1. Introduction

Obstructive sleep apnea (OSA) is a chronic disease affecting almost one billion people worldwide. It is reportedly an independent risk factor for cardiovascular disease and associated with metabolic syndrome and neurodegenerative disease. In the United States, the annual cost associated with untreated OSA was estimated to be $150 billion, with over $6.2 billion spent annually on positive airway pressure and oral appliance (OAT) therapies. Positive airway pressure is the standard of care for moderate to severe OSA, while OAT is recommended for those with mild to moderate OSA or intolerant of positive airway pressure. Patients with mild to moderate OSA tend to be less symptomatic and less tolerant of positive airway pressure.

In patients with moderate-severe OSA, the relative therapeutic effectiveness of positive airway pressure and OAT was found to be similar, due to positive airway pressure being more effective in normalizing the apnea-hypopnea index (AHI) but used less. Conflicting results have been reported when the cost-effectiveness of positive airway pressure versus OAT was modeled. When stratified by OSA severity and then compared to no therapy, the cost-utilities for OAT and positive airway pressure were estimated at $2,984 and $13,698 for United States patients with moderate to severe OSA, and $45,579 and $256,048, respectively, for French patients with mild OSA and low cardiovascular risk.

Over 65% of diagnosed patients have positional-OSA, i.e. the supine AH1 and time sleeping in the supine position contribute to an elevated overall OSA severity. Positional-OSA patients are more likely to have mild-moderate OSA and exhibit a positive treatment response to OAT. Positional-OSA patients can also be efficaciously treated with supine avoidance therapy (SAT), whereby the overall OSA severity is typically reduced to the magnitude measured in the non-supine positions. The new generation of SAT devices, which utilize vibrato-tactile feedback rather than
position restriction to elicit the behavioral response, deliver improved outcomes and compliance in positional-OSA patients.\textsuperscript{16–22} Despite these improvements in SAT technologies, it remains underutilized relative to OAT in positional-OSA patients, despite the fact that SAT and OAT effectiveness and compliance were reportedly similar\textsuperscript{19–21}. The combination of OAT and SAT, which demonstrated superior outcomes compared to either therapy alone, is also underutilized\textsuperscript{22}.

This report expands upon our efforts to establish an empirically-based cost-containment protocol for therapy selection in patients intolerant of positive airway pressure. Previously, we demonstrated that the OAT could be optimized by the use of a trial oral appliance to rule out patients who would likely exhibit a poor treatment response to a custom-fabricated oral appliance\textsuperscript{23}. In this study, we investigate the potential impact on both costs and patient care from the introduction of SAT into the protocol, used either instead of, or in combination with, OAT.

2. Methods

2.1. Subjects

This retrospective analysis included 170 patients diagnosed with OSA and who either failed or refused positive airway pressure after approval from the BioMed Institutional Review Board (San Diego, CA). Consecutive cases from May 2018 to October 2019, with a diagnostic AHI $\geq$ 5 event/h, and third-party payer-designated participation in a pilot cost-containment protocol were selected. Patients were first referred for oral appliance trial, and those who responded to the oral appliance were then authorized reimbursement for a custom oral appliance.

2.2. Description of OAT

The OAT data were derived using the Apnea Guard (Advanced Brain Monitoring, Carlsbad, CA), trial appliance, designed for up to 30-nights of use and available in three sizes. The “low” provides 5.5 mm anterior and posterior interocclusal distance, the “medium” 6.5 mm anterior and 5.5 mm posterior, and the “high” 8.0 mm and 6.5 mm, respectively. Sizes were selected based on a combination of sex and the degree of tongue scallop. Women with non-scalloped tongues were fitted with size low, and men with non-scalloped tongues were fitted with size “medium,” and men with scalloped tongues were fitted with size “high.” Tongue scalloping was based on the degree of tooth-markings on the lateral borders of the tongue using a technique similar to obtaining a Mallampati score. Protrusion was set to 70% of the distance from a “neutral” centric occlusion to maximum protrusion with the appliance in situ. The relative effectiveness of the Apnea Guard and custom oral appliances has been previously studied and shown to be equivalent\textsuperscript{23,24}.

