Laryngoscope
Investigative Otolaryngology

REVIEW OPEN ACCESS

# Why Consider Aspirin for the Treatment of Vestibular Schwannoma? A Brief Review and Randomized, Double-Blind, Placebo-Controlled Study Proposal

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**Received:** 15 November 2024 | **Revised:** 10 February 2025 | **Accepted:** 2 March 2025

**Funding:** This work was supported by the Department of Defense Congressionally Directed Medical Research Program, W81XWH-17-1-0644 (NF160065).

**Keywords:** aspirin | double-blinded prospective randomized placebo controlled trial | review | vestibular schwannoma

## ABSTRACT

**Objective:** The primary objective of this study is to review the evidence for aspirin use to prevent the growth of vestibular schwannomas (VS) and to propose a prospective trial to determine the progression-free survival of VS patients after up to 42 months of treatment with aspirin. Secondary study objectives are to determine the effect of aspirin on VS growth, hearing function, serum biomarker levels, and the quality of life, as well as to determine the tolerability of aspirin treatment and whether serum biomarker and salicylate levels predict the response to aspirin.

**Study Design:** Literature review.

**Setting:** Six academic and private medical centers.

**Methods:** Review of recent English literature regarding prophylactic aspirin use for VS.

**Results:** The retrospective reviews on the utility of aspirin to prevent VS growth are inconclusive. Eighty-four patients have been enrolled in a prospective double-blinded, placebo-controlled trial thus far to determine the effect of aspirin on VS.

**Conclusions:** Completion of a robust study design is necessary. The current aspirin dose has been well tolerated, with minimal adverse events to date.

**Level of Evidence:** Review of retrospective studies: Level 4; Proposed randomized, placebo-controlled, double-blinded clinical trial: Level 2.

## 1 | Introduction

NF2-related schwannomatosis (NF2-SWN) (formerly neurofibromatosis type 2) is an autosomal-dominant genetic disorder, the hallmark of which is the presence of bilateral VS [1] with an incidence of 1/33,000 [2]. Although histologically benign, VS leads to substantial morbidity, including sensorineural hearing loss, vestibular dysfunction, facial nerve paralysis, paralysis of other cranial nerves, brainstem compression, and even death.

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Unilateral sporadic VS have an incidence of 1/10,000 [3] and are clinically, genetically, and histologically similar to NF2-associated VS [4]. Although NF2-associated VS are multicentric and pathogenic variants may differ [5, 6], sporadic VS are the most similar tumors to NF2-associated VS [7]. Whether sporadic or NF2-associated, VS have sensorineural hearing loss and tinnitus as the presenting signs in 95% of adults and are the most commonly associated tumors in NF2-SWN [8, 9].

Current treatments for growing VS are limited to microsurgical resection, stereotactic radiation therapy, and bevacizumab treatment. Microsurgical resection carries substantial risks, including ipsilateral deafness and facial paralysis [10, 11]. Stereotactic radiation therapy is associated with sensorineural hearing loss, vestibular dysfunction, and rare malignant transformation [12].

Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, decreases NF2-related VS tumor volume in 30%–47% of patients and demonstrates a favorable hearing response in 20%–56% [13–17]. Associated adverse effects of bevacizumab include hypertension (23%–35%), proteinuria (18%–44%) and amenorrhea (16%–73%) [15, 16, 18, 19]. Other small molecule inhibitors tested against VS have shown little or no effect, including erlotinib [20], lapatinib [21], everolimus [22], AR-42 [23] and brigatinib [24]. Effective and well-tolerated therapy for VS is clearly an unmet medical need [25, 26].

## 2 | Previous Studies

The use of aspirin for the treatment of VS was reported in a retrospective study finding decreased growth in VS, and mechanistic studies with primary human VS cells in vitro found aspirin to be cytostatic. Specifically, Kandathil et al. reported the probability of VS growth in 81 patients who took aspirin was approximately half of that in 266 patients with VS who did not take aspirin (odds ratio = 0.5) [27]. The dose of aspirin used was not specified, although most frequently either 81 or 325 mg daily was reported, typically used for cardiovascular prophylaxis. This finding suggested that aspirin may inhibit VS growth and was confirmed with a subsequent volumetric analysis [28]. Moreover, mechanistic studies with primary human VS cultures found that aspirin inhibited VS cell proliferation and viability, and decreased secretion of prostaglandin E2, the downstream enzymatic product of COX-2, which is the target of aspirin. Importantly, aspirin had no effect on VS cell death or healthy Schwann cells [29]. Treatment of patient-mimicking NF2-associated schwannomas in mice with moderate doses of aspirin resulted in decreased schwannoma progression in vivo [30]. These data suggest a role for aspirin in inhibiting the proliferation of VS cells.

Additional studies have implicated inflammation in VS progression. Specifically, immunohistochemically determined expression levels of COX2 in VS tissue correlated with tumor proliferation rate [31]. Pro-inflammatory transcription factor NF-kB was identified and validated as a central molecule in VS pathobiology [32]; the presence [33] and functional activity [34–37] of tumor-associated macrophages in VS correlated with volumetric tumor growth; human VS tissue was shown to secrete pro-inflammatory ototoxic molecules including TNFa [38] and IL-6 [39]. Meta-analysis of the genes differentially expressed in VS tissue revealed inflammatory pathways as the top-ranked pathways in VS pathobiology, with potential for molecular targeting via drug repositioning [40].

