Creating an Optimal Approach for Diagnosing Sleep Apnea

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KEYWORDS

• Sleep apnea • Diagnosis • Home sleep apnea testing • Virtual sleep laboratory
• Mandibular jaw movements • Photoplethysmography • Peripheral arterial tone

KEY POINTS

- Home multi-night sleep testing reduces misclassification of sleep apnea level of severity.
- Scoring of abnormal respiratory events and sleep disturbances could be assisted by artificial intelligence to reduce burden of manual scoring and inter-scorer variability.
- Sleep testing methods should be low-cost, simple to install, and easy to use at home.
- Robust clinical trials are needed to validate new sensors, algorithms, and digital solutions.

INTRODUCTION

Sleep apnea is one of the most frequent chronic diseases, affecting nearly one billion people worldwide.[1] Its prevalence is expected to continue to increase owing to the sustained progression of obesity, sedentariness, and diabetes epidemics that represent the most common risk factors for sleep apnea.[2] At an individual level, sleep apnea is responsible for deterioration in quality of life, neurocognitive dysfunctions, and sleepiness (causing related traffic accidents).[3,4] Sleep apnea is associated with a higher risk of the occurrence and cumulation of cardiometabolic comorbidities, which in turn lead to early mortality.[5–7] The impact on health systems is substantial, and in response to the burden of sleep apnea, specific national programs have been initiated to review diagnostic methods, along with the reorganization of treatment and follow-up care pathways.[8]

Conventionally, diagnosis usually depends on overnight polysomnography in a sleep clinic, for which there are often long waiting lists, as well as being highly human-resource intensive. Once diagnosed, the efficient treatments are available to confront the medical challenge of sleep apnea. Continuous positive airway pressure (CPAP) is the first-line therapy for moderate-to-severe obstructive sleep apnea (OSA) and is highly efficient in improving quality of life and reducing symptoms and sleepiness.[9] The efficacy of CPAP is less clear concerning reduction in the risk of cardiovascular diseases and mortality, but there is strong evidence from real-word studies of a positive impact[10,11] of OSA treatment. Positive airway therapies also reduce health-related costs, particularly in the comorbid combinations of sleep apnea and chronic obstructive pulmonary disease (COPD),[12] or sleep apnea and type 2 diabetes.[13]

Although often ignored in the past, for all these reasons there is an increase in sleep apnea

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Sleep Med Clin 18 (2023) 301–309
https://doi.org/10.1016/j.jsmc.2023.05.004

awareness among health care professionals, health insurers, and individuals having risk factors of sleep apnea. Therefore, in recent years, there has been a huge increase in the demand for sleep apnea diagnosis and treatment pathway workflows. For example, a national registry study in Finland reported a continuous increase in the societal burden caused by sleep apnea over the last 20 years, constant progression in outpatient visits in primary and secondary care and an increase in the cumulative annual number of days off work for sleep apnea.[8] In the Finnish case, to meet these growing demands, diagnostic methods were simplified and more often conducted in an ambulatory setting, treatment pathways were revised, and patient follow-up was reorganized. Consequently, despite a remarkable increase in the number of patients, there was a significant decrease in societal costs per patient.[8] This is a pragmatic demonstration that the urgently needed reforms in sleep apnea diagnosis and treatment workflow are feasible, benefiting both patients and society as a whole.[14,15]

Advances to Be Made in Sleep Apnea Diagnosis

This review aims to summarize the main improvements that could be made in sleep apnea diagnosis. We do not discuss sleep apnea symptoms or specific clinical contexts. Several major issues are addressed.

1. Patients and caregivers share expectations for the rapid deployment of simplified and home sleep testing. Multi-night assessment certainly represents the future, avoiding misclassification of sleep apnea level of severity.
2. The introduction of novel technologies and sensors (after appropriate validation as medical devices) or end-to-end diagnostic solutions is necessary.
3. Scoring of abnormal respiratory events and sleep disturbances should be supported by automated devices and interpretable artificial intelligence.
4. New approaches to sleep apnea diagnosis should be appropriate to meet the size of the epidemiologic problem. Testing methods should be low-cost and easy-to-use to allow dissemination *at all scales* in diverse health systems.

