Let's Put the S*leep* – Back into *Sleep* Medicine

EXECUTIVE SUMMARY

"I didn't feel that I was sleeping better (with CPAP), it didn't seem to work for me."
RC (age 71), with moderate OSA and still looking for answers to his sleep problems.

His story is all too common. He tried CPAP but, in the end, it did not improve his sleep and it was not worth the trouble. Another CPAP machine collecting dust, wasted healthcare resources, and wasted dollars. This is an all-too-common problem wIth CPAP non-adherence mired at 34% with no real change over the past 20 years (Rotenberg et al., 2016). Some of you may be thinking – we know the apnea hypopnea index is flawed, we need a better way to diagnose sleep apnea, and everything will be better. But are we asking the right question, shouldn't we be asking **"How do we help people with OSA sleep better?"**

The Problem

"If something (e.g., a process, an outcome) cannot be measured, it cannot be improved."
(Blumenthal & McGinnis, 2015)

Polysomnography generates a tremendous amount of information but gives us relatively few results beyond AHI, sleep stages, and arousals. We have been scoring sleep for over 40 years, but we still do not have a way to reliably assess sleep quality and the impact on daytime functioning. Like AHI, the AASM scoring manual still classifies sleep into 5 bins (Berry et al., 2020) and does not recognize an estimate of sleep depth, does not recognize that stage N2 is highly variable in sleep depth, and there is considerable interscorer variability in sleep staging especially for stages N1 and N3. There are also EEG characteristics such as sleep spindles that do not correlate with sleep depth but are instead used to arbitrarily define NREM stage 2 sleep. Furthermore, sleep staging was based on 30-second epochs to accommodate paper polysomnograms and ink speed in a non-digital world. We have continued to categorize sleep largely in the same way for the past 40 years with somewhat different sensors but, by and large, the same signals and the same approach. This simply isn't good enough and we CAN do better.

Home sleep apnea testing (HSAT) devices do not use EEG, but there are ongoing efforts to utilize artificial intelligence to determine surrogates of total sleep time, arousals, and the amount of REM sleep through changes in ventilation, sympathetic tone, heart rate, and movement. Improvements in this technology may reduce some of the unique advantages of PSG. New approaches are needed to add value to PSG and to improve the utility of home sleep testing with limited EEG channels. If PSG is to survive compared to HSAT, we must add more value to the data we obtain by PSG.

Sleep disruption, resulting in impaired daytime functioning, is one of the main cited consequences of OSA. Yet, many patients with severe OSA either do not complain of non-restorative sleep, or do not experience any benefit in daytime functioning when placed on CPAP (See patient stories from video). Is it then worth asking whether the effect of OSA on sleep quality might have been exaggerated? For example, we do not know the impact of cortical arousals on the overall restorative function of sleep *in a given individual*, and, based on recent studies, there are reasons to believe that in some individuals

relatively few arousals can seriously degrade overall sleep quality while in others many more arousals can have little effect on sleep quality. We need to be able to identify individuals whose sleep is impacted by OSA and, by extension, their sleep is expected to improve when OSA is treated. Many patients without comorbidities or pronounced desaturations could be spared the CPAP experience. We can measure AHI improvement, but the real question is how has a patient's sleep quality changed? We need to accurately determine differences in sleep quality both on and off CPAP to determine how much the patient's sleep is actually benefiting. Further, maybe adherence to CPAP is so low because treating the AHI doesn't always improve sleep quality (See patient stories)?

Our Solution

The Metric

Introducing the odds ratio product (ORP): ORP is a continuous measure of sleep depth calculated from the EEG using fast-Fourier transform (FFT). ORP is measured in 3-second epochs, making it possible to track changes in sleep depth on a more fine-grained time scale. It can be measured in real time, making it possible to adjust CPAP pressure to normalize sleep.

We studied 184 severe OSA patients (57±30 AHI) who underwent split-night studies. We phenotyped patients into 4 types based on their pattern of ORP deciles (see ORP-based sleep architecture section). We hypothesized that different phenotype patterns of ORP-based decile patterns would predict improvement of sleep on CPAP. We found that Type 1, in whom most epochs were in the light/transitional sleep deciles during the diagnostic study, had a large improvement in ORP on CPAP. Type 2 phenotypes, who had a similar histogram pattern as Type 1 but with normal representation in decile 10 (i.e., full wakefulness), also showed large improvement in ORP. In Type 3 phenotypes, with excessive amounts of full wakefulness and no epochs in decile 1 (i.e., very deep sleep), suggesting hyperarousal, ORP during sleep improved but they were still left with excessive amounts of full wakefulness, and sleep efficiency remained very low (67%). Type 4 phenotypes had essentially a normal ORP sleep architecture before CPAP and showed no improvement on CPAP while sleep efficiency actually decreased.

While research continues and publication of this work is forthcoming, the fact that the type 3 and 4 phenotypes exhibited little improvement while on CPAP, demonstrates the ability of ORP to determine potential scenarios where CPAP therapy will likely not be effective. Further, it is the belief of our team, and the subject of planned research, that sleep improvement on CPAP is a fundamental driver of adherence and potential outcomes associated with CPAP therapy.

The Modality

The COVID-19 pandemic led to sleep laboratory closures and an increase in HSAT. The ability of HSAT to determine AHI in the home and at a lower cost, drove many jurisdictions to rapidly adopt HSAT for OSA diagnosis. Canada is a prime example, where outside of Ontario (where HSAT is not allowed), HSAT accounts for 80 - 90% of sleep tests conducted (**Source**: Cerebra industry analysis). The problem though is HSAT devices are designed to measure AHI and not sleep quality. This is why at-home polysomnography using Level 2 sleep studies is the answer. Furthermore, with metrics such as ORP, the information is leveraged and actionable to help understand sleep quality and help diagnose and treat sleep disorders. There are currently three companies developing at-home self-applied PSG devices, the technology is available now.

Reimbursement and the Future of Sleep Medicine

Putting the *sleep* - back into *sleep* medicine is more than just a catch phrase. The field of sleep medicine is dominated by the diagnosis of OSA, increasing through HSAT and treated with the gold standard CPAP therapy. Accordingly, reimbursement is declining as payers streamline costs around a disease and therapy with high non-adherence and recent challenges to the overall effect of CPAP therapy and OSA itself on all cause morbidity.

The missing link is sleep. We now have the metric and modality to scale our ability to diagnose a patient's sleep, not just the airway. More importantly, Level 2 studies are immediately scalable even accounting for greater accuracy in AHI allowing for immediate adoption. In fact, a Level 2 at-home PSG test was the lowest cost option for payers than an in-lab PSG and a Level 3 sleep test for any suspected OSA pre-test probabilities (See Figure 8).

Furthermore, it has the potential to provide higher reimbursement. The use of ORP-based sleep architecture and OSA phenotyping opens up a path to even higher reimbursement, with a well-defined program of clinical evidence building, health technology assessments and inclusion in AASM guidelines. Ultimately, objective measurement of sleep will open up additional areas for advancement in sleep medicine as linkages to other chronic diseases and daytime functioning are validated.

Together, these innovations will ***put the sleep back into sleep medicine***, dramatically changing the course of sleep medicine to the benefit of patients, providers, and payers.

SITUATION ANALYSIS

Background

OSA today is almost exclusively diagnosed based on the apnea hypopnea index (AHI) as recommended by the AASM (Berry et al., 2012). Traditionally, AHI was produced as a part of a polysomnogram (PSG) conducted during an overnight stay in a sleep lab. In 2007, the AASM approved the use of unattended portable monitoring home sleep apnea testing (HSAT) as a screening tool to estimate AHI in patients with a high pretest probability of moderate to severe OSA with no significant comorbid medical conditions (Collop et al., 2007).

Recent trends

1) Shift to Home Sleep Apnea Testing (HSAT)

   AHI has become the predominant, single metric of OSA diagnosis. Many jurisdictions have rapidly adopted HSAT to determine the AHI because of the lower cost. Canada is a prime example, where outside of Ontario, HSAT accounts for 80- 90% of sleep tests conducted (**Source**: Cerebra industry analysis).

   Prior to Covid-19, HSAT adoption in the United States had been mixed across regions and Level 1, in-lab PSGs accounted for 70% of sleep tests conducted. With Covid-19, this ratio reversed due to broad-scale lab closures and HSAT quickly grew to account for 70% of sleep diagnostics (EnsoData, 2021).

2) Poor Adherence is Driving Payer Policies

   Continuous Positive Airway Pressure (CPAP) is the gold standard for OSA treatment. Adherence is a major barrier to CPAP use and studies have shown the non-adherence to CPAP has remained at 34.1% since the late 90s (Rotenberg et al., 2016).

   To control costs, most payers require durable medical equipment (DME) suppliers to rent CPAP devices where coverage is dependent on compliance. As a further action, many providers have implemented pre-approval requirements for Level 1 PSG testing and are actively shifting the reimbursement market towards HSAT to reduce costs.

   This “diagnostic reductionism” represents a challenge to sleep medicine providers as profitability is driven by Level 1, in-lab testing. HSAT requires far less expertise to review and reimbursement reflects this, challenging margins for providers.

3) Clinical Benefit of CPAP Challenged

   A draft technology assessment from the Agency for Healthcare Research and Quality (AHRQ) has cast doubt on the long-term clinical benefit for the gold standard treatment for sleep apnea.

Reviewers found that CPAP studies have consistently failed to show improvements in non-sleep-related outcomes linked to OSA, such as stroke, heart attack, diabetes, and depression (MEDPAGE, 2021).

It is unclear the impact this will have on Payer policies, however this provides further ammunition to drive down expenditures on OSA diagnosis and CPAP therapy.

SWOT ANALYSIS - Current state of OSA diagnosis and therapy

Figure 1: SWOT analysis for OSA diagnosis and therapy.

PROBLEM STATEMENT

We know ongoing sleep deficiency is linked to a host of negative health outcomes including increased risk of heart disease, kidney disease, high blood pressure, diabetes, and stroke (Gottlieb et al., 2010; Punjabi et al., 2004). Yet assessing sleep quality itself is not a part of our diagnostic protocols. HSAT doesn't even measure sleep at all.

"If something (e.g., a process, an outcome) cannot be measured, it cannot be improved."
(Blumenthal & McGinnis, 2015)

The issues we've outlined - declining reimbursement, stagnant CPAP adherence, questions raised regarding the effectiveness of CPAP therapy are all symptoms of a broader issue in sleep medicine today

- the fact we haven't been able to objectively measure sleep quality. We haven't been able to do this in a lab with the wealth of PSG data available and we certainly can't do it in the home. Yet the concept of sleep quality as a core part of sleep disorder diagnostics is not a new concept.

"Severity of sleepiness was included in the 1999 AASM recommendations for classifying OSA severity, although in the absence of a reproducible standard for assessing sleepiness, this severity metric was not retained in subsequent recommendations." (Malholtra, 2021 - Beyond AHI paper).

We now have the technology to change this.
It's time we put the *sleep* back into *sleep* medicine.

If PSG is to survive compared to home sleep apnea testing, we must add more value to the data we obtain by PSG. In particular, we need to accurately determine differences in sleep quality off and on CPAP to determine how much the patient's sleep is benefitting.

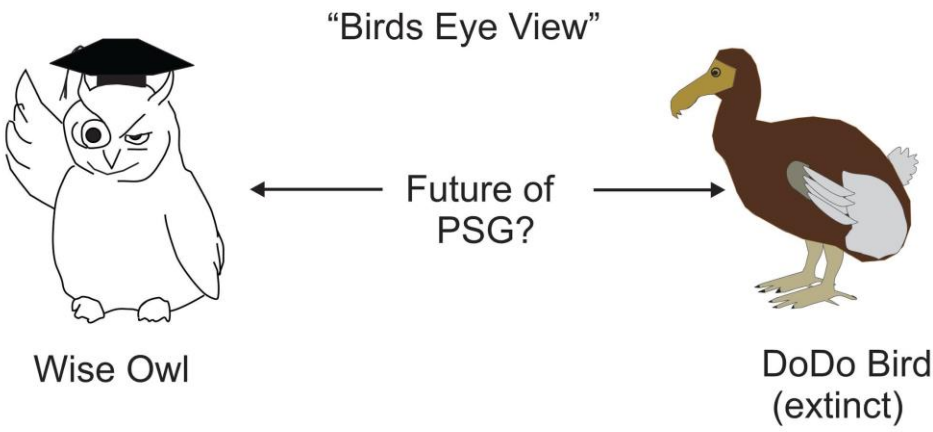

Figure 2: On the left, PSG changes like a wise old owl. On the right, PSG remains the same and faces extinction.

SOLUTION FRAMEWORK – THE METRIC

ODDS RATIO PRODUCT-BASED SLEEP ARCHITECTURE

Shortcomings of Conventional Measures of Sleep Quality:
Sleep quality is conventionally assessed by sleep efficiency (SE), percent of time in stages N1 (%N1) and N3 (%N3), and the arousal/awakening index (AI). There are several shortcomings to the use of these indices to evaluate sleep quality (See Appendix A for full description):

1) SE is not a measure of sleep quality;

2) %N1 mirrors the arousal index and has no additional significance;

3) Scorer inter-rater variability;

4) Conventional approaches for defining the three NREM stages are not based on features that reflect sleep depth;

5) Not all arousals have the same effect on sleep depth (Azarbarzin et al., 2014);

6) The conventional indices do not always change in the same direction in response to CPAP.

Odds ratio product (ORP; See Appendix B for detailed methodology) circumvents all the shortcomings of conventional indices. It is a continuous measure of sleep depth calculated from the EEG using a FFT in 3-second epochs. Unlike the stepwise stages of conventional scoring, it is a continuous metric from full wakefulness (ORP>2.25) to very deep sleep (ORP near zero). This makes it possible to detect changes in sleep depth within the same conventional stage and during wakefulness (See Figure 3). It is also measured in 3-second epochs (Younes et al 2015), making it possible to track changes in sleep depth on a very reduced time scale.

ORP correlates well with the visual appearance of the EEG (Younes et al., 2015, See Figure 3). It changes in the appropriate direction following sleep deprivation (Kuna et al., 2018), sleep restriction (Younes et al., 2020), and across the night (Qanash et al., 2017). ORP also responds dynamically to transient noise stimuli (Smith et al., 2019). Most importantly, the linear correlation between ORP at any given moment and likelihood of a spontaneous arousal occurring within the next 30 seconds was almost perfect (r^2 = 0.98) (Younes et al., 2020, Younes et al., 2015).

If ORP is the missing measure of sleep quality, the question remains – how can it be put into clinical practice? Dr. Magdy Younes, inventor of the ORP has recently developed a simple decile-based view of ORP results that can be useful to profile the sleep pattern of patients. This ORP-based sleep architecture approach provides an easy to use, visual representation of a patient's sleep and consists of dividing the entire ORP range into deciles, 0.25 each, and reporting the % of all 30-second epochs having ORP in each decile (Figure 3, bottom left). The distribution of epochs among the ORP deciles is then used to infer the impact of OSA on sleep depth and whether the patient’s sleep drive is low, normal, or high.