Despite the affirming mechanistic and bioinformatic studies highlighting the central role of inflammation in VS progression, two subsequent retrospective clinical studies failed to show aspirin associated with a reduced risk of VS growth [41, 42]. These differing retrospective outcomes motivated the present study. COX-2 inhibiting salicylates like aspirin are well tolerated, inexpensive, and widely used, making this study potentially valuable.

## 3 | Dosing Rationale

The dose of aspirin selected for this trial was based on our own preclinical data and from well-known clinical applications targeting pain and inflammation in humans. Low dose aspirin (81 mg/day) in adults has an anti-platelet effect, but 325 mg–650 mg/day has anti-inflammatory and analgesic properties. We selected 650 mg/day for our adult subjects targeting an anti-inflammatory response. Blood levels of aspirin that are considered adequate to treat inflammatory conditions range from 1.1 to 2.2 mM [43–45]. This range is comparable with dosages found efficacious in vitro. Specifically, the salicylate levels of 3.3 mg/dL were measured in media containing 5 mM aspirin, which led to a significant reduction in human VS cell proliferation in vitro [29]. Such therapeutic salicylate levels are expected to be detected in serum with a dose of aspirin around 600–800 mg [46, 47]. This dose is substantially less than the range of salicylate toxicity, as milder symptoms such as tinnitus have been reported at approximately 25–35 mg/dL serum salicylate levels [48]. The current study therefore uses a daily regimen of 325 mg of aspirin twice a day (or placebo) for individuals 12 years of age or older.

## 4 | Potential Adverse Effects of Aspirin

Aspirin toxicity is dose-related, and serious adverse effects are extremely rare at low doses. Contraindications include pregnancy or trying to become pregnant, breastfeeding, chickenpox or flu (in children), hypersensitivity to salicylates or other NSAIDs, asthma with rhinitis and/or nasal polyps, inherited bleeding disorders like hemophilia, and severe renal or hepatic failure.

Aspirin generally has a favorable adverse effect profile but does include gastric irritation and bleeding, and an increased risk of hemorrhage. Gastric irritation is treatable with antacids. The incidence of major gastrointestinal (GI) events (upper GI ulcer, peptic ulcer, serious GI bleeding) ranged from 0.8% to 2.6% [49–53]. Additional studies demonstrate that, after controlling for dose, the duration of aspirin use was not found to be associated with an increased risk of GI bleeding [54, 55].

The risks of tinnitus and hearing loss due to aspirin are dose dependent and are typically observed when the daily intake of aspirin is at least three times larger than proposed in the current

study [48]. An epidemiologic analysis of analgesic use and the risk of hearing loss revealed that longer duration (> 6 years) of aspirin use was not associated with a higher risk of hearing loss, while longer duration of ibuprofen and acetaminophen use was associated with a higher risk of hearing loss [56].

Young children have the rare potential risk of Reye's syndrome, characterized by acute noninflammatory encephalopathy and fatty degenerative liver failure following a viral illness, which is increased if aspirin is administered [57, 58]. We thus exclude children under the age of 12 years in this study.

## 5 | Other Prophylactic Uses

Aspirin has been used for the primary prevention of cardiovascular disease (CVD) and the prevention of colorectal cancer (CRC). Prophylactic use for these purposes has been a deterrent to recruitment to this study for potential subjects concerned that they needed to continue a low-dose aspirin prophylaxis. Recommendations for the prevention of CVD were altered by the United States Preventive Services Task Force (USPSTF) in 2022. It recommended that the decision to initiate low-dose aspirin use for the primary prevention of CVD in adults aged 40–59 years with a 10% or greater 10-year CVD risk should be an individual one, as evidence indicated that the benefit of aspirin use in this group was small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit. The USPSTF recommended against initiating low-dose aspirin use for the primary prevention of CVD in adults 60 years or older. The USPSTF also withdrew its recommendation regarding CRC, deeming the evidence supporting aspirin's reduction of CRC risk as “inadequate” [59]. Contrariwise, Chan opined that the USPSTF's statement was based on a narrow interpretation of new primary CVD prevention trials with limited relevance to CRC and failed to consider the broader evidence base supporting aspirin's efficacy for CRC prevention [60, 61].

As the benefit of aspirin to patients with VS is yet unknown, potential study subjects and their primary care physicians should consider the relatively weak evidence for and against aspirin prophylaxis of CVD and CRC. For the purposes of this study, participation seems feasible even for those subjects who have previously been on aspirin or other nonsteroidal anti-inflammatory drugs. Study subjects are required to undergo a 60-day aspirin discontinuation washout period to proceed.

## 6 | Potential Benefits of Study Participation

Patients may benefit from halted or reduced tumor growth. Additionally, for NF2-SWN patients randomized to the aspirin arm, they may see halted or reduced tumor growth in other NF2-related tumors. For patients who are randomized to the placebo arm, they may or may not benefit directly from placebo treatment, but they have the option of receiving open-label aspirin if the tumors progress while on placebo. Future patients with VS and NF2-SWN will certainly benefit from the conclusions of this study. The reduced morbidity due to avoiding surgery or radiation-related adverse events, may be considerable. Likewise, the unnecessary treatment can be eliminated if not shown to be effective.