Multi-Night Home Sleep Apnea Testing

The American Academy of Sleep Medicine has established clinical practice guidelines supporting home sleep apnea testing (HSAT) with technically adequate devices for the diagnosis of OSA in "uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA" (Strong Recommendation).[16] In patients with a high pretest probability of OSA without unstable comorbidities, comorbid insomnia, or suspicion of nocturnal hypoventilation, HSAT now represents the standard of care in many countries.

However, it is currently widely accepted that for patients with mild-to-moderate sleep apnea, a single night of polysomnography or HSAT can lead to misclassification of disease severity in nearly one-third of patients. This is explained by the substantial night-to-night variability in the apnea–hypopnea index (AHI)[17–19] and unevenness in sleep quality.[20] Also, up to 21% of patients might be overdiagnosed, whereas 7% might be underdiagnosed based on a single-night AHI value.[21] In-laboratory sleep studies probably exacerbate misclassifications when compared with at-home measurements as place and type of recording are modulating factors susceptible to influencing the AHI. The "first night effect" is probably higher in the sleep laboratory owing to the unusual sleep environment leading in turn to changes in sleep architecture, different sleep positions, and consequently variations in respiratory event indices.[17] Sleep body position is largely determined by the recording device used, as some devices affect the ability to sleep in a lateral decubitus position.

In summary, among the current requirements for an accurate diagnostic workup of OSA, it is now time that at-home multi-night testing becomes mainstream practice.[22] Such a multi-night sleep testing strategy has been challenged due to potentially higher health care costs and greater inconvenience to patients. However, newly available digital medicine end-to-end diagnostic solutions will significantly simplify at-home multi-night testing allowing efficient cost-effective diagnostic pathways to be implemented.[21,23–27]

Knowledge Gaps and Research Perspectives

Number of nights of sleep testing

The number of nights of sleep testing required for a reliable and accurate OSA diagnosis is still under debate.[22,28,29] The optimum number of nights required is a compromise between the inconvenience for the patient, cost-effectiveness, and the precision required for clinical decision-making. Most of the studies addressing night-to-night variability in AHI have been conducted over two or three consecutive nights. Recently, Lechat and colleagues[21] have amassed an impressive amount of home sleep data to describe the

variability and misclassification of OSA. Using a noninvasive under-mattress sensor technology, 67,278 individuals aged between 18 and 90 years underwent in-home nightly monitoring over an average of approximately 170 nights per participant.[21] The main "inflection" point of the number of nights versus diagnostic confidence curves occurs between 5 and 10 nights, after which there is only a relatively small improvement in diagnostic performance.[29] Undertreatment probability drops to 14% and overtreatment to 6% with a 5-night diagnostic test corresponding to an approximately twofold increase in overall diagnostic performance.[29]

The number of nights required is probably also related to the diagnostic performance of the diagnosis tool used and the typology of patients. Some sleep apnea phenotypes are associated with higher AHI variability, particularly mild-to-moderate OSA, OSA with comorbid insomnia and/or cardiovascular diseases, and behavioral and lifestyle factors such as alcohol consumption. A pragmatic view might be to start with 5 nights for all patients and in case of large night-to-night variability, extend to 7 to 10 nights.

