Sacrifice or preserve the superior petrosal vein in microvascular decompression surgery: a systematic review and meta-analysis

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OBJECTIVE In microvascular decompression (MVD) surgery through the retrosigmoid approach, the surgeon may have to sacrifice the superior petrosal vein (SPV). However, this is a controversial maneuver. To date, high-level evidence comparing the operative outcomes of patients who underwent MVD with and without SPV sacrifice is lacking. Therefore, this study sought to bridge this gap.

METHODS The authors searched the Medline and PubMed databases with appropriate Medical Subject Heading (MeSH) terms and keywords. The primary outcome was vascular-related complications; secondary outcomes were new neurological deficit, cerebrospinal fluid (CSF) leak, and neuralgia relief. The pooled proportions of outcomes and OR (95% CI) for categorical data were calculated by using the logit transformation and Mantel-Haenszel methods, respectively.

RESULTS Six studies yielding 1143 patients were included, of which 618 patients had their SPV sacrificed. The pooled proportion (95% CI) values were 3.82 (0.87–15.17) for vascular-related complications, 3.64 (1.0–12.42) for new neurological deficits, 2.85 (1.21–6.58) for CSF leaks, and 88.90 (84.90–91.94) for neuralgia relief. The meta-analysis concluded that, whether the surgeon sacrificed or preserved the SPV, the odds were similar for vascular-related complications (2.5% vs 1.5%, OR [95% CI] 1.01 [0.33–3.09], p = 0.99), new neurological deficits (1.2% vs 2.8%, OR [95% CI] 0.55 [0.18–1.66], p = 0.29), CSF leak (3.1% vs 2.1%, OR [95% CI] 1.16 [0.46–2.94], p = 0.75), and neuralgia relief (86.6% vs 87%, OR [95% CI] 0.96 [0.62–1.49], p = 0.84).

CONCLUSIONS SPV sacrifice is as safe as SPV preservation. The authors recommend intentional SPV sacrifice when gentle retraction fails to enhance surgical field visualization and if the surgeon encounters SPV-related neurovascular conflict and/or anticipates impeding SPV-related bleeding.

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KEYWORDS Dandy’s vein; superior petrosal vein; microvascular decompression; retrosigmoid approach; trigeminal neuralgia; meta-analysis; pain; surgical technique

MICROVASCULAR decompression (MVD) has been known as the benchmark surgical procedure for the treatment of intractable trigeminal neuralgia (TN), hemifacial spasm, glossopharyngeal neuralgia, and other cranial nerve rhizopathies.1–7 As initially described by Walter E. Dandy, the superior petrosal vein (SPV) is the most frequently encountered venous structure during posterior fossa surgery and serves as a prominent landmark in the retrosigmoid approach (Fig. 1).7,9 The SPV drains infratentorial structures into the superior petrosal sinus (SPS) in 3 distinct patterns. In type I (19% of patients), the SPV enters the SPS superolateral to the internal acoustic meatus (IAM); type II (72%), the SPV joins the SPS between IAM and Meckel’s cave just lateral to the trigeminal trunk; and type III (9%), the SPV empties into the SPS superior or medial to Meckel’s cave.11 Therefore, in the majority of patients, the SPV crosses the retrosigmoid corridor lateral to the trigeminal nerve, thereby obscuring the surgeon’s view.9,11,12

During the retrosigmoid approach for MVD surgery,
surgeons may have to sacrifice the SPV. However, this is a controversial maneuver. Proponents recommend sacrificing the SPV to enhance surgical exposure, prevent inadvertent vein avulsion and subsequent hemorrhage, attenuate overzealous retraction, and release the impinged nerve when the conflicting vessel appears to be the SPV itself.

On the other hand, opponents indicate that complications can arise after vein sacrifice, and surgeons should try to preserve the SPV as much as possible. Several case reports have attributed perioperative complications to SPV sacrifice, including peduncular hallucinosis, transient global brainstem dysfunction, contralateral hearing loss, delayed contralateral TN, cerebellar ataxia due to infarction, and fatal hemorrhagic infarction. Conversely, there are reports of uneventful SPV ligation and peduncular hallucinosis due to cerebellar retraction. These controversies keep the dilemma ongoing.