## 7 | Biomarker Analysis

Increasing evidence is emerging of serologic biomarkers of VS growth and hearing loss [36, 37]. The current study incorporates biomarker analysis, such as TNFα and prostaglandin E2 levels, as well as confirms serum levels of salicylates in study participants. These data may aid in determining treatment risks and benefits to patients who present with VS, including predicting responses to aspirin treatment.

## 8 | Study Design/Methods

After IRB approval 2019P000045 from Mass General Brigham, the following study was ensured.

In the randomized treatment phase of this study, patients aged 12 years or older with VS are recruited into one of two randomized groups who receive either 325 mg aspirin twice daily or a placebo. For patients whose weight is less than 50 kg, the aspirin dose is 81 mg twice daily. Patients stay on aspirin as long as there is no more than a 20% increase volume in VS size from baseline. All patients are followed throughout the duration of the study (42 months post-baseline), unless they receive other definitive treatment or progress as defined below. If tumor volume progresses > 20% from baseline, the blind is broken, and the subjects have the option to participate in the Open Label Follow-Up Phase as follows:

- Subjects whose tumors progressed on placebo may opt to receive aspirin and continue to be followed in the Open Label Phase until they progress further (an additional 20%) or they reach 42 months post-baseline.
- Subjects whose tumors progressed on aspirin may continue to take aspirin and be followed in the Open Label Phase until they progress further (an additional 20%) or they reach 42 months post-baseline. See Figure 1. Subjects whose tumors progress during the Blinded Randomized Treatment Phase may decide to come off treatment and pursue surgery or radiation.

Subjects are notified of what group they were randomized into when their study participation has ended. Subjects have the option of taking over-the-counter aspirin treatment once their study participation has ended.

Subjects who experience an adverse event of grade 3 (severe or medically significant but not immediately life-threatening) or grade 4 (life-threatening) that is determined to be related to aspirin treatment are removed from the treatment but continue to be followed.

## 9 | Inclusion Criteria

All subjects that participate in this study must meet the following criteria:

1. Ability to provide informed consent.
2. Pediatric patients must provide assent in addition to their parents'/guardians' consent.

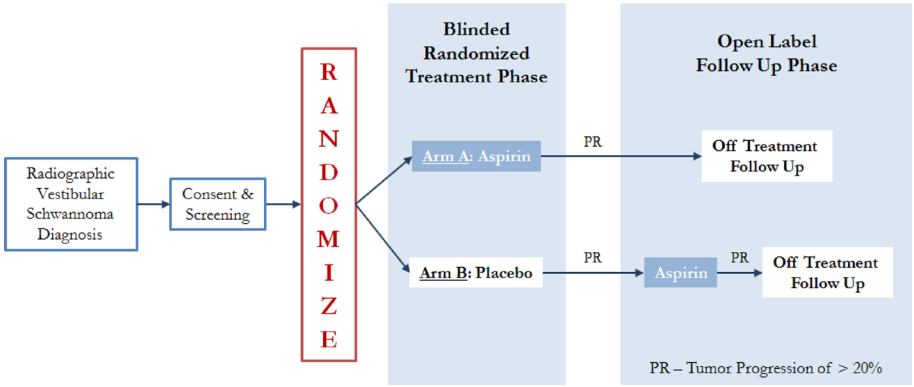


**FIGURE 1** | Schematic of Study Design. The randomized and open-label phases of the study are depicted. PR is tumor progression of > 20% by volume.

3. Age ≥ 12 years.
4. VS categorized as NF2-SWN associated or sporadic.
5. Newly diagnosed VS within the last 2 years or any growing VS (tumors are considered growing if it they show ≥ 2 mm increase in any dimension or > 20% change in volume between scans at least 6 months apart).
6. Confirmed radiographic diagnosis of VS by an MRI scan. Images must be present at baseline.
7. Ability to swallow capsules.

## 10 | Exclusion Criteria

The presence of any of the following excludes potential subjects from participation:

1. Use of aspirin (or aspirin containing products) more than four times in a single week within the last 2 months. However, patients may complete a 60-day washout period.
2. Use of systemic steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) more than four times in a single week in the last two months. Patients may complete a 60-day washout period.
3. Refusal to refrain from the use of aspirin, aspirin-containing products, NSAIDs, and steroids throughout the course of the study.
4. Anticoagulation
5. Prior treatment for vestibular schwannoma as follows:
    - Radiation. For patients with bilateral vestibular schwannomas, of which only one has been irradiated, patients are eligible if the tumor on the non-irradiated side is designated the target lesion.
    - Bevacizumab within 60 days prior to enrollment. Patients who have more than a 60-day washout period are eligible.
    - Surgical resection of the target lesion must occur within 6 months prior to enrollment. Patients with prior surgical resection of the target lesion must have a post-op scan that shows residual tumor growth to be eligible.
6. Known allergy to aspirin.
7. Impairment of gastrointestinal function or gastrointestinal disease.
8. Patients are at an increased risk of gastrointestinal or other bleeding.
9. Pregnant or lactating women.
10. Patients with serious medical illnesses.
11. Hydrocephalus.
12. History of febrile or flu-like illness in subjects less than 18 years of age.

## 11 | Randomization

Randomization to aspirin or placebo treatment is achieved by a permuted block design stratified by clinical center, NF-2 versus sporadic etiology, and tumor growth status (growing or unknown) to maintain balance across these factors. The lead study pharmacist also maintains the randomization status of study subjects across all sites.

