

AMERICAN THORACIC SOCIETY DOCUMENTS

Research Priorities for Translating Endophenotyping of Adult Obstructive Sleep Apnea to the Clinic

An Official American Thoracic Society Research Statement

Thomas M. Tolbert, Christopher N. Schmickl, Laura K. Gell, Brendan T. Keenan, Diego R. Mazzotti, Sara Op de Beeck, Amal M. Osman, Cinthya Peña-Orbea, Scott A. Sands, Tamar Sofer, Andrey V. Zinchuk, Erna S. Arnardóttir, Ali Azarbarzin, Susmita Chowdhuri, Peter A. Cistulli, Amy S. Jordan, Yuanming Luo, Sanjay R. Patel, Jean-Louis Pépin, Susan Redline, Richard J. Schwab, Andrew Wellman, and Danny J. Eckert; on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

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Abstract

Background: Obstructive sleep apnea (OSA) pathogenesis, clinical manifestations, and consequences vary markedly among patients. Yet OSA heterogeneity goes largely unaddressed in current management pathways, which are characterized by high treatment failure rates of ~50%. Growing knowledge of OSA pathogenesis has stimulated new lines of investigation for therapies targeted to specific underlying mechanisms or “endotypes.” OSA endotypes include the primary anatomic predisposition to pharyngeal collapse, as well as “nonanatomic” mechanisms of low arousal threshold, unstable control of breathing (high loop gain), and impaired pharyngeal dilator muscle function. Identification of interindividual differences in OSA endotypes and disease expression, or “OSA phenotypes,” offers promise for a more targeted approach to OSA management in which appropriate treatments are tailored to individual needs. However, these concepts have largely been limited to the research setting, and more evidence is needed to support clinical translation.

Goals: To outline the rationale for clinical use, challenges, and key research priorities required to translate OSA endophenotyping for delivery of a more tailored approach to improve patient care and outcomes.

Methods: An international multidisciplinary working group with expertise in OSA epidemiology, pathophysiology, diagnostics, and treatments was convened. The group met at the American Thoracic Society 2024 International Conference to discuss the current state of OSA endophenotyping and required research objectives. This research statement, authored with input from all members, summarizes the group discussion, identified key areas, and research priorities.

Results: The working group identified research priorities that cover the spectrum from discovery to translation/implementation, including technical standards, validation, establishment of clinical cutoffs and minimal clinically important differences, generalizability across diverse populations, stability and reproducibility of measurement, prospective study design and conduct, clinical utility, and impact analysis.

Conclusions: This research statement provides a road map of the opportunities and key steps required to generate the evidence necessary to translate OSA endophenotyping concepts into clinical care at scale.

Keywords: precision sleep medicine; sleep-disordered breathing; pathophysiology; upper airway; respiratory physiology

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ORCID IDs: 0000-0002-2275-8192 (T.M.T.); 0000-0001-5417-9980 (C.N.S.); 0000-0002-9070-847X (B.T.K.); 0000-0003-3924-9199 (D.R.M.); 0000-0002-5978-9814 (S.O.d.B.); 0000-0001-6987-3262 (A.M.O.); 0000-0001-7850-8961 (C.P.-O.); 0000-0003-3752-0328 (S.A.S.); 0000-0001-8520-8860 (T.S.); 0000-0003-0488-9778 (A.V.Z.); 0000-0003-0877-3529 (E.S.A.); 0000-0002-4986-4753 (A.A.); 0000-0002-5927-1169 (S.C.); 0000-0002-7920-4924 (P.A.C.); 0000-0001-8561-9766 (A.S.J.); 0000-0002-9142-5172 (S.R.P.); 0000-0003-3832-2358 (J.-L.P.); 0000-0002-6585-1610 (S.R.); 0000-0003-3503-2363 (D.J.E.).

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The objectives of this obstructive sleep apnea (OSA) endophenotyping research statement are to 1) concisely review the latest knowledge on OSA pathophysiology and the current evidence on the potential of endophenotyping concepts to deliver a more tailored approach to improve patient care and outcomes, 2) identify knowledge gaps, and 3) highlight what we need to know to incorporate endophenotyping into the clinical setting. To advance these objectives, the working group identified four key areas and 11 research priorities:

Key Areas

1. Technical standards and data sharing
2. External and prospective validation
3. Design and conduct of prospective studies
4. Knowledge exchange and impact analysis

Research Priorities

1. Examine the impact of variations in scoring of sleep, arousal, and respiratory events on the physiologic and clinical utility of endotypes.
2. Establish standards for sleep study signal quality and methods to assess whether quality is sufficient for the appropriate use of endophenotypic metrics.
3. Establish large data repositories with standard data formats for the development of new and existing endophenotypic metrics at scale.

4. Establish endophenotypic metric thresholds on the basis of physiologically or clinically important outcomes.
5. Examine the generalizability of endophenotypic metrics across diverse patient groups.
6. Examine changes in endophenotypic metrics with aging, changing health status, and treatments.
7. Investigate joint effects, including interplay and interrelationships among endotypes, patient clinical characteristics, OSA disease severity metrics, and downstream health effects.
8. Use precision medicine principles to design studies of endophenotype-informed therapeutic decisions.
9. Prespecify hypotheses, analysis plans, and appropriate outcomes in endophenotyping studies.
10. Establish a clinical registry for collaborative OSA endophenotyping knowledge exchange among researchers and clinical decision makers.
11. Assess the potential clinical and financial benefits and pitfalls of endophenotype-informed treatment selection with comparative effectiveness research.

Introduction

Obstructive sleep apnea (OSA) is a common chronic respiratory condition characterized by repetitive upper airway collapse during sleep (1). There is considerable interindividual variation in the mechanisms that drive

repetitive upper airway collapse in OSA (2). These mechanisms include an anatomic predisposition to airway obstruction and “nonanatomic” contributors such as unstable ventilatory control, poor pharyngeal dilator muscle function, and a low respiratory arousal threshold (i.e., waking up too easily to minor airway obstruction) (2). Whether driven by one or a combination of these mechanisms, repetitive airway collapse can produce physiologic consequences that contribute to downstream adverse health and safety impacts that can differ markedly among patients. For example, significant hypoxemia accompanies respiratory events in some but not all patients. Left untreated, airway obstruction and the accompanying physiologic disturbances contribute to adverse health and safety consequences, which also vary markedly among patients. Indeed, some patients are sleepy and at higher risk of attention and vigilance failure; others are not. Some appear to be at elevated risk of cardiovascular disease; others may not be. Heterogeneity is thus observed in all three domains: pathogenic mechanisms, physiologic impacts, and disease expression. Figure 1 provides a conceptual schema.

Despite this multilevel heterogeneity, a single frequency metric, the apnea–hypopnea index (AHI), dominates diagnosis and treatment decisions, though it has widely acknowledged limitations (3, 4). Treatment is currently limited to a handful of options that principally address the anatomic mechanism: continuous positive airway pressure (CPAP), oral appliance therapy (OAT), various surgical

Correspondence and requests for reprints should be addressed to Thomas M. Tolbert, M.D., Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1232, New York, NY 10029. E-mail: thomas.tolbert@mountsinai.org.

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Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

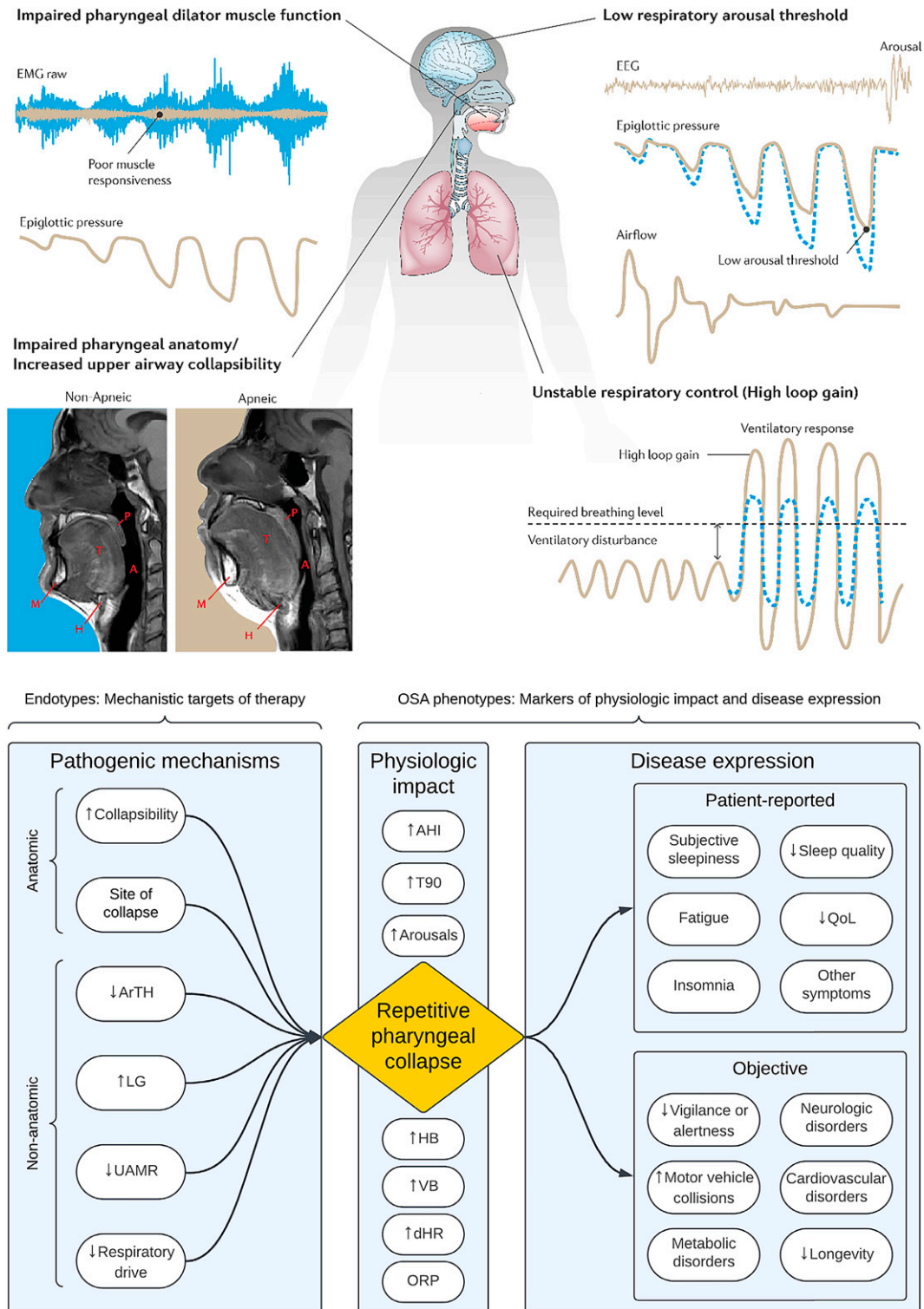


Figure 1. Examples of the contributions of mechanistic endotypes (in the upper panel schematic, tan shading indicates an impaired endotype, and blue shading indicates a favorable endotype) and OSA phenotypes to repetitive upper airway collapse during sleep. Midsagittal magnetic resonance imaging slices compare a patient with apnea with impaired pharyngeal anatomy (crowded upper airway) versus a patient without apnea: the patient with apnea demonstrates greater tongue volume, a larger and longer soft palate, narrower airway caliber, a retrognathic mandible, and a lower hyoid position. A = airway caliber; AHI = apnea-hypopnea index; ArTH = arousal threshold; dHR = pulse-rate response; H = hyoid position; HB = hypoxic burden; LG = loop gain; M = mandible; ORP = odds ratio product; OSA = obstructive sleep apnea; P = soft palate; QoL = quality of life; T = tongue volume; T90 = time below 90% oxygen saturation; UAMR = upper airway muscle response; VB = ventilatory burden.

interventions, and supine avoidance devices (5). Clear guidelines for how best to select among these treatment options are lacking, and a “one-size-fits-all” recommendation for CPAP as first-line therapy remains dominant (3, 4). Unfortunately, nearly half of patients prescribed CPAP will discontinue treatment within three years, and considerable attempts to improve adherence have had limited success (6, 7). Novel emerging treatments for OSA, such as medications to stimulate upper airway musculature and stabilize ventilatory control, or to reduce weight to improve upper airway anatomy (8), promise to expand the therapeutic armamentarium (5). However, consistent with variable underlying pathophysiology, substantial interindividual variability in the therapeutic efficacy of OSA pharmacotherapies is expected (9).

Helping patients and providers make more informed treatment decisions is a major goal of the emerging field of *precision sleep medicine*, a process of leveraging a wide variety of multimodal data to classify patients into increasingly specific subpopulations with distinct prognoses and treatment needs (10, 11). Sleep metrics recently developed under this precision principle are intended to capture specific aspects of OSA heterogeneity: the mechanisms underlying respiratory events, the physiologic impact of these events, or the variable susceptibility to downstream physical and mental health problems (disease expression) (12, 13). Once limited to research settings, many of these metrics are now, or are soon to be, derivable from routine clinical data (14–20). Efforts to study and ready these metrics for clinical applications, a process often described under the broad term “endophenotyping,” have generated both excitement and skepticism among sleep researchers and clinicians (21–24). Although some have highlighted the transformative potential of endophenotyping in the clinical approach to OSA, others have pointed to knowledge gaps and resulting uncertainties in the validity of endophenotyping.

We therefore convened an *ad hoc* working group of leading experts in OSA epidemiology, pathophysiology, and treatment to identify knowledge gaps limiting clinical use of OSA endophenotypes and to define research priorities to close these knowledge gaps. In this resulting research statement, we provide a development framework for an endophenotypic metric from conception to clinical deployment, with

examples of existing metrics and their approximate positions in this idealized development process. Finally, we provide recommendations to further the progress of endophenotypic metrics toward translation to clinical use.

Methods

Working group members were recruited on the basis of their expertise in OSA epidemiology, pathophysiology, diagnostics, and/or treatments. Members disclosed potential conflicts of interest, which were managed in accordance with American Thoracic Society (ATS) policies and procedures. Working group discussions occurred primarily during a hybrid in-person and video teleconference meeting in May 2024. Before the meeting, the working group co-chairs (D.J.E. and T.M.T.) solicited other members on important topics to assemble a preliminary meeting agenda. The agenda was subsequently finalized in an iterative process through electronic distribution for feedback. During the meeting, a designated speaker provided a brief overview of a selected topic, and all members then participated in discussion of the topic. Speakers were early- or midcareer investigators. Each speaker was paired with an established investigator to develop the talk overview before the meeting. At the conclusion of the meeting, members agreed on an outline for an idealized development framework for OSA endophenotypic metrics, and key areas of existing research gaps were identified for the focus of the present statement.

Terminology

Broadly, OSA metrics developed using precision principles share a common goal: to provide information usable in a clinical context to better inform clinical decision making and improve outcomes for patients (2, 11). Various terms have been used (e.g., “endotypes,” “pathophysiological phenotypes,” “phenotypes,” “traits,” and “treatable traits”), but definitions and distinctions among terms have not always been clear. With the aim to provide useful terminology comprehensible to a general audience of researchers and clinicians, this statement provides conceptual definitions of “endotype,” “OSA phenotype,” and “endophenotype.”

Conceptual Definition of “Endotype”

For the purposes of this statement, “endotype” refers *either to the physiologic standard measurement of an underlying pathogenic mechanism of repetitive airway collapse during sleep or to any surrogate metric intended to provide the same clinically actionable information*. That is, an endotype either directly quantifies a specific mechanism of repetitive airway collapse or provides a sufficiently accurate estimate of the mechanism of interest to add physiologic insight that may inform clinical decision making. Currently available endotypes estimate one of several key mechanisms: elevated upper airway collapsibility, low arousal threshold (ArTH), high loop gain (LG) (25), diminished upper airway dilator muscle responsiveness (UAMR) (2), and emerging potential endotypes such as site of upper airway collapse (26, 27) and reduced neural respiratory drive (28, 29). These mechanisms were initially characterized through extensive research in specialized physiology laboratories using “physiologic standard” measurements too cumbersome for clinical care. For example, critical closing pressure (Pcrit) is widely accepted as a physiologic standard measurement for upper airway collapsibility during sleep (30). However, the complex apparatus and maneuvers required to quantify Pcrit preclude its use in clinical settings (30). Accordingly, estimates of the upper airway collapsibility endotype (17, 20, 31, 32) have been developed with the goal of achieving greater uptake and scalability for quantifying collapsibility beyond the physiology research laboratory.