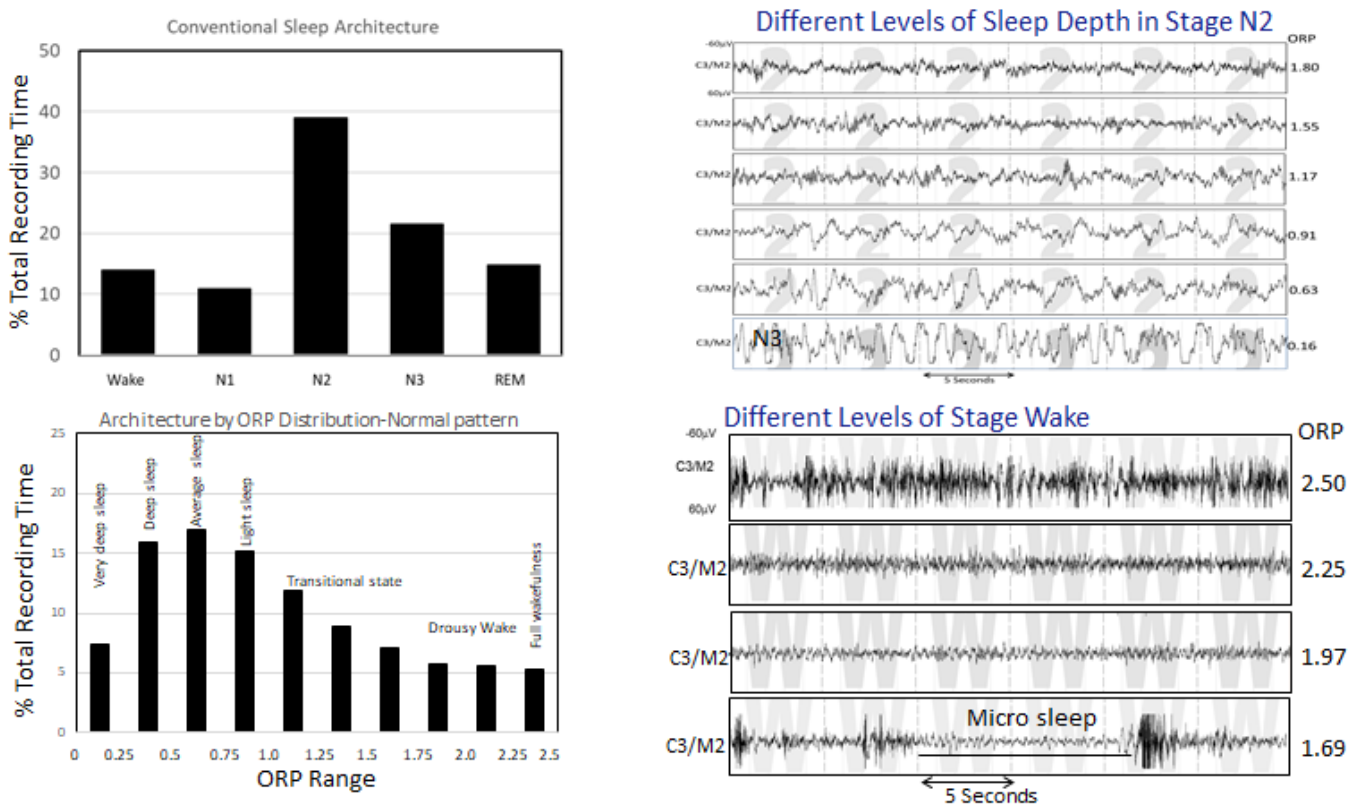

Figure 3 (See Appendix F for high resolution figures): Contrasting ORP-based sleep architecture with conventional sleep architecture. The top right panel shows five epochs scored as stage N2 and a sixth epoch scored as N3. As sleep gets deeper (top to bottom) it is reflected in the ORP values. The bottom right panel shows 4 epochs scored as wake which shows a similar phenomenon. The top left panel shows conventional sleep architecture while the bottom left panel is the proposed ORP-based architecture with 10 deciles (i.e., very deep to transitional state to full wakefulness).

Normal Healthy Sleepers

The first step to developing the ORP-based sleep architecture approach was to define the normal patterns in different demographics and the influence of common sleep disorders on this architecture. To this end, we analyzed sleep records from the Sleep Heart Health Study (SHHS1; n=>5,000; Quan et al., 1997) and from a previously published study on the effect of sleep deprivation in twins (Kuna et al., 2012). ORP-based sleep architecture was established for normal healthy sleepers based on different age groups, gender, and before and after sleep deprivation (See Appendix C, Figure C1).

OSA

The next step was to define ORP-based decile patterns in patients with different levels of OSA severity. Surprisingly, there was little of an effect on ORP-based sleep architecture in mild to moderate OSA compared to “No Disease” (See Figure 4, A-C). It wasn’t until OSA was severe (See Figure 4, D-E), when we saw differences in the deciles compared to “No Disease” subjects.

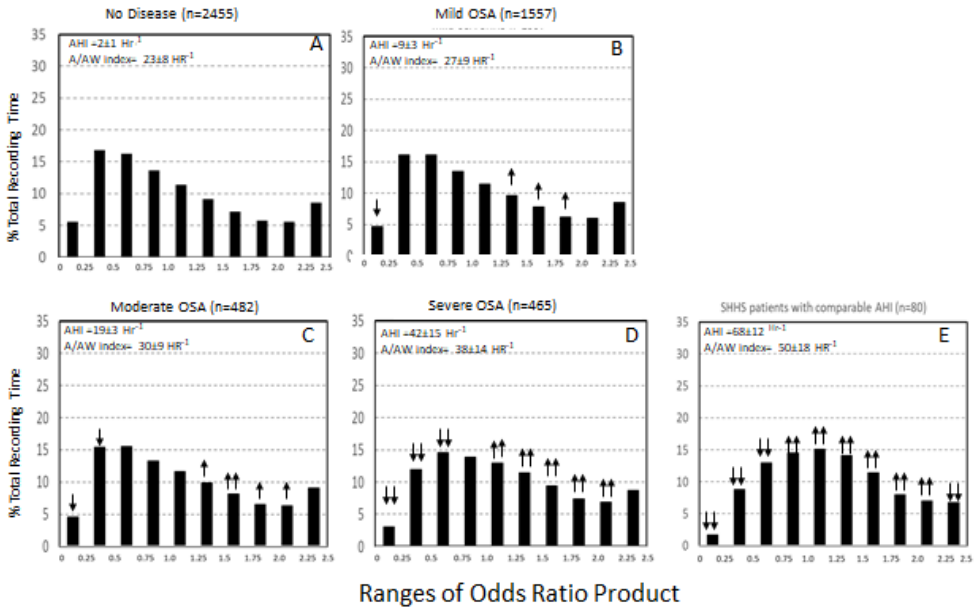

Figure 4 (See Appendix F for high resolution figures): ORP-based sleep architecture in SHHS subjects with no identified sleep disorder (A) and with OSA of different severity (A-E). Panel E is from a subgroup of subjects in the severe OSA group (D) with an AHI >60/hr. The up arrows indicate significantly higher than the "No Disease" group, and vice versa. One arrow indicates p<1E-5. Two arrows denote p <1E-10. Note that the changes from "No Disease'', while highly significant, are barely noticeable in the mild and moderate OSA groups. For both severe (D) and very severe (E) OSA, there was a large percent of epochs in transitional sleep (ORP 1.0-1.75).

<u>Insomnia</u>

ORP-based sleep deciles were also measured in people with insomnia (See Appendix C, Figure C2). In patients with insomnia with short sleep duration (SE=69±9%) there were fewer epochs in deep sleep and considerably more epochs in the wake range (ORP >1.75, See Appendix, Figure C2B). Furthermore, the increase in wake epochs was predominantly in epochs with full wakefulness. No differences were detected in subjects with insomnia and normal sleep duration (See Appendix C, Figure C2C). The pattern in insomnia & OSA was intermediate between insomnia with short sleep duration and moderate/severe OSA (See Appendix C, Figure C2D).

In summary, apart from documenting the changes in ORP-based architecture with demographics, OSA and insomnia, the reciprocal relation between % epochs in the first and last deciles suggested a framework for phenotyping patients. Thus, very few epochs in the first decile indicates either a) low sleep pressure (e.g., a hyperarousal state), or b) a disorder that disrupts sleep continuity and precludes progression to deep sleep (e.g., OSA, PLM disorder, other causes of sleep fragmentation). These two possibilities can be distinguished by the fraction of epochs in the last decile (full wakefulness). Possibility "a" should be associated with a high number of epochs in the 10th decile, while possibility "b" should be associated with normal (normal sleep pressure) or reduced number of epochs in the last decile (high sleep pressure).

It should be emphasized that fraction of epochs in decile 1 is not the same as %N3 since ORP in N3 extends up to 0.75 or even more depending on the extent of beta activity when delta waves meet the 6 seconds/epoch (Younes M., 2017). Likewise, percent of epochs in the 10th decile is not the same as %wake epochs since epochs are typically scored wake when ORP is >1.75 (Younes et al 2015). These two deciles have special significance in that they represent very deep sleep and full wakefulness.

Phenotyping Patients

Based on the above framework, we hypothesized that patients with combined low representation in deciles 1 and deciles 10 were the patients with high sleep pressure and in whom CPAP would have the most beneficial impact on sleep quality. By contrast, OSA patients with few to no epochs in decile 1 and high representation in decile 10 are likely to be patients with comorbid insomnia and OSA (COMISA). CPAP may improve their sleep depth when asleep but the excessive time in full wakefulness may not improve (Younes & Giannouli, 2020). Other combinations will exist (e.g., normal amounts in both deciles) and it would be of interest to know how they might respond.

We studied 184 severe OSA (57±30 AHI) patients who underwent split-night studies. A preliminary typing scheme was applied to this data (See Figure 5). Fifty-nine percent of patients had 0% epochs in decile 1 when only 8% of the normal sleepers in the SHHS had 0% in decile 1. This group was further divided into three subgroups based on the % epochs in decile 10 (low, normal, high) and these were assigned types 1 to 3 (Figure 5). The remaining patients (41%) were placed in group 4.

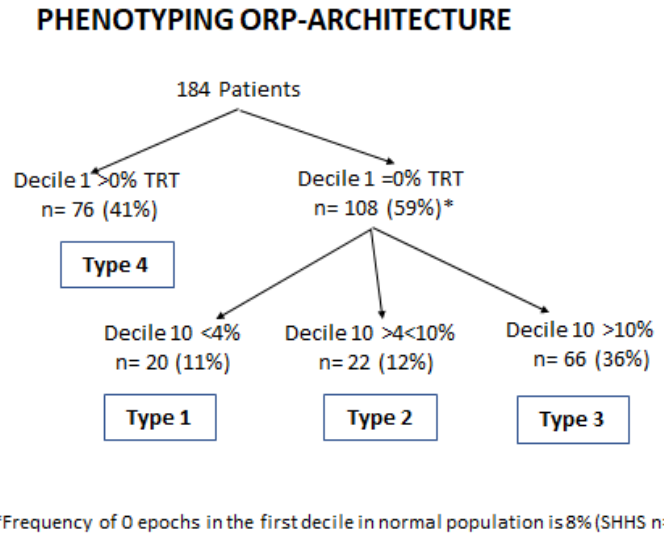

Figure 5 (See Appendix F for high resolution figures): Preliminary phenotyping scheme based on percent of epochs in the first and last deciles of the ORP-based histogram.

Figure 6 shows the ORP-based architecture in the four phenotypes during the diagnostic and CPAP portions of the studies. Type 1 had most epochs in the light sleep/transitional sleep deciles. As predicted, this phenotype had a large leftward shift in the histogram when placed on CPAP. ORP_{NR} decreased from 1.13 to 0.88. Type 2, with a similar pattern but a normal representation in decile 10 (4-10%) had a similarly important left shift and improvement in ORP_{NR} (1.23 to 0.87). In type 3, with excessive amount of full wakefulness along with no epochs in decile 1, both suggesting hyperarousal, ORP during sleep improved (1.34 to 0.95) but the patients were still left with excessive amounts of full wakefulness and sleep efficiency remained very low (67%). Type 4 had essentially a normal ORP architecture before CPAP (compare their diagnostic histogram with the normal histogram in the upper inset). In these patients there was no improvement on average on CPAP, while sleep efficiency actually decreased.

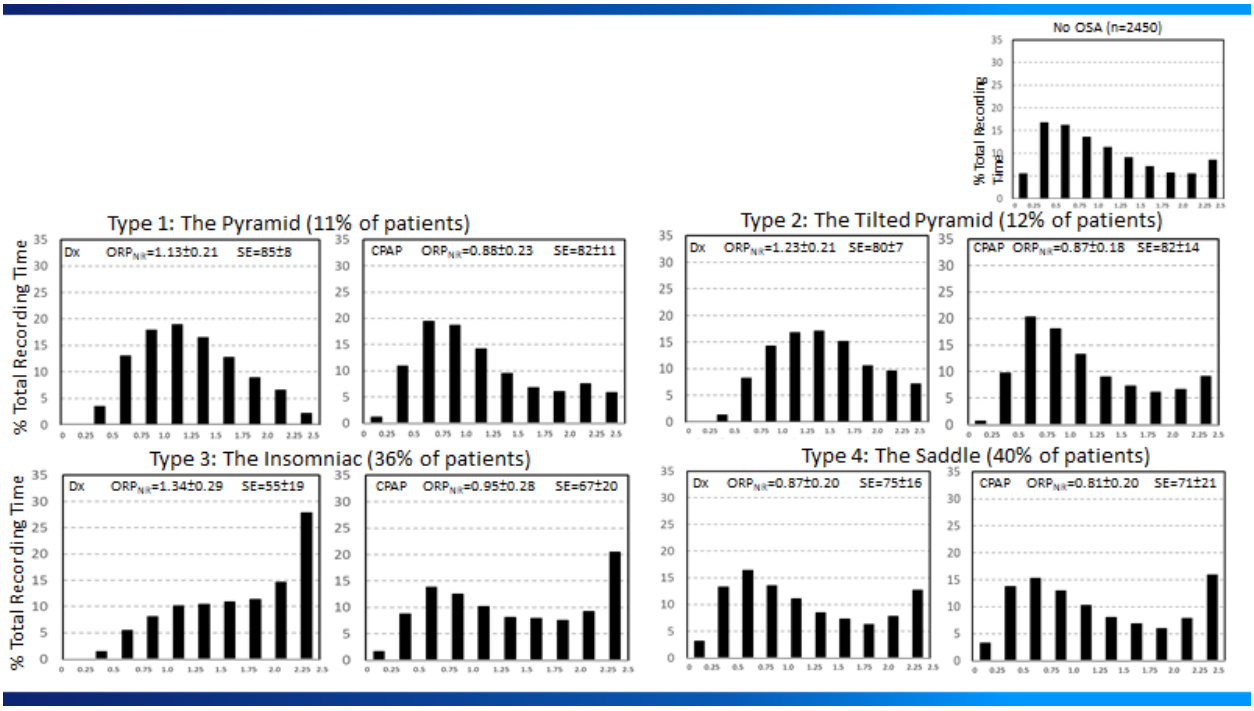

Figure 6 (See Appendix F for high resolution figures): Panels illustrating the four phenotypes of ORP-based architecture before and on CPAP.