To date, high-level evidence comparing the odds of complications after SPV sacrifice versus preservation is lacking. This systematic review and meta-analysis seeks to bridge this gap. We hypothesized that the risks of complications were not significantly different between MVD with and without SPV sacrifice.

Methods

Study Design

This systematic review and meta-analysis was conducted according to the guidelines set forth by PRISMA. The study’s question per the patient, intervention, comparator, and outcome (PICO) format was as follows: patients were individuals who had TN, glossopharyngeal neuralgia, or hemifacial spasm and underwent MVD; intervention was SPV sacrifice, either inadvertently or intentionally; comparator was SPV preservation; and outcomes were vascular-related complications, neurological deficits, CSF leak, and neuralgia relief.

Outcomes

The primary outcome was vascular-related complications, including sinus thrombosis, edema, or ischemia involving the cerebellum or brainstem; secondary outcomes were postoperative new neurological deficits (i.e., postoperative cranial nerve deficit), cerebrospinal fluid (CSF) leak (with or without meningitis), and neuralgia relief.

Eligibility Criteria

Studies that met the following criteria were considered eligible for inclusion: 1) comparative studies involving both the intervention and comparator; 2) studies with at least 4 patients in each group; and 3) studies with clearly reported outcomes. Case reports, noncomparative articles, review papers, and articles with unclear outcome reports were excluded. We considered only full-text English articles.

Search Strategy

We searched Medline and PubMed databases from inception to October 20, 2021. The following Medical Subject Heading (MeSH) terms and potential keywords were used in various combinations: 1) “Trigeminal Neuralgias” or “Tic Convulsive” or “Trigeminal Neuralgia” or “Tic Doloureux” or “Fothergill Disease” or “Trifacial Neuralgia” or “Trifacial Neuralgias” or “Tic Doloureux” or “Epileptiform Neuralgia” or “Epileptiform Neuralgias” or “Trigeminal Neuralgia” or “Hemifacial Spasms” or “Hemifacial Spasm” or “Unilateral Facial Spasm” or “Unilateral Facial Spasm” or “Hemifacial Myokymia” or “Facial Spasm” or “Glossopharyngeal Neuralgia” or “Glossopharyngeal Neuralgias”; 2) “Decompression Surgery” or “Microvascular Decompression Surgery” or “Microvascular Decompression Surgeries” or “Microvascular Decompression” or “Microvascular Decompression Surgeries” or “MVD” or “Microvascular Surgery” or “Microvascular Surgeries”; and 3) “Superior Petrosal Vein” or “Petrosal Vein” or “Dandy’s Vein” or “Vein of Dand” or “Superior Petrosal Sinus” or “Petrosal Sinus” or “Superior Petrosal Complex” or “Superior Petrosal Venous System” or “SPV” or “SPVS”.

One author (S.A.S.) performed the search and screened the records on the basis of title and abstract. Irrelevant records were excluded, and the remaining full-text articles were reviewed for eligibility. We supplemented our search by manually screening the text and references of the potentially eligible studies.

Data Extraction

Two authors (S.A.S. and A.S.) separately extracted the data into two Microsoft Excel sheets, and then the files were cross-checked and verified against the source materials. The corresponding author (J.H.) adjudicated any unresolved discordance. The following data were extracted: first author’s name, publication year, country of origin, study design, sample size, age and sex characteristics, outcomes of interest, and follow-up duration.
Risk of Bias Assessment

The Risk of Bias in Nonrandomized Studies of Intervention (ROBINS-I) tool was used to assess the bias of the included studies.

Statistical Analysis

The baseline demographic and clinical characteristics of the included studies were summarized with descriptive statistics. Pooled proportions of outcomes (i.e., number of events divided by number of patients) with associated 95% CIs were calculated with the logit transformation method and the DerSimonian and Laird random-effects model by using RStudio version 4.1.2. The ORs for the categorical outcomes with associated 95% CIs were calculated with the Mantel-Haenszel method by using Review Manager (RevMan) version 5.4.1 (The Cochrane Collaboration). With consideration of the clinical diversities and methodological differences between studies, the random-effects model was applied. Heterogeneities between studies were detected using the I² test statistic, which attributes proportions of total variation to differences between studies rather than sampling error. All statistical tests were 2-sided, and p < 0.05 was considered statistically significant.