Conceptual Definition of “OSA Phenotype”

Historically, “phenotype” has been used broadly to capture multiple demographic, anthropometric, symptomatic aspects, and comorbidities of a given patient with OSA (e.g., “middle-aged man with obesity, daytime sleepiness, and diabetes” vs. “an otherwise healthy young woman with snoring and insomnia”). The working group extensively debated how to deploy “phenotype” for the purpose of advancing precision sleep medicine. Ultimately, the consensus was to describe a narrow, intuitive concept for operational use in research and clinical settings, rather than to provide a universally generalizable definition of “phenotype.” This statement therefore uses the term “OSA phenotype” to refer

specifically to a metric or combination of metrics that capture the physiologic impact and/or disease expression resulting from repetitive airway collapse during sleep (e.g., “elevated hypoxic burden,” “excessively sleepy,” “excessively sleepy with elevated hypoxic burden”). For example, the physiologic impact metric hypoxic burden quantifies the disturbance to gas exchange (33), while odds ratio product (ORP), an EEG-based metric of sleep stability, shows promise to more comprehensively quantify sleep disturbance versus traditional polysomnography metrics. Other phenotype metrics capture disease expression by grouping patients according to known or suspected consequences of repetitive obstructive respiratory events and the accompanying physiologic disturbances. For example, three to five “symptom subtypes” have been identified using cluster analyses of large cohorts and are expected to have use in clinical diagnosis and decision making (34–43).

Like “OSA phenotype,” the more general “phenotype” may include downstream consequences of OSA but might also capture aspects believed to be causally *upstream* of OSA, such as patient-level risk factors. “Phenotype” might also include aspects without any clear causal relationship with OSA but still useful for grouping patients in clinical or research settings. Aging, male sex, and weight gain, all common risk factors for OSA, might all fall under a phenotype, perhaps useful in some clinical contexts, of “older man with elevated body mass index and OSA who feels sleepy during the day.”

However, only the symptom of sleepiness would fall under “OSA phenotype.” Regardless, this statement’s use of “OSA phenotype” as a narrow, pragmatic term should not be misconstrued as invalidating the broader term “phenotype,” which may be preferred in some settings.

Conceptual Definition of “Endophenotype”

“Endophenotypes” refer collectively to endotypes and OSA phenotypes, as described above. However, the singular “endophenotype” may be used to describe a metric that is not clearly one or the other. For example, LG can decrease after CPAP therapy (44–46). This suggests that high LG may be a reversible consequence of OSA rather than a cause, at least in some patients (44–48). An alternative interpretation is that changes in the mechanisms that drive OSA are expected given that OSA itself is known to vary markedly from night to night in a given patient (49). Similarly, ArTH may also decrease after CPAP therapy (44, 46, 50–52). Referring to LG or ArTH as an endophenotype acknowledges this uncertainty in cause and effect. However, for the sake of conceptual clarity, this statement considers LG and ArTH endotypes.

In the clinical setting, no metric should be interpreted in isolation. Even the best validated endotype, OSA phenotype, or endophenotype should not replace well-reasoned clinician judgement but should be interpreted in the context of the patient’s background, concerns, comorbidities, and goals of therapy. This statement therefore

uses the term “endophenotype-informed” rather than “endophenotype-guided” when describing treatment decisions that integrate information from endophenotypes. In principle, an effective therapy intended to target a specific endotype should reduce the burden of upper airway obstruction, and a measurable improvement in one or more physiologic disturbances and/or patient-centered outcomes should result. The group therefore agreed that physiologic impact metrics and disease expression metrics may be used to assess the effectiveness of endotype-informed therapeutic decisions (Figure 1).

Development Framework

Our idealized developmental process is informed by the general precision medicine framework described by König and colleagues, as well as established frameworks for the development of clinical decision rules (10, 53–55) and prediction models (56). When appropriate, we highlight lessons from efforts toward precision care in oncology, rheumatology, and obstructive airway disease, including the treatable traits paradigm (57–60). As depicted in Figure 2, metrics for clinical decision making proceed through three overarching processes: *derivation/discovery*, *external and prospective validation*, and *impact analysis* (55). However, these processes are fluid: precision medicine is a continuous, iterative process with feedback loops to allow findings in one domain to inform

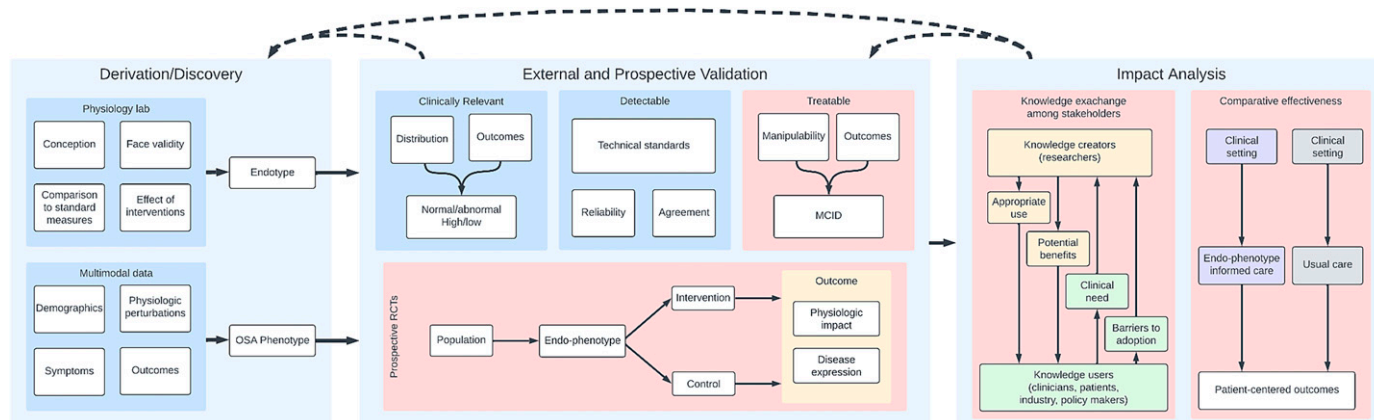


Figure 2. Idealized development framework for OSA endophenotypes. Three major domains are depicted corresponding to the research priorities outlined in this statement: derivation/discovery, external and prospective validation, and impact analysis. Inset boxes in blue indicate knowledge areas with existing or emerging data. Inset boxes in red indicate comparatively underexplored knowledge areas. Note that clinical implementation is a vital domain that is not depicted in this figure given the current stage of endophenotyping knowledge. MCID = minimal clinically important difference; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

investigations in another (10). Indeed, strict adherence to the overall order is neither expected nor required. Findings from validation studies may influence refinement in derivation studies, just as impact analysis may suggest further steps needed in validation (55, 56).

Derivation/Discovery

Endotypes. Based on established physiologic principles, OSA endotypes have been conceived and quantified according to physiologic standard measurements in the research laboratory (2). This usually involves small samples using relatively invasive techniques as the physiologic standard, such as esophageal or epiglottic pressure, end-tidal CO₂ monitoring, diaphragm EMG, and CPAP dial-down protocols. Recently developed endotype metrics have focused on scores or estimates that use clinical sleep study data in lieu of technically complex measurements from the physiology laboratory. Accordingly, recent derivation and discovery efforts for OSA endotypes have involved direct comparison between sleep study data and one or more standard physiologic measurements. For “point-of-care” endotypes, comparison between simple, readily available metrics and the physiologic standard has been used. Examples include the fraction of respiratory events that are hypopneas ($F_{\text{hypopneas}}$) as a predictor of collapsibility measured by Pcrit (17, 61), as well as a score using standard sleep study parameters to estimate low ArTH quantified using an epiglottic pressure sensor (14). More complex sleep study–based endotypes use advanced computational analysis methods. For example, phenotyping using polysomnography (PUP) involves granular breath-by-breath analysis of sleep study signals to produce estimates of endotypes validated by direct comparison with physiologic standard CPAP dial-down measurements (15, 62–64). A crucial point is that whether derivation is straightforward or technically complex, endotypes derived in this way provide *surrogates* or *estimates* of physiologic standard measurements, rather than replacement of direct physiologic standards.

Some endotype estimates do not use sleep study data but have also been validated against physiologic standard measurements. Examples include awake breath holding to estimate LG (65) and awake chemosensitivity testing (66). However, direct comparison with physiologic standards may not be

strictly necessary. Two metrics to infer high LG—a simple point-of-care estimate (16) and the advanced computational method of “self-similarity” (18, 19)—were developed without direct comparison with a physiologic standard. In principle, any surrogate measure that is “guided by scientifically based, *a priori* knowledge about the possibly biologically relevant variables” may prove acceptable (10).

Like endotypes, OSA phenotypes that capture the physiologic impact of upper airway collapse may initially be derived from detailed physiology sleep studies, as in the development of the AHI (3). More recently developed metrics use computational signal processing methods to quantify specific physiologic perturbations from sleep study data, such as hypoxic burden, ventilatory burden, and ORP (33, 67, 68). Disease expression OSA phenotypes may arise from clinical experience, as in the straightforward observation that some people with OSA report excessive daytime sleepiness whereas others do not. The symptom clusters provide examples of disease expression OSA phenotypes derived from more sophisticated examination of multimodal data in large cohorts.

These examples of different methods to derive and establish the face validity of endotypes and OSA phenotypes should not be considered exhaustive. Newer methods that leverage increasingly rich multimodal data are expected to provide clinically feasible inferences into the mechanisms that drive OSA and its consequences. For example, machine learning approaches that use clinical characteristics and sleep study data have recently been developed to derive endotypes potentially predictive of non-CPAP treatment responses (20, 69). Unlike many machine learning approaches that involve “black box” predictions, the techniques used in these studies provide insight into how the predictions are performed to allow greater clinical oversight to inform decision making (20, 69). Regardless of the method used for derivation/discovery, use in clinical care requires prospective validation and impact analysis (53–55).

External and Prospective Validation

In the research setting, endophenotypes can help stratify patients into more homogeneous groups and enhance knowledge of the underlying pathogenic mechanisms of OSA and its associated adverse consequences. However, in the context of clinical translation, external and prospective validation is required to demonstrate that

a candidate endophenotype is clinically “relevant, detectable, and treatable” (59, 60). That is, through validation in cohorts distinct from the derivation cohort and through prospective clinical studies, an ideal endophenotype needs to be 1) *clinically relevant*, in that it is predictive of an important clinical outcome; 2) *detectable* from available clinical data using validated measurement methods; and/or 3) *treatable*, in that an available therapy can target the endophenotype to affect a clinically important outcome. We elaborate on each of these criteria in the below key areas briefly.

A *clinically relevant* endophenotype has predictive value to identify, among the wide variety of patients with OSA, those who will physiologically respond to a *specific* treatment or treatments and/or those who will *benefit* from treatment through improvement in disease expression. Any candidate endophenotype therefore requires a defined distribution with sufficient variance to reliably stratify patients into groups with different needs. Examination against outcomes data can help determine thresholds for “normal” versus “abnormal” or “high” versus “low.” Even if a metric is intended as a continuous parameter without categorical thresholds, clinicians need some sense of what is high and/or what is low.

A *detectable* endophenotype has established technical standards for measurement in the clinical setting. That is, can the metric derived in the research setting be measured in the clinical setting with adequate accuracy to be useful? The metric should also have sufficient reproducibility (*reliability* and *agreement*) to provide confidence in its value. For example, does a metric consistently stratify or rank patients relative to one another (*reliability*)? Also, to what extent does the metric change if it is measured at two points in the same patient, and what is the meaning of this change (*agreement*)? Such questions are complicated by potentially different testing circumstances, night-to-night physiologic variability, biological changes across the lifespan, duration of disease, and a history of prior treatment. Ideally, an endophenotype should have comparable or better reproducibility than conventional measures such as the AHI.

A *treatable* endophenotype is manipulable through an intervention, and such manipulation has a measurable effect on a clinically important outcome (70). Examination of change in the metric vis-à-vis a patient-centered or clinically

important outcome helps establish the *minimal clinically important difference* (MCID), the minimum change in the metric necessary to produce a nonnegligible change in outcome (71). Note that some disease expression OSA phenotypes (e.g., daytime sleepiness) may be viewed as patient-centered outcomes in and of themselves.

Each of the aforementioned characteristics—clinical relevance, detectability, and treatability—may first be examined through secondary analysis of observational cohorts or existing clinical trials. Ultimately, however, prospective clinical validation is needed to demonstrate that an endophenotype can truly inform clinical decision making. For example, study designs that stratify patients into groups according to endophenotype are required to demonstrate improved patient-centered outcomes relative non-endophenotype-informed “usual care.” Thus, prospective endophenotype-informed clinical trials are a priority, and initial attempts toward this objective have commenced (55, 72, 73).

Impact Analysis and Implementation

Even with the addition of well-designed prospective trials, further steps are required to demonstrate that a candidate endophenotype can meaningfully affect outcomes in “real world” clinical settings, beyond the optimal conditions in research studies (74). Furthermore, the impact of any given endophenotype may evolve over time with growing knowledge of OSA pathophysiology and consequences and the emergence of new therapeutic options. A continuous, iterative process of impact analysis is needed to assess and monitor effects on clinical decision making and patient-centered outcomes during and after adoption of an endophenotype into clinical use (55).

Finally, an endophenotype-informed approach that demonstrates a robust impact on outcomes will require efforts toward clinical implementation, in part through knowledge translation and dissemination to clinical providers (e.g., via incorporation into clinical guidelines). Currently, endophenotyping remains in research stages, without demonstrated impacts on key clinical outcomes, and as such, widespread clinical implementation is premature. However, steps can be taken now to lay the groundwork for impact analysis and to anticipate and address barriers to clinical implementation.

Knowledge Gaps and Research Priorities

No currently available endophenotypic metric has met every milestone of this idealized development framework. Table 1 provides a nonexhaustive list of the handful that have demonstrated promise in small physiology studies, cross-sectional studies, or secondary retrospective analyses of cohort or clinical trial data. Many have been examined in cohorts distinct from derivation cohorts, providing insight into their distributions and potential connections to outcomes. Reproducibility has been examined for several metrics, but MCIDs have yet to be reported. Indeed, beyond subjective daytime sleepiness (75), MCIDs for key OSA metrics (including the AHI) are lacking. As noted, the use of endophenotypes to guide prospective clinical trials is in its infancy, and the potential barriers and impact of endophenotyping in real-world clinical settings has not been extensively examined.

With a view toward addressing these knowledge gaps, the remainder of this statement provides research priorities grouped into four key areas: technical standards and data sharing, external and prospective validity, study design, and knowledge exchange and impact analysis.

Key Area I: Technical Standards and Data Sharing

Many proposed endotypes and OSA phenotypes do not require diagnostics or instrumentation beyond routine clinical care. However, sleep study–based endophenotypes are at least somewhat contingent on human or automated sleep staging, arousal scoring, and/or respiratory event scoring. Furthermore, any metric that analyzes sleep study signals (e.g., computationally advanced endotypes such as PUP and physiologic impact metrics such as hypoxic burden and ORP) is at least somewhat reliant on adequate signal quality. Variations in scoring and signal quality both contribute to *data heterogeneity* (76), which creates barriers to two major goals:

1. Maintaining validity and supporting scalability of endophenotypes in a clinical setting (60).
2. Collaborative data sharing among researchers and clinicians to support endophenotype discovery, cross-laboratory validation, and eventual implementation and monitoring.

With the objective of achieving these goals, this key area focuses on knowledge gaps in the technical aspects of endophenotypes and research priorities to address them.

Research priority 1: Examine the impact of variations in scoring of sleep, arousal, and respiratory events on the physiologic and clinical utility of endotypes.