<u>Other Applications of the ORP-based architecture</u>

One potential application of this technology is identifying the mechanism of non-restorative sleep when the conventional sleep architecture is normal. Figure 7 shows two examples where the ORP-based architecture was quite abnormal, suggesting different mechanisms. In subject 1 the pattern suggests a disorder that interrupts the progression to deep sleep resulting in increased sleep pressure. In the absence of sleep pathology during the PSG, the cause may be found in non-sleep disorders that provide excessive arousal stimuli (e.g., itching, joint pain). The architecture in subject 2 suggests high sleep quality but inadequate sleep time, resulting in high sleep pressure. This patient may be improved by spending more time in bed. These suggestions are highly speculative, but we plan to study patients with non-restorative sleep with normal PSG to determine whether such mechanisms can be identified, and whether the symptoms can be improved by interventions.

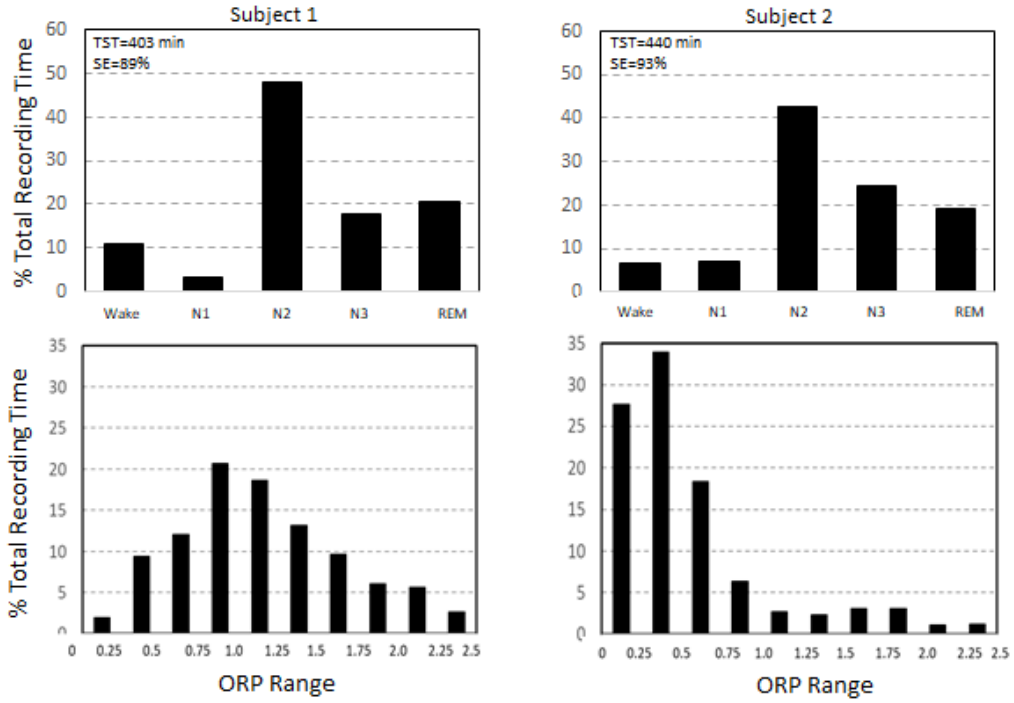

Figure 7 (See Appendix F for high resolution figures): Two patients with non-restorative sleep and normal conventional sleep architecture (top). In subject 1, the ORP histogram shows the pyramid pattern suggesting a disorder that precludes progression to deep sleep (reduced epochs in deep and stable sleep (0.0-0.75) with reduced epochs in the last decile as well. In the second subject the pattern is very similar to subjects with severe sleep deprivation (See Appendix C, Figure C1J).

Future Directions (See Appendix D for full explanation)

There are many future directions for use of the ORP-based sleep architecture method.

1) Development of models to predict sleep improvement among individuals within each type.
2) Determine the extent of sleep improvement on CPAP influences CPAP adherence.
3) Whether sleep improvement during a split study reflects long term sleep improvement.
4) Determine if CPAP adherence in Type 3 patients (i.e., OSA and high amounts of full wakefulness) will improve with concomitant insomnia treatment.

SOLUTION FRAMEWORK – THE MODALITY

A validated, objective measure of sleep quality and an exciting new methodology to dramatically improve OSA diagnosis and therapy direction. Mission accomplished right? Wrong. This alone will not change the course of sleep disorder diagnostics. The message from the market is clear, payers are driving costs of sleep testing down and the PSG must respond. Patients have spoken as well, and they prefer the convenience of sleep testing in the home. The best metrics in the world won't change this trend and to truly disrupt sleep medicine and bring sleep back to the forefront of care, we need to do PSGs in the home, scalably and cost effectively.

The good news is, multiple companies have developed or are developing self-applied, Level 2 in-home PSGs for the North American market. One example is the Prodigy Sleep System currently approved by Health Canada and actively being developed for the US market.

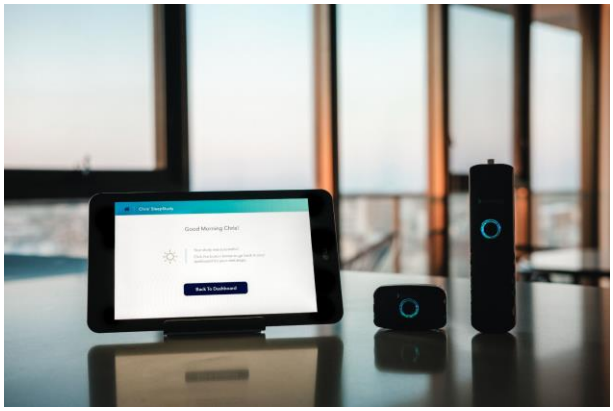

Image 1: Tablet guides the patient experience.

Image 2: Comfortable, self-applied PSG.

In-home PSGs are not new. The ability for a patient to reliably self-administer the study is and this is the critical component. Each system has its own methodology, however the unique ability for ORP to be derived solely from frontal EEGs has unlocked the potential for self-applied EEG with the Prodigy Sleep System. Full validated vs. Level 1 in-lab PSG (Younes et al., 2017), the Prodigy device has >90% single night study success rate, on par with commonly used Level 3 HSAT devices.

Sleep Diagnostic Economic Modelling

One potential challenge to self-applied PSG is reimbursement. Level 2 studies are not supported in many jurisdictions and in the United States a single G-code (G0398) exists for Level 2 studies. Not all payers recognized G-codes and payers, not unexpectedly, consider Level 2 studies generally on par with Level 3 HSAT and reimbursement Levels only covers the incremental costs to conduct the test. The main reason for this is a Level 2 study is typically reduced to an AHI metric for OSA diagnosis, no different than Level 3 HSAT.

This is where Payer engagement and evidence building is required. Level 3 HSAT is intended to be used as a screening tool for OSA patients **with a high pre-test probability**. As a screening tool, HSAT produces false positives as well as false negatives. They cannot assess co-morbid non-respiratory sleep disorders such as periodic limb movements, nor can they evaluate sleep.

Dr. Najib Ayas, an Associate Professor of Medicine at the University of British Columbia with over 200 scientific publications and the leading expert on obstructive sleep apnea in Canada, has shown that Level 2 studies can be economically attractive in assessing patients with suspected OSA.

Building on past work evaluating Level 3 HSAT (Ayas et al., 2010), a theoretical economic model was developed comparing sleep testing using Level 1 PSG alone compared to screening with either Level 3 HSAT or conducting in-home Level 2 PSG as the first step in patients with suspected sleep apnea.

Applying the model to the British Columbia market yielded surprising results as Level II studies were the lowest cost diagnostic delivery method (See Figure 8).

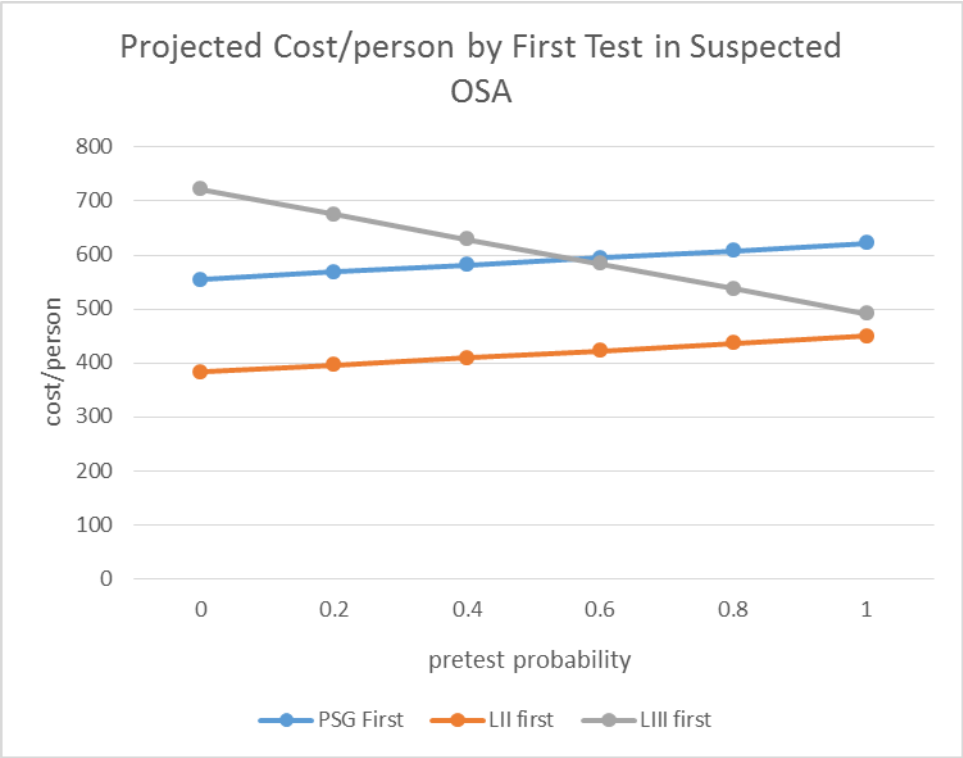

Figure 8 (See Appendix F for high resolution figures): Sleep diagnostic costs per patient based on OSA pre-test probability with three types of testing (confidential - unpublished data under review)

At a 50% pre-test probability of OSA, the cost advantage of a Level 2 study followed by PSG compared to Level 3 followed by PSG was $190 per study. Numerous assumptions were made in the analysis, but the main drivers of the lower cost are that Level 2 PSG is not a screening study. Successful study results contain largely the same information available in a Level 1 study with the only additional factor being technical user requirements for setting up their own studies.

Perhaps more interestingly, sensitivity analysis on the 50% pretest probability scenario indicated a Level 2 study would need to be priced above $450 per study before cost-equivalence was reached with a Level 3 testing program. This Level should be more than adequate to enable an interpretation fee for sleep doctors.

P.I.C.O.S. FRAMEWORK

The PICOS framework provides the foundation for evidence and is used by many payers and HTA bodies globally to understand and evaluate the value of new technologies and solutions.

P	Target Patient Population	OSA patients without symptoms of daytime tiredness. OSA patients who also exhibit symptoms of insomnia.
I	**I**ntervention	Level 2 PSG test with ORP-based sleep architecture analysis.
C	**C**omparison / **C**omparator	Level 3 HSAT defining therapy based solely on AHI. Level 1 as the gold standard, economic comparison.
O	**O**utcome/s	Improved compliance rates for patients who are prescribed CPAP therapy and reduced spend on non-adhering CPAP patients. Improved patient outcomes as therapies are tailored to the individual patient (personalized medicine) whether it be OSA in the absence of sleep issues or COMISA Patients where Insomnia is the primary issue. Reduce total sleep diagnostic spend as Level 2 studies replace Level 3 HSAT. Improved Provider reimbursement as Level 2 interpretation fees for in-home studies match Level 1 lab fees.
S	**S**etting	In-home, self-applied Level 2 study with set patient criteria ensuring high study success rate.

Figure 9 (See Appendix F for high resolution figures): PICOS framework for OSA patients.

With the PICOS framework clearly defined, evidence building is the priority to demonstrate the combination of ORP and in-home, self-applied PSG is solving the identified problem. In addition, Payers and Providers will want to see evidence that the solution is able to be integrated into the care continuum with minimal disruption.

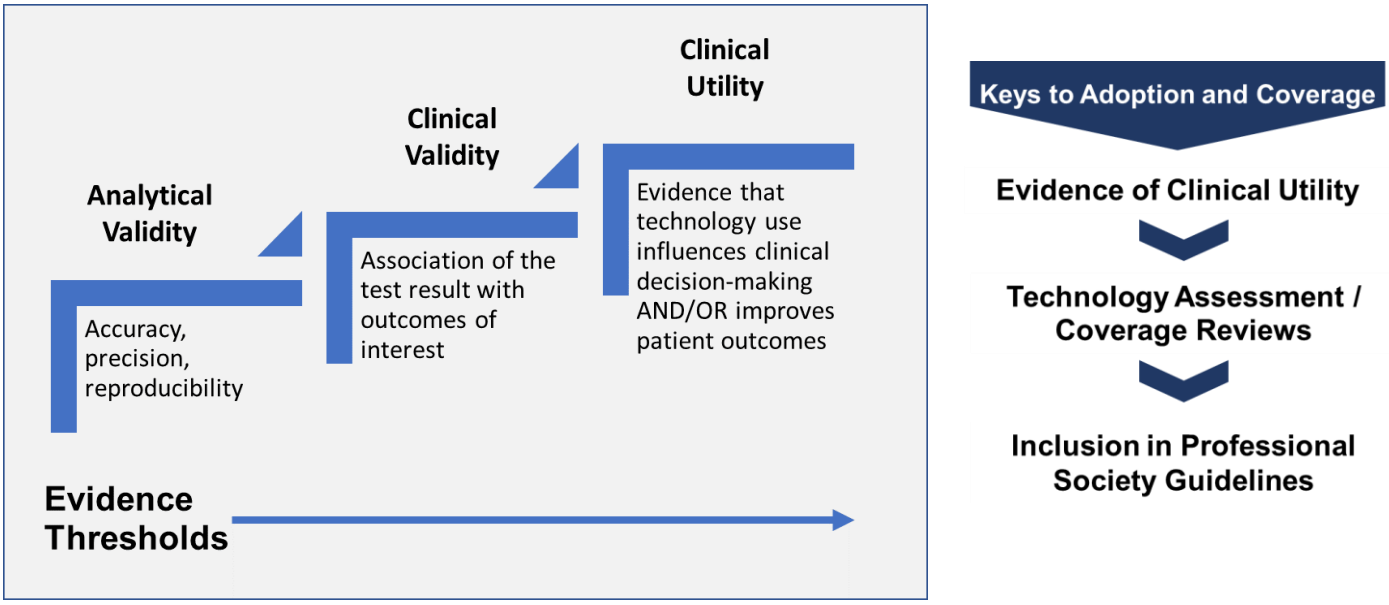

Figure 10 (See Appendix F for high resolution figures): Keys to adoption and coverage for ORP.