Apnea–hypopnea index variability: A new metric for sleep apnea diagnosis and clinical decision-making

Sole reliance on the AHI for the classification of OSA severity has been challenged[30] as it may not precisely reflect the OSA-related hypoxic burden and acute cardiovascular responses that are the best predictors of long-term hard outcomes and mortality.[11] In the quest for metrics to better characterize OSA severity and to guide therapeutic decisions, information gained by multinight recordings might change practices. It is unknown whether the mean, median, or standard deviation of AHI will be a better predictor of outcomes. This question has been recently nicely addressed for atrial fibrillation[31] and the occurrence of malignant ventricular arrhythmias in heart failure patients appropriately treated with implantable cardioverter-defibrillators.[32] There was a significant association between the variability in sleep-disordered breathing recorded over several nights and the number of appropriate shocks. Very recently, it has been shown that a single-night assessment of OSA failed to detect any association with hypertension. Conversely, the association with hypertension was clearly detected when AHI was measured over $\geq$28 nights.[33] These details are of fundamental importance when aiming to develop risk prediction analyses or performing clinical trials in the OSA field. Also, studies assessing the link between the variability of AHI at diagnosis and simple clinical outcomes such as excessive daytime sleepiness, quality of life, or long-term CPAP adherence are missing so far.

Implementation of Novel Technologies, Sensors, and End-to-End Solutions

Polysomnography provides three main categories of information required for accurate sleep apnea diagnosis (**Fig. 1**): sleep characterization (ie, architecture, microstructure, and fragmentation); number and nature of respiratory events (ie, apneas, hypopneas, respiratory effort-related arousals, and central vs obstructive components); and acute cardiorespiratory responses (ie, sympathetic activity and hypoxic burden). To capture all these data, multiple sensors are needed requiring long installation times, specialized technical expertise for scoring, and continuous monitoring during the night of the multiple recording channels by a sleep professional. Automated scoring of polysomnography has been introduced to ease the task of sleep technicians and render the scoring more objective.[34,35]

A major step forward for the easy implementation and smooth running of new diagnostic procedures would be to validate and render available a limited number of innovative sensors and metrics, able to summarize all the information needed to determine sleep disorder pathophysiology and classify disease severity. Indeed, a plethora of technologies has emerged to diagnose sleep apnea in the home setting. Mandibular jaw movements (MJMs),[23–25,36] photoplethysmography (PPG), and peripheral arterial tone[26,37] are among the most promising techniques that have already been shown to perform well in different research and clinical settings.

Mandibular Jaw Movements

There are new technologies for detecting and recording MJM in the home setting. A sensor taped on the chin captures inertial energy in a three-dimensional system of measurement providing data from a total of six derived channels (Sunrise).[23–25] At a given point in time, some channels are more informative than others depending on the position of the body, head, and mandible.

The mandibular jaw plays the role of a prop stabilizing the pharynx, ensuring upper airway patency, and reducing upper airway resistance in the presence of negative and suctioning pressure inside the airways during inspiration. MJMs reflect both respiratory drive and variations in the respiratory effort (RE), which typically occur during abnormal respiratory events. This reliable measurement of respiratory drive/effort allows an