### 11.1 | Response Criteria

*Radiographic response* is defined as at least a 20% decrease in the VS volume, taking as reference the baseline volume. *Progressive disease* is defined as at least a 20% increase in the VS volume, taking as reference the baseline volume during treatment. *Stable disease* is defined as not meeting criteria for radiographic response or for progressive disease. MRIs will be obtained at 6 months and yearly thereafter unless > 20% volume growth is detected.

Hearing response criteria are defined relative to the baseline word recognition (WR) score (Plotkin et al. 2009b): *hearing improvement* is defined as improvement in word recognition (WR) score above the 95% critical difference; *stable hearing* is defined

as persistence of WR score within the 95% critical difference; *progressive hearing loss* is defined as a decline in WR score below the 95% critical difference.

Serologic response criteria are defined relative to the baseline biomarker levels of TNFα and prostaglandin E2. Serum salicylate levels are measured to assess compliance with therapy.

Quality of Life response criteria are defined relative to baseline scores on the following surveys: Penn Acoustic Neuroma Quality of Life (PANQOL) survey for non-NF patients, NF2 Quality of Life (NFTI) survey for NF2 patients, and tinnitus interference questionnaire for all patients. These surveys are reliable, widely used, and have been validated in multiple studies.

## 12 | Progress to Date

To date, 84 study subjects have enrolled of a projected 300 necessary for statistical rigor. Three failed screening, 18 subjects have withdrawn for the reasons of personal preference, change of insurance, election for surgery, need for aspirin or other NSAIDs for other symptoms, and three for symptoms related to aspirin (gastrointestinal discomfort). Nine subjects have terminated for tumor growth, 11 have completed the 42 months on study, and one is in the open label phase with 20 active study subjects. See Figure 2 timeline.

## 13 | Challenges

Several challenges have been encountered. Alignments in a multicenter study with the individual Investigational Review Boards (IRB) and the Department of Defense (DoD) Human Research Protections Office (HRPO) are challenging. Covid-19 prevented potential study subjects from attending clinics for several years. Recruitment is also affected by the patient's ability to choose to take over-the-counter aspirin rather than be assigned randomly in this study. Some subjects take aspirin on their own. Other drug trials also compete for NF2 patients.

The number of enrolled subjects who have withdrawn from the study is higher than anticipated. Perhaps the indolent nature of tumor growth and patients' lack of urgency or relative sense of well-being has played a role. Fortunately, the funding for the study provided by the Department of Defense has been granted no-cost extensions to allow continued accrual. The first interim statistical analysis is planned when there are 100 evaluable subjects. Perhaps a difference between groups will be detected because the current study design entails a larger dose of aspirin (650 mg) consistently taken than in the previous retrospective studies where most patients took 81 or 325 mg.

## 14 | Secondary Biomarker Endpoints

To test whether baseline levels of the specific molecules in the blood predict response to therapy, a panel of serum biomarkers will be analyzed [36, 37]. Mediation analysis will be applied [62]. Improved identification of individuals for whom the protective benefits of aspirin outweigh the potential sideeffects may allow a precision medicine approach to emerge.

## 15 | Statistical Considerations

The primary study outcome is progression-free survival. Our retrospective study of 347 VS patients whose tumors were clinically documented with serial MRI scans revealed that patients taking aspirin for unrelated reasons were less likely to have tumor growth than those not taking aspirin, with the proportion of patients experiencing tumor growth being 0.41 in those taking aspirin and 0.58 in those not taking aspirin [27]. The power analysis was performed based on two prior studies demonstrating volumetric growth in untreated vestibular schwannomas in 59% and 66% of subjects, respectively, with a mean follow-up of 4.5 and 3.8 years respectively [28, 63]. Based on these data and with our planned follow-up of 42 months and 150 patients per group (treatment versus control), a log-rank test for a difference in progression-free survival will have 80% power to detect a significant treatment effect at a 0.05 two-sided significance level.

Analyses will use all available data and follow the intention-to-treat principle. No deaths are anticipated. Loss to follow-up should be low because patients whose tumor volume increases by more than 20% will continue to be followed despite being taken off treatment. Patients who progress will be removed from treatment or crossed over for ethical and safety reasons. The causal effect of treatment can only be estimated on the primary outcome since all patients in the risk set at each event time will still be on the initially assigned aspirin or placebo treatment.

Specific analyses planned for primary and secondary objectives of the study are specified in Table 1, along with the corresponding endpoints and statistical analytical tools.

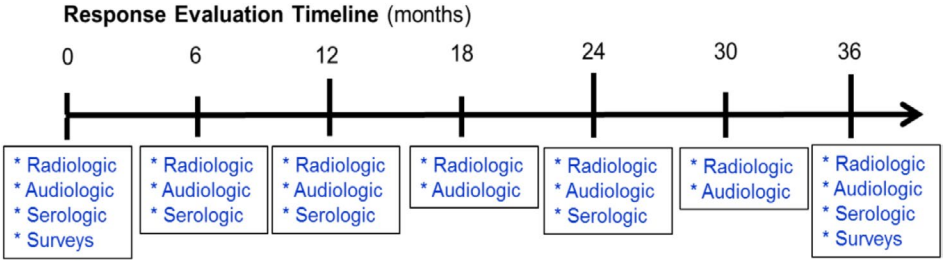


**FIGURE 2** | Response evaluation timeline. All patients will have up to 42 months of follow up time. The final surveys will be administered at the time of study completion.