The analytical validity of ORP is well established and on-going engagement with the AASM committee on A.I. methodologies key to achieving an AASM statement whereby ORP is recognized as a measure of sleep quality.

Analytical Validity of ORP-based sleep architecture and phenotyping is set to be submitted for 1st publication shortly. Clinical validity will be determined through analysis with high quality data sets including both diagnostic and CPAP therapy PSG assessment as well as compliance data. These studies can be completed as blind retrospective studies where only initial PSG assessment data is available, revealing sleep improvement and compliance to test against the model.

Clinical utility will be the subject of current and planned prospective trials validating the clinical recommendations as well as confirming the modelled positive healthcare economics with shifting from Level 3 HSAT to Level 2 testing.

Furthermore - a formal Health Technology Assessment has been initiated with partners in the Province of Ontario requesting 3rd party review of the Level 2 in-home PSG.

ADVANCING REIMBURSEMENT

A key part of our challenge - "….and results in higher reimbursement"

Improving provider reimbursement is a key outcome of shifting to PSG based diagnostics as physicians are remunerated for the expertise required to evaluate and treat sleep comprehensively as compared to today's sole focus on the AHI. The existing G-code for Level 2 studies, however, does little to reflect the expertise Providers bring to sleep analysis and ultimately obtaining a separate fee-for-service for Level 2 studies + an ORP based-sleep architecture assessment will be required. This will take several steps over time.

1) Enter market as a stand-alone Level II test and bill under G0398 as a starting point. At the same time, address payer perceptions that Level II tests require a technician for set-up.

2) Execute primary and secondary research program building evidence for ORP-based sleep architecture and phenotyping ability to identify patients where CPAP will not improve their sleep.
3) Continue to build relationships with Key Opinion leaders.
4) Segment patient population that will benefit most from Level II + ORP vs Level I as reference standard + Level II tests w/out ORP.
5) Establish and test clinical trial protocols with payers to ensure that intended outcomes will drive coverage and payment.
6) Work with a health economist to determine and include Healthcare Economic outcomes in protocols identified by payers as key.
7) Identify clinical research partners and complete studies under an IRB.
8) Bill as a Level II test during study (confirm with specific payer policies and IRB).
9) Publication of studies validated impact on CPAP compliance and improved healthcare economics.
10) Complete Dossier for Payers and Providers to drive coverage policy changes and adoption.
11) Convert "G" code to an amended CPT code that includes ORP-based sleep architecture in the descriptor.

ANTICIPATED OUTCOMES - SLEEP IS THE FUTURE OF SLEEP MEDICINE

Sufficient sleep is critical for all aspects of our health and wellbeing. We are currently facing a sleep insufficiency epidemic, which includes a large proportion of people not being diagnosed or effectively treated for OSA and other sleep disorders. OSA itself is associated with a range of health and medical comorbidities, including stroke, cardiovascular disease, diabetes and obesity.

Addressing this epidemic, we've outlined four fundamental advancements:

1) ORP - objective measurement of sleep quality
2) ORP-based sleep architecture - OSA phenotyping
3) In home, self-applied PSG - scalable sleep diagnostic testing
4) Enhanced value from PSG data - Improved reimbursement for Level 2 tests

The ability to accurately measure an individual's sleep profile enables precision medicine where sleep medicine physicians will be able to determine if CPAP actually improves the person's sleep quality. This is especially important in those with mild OSA where even a low number of arousals can negatively impact sleep quality. Yet, this could also be useful in moderate to severe OSA where treating the AHI doesn't necessarily improve sleep quality.

This opens up a more specific and targeted therapy pathway looking at alternative treatments that may reduce OSA without the inconvenience of CPAP. This phenotyping will extend beyond alternative OSA

therapies to a holistic approach to sleep medicine and the integration of other therapies like cognitive therapy for insomnia (CBT-i) either independently or in conjunction with OSA treatment.

The implications for therapy follow-up and long-term adherence are also substantial. Today we are able to determine adherence on CPAP and an estimate of residual AHI but are unable to determine the quality of sleep at home on CPAP. The technology exists to do this but it requires the ability to determine sleep quality on relatively few EEG channels with self-applied electrodes outside the hair line. Using ORP as the metric of sleep quality makes this possible to ensure on-going focus and adaptation to the changing sleep issues our patients have as they adapt to therapy.

The consequences of OSA include intermittent hypoxia and sleep disruption. This has a negative impact on brain health. It is therefore not surprising that patients with OSA are at a higher risk of depression, cognitive decline, and dementia. Cognition is impaired in OSA patients across a number of domains, from attention, to memory, to decision making. However, OSA patients vary considerably with regards to the cognitive impact attributable to OSA, and this doesn't always relate to their AHI. And, when we treat patients with CPAP, there doesn't seem to be a clear dose response relationship between CPAP use and cognitive improvement (Jackson et al., 2018).

This suggests there are other aspects of a patient's sleep that are not being adequately treated, and are impacting daytime function. Therefore, our current measures of sleep apnea severity do not tell us about how someone is improving in terms of their daytime function, and potentially, other areas of their health. ORP is just the start as there are other digital metrics to be investigated providing insights into other areas of health, spindle characteristics being one example (Purcell et al., 2017).

Ultimately, the importance of sleep in chronic disease development will play out in a healthier, safer and more productive world with significant improvement on health outcomes at a population Level. This squarely places sleep medicine at the center of the movement from fee for services to alternative, outcome-based payment methodologies as the entire healthcare system re-tools and shifts more resources to preventative care.

Together, these innovations will ***put the sleep back into sleep medicine***, dramatically changing the course of sleep medicine to the benefit of Patients, Providers and Payers.

References (See Appendix E).

Appendix A

Shortcomings of Conventional Measures of Sleep Quality

1) *SE is not a measure of sleep quality*: since it only reflects the fraction of time spent asleep, and not the quality of sleep. In a recent study we found that the extent of wake time in patients with OSA is primarily related to an underlying insomnia disorder (Younes and Giannouli, 2020).

2) *With the current AASM guidelines* to change sleep stage to N1 after arousals until a spindle is seen, *%N1 essentially mirrors the arousal index and has no additional significance* in terms of sleep depth in these patients. This problem is compounded by the reduced number of spindles in patients with OSA (Purcell et al 2017) which would maintain N1 for a longer period after arousals. Thus, a high %N1 does not necessarily indicate poor sleep quality in patients with OSA who have a high arousal index, and a decrease in %N1 on CPAP, with the associated reduction in arousal index, does not necessarily reflect improvement in sleep quality.

3) *Inter-rater variability* A recent study has demonstrated the marked inconsistency in scoring %N1 and % N3 among highly qualified academic sleep technologists (Younes et al., 2018).

4) *Conventional approaches for defining the three NREM stages*, (i.e., spindles and delta wave duration > 6 seconds/ epoch) *are not based on features that reflect sleep depth*. Thus, spindles are sporadic events that subserve memory and cognition, (Clawson et al., 2016) but are not related to sleep depth. In fact, their frequency decreases as sleep becomes deeper. (Curcio et al., 2003, De Gennaro et al., 2003) Likewise, the large delta waves used to define stage 3 are also sporadic events that occur during deep sleep and were recently shown not to be a continuous marker of sleep depth (Younes et al., 2020).

5) The arousal index is simply a number. *Not all arousals have the same effect on sleep depth*. The intensity and duration of arousals vary substantially within and between individuals (Azarbarzin et al., 2014). Furthermore, as shown recently, the rate at which sleep depth increases following arousals is highly variable between individuals, with some reaching deep sleep within seconds after the end of arousals, while in others progression to deep sleep takes place over minutes and only if no subsequent arousal occurs (Younes et al., 2016). Only in the latter group do arousals affect average sleep depth.

6) *The conventional indices do not always change in the same direction in response to CPAP*. For example, N1% may decrease (improve) while N3% and/or SE decrease (poorer sleep). We have recently found that only in 40 of 181 patients did all 5 variables improve on CPAP (Quanash et al., 2017). When the variables change in opposite directions it is not possible to conclude whether overall sleep quality has improved.

Appendix B

How Odds Ratio Product (ORP) is Measured

ORP values are generated from C3 and C4 signals at 3-s intervals as detailed previously. (Younes et al., 2015). In brief, a fast Fourier transform is separately applied to each EEG signal. The frequency spectrum from 0.33 to 35.0 Hz was divided into four ranges and total power in each range was calculated: 0.3-2.3 Hz (slow delta), 2.7-6.3 Hz (fast delta + theta; Range-2 in brief); 7.3-14.0 Hz (alpha-sigma), and 14.3-35.0 Hz (beta). A reference dataset composed of 56 clinical PSGs (>400,000 3-s epochs) obtained from patients with various sleep disorders was assembled. The entire range of powers in each of the four frequency ranges was divided into deciles (0-9). For each 3-s epoch in the file power in each range is assigned a rank (0-9) based on its relative location within the reference dataset. This results in a four-digit signature for each 3-s epoch, representing the ranks of slow delta, Range-2, alpha-sigma, and beta powers, respectively. A look-up table was developed from manually scored PSGs contained the probability of each of the possible 10,000 signatures occurring in a 30-s epoch scored wake or during arousals (Younes et al. Sleep 2015) resulting in probability values from 0% to 100%. The probability the 4-digit signature from each 3-s epoch in the test files was converted to probability from this look-up table. The probability is normalized by dividing by 40 (% of 30-s epochs manually scored awake in the reference PSGs) producing the odds ratio product (ORP), with a range of 0 (deep sleep) to 2.5 (full wakefulness).

Odds ratio product (ORP) circumvents all the shortcomings of conventional indices. First, it is a single metric of sleep depth; there is no uncertainty related to opposite changes in different metrics (Appendix A, #6). Second, unlike the stepwise stages of conventional scoring, it is a continuous metric from full wakefulness (ORP>2.25) to very deep sleep (ORP near zero). Thus, it is consistent with what we know from basic research, that sleep depth progression is a gradual process associated with gradual and reciprocal changes in powers of high and low frequencies (Uchida et al 1992, Merica et al 1997, Mann et al 1997). In addition, it makes it possible to detect changes in sleep depth within the same conventional stage (Figure 3). Third, ORP does not rely on spindles or delta waves (Younes et al 2015), which are not directly related to sleep depth (Appendix A, # 4). Fourth, it is measured in 3-second epochs (Younes et al 2015), making it possible to track changes in sleep depth on a very reduced time scale. Fifth, it can distinguish different Levels of wakefulness (Figure 3). Sixth, it can be measured in real time, making it possible to adjust CPAP pressure to normalize sleep, and not only respiratory signals.

Appendix C

Preliminary Studies

Normal Healthy Sleepers

The Sleep Heart Health Study (SHHS1) is a community-based prospective study involving 6441 adults >40 years of age. PSGs were available in 5804 subjects and were obtained through the National Sleep Research Resource (NSRR; sleepdata.org). The SHHS study provided information on demographics, conventional visual analysis of PSG data, questionnaires on quality of life, symptoms of various sleep disorders (insomnia, restless legs, sleepiness, etc.), and co-morbidities among many others. For the current study, ORP data was generated and the distribution of 30-second epochs among ORP deciles was determined. The results will be reported according to age, gender, body mass index (BMI), presence and severity of OSA and presence of insomnia with and without OSA. OSA was categorized as mild (AHI 5-15 Hr-1), moderate (AHI 15-30 Hr-1), severe (AHI 30-50 Hr-1) and very severe AHI>50 Hr-1. The last category was selected to match the severity of the patients later studied to determine the impact of CPAP on sleep depth/quality (see below). A diagnosis of insomnia was assigned if the subject answered yes on any of the usual questions and indicated that any of these symptoms occurred 16-30 times per month. The diagnosis of insomnia + OSA was assigned to subjects with insomnia in whom AHI was greater than 5 Hr-1. Subjects with neither insomnia nor OSA were classified as “No disease”.

The other study examined the heritability of performance deficit accumulation during acute sleep deprivation in 100 twin pairs (200 subjects) with no sleep pathology (Kuna et al., 2012). It was used to obtain the ORP-based architecture in healthy subjects <40 years of age, who were missing in the SHHS.

Figure C1, top, shows the changes in ORP architecture with age. Data of normal young adults (20-40 years) are from the twin study while data for the 40-90 years old subjects are from 2452 SHHS1 subjects with “no disease”. Consistent with results of conventional sleep architecture that show a generally lighter sleep in the elderly, figure C1 (A-D) shows a reciprocal relation between frequency of epochs in the lowest (very deep sleep) and highest (full wakefulness). Female gender was associated with a slightly lower frequency in the first decile and higher frequency in the tenth decile (Figure C1 (E-F)). BMI had no impact on the ORP-based architecture (Figure C1 (G-H)). Figure C1 (I and H) show that following sleep deprivation, there was a marked shift to the left with much higher frequency in the deeper sleep deciles and markedly reduced frequency in the 10^{th} decile. Thus, the paradoxical relation between epochs in the first and last deciles was maintained throughout these observations and indicates that increased sleep pressure is manifest by higher frequency in epochs with very deep sleep and lower frequency in epochs with full wakefulness, and vice versa.