Any endotype has two distinct but likely overlapping characteristics: 1) physiologic merit, or whether and to what extent the endotype is truly representative of the corresponding physiologic standard, and 2) clinical utility, or whether an endotype can meaningfully inform clinical decision making. Variations in scoring and unreliable signal data pose potential threats to each of these. That is, the estimate produced by the endotype may “break down” if scoring does not adhere to methods used during validation research. However, for all current endotypes, there are limited data on the degree to which scoring may vary before physiologic validity or clinical utility is compromised. Studies should therefore examine the impact of variations in definitions and scoring of sleep stages, respiratory events, and arousals on endotype physiologic validity and clinical utility.

SLEEP SCORING. Variations in manual scoring of sleep versus wake and non-REM (NREM) versus REM sleep may affect some sleep study–based endotypes (e.g., PUP endotypes are derived from NREM sleep in accordance with the physiologic standard CPAP dial-downs). Little research has investigated whether endotype estimates are robust to differences in scoring.

RESPIRATORY EVENT SCORING. Variable definitions of “hypopnea” are of particular concern for endotype estimates (77). Metrics validated in cohort studies in which *any* period of significant airflow reduction was considered a hypopnea (i.e., regardless of desaturation or arousal), might produce different results when used under a more stringent definition. For example, Landry and colleagues demonstrated that a hypopnea definition requiring at least 4% desaturation weakened the potential value of PUP-estimated LG in predicting treatment response to upper airway surgery (78). This issue is not limited to computationally advanced sleep study–based endotypes. For example, $F_{\text{hypopneas}}$ is also clearly dependent on hypopnea scoring. Derivation and external validation studies of any candidate endotype should therefore report the specific hypopnea definition used as well as

Table 1. Endophenotypic Metrics with the Potential to Support Clinical Decision Making

	Metric	Clinical Decision Support Potential		
		Clinically Relevant?	Detectable?	Treatable?
Endotypes: mechanisms predisposing to repetitive UA collapse in sleep	UA collapsibility	• ↑ Collapsibility → OAT failure (166)	• Estimable with PUP from EEG and NC airflow; ICC > 0.8 (112, 120, 124) • Simple PSG-based model available, reproducibility unknown (17)	• CPAP → ↓ collapsibility (46) • Weight loss, surgery, OAT, position change → ↓ collapsibility (81, 132–134)
	ArTH	• ↓ ArTH → CPAP nonadherence, poor HGNS efficacy, poor surgery efficacy (87, 107, 108)	• Estimable with PUP from EEG and NC airflow; ICC > 0.8 (112, 120, 124) • Estimable from traditional respiratory indices; reproducibility unknown (14)	• Hypnotics → ↑ ArTH (modest, without major change in OSA severity) (138) • ↑ ArTH → ↑ executive function with CPAP (83)
	LG	• ↑ LG → response to oxygen, acetazolamide • ↑ LG → nonresponse to UA surgery, HGNS, OAT • ↑ SS → residual events with CPAP (19) • ↓ UAMR → HGNST failure (90)	• Estimable with PUP from EEG and NC airflow; ICC > 0.8 (112, 120, 124) • Estimable from traditional respiratory indices (16) and with SS from RIP (18, 19); reproducibility unknown	• Oxygen, acetazolamide → ↓ LG (135) • ↑ LG → ↓ BP with CPAP (95)
	UAMR		• Estimable with PUP from EEG and NC airflow; ICC < 0.8 (112, 120, 124)	• Emerging pharmacotherapy (167–169) and nerve stimulation → ↑ UAMR (170, 171)
OSA phenotypes: markers of OSA physiologic impact or disease expression	Symptom subtypes (34)	• Sleepy → ↑ CV risk (38, 42, 94) • Useful for understanding specific symptom benefits (172)	• “Excessively sleepy” potentially identifiable using decision tree (173) • Over 5 yr, 44% transition between symptom subtypes (174); shorter term reproducibility unknown	• CPAP → ↓ sleepiness, ? ↓ CV risk (96, 101)
	Event-related HB	• ↑ HB → ↑ CV risk (33, 43, 99, 100)	• Quantified from oximetry in studies with airflow (NC or thermistor); reproducibility unknown	• CPAP → ↓ HB, ? ↓ CV risk (98, 101, 102)
	VB	• ↑ VB → ↑ CV risk, ↑ mortality risk (67)	• Quantified from NC airflow; ICC > 0.8 (67)	• ↑ VB → ↓ sleepiness with CPAP (143)
	ΔHR	• ↑ ΔHR → ↑ CV risk (175)	• Quantified from ECG (respiratory events required); ICC 0.72–0.92 (176)	• ↑ ΔHR → ↓ CV risk with CPAP therapy (177)

Definition of abbreviations: ArTH = arousal threshold; BP = blood pressure; CPAP = continuous positive airway pressure; CV = cardiovascular; ΔHR = pulse-rate response; HB = hypoxic burden; HGNS = hypoglossal nerve stimulation; HGNST = hypoglossal nerve stimulation therapy; ICC = intraclass correlation coefficient; LG = loop gain; NC = nasal cannula; OAT = oral appliance therapy; OSA = obstructive sleep apnea; PSG = polysomnography; PUP = phenotyping using polysomnography; RIP = respiratory inductance plethysmography; SS = self-similarity; UA = upper airway; UAMR = upper airway muscle response; VB = ventilatory burden. Refer to the text for further detail.

Table 2. Four Key OSA Endotypes and Examples of Associations with Treatment Success or Failure to Current and Emerging Therapies and Knowledge Gaps

Treatment Intervention	Endotype				
	High Upper Airway Collapsibility	Low Arousal Threshold	High Loop Gain	Poor Upper Airway Muscle Responsiveness	Combinations of Endotypes
Continuous positive airway pressure	+ (89)	– (87, 91, 178)	+ (89)	?	?
Oral appliance therapy	– (166)	– (141)	– (166)	+ (140)	+ (140)
Upper airway surgery	?	– (109)	– (109, 111, 179)	– (180)	+ (109, 179, 180)
Supine avoidance therapy	?	?	?	?	?
Hypoglossal nerve stimulation	+ (90)	– (90)	– (90)	– (90)	+ (90)
Emerging pharmacotherapies to target nonanatomic endotypes (e.g., noradrenergic/antimuscarinic agents, carbonic anhydrase inhibitors, potassium channel blockers)	– (168)	?	+ (181) – (182)	+ (183)	?
Weight loss, pharmacological or surgical	?	?	?	+ (184)	?
Weight loss, lifestyle interventions (i.e., through diet and/or physical activity) (185)	?	?	?	?	?
Supplemental O ₂ therapy	– (85)	?	+ (186, 187)	– (85)	+ (85)

Definition of abbreviation: OSA = obstructive sleep apnea.

The table provides conceptual examples derived from current proof-of-concept studies on specific baseline OSA endotypes and their ability to help predict treatment success or failure, noting that emerging research highlights the superior predictive potential of incorporating multiple endotypes (and other relevant metrics). Question marks indicate cases for which there are either no data or uncertainty/disparate findings as to whether the highlighted endotype is associated with treatment success or failure (i.e., these are areas for future research), negative signs indicate that the endotypes as defined in the title are associated with treatment failure, and positive signs indicate that the endotypes as defined in the title are associated with treatment success. Refer to the text for further detail.

the potential effects of variable hypopnea definitions.

An approach used in several large cohort studies (e.g., the Multi-Ethnic Study of Atherosclerosis, the Sleep Heart Health Study, Osteoporotic Fractures in Men) would be helpful to test an endotype under different hypopnea definitions: all discrete periods of sufficient airflow reduction are marked as candidate hypopneas. These candidate hypopneas can then be tagged as “true” hypopneas depending on the degree of accompanying desaturation and/or arousal, allowing efficient investigation under different definitions. The extent to which central versus obstructive hypopneas influence key metrics, which are not well differentiated with current clinical diagnostic tools, also requires investigation (79, 80).

AROUSAL SCORING. Computationally advanced endotypes that rely on arousal scoring depend not only on the presence of a scored arousal but also on accurate identification of start and end times of each arousal, a degree of accuracy beyond current routine clinical practice. Even point-of-care endotype surrogates that do not require such a degree of precision may still be affected by variable arousal scoring. The fraction of

respiratory events terminating in arousal is a point-of-care surrogate used to infer a low ArTH. This is likely to be largely robust to event type and precise timing but may suffer from marked interindividual heterogeneity or arousal scoring differences.

BODY POSITION. Physiologic mechanisms are affected by changes in body position, including the head and neck (81, 82). Small studies have examined the effects of body position on some endotypes, but assessing these effects at scale is complicated by the lack of a consistent coding scheme (i.e., for supine, left, right, prone, and upright) and a paucity of head and neck position data due to a lack of clinically feasible monitoring technology.

INTERSCORER VARIATION AND AUTOMATED VERSUS MANUAL SCORING OF SLEEP, RESPIRATORY EVENTS, AND AROUSALS. Even under consistent definitions of sleep stages, respiratory events, and arousals, differences in manual scoring between individuals may produce variable endotype estimates. Studies are therefore needed to examine the impact of interscorer variation. The development of automated scoring algorithms with sufficient accuracy to ensure metric accuracy could obviate manual scoring altogether and is a priority for the field (83). However, automated scoring

algorithms will not altogether bypass these issues without consistent event definitions. Studies are also needed to determine whether endotype estimates significantly differ under different automated scoring algorithms.

A final point is that the foregoing issues are not limited to endotypes. OSA phenotypes that incorporate physiologic impact metrics dependent on manual scoring (e.g., AHI, hypoxic burden) may also be affected by variable event definitions and interscorer variation. Some physiologic impact metrics (e.g., ORP) have “built-in” automated scoring of sleep, respiratory events, and arousals, a feature that may improve consistency in metric output but does not necessarily imply robust physiologic validity or improved clinical utility.

Research priority 2: Establish standards for sleep study signal quality and methods to assess whether quality is sufficient for the appropriate use of endophenotypic metrics. Like variations in scoring, variable signal quality may affect physiologic validity and clinical value. The technical complexity and corresponding “tolerance” of poor signal quality can vary widely among endophenotypic metrics. For example, $F_{\text{hypopneas}}$ fraction of respiratory events

terminating in arousal, and other point-of-care endotypes are derivable from data already immediately available from patient characteristics or traditional sleep study indices (14, 16, 17, 20). In contrast, more complex endotypes (e.g., PUP, self-similarity) and physiologic impact metrics (e.g., hypoxic burden, ventilatory burden, ORP) require additional, computer-based signal processing (84). It has not been established whether the ostensible additional accuracy produced by these advanced analyses is necessary or if simpler endotypes will suffice for clinical care. Regardless, clinical settings will vary in their capacity to both capture high-quality data and process it with advanced computational methods (60, 84). Therefore, future studies to discover new endophenotypic metrics or to validate existing ones should fully and transparently report the signals used, their quality, and any preprocessing steps (56). An indication of a metric's sensitivity to signal quality compromise is needed. One approach is to "stress test" with simulated conditions of compromised signal quality by starting with high-quality data and artificially introducing issues common to clinically acquired signals.

Although technically complex, the methods used in the derivation of PUP endotypes are publicly available, providing examples of issues raised by signal quality and potential steps to address them. PUP derives ventilation from a nasal pressure signal and uses a model-fitting parameter approach to estimate ventilatory drive during scored obstructive respiratory events (15, 62, 63). Many publications have used PUP to analyze sleep studies with high-quality nasal pressure recordings (15, 63, 85–89). However, other studies have used nasal pressure recordings that suffered from artifacts common to in-laboratory clinical data (62, 83, 90). Ongoing research seeks to quantify the robustness of PUP estimates to signal quality issues like filtering artifacts or to patient-related circumstances such as mouth breathing. Details of these and other examples are provided in the data supplement.

Research priority 3: Establish large data repositories with standard data formats for the development of new and existing endophenotypic metrics at scale. At every step in endophenotype development, from conception to use in clinical care, multimodal data in large numbers of individuals improves the robustness of findings. Well-characterized clinical cohorts with outcomes tracked at

several time points (at diagnosis before treatment, while on treatment, and after years of follow-up) would greatly enhance the understanding of endophenotype-informed clinical decision making. Leading sleep investigators have made strides toward building rich data sources through collaborative data sharing, including the National Sleep Research Resource (NSRR). National and international collaborations should augment these efforts by making raw sleep study data, processed data, and relevant code available while respecting data privacy policies. Launching, developing, and maintaining repositories requires considerable effort and sustained commitment to collaboration among researchers. Within the field of sleep research, the NSRR, together with the European Sleep Apnea Database, provide models for success. Researchers should also look to non-sleep-focused databases, such as The Cancer Imaging Archive (<https://www.cancerimagingarchive.net>) and the Human Reference Atlas (<https://humanatlas.io>), as successful projects bringing together complex, multimodal data.

As highlighted by recent reporting from the NSRR, a lack of standard formatting produces heterogeneity in several aspects of sleep study data: differences in sensor hardware and signal processing; ambiguous signal labeling; and a lack of standard annotations of sleep stages, arousals, respiratory events, and positions. This data heterogeneity reduces the efficiency of collating and analyzing sleep studies on the large scales necessary for precision sleep research (76). Practical lessons from the NSRR can inform efforts to improve data compatibility at both the clinic level and throughout the wider sleep field. These include adherence to federal data sharing requirements, such as the "findable, accessible, interoperable, and reusable" principles and the NIH's Data Management and Sharing Policy. Use of the European Data Format eases the burden of data harmonization, but further standardization is needed across multiple data levels, including signal preprocessing, scoring annotations, and metadata.

Importantly, endophenotypes do not arise from signal data in isolation but are increasingly the products of coded algorithmic analyses of these data. Development and validation of computer-based endophenotypes naturally involves the interrogation and optimization of coding language, and

heterogeneity of endophenotypes may result from coding differences. Therefore, sharing should not be limited to clinical information and signals but should also include documentation of any coded algorithms used to analyze these data in language understandable to unaffiliated researchers, either as annotated computer code or in the form of readable "pseudocode" detailing methodological steps. Best practices to enhance readability and reproducibility include specifying formats for input data, providing sufficient documentation (e.g., read-me files and workable examples), and transparent version tracking. When processed data are deposited into repositories such as the NSRR, applicable code or pseudocode can be provided as part of study documentation or via links to online platforms (e.g., <http://www.github.com>, <http://www.zenodo.org>).

Key Area II: External and Prospective Validation

Clinician confidence in the validity, reproducibility, and meaning of endophenotypes is needed for use in the clinical setting. This requires external validation (i.e., beyond derivation cohorts) of endophenotypes in representative populations, as well as prospective validation in well-designed studies. Challenges and research priorities in external and prospective validation are discussed in this key area. Considerations include the following:

1. Clinicians will need a sense of when an endophenotype might be clinically actionable according to whether it is normal or abnormal or high or low. Investigations are needed to determine whether and how endophenotypes differ across patient subgroups and demographics (88, 91). Measurement and interpretation of these metrics should be free from technological (92) or other systemic biases to avoid worsening current health disparities.
2. Better understanding of how endophenotypes vary over the lifespan (e.g., from childhood to adolescence to adulthood, during pregnancy, or through menopause) is needed. Similarly, the impact of evolving health status on endophenotypes requires investigation (e.g., whether comorbidities and/or a history of OSA treatment influence

OSA endophenotypes and treatment predictions).

3. In isolation, a given endophenotypic metric may be inadequate to informing clinical decisions because of complex interactions with other aspects of OSA (including other endophenotypic metrics) and patient characteristics. Investigations of this potential interplay are needed to determine when and how to use endophenotypes alone or in combination.

Research priority 4: Establish endophenotypic metric thresholds on the basis of physiologically or clinically important outcomes. A clinically relevant endophenotype should have predictive value in one or more of three domains: 1) risk of adverse sequelae, 2) physiologic response to a specific treatment or treatments, or 3) benefit from treatment. To some extent, these domains overlap: a hypothetical metric that predicts resolution of respiratory events with OAT and reduces the risk of stroke would cover all three domains. However, the domains are not equivalent. An elevated risk of long-term sequelae does not necessarily translate to treatment benefit (93). For example, some studies (35, 38, 42, 94), but not all (43, 95, 96), suggest that the excessively sleepy symptom subtype is associated with increased risk of future cardiovascular events. Similarly, the sleep apnea-specific hypoxic burden (33, 97, 98) has shown promise with respect to differentiating patients at increased cardiovascular risk (33, 43, 97, 99, 100). However, findings are mixed as to whether treatment mitigates the increased risk in these individuals (95, 96, 98, 101, 102). Similarly, some patients might show apparent physiologic resolution of OSA with a specific treatment but without any appreciable patient-centered or other key clinically important benefits.