Results

Study Selection

Our search strategy resulted in 2069 records, from which 26 duplicate records and 259 non–English language records were removed. We screened the remaining 1784 records on the basis of the titles and abstracts and excluded 1750 studies on irrelevant topics. We reviewed the full text of the remaining 34 articles to assess for eligibility, of which 28 articles were excluded due to the following exclusion criteria: case reports (n = 13), noncomparative studies (n = 5), review articles (n = 3), and fewer than 4 patients in the study groups (n = 2). Therefore, we included 6 studies in this systematic review (Fig. 2).
Characteristics of the Included Studies

The included studies were published between 2015 and 2021 and were conducted in the United States (n = 3), United Kingdom (n = 1), France (n = 1), and Japan (n = 1). All included studies were retrospective observational studies, including 1143 microvascular decompression cases, of which 618 underwent SPV sacrifice. The mean age ranged from 32 to 54 years, and 367 (32.4%) patients were male. The SPV was resected to increase surgical exposure, relieve nerve compression, and prevent impeding SPV bleeding. In the population of this systematic review, the pooled proportion (95% CI) values were 3.82 (0.87–15.17) for vascular-related complications, 3.64 (1.0–12.42) for new neurological deficits, 2.85 (1.21–6.58) for CSF leak with and without meningitis, and 88.90 (84.90–91.94) for neuralgia improvement (Table 1).

Risk of Bias Assessment

The included studies were retrospective nonrandomized studies and were at moderate risk of selection bias and classification bias (Fig. 3).

Meta-Analysis of the Outcomes

Primary Outcome

Vascular-Related Complications. Sixteen events occurred in the SPV-sacrificed cohort versus 8 events in the SPV-preserved group, and the meta-analysis concluded that the odds of vascular-related complications were not significantly different between the sacrificed and preserved cohorts (2.5% vs 1.5%, OR [95% CI] 1.01 [0.33–3.09], p = 0.99, I² = 0) (Fig. 4).

Secondary Outcomes

New Neurological Deficits. Eight new deficits occurred in the SPV-sacrificed group versus 15 new deficits in the SPV-preserved group, and the meta-analysis concluded that the risks of new deficit were not significantly different between groups (1.2% vs 2.8%, OR [95% CI] 0.55 [0.18–1.66], p = 0.29, I² = 0) (Fig. 5).

CSF Leak With or Without Meningitis. Thirteen events in the SPV-sacrificed group relative to 10 events in the SPV-preserved group occurred, and meta-analysis revealed that the risk of CSF leak was not significant between the 2 groups (3.1% vs 2.1%, OR [95% CI] 1.16 [0.46–2.94], p = 0.75, I² = 0) (Fig. 5).

Neuralgia Relief. In total, 273 of 315 SPV-sacrificed patients and 370 of 425 SPV-preserved patients reported neuralgia relief at the follow-up visits. The meta-analysis showed that the 2 groups were not significantly different (86.6% vs 87%, OR [95% CI] 0.96 [0.62–1.49], p = 0.84, I² = 0) (Fig. 6).

Discussion

MVD via a retrosigmoid approach is the mainstay treatment for refractory TN, hemifacial spasm, and other cranial nerve rhizopathies. Vascular conflict is the underlying pathology of these types of neuralgia, with the arteries as the most frequent offenders. After bone removal, “turning the corner” (i.e., exposing the cerebellar pontine angle) and engaging with “the vein of Dandy’s” (i.e., the SPV) is the most critical step of the retrosigmoid approach and must be executed masterfully.

The veins of the posterior fossa are classified into 3 major groups: the galenic group draining into the vein of Galen; the tentorial group emptying into the tentorial sinuses; and the petrosal group draining into the petrosal sinuses. The SPV is the upper division of the petrosal group and drains the anterior aspect of the brainstem and cerebellum. The main affluents of the SPV are the transverse pontine and pontotrigeminal veins, as well as the veins of the cerebellopontine fissure and the middle cerebellar peduncle. These tributaries merge and form the SPV, usually along the adjacent anterolateral margin of the cerebellum. Then, the SPV courses anterolaterally to join the SPS at a variable point along the petrosal ridge. The SPV is a prominent landmark during the retrosigmoid approach to the posterior fossa, and the operational field of view is determined on the basis of the drainage patterns of the SPV to the SPS. In type I (19% of patients), the SPV drains into the SPS above or lateral to the IAM at a point superolateral to the medial limit of the facial nerve at its point of entry into IAM; in type II (72%), the SPV drains into the SPS between IAM and Meckel’s cave at a point lateral to the trigeminal nerve; and in type III (9%), the SPV joins the SPS superior or medial to Meckel’s cave at a point medial to the lateral limit of the trigeminal nerve. Therefore, in most patients, the SPV crosses laterally to Meckel’s cave and obscures the rectosigmoid corridor, and the surgeon must decide whether to sacrifice or retract the vein; however, this decision is controversial.