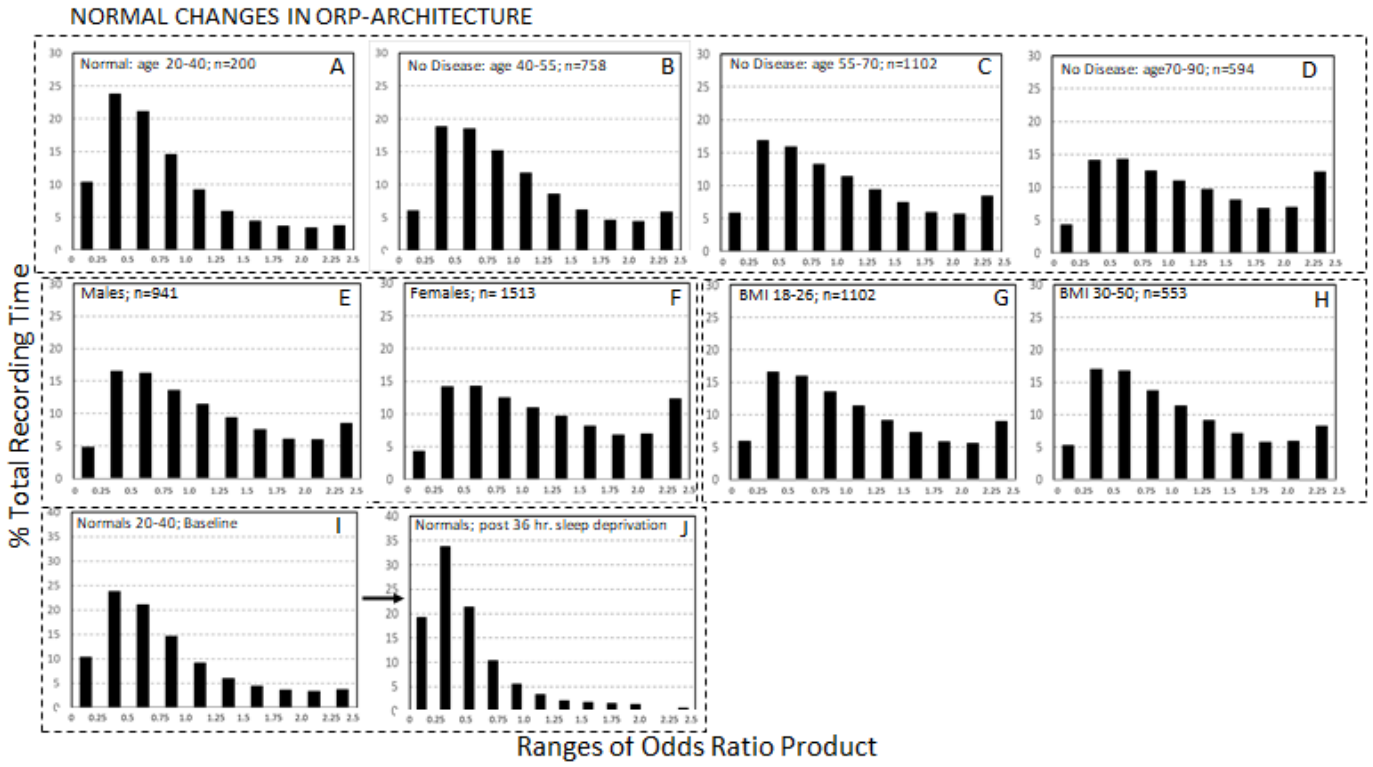

Figure C1: ORP-based architecture in SHHS subjects with no identified sleep disorder as a function of age (A-D), gender (E-F), body mass index (G-H) and the response to 36 hours of sleep deprivation in 200 healthy young subjects (I-J). Note the reciprocal relation between frequency of epochs in the first and last deciles under all conditions.

Insomnia and OSA

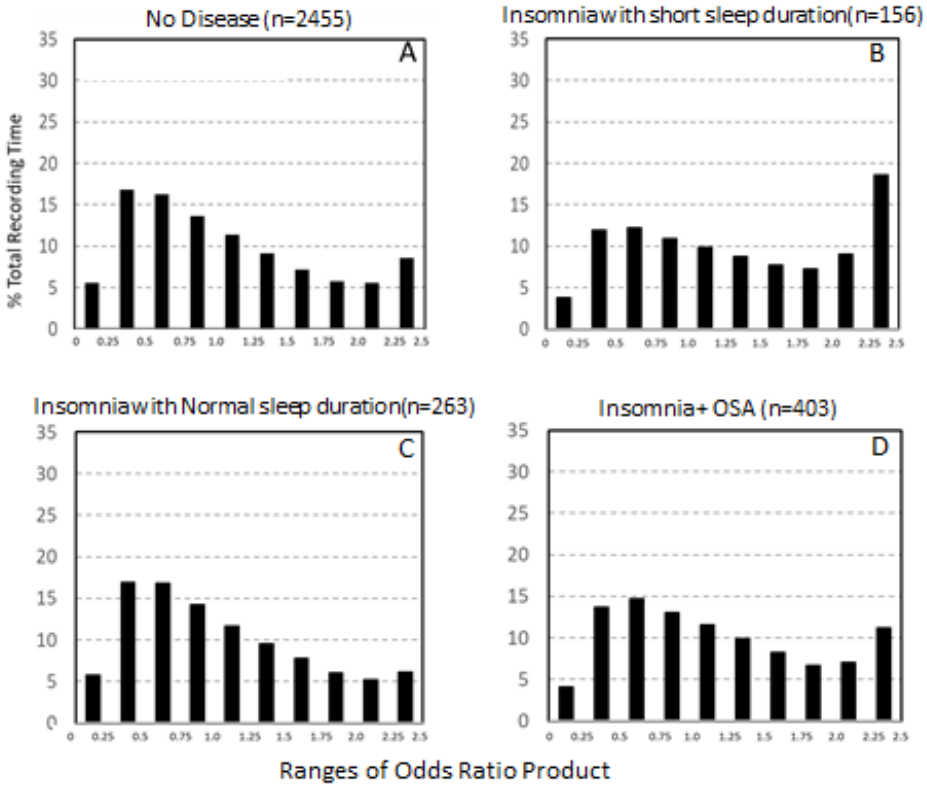

Figure C2: ORP-based architecture in SHHS subjects with no identified sleep disorder (A) and in subjects with insomnia with short sleep duration (B), insomnia with normal sleep duration (C) and insomnia plus OSA.

Appendix D

Future Directions

These preliminary findings demonstrate the potential of this type of phenotyping in predicting response of sleep quality to CPAP. Further improvements and extended applications are ongoing or planned and include:

1) Development of models to predict sleep improvement among individuals within each type: Not all members of a given type improve or deteriorate to the same extent. For example, in type 1 the change in ORP_{NR} on CPAP was (mean; range) -0.25; -0.60 to 0.12, while in types 2 and 3 the corresponding values were -0.37; -0.78 to 0.21 and -0.42; -1.24 to 0.26, respectively. In type 4 there was little net improvement (-0.07; -0.42 to 0.58). Preliminary modeling using additional variables from the ORP histogram as well as other variables from conventional scoring have shown promise with r^2 ranging 0.53 in type 1, 0.65 in type 2, 0.43 in type 3 and 0.50 in type 4. Further refinement of these models is planned as studies are added.

2) Determining whether the extent of sleep improvement on CPAP influences CPAP adherence. The issue of whether sleep improvement is an important determinant of CPAP adherence is an important one. Studies are currently ongoing in collaboration with other scientists who accumulated information on CPAP adherence over time. It is too early to come to a definitive conclusion, but early results are very promising.

3) Whether sleep improvement during a split study reflects long term sleep improvement. We plan studies to address this issue. However, since the range of changes in ORP_{NR} with CPAP in split studies (Qanash et al., 2017) and with long term CPAP (Penner et al., 2019) are very similar, we expect that results observed during split studies will persist in the long term.

4) To determine if CPAP adherence in type 3 patients with OSA and increased time in decile 10 will improve with concomitant use of insomnia treatment. Sweetman et al reported that patients with COMISA have, on average, better CPAP adherence and improvement in insomnia symptoms when receiving cognitive behavioral therapy for insomnia (Sweetman et al., 2019) . It is possible that selection of patients for concomitant insomnia therapy with CPAP (i.e., type 3) will be improved using the ORP-based architecture. We are currently collaborating with Dr. Sweetman's group to address this issue.

Appendix E

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Figure 1:

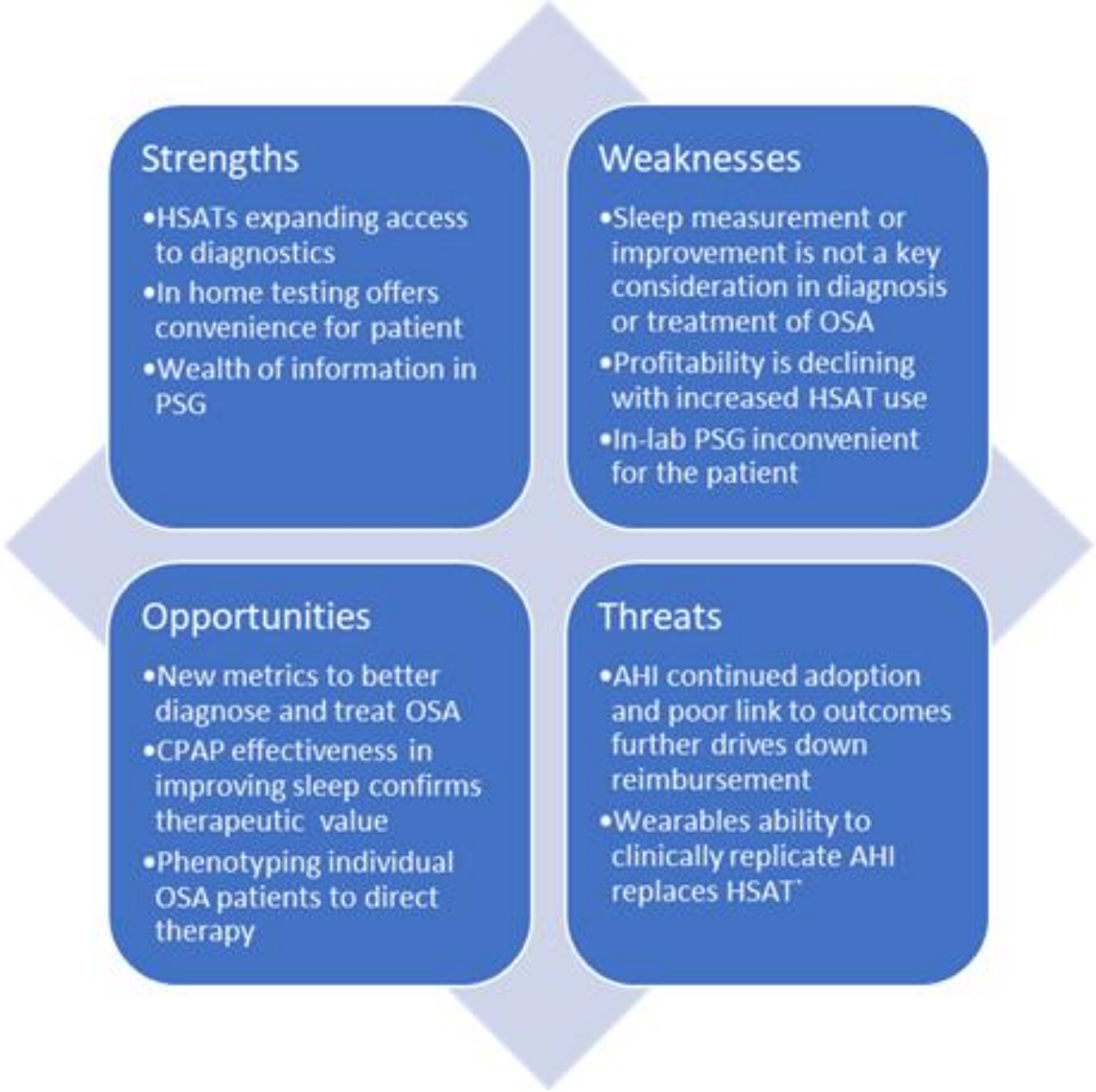

Strengths
•HSATs expanding access to diagnostics
•In home testing offers convenience for patient
•Wealth of information in PSG
Weaknesses
•Sleep measurement or improvement is not a key consideration in diagnosis or treatment of OSA
•Profitability is declining with increased HSAT use
•In-lab PSG inconvenient for the patient
Opportunities
•New metrics to better diagnose and treat OSA
•CPAP effectiveness in improving sleep confirms therapeutic value
•Phenotyping individual OSA patients to direct therapy
Threats
•AHI continued adoption and poor link to outcomes further drives down reimbursement
•Wearables ability to clinically replicate AHI replaces HSAT`

Figure 2:

