomized with comparator: 1 Clinicaltrials.gov</li><li>• Recruiting: 0</li></ul>
Question 2: Radiation therapy for VS	Total: 0	Total: 66 <ul style="list-style-type: none"><li>• Retrospective with comparator: 10</li><li>• Without comparator: 54 Clinicaltrials.gov</li><li>• Recruiting: 2</li></ul>
Question 3: Surgery for VS	Total: 0	Total: 18 <ul style="list-style-type: none"><li>• With comparator: 2</li><li>• Without comparator: 15 Clinicaltrials.gov</li><li>• Recruiting: 1</li></ul>

Question	Systematic reviews (7/2018-7/2021)	Primary studies (7/2016-7/2021)
Question 4: Pharmacotherapy for VS	Total: 0	Total: 6 <ul style="list-style-type: none"> <li>Without comparator: 5 Clinicaltrials.gov</li> <li>Recruiting: 1</li> </ul>

Abbreviations: KQ=key question; VS=vestibular schwannoma.

See Appendix B for detailed assessments of all EPC selection criteria.

## Summary of Selection Criteria Assessment

Current guidelines pertaining to diagnosis and treatment of VS are outdated. The nominators would use a new systematic review to update current guidelines to influence practice. While we found only one study on diagnosis with MRI, we found a larger body of evidence for the effectiveness of radiation, surgical, and pharmacological interventions. The majority of these studies address the effectiveness, rather than comparative effectiveness, of interventions. Most of the studies are retrospective or prospective analyses of a group, or pre- and post-intervention methodology.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

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## Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

### Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

### Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years 7/23/2018 - 7/23/2021 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
  - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
  - EHC Program <https://effectivehealthcare.ahrq.gov/>
  - US Preventive Services Task Force <https://www.uspreventiveservicestaskforce.org/>
  - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- US Department of Veterans Affairs Products publications
  - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- University of York Centre for Reviews and Dissemination database <https://www.crd.york.ac.uk/CRDWeb/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospero/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>
- Epistemonikos <https://www.epistemonikos.org>

### Impact of a New Evidence Review

The potential impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

### Feasibility of New Evidence Review

We conducted a limited literature search in PubMed for studies published in the last five years (7/23/2016 -7/23/2021). We reviewed all identified titles and abstracts for KQs 1-3 and a random sample of 200 titles and abstracts for KQ4 for inclusion, and classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

### Search strategy

(((((("2016"[Date - MeSH] : "3000"[Date - MeSH])) AND ("english"[Language])) AND ("humans"[Filter])) AND ("adult"[Filter])) AND (((("neuroma, acoustic"[MeSH Terms]) OR

(vestibular[Title/Abstract] AND schwannoma[Title/Abstract])) OR ("vestibular  
 schwannoma"[Title/Abstract]))  
 AND  
 "neuroma, acoustic/diagnostic imaging"[MeSH Terms]  
 RCTs (((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR  
 (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized  
 controlled trial[pt])  
 (((("2016"[Date - MeSH] : "3000"[Date - MeSH])) AND ("english"[Language])) AND  
 ("humans"[Filter])) AND ("adult"[Filter])) AND (((("neuroma, acoustic"[MeSH Terms]) OR  
 (vestibular[Title/Abstract] AND schwannoma[Title/Abstract])) OR ("vestibular  
 schwannoma"[Title/Abstract]))  
 AND  
 ("radiotherapy"[MeSH Terms] OR ("radiation"[Title/Abstract] OR  
 "radiotherapy"[Title/Abstract])) AND "therapy"[MeSH Subheading]  
 (((("2016"[Date - MeSH] : "3000"[Date - MeSH])) AND ("english"[Language])) AND  
 ("humans"[Filter])) AND ("adult"[Filter])) AND (((("neuroma, acoustic"[MeSH Terms]) OR  
 (vestibular[Title/Abstract] AND schwannoma[Title/Abstract])) OR ("vestibular  
 schwannoma"[Title/Abstract]))  
 AND  
 "surgery"[MeSH Subheading]

[Clinical Trials.gov Link](#)

## Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

## Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
<b>1. Appropriateness</b>	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the US?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
<b>2. Importance</b>	
2a. Represents a significant disease burden; large proportion of the population	Yes. While the incidence of VS is not high, at approximately 1 per 100,000 person years in the US, <sup>1</sup> clinical management is controversial and highly variable. The current guidelines by the CNS were published in 2017 and are based on evidence published through 2014. <sup>6</sup> An updated systematic review would help inform a clinical practice guideline update.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. The current guidelines by the CNS were published in 2017 and are based on evidence published through 2014. <sup>6</sup> An updated systematic review would help inform a clinical practice guideline update.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. In 2014, the average total cost of three years of surgical treatment for VS was \$80,074. <sup>5</sup>
<b>3. Desirability of a New Evidence Review/Absence of Duplication</b>	
3. A recent high-quality systematic review or other evidence review is not available on this topic	Yes, A recent high-quality systematic review or other evidence review is not available on this topic
<b>4. Impact of a New Evidence Review</b>	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. The current guidelines by CNS were published in 2017 and are based on evidence published through 2014. <sup>6</sup> It is important for guidelines to be consistent with current evidence.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. Clinical management remains controversial with substantial variation across the nation and globally.
<b>5. Primary Research</b>	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	KQ1: 1 out of entire search yield; KQ2: 66 out of entire search yield; KQ3: 18 out of entire search yield; KQ4: 6 out of a sample the search yield. The estimated size of a new systematic review is medium.
<b>6. Value</b>	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes. An updated guideline on the topic would influence practice.

6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. The nominator represents a guideline group that plans to use a new systematic review to update current guidelines.
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Abbreviations: AHRQ=Agency for Healthcare Research and Quality; CNS= Congress of Neurological Surgeons; KQ=key question; US=United States; VS=vestibular schwannomas.