

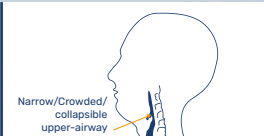
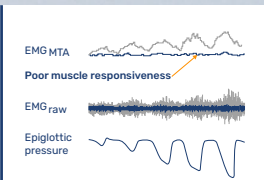
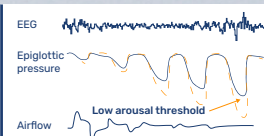
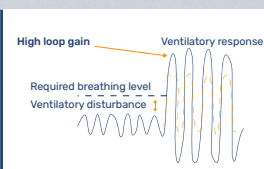
# How Endotyping Could Shape the Future of Sleep Medicine

Through scientific collaborations and Nox Flow™ technology, Nox is driving research to uncover how sleep apnea emerges in individual patients.

A deeper understanding of how sleep apnea emerges in each patient could pave the way for a more targeted, individualized approach to sleep medicine. While continuous positive airway pressure (CPAP) remains the most effective therapy for sleep apnea, many patients struggle to tolerate it, highlighting the need for alternative treatment strategies tailored to individual pathophysiology. Although not standard today, endotyping, the process of identifying the underlying physiology that contributes to the sleep apnea for each patient, opens the door to personalized precision medicine.

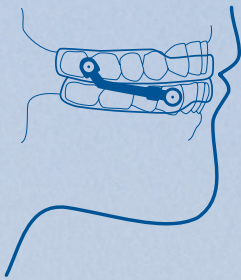
At Nox Medical, we are at the forefront of sleep apnea endotyping research<sup>1,2</sup>, having collaborated with leading researchers to develop *DeepRESP*<sup>3</sup>, an AI tool that uses RIP-derived flow data to precisely identify endotypes. It builds on the validated Sands et al. PUP<sup>4,5</sup> (Endo-Phenotyping Using Polysomnography) methodology and is delivered through a secure, cloud-based platform, Nox Connect.

So far, scientists have identified four key endotypes for sleep apnea<sup>6,7,8,9,10,11,12</sup>.

	<p><b>Collapsibility</b> Collapsibility is characterized by a tendency of the pharyngeal tissues to obstruct the airway during sleep, a primary cause of OSA.</p>
	<p><b>Compensation</b> Compensation refers to the effectiveness of the muscles in the tongue and airway that work to keep the upper airway open and counteract upper airway collapsibility. Reduced activation of these muscles can fail to compensate for airway obstruction during sleep.</p>
	<p><b>Arousal Threshold</b> Arousal threshold is the level of ventilatory effort that causes an awakening from sleep. Lower arousal threshold can lead to more awakenings and can destabilize breathing.</p>
	<p><b>Loop Gain</b> Loop gain describes how strongly ventilatory effort increases in response to interruptions to breathing. High loop gain can destabilize breathing, causing cyclical episodes of respiratory events, contributing to both obstructive and central sleep apnea.</p>

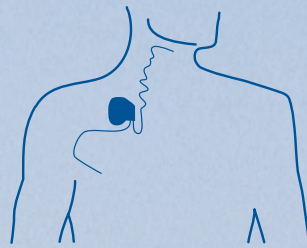
1 Finnsson E, et al. (2023). *Front Sleep*, 2. doi:10.3389/frsle.2023.1188052  
 2 Finnsson E, et al. (2020). *Sleep*, 43(Suppl 1):A171-72. doi:10.1093/sleep/zsaa056.445  
 3 FDA cleared software medical device DeepRESP K241960  
 4 Terrill PI, et al. (2015). *Eur Respir J*, 45(2):408-18. doi:10.1183/09031936.00062914  
 5 Sands SA, et al. (2018). *Am J Respir Crit Care Med*, 197(9):1187-97. doi:10.1164/rccm.201707-14350C  
 6 Younes M, et al. (2007). *J Appl Physiol*, 103:1929-41. doi:10.1152/jappphysiol.00561.2007  
 7 Ratnavadivel R, et al. (2010). *Thorax*, 65:107-12. doi:10.1136/thx.2008.112953  
 8 Wellman A, et al. (2011). *J Appl Physiol*, 110:1627-37. Doi: 10.1152/jappphysiol.00972.2010  
 9 Eckert DJ, et al. (2013). *Am J Respir Crit Care Med*, 188:996-1004. doi: 10.1164/rccm.201303-04480C  
 10 Sands SA, et al. (2018). *Eur Respir J*, 52:1800674. doi: 10.1183/13993003.00674-2018  
 11 Light M, et al. (2019). *Sleep Med Clin*, 14:391-98. doi: 10.1016/j.jsmc.2019.05.005  
 12 Malhotra A, et al. (2020). *Curr Opin Pulm Med*, 26:609-14. doi: 10.1097/MCP.0000000000000724