Even a metric robustly associated with a clinically important outcome may be of little use as a clinical decision support tool if its interpretation is not straightforward. Defining the distribution of metrics and establishment of thresholds (normal vs. abnormal and/or low vs. high) would make metrics more viable as clinical decision tools and would help stratify patients in prospective trials. Threshold levels have been proposed for physiologic standard metrics such as Pcrit, and data are available that show comparable or greater performance characteristics of physiologic standards compared with traditional metrics such as the AHI (2, 20, 103, 104). However, these

detailed physiologic data were derived from relatively small cohorts, and physiologic standards methodology are too cumbersome for wide clinical deployment. It is plausible that threshold for “normality” may vary by age, sex, and other characteristics that have not been yet addressed.

In contrast, PUP-estimated endotypes have been examined across multiple large cohorts, producing distributions that might reasonably serve as reference ranges (88, 105, 106). A growing number of studies attest to the potential for PUP-estimated endotypes to predict physiologic response to specific treatments. Indeed, PUP and other algorithm-based estimates of low ArTH have been associated with treatment failure for a variety of treatment modalities, including CPAP (87, 91, 107, 108), hypoglossal nerve stimulation therapy (90), and other surgical interventions in some (109) but not all (110) studies. High PUP-estimated LG has also been associated with surgical treatment failure (111). However, consensus thresholds for PUP endotype values are lacking. Studies often report statistical differences in an endotype between responders and nonresponders to a given therapy but do not provide thresholds to categorize patients into normal versus abnormal or low versus high groups on the basis of the endotype of interest (112). For example, Op de Beeck and colleagues demonstrated significantly lower baseline PUP-estimated LG in responders to oral appliance therapy relative to nonresponders but did not specify a cutoff for distinguishing low and high LG categories (86, 90). Furthermore, PUP estimates are not possible in the absence of respiratory events, so at least *some* degree of elevation in the AHI is needed to calculate PUP-derived endotypes. Therefore, establishing normal values for PUP endotypes (i.e., in individuals without OSA) may not be possible, though this does not preclude establishing high and low values among patients with OSA.

Research priority 5: Examine the generalizability of endophenotypic metrics across diverse patient groups. A hypothetical “perfect” endophenotype is usable for any patient with OSA who presents to a sleep practitioner, whether young or elderly, male or female, and independent of ethnic descent or of the presence of comorbidities such as obesity. Testing a metric under the myriad combinations of each of these characteristics may not always be feasible, but clinicians

need at least some degree of confidence that the metric is applicable to the patient in front of them.

Conceptually, if a test measures the true underlying mechanisms that contribute to OSA and the measurement tools are free from biases specific to certain populations (e.g., oximetry in people with different skin tones) then findings should be generalizable across demographic groups. For example, even if a metric is more common in one group versus another (e.g., a low ArTH is more common in people without vs. with obesity [91]), the accuracy of the metric’s estimates should be equivalent across groups, assuming the metric accurately reflects underlying physiology free of bias. Endophenotyping tools require careful testing across diverse populations to ensure that this condition is met. A pertinent and underexplored example is whether the accuracy of hypoxic burden determined from pulse oximetry is affected by differences in skin pigmentation (113).

Similarly, the physiologic validity of endotype estimates in groups that were not well represented in initial derivation studies is difficult to determine. PUP-estimated endotypes were initially derived in comparison with physiologic reference standard measurements in cohorts consisting predominantly of White men (15). Subsequent studies have suggested differences in PUP estimates across sex and in individuals of Asian descent consistent with known differences in physiologic standards. However, differing roles for collapsibility have been observed for Black and White individuals using Pcrit (114) compared with PUP-estimated collapsibility (88). Comparison across such studies is difficult given population and methodological inconsistencies, but any apparently discordant findings between physiologic standard measurements and endotype estimates warrant reexamination of both methods together (e.g., in the physiology laboratory) for the populations in question. In general, unexpected or counterintuitive findings using endophenotypic estimates should motivate a return to the derivation/discovery stage for reexamination and confirmation.

Research priority 6: Examine changes in endophenotypic metrics with aging, changing health status, and treatments. OVERVIEW ON “CHANGE” AND REPRODUCIBILITY. It is important for both the *detectability* and *treatability* of a metric that clinicians

understand the meaning of differences among patients, as well as apparent change in a metric over time. Good reproducibility requires both high *reliability* and good *agreement* (112, 115, 116). Reliability describes how consistently a metric stratifies different individuals relative to one another: a reliable metric will consistently rank an individual with a high value above an individual with a low value (117). *Agreement* refers to the degree to which a metric may change when measured at different time points in a given individual because of measurement noise alone (118). A metric may consistently stratify individuals yet suffer from poor agreement because of high variation on repeat measurement in a single individual. Acceptable reproducibility metrics include the intraclass correlation coefficient (ICC) for reliability (117) and the smallest real difference (SRD) for agreement (119).

MEASUREMENT ERROR VERSUS OTHER SOURCES OF CHANGE. Change in sleep study–based endophenotypes across consecutive nights in the absence of any intervention or changes in conditions (e.g., change in the amount of supine sleep, in head and neck positions, or in sleep architecture) might reasonably be attributed to measurement noise, permitting the calculation of ICC and SRD (112, 120). However, other non-noise sources of change include environmental factors (e.g., acclimation to testing or the “first-night effect”), variable sleep architecture, and night-to-night variability in OSA itself, which can be substantial in some cases (49). Variations in the proportions of NREM and REM sleep are of particular interest, as endotypes have largely been derived from NREM sleep, potentially limiting the understanding of variable REM duration on pathophysiologic mechanisms (14, 121), as well as the applicability to REM-predominant OSA (122). Sources of night-to-night change also raise the underexplored question of whether testing on one occasion (single-night testing) is adequate or if repeated, multnight testing is needed for optimal predictive performance. Indeed, variability in metrics across multiple nights may, in itself, be an important predictor of outcomes (123).

Over longer intervals, change is likely to reflect a combination of measurement noise and intercurrent biological changes due to aging or other sources of evolving health status, such as developing comorbidities or a history of therapeutic interventions (124).

Recent studies comparing men and women have suggested distinct interactions of PUP-estimated endotypes with health status and aging. For example, obesity may distinctly influence endotypes across sexes (125). Aging also appears to have different effects on endotypes in men and women (126), and the role of menopause remains an important but underexplored question (127). In general, further investigations are needed to determine if changes in endophenotypes across the lifespan are distinct in different groups.

INFLUENCE OF TREATMENTS. In the context of targeted therapy, a key question is to what extent a metric needs to change to sufficiently alter key outcomes (i.e., the MCID). The distribution and agreement (SRD) of a metric has implications for clinical interpretability: ideally, the MCID is narrow relative to the range of the distribution but greater than the SRD (128). If the SRD of a metric is greater than its MCID, the metric may fail to detect a clinically important change.

In general, extensive reproducibility data, MCID values, and prospective clinical validation studies are lacking for most endophenotypes. Such studies are urgently needed. Furthermore, reliability, agreement, and MCID are not intrinsic properties of a metric itself but may vary depending on the characteristics of the study population and the outcomes of interest (128). Change in a metric must therefore be evaluated across diverse groups of individuals, including those traditionally underrepresented in OSA studies.

PUP-estimated endotypes have demonstrated moderate to good within-night (124) and short-term (night-to-night [120, 112]) *reliability*. This is generally better for PUP-estimated collapsibility, ArTH, and LG (ICCs of 0.80 or greater) but modest for UAMR (ICCs of 0.59–0.67) (112, 120). Data on night-to-night *agreement* are less favorable (112, 120, 129–131). The SRDs suggest that an individual’s endotype estimate on the basis of PUP could change by as much as 20–30% of the observed range of values because of measurement noise alone, which may limit the ability of these estimates to establish endotype manipulability.

Over longer periods (i.e., years), greater variation is observed in PUP estimates. A longitudinal cohort study showed a significant decrease in PUP-estimated ArTH and an increase in PUP-estimated UAMR by repeating analyses in the same individuals across a 6.5-year time span (124). Sex-specific differences in older versus

younger individuals were reported in a recent cross-sectional study (126).

Several proof-of-concept studies have demonstrated changes in physiologic standard and sleep study–based endotypes with various treatments. Collapsibility assessed using Pcrit improves with weight loss (132), surgery (133), OAT (134), and body position changes (81). LG determined by CPAP drops decreases with supplemental oxygen (135) and acetazolamide (136). Like physiologic standard assessment, PUP-estimated LG also decreases with supplemental oxygen (62, 85) and acetazolamide (62). Conversely, most attempts to increase the ArTH with hypnotics have yielded either neutral effects or only modest benefit (137, 138). Regarding outcomes, most intervention studies that have incorporated OSA endotypes conducted to date have assessed AHI reduction as the primary outcome. Thus, the minimal changes needed for reduction in obstructive respiratory events are calculable, but further study is needed to establish MCID values for truly “clinically important” outcomes, recognizing that OSA may influence multiple outcomes.

Physiologic standard and sleep study–based endotypes may also be informative to understand important mechanistic changes with emerging therapies, for example, whether reductions in AHI with GLP-1 agonist therapy are attributable solely to anatomy (i.e., reduced pharyngeal collapsibility, reduction in the size of the pharyngeal soft tissue structures) or whether nonanatomic endotypes also play a role (8). There is also the potential to investigate age at onset of OSA (139) and the relationship with disease severity and other outcomes. Investigating these key questions in different patient populations is important to allow appropriate interpretation of intervention studies.

Research priority 7: Investigate joint effects, including interplay and interrelationships among endotypes, patient clinical characteristics, OSA disease severity metrics, and downstream health effects. As summarized in Table 2, there is accumulating evidence from multiple proof-of-concept studies that endotypes derived directly by physiologic assessment or by estimates from standard polysomnography can help better predict treatment outcomes across a range of modalities compared with current standard-of-care approaches (5). However, given the different pathophysiologic pathways to OSA,

several recent findings indicate that knowledge of the *interplay* among endotypes as well as OSA phenotypes and clinical characteristics, rather than any single metric alone, is required for optimal treatment prediction (72).

Joint effects among physiologic standard endotypes have long been acknowledged (2), and the interplay among PUP estimates is an area of active investigation. For example, in the context of mild upper airway collapsibility, the combination of high LG and preserved UAMR has been associated with reductions in AHI using oxygen therapy (85). Endotype treatment predictors for oral appliance therapy include mild to moderate airway collapsibility, lower LG, higher ArTH, and poor UAMR (86, 140, 141).

Accruing evidence suggests that nonanatomic endotypes (ArTH, LG, and UAMR) need to be considered in the context of low or high collapsibility. Patients with highly collapsible pharyngeal airways are expected to not benefit from therapies directed toward nonanatomic endotypes, regardless of whether nonanatomic endotypes are abnormal. For example, targeting high LG in a patient with a highly collapsible upper airway may have little physiologic effect unless the collapsibility is targeted first. Thus, testing for high LG may not be useful in this context. A long proposed but largely untested “triage”

approach suggests using a simple collapsibility metric (31, 32, 142) to decide which patients should receive anatomy-directed therapy (e.g., CPAP) without further evaluation and which patients may benefit from more advanced precision testing (2, 30) (Figure 3). The PALM scale (Pcrit, ArTH, LG and muscle response) is a version of this approach based on concepts derived from physiologic standard testing (2). The PALM scale was recently investigated prospectively (72, 73), but further validation is needed, and the requirement for physiologic standard measures precludes widespread use in clinical settings. Still, investigations of the concept using more clinically feasible methods are warranted, for example, testing whether the upper airway collapsibility index (31) successfully triages patients to CPAP versus further assessment with PUP-estimated ArTH, LG, and UAMR (15) to direct alternative therapies.

Like endotypes, OSA phenotypes may interact with one another, as suggested by findings that hypoxic burden is associated with excessive sleepiness and recent data linking ventilatory burden to sleepiness (143). Furthermore, early evidence suggests joint effects among endotypes and OSA phenotypes, as in the observation that high PUP-estimated LG is predictive of blood pressure response to CPAP therapy (95). Studies are needed to better characterize

the interplay among endophenotypes with the potential for use in the clinical setting, including PUP endotypes, respiratory effort metrics (e.g., mandibular movements) (144), hypoxic and ventilatory burdens (33, 67), simple CPAP interventions or therapeutic pressure (32, 145), and algorithms that use standard clinical sleep study report metrics (14, 69).

Key Area III: Design and Conduct of Prospective Studies

As summarized in the previous key areas, considerable retrospective data indicate that endophenotypes (or their combinations) may predict treatment response. However, most analyses are from existing observational and interventional studies without specified *a priori* hypotheses or analysis plans, raising concern for type I errors. In addition, a diverse patient population was not always investigated, and key patient-centered outcomes were frequently not available. As such, well-designed prospective studies in diverse patient populations are needed to investigate the ability of endophenotypes to guide treatment selection for improved outcomes (73).

Research priority 8: Use precision medicine principles to design studies of endophenotype-informed therapeutic decisions. Experience in precision medicine study design from other fields (e.g., oncology,

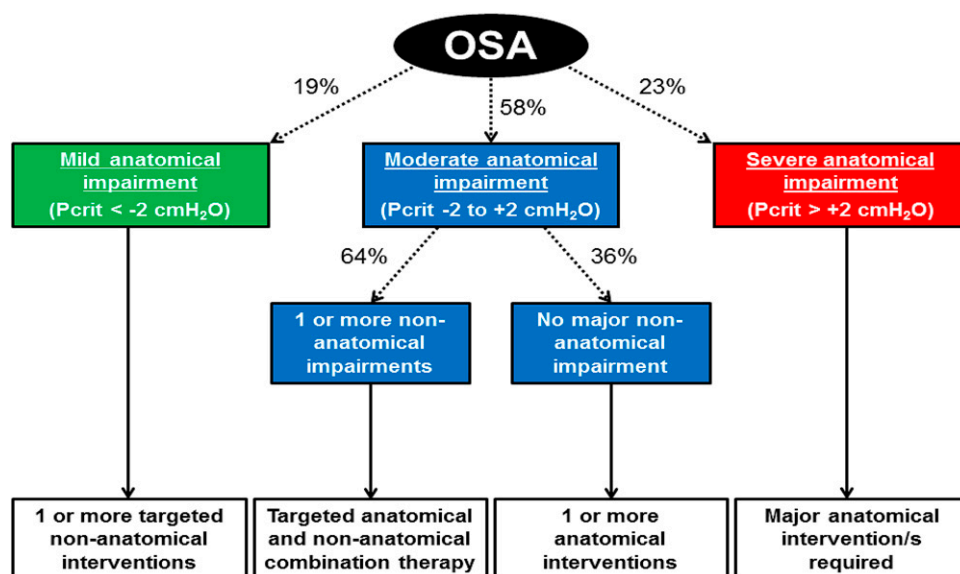


Figure 3. A flow diagram of the PALM scale (Pcrit, arousal threshold, loop gain and muscle responsiveness) categorization concepts and an example of a potential treatment triage decision tree according to 1) the extent of anatomic versus 2) nonanatomic endotype impairment. Percentage estimates are derived from Eckert and colleagues (2), and the figure has been adapted with permission from Eckert (30). Refer to the text for further detail. Note that although this conceptual framework has been applied in small prospective and retrospective treatment intervention trials, further validation is required to translate these concepts into clinical practice. OSA = obstructive sleep apnea; Pcrit = critical closing pressure of the upper airway during sleep.

rheumatology) should inform the approach to trials in precision sleep medicine. Although oncology and rheumatology trials typically target molecular markers, endophenotype-informed OSA management shares a common goal: to match the right patient with the appropriate therapy or therapies in expectation of associated benefits to patient-centered outcomes (57–59). Precision efforts in oncology and rheumatology have recognized that conventional randomized controlled trials, while the “gold standard” for establishing therapeutic efficacy and risk–benefit profile of experimental therapies, may fail to account for heterogeneity in disease mechanisms and reasons for therapeutic failure (58). “Biomarker-driven” trial designs are intended to overcome these barriers. As conceptually depicted in Figure 4, similar endophenotype-informed trial designs are needed for OSA.