**TABLE 1** | The study's objectives and endpoints.

| | Objective | Endpoints |
|---|---|---|
| Primary | To determine progression-free survival (PFS) of VS patients after up to 42 months of treatment with aspirin | Time to tumor progression<br>Analysis: Cox model |
| Secondary/exploratory | To determine the effect of aspirin on VS growth | % change in VS radiographic volume at 6–12 month intervals compared with baseline<br>Analysis: Random effects model |
| | To determine the effect of aspirin on hearing function | Proportion of patients with hearing loss compared with baseline at 12 and 24 months<br>Analysis: Logistic regression |
| | To determine the effect of aspirin on serum biomarkers TNFα and prostaglandin E2 | Mean change in protein biomarkers (based on ELISA assays) compared with baseline at 12 and 24 months and at completion of the study<br>Analysis: Random effects model |
| | To determine the effect of aspirin on serum salicylate levels | Mean change in serum salicylate levels compared with baseline at 12 and 24 months and at completion of the study<br>Analysis: Random effects model |
| Secondary/exploratory | To determine whether baseline levels of TNFα and prostaglandin E2 predict response to aspirin (serologic prediction) | Progression free survival<br>Analysis: Cox model with interactions<br>% change in VS volume at 6-month intervals<br>Analysis: Random effects model with interactions<br>Proportion of patients with hearing loss at 12 and 24 months<br>Analysis: Logistic regression with interactions |
| | To determine whether changes in TNFα and prostaglandin E2 levels mediate the treatment effect of aspirin (serologic mediation analysis) | Time to progression<br>% change in VS volume at 6–12 month intervals<br>Proportion of patients with hearing loss at 12 and 24 months<br>Analysis: Mediation analysis |
| | To determine whether changes in salicylate levels mediate the treatment effect of aspirin | Time to progression<br>% change in VS volume at 6–12 month intervals<br>Proportion of patients with hearing loss at 12 and 24 months<br>Analysis: Mediation analysis |
| | To determine the tolerability of aspirin treatment | Number of adverse events per patient per unit follow up time<br>Analysis: Negative binomial regression |
| | To determine the effect of aspirin treatment on quality of life | Scores on PANQOL survey (non-NF2 VS-specific quality of life for patients with sporadic VS), NFTI survey (NF2-specific quality of life for patients with NF2) and on tinnitus interference questionnaire at the beginning and end of study<br>Analysis: Random effects model |

*Note:* For each endpoint, statistical analysis is highlighted in blue.

## 16 | Considerations Regarding NF2-SWN Subjects

This Phase 2 study is not powered to detect a treatment by tumor etiology in the NF-2 patients alone. As an exploratory objective, these effects will be estimated and will provide valuable data for planning a potential Phase 3 study.

## 17 | Data Safety and Monitoring

The Data and Safety Monitoring is ongoing with the continuous evaluation of safety, data quality, and data timeliness. Frequency and severity of adverse events are reported. The Medical Monitor reviews all unanticipated problems involving

risks to subjects and provides an independent report of events to the IRB, the Data Safety and Monitoring Board (DSMB), and the Human Research Protection Office (HRPO) for the U.S. Army Medical Research and Materiel Command. The Data Safety and Monitoring Board (DSMB) serves as the independent data and safety monitoring board. The revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 are utilized.

## 18 | Participating Sites

Massachusetts Eye and Ear (Boston, MA), Stanford University (Palo Alto, CA), the Mayo Clinic (Rochester, MN), the University of Utah (Salt Lake City, UT), the University of Miami (Miami, FL) and the Barrow Neurological Institute (Phoenix, AZ).

## 19 | Conclusions

The authors encourage referral and patient participation. We look forward to completion in a rigorous fashion, which will hopefully answer the question regarding the efficacy of aspirin in the treatment of vestibular schwannomas.


### Acknowledgments

We gratefully acknowledge support from the Department of Defense Congressionally Directed Medical Research Program Grant W81XWH-17-1-0644 (NF160065) and the Acoustic Neuroma Association in disseminating information. This study is posted on clinicaltrials.gov, ID: NCT03079999.


### Conflicts of Interest

D. Bradley Welling is a consultant for Salubritas Therapeutics Inc.; Brian A. Neff is a consultant for Akuous. The other authors declare no conflicts of interest.

### References


1. W. J. Neary, V. E. Newton, M. Vidler, et al., "A Clinical, Genetic and Audiological Study of Patients and Families With Bilateral Acoustic Neurofibromatosis," *Journal of Laryngology and Otology* 107, no. 1 (1993): 6–11.

2. D. G. Evans, E. Howard, C. Giblin, et al., "Birth Incidence and Prevalence of Tumor-Prone Syndromes: Estimates From a UK Family Genetic Register Service," *American Journal of Medical Genetics* 152A, no. 2 (2010): 327–332.

3. S. Stangerup and P. Caye-Thomasen, "Epidemiology and Natural History of Vestibular Schwannomas," *Otolaryngologic Clinics of North America* 45 (2012): 257–268.

4. P. H. Aguiar, M. Tatagiba, M. Samii, E. Dankoweit-Timpe, and H. Ostertag, "The Comparison Between the Growth Fraction of Bilateral Vestibular Schwannomas in Neurofibromatosis 2 (NF2) and Unilateral Vestibular Schwannomas Using the Monoclonal Antibody MIB 1," *Acta Neurochirurgica* 134, no. 1–2 (1995): 40–45.