To date, sacrificing or preserving Dandy’s vein has remained a neurosurgical dilemma, and high-level evidence of the risks of sacrifice versus preservation is lacking. To the best of our knowledge, this is the first systematic review and meta-analysis to compare the outcomes of MVD surgery performed with and without SPV sacrifice.

This meta-analysis showed that postoperative morbidities occurred at a relatively low rate. In the cohort of 1143 cranial rhizopathy patients who underwent MVD, the pooled proportions of events per 100 patients were 3.8 for vascular-related complications, 3.6 for new neurological deficits, and 2.8 for CSF leak. Furthermore, there were no fatal complications. The meta-analysis showed that the 2 groups were comparable in terms of postoperative morbidities and treatment success.

Morbidity

This study showed that pooled vascular-related complications occurred at rates of 4.7 and 4.1 per 100 patients in the SPV-sacrificed and SPV-preserved cohorts, respectively. These results are consistent with the previously reported rate of complications of 6.2% after SPV sacrifice. Furthermore, the meta-analysis concluded that the risks of vascular-related complications were not statistically different between patients with sacrificed and preserved SPV. These findings indicate that 1) vascular-related complications are infrequent; 2) the petrosal venous complex has sufficient collaterals and therefore most individuals tolerate SPV sacrifice well; and 3) other factors such as venous
# Table 1. Systematic review and meta-analysis of outcomes

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Country</th>
<th>Study Group</th>
<th>Pts (no.)</th>
<th>Age (yrs)</th>
<th>Male Sex</th>
<th>Pt Description</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Vascular-Related Complication</th>
<th>New Neurological Deficit</th>
<th>CSF Leak w/o or w/ Meningitis</th>
<th>Neuralgia Relief</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dumot &amp; Sindou, 2015</td>
<td>France</td>
<td>Total</td>
<td>19</td>
<td>32†</td>
<td>9 (47)</td>
<td>TN due to SPV conflict</td>
<td>MVD w/ coagulation division of SPV trunk &amp;/or pontine affluent &amp;/or mesencephalic affluent of SPV</td>
<td>MVD w/ preservation of SPV by using Teflon pieces</td>
<td>1 (5.2)</td>
<td>3 (15.7)</td>
<td>NR</td>
<td>NR</td>
<td>4.7 yrs†</td>
</tr>
<tr>
<td>Liebelt et al., 2017</td>
<td>USA</td>
<td>Total</td>
<td>95</td>
<td>NR</td>
<td>37 (22)</td>
<td>TN</td>
<td>MVD w/ coagulation division of SPV to enhance surgical exposure</td>
<td>MVD w/ preservation of SPV</td>
<td>8 (8.4)</td>
<td>1 (1)</td>
<td>6 (6.3)</td>
<td>NR</td>
<td>3 mos</td>
</tr>
<tr>
<td>Pathmanaban et al., 2017</td>
<td>UK</td>
<td>Total</td>
<td>224</td>
<td>57‡</td>
<td>83 (37)</td>
<td>TN</td>
<td>MVD w/ SPV sacrifice</td>
<td>MVD w/ SPV preservation</td>
<td>7 (3.1)</td>
<td>0</td>
<td>NR</td>
<td>208 (92.8)</td>
<td>3 mos</td>
</tr>
<tr>
<td>Blue et al., 2020</td>
<td>USA</td>
<td>Total</td>
<td>201</td>
<td>61‡</td>
<td>51 (26)</td>
<td>TN, HFS, &amp; GPN</td>
<td>MVD w/ sacrifice of SPV or affluent(s) of SPV to enhance surgical exposure</td>
<td>MVD w/ SPV preservation</td>
<td>0</td>
<td>4 (2)</td>
<td>2 (1)</td>
<td>145/166 (87.3)</td>
<td>1 mo</td>
</tr>
<tr>
<td>Xia et al., 2020</td>
<td>USA</td>
<td>Total</td>
<td>592</td>
<td>54†</td>
<td>187 (31)</td>
<td>TN &amp; HFS</td>
<td>MVD w/ sacrifice of SPV or affluent(s) of SPV to enhance surgical exposure</td>
<td>MVD w/ SPV preservation</td>
<td>2 (0.3)</td>
<td>11 (1.8)</td>
<td>15 (2.5)</td>
<td>457/562 (86.6)</td>
<td>1 mo</td>
</tr>
<tr>
<td>Kasuya et al., 2021</td>
<td>Japan</td>
<td>Total</td>
<td>12</td>
<td>4 NR</td>
<td>NR</td>
<td>TN due to SPV conflict</td>
<td>MVD w/ coagulation &amp; sacrifice of SPV</td>
<td>MVD w/ SPV preservation by using transposition &amp; fixation technique</td>
<td>6 (50)</td>
<td>4 (33.3)</td>
<td>NR</td>
<td>11 (91.6)</td>
<td>4.5 yrs†</td>
</tr>
<tr>
<td>Overall no. &amp; pooled proportions (95% CI)</td>
<td></td>
<td>Total</td>
<td>1143</td>
<td>3.82 (0.87–15.17)</td>
<td>3.64 (1.0–12.42)</td>
<td>2.85 (1.21–6.58)</td>
<td>88.90 (84.90–91.94)</td>
<td>4.73 (1.44–14.43)</td>
<td>2.76 (0.54–12.99)</td>
<td>3.32 (1.22–8.77)</td>
<td>86.52 (82.29–89.87)</td>
<td>4.17 (0.61–23.54)</td>
<td>4.99 (1.52–15.13)</td>
</tr>
</tbody>
</table>