2.3. Data acquisition and analysis

Two-night home sleep apnea studies were performed: a no-treatment baseline on Night 1 and OAT on Night 2, with hypopneas requiring a 3% oxyhemoglobin desaturation. For this study, the OAT responder criteria required at least a 50% reduction in overall AHI, or a post-treatment AHI $\geq$ 10 events/h with a post-treatment AHI $< 10$ events/h\textsuperscript{25}. The OAT percent AHI reduction was derived from the diagnostic or baseline study based on the greater overall severity. At least 20-minutes of supine and non-supine time was required to report positional AHI values and to determine positional-OSA. Positional-OSA were characterized when the overall non-supine AHI ratio was $\geq 1.4$\textsuperscript{13}. Patients with less than 20-minutes non-supine (supine) time were labeled supine (non-supine) dominant. The overall benefit of SAT was estimated using the positional AHI data from: (a) the same diagnostic or baseline study applied to the OAT analysis, and (b) the Night 2 OAT results. Two-tailed Mann-Whitney U and Chi-squared with Fisher Exact probability tests were used to compare conditions across continuous and ordinal data, respectively.

2.4. Cost Comparison analyses

Ten-year cost-comparison analyses were applied under the assumption that both OAT and SAT had a 5-year useful life and equivalent long-term compliance\textsuperscript{19,20}. Medical insurance reimbursement for OAT in the United States ranges from $2,000 to $2,500. The price for a vibro-tactile SAT feedback device that monitors user compliance currently costs $400 but could increase to $700 under conditions of medical insurance reimbursement, i.e. provided by a homecare company with confirmation of 90-day usability compliance. An optional mattress topper and side-sleeper pillow costing $200 could be added to the SAT total cost to reduce the likelihood of shoulder and/or neck pain. Given 70% of positional-OSA patients remained positional after an average of 6.6 years, this study assumed that 60% of those treated with SAT for years-1 through –5 would remain positional-OSA through year-10\textsuperscript{26}, while the balance would increase in severity and require the combination of OAT and SAT for years-6 through –10.

Differences in all-cause mortality, extracted from the Wisconsin Sleep Cohort 18-year follow-up study, were used to estimate the life-years-gained (LYG) attributed to different therapeutic outcomes (see Table 1)\textsuperscript{27}. The LYG calculations for each time point were based on the difference in mortality multiplied by one-half of the time since diagnosis. For

| Table 1. Mortality rates and life years gained (LYG) associated with untreated OSA across time. |
|---------------------------------------------------------------|
| Untreated OSA severity | Year-5 | Year-10 | Year-15 | Year-18 |
|------------------------|--------|--------|--------|--------|
| Mortality rates (%) in years subsequent to OSA diagnosis     |        |        |        |        |
| Normal                 | 1.3    | 2.2    | 4.3    | 6.3    |
| Mild                   | 1.3    | 4.3    | 6.2    | 10.5   |
| Moderate               | 1.9    | 3.5    | 6.2    | 17.0   |
| Severe                 | 6.8    | 20.0   | 32.7   | 44.0   |
| LYG resulting from OSA severity category changes             |        |        |        |        |
| Mild to normal        | 0.000  | 0.105  | 0.143  | 0.378  |
| Moderate to normal    | 0.015  | 0.065  | 0.143  | 0.963  |
| Moderate to mild      | 0.015  | –0.040 | 0.000  | 0.585  |
| Severe to mild        | 0.138  | 0.785  | 1.988  | 3.015  |
| Severe to moderate    | 0.123  | 0.825  | 1.988  | 2.430  |

Abbreviation. OSA, obstructive sleep apnea.
example, the LYG at 10-years between the normal range and mild OSA was 0.105 based on the difference in mortality rates (4.3% versus 2.2%) multiplied by 5 (10-year mid-point).

Given the limited information available on long-term OAT and SAT compliance and associated post-treatment changes in OSA severity, the cost-effectiveness of OAT versus SAT was made at the 10-year point. The LYG at 10-years between mild OSA to normal (i.e. 0.105) was used to compute the incremental cost-effectiveness ratio (ICER) when the post-OAT overall AHI was $\geq 5$ and the non-supine AHI was $< 5$.

The cost-benefit associated with combination therapy was applied to patients with a post-OAT AHI $\geq 10$ events/h with positional-OSA. Given OSA is a chronic disease and reduced severity is associated with improved long-term survivability, the ICER analyses for combination therapy at year-10 were based on LYG estimates derived from mortality rates at year-18, and then discounted by 70% and 85%. For the sensitivity assessment, ICERs were computed for cases in which combination therapy might normalize the OSA severity, or potentially shift the AHI to a less severe OSA category.

### 3. Results

#### 3.1. Stratification and outcome analyses

Fifty-nine percent of the patients met the OAT responder criteria. Responders were characterized by significantly lower non-supine AHI values, with proportionally fewer cases with severe OSA and more cases with positional-OSA (Table 2). A greater proportion of non-responders had post-OAT overall AHI $\geq 10$ events/h with residual positional-OSA. OAT did not resolve the significantly greater overall and supine AHI values observed in men when compared to women.