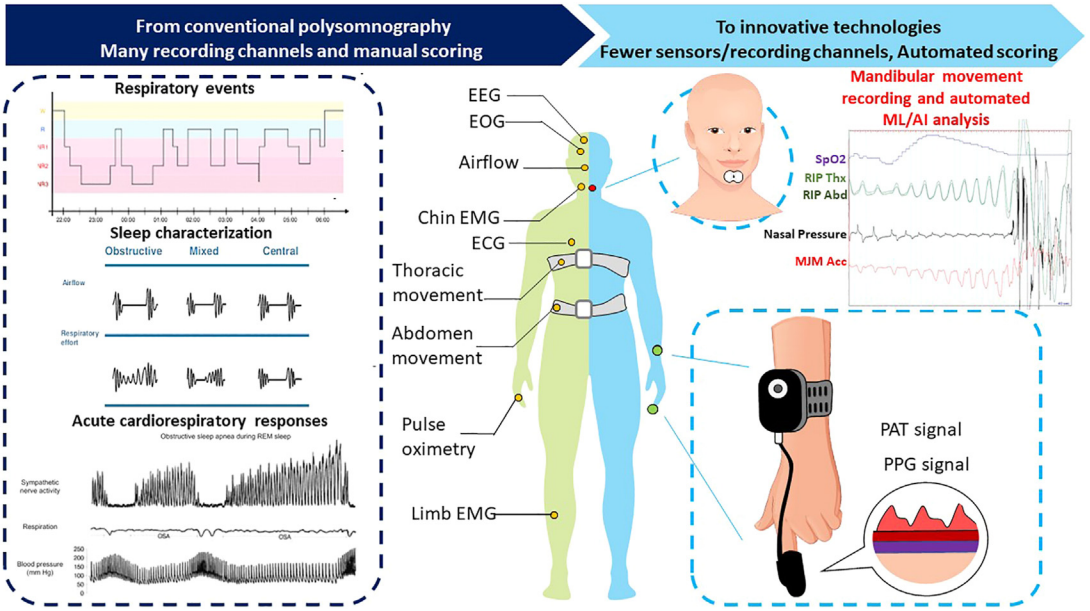

Fig. 1. Transition from the conventional sleep apnea diagnostic pathway based on overnight polysomnography in a sleep clinic to home multi-night testing based on new innovative sensors and digital solutions. Polysomnography (PSG) in a sleep clinic includes many different recording channels: brain activity (EEG), eye movements (EOG), muscle activity (EMG), heart rhythm (ECG), abdominal movement (ABD), and so forth. Home sleep testing has fewer recording channels: mandibular jaw movements (MJM), peripheral arterial tonometry (PAT), and photoplethysmography (PPG).

accurate identification of obstructive versus central events[38] and a unique characterization of the cumulative burden of RE throughout the night.[36]

MJMs are the net result of the activation of brainstem respiratory and sleep centers and their respective interactions.[24] This interaction modulates the amplitude and frequency of MJM across the different sleep stages allowing sleep staging.[24] During light sleep (N2), the amplitude of MJM is of several tenths of a millimeter and varies slightly. The amplitude of MJM increases during normal deepening of sleep into non-rapid eye movement sleep (N3) when upper airway resistance is known to increase. N3 MJM is also more stable than during N2. Rapid eye movement (REM) sleep is easily identified by irregular frequencies and changing amplitudes in MJM reflecting tonic and phasic sleep. MJM amplitudes during REM are on average smaller than non-REM sleep amplitudes.

At present, the only known limitation of MJM is difficulty in fixing the sensor to the chin of men with abundant beards.

Photoplethysmography and peripheral arterial tonometry

PPG and peripheral arterial tonometry (PAT) are noninvasive measurements reflecting sympathetic activity. PPG measures small variations in light absorption associated with changes in tissue perfusion, usually at the fingertip.[39] The pulsatile component of the waveform reflects changes in blood volume occurring with each heartbeat and the amplitude between pulsatile changes reflects autonomic tone.[39] PAT measures the pulsatile arterial volume at the finger, which depends on sympathetic activity, providing a window into the autonomic nervous system.

Most respiratory events in sleep apnea end in cortical and/or autonomic arousals leading to peripheral sympathetic activation. Intrinsically, PAT and PPG signals have the potential to identify micro-arousals associated with these surges in sympathetic activity ending the respiratory events. Sympathetic activation causes vasoconstriction and heart rate acceleration resulting in attenuation of the PAT and PPG signals. The interval between micro-arousals then corresponds to the frequency of respiratory events. The combination with other signals, such as SaO_2, snoring, and thoracic impedance, can improve performances and complete PAT and PPG information. In addition, measurement of the tonic and phasic sympathetic tones and their variations also allows an estimation of sleep stages and total sleep time.