For example, a currently ongoing pilot trial, TOP-CPAP (Endotype-targeted Therapy to Rescue OSA Patients Struggling with CPAP Adherence), is recruiting patients with low adherence to CPAP therapy to test whether the addition of eszopiclone will improve adherence (NCT 05951023). Randomization is stratified on the basis of ArTH similar to Figure 4B to test the hypothesis that low ArTH predicts greater improvement in adherence than normal or high ArTH with the addition of eszopiclone.

Research priority 9: Prespecify hypotheses, analysis plans, and appropriate outcomes in endophenotyping studies.

Although prospective, randomized, interventional trials are needed, observational, nonrandomized, or noncontrolled studies can be an important source of evidence as well. To leverage such data, researchers should consider design and analysis plans that attempt to emulate a randomized trial design. A recent nonrandomized interventional study, for example, demonstrated the use of physiologic standard endotypes to guide adjuvant therapies in patients without a full response to OAT (72, 73). The NICEPAP (Novel Physiologic Predictors of Positive Airway Pressure Effectiveness) study is a prospective, observational study to examine whether endotypes are predictive of CPAP adherence, efficacy, and quality of life, in addition to multiple secondary outcomes (146). Like NICEPAP, analytic plans for future OSA endophenotyping studies at the validation/impact analysis stages should be made publicly available *a priori*.

Performance characteristics of the endophenotype of interest (reliability, agreement, MCID) should inform trial size and statistical power considerations. Efficacy targets may vary depending on the stage of development (Figure 2). At the derivation/discovery stage, demonstrating successful mechanism targeting (e.g., improved airway collapsibility by Pcrit), relief of physiologic impact (e.g., reduced AHI or hypoxic burden), or a combination of both may provide a physiologic rationale for the tested therapy. For example, Sands and colleagues recently conducted a double-blind, randomized, crossover trial to investigate the response to drug therapy (147). AHI was the primary outcome; hypoxic burden and arousal index were secondary. These drugs may therefore be considered “rational” in that they have been shown to alter the OSA disease process.

Ultimately, however, further stages of development require demonstration of improvement in important clinical endpoints, as addressing physiologic impact does not necessarily imply patient-centered benefits. Accumulating evidence indicates that reduction of the AHI does not necessarily translate to improvement in patient-centered outcomes (53, 148–152). A truly effective treatment should alter the OSA disease process and symptom burden, improve quality of life, and/or reduce the risk of long-term sequelae. Accordingly, for prospective validation or impact analysis, studies testing endophenotype-informed therapeutic decisions should include at least one metric from each of the following two categories:

1. Altered OSA disease process by reduced adverse *physiologic impact*
 - Current: AHI, time below 90% oxygen saturation, sleep quality (e.g., sleep efficiency).
 - Emerging: Hypoxic burden, ventilatory burden, heart-rate response, ORP.
 - Wherever possible, a physiologic impact metric should be accompanied by or integrate a measurement of therapeutic adherence to demonstrate a true reduction in the burden of physiologic perturbation. For example, the “effective AHI” (153, 154) combines the AHI and adherence to capture both the efficacy of a treatment and the actual use of treatment, thus also facilitating fair comparisons across adherence-dependent and

adherence-independent (e.g., upper airway surgery) therapies.

2. Therapeutic effect according to improved OSA *disease expression*
 - Patient-reported outcomes
 - Subjective sleepiness (e.g., Epworth Sleepiness Scale, Patient-reported Outcomes Measurement Information System [PROMIS] sleep-related impairment item)
 - Fatigue (e.g., PROMIS fatigue item, Fatigue Severity Scale)
 - Insomnia symptoms (e.g., Insomnia Severity Index)
 - Subjective sleep quality: PROMIS sleep disturbance item (155), Pittsburgh Sleep Quality Index
 - Quality of life (e.g., Sleep Apnea Quality of Life Index, Functional Outcomes of Sleep Questionnaire), Patient Generated Index
 - Other symptoms (e.g., nocturnal gasping/choking, nocturia, brain fog, depressed mood, bothersome snoring, erectile dysfunction)
 - Objective outcomes (established or suspected):
 - Blood pressure
 - Metabolic markers (blood glucose handling parameters, glycated hemoglobin)
 - Neurocognitive (objective sleepiness/vigilance, attention, learning, memory, executive function)
 - Motor vehicle accident risk
 - Disorders: hypertension, myocardial infarction, heart failure, metabolic syndrome, nonalcoholic fatty liver disease, mild cognitive impairment, dementia, etc.

Key Area IV: Knowledge Exchange and Impact Analysis

Previous key areas highlighted research needed to address current knowledge gaps before clinical implementation of endophenotyping tools. However, even when these gaps are closed, there is no guarantee that endophenotyping will enter routine clinical practice (53). Translation of research knowledge to the clinical space is a complex process requiring the involvement of multiple stakeholders, including knowledge *creators* (i.e., researchers) and knowledge *users* (i.e., clinical sleep medicine providers, patients, industry, and policymakers). Thus far, OSA endophenotyping has been

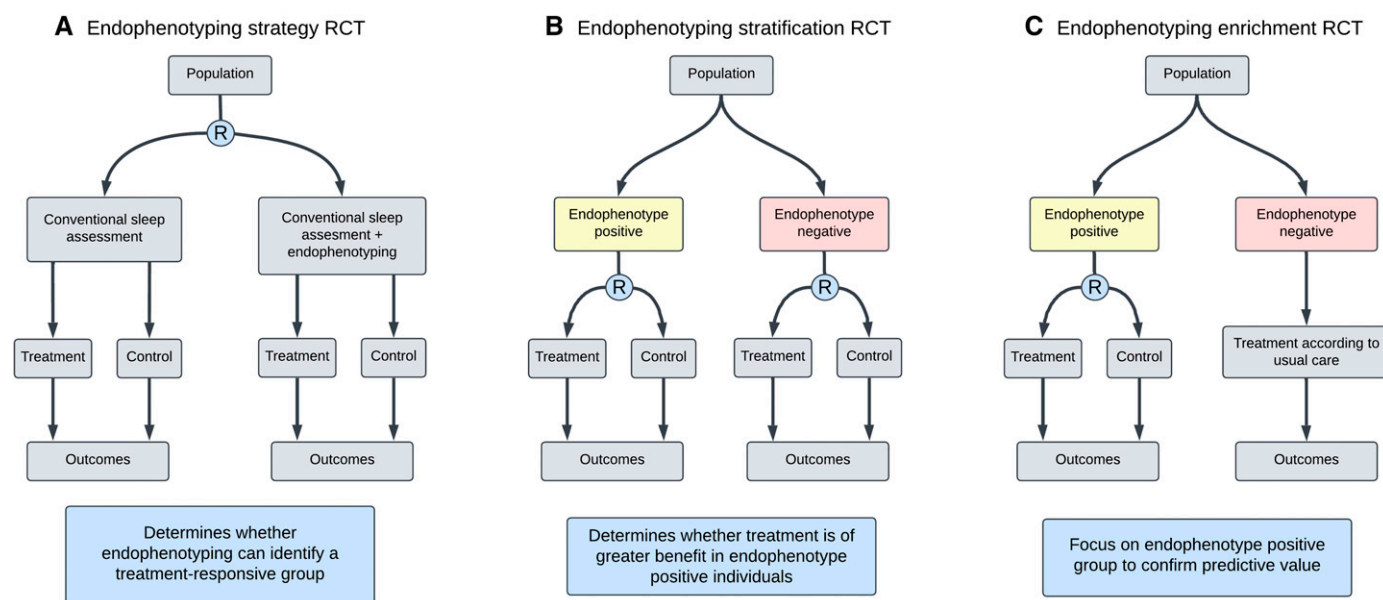


Figure 4. Conceptual endophenotype-informed trial designs. A conventional randomized controlled trial (RCT) stratifies patients with diagnoses of obstructive sleep apnea (OSA) to treatment or control without regard for underlying heterogeneity in pathogenic mechanisms (endotypes) or physiologic impacts and disease expression (OSA phenotypes). In contrast, endophenotype-informed RCTs can test the role of endophenotypes in clinical decision making. (A) An endophenotyping strategy RCT assigns patients to either conventional assessment (e.g., clinical evaluation and polysomnography) or conventional assessment *plus* endophenotyping. Patients in each arm receive the treatment or control intervention depending on the findings of the assessments. Such a study design may determine whether use of an endophenotype can identify a treatment-responsive subgroup. For example, conventional assessment for hypoglossal nerve stimulation therapy includes drug-induced sleep endoscopy (DISE). Conventional DISE could be compared with DISE *plus* endotyping to identify patients with high arousal threshold and adequate upper airway muscle response to test whether endotyping patients better identifies responders (90). (B) An endophenotyping stratification RCT ensures equal distributions of endophenotype-positive and endophenotype-negative patients in treatment and control arms. Such a study design is appropriate to test whether the presence of an endophenotype is associated with differential responses to a specific treatment. For example, the ongoing TOP-CPAP (Endotype-targeted Therapy to Rescue OSA Patients Struggling with CPAP Adherence) pilot trial stratifies the randomization of patients with low continuous positive airway pressure (CPAP) adherence on the basis of arousal threshold to test whether low arousal threshold predicts greater improvement in CPAP adherence than normal or high arousal threshold (NCT 05951023). (C) An endophenotyping enrichment RCT focuses on endophenotype-positive patients to test whether the endophenotype is predictive of response to a specific treatment. Such a study design could be used to test the “triage approach” suggested in Figure 3: patients with low collapsibility and one or more “nonanatomic” endotypes could be randomized to a non-CPAP treatment or control, while patients with high collapsibility receive CPAP. Adapted from Pitzalis and colleagues (58) with permission. R = randomization. Adapted by permission from Reference 156.

the focus of knowledge creators with limited involvement of the ultimate knowledge users. The gap between these two groups raises potential barriers to eventual implementation of endophenotypes in real-world clinical settings (157). In addition to a simple lack of awareness, clinicians may choose not to use an endophenotype for a variety of reasons:

- Their patients and/or practice settings differ substantially from those in whom the endophenotype was validated (11).
- The endophenotype is viewed as unnecessary in light of a perceived intuition for making clinical decisions (54).
- The endophenotype is too difficult to incorporate and efficiently use in a clinical setting (11).

- The costs of employing the endophenotype may outweigh expected benefits, especially in resource-limited settings (60).

This key area focuses on initial steps available to close the gap between knowledge creators and knowledge users. Promoting knowledge exchange between researchers and clinical decision makers early and throughout the process can help codevelop strategies to reduce barriers like those listed above and incorporate effective mitigation strategies (158). Specifically, knowledge exchange “involves collaborative problem-solving between researchers and decision makers and results in mutual learning through the process of planning, producing, disseminating, and applying existing or new research in decision-making” (157).

The research priorities described here are intended to address two key unanswered questions:

1. Will clinicians use endophenotypes to inform clinical decision making?
2. Will their use significantly affect clinical decisions and patient outcomes?

Research priority 10: Establish a clinical registry for collaborative OSA endophenotyping knowledge exchange among researchers and clinical decision makers. Researchers have speculated that the physiologic concepts underlying endophenotypic metrics are already influencing clinicians in treatment selection for patients with OSA (21). This is in contrast with guidelines, which base

treatment decisions largely on the presence and severity of OSA according to the AHI, clinician and patient preferences, and/or the failure of a trial of CPAP therapy (159–161). Whether clinician preferences are or should be influenced by physiologic reasoning is not specified. Nor is it known whether knowledge of underlying physiology would meaningfully change treatment decisions or patient-centered outcomes.

Registries created for other chronic respiratory conditions, such as pulmonary fibrosis (Pulmonary Fibrosis Foundation) and sarcoidosis (Sarcoidosis Advanced Registry for Cures), offer patients and providers the opportunity to advance knowledge and track outcomes at scale. The creation of OSA registries accessible to researchers, clinicians, and patients would lay the groundwork for collaborative knowledge exchange. Researchers could speak to the potential benefits of endophenotyping and provide education on appropriate use, while clinicians and patients could feedback their observations and experience of endophenotypic metrics to the research world. This effort would acknowledge that endophenotyping methods may not yet have a sufficient evidence base for integration into treatment guidelines while engaging clinicians and patients in ongoing efforts to use and assess endophenotyping methods.

A registry would also help support many of the priorities identified in other key areas by providing longitudinal data at a larger scale that could be shared in a collaborative manner. No less important, knowledge exchange would open channels for needed education on endophenotyping, including the underlying pathophysiologic concepts, potential limitations, and the necessary steps that remain to be completed before widespread clinical uptake. For example, a sufficiently validated sleep study–based endotype will require training of sleep specialists and technicians in the relevant technical aspects before and during clinical implementation.

To an extent, a clinical registry would conceptually overlap with the research databases discussed in research priority 3 of this document. However, knowledge exchange between researchers and clinical decision makers faces barriers distinct from those of research collaboration, and tailored approaches specific to the “end user” are needed to encourage clinician involvement in translating endophenotyping. Sharing of

PUP’s underlying source code has generated fruitful collaborations among researchers, but the lack of a graphical user interface limits uptake in the clinical setting. Broad success of a clinical registry incorporating PUP metrics is unlikely in the absence of interactive user-friendly software to engage clinical decision makers. Relatively simple tools may be paired with correspondingly intuitive graphical user interfaces, as in Automatic Blood Oxygen Saturation Analysis, a free MATLAB-based software package (162). More complex tools require ongoing end-user support and software maintenance. As research funding mechanisms do not typically provide resources beyond the investigational period, continuous user support often requires partnership with industry, potentially at the cost of code transparency. Cerebra ORP and hypoxic burden software from the Siesta Group provides user-friendly interfaces, but the underlying algorithms are proprietary. Ideally, an endophenotyping tool strikes a balance between these development philosophies by providing both transparent methods sharable among researchers and a user-friendly design enabling seamless integration into clinical care. The field should advocate for mechanisms to better support the latter.

Research priority 11: Assess the potential clinical and financial benefits and pitfalls of endophenotype-informed treatment selection with comparative effectiveness research. The highly controlled, “optimal” conditions in research trials are not necessarily reflective of real-world clinical settings. Nor is it known to what extent use of endophenotypes will meaningfully change clinician preferences and behaviors. Assuming that high-quality prospective validation studies are reported, they will attest to the potential benefits of endophenotype-informed care under optimal conditions (“efficacy”) (74). However, the performance of endophenotyping in actual clinical settings (“effectiveness”) remains to be established by comparative effectiveness research (CER), defined by the U.S. Department of Health and Human Services as “research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in ‘real world’ settings” (74). A previous ATS research statement provided guidance on the use of CER in pulmonary, critical care, and sleep medicine (74). Ultimately, CER studies that address the

clinical and cost-effectiveness of care using OSA endophenotype-informed approaches versus usual care in specific scenarios are needed for translation. The rising prominence of home sleep testing evokes pertinent examples: emerging evidence suggests that PUP-estimated endotypes can be derived from home sleep tests and have the potential to influence treatment (64, 163, 164). However, PUP requires a nasal cannula airflow signal, which is not included in many current and emerging home sleep testing devices, such as “wearable” wrist and/or finger sensors, as well as devices that do not come into contact with patients (bed-based “nearables” and audio- or video-based “airables”) (165). A practicing sleep clinician who routinely tests for OSA using such a device would need to balance the potential utility of PUP-estimated endotypes against the cost of deviating from usual practice for a test that includes a nasal cannula. Broadly, the large burden of undiagnosed OSA and the trend toward testing with devices that use limited and/or varying signals suggest a “tiered endophenotyping approach” may be necessary for metrics that require more extensive and costly data (e.g., in-laboratory polysomnography, drug-induced sleep endoscopy). That is, endophenotyping may be best reserved (initially) for certain subsets of patients (e.g., those who fail to respond to or decline the standard treatment approach with CPAP, patients considering surgical therapies) rather than applying such an approach to all patients with newly diagnosed OSA. In general, the costs and benefits of endophenotyping are expected to change with evolving practice paradigms, and CER is needed to help clinicians balance advantages and drawbacks.