FU = follow-up; GPN = glossopharyngeal neuralgia; HFS = hemifacial spasm; NR = not reported; Pt = patient; SPV-P = SPV-preserve; SPV-S = SPV-sacrifice; UK = United Kingdom.

Values are shown as number (%) unless indicated otherwise.

* All included studies were retrospective and observational.
† Mean values are shown.
‡ Median values are shown.
§ Reported 58 patients (39 females and 19 males; mean age 59.4 years) with TN due to isolated venous conflict; of these, 12 SPV-related neuralgia cases were enrolled in the systematic review and meta-analysis.
¶ The pooled proportions show the estimated number of events per 100 patients.
anomalies and/or improper execution of surgery are potential offenders in patients with complications.

Numerous case reports have attributed perioperative complications to SPV resection. However, the territory and resection of SPV cannot explain all these events. Here, we have provided details of some of these events. Peduncular hallucinosis is a dream-like visual hallucination that is presumably due to lesions affecting paramedian reticular formations and the pontine-geniculate-occipital pathway. To date, of the 4 studies that reported transient peduncular hallucinosis after MVD surgery, 3 postulated that SPV resection was the underlying cause. However, in the study by Tsukamoto et al., SPV was avulsed inadvertently, leading to posterior fossa hemorrhage. It seems that subsequent perforating artery vasospasm was the culprit etiology that led to hallucinosis. Interestingly, Miyazawa et al. preserved the SPV, and cerebellar retraction was the underlying cause of peduncular hallucinosis.

Strauss et al. sacrificed the pontotrigeminal affluent of the SPV during MVD of TN. Three days later, the patient sustained contralateral hearing loss due to inferior colliculus congestion attributed to the SPV territory. Although the lateral mesencephalic vein of the inferior colliculus has an anastomosis with the pontotrigeminal vein, it has also other collaterals and predominantly drains into the basal vein. In addition, the collicular plate has a rich venous plexus that mainly drains into galenic vein groups. Such a case is rare (0.08% of patients) and occurs in the setting of venous aberration and/or iatrogenic vessel injury. The most dreadful complication attributed to SPV resection is fatal hemorrhagic infarction. However, Singh et al. reported extensive infarction after SPV avulsion in a case with an underlying anomaly of the right transverse sinus, right sigmoid sinus, and internal jugular vein. Of note, the SPV territory cannot justify the extension of infarction to the supratentorial region, thalamus, and temporal lobe, as reported by Anichini et al. In later studies, most vascular-related complications were edema and sinus thrombosis, and no vascular-related complications occurred in the SPV-sacrificed groups of 2 cohort studies.