The combination of simultaneous assessment of PAT/PPG with two or three additional signals

(including SaO_2) allows us to derive a comprehensive characterization of sleep architecture and the main indices of sleep apnea severity. Two devices integrated into digital solutions are already available on the market (ie, WatchPAT and NightOwl). They work with acceptable levels of performances.[37,40] However, misclassification can occur for mild- and moderate-severity classes of sleep apnea, whereas the recognition of severe sleep apnea is good. Once again (see paragraph above), use over multiple nights represents a solution to increase the robustness of these ambulatory home-based diagnostic tools.

Automated Devices and Artificial Intelligence for Scoring Respiratory Events and Sleep Disturbances

The manual scoring of respiratory and sleep events requires expert specialist staff and is very time- and human-resource-consuming. Moreover, manual scoring and the classification of sleep epochs have two essential drawbacks.

Manual scoring is associated with large intra- and inter-scorer variability

This significant limitation persists even in well-trained teams and despite well-established scoring criteria. In a recent study,[25] we compared home sleep testing using mandibular movements (MJMs) with at-home polysomnography that was blindly scored by two expert centers (in Grenoble and London). There was significant variability among the experienced experts (ie, inter-scorer agreement reached only 80%) despite the use of standardized scoring criteria. These discrepancies have been known for many years and are present even in centers with highly trained staff.[41] The magnitude of this difference between centers was similar to the difference between the machine learning automated scoring of MJMs compared with the respiratory disturbance index calculated from both the Grenoble and London PSG manual scorings. This demonstrates that the automatic scoring of sleep and respiratory events offers many advantages beyond simply a reduction in the human resources needed for routine manual scoring and a reduction in the subjectivity associated with manual scoring. Overall, automated algorithms for scoring sleep and respiratory events have now achieved an acceptable level of accuracy and agreement close to 85% with manual scoring.[42] A common strategy being introduced in the routine practice of many sleep laboratories is to start with automated scoring followed by an auto-edited approach, especially when there are inconsistencies between pretest probability and the results of the automated scoring.

Epoch-Based Manual Scoring Fails to Capture Much Information Contained in the Signals

The recognition of a respiratory event limited to preestablished criteria leads to an artificial disconnection between interlinked physiologic and pathophysiologic events with the loss of the understanding of temporal links or the dynamics of specific event trajectories. This reduces the richness of the physiologic signals available with the loss of important information relevant to the patient's diagnostic characterization and therapeutic decision-making. It is now well known that AHI is not the perfect metric for sleep-disordered breathing[29] and is poorly correlated with outcomes. Other, previously often overlooked quantifiable overall features within polysomnographic data such as the hypoxic burden or acute cardiovascular responses to respiratory events have recently been demonstrated as being more strongly related to poor prognosis than AHI.[30] No doubt, in the near future, diagnostic nights will include metrics more representative of what is truly related to symptoms, quality of life, and hard outcomes. Current conventional scoring does not capture the cumulative burden of sympathetic tone, sleep microstructure, and RE, all key consequences of the repetitive occurrence of respiratory events during sleep. Overnight sympathetic tone is possible to capture by PPG and PAT signals and we need studies showing the impact of the cumulative elevation in sympathetic activity during the night on hard outcomes in the context of OSA. It has been recently demonstrated that fine-tuning microstructure changes (ie, slow-wave activity and sleep spindles) allow the identification of indices that are strong predictors of incident hypertension.[43] Increased RE is one of the main features of OSA and is associated with sympathetic overactivity, leading to increased vascular wall stiffness and remodeling. We have recently demonstrated that the proportion of sleep time spent with increased RE (automatically derived from MJM by machine learning analyses) is potentially a reliable new metric to predict prevalent hypertension in patients with OSA.[36]

Automation and interpretable artificial intelligence

Overall, it appears obvious that algorithmic metrics and artificial intelligence have the capabilities to enrich diagnosis and support risk prediction in OSA by conveying more information than classical PSG metrics. They will provide metrics that reflect more accurately the sleep-related dynamics of disease burden and the associated risks. To convince the sleep community, and in particular