Summary and Conclusions

The pathogenesis, clinical manifestations, and consequences of OSA vary markedly among patients. Yet OSA heterogeneity goes largely unaddressed by current diagnostic and treatment practices. Instead, most patients are diagnosed on the basis of AHI from a single-night sleep study followed by a trial of CPAP therapy. This clinical model yields high failure treatment rates of ~50%. “Second-line” non-CPAP therapies such as oral appliances, upper airway surgery, hypoglossal nerve stimulation, and supine avoidance therapy are typically reserved for

those who do not respond or adhere to CPAP. Variable and largely unpredictable efficacy and treatment uptake and adherence characterize this trial-and-error approach, risking confusion, frustration, and unaddressed burdens of untreated and undertreated OSA. Growing knowledge of OSA pathogenesis has stimulated new lines of investigation for targeted therapy. GLP-1 agonists for weight loss likely directly affect the primary anatomic predisposition to pharyngeal collapse. Emerging OSA pharmacotherapies and combination therapies are intended to target specific underlying mechanisms or “endotypes” beyond the primary anatomic predisposition to pharyngeal collapse. These include low

ArTH, unstable control of breathing (high LG), and impaired pharyngeal dilator muscle function. In the research setting, interindividual differences in OSA endotypes and clinical manifestations between patients or “OSA phenotypes” offer promise for a more targeted approach to OSA management in which the appropriate treatment or treatments are tailored to individual needs. Yet these concepts have been limited largely to the research setting. Accordingly, the current research statement has attempted to outline the challenges and the potential to translate OSA endophenotyping to deliver a more tailored approach to care to improve outcomes. Specifically, a research road map from

discovery to impact analysis is provided that covers a range of priority areas for clinical translation, including technical standards, validation, establishment of clinical cutoffs, determination of MCIDs, generalizability across diverse populations, stability of measurement, and the design and conduct of prospective studies. Meeting these needs will provide the evidence required to implement these concepts into clinical care at scale. ■

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Members of the subcommittee are as follows:

DANNY J. ECKERT, Ph.D. (*Chair*)^{1,2}
 THOMAS M. TOLBERT, M.D. (*Co-Chair*)³
 ERNA S. ARNARDÓTTIR, Ph.D.^{4,5}
 ALI AZARBARZIN, Ph.D.²
 SUSMITA CHOWDHURI, M.D., M.S.⁶
 PETER A. CISTULLI, M.D., Ph.D., M.B.A.^{7,8}
 LAURA K. GELL, Ph.D.²
 AMY S. JORDAN, Ph.D.⁹
 BRENDAN T. KEENAN, M.S.¹⁰
 YUANMING LUO, M.D., Ph.D.^{1,2,11}
 DIEGO R. MAZZOTTI, Ph.D.^{12,13}
 SARA OP DE BEECK, Ph.D.^{14,15}
 AMAL M. OSMAN, Ph.D.¹
 SANJAY R. PATEL, M.D., M.S.¹⁶
 CINTHYA PEÑA-ORBEA, M.D.¹⁷
 JEAN-LOUIS PÉPIN, M.D., Ph.D.¹⁸
 SUSAN REDLINE, M.D., M.P.H.²
 SCOTT A. SANDS, Ph.D.²
 CHRISTOPHER N. SCHMICKL, M.D., Ph.D.¹⁹
 RICHARD J. SCHWAB, M.D.¹⁰
 TAMAR SOFER, Ph.D.^{20,21}
 ANDREW WELLMAN, M.D., Ph.D.²
 ANDREY V. ZINCHUK, M.D., M.H.S.²²

Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; ¹¹State Key Laboratory of Respiratory Disease, Guangzhou Medical University, Guangzhou, China; ¹²Division of Medical Informatics and ¹³Division of Pulmonary Critical Care and Sleep Medicine, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas; ¹⁴Translational Neurosciences, Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium; ¹⁵Department of ENT, Head and Neck Surgery, Antwerp University Hospital, Edegem, Belgium; ¹⁶Center for Sleep and Cardiovascular Outcomes Research, University of Pittsburgh, Pittsburgh, Pennsylvania; ¹⁷Sleep Disorders Center, Neurologic Institute, Cleveland Clinic, Cleveland, Ohio; ¹⁸University Grenoble-Alpes and HP2 Laboratory, INSERM, La Tronche, France; ¹⁹Division of Pulmonary, Critical Care, and Sleep Medicine, University of California, San Diego, La Jolla, California; ²⁰Cardiovascular Division, Department of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts; ²¹Department of Biostatistics, Harvard T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts; and ²²Department of Medicine, School of Medicine, Yale University, New Haven, Connecticut

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¹Adelaide Institute for Sleep Health, Flinders University, Bedford Park, South Australia, Australia; ²Division of Sleep Medicine and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; ³Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; ⁴School of Technology, Sleep Institute, Reykjavik University, Reykjavik, Iceland; ⁵Landspítali, The National University Hospital of Iceland, Reykjavik, Iceland; ⁶John D. Dingell VA Medical Center and Wayne State University, Detroit, Michigan; ⁷Department of Respiratory and Sleep Medicine, Royal North Shore Hospital, St. Leonards, New South Wales, Australia; ⁸Faculty of Medicine and Health, University of Sydney, Sydney, Australia; ⁹Melbourne School of Psychological Sciences, University of Melbourne, Parkville, Victoria, Australia; ¹⁰Division of Sleep Medicine,

Technologies, Philips, Powell Mansfield, and SleepRes; served as a fiduciary officer for BreathePA; and received research support from Apnimed, Bayer, Mineralys, Philips Respironics, SleepRes, and Sommetrics. J.L.P. served as a consultant for BioProject, Eli Lilly, Idorsia, ResMed, Takeda, and Zoll Itamar; served in a leadership role for Grenoble Alpes University Foundation; received honoraria from BioProject, Eli Lilly, Idorsia, Pharmanovia, ResMed, Sefam, and Zoll-Respicardia; and received research support from the French National Research Agency. S.R. is an employee and fiduciary officer of the National Sleep Foundation; served on an advisory board for Apnimed; served as a

consultant for Apnimed and Eli Lilly; and served in a leadership role for the Alliance of Sleep Apnea Partners and the *Journal of Sleep Health*. R.J.S. served on an advisory board for ExciteOSA, Onera Health, and Sleep Evolution; served as a consultant for Eli Lilly; received research support from CryOSA, Eli Lilly, Inspire, and ResMed; and received royalties from Eli Lilly, Merck Manual, and UpToDate. A.W. served as a consultant for Apnimed, iNOS, Inspire, Mosanna, Nox Medical, and Takeda; holds financial interest in Apnimed, iNOS, and Mosanna; holds a patent on pharmacological therapy for Obstructive Sleep Apnea; and received research support from the NIH and ProSomnus. D.J.E. served on an

advisory board for Apnimed, Eisai, Invicta Medical, Mosanna, and SleepRes; served as a consultant for Apnimed, Bayer, Invicta Medical, Mosanna, Open Airway Dental Solutions Australia, and Takeda; holds both pending and issued patents about methods for estimating key phenotypic traits for obstructive sleep apnea; and received research support from Bayer, Eli Lilly, Invicta Medical, the National Health and Medical Research Council, the NIH, Open Airway Dental Solutions Australia, SomnoMed, Takeda, and Withings. T.M.T., D.R.M., C.P.O., S.C., A.S.J., and Y.L. reported no commercial or relevant non-commercial interests from ineligible companies.

References

- Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, *et al*. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7: 687–698.
- Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea: identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013;188: 996–1004.
- Pevernagie DA, Gnidovec-Strazisar B, Grote L, Heinzer R, McNicholas WT, Penzel T, *et al*. On the rise and fall of the apnea-hypopnea index: a historical review and critical appraisal. *J Sleep Res* 2020;29: e13066.
- Malhotra A, Ayappa I, Ayas N, Collop N, Kirsch D, McArdle N, *et al*. Metrics of sleep apnea severity: beyond the apnea-hypopnea index. *Sleep* 2021;44:zsab030.
- Pepin JL, Eastwood P, Eckert DJ. Novel avenues to approach non-CPAP therapy and implement comprehensive obstructive sleep apnoea care. *Eur Respir J* 2022;59:2101788.
- Baratta F, Pastori D, Bucci T, Fabiani M, Fabiani V, Brunori M, *et al*. Long-term prediction of adherence to continuous positive air pressure therapy for the treatment of moderate/severe obstructive sleep apnea syndrome. *Sleep Med* 2018;43:66–70.
- Pépin JL, Bailly S, Rinder P, Adler D, Szeftel D, Malhotra A, *et al*. CPAP therapy termination rates by OSA phenotype: a French nationwide database analysis. *J Clin Med* 2021;10:936.
- Malhotra A, Grunstein RR, Fietze I, Weaver TE, Redline S, Azarbarzin A, *et al*. SURMOUNT-OSA Investigators. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N Engl J Med* 2024;391: 1193–1205.
- Aishah A, Eckert DJ. Phenotypic approach to pharmacotherapy in the management of obstructive sleep apnoea. *Curr Opin Pulm Med* 2019; 25:594–601.
- König IR, Fuchs O, Hansen G, von Mutius E, Kopp MV. What is precision medicine? *Eur Respir J* 2017;50:1700391.
- Light JM, Owens RL, Schmickl CN, Malhotra A. Precision medicine for obstructive sleep apnea. *Sleep Med Clin* 2019;14:391–398.
- Edwards BA, Redline S, Sands SA, Owens RL. More than the sum of the respiratory events: personalized medicine approaches for obstructive sleep apnea. *Am J Respir Crit Care Med* 2019;200: 691–703.
- Hajipour M, Baumann B, Azarbarzin A, Allen AJH, Liu Y, Fels S, *et al*. Association of alternative polysomnographic features with patient outcomes in obstructive sleep apnea: a systematic review. *J Clin Sleep Med* 2023;19:225–242.
- Edwards BA, Eckert DJ, McSharry DG, Sands SA, Desai A, Kehlmann G, *et al*. Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2014;190: 1293–1300.
- Sands SA, Edwards BA, Terrill PI, Taranto-Montemurro L, Azarbarzin A, Marques M, *et al*. Phenotyping pharyngeal pathophysiology using polysomnography in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2018;197:1187–1197.
- Schmickl CN, Orr JE, Kim P, Nokes B, Sands S, Manoharan S, *et al*. Point-of-care prediction model of loop gain in patients with obstructive sleep apnea: development and validation. *BMC Pulm Med* 2022;22: 158.
- Vena D, Taranto-Montemurro L, Azarbarzin A, Op de Beeck S, Marques M, Vanderveken OM, *et al*. Clinical polysomnographic methods for estimating pharyngeal collapsibility in obstructive sleep apnea. *Sleep* 2022;45:zsac050.
- Oppersma E, Ganglberger W, Sun H, Thomas RJ, Westover MB. Algorithm for automatic detection of self-similarity and prediction of residual central respiratory events during continuous positive airway pressure. *Sleep* 2021;44:zsaa215.
- Nassi TE, Oppersma E, Labarca G, Donker D, Westover MB, Thomas RJ. Morphological prediction of CPAP associated acute respiratory instability. *Ann Am Thorac Soc* 2024;22:138–149.
- Dutta R, Delaney G, Toson B, Jordan AS, White DP, Wellman A, *et al*. A novel model to estimate key obstructive sleep apnea endotypes from standard polysomnography and clinical data and their contribution to obstructive sleep apnea severity. *Ann Am Thorac Soc* 2021;18: 656–667.
- Edwards BA, Jordan AS, Schmickl CN, Owens RL. Point: are OSA phenotypes clinically useful? Yes. *Chest* 2023;163:25–28.
- Tolbert TM, Parekh A, Rapoport DM, Ayappa I. Counterpoint: are OSA phenotypes clinically useful? No. *Chest* 2023;163:28–32.
- Sands SA, Edwards BA. Pro: can physiological risk factors for obstructive sleep apnea be determined by analysis of data obtained from routine polysomnography? *Sleep* 2023;46:zsac310.
- Younes M, Schwab R. Con: can physiological risk factors for obstructive sleep apnea be determined by analysis of data obtained from routine polysomnography? *Sleep* 2023;46:zsac158.
- Asyali MH, Berry RB, Khoo MC. Assessment of closed-loop ventilatory stability in obstructive sleep apnea. *IEEE Trans Biomed Eng* 2002;49: 206–216.
- Op de Beeck S, Van de Perck E, Vena D, Kazemeini E, Deltjens M, Willemen M, *et al*. Flow-identified site of collapse during drug-induced sleep endoscopy: feasibility and preliminary results. *Chest* 2021;159: 828–832.
- Op de Beeck S, Vena D, Mann D, Azarbarzin A, Huyett P, Van de Perck E, *et al*. Polysomnographic airflow shapes and site of collapse during drug-induced sleep endoscopy. *Eur Respir J* 2024;63:2400261.
- Luo YM, Wu HD, Tang J, Jolley C, Steier J, Moxham J, *et al*. Neural respiratory drive during apnoeic events in obstructive sleep apnoea. *Eur Respir J* 2008;31:650–657.
- Gell LK, Vena D, Alex RM, Azarbarzin A, Calianese N, Hess LB, *et al*. Neural ventilatory drive decline as a predominant mechanism of obstructive sleep apnoea events. *Thorax* 2022;77:707–716.
- Eckert DJ. Phenotypic approaches to obstructive sleep apnoea—new pathways for targeted therapy. *Sleep Med Rev* 2018;37:45–59.
- Osman AM, Carberry JC, Burke PGR, Toson B, Grunstein RR, Eckert DJ. Upper airway collapsibility measured using a simple wakefulness