By using the sleep apnea endotypes, physicians and others could then evaluate each patient's sleep disordered breathing with the patient's underlying physiology in mind to choose an ideal treatment modality. For instance, patients with less collapsibility and lower loop gain seem to respond favorably to oral appliance therapy<sup>13</sup>. In other cases, those patients with lower loop gain, good compensation, and higher arousal threshold might be candidates for hypoglossal nerve stimulation<sup>14</sup>. Furthermore, a growing pipeline of pharmacologic therapies targets mechanisms like airway muscle tone<sup>15</sup>, arousal thresholds<sup>16</sup>, and ventilatory control<sup>17</sup>. As these advance, physiologic endotyping will be key to identifying responders and enabling personalized treatment for obstructive sleep apnea.



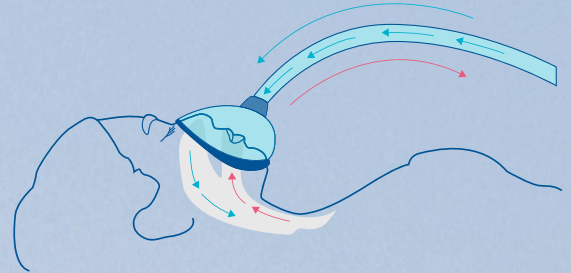
#### Oral appliance therapy

- » Less collapsibility
- » Lower loop gain



#### Hypoglossal nerve stimulation

- » Lower loop gain
- » Good compensation
- » Higher arousal threshold



#### Continuous Positive Airway Pressure

- » Lower loop gain
- » High collapsibility
- » High Arousal Threshold

## A Wealth of Data Captured From Nox Flow™ Technology

Sleep apnea endotypes are defined in terms of flow and effort. Thus, in order to properly assess these traits, accurate flow measurement is essential. Nox Medical diagnostic devices ensure exceptionally reliable flow measurements by integrating nasal cannula signals with Nox Flow™ technology (flow signals derived from the respiratory inductance plethysmograph (RIP) belts)<sup>18</sup>. With high-fidelity flow signals, Nox Medical diagnostic devices are well positioned to capture the critical data required for this analysis.

Although further research and clinician guidance are needed on how to interpret trait data and predict therapy responses, endophenotyping shows promise in identifying patients likely to benefit from specific treatment based on underlying disease mechanism. With high-fidelity flow signals, Nox Medical diagnostic tests are well positioned to capture the complex data required for this analysis.

13 Edwards BA, et al. (2016). Am J Respir Crit Care Med, 194(11). doi: 10.1164/rccm.201601-00990C

14 Op de Beeck S, et al. (2020). Am J Respir Crit Care Med, 203(6):746–55. doi:10.1164/RCCM.202006-21760C

15 Taranto-Montemurro L, et al. (2019). Am J Respir Crit Care Med, 199(10):1267–1276. doi: 10.1164/rccm.201808-14930C

16 Schmickl CN, et al. (2020). Am J Respir Crit Care Med, 202(11):1592–95. doi:10.1164/rccm.202003-0502LE

17 Edwards BA, et al. (2012). J Physiol, 590(5):1199–211. doi: 10.1113/jphysiol.2011.223925

18 Montazeri K, et al. (2021). Sleep and Breathing, 25:1535–41. doi:10.1007/s11325-020-02268-x

**DISCLAIMER:** Nox Flow is a calibrated RIP flow signal from Nox Medical devices.

The following are medical devices cleared for clinical use by the FDA at the direction of a physician: Nox T3 system, Nox A1 system, Noxturnal, Noxturnal Web, Nox RIP belts and Nox AI Scoring (DeepRESP K241960).

For more information on specific Nox Medical devices as part of the service offering, please consult manufacturer's instruction for use and contraindications at [noxmedical.com/downloads-USA](https://noxmedical.com/downloads-USA)

The Nox Connect is not a medical device. It serves as an interface with Nox Medical devices that meet the necessary regulatory requirements for legal sale in applicable jurisdictions.