Twenty-one percent of the patients (35/170) had pre-treatment positional-OSA with non-supine OSA severity in the normal range. These cases were equally distributed among OAT responders and non-responders and trended toward a greater percentage among women relative to men.

The AHI severity was reduced by an average of $48 \pm 42\%$ with OAT versus a potential AHI reduction of $81 \pm 16\%$ with SAT ($p < .0001$).

Due to pre-treatment supine dominant sleep, the benefit of SAT could not be estimated in 19% of the cohort, with 15% having pre-treatment moderate or severe OSA.

#### 3.2. Combination Therapy analyses

Patients who responded to OAT were less likely to have a post-treatment AHI $\geq 10$ events/h with residual positional-OSA (10% versus 23%, $p < .05$). Across the 10 responders and 16 non-responders, the AHI values were reduced by $26 \pm 44\%$ with OAT versus $70 \pm 21\%$ if OAT and SAT were combined ($p < .00001$). Figure 1 presents the AHI distributions across three conditions stratified by OAT response. If combination therapy had been utilized, the AHI severity might be further optimized in both responders ($p < .00005$) and non-responders ($p < .005$), and the significant post-OAT AHI differences between responders and non-responders eliminated ($p < .002$).

![Figure 1. AHI distributions (mean ± SE) in responders and non-responders with post-OAT AHI ≥10 events/h with residual positional-OSA.](image)

### Table 2. Demographic and OSA severity characteristics for 170 patients stratified by OA response and sex.

|                          | Responders | Non-responders | $p$  | Men     | Women    | $p$  |
|--------------------------|------------|----------------|------|---------|----------|------|
| Patients, % (n)          | 58.8 (100) | 41.2 (70)      |      | 59.4 (101) | 40.6 (69) |      |
| Age, years               | 53.7 ± 13.2| 54.9 ± 13.6    | ns   | 52.0 ± 13.0 | 57.3 ± 13.3 | .008 |
| BMI, kg/m²               | 29.3 ± 5.4 | 31.3 ± 7.2     |      | 29.7 ± 4.9 | 30.8 ± 7.7 | ns   |
| Pre-treatment            |            |                |      |          |          |      |
| AHI – Overall, mean ± SD | 23.7 ± 13.8| 27.9 ± 18.2    | ns   | 28.7 ± 17.3 | 20.6 ± 11.9 | .0005|
| – Supine                 | 33.4 ± 20.8| 36.3 ± 23.7    | ns   | 39.6 ± 23.9 | 27.5 ± 16.8 | .0006|
| – Non-supine             | 13.2 ± 12.7| 20.7 ± 19.6    | .034 | 18.7 ± 17.6 | 12.4 ± 13.1 | .017 |
| OSA – Mild, % (n)        | 28.0 (28)  | 22.9 (16)      | ns   | 20.8 (21)  | 33.3 (23)  | .076 |
| – Moderate               | 50.0 (50)  | 40.0 (28)      | ns   | 44.6 (45)  | 47.8 (33)  | ns   |
| – Severe                 | 22.0 (22)  | 37.1 (26)      | .038 | 34.7 (35)  | 18.8 (13)  | .037 |
| Non-sup dominant, % (n)  | 5.0 (5)    | 4.3 (3)        | ns   | 5.9 (6)    | 2.9 (2)    | ns   |
| Supine dominant          | 20.0 (20)  | 18.6 (13)      | ns   | 14.9 (15)  | 26.1 (18)  | .078 |
| Positional-OSA           | 58.0 (58)  | 37.1 (26)      | .008 | 47.5 (48)  | 52.2 (36)  | ns   |
| Positional-OSA with non-sup < 5 | 20.0 (20) | 20.0 (14) | ns   | 15.8 (16)  | 26.1 (18)  | .119 |

Abbreviations. OSA, obstructive sleep apnea; AHI, apnea-hypopnea indexes.
Twenty-nine patients (17%) slept exclusively supine (i.e. supine dominant) while undergoing OAT. Of these, 11 had a post-treatment AHI ≥10 and <30 events/h.

### 3.3. Cost Comparison analyses

The first cost comparison analysis included the 129 patients who were neither supine nor non-supine dominant prior to treatment. For each patient treated with OAT, the 10-year cost for delivery of the two appliances would range from $4,000 to $5,500. The average cost for SAT over the same period would range from $2,000 to $2,800 based on the provision of two position therapy devices, plus delivery of OAT to 40% of the patients assumed to have increased OSA severity after year-5. In the 18 cases when post-OAT and pre-treatment non-supine AHI values were in the normal range, the ICER associated with SAT ranged from -2,000 to $2,200, i.e. the difference in cost of the two therapies. In the 17 cases when the post-OAT AHI was outside the normal range and the pre-treatment non-supine AHI was normal, the ICER for SAT instead of OAT ranged from $19,048 to $20,952 based on the differences in cost divided by the year-10 LYG corresponding to the shift from mild OSA to normal (i.e. LYG = 0.105).