- test closely relates to the pharyngeal critical closing pressure during sleep in obstructive sleep apnea. *Sleep* 2019;42:zs080.
32. Osman AM, Tong BK, Landry SA, Edwards BA, Joosten SA, Hamilton GS, *et al.* An assessment of a simple clinical technique to estimate pharyngeal collapsibility in people with obstructive sleep apnea. *Sleep* 2020;43:zsaa067.
 33. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, *et al.* The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J* 2019;40:1149–1157.
 34. Keenan BT, Ye L, Pien GW, Magalang UJ, Benediktsdottir B, Gislason T, *et al.* Symptom subtypes of obstructive sleep apnea 10 years later: past, present and future. *Sleep* 2025;48:zsaf082.
 35. Ye L, Pien GW, Ratcliffe SJ, Bjornsdottir E, Arnardottir ES, Pack AI, *et al.* The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J* 2014;44:1600–1607.
 36. Keenan BT, Kim J, Singh B, Bittencourt L, Chen NH, Cistulli PA, *et al.* Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. *Sleep* 2018;41:zsx214.
 37. Kim J, Keenan BT, Lim DC, Lee SK, Pack AI, Shin C. Symptom-based subgroups of Koreans with obstructive sleep apnea. *J Clin Sleep Med* 2018;14:437–443.
 38. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med* 2019;200:493–506.
 39. Allen AH, Beaudin AE, Fox N, Raneri JK, Skomro RP, Hanly PJ, *et al.* Symptom subtypes and cognitive function in a clinic-based OSA cohort: a multi-centre Canadian study. *Sleep Med* 2020;74:92–98.
 40. Morris JL, Mazzotti DR, Gottlieb DJ, Hall MH. Sex differences within symptom subtypes of mild obstructive sleep apnea. *Sleep Med* 2021;84:253–258.
 41. González KA, Tarraf W, Wallace DM, Stickel AM, Schneiderman N, Redline S, *et al.* Phenotypes of obstructive sleep apnea in the Hispanic Community Health Study/Study of Latinos. *Sleep* 2021;44:zsab181.
 42. Labarca G, Dreyse J, Salas C, Letelier F, Jorquera J. A validation study of four different cluster analyses of OSA and the incidence of cardiovascular mortality in a Hispanic population. *Chest* 2021;160:2266–2274.
 43. Trzepizur W, Blanchard M, Ganem T, Balusson F, Feuilloley M, Girault JM, *et al.* Sleep apnea specific hypoxic burden, symptom subtypes and risk of cardiovascular events and all-cause mortality. *Am J Respir Crit Care Med* 2022;205:108–117.
 44. Loewen A, Ostrowski M, Laprairie J, Atkar R, Gnitecki J, Hanly P, *et al.* Determinants of ventilatory instability in obstructive sleep apnea: inherent or acquired? *Sleep* 2009;32:1355–1365.
 45. Salloum A, Rowley JA, Mateika JH, Chowdhuri S, Omran Q, Badr MS. Increased propensity for central apnea in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 2010;181:189–193.
 46. Tolbert TM, Parekh A, Rapoport DM, Ayappa I. Phenotyping using polysomnography attributes reduced respiratory events after CPAP therapy to improved upper airway collapsibility. *Ann Am Thorac Soc* 2025;22:438–449.
 47. Younes M. CrossTalk proposal: elevated loop gain is a consequence of obstructive sleep apnoea. *J Physiol* 2014;592:2899–2901.
 48. Orr JE, Edwards BA, Malhotra A. CrossTalk opposing view: loop gain is not a consequence of obstructive sleep apnoea. *J Physiol* 2014;592:2903–2905.
 49. Lechat B, Naik G, Reynolds A, Aishah A, Scott H, Loffler KA, *et al.* Multinight prevalence, variability, and diagnostic misclassification of obstructive sleep apnea. *Am J Respir Crit Care Med* 2022;205:563–569.
 50. Berry RB, Kouchi KG, Der DE, Dickel MJ, Light RW. Sleep apnea impairs the arousal response to airway occlusion. *Chest* 1996;109:1490–1496.
 51. Haba-Rubio J, Sforza E, Weiss T, Schroder C, Krieger J. Effect of CPAP treatment on inspiratory arousal threshold during NREM sleep in OSAS. *Sleep Breath* 2005;9:12–19.
 52. Eckert DJ, Younes MK. Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. *J Appl Physiol* (1985) 2014;116:302–313.
 53. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules: a review and suggested modifications of methodological standards. *JAMA* 1997;277:488–494.
 54. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS; Evidence-Based Medicine Working Group. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. *JAMA* 2000;284:79–84.
 55. Wallace E, Smith SM, Perera-Salazar R, Vaucher P, McCowan C, Collins G, *et al.* International Diagnostic and Prognosis Prediction (IDAPP) Group. Framework for the impact analysis and implementation of clinical prediction rules (CPRs). *BMC Med Inform Decis Mak* 2011;11:62.
 56. Pencina MJ, Goldstein BA, D'Agostino RB. Prediction models—development, evaluation, and clinical application. *N Engl J Med* 2020;382:1583–1586.
 57. Biankin AV, Piantadosi S, Hollingsworth SJ. Patient-centric trials for therapeutic development in precision oncology. *Nature* 2015;526:361–370.
 58. Pitzalis C, Choy EHS, Buch MH. Transforming clinical trials in rheumatology: towards patient-centric precision medicine. *Nat Rev Rheumatol* 2020;16:590–599.
 59. Gibson PG, McDonald VM, Thomas D. Treatable traits, combination inhaler therapy and the future of asthma management. *Respirology* 2023;28:828–840.
 60. Agusti A, Gibson PG, McDonald VM. Treatable traits in airway disease: from theory to practice. *J Allergy Clin Immunol Pract* 2023;11:713–723.
 61. Genta PR, Schorr F, Edwards BA, Wellman A, Lorenzi-Filho G. Discriminating the severity of pharyngeal collapsibility in men using anthropometric and polysomnographic indices. *J Clin Sleep Med* 2020;16:1531–1537.
 62. Terrill PI, Edwards BA, Nemati S, Butler JP, Owens RL, Eckert DJ, *et al.* Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. *Eur Respir J* 2015;45:408–418.
 63. Sands SA, Terrill PI, Edwards BA, Taranto Montemurro L, Azarbarzin A, Marques M, *et al.* Quantifying the arousal threshold using polysomnography in obstructive sleep apnea. *Sleep* 2018;41:zsx183.
 64. Orr JE, Sands SA, Edwards BA, Deyoung PN, Deacon N, Jen R, *et al.* Measuring loop gain via home sleep testing in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2018;197:1353–1355.
 65. Messineo L, Taranto-Montemurro L, Azarbarzin A, Oliveira Marques MD, Calianese N, White DP, *et al.* Breath-holding as a means to estimate the loop gain contribution to obstructive sleep apnoea. *J Physiol* 2018;596:4043–4056.
 66. Wang D, Martins RT, Rowsell L, Wong KK, Yee BJ, Grunstein RR, *et al.* Comparison of awake respiratory control versus sleep obstructive sleep apnea endotypes. *J Appl Physiol* (1985) 2024;137:1524–1534.
 67. Parekh A, Kam K, Wickramaratne S, Tolbert TM, Varga A, Osorio R, *et al.* Ventilatory burden as a measure of obstructive sleep apnea severity is predictive of cardiovascular and all-cause mortality. *Am J Respir Crit Care Med* 2023;208:1216–1226.
 68. Younes M, Ostrowski M, Soiferman M, Younes H, Younes M, Raneri J, *et al.* Odds ratio product of sleep EEG as a continuous measure of sleep state. *Sleep* 2015;38:641–654.
 69. Dutta R, Tong BK, Eckert DJ. Development of a physiological-based model that uses standard polysomnography and clinical data to predict oral appliance treatment outcomes in obstructive sleep apnea. *J Clin Sleep Med* 2022;18:861–870.
 70. Joosten SA, Edwards BA, Landry SA. The arousal threshold: the “weakest link” in obstructive sleep apnea pathogenesis? *Am J Respir Crit Care Med* 2024;210:1396–1397.
 71. Wu X, Liu J, Tanadini LG, Lammertse DP, Blight AR, Kramer JL, *et al.* Challenges for defining minimal clinically important difference (MCID) after spinal cord injury. *Spinal Cord* 2015;53:84–91.
 72. Aishah A, Tong BKY, Osman AM, Pitcher G, Donegan M, Kwan BCH, *et al.* Stepwise add-on and endotype-informed targeted combination therapy to treat obstructive sleep apnea: a proof-of-concept study. *Ann Am Thorac Soc* 2023;20:1316–1325.
 73. Eckert D, Tong B, Aishah A, Naik G, Chiang A, Pitcher G, *et al.* Stepwise and targeted therapy to treat sleep apnea: a novel, physiology-informed, personalised approach using oral appliance therapy plus combination therapy in incomplete responders [abstract]. *Am J Respir Crit Care Med* 2024;209:A1059.

74. Carson SS, Goss CH, Patel SR, Anzueto A, Au DH, Elborn S, *et al.*; American Thoracic Society Comparative Effectiveness Research Working Group. An official American Thoracic Society research statement: comparative effectiveness research in pulmonary, critical care, and sleep medicine. *Am J Respir Crit Care Med* 2013;188:1253–1261.
75. Crook S, Sievi NA, Bloch KE, Stradling JR, Frei A, Puhan MA, *et al.* Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomised controlled trials. *Thorax* 2019;74:390–396.
76. Zhang Y, Kim M, Prerau M, Mobley D, Rueschman M, Sparks K, *et al.* The National Sleep Research Resource: making data findable, accessible, interoperable, reusable and promoting sleep science. *Sleep* 2024;47:zsae088.
77. Thomson LDJ, Landry SA, Singleton R, Wong AM, Joosten SA, Beatty CJ, *et al.* The effect of hypopnea scoring on the arousal threshold in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2020;202:1308–1311.
78. Landry SA, Joosten SA, Thomson LDJ, Turton A, Wong AM, Leong P, *et al.* Effect of hypopnea scoring criteria on noninvasive assessment of loop gain and surgical outcome prediction. *Ann Am Thorac Soc* 2020;17:484–491.
79. Mooney AM, Abounasr KK, Rapoport DM, Ayappa I. Relative prolongation of inspiratory time predicts high versus low resistance categorization of hypopneas. *J Clin Sleep Med* 2012;8:177–185.
80. Randerath WJ, Trembl M, Priegnitz C, Stieglitz S, Hagemeyer L, Morgenstern C. Evaluation of a noninvasive algorithm for differentiation of obstructive and central hypopneas. *Sleep* 2013;36:363–368.
81. Joosten SA, Edwards BA, Wellman A, Turton A, Skuza EM, Berger PJ, *et al.* The effect of body position on physiological factors that contribute to obstructive sleep apnea. *Sleep* 2015;38:1469–1478.
82. Walsh JH, Maddison KJ, Platt PR, Hillman DR, Eastwood PR. Influence of head extension, flexion, and rotation on collapsibility of the passive upper airway. *Sleep* 2008;31:1440–1447.
83. Zinchuk AV, Kushida CA, Walker A, Wellman A, Azarbarzin A, Alex RM, *et al.* Arousal threshold modifies the effect of CPAP on executive function among individuals with obstructive sleep apnea. *Eur Respir J* 2025;65:2401183.
84. Finnsson E, Ólafsdóttir GH, Loftsdóttir DL, Jónsson S, Helgadóttir H, Ágústsson JS, *et al.* A scalable method of determining physiological endotypes of sleep apnea from a polysomnographic sleep study. *Sleep* 2021;44:zsaa168.
85. Sands SA, Edwards BA, Terrill PI, Butler JP, Owens RL, Taranto-Montemurro L, *et al.* Identifying obstructive sleep apnoea patients responsive to supplemental oxygen therapy. *Eur Respir J* 2018;52:1800674.
86. Op de Beeck S, Dieltjens M, Azarbarzin A, Willemen M, Verbraecken J, Braem MJ, *et al.* Mandibular advancement device treatment efficacy is associated with polysomnographic endotypes. *Ann Am Thorac Soc* 2021;18:511–518.
87. Zinchuk AV, Chu JH, Liang J, Celik Y, Op de Beeck S, Redeker NS, *et al.* Physiological traits and adherence to sleep apnea therapy in individuals with coronary artery disease. *Am J Respir Crit Care Med* 2021;204:703–712.
88. Sands SA, Alex RM, Mann D, Vena D, Terrill PI, Gell LK, *et al.* Pathophysiology underlying demographic and obesity determinants of sleep apnea severity. *Ann Am Thorac Soc* 2023;20:440–449.
89. Cheng WJ, Finnsson E, Agustsson JS, Sands SA, Hang LW. Continuous positive airway pressure and adherence in patients with different endotypes of obstructive sleep apnea. *J Sleep Res* 2024;33:e13999.
90. Op de Beeck S, Wellman A, Dieltjens M, Strohl KP, Willemen M, Van de Heyning PH, *et al.*; STAR Trial Investigators. Endotypic mechanisms of successful hypoglossal nerve stimulation for obstructive sleep apnea. *Am J Respir Crit Care Med* 2021;203:746–755.
91. Gray EL, McKenzie DK, Eckert DJ. Obstructive sleep apnea without obesity is common and difficult to treat: evidence for a distinct pathophysiological phenotype. *J Clin Sleep Med* 2017;13:81–88.
92. Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. Racial bias in pulse oximetry measurement. *N Engl J Med* 2020;383:2477–2478.
93. Yeh RW, Kramer DB. Decision tools to improve personalized care in cardiovascular disease: moving the art of medicine toward science. *Circulation* 2017;135:1097–1100.
94. Allen AJH, Jen R, Mazzotti DR, Keenan BT, Goodfellow SD, Taylor CM, *et al.* Symptom subtypes and risk of incident cardiovascular and cerebrovascular disease in a clinic-based obstructive sleep apnea cohort. *J Clin Sleep Med* 2022;18:2093–2102.
95. Schmickl CN, Orr JE, Sands SA, Alex RM, Azarbarzin A, McGinnis L, *et al.* Loop gain as a predictor of blood pressure response in patients treated for obstructive sleep apnea: secondary analysis of a clinical trial. *Ann Am Thorac Soc* 2024;21:296–307.
96. Eulenburg C, Celik Y, Redline S, Munstern E, Glantz H, Strollo PJ, *et al.* Cardiovascular outcomes in adults with coronary artery disease and obstructive sleep apnea with versus without excessive daytime sleepiness in the RICCADSA clinical trial. *Ann Am Thorac Soc* 2023;20:1048–1056.
97. Azarbarzin A, Sands SA, Taranto-Montemurro L, Vena D, Sofer T, Kim SW, *et al.* The sleep apnea-specific hypoxic burden predicts incident heart failure. *Chest* 2020;158:739–750.
98. Pinilla L, Esmaeili N, Labarca G, Martinez-Garcia M, Torres G, Gracia-Lavedan E, *et al.* Hypoxic burden to guide CPAP treatment allocation in patients with obstructive sleep apnoea: a post hoc study of the ISAACC trial. *Eur Respir J* 2023;62:2300828.
99. Kim JS, Azarbarzin A, Wang R, Djonlagic IE, Punjabi NM, Zee PC, *et al.* Association of novel measures of sleep disturbances with blood pressure: the Multi-Ethnic Study of Atherosclerosis. *Thorax* 2020;75:57–63.
100. Martínez-García MA, Sánchez-de-la-Torre M, White DP, Azarbarzin A. Hypoxic burden in obstructive sleep apnea: present and future. *Arch Bronconeumol* 2023;59:36–43.
101. Gerves-Pinque C, Bailly S, Goupil F, Pigeanne T, Launois S, Leclair-Visonneau L, *et al.* Positive airway pressure adherence, mortality, and cardiovascular events in patients with sleep apnea. *Am J Respir Crit Care Med* 2022;206:1393–1404.
102. Azarbarzin A, Zinchuk A, Peker Y, Sands SA. Reply to: heart rate response in obstructive sleep apnea: a clue to reveal cardiovascular benefit from continuous positive airway pressure? *Am J Respir Crit Care Med* 2022;206:1181–1182.
103. Kirkness JP, Peterson LA, Squier SB, McGinley BM, Schneider H, Meyer A, *et al.* Performance characteristics of upper airway critical collapsing pressure measurements during sleep. *Sleep* 2011;34:459–467.
104. Wellman A, Eckert DJ, Jordan AS, Edwards BA, Passaglia CL, Jackson AC, *et al.* A method for measuring and modeling the physiological traits causing obstructive sleep apnea. *J Appl Physiol (1985)* 2011;110:1627–1637.
105. Won CHJ, Reid M, Sofer T, Azarbarzin A, Purcell S, White D, *et al.* Sex differences in obstructive sleep apnea phenotypes, the Multi-Ethnic Study of Atherosclerosis. *Sleep* 2020;43:zsz274.
106. Finnsson E, Amardóttir E, Cheng W-J, Alex RM, Sigmarsdóttir ÞB, Helgason S, *et al.* Sleep apnea endotypes: from the physiological laboratory to scalable polysomnographic measures. *Front Sleep* 2023;2:1188052.
107. Zinchuk AV, Redeker NS, Chu JH, Liang J, Stepnowsky C, Brandt CA, *et al.* Physiological traits and adherence to obstructive sleep apnea treatment in patients with stroke. *Am J Respir Crit Care Med* 2020;201:1568–1572.
108. Wu H, Fang F, Wu C, Zhan X, Wei Y. Low arousal threshold is associated with unfavorable shift of PAP compliance over time in patients with OSA. *Sleep Breath* 2021;25:887–895.
109. Li Y, Ye J, Han D, Cao X, Ding X, Zhang Y, *et al.* Physiology-based modeling may predict surgical treatment outcome for obstructive sleep apnea. *J Clin Sleep Med* 2017;13:1029–1037.
110. Wong AM, Landry SA, Joosten SA, Thomson LDJ, Turton A, Stonehouse J, *et al.* Examining the impact of multilevel upper airway surgery on the obstructive sleep apnoea endotypes and their utility in predicting surgical outcomes. *Respirology* 2022;27:890–899.
111. Joosten SA, Leong P, Landry SA, Sands SA, Terrill PI, Mann D, *et al.* Loop gain predicts the response to upper airway surgery in patients with obstructive sleep apnea. *Sleep* 2017;40:zsx094.
112. Tolbert TM, Schoenholz RL, Parekh A, Berkaliyeva A, Osorio RS, Ayappa I, *et al.* Night-to-night reliability and agreement of obstructive sleep apnea pathophysiologic mechanisms estimated with phenotyping using polysomnography in cognitively normal elderly subjects. *Sleep* 2023;46:zsad058.