It is worth noting that the complications in the SPV-sacrificed cohort included those associated with inadvertent SPV avulsion. SPV avulsion usually occurs owing to overzealous cerebellar retraction leading to torrential hemorrhage. Controlling such hemorrhage is challenging because the venous ends retract within the arachnoid sleeve or dural folds, and repeated attempts to stop bleeding further damage the tissue. However, the chance of complications is lower if the surgeons resect the SPV in a controlled manner.

Cranial nerve injuries constituted the new postoperative neurological deficits in the reviewed studies. Trying to preserve the SPV as much as possible may sound appealing, but doing so is cumbersome and tricky. Although the meta-analysis showed comparable odds of new postoperative neurological deficit, patients with sacrificed SPV had fewer new neurological deficits. When the SPV encroaches into the surgical field of view, it must be either sacrificed or retracted. Apart from retraction-related injuries, continuing the operation despite an inadequate view increases the risk of iatrogenic injury to adjacent structures such as cranial nerves.

Despite advancements in MVD techniques, CSF leak is a concerning postoperative morbidity with a reported rate of 1.5% to 14.5%. The pooled proportion of CSF leaks was 2.85 per 100 patients. Several factors may predispose patients to CSF leak, of which dural and bony closure are the most important, and this meta-analysis showed that the odds of CSF leak were similar with and without SPV sacrifice.

**Neuralgia Relief**

It is unclear whether SPV preservation or sacrifice al-
ters treatment outcomes. Some authors hypothesized that SPV preservation may reduce the success rate due to impeded access.\textsuperscript{17,18} The meta-analysis showed that 89\% of patients achieved neuralgia relief with MVD surgery and further concluded that the likelihood of MVD success is comparable regardless of whether the surgeon sacrifices or preserves the SPV.

Limitations

We acknowledge several limitations. First, we included retrospective cohort studies with moderate risk of bias. However, conducting a prospective randomized trial to compare sacrifice versus preservation of the SPV would be challenging due to ethical underpinnings\textsuperscript{53} and the low proportion of the events would require a relatively large sample size. In this systematic review of 1143 patients, the primary outcome event rate was 0.02 (16/618) in the SPV-sacrificed group and 0.01 (8/525) in the SPV-preserved group. With consideration of the statistical characteristics of this study ($\rho_1 = 0.02$, $\rho_2 = 0.01$, $\alpha = 0.05$, and $\beta = 0.8$), a randomized controlled trial in this setting requires at least 456 randomized patients in each arm (i.e., 912 patients in total). Therefore, the current meta-analysis reached the optimal information size and has sufficient statistical power. Second, these studies did not report the outcomes of MVD stratified on the basis of underlying cranial nerve rhizopathies and intentional versus inadvertent venous sacrifice. Therefore, we were unable to perform a subgroup meta-analysis. Third, we only searched the Medline and PubMed databases and included studies with English text. Fourth, other postoperative outcomes, such as hospital stay, reoperation, and neuralgia recurrence, were not evaluated.

Conclusions

The risks of operation-related morbidities and treatment success rates were not statistically different between patients with and without sacrificed SPV. Most individuals have well-established collaterals and properly tolerate SPV resection. Vascular-related complications are rare and limited to edema and venous thrombosis. Devastating complications can arise due to underlying venous anomalies or improper execution of surgery. SPV sacrifice is as safe as its preservation. We recommend
SPV sacrifice when gentle retraction fails to increase the surgical view and if the surgeon encounters SPV-related neurovascular conflict and/or anticipates impeding SPV-related bleeding.

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Disclosures
Dr. Bettegowda is a consultant for DePuy-Synthes, Bionaut Labs, and Galectin Therapeutics; and is the founder of OrisDx. Dr. Huang owns stock in Longevity.

Author Contributions
Conception and design: Huang, Sattari, Xu, Hung, Bettegowda. Acquisition of data: Huang, Sattari, Shahbandi, Xu, Hung, Bettegowda. Analysis and interpretation of data: all authors. Drafting the article: Huang, Sattari, Shahbandi. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Huang. Statistical analysis: Sattari, Feghali. Study supervision: Huang, Xu, Hung, Bettegowda.

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