5. D. B. Welling, M. Guida, F. Goll, et al., "Mutational Spectrum in the NF2 Gene in Sporadic and Familial Schwannomas," *Human Genetics* 98, no. 9 (1996): 189–193.

6. S. I. Nam, F. H. Linthicum, Jr., and S. N. Merchant, "Temporal Bone Histopathology in Neurofibromatosis Type 2," *Laryngoscope* 121, no. 7 (2011): 1548–1554.

7. R. A. Sobel, "Vestibular (Acoustic) Schwannomas: Histologic Features in Neurofibromatosis 2 and in Unilateral Cases," *Journal of Neuropathology and Experimental Neurology* 52, no. 2 (1993): 106–113.

8. I. Gugel, F. Grimm, C. Teuber, et al., "Presenting Symptoms in Children With Neurofibromatosis Type 2," *Child's Nervous System* 36, no. 10 (2020): 2463–2470.

9. M. S. Dirks, J. A. Butman, H. J. Kim, et al., "Long-Term Natural History of Neurofibromatosis Type 2- Associated Intracranial Tumors," *Journal of Neurosurgery* 117, no. 1 (2012): 109–117, https://doi.org/10.3171/2012.3.JNS111649.

10. D. G. Hardy, R. Macfarlane, D. Baguley, and D. A. Moffat, "Surgery for Acoustic Neurinoma," *Journal of Neurosurgery* 71, no. 6 (1989): 799–804.

11. A. K. Demetriades, N. Saunders, P. Rose, et al., "Malignant Transformation of Acoustic Neuroma/Vestibular Schwannoma 10 Years After Gamma Knife Stereotactic Radiosurgery," *Skull Base* 20, no. 5 (2010): 381–387, https://doi.org/10.1055/s-0030-1253576.

12. C. E. Gilkes and D. G. Evans, "Review of Radiation Therapy Services for Neurofibromatosis (NF2) Patients in England," *British Journal of Neurosurgery* 28, no. 1 (2014): 16–19.

13. M. Fujii, M. Ichikawa, K. Iwatate, et al., "Bevacizumab Therapy of Neurofibromatosis Type 2 Associated Vestibular Schwannoma in Japanese Patients," *Neurologia Medico-Chirurgica* 60, no. 2 (2020): 75–82, https://doi.org/10.2176/nmc.oa.2019-0194.

14. P. Sverak, M. E. Adams, S. J. Haines, et al., "Bevacizumab for Hearing Preservation in Neurofibromatosis Type 2: Emphasis on Patient-Reported Outcomes and Toxicities," *Otolaryngology and Head and Neck Surgery* 160, no. 3 (2019): 526–532, https://doi.org/10.1177/0194599818809085.

15. J. Shi, D. Lu, R. Gu, et al., "Reliability and Toxicity of Bevacizumab for Neurofibromatosis Type 2-Related Vestibular Schwannomas: A Systematic Review and Meta-Analysis," *American Journal of Otolaryngology* 42, no. 6 (2021): 103148, https://doi.org/10.1016/j.amjoto.2021.103148.

16. V. M. Lu, K. Ravindran, C. S. Graffeo, et al., "Efficacy and Safety of Bevacizumab for Vestibular Schwannoma in Neurofibromatosis Type 2: A Systematic Review and Meta-Analysis of Treatment Outcomes," *Journal of Neuro-Oncology* 144, no. 2 (2019): 239–248, https://doi.org/10.1007/s11060-019-03234-8 2019 Jun 28. PMID: 31254266.

17. J. O. Blakeley, X. Ye, D. G. Duda, et al., "Efficacy and Biomarker Study of Bevacizumab for Hearing Loss Resulting From Neurofibromatosis Type 2-Associated Vestibular Schwannomas," *Journal of Clinical Oncology* 34, no. 14 (2016): 1669–1675.

18. S. R. Plotkin, V. L. Merker, C. Halpin, et al., "Bevacizumab for Progressive Vestibular Schwannoma in Neurofibromatosis Type 2: A Retrospective Review of 31 Patients," *Otology & Neurotology* 33, no. 6 (2012): 1046–1052, https://doi.org/10.1097/MAO.0b013e31825e73f5.

19. S. R. Plotkin, D. G. Duda, A. Muzikansky, et al., "Multicenter, Prospective, Phase II and Biomarker Study of High-Dose Bevacizumab as Induction Therapy in Patients With Neurofibromatosis Type 2 and Progressive Vestibular Schwannoma," *Journal of Clinical Oncology* 37, no. 35 (2019): 3446–3454. Erratum in: Journal of Clinical Oncology, 2020, 38(6), 656.

20. S. R. Plotkin, C. Halpin, M. J. McKenna, J. S. Loeffler, T. T. Batchelor, and F. G. Barker, 2nd, "Erlotinib for Progressive Vestibular Schwannoma in Neurofibromatosis 2 Patients," *Otology & Neurotology* 31 (2010): 1135–1143.

21. M. A. Karajannis, G. Legault, M. Hagiwara, et al., "Phase II Trial of Lapatinib in Adult and Pediatric Patients With Neurofibromatosis Type

2 and Progressive Vestibular Schwannomas," *Neuro-Oncology* 14, no. 9 (2012): 1163–1170.