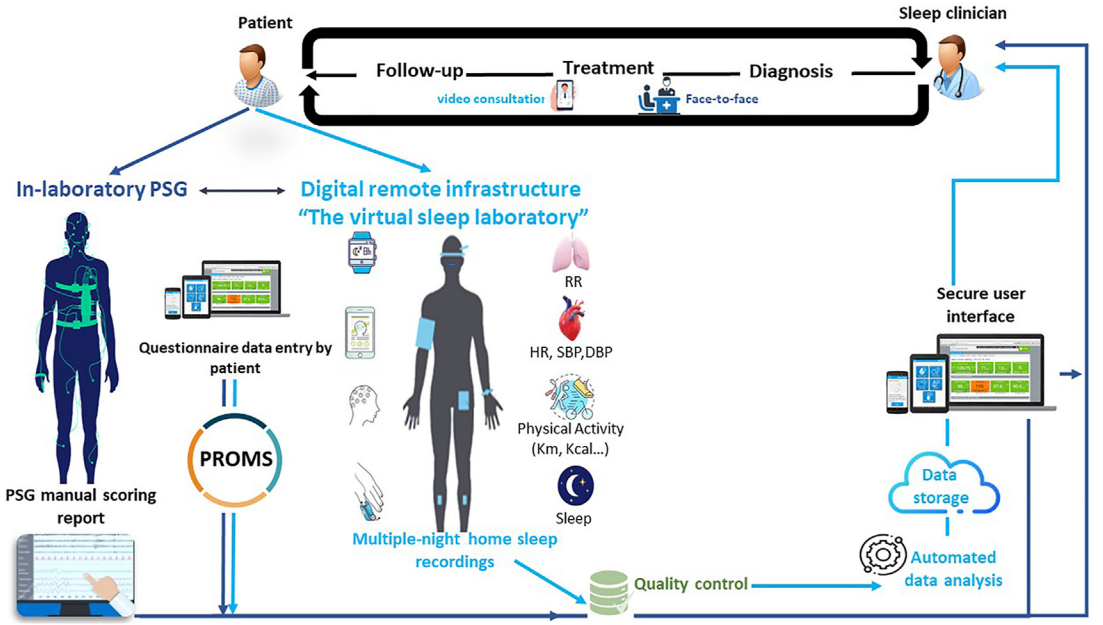

Fig. 2. The place of digital solutions in the sleep apnea diagnostic pathway. The virtual sleep laboratory would collect measurements made by the patient themselves or with the help of a carer, nurse, or sleep technician, such as patient reported outcome measures (PROMS), respiratory rate (RR), heart rate (HR), blood pressure (SBP and DBP), physical activity, daytime sleepiness, self-reported sleep disturbance, and then data from home sleep tests over several nights using innovative sensors. Comorbidities might necessitate a conventional polysomnography. Data could initially be analyzed using automated ML algorithms with recourse to the sleep clinician when in doubt. The treatment decision should be made at a face-to-face or video consultation with the sleep physician in the light of all available data. DPB, diastolic blood pressure; ML, machine learning; SBP, systolic blood pressure.

clinicians, of their relevance and value algorithmic codes and software should be made readily available, open access, and easily sharable between laboratories worldwide to allow replicability. Machine learning and artificial intelligence are powerful tools but are often considered "black box" methods due to their complexity, generating disillusionment and distrust. It is crucial that the models and outputs remain reasonably interpretable by sleep experts in terms of physiologic and pathophysiologic patterns.[44] Direct collaborations between the end users (clinicians), and the target audience (patients) in model conception and development are mandatory and will increase trustworthiness and hence dissemination in the field. It is a new challenge for scientific sleep societies to propose a set of best practices for validation studies and guidelines regarding the use of these tools and the new metrics they generate. Accordingly, a recent systematic review found that despite the large number of medical machine learning-based algorithms and digital tools in development for medicine, only a few randomized controlled trials (RCTs) of rather low quality have been conducted for these technologies.[45]