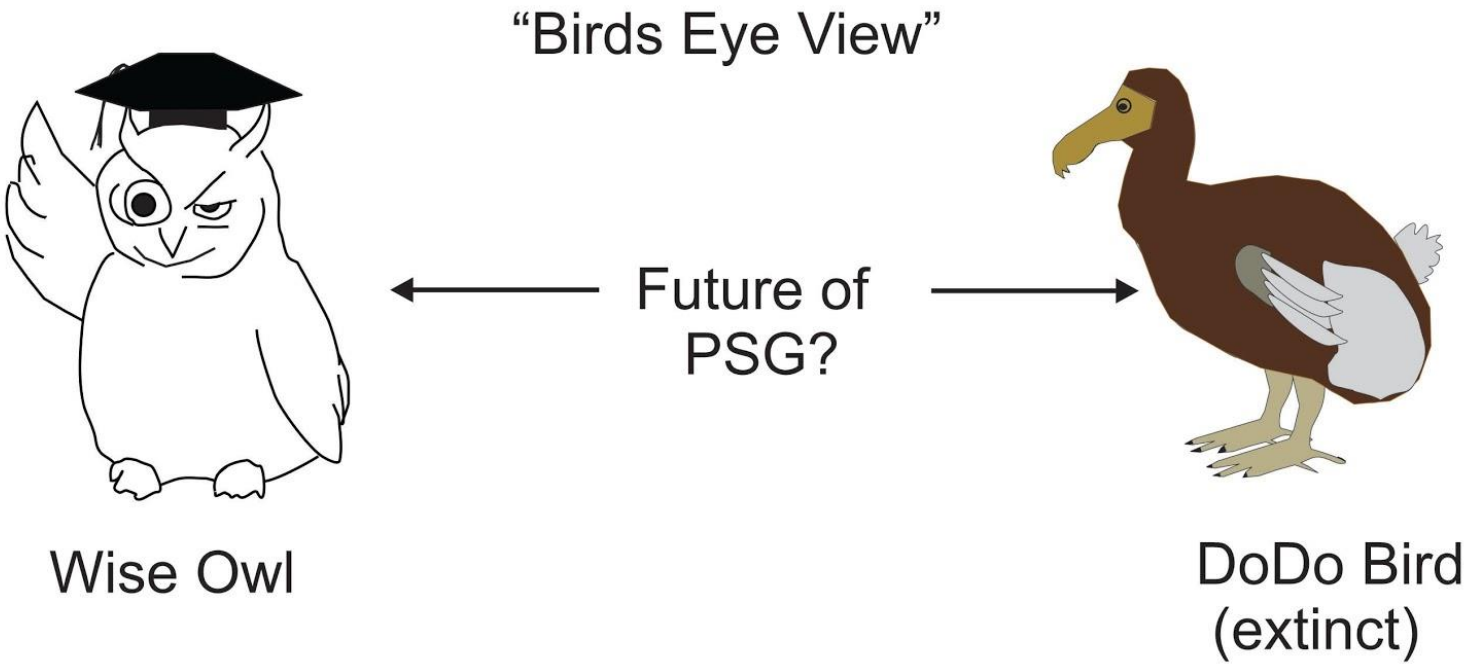
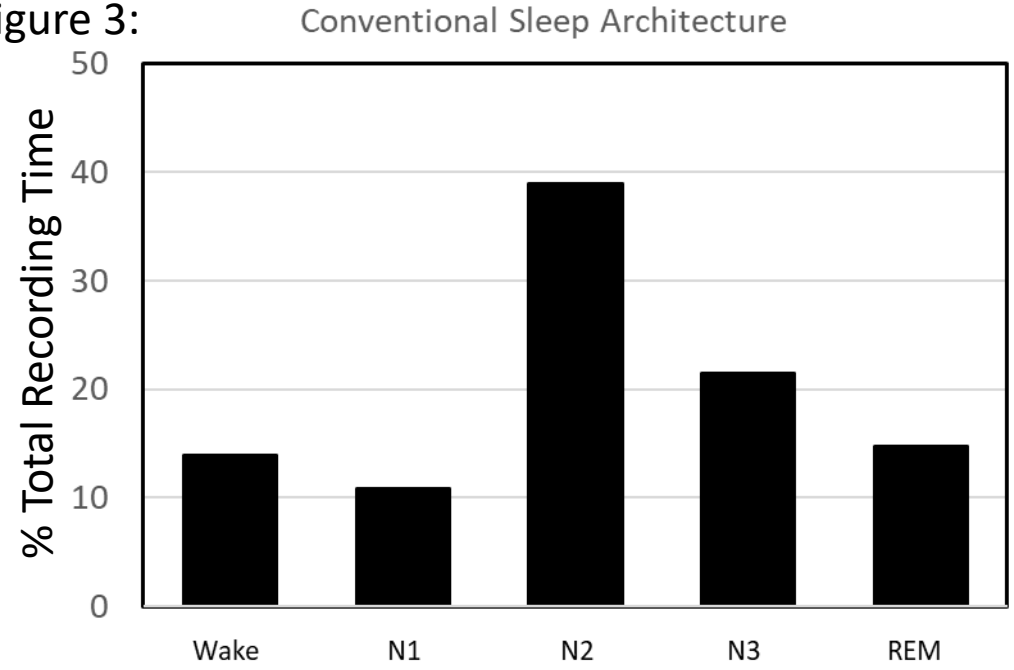
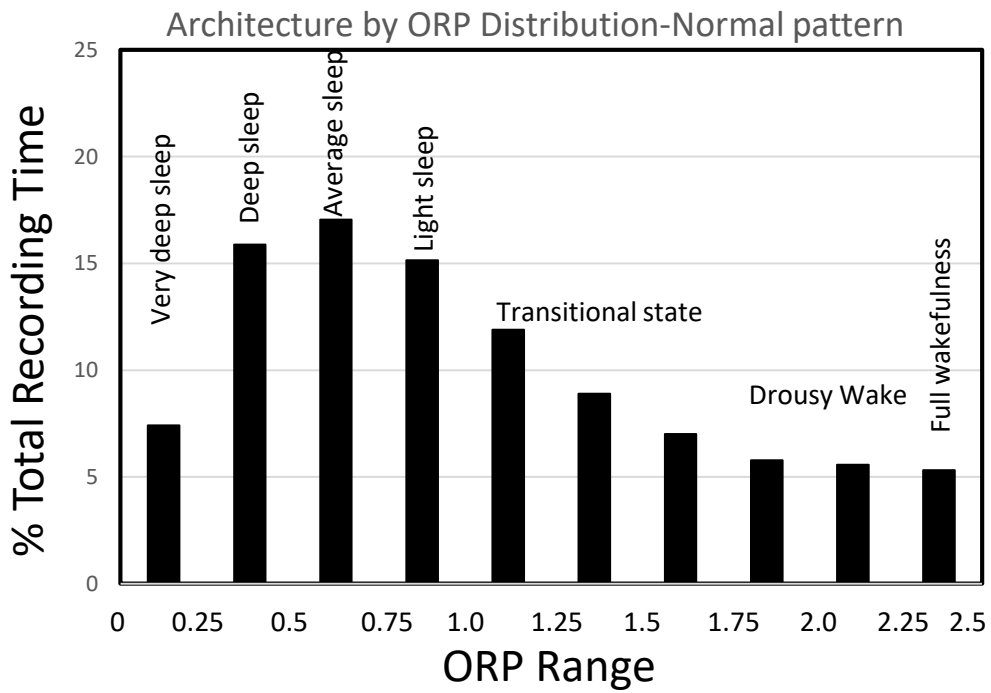
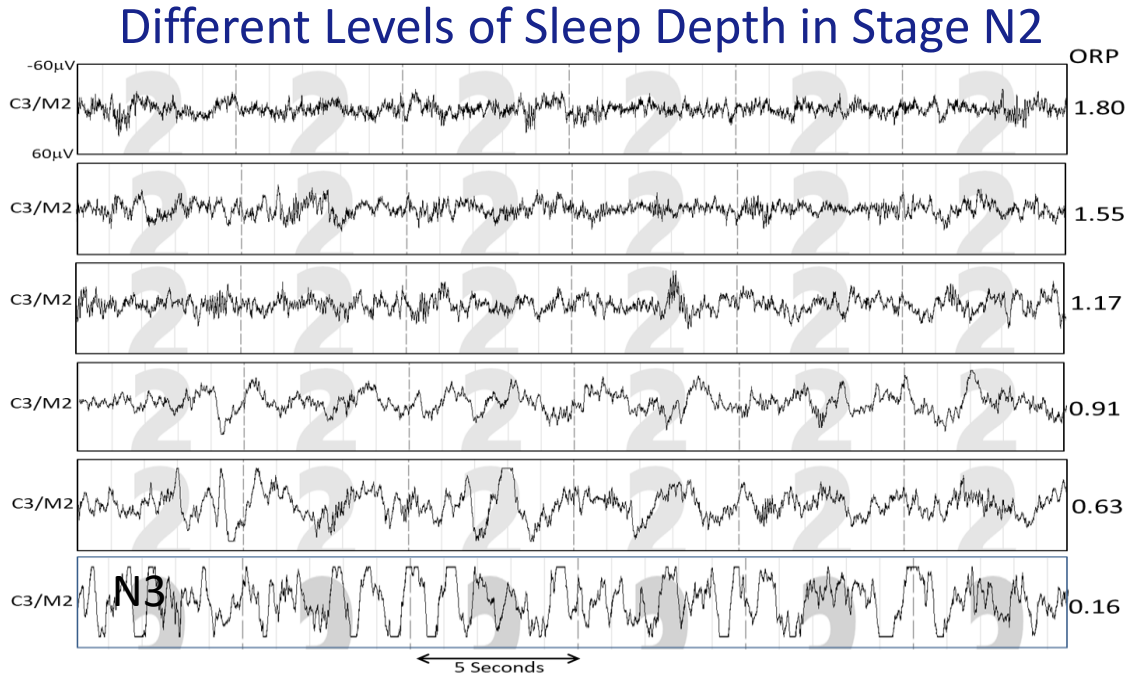


Figure 3:


Conventional Sleep Architecture
% Total Recording Time
50
40
30
20
10
0
Wake
N1
N2
N3
REM


Architecture by ORP Distribution-Normal pattern
% Total Recording Time
25
20
15
10
5
0
Very deep sleep
Deep sleep
Average sleep
Light sleep
Transitional state
Drousy Wake
Full wakefulness
0
0.25
0.5
0.75
1.0
1.25
1.5
1.75
2.0
2.25
2.5
ORP Range


Different Levels of Sleep Depth in Stage N2
-60µV
C3/M2
60µV
ORP
1.80
1.55
1.17
0.91
0.63
0.16
N3
5 Seconds

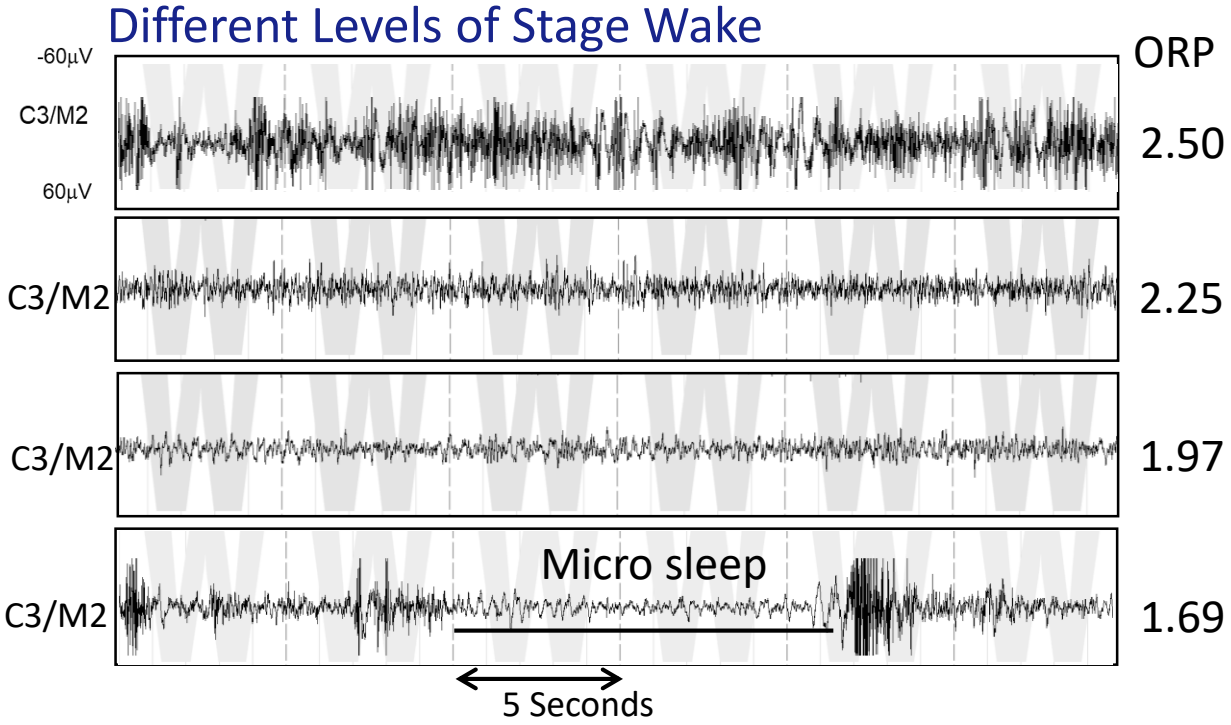

Different Levels of Stage Wake
-60µV
C3/M2
60µV
ORP
2.50
2.25
1.97
1.69
Micro sleep
5 Seconds

Figure 4:

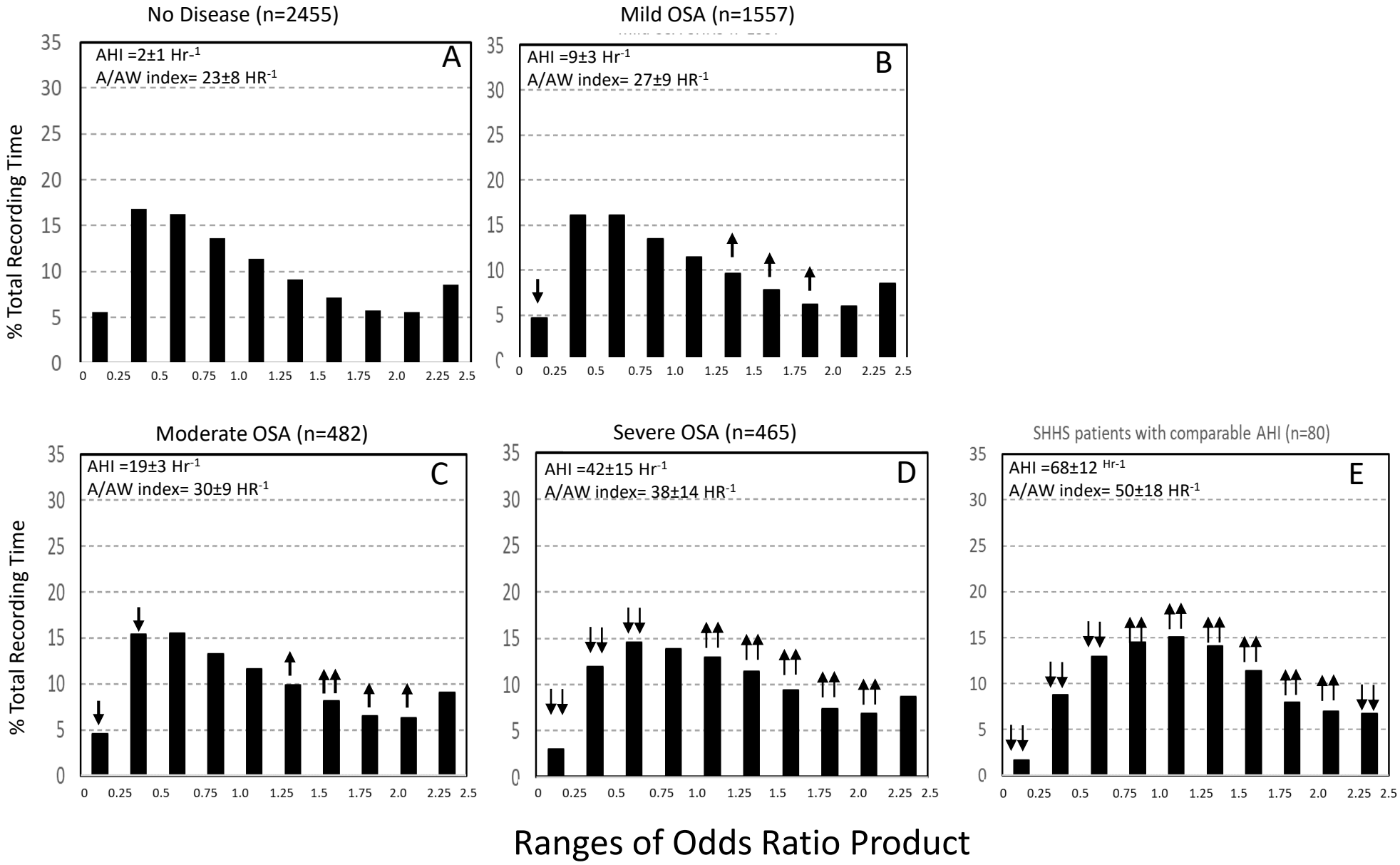
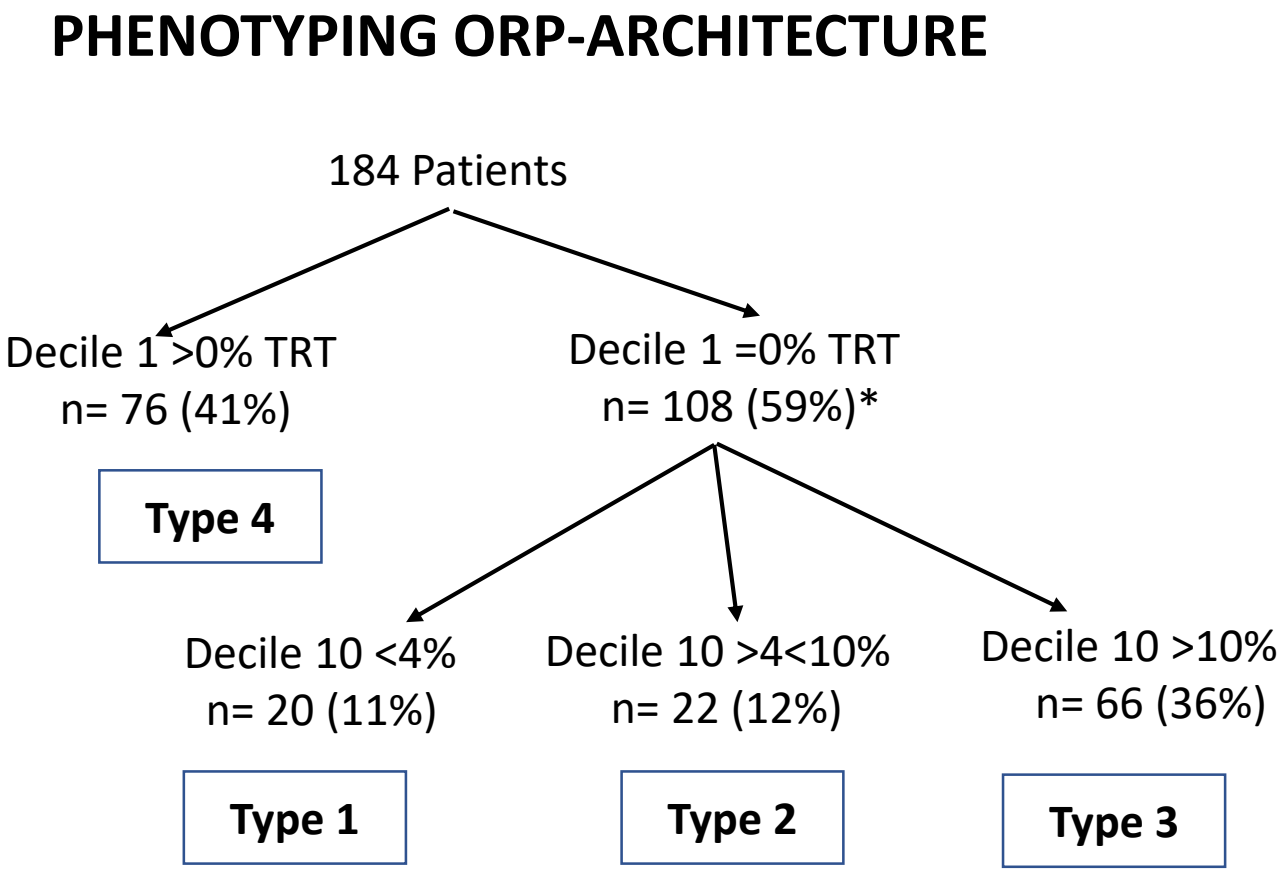
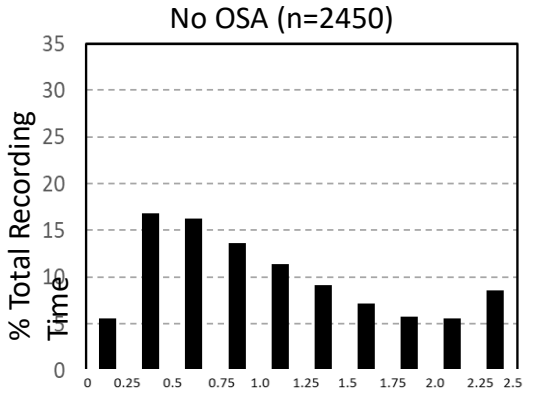