22. S. Goutagny, E. Raymond, M. Esposito-Farese, et al., "Phase II Study of mTORC1 Inhibition by Everolimus in Neurofibromatosis Type 2 Patients With Growing Vestibular Schwannomas," *Journal of Neurooncology* 122, no. 2 (2015): 313–320.

23. D. B. Welling, K. A. Collier, S. S. Burns, et al., "Early Phase Clinical Studies of AR-42, a Histone Deacetylase Inhibitor, for Neurofibromatosis Type 2-Associated Vestibular Schwannomas and Meningiomas," *Laryngoscope Investigative Otolaryngology* 6, no. 5 (2021): 1008–1019.

24. S. R. Plotkin, K. H. Yohay, P. L. Nghiemphu, et al., "Brigatinib in *NF2*-Related Schwannomatosis With Progressive Tumors," *New England Journal of Medicine* 390, no. 24 (2024): 2284–2294, https://doi.org/10.1056/NEJMoa2400985.

25. Y. Ren, D. Chari, S. Vasilijic, D. B. Welling, and K. M. Stankovic, "New Developments in Neurofibromatosis Type 2 and Vestibular Schwannoma," *Neuro-Oncology Advances* 3, no. 1 (2020): vdaa153.

26. D. B. Welling, "Targeted Therapies in the Treatment of Vestibular Schwannomas: Current State and New Horizons," *Otolaryngologic Clinics of North America* 56, no. 3 (2023): 543–556.

27. C. K. Kandathil, S. Dilwali, C. C. Wu, et al., "Aspirin Intake Correlates With Halted Growth of Sporadic Vestibular Schwannoma In Vivo," *Otology & Neurotology* 35, no. 2 (2014): 353–357.

28. C. Kandathil, M. E. Cunnane, H. Curtin, and K. M. Stankovic, "Correlation Between Aspirin Intake and Reduced Growth of Human Vestibular Schwannoma: Volumetric Analysis," *Otology & Neurotology* 37, no. 9 (2016): 1428–1434.

29. S. Dilwali, S. Y. Kao, T. Fujita, L. Landegger, and K. M. Stankovic, "Non-steroidal Anti-Inflammatory Medications Are Cytostatic Against Human Vestibular Schwannomas," *Translational Research* 166, no. 1 (2015b): 1–11.

30. A. Schulz, R. Büttner, C. Hagel, et al., "The Importance of Nerve Microenvironment for Schwannoma Development," *Acta Neuropathologica* 132, no. 2 (2016): 289–307.

31. B. Hong, C. A. Krusche, K. Schwabe, et al., "Cyclooxygenase-2 Supports Tumor Proliferation in Vestibular Schwannomas," *Neurosurgery* 68 (2011): 1112–1117.

32. S. Dilwali, M. C. Briët, S. Y. Kao, et al., "Preclinical Validation of Anti-Nuclear Factor-Kappa B Therapy to Inhibit Human Vestibular Schwannoma Growth," *Molecular Oncology* 9, no. 7 (2015): 1359–1370.

33. M. de Vries, I. Briaire-de Bruijn, M. J. A. Malessy, S. F. de Bruïne, A. G. van der Mey, and P. C. Hogendoorn, "Tumor- Associated Macrophages Are Related to Volumetric Growth of Vestibular Schwannomas," *Otology & Neurotology* 34, no. 2 (2013): 347–352.

34. D. Lewis, C. A. Donofrio, C. O'Leary, et al., "The Microenvironment in Sporadic and Neurofibromatosis Type II-Related Vestibular Schwannoma: The Same Tumor or Different? A Comparative Imaging and Neuropathology Study," *Journal of Neurosurgery* 134, no. 5 (2020): 1419–1429.

35. C. J. Hannan, D. Lewis, C. O'Leary, et al., "The Inflammatory Microenvironment in Vestibular Schwannoma," *Neuro-Oncology Advances* 2, no. 1 (2020): vdaa023, https://doi.org/10.1093/noajnl/vdaa023.

36. S. Vasilijic, N. A. Atai, H. Hyakusoku, et al., "Identification of Immune-Related Candidate Biomarkers in Plasma of Patients With Sporadic Vestibular Schwannoma," *Science Advances* 9, no. 45 (2023): eadf7295.

37. K. M. Stankovic, S. Batts, D. B. Welling, and S. Vasilijic, "Immune Profiling of Secreted Factors From Human Vestibular Schwannoma Cells and Tumor-Associated Macrophages," *Laryngoscope* 134, no. Suppl 5 (2024): S1–S14.

38. S. Dilwali, L. Landegger, V. Y. R. Soares, D. G. Deschler, and K. M. Stankovic, "Secreted Factors From Human Vestibular Schwannomas Can Cause Cochlear Damage," *Scientific Reports* 5 (2015): 18599.

39. L. Wu, S. Vasilijic, Y. Sun, et al., "Losartan Prevents Tumor-Induced Hearing Loss and Augments Radiation Efficacy in NF2 Schwannoma Rodent Models," *Science Translational Medicine* 13, no. 602 (2021): eabd4816.

40. J. E. Sagers, A. S. Brown, S. Vasilijic, et al., "Computational Repositioning and Preclinical Validation of Mifepristone for Human Vestibular Schwannoma," *Scientific Reports* 8, no. 1 (2018): 5437.