The next cost comparison analysis was applied to the 102 patients with at least mild non-supine AHI values and neither OAT supine nor non-supine dominant. Of these, 26 had a post-OAT overall AHI ≥10 events/h with residual positional-OSA. If combination therapy was provided to these patients, a further AHI reduction of 68±21% could be achieved. In 9 of these cases, the post-OAT non-supine AHI was in the normal range. Thus, the addition cost for SAT as an adjuvant to OAT through year-10 (i.e. $1,200 or $1,800) would result in ICERs ranging from $10,582 to $15,873, depending on a 30% or 85% LYG discount (see Table 3). In six cases, the shift from moderate to mild OSA severity attributed to the addition of SAT was associated with a mean AHI reduction of 50±11%, and ICER values ranging from $6,838 to $20,513. In six additional cases, the combination of OAT and SAT could shift the OSA from severe to moderate, resulting in a mean AHI reduction of 54±9% and ICERs ranging from $1,646 to $4,938. In the remaining five cases, combination therapy could reduce the mean AHI values by 36±8% compared to OAT alone, with ICER values ranging from $6,838 to $20,513 based on the assumption that those with mild overall OSA and moderate/severe supine AHI values would avoid night-to-night variability in supine sleep time that could elevate the overall OSA severity into the moderate category.

### 4. Discussion

To our knowledge, this is the first study to investigate the cost-benefit of SAT. We identified 36% of patients diagnosed with OSA as potential beneficiaries of SAT, either as a first-line therapy or in combination with OAT. SAT should be the first treatment choice in the 21% of cases with pre-treatment non-supine AHI values in the normal range, given negative ICERs associated with SAT being both more effective and less expensive than OAT in this group. The ICER estimates also advocated for the use of SAT as an adjuvant to OAT in the 15% of cases with a post-OAT AHI ≥10 events/h with residual positional-OSA. While the consideration of health in monetary terms can be controversial, cost-effectiveness analysis is an important tool that can be used by both clinicians and third parties to evaluate the allocation of resources between different therapy options. The ICERs from this study, supporting increased utilization of SAT, were below the $50,000 threshold typically used by United States third-party payers when considering reimbursement for a new therapy.

The objective of this study was to provide empirical evidence to support the inclusion of SAT into our cost-containment protocol. Given the sample size was relatively small, and by selecting those applications of SAT that were clearly dominant, we limited the cost-benefit analysis to a deterministic approach with sensitivity analyses based on cost and the potential impact of improved therapeutic outcomes on survivability. Additionally, this study limited its estimation of LYG to the Young et al. stratification of OSA severity and 18-year all-cause mortality. The LYG associated with the shift from mild OSA to normal at year-10 (i.e. 0.105) was very similar to the LYG resulting from the OSA severity shift at 18-year and then discounted by 70% (i.e. 0.378 × 30% = 0.113), suggesting the ICERs × 30% provided a reasonable estimate of the long-term cost-benefit of SAT as an alternative to, or in combination with, OAT.

The SAT selection criteria developed in this study ensured that patients satisfied one set of conditions but not both i.e. either SAT instead of OAT when the pre-treatment non-supine AHI < 5, or the combination of the two therapies when the post-OAT AHI ≥10 event/h with residual positional-OSA. It should also be noted that potential benefit of
SAT may have been underestimated by the fact that 19% of the cohort were supine dominant at baseline and 17% while undergoing the OAT trial. Given as many as 15% of these patients had moderate or severe OSA and the ICERS associated with a shift from severe or moderate into lower OSA severity categories were compelling, further investigation into the benefit of a SAT trial in patients who sleep exclusively supine is warranted.

While this investigation highlights the potential impact of SAT as an alternative to or in combination with OAT, the generalizability of these findings are dependent on a number of factors. The percentage of patients who might benefit from SAT as the first treatment choice might vary in a population with different age, sex, BMI, and/or OSA severity distributions. These results, however, were markedly similar to findings observed in other cohorts. For example, the percentage of positional-OSA patients with a non-supine AHI events/h in the normal range in our cohort was equivalent to a recent study of 6,437 patients. Women had lower pre-treatment overall, supine, and non-supine AHI values compared to men, and by-sex differences remained post-OAT. Pre-treatment positional-OSA was observed in over twice as many OAT responders as non-responders, and a greater proportion of OAT non-responders had overall AHIs in the severe range accompanied by significantly greater non-supine AHI values.

The results from this study reinforce the fact that SAT is underutilized, given one-fifth of the OSA patients with non-supine AHIs in the normal range had to fail positive airway pressure therapy before an alternative was considered. The proportion of patient who might benefit from combination therapy is dependent on OAT outcomes and influenced by the dentist’s choice of custom appliance functional settings, i.e. jaw-forward protrusion, vertical dimension of occlusion, and/or control of vertical mouth opening. For example, based on the trial oral appliance used in this study, 15% of patients were observed with a post-OAT AHI ≥10 events/h with residual positional-OSA. In contrast, 63% of the 84 patients from this cohort had a post-OAT AHI ≥10 event/h with residual positional-OSA when fitted with a custom oral appliance according to conventional dental protocols. While it is possible to improve custom OAT outcomes with repetitive home sleep apnea studies or polysomnographic titration studies to help optimize the functional settings, the direct and indirect costs of office visits and titration studies would increase the total cost of OAT and/or exceed the incremental cost needed to add SAT.

Pre-treatment non-supine AHI event/h were used to predict the benefit of SAT in this study. This assertion was based on our prior observation of a slight bias toward increased pre-treatment non-supine AHI values versus the overall AHI values measured after four-weeks of SAT. To minimize outcome bias resulting from night-to-night variability in OSA severity, the diagnostic or baseline home sleep study with the greater overall AHI value was utilized, and supine and non-supine AHI values were based on at least 20-min of sleep time. Post-hoc analysis of differences in the diagnostic versus baseline non-supine AHI values suggest the proportion of patients expected to benefit from SAT as a first-line therapy in this study was slightly under-estimated. Conversely, the cost-benefit of SAT may have been overestimated given its long-term compliance is not as well studied as that of OAT.

One limitation of this study is that it relied on the AHI as its key outcome measure, despite the criticism that the AHI does not capture all of the relevant clinical features of OSA. Many OSA cost-effectiveness models also include Epworth Sleepiness Scores (ESS) as a surrogate for the likelihood of a motor vehicle accidents. In this study, ESS were incorporated into the all-cause mortality estimates of the Wisconsin cohort, given 35% of their women and 23% of their men diagnosed with OSA, and 18% of their women and 7% of their men in the normal range, reported excessive daytime sleepiness in 2 or more days per week. Further, two cross-over studies of mild-moderate OSA patients found limited differences in the mean ESS reductions resulting from OAT versus SAT.

This study did not include snoring as a criterion for determining OAT versus SAT cost-effectiveness. That is because snoring, in the absence of apneas and hypopneas, is not a recognized medical condition covered by insurance reimbursement in the United States. Although SAT has been reported to reduce loud snoring in supine dependent non-apneic and apneic patients, there is some likelihood that snoring will remain bothersome to the bed partner. The proposed therapy selection criteria assumes lower cost alternatives to a custom oral appliance would be considered for non-apneic snoring.

In addition to cost-effectiveness, there are a number of clinical considerations that impact OSA therapy recommendations. For example, patients require appropriate dentition for OAT (i.e. at least eight teeth in the upper and lower arch). With SAT, long-term compliance may be limited if patients are not counselled as to mattress and pillow choices that minimize side effects from non-supine sleep.

One of the advantages of vibrotactile SAT is, like positive airway pressure, patients can undergo a trial to determine their willingness to use SAT, based on objective monitoring of utilization/compliance.

In conclusion, the prevalence of OSA necessitates a careful economic analysis of the proper therapy to preserve healthcare resources. Given OSA is phenotypically a diverse disease, this study identified conditions under which SAT is justified as a first-line therapy or for use in combination with OAT in patients with positional-OSA. Given the ongoing and long-term struggle to provide therapeutic options for the treatment of OSA, the selective use of OAT and SAT should be considered in an effort to improve outcomes. The potential economic benefit resulting from adoption of these therapy selection criteria was compelling.

Transparency

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Declaration of financial/other relationships

DL, PW, and RO are shareholders in Advanced Brain Monitoring, Inc. and would benefit financially if the Apnea Guard-Trial oral appliance or the Night Shift-Sleep Positioner was to be sold to a third party. ES is Medical Director of Pronosmus Sleep Technologies and has no conflicts for this study. The other authors had no conflicts of interest.

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Author contributions

DL and BB designed the study. DL and RO performed that statistical analyses. All authors were involved in the interpretation of the results and preparation of the manuscript.

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Previous presentations

None.

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