New Diagnostic Approaches Appropriate to the Size of the Epidemiologic Problem

Despite the potential of innovative diagnostic pathways to improve multiple aspects of patient care, barriers to their large-scale clinical adoption exist. There is a need to reinvent not only the diagnosis tools but also the patient's complete journey from suspicion of OSA to long-term treatment follow-up. For the workup of patients suspected of sleep apnea, technological innovation should certainly be introduced in the form of a remote digital infrastructure, often called a "virtual sleep laboratory"[27] (**Fig. 2**). The virtual sleep laboratory would propose preliminary screening with, if appropriate, a recommendation for a home sleep test (ideally over multiple nights), data collection, and interpretation in a digital pipeline, strictly following data privacy rules. This type of framework should also propose an initial clinical evaluation that includes appropriate patient-reported outcomes as these will contribute to compliance with therapy. A second virtual or face-to-face consultation would allow treatment decision-making shared with the patient and inclusion in the treatment follow-up management pathway. A

specialized nurse or sleep technician could supervise quality control and the progress of the patients through the diagnostic pathway and ensure that the sleep physician has access to home sleep test results for the final treatment decision. Complex cases, including patients with comorbidities, might be directly redirected to the classical diagnostic pathway of in-laboratory evaluation after the first consultation or after home sleep testing. Although such an organization is highly attractive to improve access to sleep apnea diagnosis, there are two major issues to address. First, the governance and management of these virtual infrastructures should certainly remain under the supervision of board-certified sleep physicians rather than private companies. Second, the dissemination of these digital solutions will push national health agencies to find new reimbursement models covering all aspects of the diagnostic pathways and not each activity separately (ie, consultations, HSAT) throughout the diagnostic workflow. Some studies have already examined the feasibility of such approaches and patient satisfaction. For example, virtual management has been evaluated in atrial fibrillation outpatient clinics[27] showing a shorter time to diagnosis and high patient satisfaction. Of note, previously undiagnosed sleep apnea was frequently detected and the patient prescribed sleep-disordered breathing treatments in association with atrial fibrillation ablation.[27]

CONCLUSION AND PERSPECTIVES

The increase in awareness and knowledge about sleep apnea among both the general public and health professionals necessitates a quick and effective response to meet the growth in demand for health care services dedicated to the diagnosis and follow-up of OSA patients.[15,46] In this review, we have identified new initiatives, key areas for further research, gaps in our knowledge, and issues to be solved before being able to translate and scale up promising innovations into routine practice. The expansion and dissemination of these new technologies into clinical settings require greater communication between sleep medicine experts, sleep-learned societies, and companies. It is the role of policymakers and the scientific community to ask for a robust demonstration of performance and cost-effectiveness in improving key patient-centered outcomes.[34,47] There is a potential that the implementation of digital technology and cloud-based analysis and data sharing will foster complementarity and interchange between conventional sleep laboratories and virtual sleep laboratories, improving access to care and reducing health care fragmentation.

CLINICS CARE POINTS

- New technologies should permit diagnostic sleep tests to be performed over several nights at home.
- Night-to-night variability in the apnea–hypopnea index should be included in obstructive sleep apnea severity classification.
- Alongside and in addition to classical sleep laboratories the "virtual sleep laboratory" should be developed.

DISCLOSURE

J.L. Pepin and J.B. Martinot are non-remunerated scientific advisors to Sunrise. J.L. Pepin has received research grants and consultancy fees from Itamar Medical. None of the other authors have a conflict of interest with respect to this review.

FUNDING

French National Research Agency (ANR) in the framework of the "Investissements d'avenir" program (ANR-15-IDEX-02) and the Grenoble Alpes University Foundation chairs of excellence: "e-health and integrated care and trajectories medicine" and "MIAI artificial intelligence." This work has been partially supported by the Grenoble Alpes Multidisciplinary Institute in Artificial Intelligence (MIAI) (ANR-19-P3IA-0003).

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