No Disease (n=2455)
Mild OSA (n=1557)
Moderate OSA (n=482)
Severe OSA (n=465)
SHHS patients with comparable AHI (n=80)
AHI =2±1 Hr-1
A/AW index= 23±8 HR-1
A
AHI =9±3 Hr-1
A/AW index= 27±9 HR-1
B
AHI =19±3 Hr-1
A/AW index= 30±9 HR-1
C
AHI =42±15 Hr-1
A/AW index= 38±14 HR-1
D
AHI =68±12 Hr-1
A/AW index= 50±18 HR-1
E
% Total Recording Time
0 5 10 15 20 25 30 35
0 0.25 0.5 0.75 1.0 1.25 1.5 1.75 2.0 2.25 2.5
Ranges of Odds Ratio Product

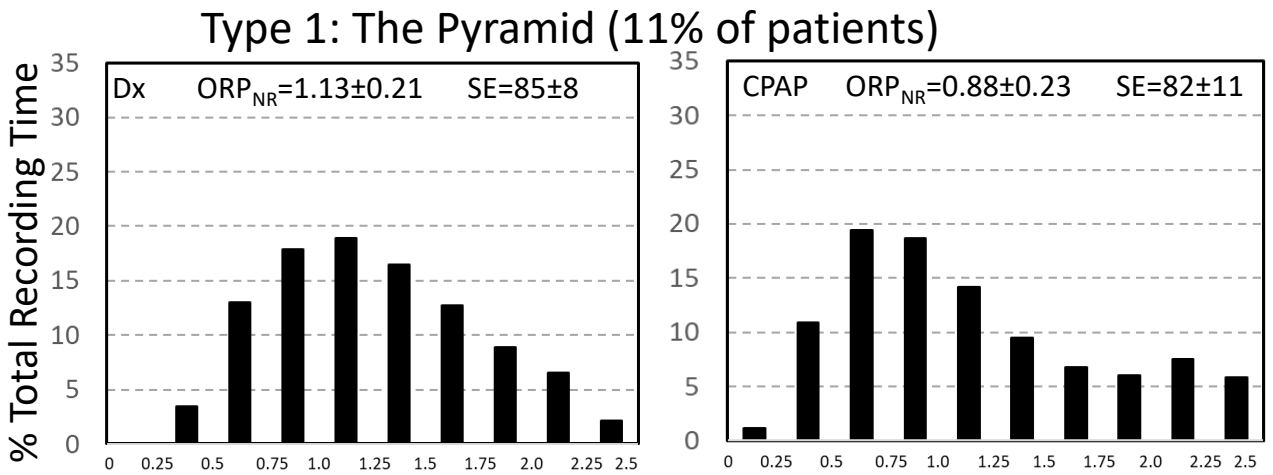
Figure 5:

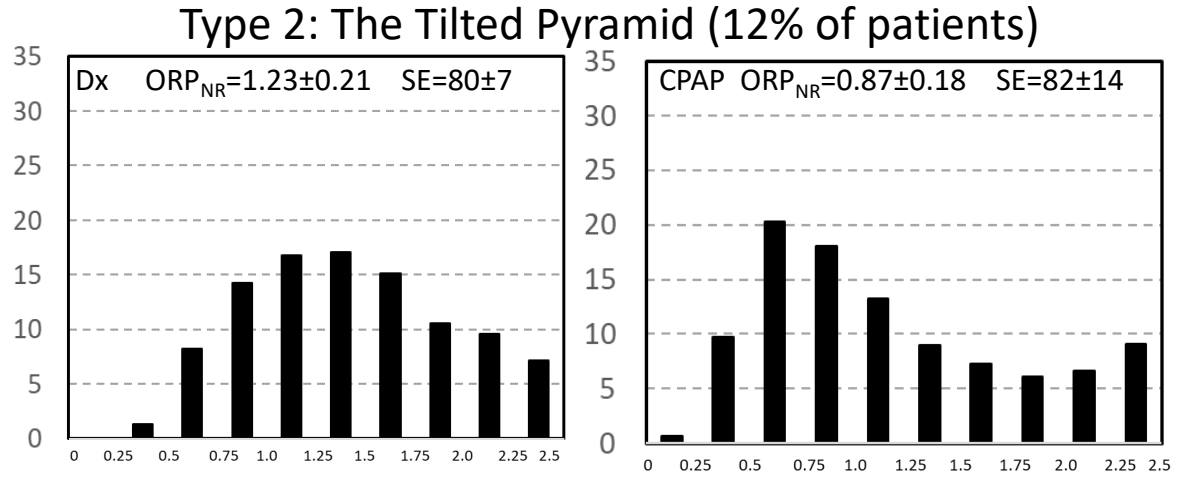


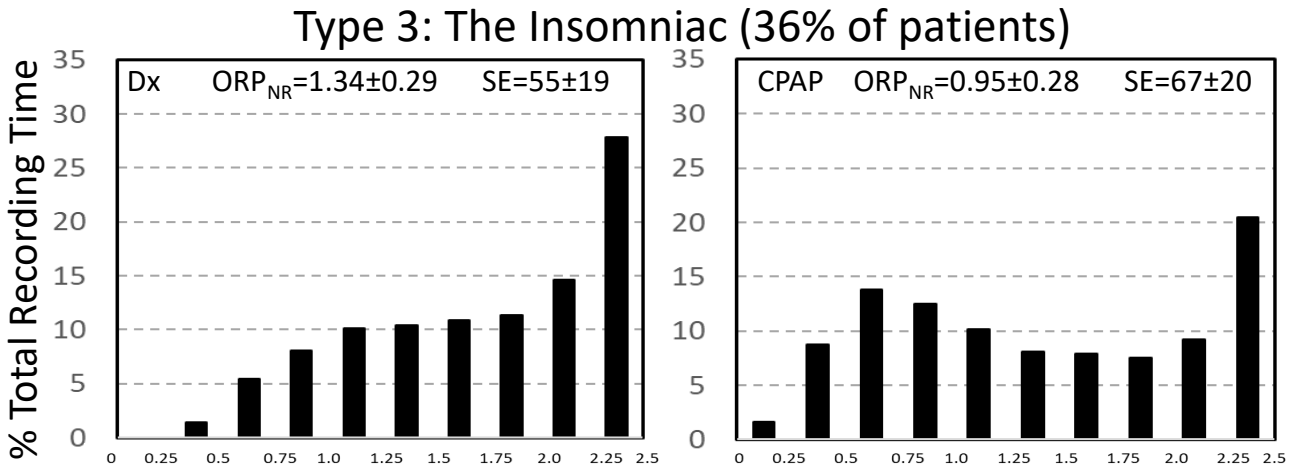
*, Frequency of 0 epochs in the first decile in normal population is 8% (SHHS n=2454)

Figure 6:


No OSA (n=2450)
% Total Recording Time


Type 1: The Pyramid (11% of patients)
% Total Recording Time
Dx ORP$_{NR}$=1.13±0.21 SE=85±8
CPAP ORP$_{NR}$=0.88±0.23 SE=82±11


Type 2: The Tilted Pyramid (12% of patients)
Dx ORP$_{NR}$=1.23±0.21 SE=80±7
CPAP ORP$_{NR}$=0.87±0.18 SE=82±14


Type 3: The Insomniac (36% of patients)
% Total Recording Time
Dx ORP$_{NR}$=1.34±0.29 SE=55±19
CPAP ORP$_{NR}$=0.95±0.28 SE=67±20

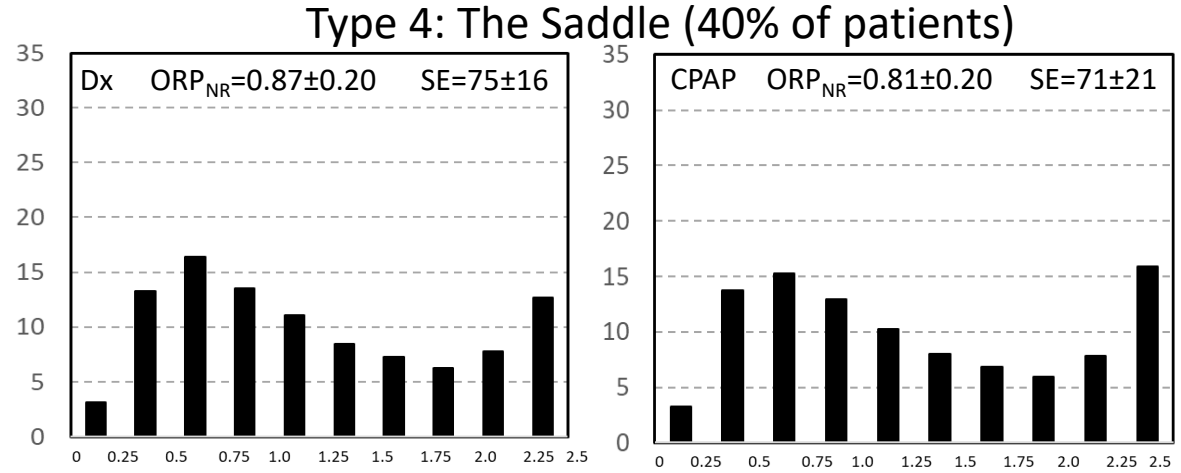

Type 4: The Saddle (40% of patients)
Dx ORP$_{NR}$=0.87±0.20 SE=75±16
CPAP ORP$_{NR}$=0.81±0.20 SE=71±21

Figure 7:

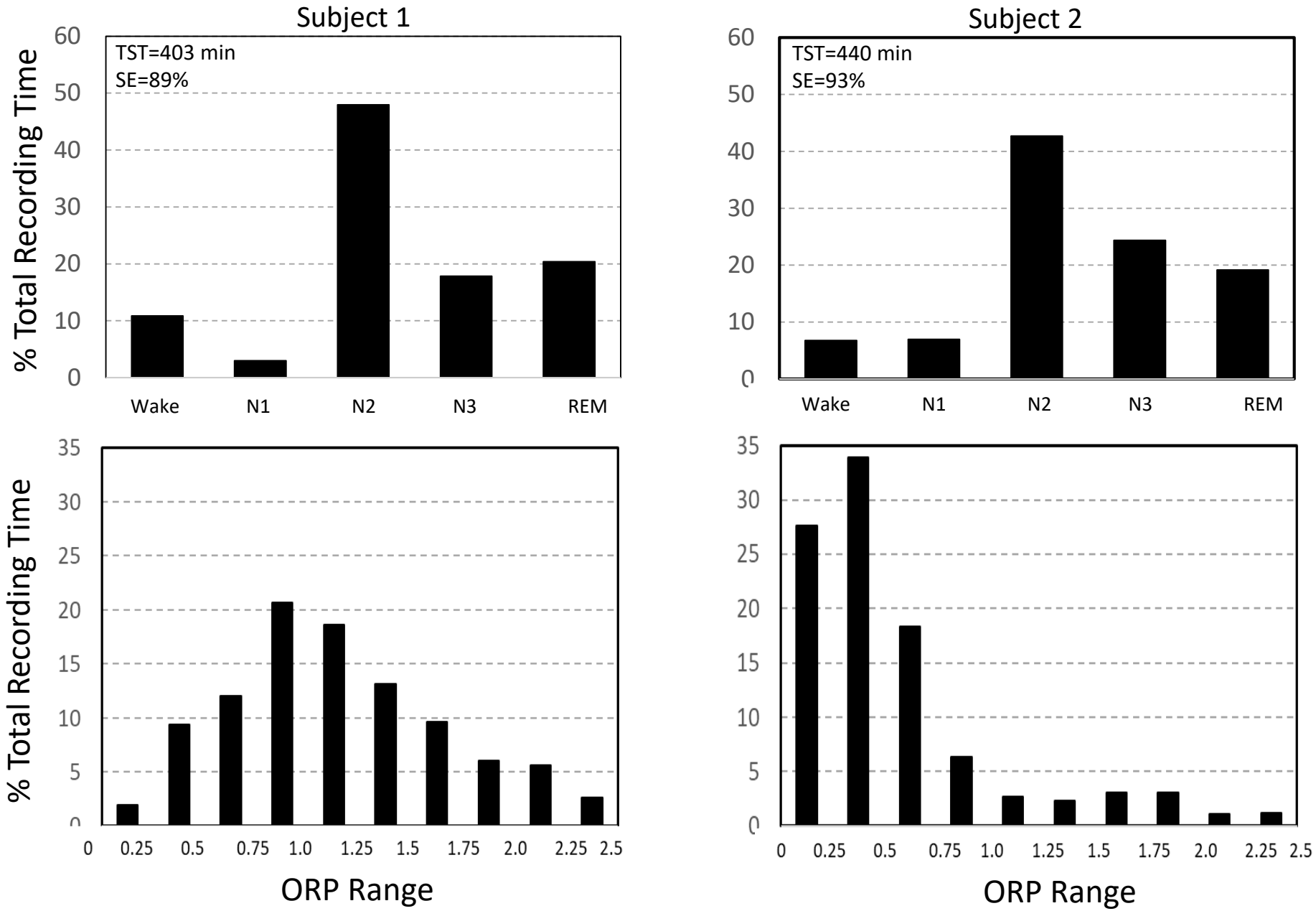

Subject 1
TST=403 min
SE=89%
% Total Recording Time
60
50
40
30
20
10
0
Wake
N1
N2
N3
REM
Subject 2
TST=440 min
SE=93%
% Total Recording Time
35
30
25
20
15
10
5
0
0
0.25
0.5
0.75
1.0
1.25
1.5
1.75
2.0
2.25
2.5
ORP Range