41. J. P. Marinelli, K. A. Lees, N. M. Tombers, C. M. Lohse, and M. L. Carlson, "Impact of Aspirin and Other NSAID Use on Volumetric and Linear Growth in Vestibular Schwannoma," *Otolaryngology and Head and Neck Surgery* 160, no. 6 (2019): 1081–1086.

42. J. B. Hunter, B. P. O'Connell, G. B. Wanna, et al., "Vestibular Schwannoma Growth With Aspirin and Other Nonsteroidal Anti-Inflammatory Drugs," *Otology & Neurotology* 38, no. 8 (2017): 1158–1164, https://doi.org/10.1097/MAO.0000000000001506.

43. L. Goodman and A. Gilman, *Goodman & Gilman's the Pharmacological Basis of Therapeutics* (McGraw-Hill, Health Professions Division, 1996).

44. G. D. Williams, E. P. Kirk, C. J. Wilson, C. A. Meadows, and B. S. Chan, "Salicylate Intoxication From Teething Gel in Infancy," *Medical Journal of Australia* 194, no. 3 (2011): 146–148.

45. H. E. Paulus, M. Siegel, E. Mongan, R. Okun, and J. J. Calabro, "Variations of Serum Concentrations and Half-Life of Salicylate in Patients With Rheumatoid Arthritis," *Arthritis and Rheumatology* 14 (1971): 527–532.

46. C. Cerletti, M. Bonati, A. del Maschio, et al., "Plasma Levels of Salicylate and Aspirin in Healthy Volunteers: Relevance to Drug Interaction on Platelet Function," *Journal of Laboratory and Clinical Medicine* 103 (1984): 869–877.

47. S. R. Samlan, M. T. Jordan, S. B. Chan, M. S. Wahl, and R. L. Rubin, "Tinnitus as a Measure of Salicylate Toxicity in the Overdose Setting," *Western Journal of Emergency Medicine* 9 (2008): 146–149.

48. E. N. Myers, J. M. Bernstein, and G. Fostiropolous, "Salicylate Ototoxicity: A Clinical Study," *New England Journal of Medicine* 273 (1965): 587–590.

49. Steering Committee of the Physicians' Health Study Research Group, "Preliminary Report: Findings From the Aspirin Component of the Ongoing Physicians' Health Study," *New England Journal of Medicine* 318 (1988): 262–264.

50. Steering Committee of the Physicians' Health Study Research Group, "Final Report on the Aspirin Component of the Ongoing Physicians' Health Study," *New England Journal of Medicine* 321, no. 3 (1989): 129–135.

51. R. Peto, R. Gray, R. Collins, et al., "Randomised Trial of Prophylactic Daily Aspirin in British Male Doctors," *British Medical Journal* 296, no. 6618 (1988): 313–316.

52. Medical Research Council's General Practice Research Framework, "Thrombosis Prevention Trial: Randomised Trial of Low-Intensity Oral Anticoagulation With Warfarin and Low-Dose Aspirin in the Primary Prevention of Ischaemic Heart Disease in Men at Increased Risk," *Lancet* 351, no. 9098 (1998): 233–241.

53. G. de Gaetano and the Collaborative Group of the Primary Prevention Project, "Low-Dose Aspirin and Vitamin E in People at Cardiovascular Risk: A Randomised Trial in General Practice," *Lancet* 357, no. 9250 (2001): 89–95.

54. E. S. Huang, L. L. Strate, W. W. Ho, S. S. Lee, and A. T. Chan, "A Prospective Study of Aspirin Use and the Risk of Gastrointestinal Bleeding in Men," *PLoS One* 5, no. 12 (2010): e15721.

55. E. S. Huang, L. L. Strate, W. W. Ho, S. S. Lee, and A. T. Chan, "Long Term Use of Aspirin and the Risk of Gastrointestinal Bleeding," *American Journal of Medicine* 124, no. 5 (2011): 426–433.

56. B. Lin, S. G. Curhan, M. Wang, R. Eavey, K. M. Stankovic, and G. C. Curhan, "Duration of Analgesic Use and Risk of Hearing Loss in Women," *American Journal of Epidemiology* 185, no. 1 (2017): 40–47.

57. K. Schrör, "Aspirin and Reye Syndrome. A Review of the Evidence," *Pediatric Drugs* 9 (2007): 191–200.

58. J. Chapman and J. K. Arnold, "Reye Syndrome," in *StatPearls [Internet]* (StatPearls Publishing, 2024).

59. K. W. Davidson, M. J. Barry, C. M. Mangione, et al., "Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement," *JAMA* 327, no. 16 (2022): 1577–1584, https://doi.org/10.1001/jama.2022.4983.

60. A. T. Chan, "Aspirin and the USPSTF-What About Cancer?," *JAMA Oncology* 8, no. 10 (2022): 1392–1394.

61. D. A. Drew and A. T. Chan, "Aspirin in the Prevention of Colorectal Neoplasia," *Annual Review of Medicine* 72, no. 1 (2021): 415–430.

62. L. Valeri and T. J. Vanderweele, "Mediation Analysis Allowing for Exposure-Mediator Interactions and Causal Interpretation: Theoretical Assumptions and Implementation With SAS and SPSS Macros," *Psychological Methods* 18, no. 2 (2013): 13–50.

63. D. D. Massick, D. B. Welling, E. E. Dodson, et al., "Tumor Growth and Audiometric Change in Vestibular Schwannomas Managed Conservatively," *Laryngoscope* 110, no. 11 (2000): 1843–1849.