113. Gottlieb ER, Ziegler J, Morley K, Rush B, Celi LA. Assessment of racial and ethnic differences in oxygen supplementation among patients in the intensive care unit. *JAMA Intern Med* 2022;182:849–858.
114. Puri S, Panza GS, Kissane D, Jones S, Reck K, Lin HS, *et al*. Racial differences in upper airway collapsibility and loop gain in young adult males. *Sleep* 2023;46:zsad091.
115. de Vet HC, Terwee CB, Knol DL, Bouter LM. When to use agreement versus reliability measures. *J Clin Epidemiol* 2006;59:1033–1039.
116. Hernaez R. Reliability and agreement studies: a guide for clinical investigators. *Gut* 2015;64:1018–1027.
117. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *J Strength Cond Res* 2005;19:231–240.
118. Liaw LJ, Hsieh CL, Lo SK, Chen HM, Lee S, Lin JH. The relative and absolute reliability of two balance performance measures in chronic stroke patients. *Disabil Rehabil* 2008;30:656–661.
119. Beckerman H, Roebroeck ME, Lankhorst GJ, Becher JG, Bezemer PD, Verbeek AL. Smallest real difference, a link between reproducibility and responsiveness. *Qual Life Res* 2001;10:571–578.
120. Strassberger C, Hedner J, Sands SA, Tolbert TM, Taranto-Montemurro L, Marciniak A, *et al*. Night-to-night variability of polysomnography-derived physiologic endotypic traits in patients with moderate to severe OSA. *Chest* 2023;163:1266–1278.
121. Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, Catcheside PG. Marked reduction in obstructive sleep apnea severity in slow wave sleep. *J Clin Sleep Med* 2009;05:519–524.
122. Appleton SL, Vakulin A, Martin SA, Lang CJ, Wittert GA, Taylor AW, *et al*. Hypertension is associated with undiagnosed OSA during rapid eye movement sleep. *Chest* 2016;150:495–505.
123. Lechat B, Löffler KA, Reynolds AC, Naik G, Vakulin A, Jennings G, *et al*. High night-to-night variability in sleep apnea severity is associated with uncontrolled hypertension. *NPJ Digit Med* 2023;6:57.
124. Alex RM, Sofer T, Azarbarzin A, Vena D, Gell LK, Wellman A, *et al*. Within-night repeatability and long-term consistency of sleep apnea endotypes: the Multi-Ethnic Study of Atherosclerosis and Osteoporotic Fractures in Men study. *Sleep* 2022;45:zsac129.
125. Nokes B, Orr JE, White S, Luu S, Chen Z, Alex R, *et al*. Effect of obesity on sleep apnea pathogenesis differs in women versus men: multiple mediation analyses in the retrospective SNOOzzzE cohort. *J Appl Physiol* (1985) 2024;136:1516–1525.
126. Hang LW, Tsai YC, Finnsson E, Ågústsson JS, Sands SA, Cheng WJ. Sex-specific age-related worsening of pathological endotypic traits in patients with obstructive sleep apnea. *Sleep* 2025;48:zsae185.
127. Koo SK, Ahn GY, Choi JW, Kim YJ, Jung SH, Moon JS, *et al*. Obstructive sleep apnea in postmenopausal women: a comparative study using drug induced sleep endoscopy. *Braz J Otorhinolaryngol* 2017;83:285–291.
128. Streiner DL, Norman GR, Cairney J. Health measurement scales: a practical guide to their development and use. New York: Oxford University Press; 2015.
129. Hoff E, Strassberger C, Zou D, Grote L, Stenlof K, Hedner J. Modification of endotypic traits in OSA by the carbonic anhydrase inhibitor sulthiame. *Chest* 2024;165:704–715.
130. Strassberger C, Hedner J, Marciniak A, Zou D, Grote L. Response. *Chest* 2023;164:e161–e162.
131. Keenan BT, Magalang UJ, Schwab RJ. Night-to-night reliability and agreement of physiological endotypes: two steps forward, one step back. *Sleep* 2023;46:zsad116.
132. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, *et al*. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991;144:494–498.
133. Schwartz AR, Schubert N, Rothman W, Godley F, Marsh B, Eisele D, *et al*. Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1992;145:527–532.
134. Marques M, Genta PR, Azarbarzin A, Taranto-Montemurro L, Messineo L, Hess LB, *et al*. Structure and severity of pharyngeal obstruction determine oral appliance efficacy in sleep apnoea. *J Physiol* 2019;597:5399–5410.
135. Edwards BA, Sands SA, Owens RL, White DP, Genta PR, Butler JP, *et al*. Effects of hyperoxia and hypoxia on the physiological traits responsible for obstructive sleep apnoea. *J Physiol* 2014;592:4523–4535.
136. Edwards BA, Sands SA, Eckert DJ, White DP, Butler JP, Owens RL, *et al*. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. *J Physiol* 2012;590:1199–1211.
137. Carter SG, Eckert DJ. Effects of hypnotics on obstructive sleep apnea endotypes and severity: novel insights into pathophysiology and treatment. *Sleep Med Rev* 2021;58:101492.
138. Messineo L, Sands SA, Labarca G. Hypnotics on obstructive sleep apnea severity and endotypes: a systematic review and meta-analysis. *Am J Respir Crit Care Med* 2024;210:1461–1474.
139. Olaithe M, Hagen EW, Barnett JH, Eastwood PR, Bucks RS. OSA-onset: an algorithm for predicting the age of OSA onset. *Sleep Med* 2023;108:100–104.
140. Bamagoos AA, Cistulli PA, Sutherland K, Madronio M, Eckert DJ, Hess L, *et al*. Polysomnographic endotyping to select patients with obstructive sleep apnea for oral appliances. *Ann Am Thorac Soc* 2019;16:1422–1431.
141. Antonaglia C, Vidoni G, Contardo L, Giudici F, Salton F, Ruaro B, *et al*. Low arousal threshold estimation predicts failure of mandibular advancement devices in obstructive sleep apnea syndrome. *Diagnostics (Basel)* 2022;12:2548.
142. Wellman D, Messineo L, Esmaeili N, Aishah A, Azarbarzin A, White D, *et al*. Estimation of upper airway collapsibility and arousal threshold in OSA patients using pulse oximetry [abstract]. *Am J Respir Crit Care Med* 2024;209:A2983.
143. Staykov E, Mann DL, Kainulainen S, Leppänen T, Töyräs J, Azarbarzin A, *et al*. Ventilatory burden predicts change in sleepiness following positive airway pressure in sleep apnea [preprint]. medRxiv; 2024 [accessed 2025 Mar 27]. Available from: <https://www.medrxiv.org/content/10.1101/2024.11.12.24316879v1>.
144. Martinot J-B, Pépin J-L. Mandibular jaw movements as a non-invasive measure of respiratory effort during sleep: application in clinical practice. *Front Sleep* 2023;2:1145620.
145. Landry SA, Joosten SA, Eckert DJ, Jordan AS, Sands SA, White DP, *et al*. Therapeutic CPAP level predicts upper airway collapsibility in patients with obstructive sleep apnea. *Sleep* 2017;40:zsx056.
146. Anwar AI, Byrne S, Sharma A, Sands S, Wellman A, Redeker NS, *et al*. Novel physiologic predictors of positive airway pressure effectiveness (NICEPAP) study: rationale, design and methods. *Sleep Breath* 2024;28:2005–2015.
147. Sands SA, Collet J, Gell LK, Calianese N, Hess LB, Vena D, *et al*. Combination pharmacological therapy targeting multiple mechanisms of sleep apnoea: a randomised controlled cross-over trial. *Thorax* 2024;79:259–268.
148. Kushida CA, Nichols DA, Holmes TH, Quan SF, Walsh JK, Gottlieb DJ, *et al*. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-Term Efficacy Study (APPLES). *Sleep* 2012;35:1593–1602.
149. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, *et al*. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;373:1095–1105.
150. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, *et al*. SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;375:919–931.
151. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea: the RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016;194:613–620.
152. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, *et al*. Spanish Sleep Network. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med* 2020;8:359–367.
153. Every JD, Mackay SG, Sideris AW, Do TQ, Jones A, Weaver EM. Mean disease alleviation between surgery and continuous positive airway pressure in matched adults with obstructive sleep apnea. *Sleep* 2023;46:zsad176.

154. Kaffenberger TM, Soose RJ, Strollo PJ, Vanderveken OM. Three-dimensional mean disease alleviation (3D-MDA): the next step in measuring sleep apnea treatment effectiveness. *Sleep Med* 2025; 125:27–30.
155. Buysse DJ, Yu L, Moul DE, Germain A, Stover A, Dodds NE, *et al.* Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep* 2010;33: 781–792.
156. Pitzalis C, Choy EHS, Buch MH. Transforming clinical trials in rheumatology: towards patient-centric precision medicine. *Nat Rev Rheumatol* 2020;16:590–599.
157. Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, *et al.* Lost in knowledge translation: time for a map? *J Contin Educ Health Prof* 2006;26:13–24.
158. Prihodova L, Guerin S, Tunney C, Kernohan WG. Key components of knowledge transfer and exchange in health services research: findings from a systematic scoping review. *J Adv Nurs* 2019;75: 313–326.
159. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, *et al.* Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *J Clin Sleep Med* 2015;11:773–827.
160. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med* 2019;15:301–334.
161. Kent D, Stanley J, Aurora RN, Levine CG, Gottlieb DJ, Spann MD, *et al.* Referral of adults with obstructive sleep apnea for surgical consultation: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med* 2021;17:2507–2531.
162. Karhu T, Leppänen T, Töyräs J, Oksenberg A, Myllymaa S, Nikkonen S. ABOSA—freely available automatic blood oxygen saturation signal analysis software: structure and validation. *Comput Methods Programs Biomed* 2022;226:107120.
163. Eckert D, Dutta R, Levendowski D. Application of a physiology based OSA endotype model to predict oral appliance outcomes using home sleep study data [abstract]. *Sleep* 2024;47:A257.
164. Eckert D, Dutta R, Levendowski D. 0471 Simplified endotyping using home sleep study data to inform targeted therapy for obstructive sleep apnea [abstract]. *Sleep* 2024;47:A203.
165. Pinilla L, Chai-Coetzer CL, Eckert DJ. Diagnostic modalities in sleep disordered breathing: current and emerging technology and its potential to transform diagnostics. *Respirology* 2025;30:286–302.
166. Edwards BA, Andara C, Landry S, Sands SA, Joosten SA, Owens RL, *et al.* Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2016;194:1413–1422.
167. Taranto-Montemurro L, Edwards BA, Sands SA, Marques M, Eckert DJ, White DP, *et al.* Desipramine increases genioglossus activity and reduces upper airway collapsibility during non-REM sleep in healthy subjects. *Am J Respir Crit Care Med* 2016;194:878–885.
168. Taranto-Montemurro L, Messineo L, Azarbarzin A, Vena D, Hess LB, Calianese NA, *et al.* Effects of the combination of atomoxetine and oxybutynin on OSA endotypic traits. *Chest* 2020;157:1626–1636.
169. Taranto-Montemurro L, Messineo L, Sands SA, Azarbarzin A, Marques M, Edwards BA, *et al.* The combination of atomoxetine and oxybutynin greatly reduces obstructive sleep apnea severity: a randomized, placebo-controlled, double-blind crossover trial. *Am J Respir Crit Care Med* 2019;199:1267–1276.
170. Li Y, Schwartz AR, Zealea D, Shotwell MS, Hall ME, Lindsell CJ, *et al.* Ansa cervicalis stimulation effects on upper airway patency: a structure-based analysis. *Eur Respir J* 2025;65:2400901.
171. Schwartz AR, Barnes M, Hillman D, Malhotra A, Kezirian E, Smith PL, *et al.* Acute upper airway responses to hypoglossal nerve stimulation during sleep in obstructive sleep apnea. *Am J Respir Crit Care Med* 2012;185:420–426.
172. Pien GW, Ye L, Keenan BT, Maislin G, Björnsdóttir E, Arnardóttir ES, *et al.* Changing faces of obstructive sleep apnea: treatment effects by cluster designation in the Icelandic Sleep Apnea Cohort. *Sleep* 2018; 41:zsx201.
173. Mazzotti DR, Keenan BT, Thorarinsdóttir EH, Gislason T, Pack AI; Sleep Apnea Global Interdisciplinary Consortium. Is the Epworth Sleepiness Scale sufficient to identify the excessively sleepy subtype of OSA? *Chest* 2022;161:557–561.
174. Morris JL, Scott PW, Magalang U, Keenan BT, Patel SR, Pack AI, *et al.* Symptom subtype progression in obstructive sleep apnea over 5 years. *J Clin Sleep Med* 2024;20:1773–1783.
175. Azarbarzin A, Sands SA, Younes M, Taranto-Montemurro L, Sofer T, Vena D, *et al.* The sleep apnea-specific pulse-rate response predicts cardiovascular morbidity and mortality. *Am J Respir Crit Care Med* 2021;203:1546–1555.
176. Azarbarzin A, Ostrowski M, Younes M, Keenan BT, Pack AI, Staley B, *et al.* Arousal responses during overnight polysomnography and their reproducibility in healthy young adults. *Sleep* 2015;38:1313–1321.
177. Azarbarzin A, Zinchuk A, Wellman A, Labarca G, Vena D, Gell L, *et al.* Cardiovascular benefit of continuous positive airway pressure in adults with coronary artery disease and obstructive sleep apnea without excessive sleepiness. *Am J Respir Crit Care Med* 2022;206:767–774.
178. Zinchuk A, Edwards BA, Jeon S, Koo BB, Concato J, Sands S, *et al.* Prevalence, associated clinical features, and impact on continuous positive airway pressure use of a low respiratory arousal threshold among male United States veterans with obstructive sleep apnea. *J Clin Sleep Med* 2018;14:809–817.
179. Wang X, Zhang J, Zou J, Zhou T, Zhou E, Shen L, *et al.* Polysomnographic endotypes of successful multilevel upper airway surgery for obstructive sleep apnea. *Sleep* 2025;48:zsaf012.
180. Zhao D, Li Y, Xian J, Qu Y, Cao X, Ye J. The combination of anatomy and genioglossus activity in predicting the outcomes of velopharyngeal surgery. *Otolaryngol Head Neck Surg* 2017;156: 567–574.
181. Altree TJ, Aishah A, Loffler KA, Grunstein RR, Eckert DJ. The norepinephrine reuptake inhibitor reboxetine alone reduces obstructive sleep apnea severity: a double-blind, placebo-controlled, randomized crossover trial. *J Clin Sleep Med* 2023;19:85–96.
182. Osman AM, Toson B, Naik GR, Mukherjee S, Delbeck M, Hahn M, *et al.* A novel TASK channel antagonist nasal spray reduces sleep apnea severity in physiological responders: a randomized, blinded, trial. *Am J Physiol Heart Circ Physiol* 2024;326:H715–H723.
183. Taranto-Montemurro L, Sands SA, Edwards BA, Azarbarzin A, Marques M, de Melo C, *et al.* Desipramine improves upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation. *Eur Respir J* 2016;48:1340–1350.
184. Beatty C, Wong A, Landry S, Thomson LDJ, Collet J, Joosten SA, *et al.* The impact of surgical weight loss on the physiological endotypes causing obstructive sleep apnea [abstract]. *Sleep Adv* 2023;4: A22–A23.
185. Araghi MH, Chen YF, Jagielski A, Choudhury S, Banerjee D, Hussain S, *et al.* Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis. *Sleep* 2013;36: 1553–1562, 1562A–1562E.
186. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: role of loop gain. *Respir Physiol Neurobiol* 2008;162:144–151.
187. Wang D, Wong KK, Rowsell L, Don GW, Yee BJ, Grunstein RR. Predicting response to oxygen therapy in obstructive sleep apnoea patients using a 10-minute daytime test. *Eur Respir J* 2018;51:1701587.