Figure 8:

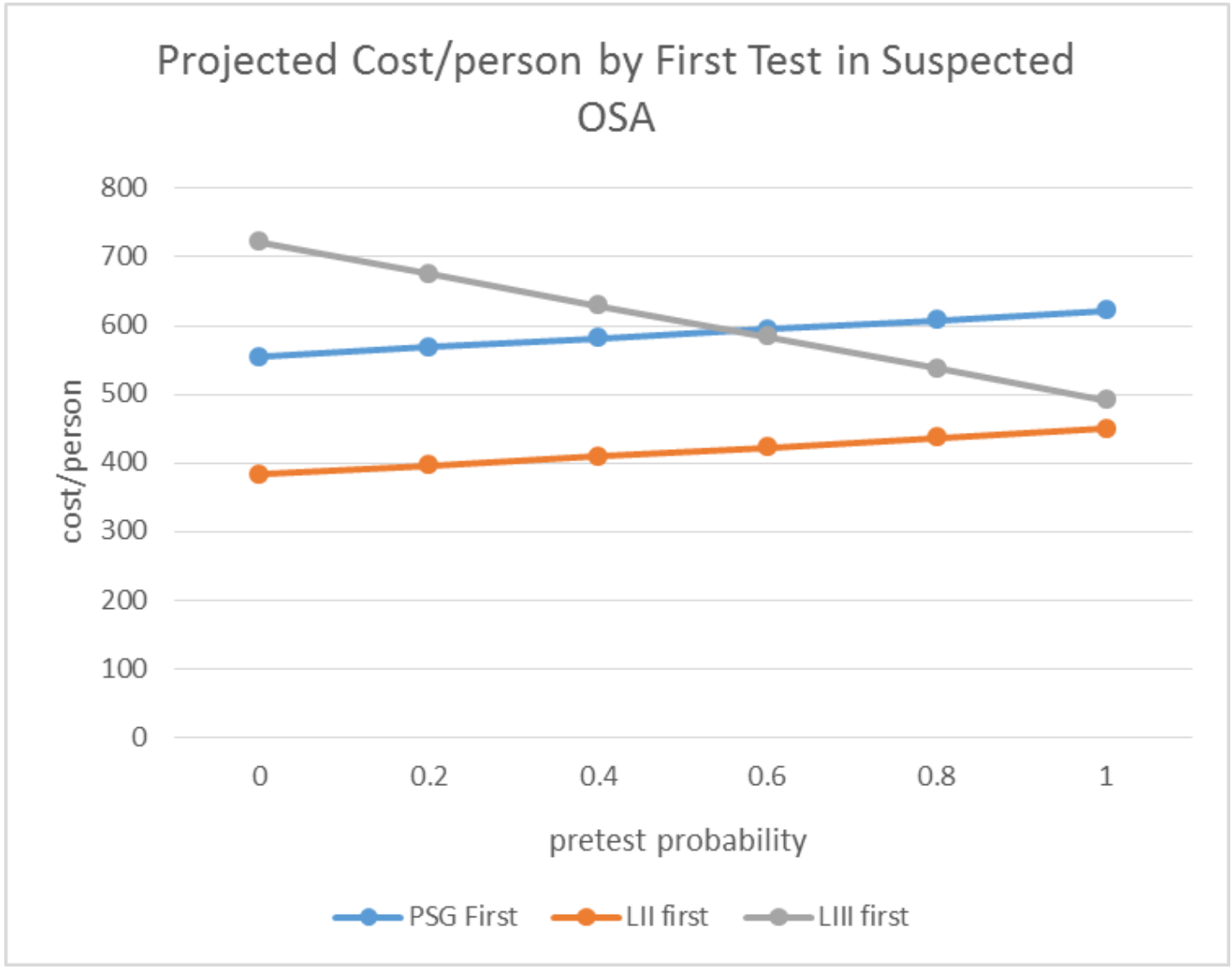
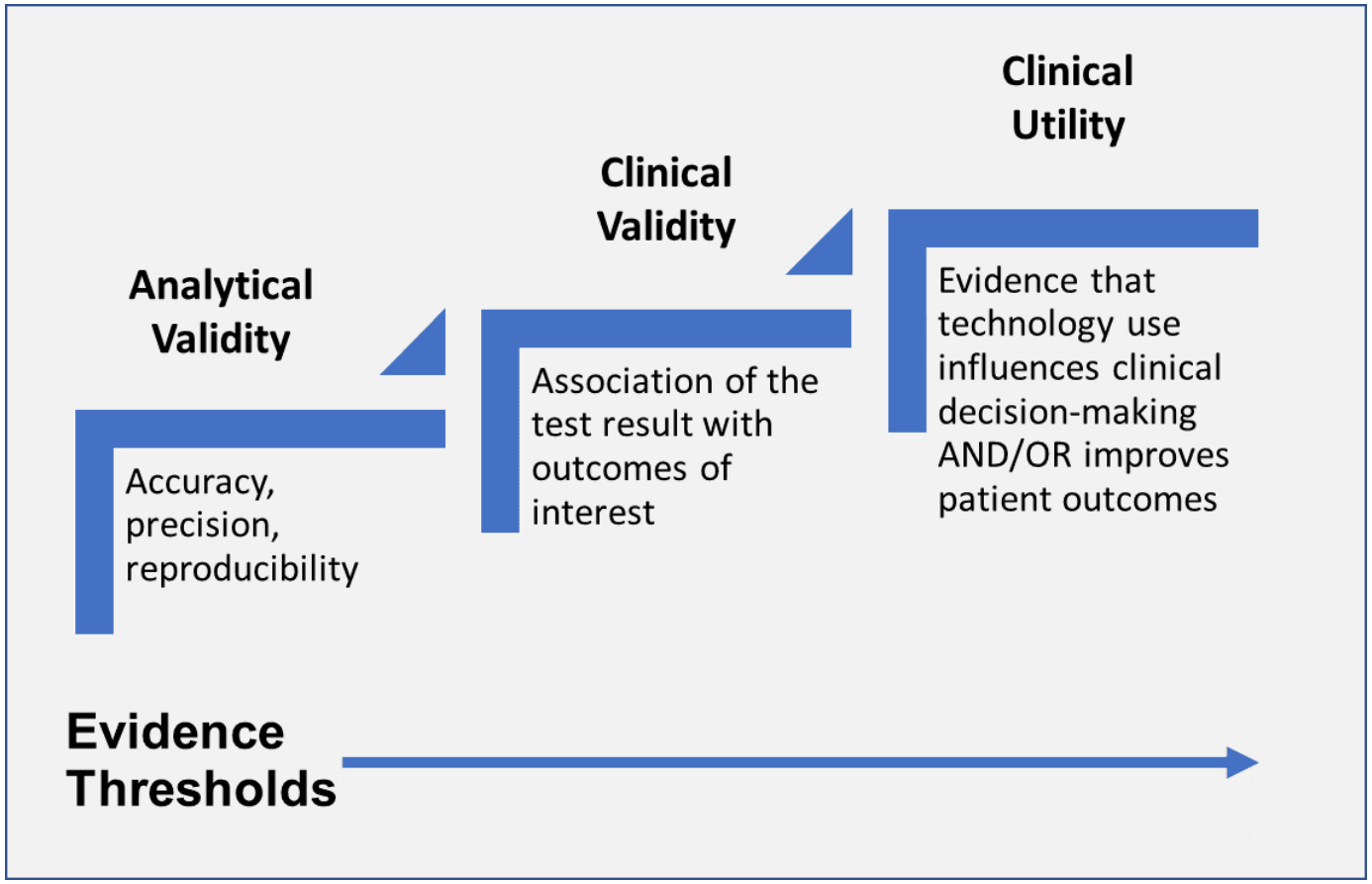

Projected Cost/person by First Test in Suspected OSA
800
700
600
500
400
300
200
100
0
cost/person
0
0.2
0.4
0.6
0.8
1
pretest probability
PSG First
LII first
LIII first

Figure 9:

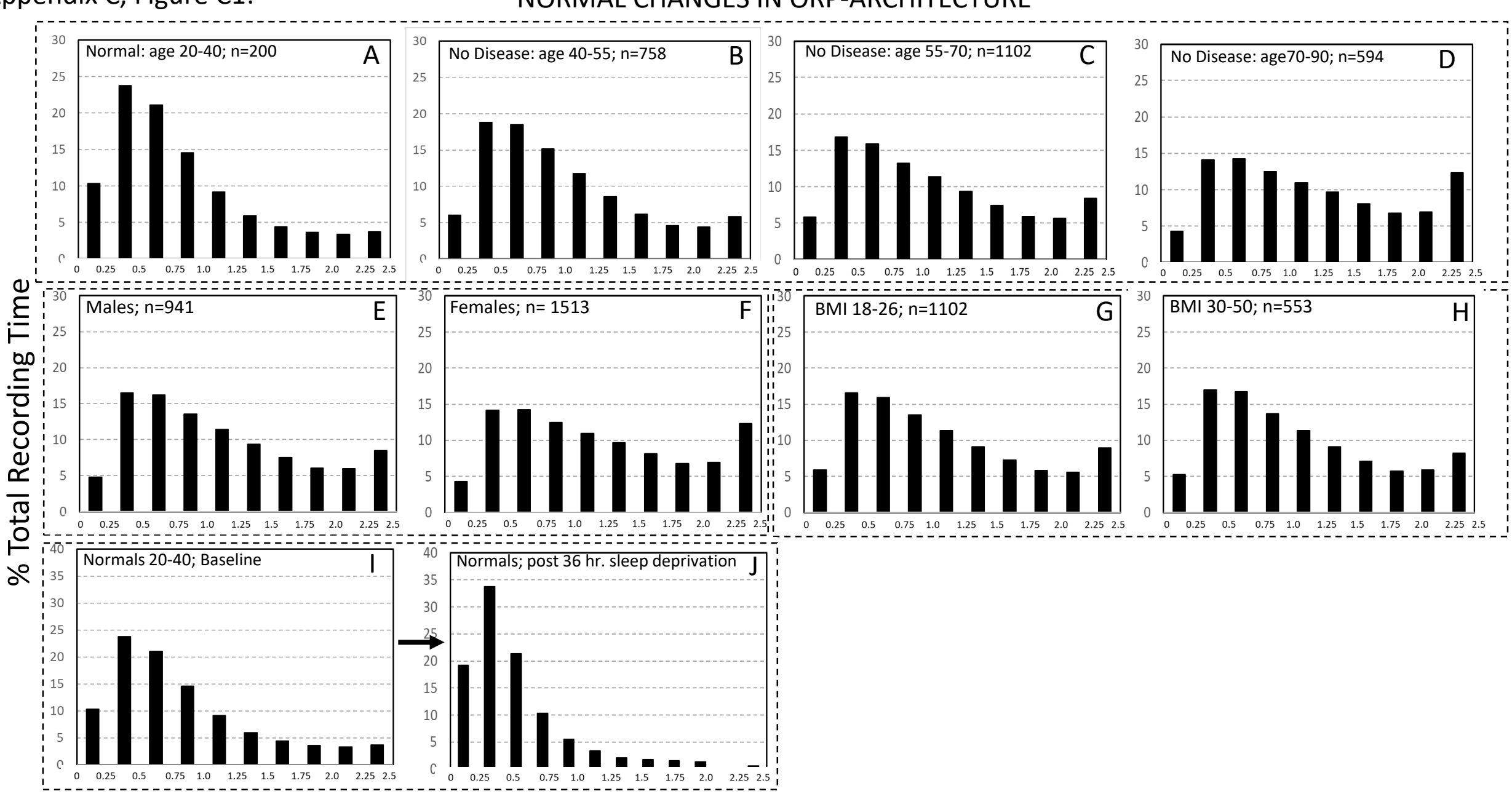
P	Target Patient Population	OSA patients without symptoms of daytime tiredness. OSA patients who also exhibit symptoms of insomnia.
I	**I**ntervention	Level 2 PSG test with ORP-based sleep architecture analysis.
C	**C**omparison / **C**omparator	Level 3 HSAT defining therapy based solely on AHI. Level 1 as the gold standard, economic comparison.
O	**O**utcome/s	Improved compliance rates for patients who are prescribed CPAP therapy and reduced spend on non-adhering CPAP patients. Improved patient outcomes as therapies are tailored to the individual patient (personalized medicine) whether it be OSA in the absence of sleep issues or COMISA Patients where Insomnia is the primary issue. Reduce total sleep diagnostic spend as Level 2 studies replace Level 3 HSAT. Improved Provider reimbursement as Level 2 interpretation fees for in-home studies match Level 1 lab fees.
S	**S**etting	In-home, self-applied Level 2 study with set patient criteria ensuring high study success rate.

Figure 10:


Analytical Validity
Accuracy, precision, reproducibility
Clinical Validity
Association of the test result with outcomes of interest
Clinical Utility
Evidence that technology use influences clinical decision-making AND/OR improves patient outcomes
Evidence Thresholds


Keys to Adoption and Coverage
Evidence of Clinical Utility
Technology Assessment / Coverage Reviews
Inclusion in Professional Society Guidelines

Appendix C, Figure C1:



Appendix C, Figure C2: