Obstructive Sleep Apnea
– From Diagnosis to Treatment –

Nyxoah®

Introduction and Agenda

Introduction
David DeMartino – Chief Strategy Officer, Nyxoah

Nyxoah Overview
Olivier Taelman – Chief Executive Officer, Nyxoah

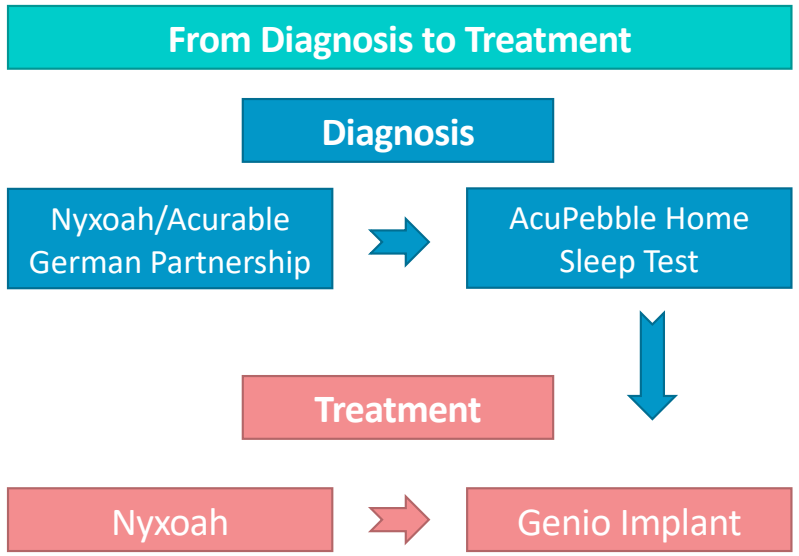
Acurable Overview
Emilio Sanz – Chief Executive Officer, Acurable

Hypoglossal Nerve Stimulation and the Need for CPAP Alternatives
Prof. Dr. med. Joachim T. Maurer

Experience with Genio
Prof. Dr. med. Clemens Heiser

The AcuPebble Opportunity
Prof. Dr. med. J. Ulrich Sommer

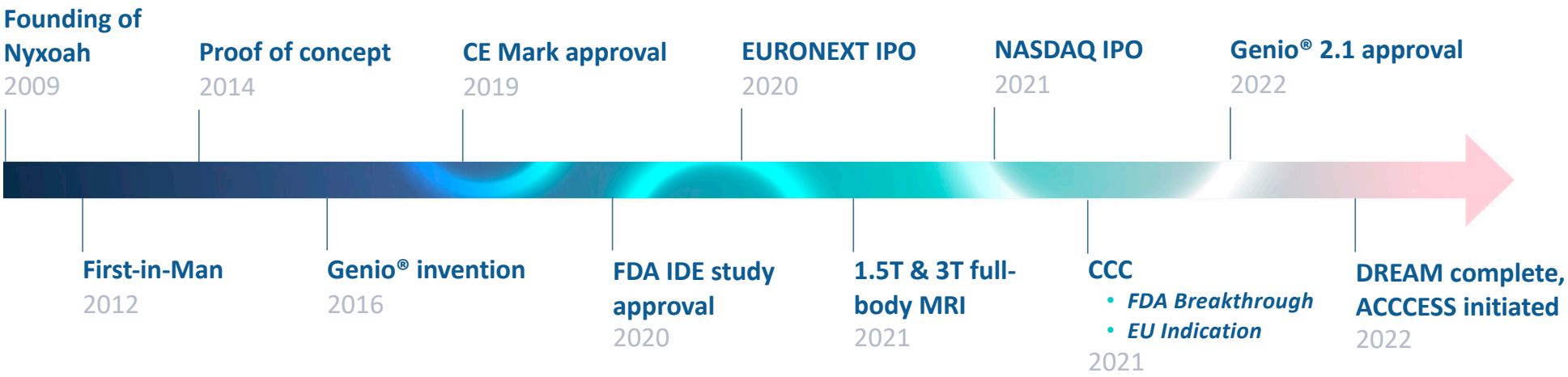
Closing Remarks
David DeMartino - Chief Strategy Officer, Nyxoah



Nyxoah®

Olivier Taelman
Chief Executive Officer, Nyxoah

Nyxoah
Our History



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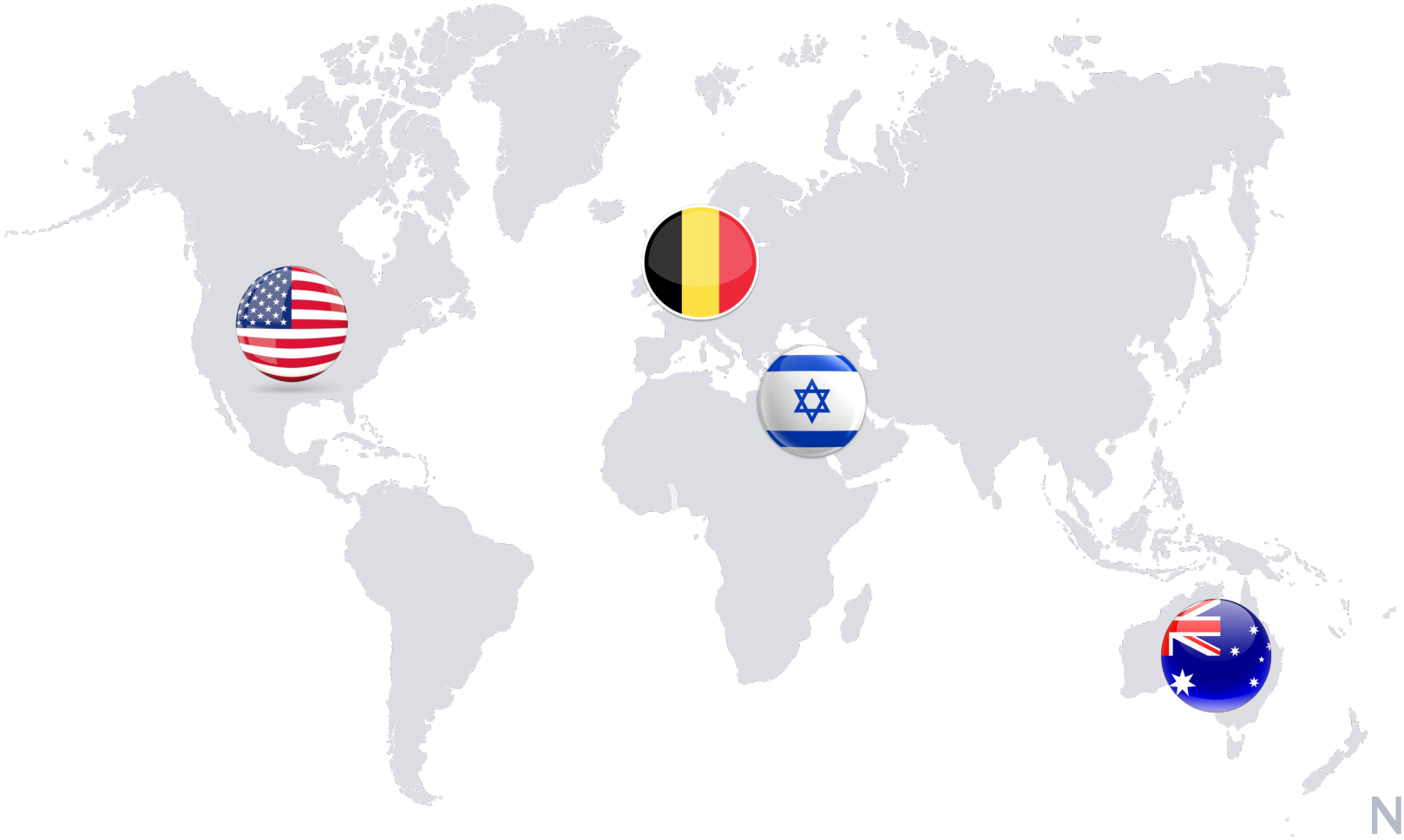
A global company with over 150 employees

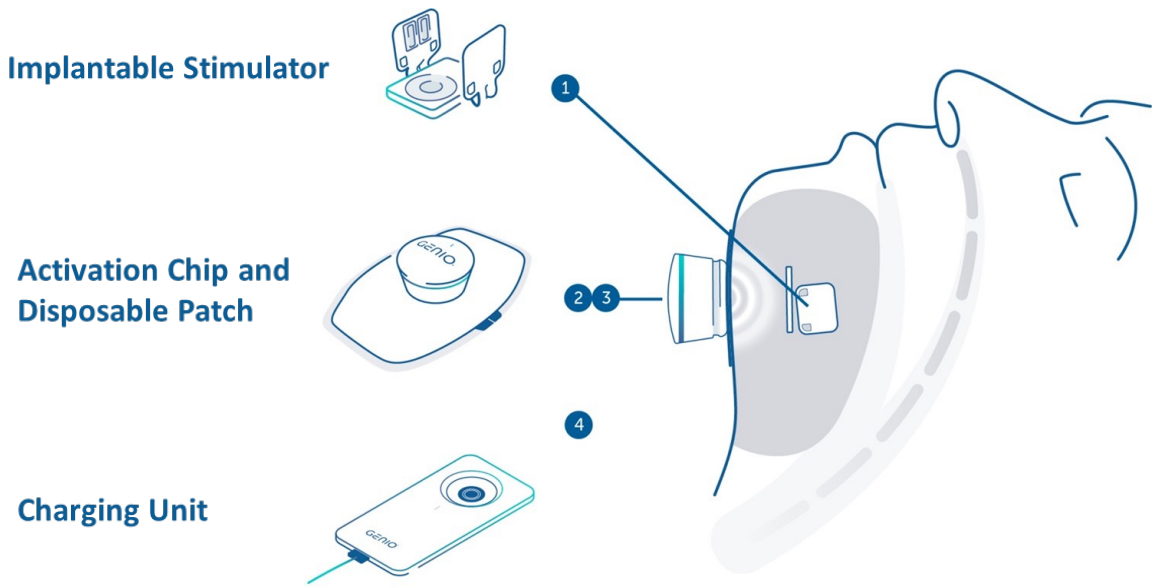


Improving Lives Through Restful Nights

A patient-centric solution TODAY…

- Single incision procedure
- Leadless and battery-free
- Full-body 1.5T and 3T MRI compatible
- Bilateral stimulation
- Indicated for both CCC and non-CCC
- Scalable platform

… An intelligent medtech solution TOMORROW



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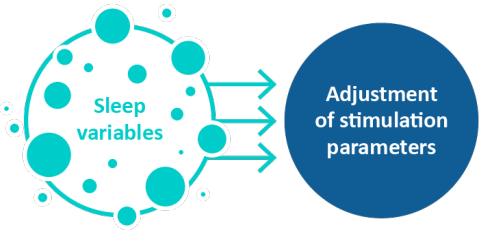
A Patient-Centric Approach to Innovation

Maximize therapy efficacy

- Integrated sensors as a baseline for future developments
  - Position sensors – Accelerometer and gyroscope
  - Sound sensor – Microphone
- Incorporating learnings from physicians
  - NAPS team: R&D, clinical, T&E, Physicians



Patient ownership and compliance

- Patient Feedback App
- Patient Remote Control allowing stimulation adjustments

Patient driven innovation

- Implant for life / Scalable technology platform
- Novel treatment
  - Complete Concentric Collapse
  - Ansa Cervicalis

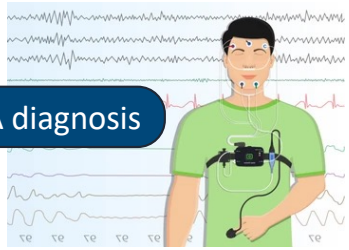
Nyxoah

The Nyxoah "Care4" Program
Building an OSA Ecosystem

1 Discover
- Snoring
- Daytime sleepiness

Prioritize PSG waiting lists

2 Moderate to severe OSA diagnosis
- Sleep Lab Polysomnography



3 CPAP – First line

4 Refractory to CPAP
- Refusal – Failure – Poor compliance

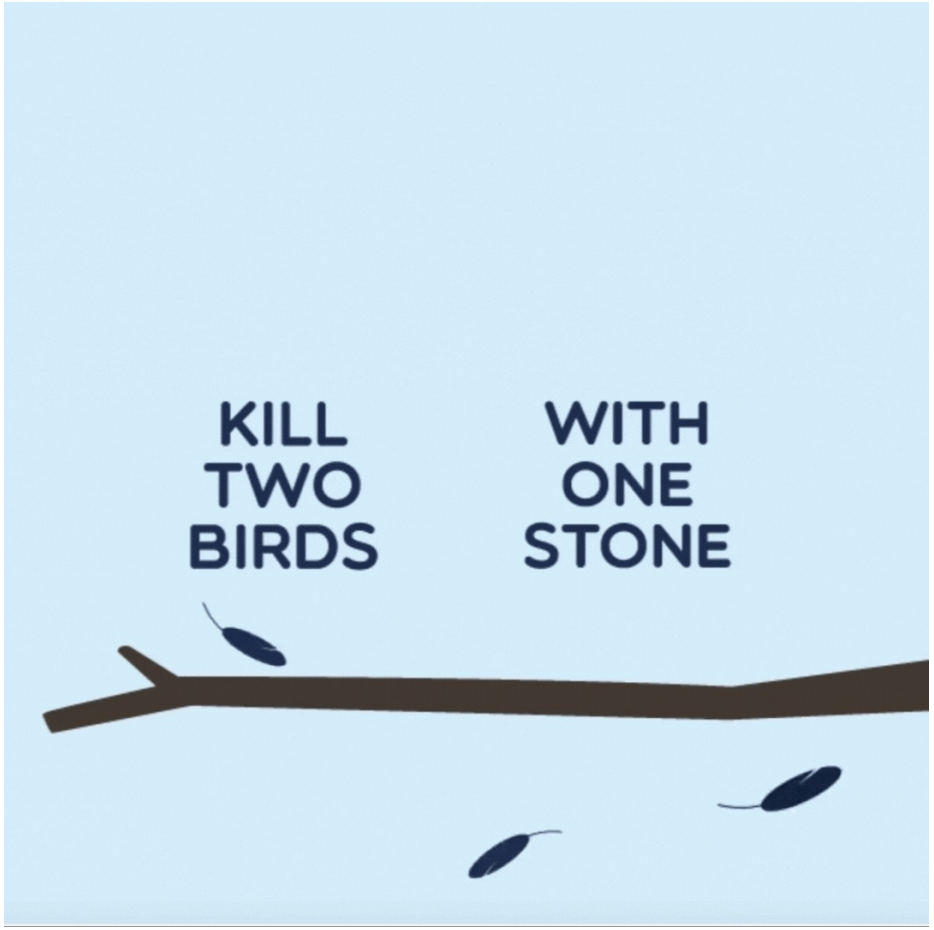
Confirm prior PSG

5 Genio®
- Implant – Activation – Titration

Genio
Monitoring & Optimization

Restful Nights

Kill Two Birds with One Stone…



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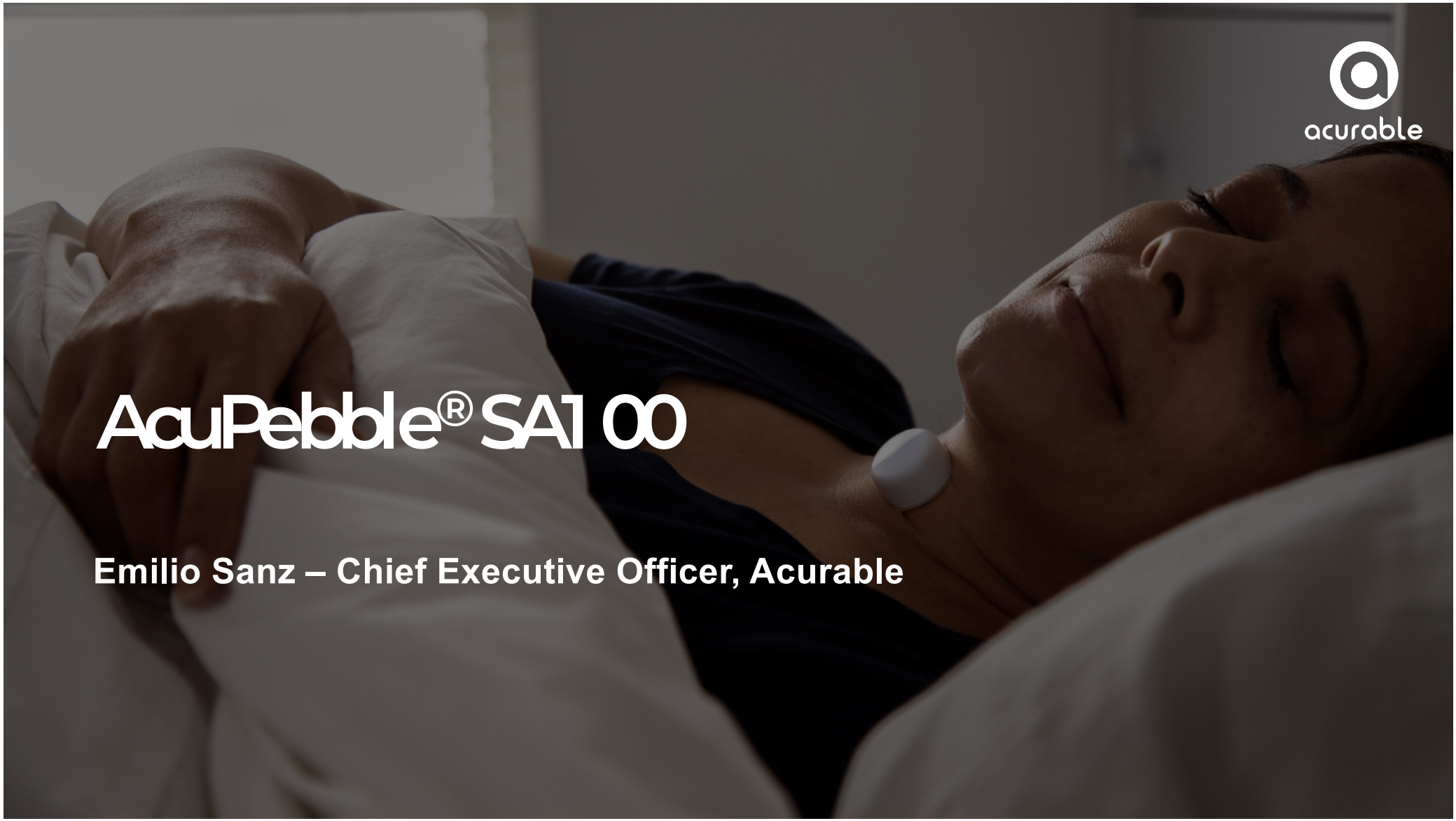
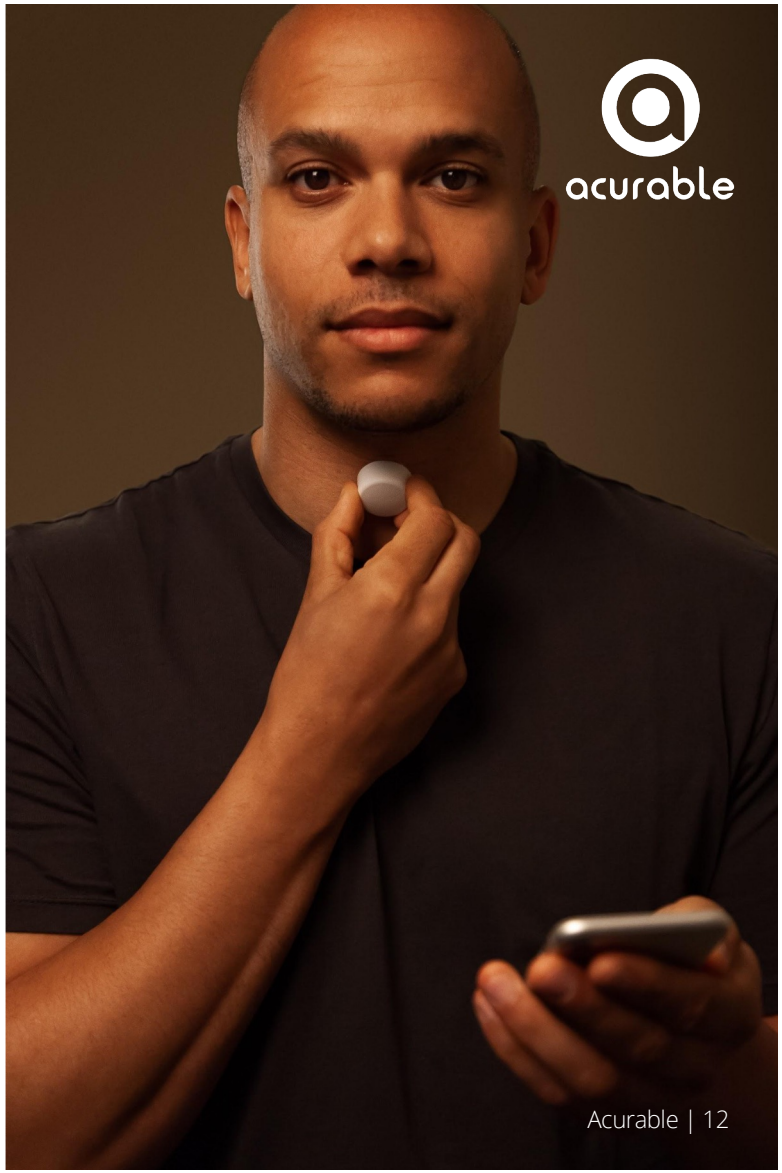

acurable
AcuPebble® SA100
Emilio Sanz – Chief Executive Officer, Acurable

Our solution: AcuPebble® SA100

The first medical device to obtain the CE mark for the **automated diagnosis** of obstructive sleep apnoea

- Over a decade of research — Imperial College London
- Clinically validated accuracy — BMJ Open
- Top technology awards — XPRIZE AWARD
- Supported by NHS England — NHS The AHSN Network



AcuPebble® SA100 makes diagnosis simple

Using AcuPebble SA100 is as simple as **peeling off an adhesive and putting it on**

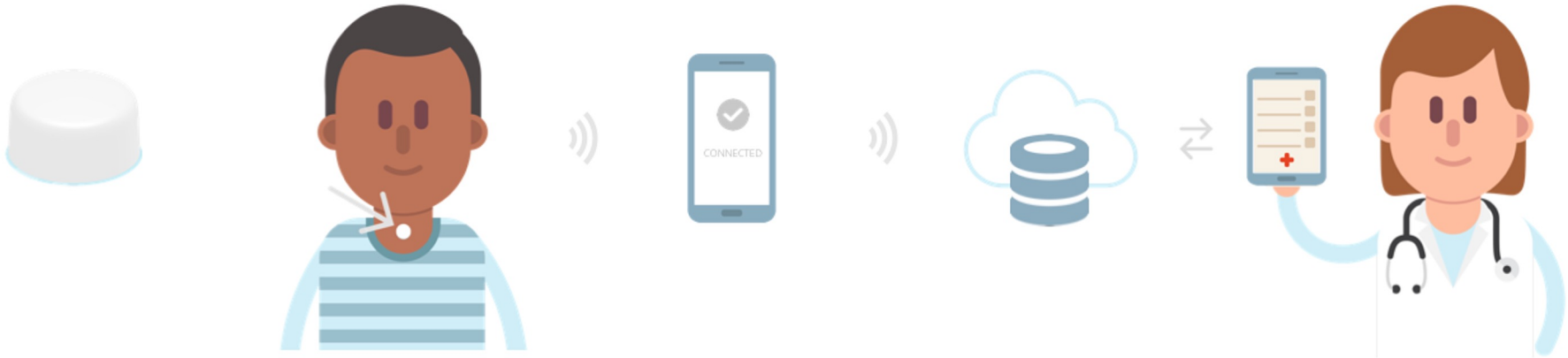
AcuPebble sensor
Size 2.9 cm
Weight 7 gr

Patient
Fix to neck exterior using medical adhesive

Mobile
Wireless transfer to nearby mobile device

Cloud
Upload to secure data platform for analysis

Doctor
Remote access to patient's results via web app



Clinically validated accuracy

POWERED CLINICAL TRIAL (150 adult patients)

- Proved sleep apnoea diagnosis **equivalence to ambulatory gold-standard** (polygraphy followed by specialist interpretation).
- Validated **AHI and ODI based diagnosis** for 3% and 4% desaturation criteria with very high accuracy (**94% PPV, 98% NPV**)[1]
- **Proved usability** with 100% of patients able to complete the test without training or assistance.
- Results published in **BMJ Open.**

(1) Trial completed at Royal Free London hospital in 2019. Results published in BMJ Open
PPV = Positive Predictive Value; NPV = Negative Predictive Value.

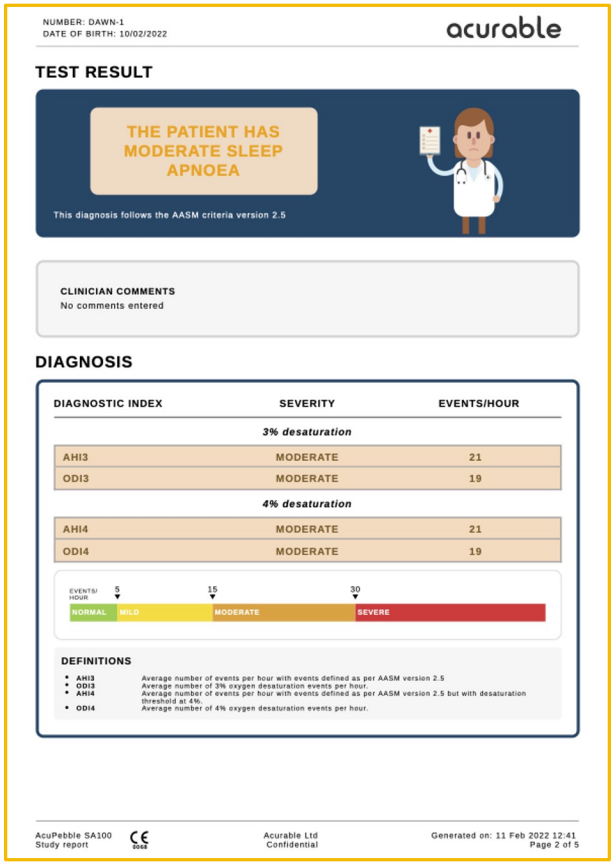
Detailed study report available in minutes

DIAGNOSIS DETAILS

- Overall diagnosis (test result and severity).
- **AHI and ODI** diagnostic indexes for 3% and 4% desaturation criteria, using estimation of sleep time.
- Classification of apnoea events (obstructive vs. central, apnoea vs. hypopnea)

ADDITIONAL INFORMATION

- Comprehensive **snoring analysis** (sleep time snoring and severity).
- Respiratory and cardiac features analysis.
- Oxygen saturation analysis (via integration with oximeter)



NUMBER: DAWN-1
DATE OF BIRTH: 10/02/2022

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TEST RESULT

THE PATIENT HAS MODERATE SLEEP APNOEA

This diagnosis follows the AASM criteria version 2.5

CLINICIAN COMMENTS
No comments entered

DIAGNOSIS

DIAGNOSTIC INDEX	SEVERITY	EVENTS/HOUR
3% desaturation		
AHI3	MODERATE	21
ODI3	MODERATE	19
4% desaturation		
AHI4	MODERATE	21
ODI4	MODERATE	19

EVENTS/HOUR 5 15 30
NORMAL | MILD | MODERATE | SEVERE

DEFINITIONS

- **AHI3** Average number of events per hour with events defined as per AASM version 2.5
- **ODI3** Average number of 3% oxygen desaturation events per hour.
- **AHI4** Average number of events per hour with events defined as per AASM version 2.5 but with desaturation threshold at 4%.
- **ODI4** Average number of 4% oxygen desaturation events per hour.

AcuPebble SA100
Study report

Acurable Ltd
Confidential

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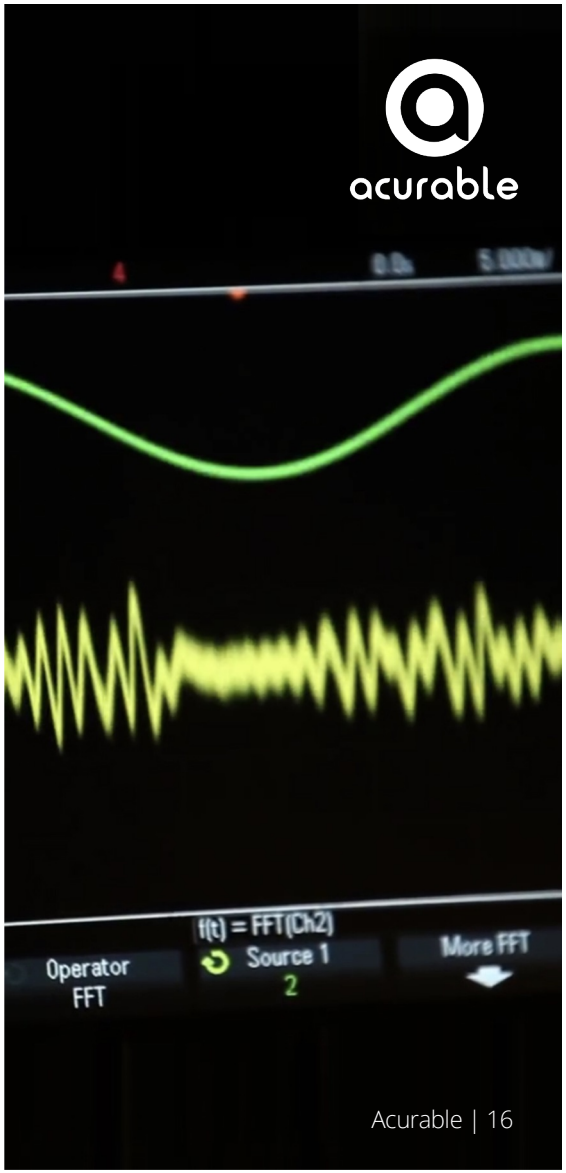
Based on acoustic sensing

HOW IT WORKS

1. Physiological body processes such as the respiratory and cardiac functions generate **sounds rich in information**.

1. **AcuPebble sensor records** these internal body sounds which are transferred to a mobile device wirelessly.

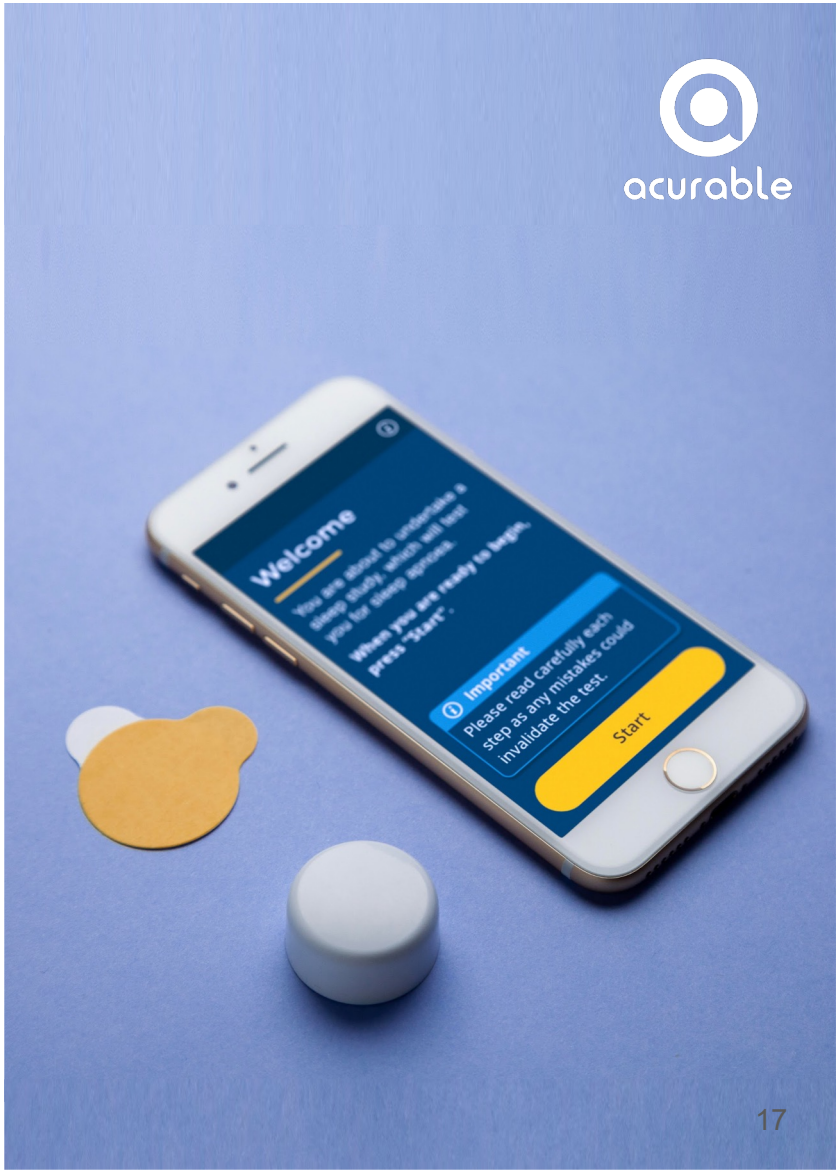
1. Sophisticated signal processing **algorithms automatically extract with high accuracy physiological biomarkers** which are subsequently used for sleep apnoea diagnosis.



Most common use cases

USE CASES

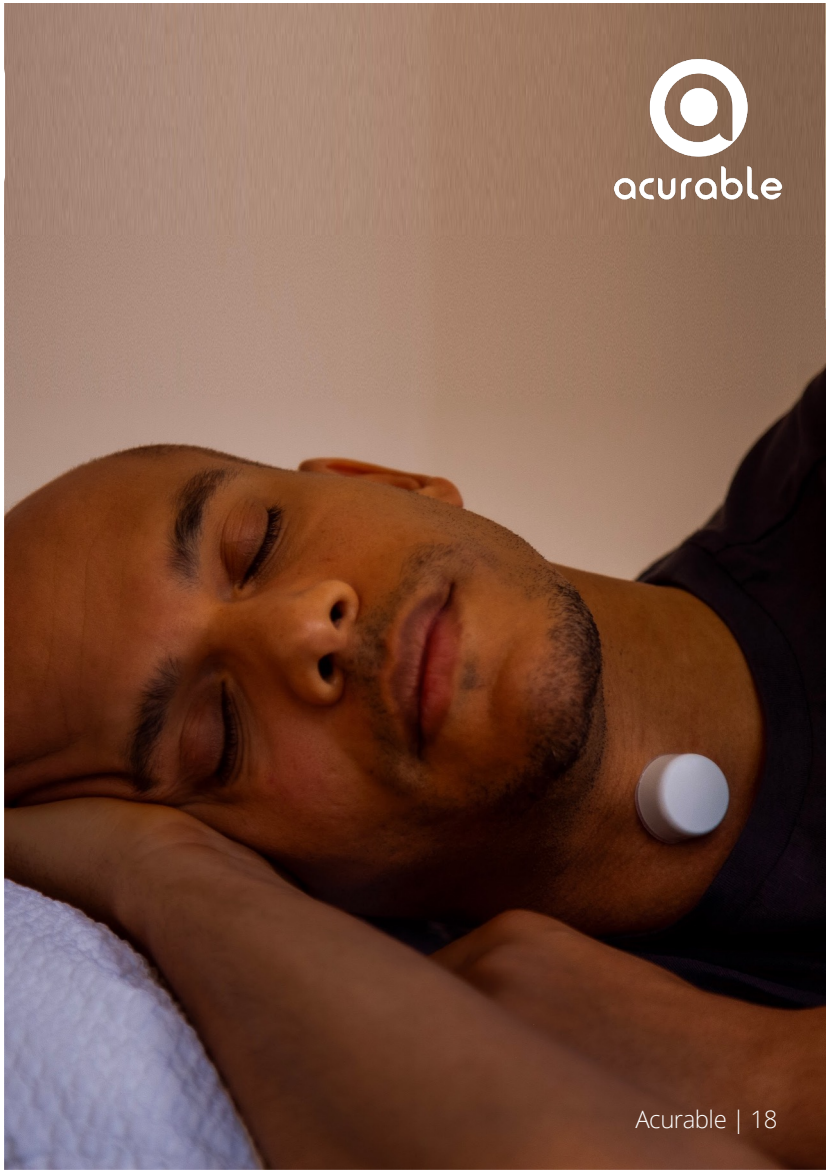
- **Diagnosis/Screening** of patients for sleep apnoea treatment
- **Titration** of therapeutic devices to achieve optimal adjustment
- **Monitoring** of treatment to track patient evolution and improve compliance



Benefits AcuPebble® SA100

AcuPebble SA100 is a valid alternative to the ambulatory gold-standard with 4 key advantages:

- **Automated**: provides an accurate report with no manual interpretation needed in minutes.
- **Efficient**: requires fewer resources and saves valuable clinician time.
- **Easy to use**: no training required and instructions in the accompanying mobile app.
- **Comfortable**: ensures a more natural night's sleep at home for the patient.



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emilio@acurable.com

Document version 1.8 // Date 2-Nov-2022

Hypoglossal Nerve Stimulation and the Need for CPAP Alternatives

Prof. Dr. med. Joachim T. Maurer
Division of Sleep Medicine
Department of ORL-HNS, University Hospital Mannheim

Conflict of interest – 36 months

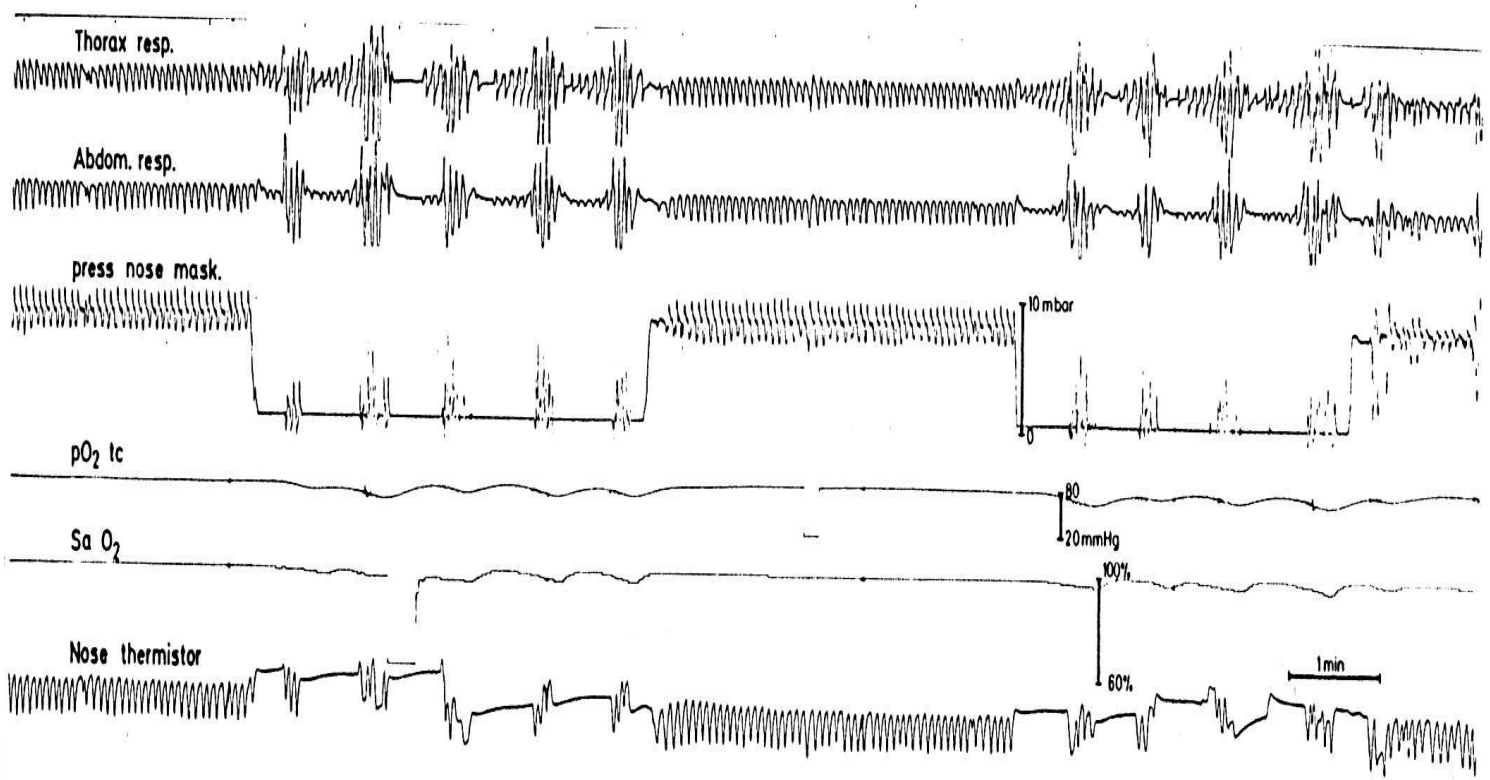
- University Hospital Mannheim: Contracts with Inspire, LivaNova, Nyxoah, Medel
- J.T. Maurer: Honoraria for presentations and/or surgical training from Inspire, LivaNova, Neuwirth Med. Products, Nyxoah

CPAP as new treatment for OSA

Colin Sullivan invented CPAP in 1981 to bridge the time gap until UPPP could be performed.

Today less than 500 g!

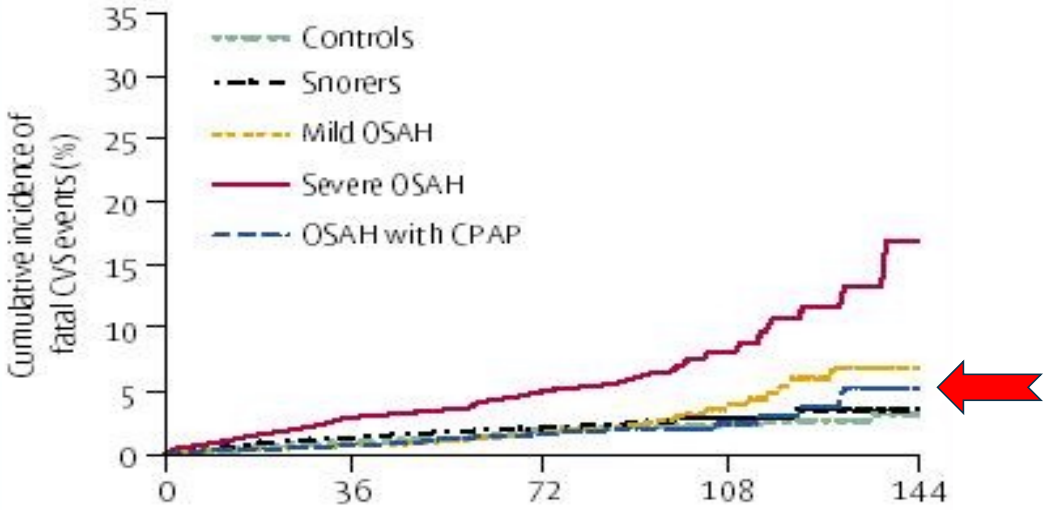
Immediate CPAP effect - 1986 in Marburg

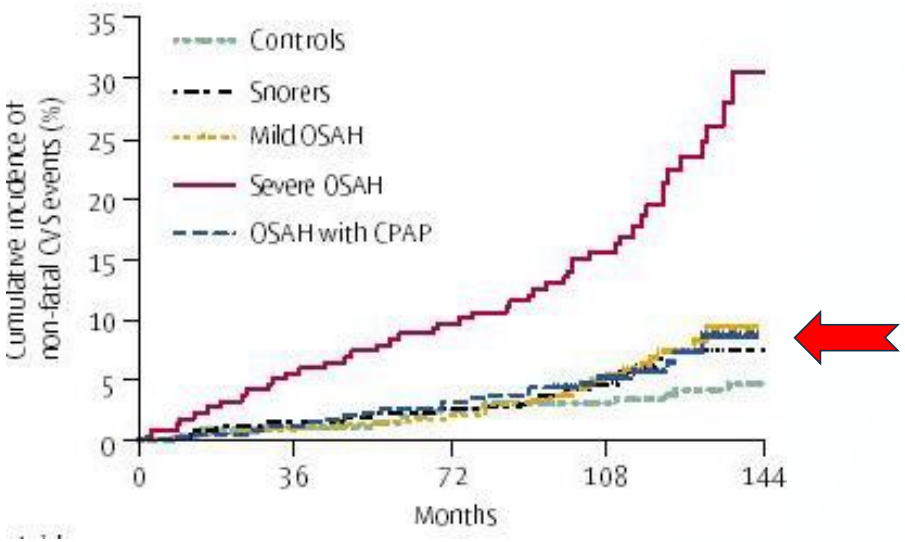


Thanks to HF Becker, Marburg/Hamburg

Cardiovascular morbidity and mortality in OSA

n=1387

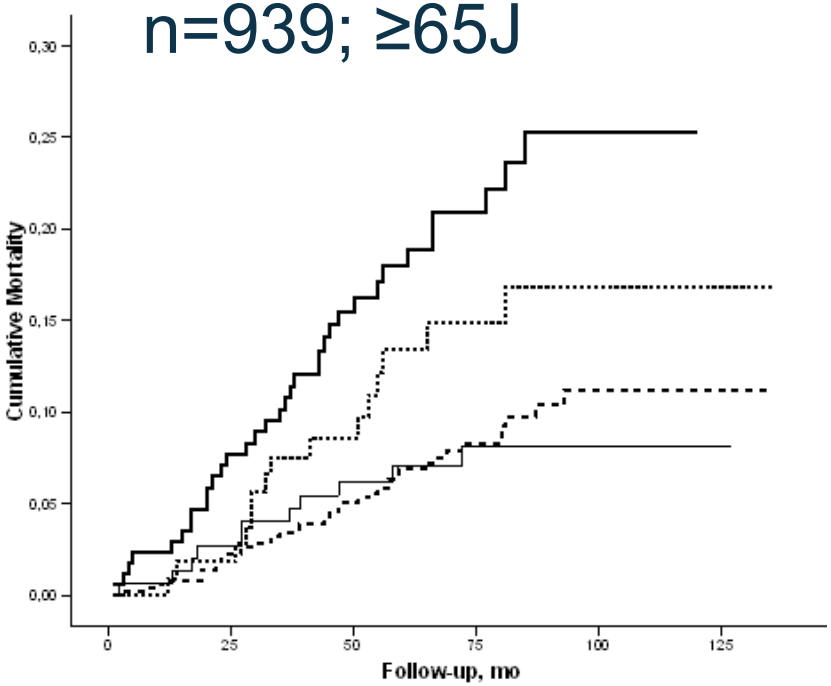




Reduced morbidity and mortality, if regulkarly used (Marin JM et al 2005)
3,3 h/night are not enough (McEvoy et al 2017)

Cardiovascular mortality in elderly patients with OSA

n=939; ≥65J

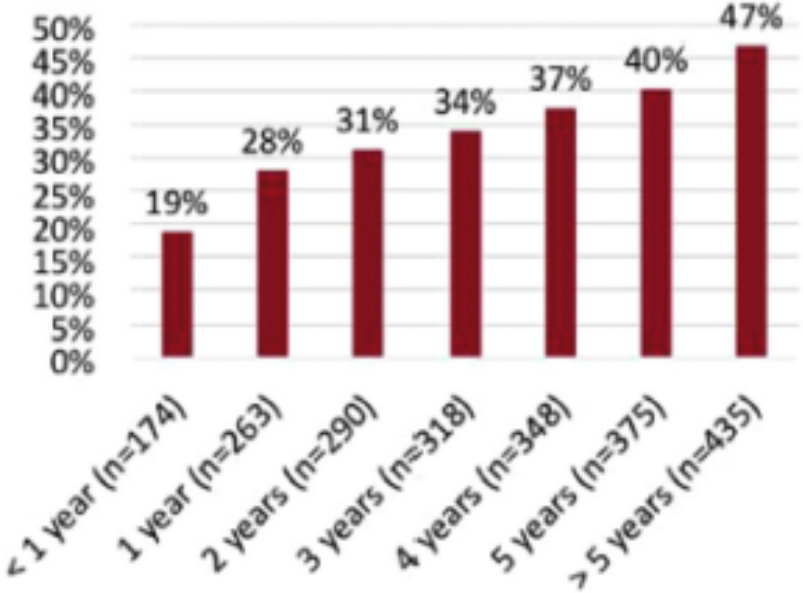


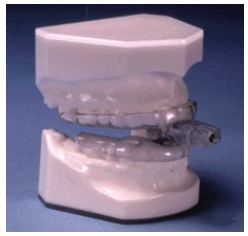
AHI≥30, n=173

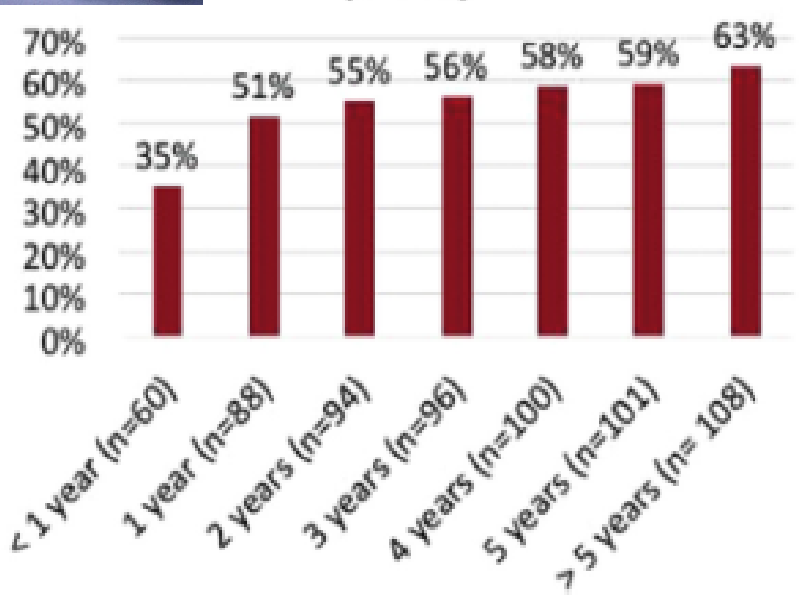
AHI 15-29, n=108
CPAP therapy ≥ 4h, n=503
Controls AHI < 15, n=155

Martinez-Garcia et al., AJRCCM, 2012)

Are PAP and MAD used sufficiently?

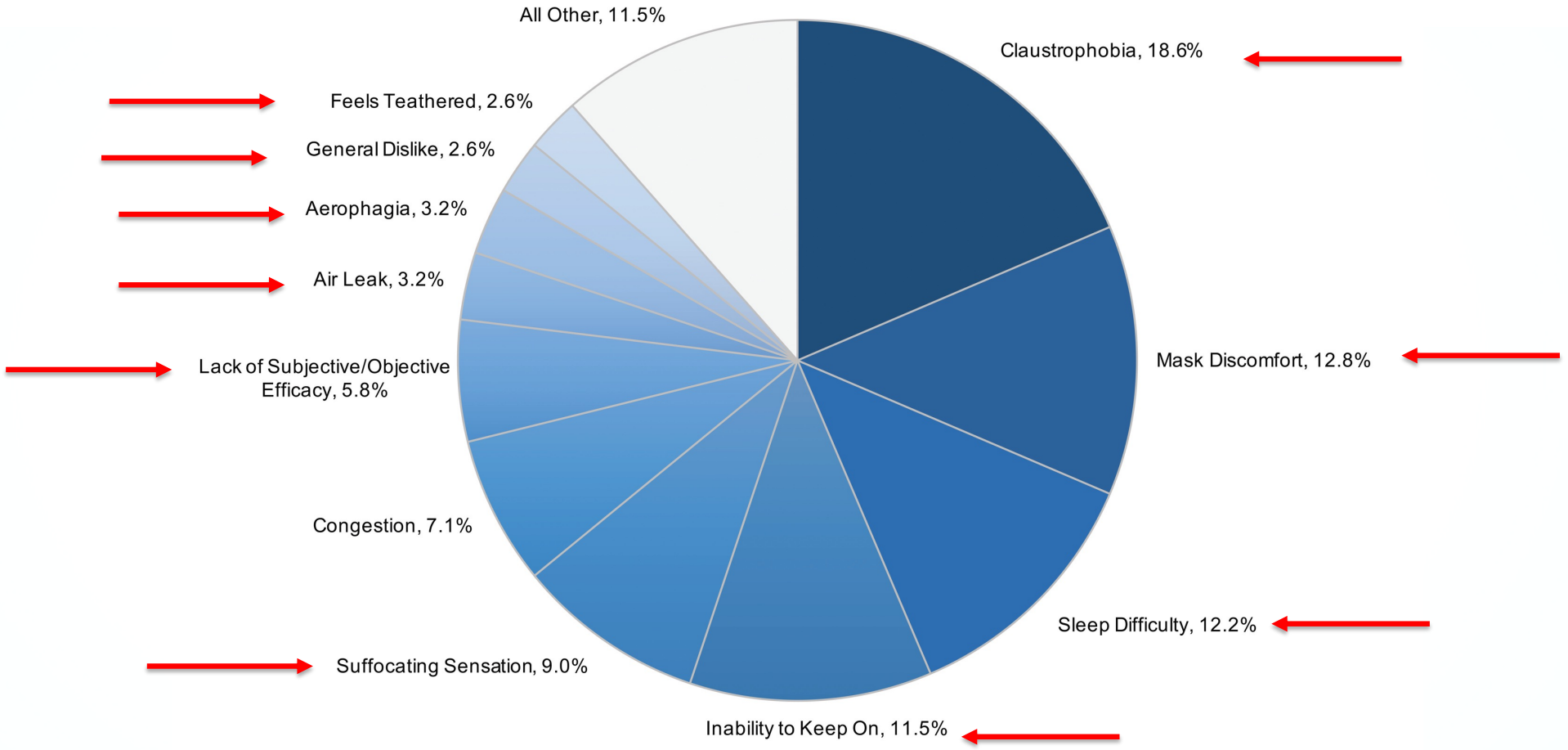






Soose RJ et al., 2017 World J Otolaryngol Head Neck Surg

Reasons for CPAP failure (n=156)



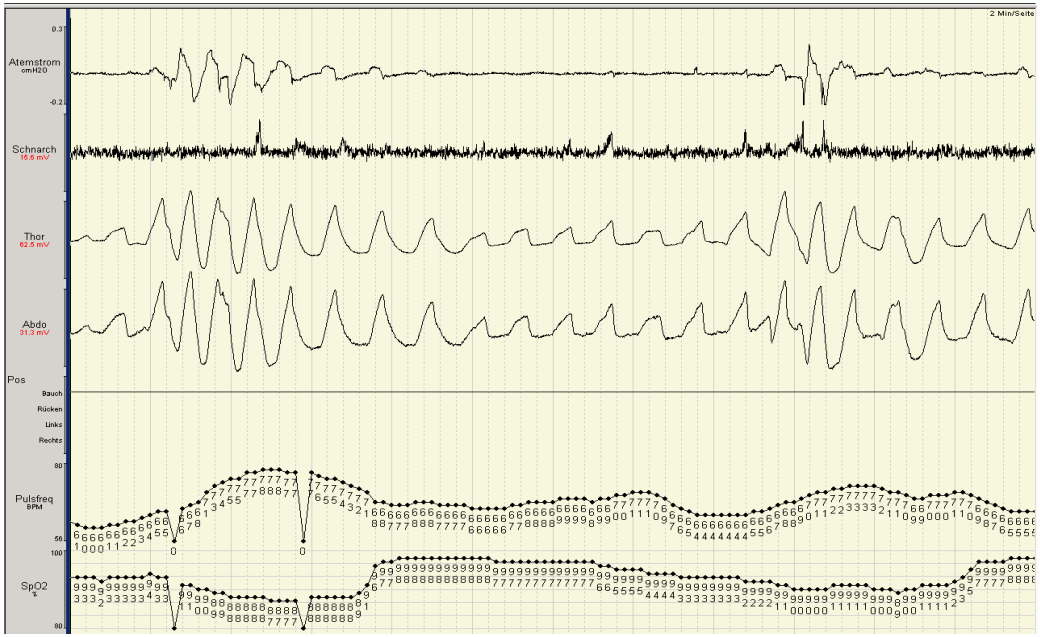
Lam et al JCSM 2017

What to do if PAP and / or MAD are not successful?

- Eliminate the obstacles ⟶ Nasal surgery
- Add another treatment ⟶ MAD + Palatal surgery
- Switch to alternative treatment ⟶ MMA, TE + palatal surgery

- Functional treatment using hypoglossal nerve stimulation

Neurostimulation: When and when not?



„Normal“ anatomy

Impaired function

Concepts of neurostimulation in OSA

- Efferent neurostimulation
  - Active AP-opening by advancement of tongue and soft palate
  - Circumferential stiffening of pharyngeal wall by tracheal/laryngeal caudal tug

- Afferent neurostimulation
  - Improving muscle responsiveness to negative pressure

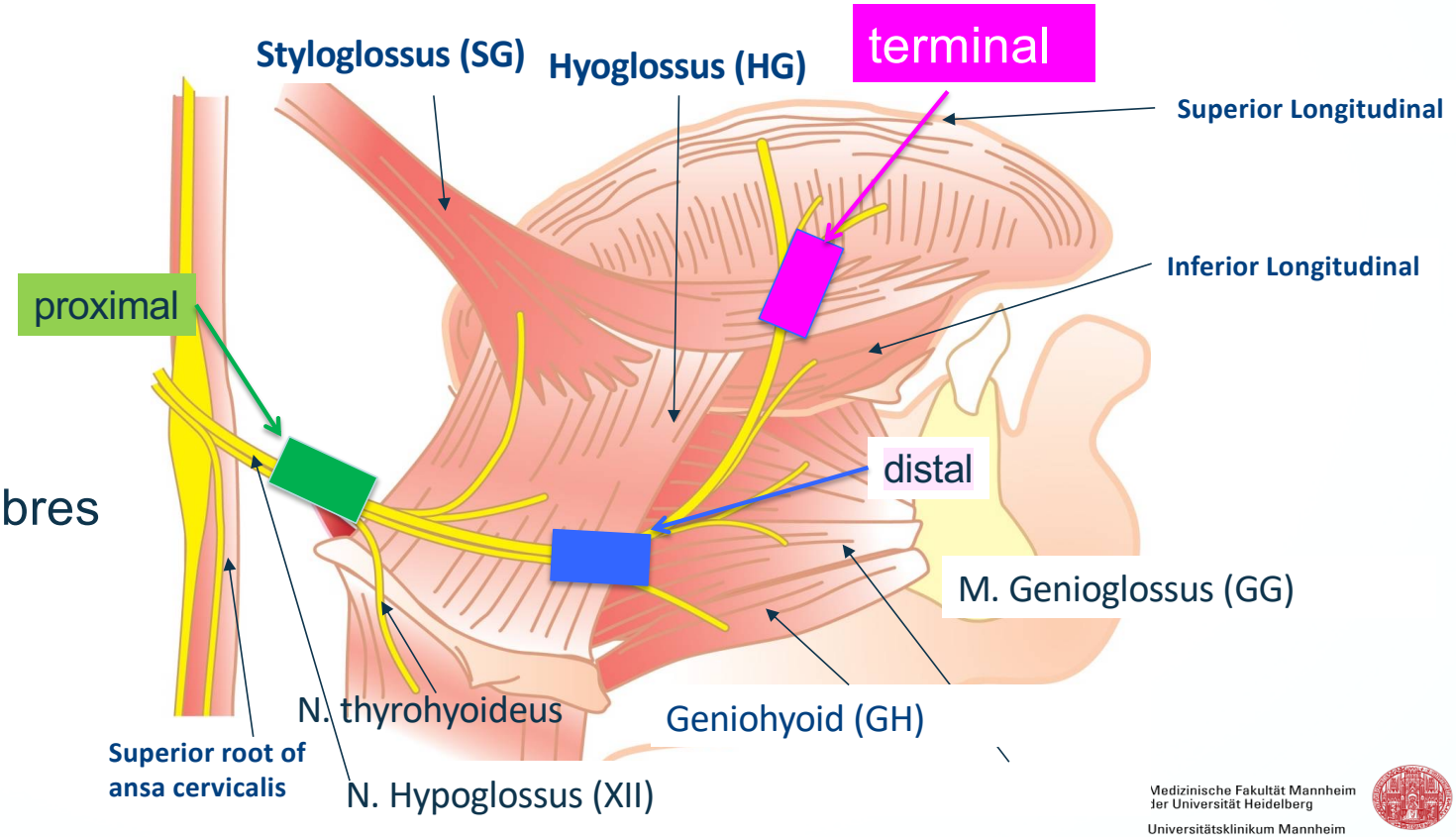
Hypoglossal nerve stimulation: Opening the airway in an antero-posterior dimension

Lateral

- proximal
- distal

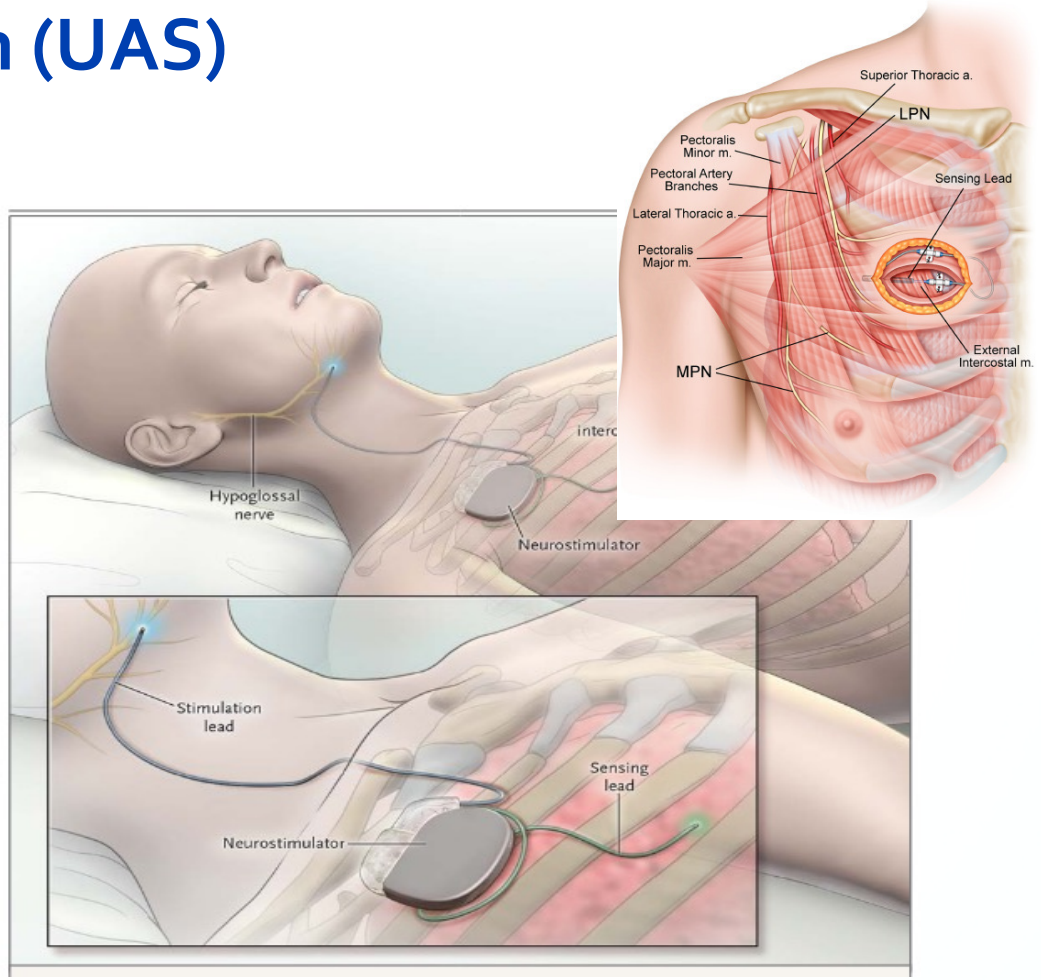
Median

- terminal fibres



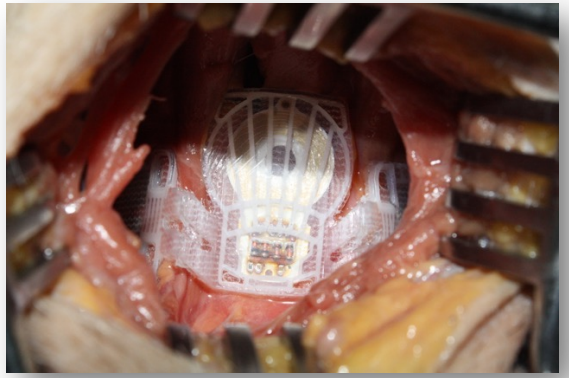
Upper Airway Stimulation (UAS)

- Distal selective stimulation
- Exclusion of retractor branches
- Unilateral
- Battery implanted
- Fixed stimulation settings for entire night



Genio (Nyxoah)

- Bilateral stimulation
- External battery
- MRI full body (3 Tesla) scan is possible
- Approved for complete concentric collapse in 2021
- Fixed stimulation settings for entire night



Challenge in hypoglossal nerve stimulation

- Long-term data is needed
- Better predictors of response required
- Self-adapting stimulation parameters according to varying needs required
  - night-to night variability, body position, sleep stage
- Implants usable for sensing and treatment adjustment

Conclusion

- CPAP is standard of care in OSA treatment for any severity
- Oral appliances are possible in mild to moderate OSA
- PAP and MAD fail long-term use in appr. 50% of patients

- Hypoglossal nerve stimulation is indicated for moderate to severe OSA and PAP-failure
- Auto-adjusting stimulation is awaited by the medical community

Klinikum rechts der Isar
Technische Universität München

Bilateral stimulation of the hypoglosal nerve

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Conflict of interest

My conflicts of interest related to the following companies within the last 12 months:

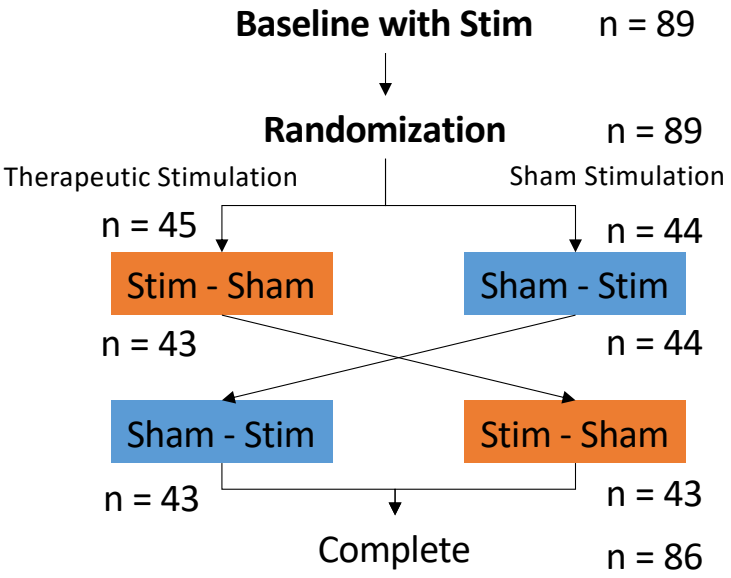
Nyxoah, Inspire Medical System, Löwenstein Medizintechnik, Neuwirth Medical Systems, XM Consult

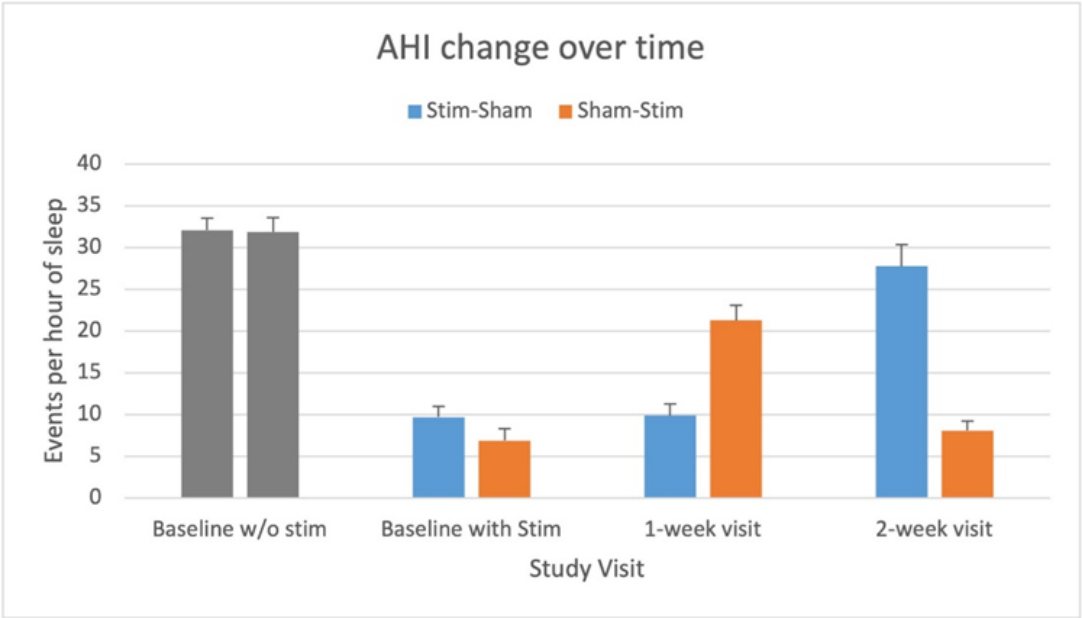
- Fees for lectures and/or consulting activities
- Accommodation and travel expenses
- Research and study funds

	unilateral HNS Inspire® IV	bilateral HNS Nyxoah Genio System™	target HNS THN System, LivaNova
Implantable device	**3 pieces** (IPG, stimulation & sensor electrode)	**1** piece (stimulation electrode)	**2** pieces (IPG, stimulation lead)
placement stimulation electrode	distal (selective) **medial branches of HN**	distal (selective) **medial branches** of HN **bilateral**	**main trunk** of HN
breathing cycle dependent	yes (intercostal sensor,pressure sensor)	duty cycle dependent	no
battery life expectancy	~ 10.7 years	external battery & IPG (induction)	~10 to 15 years
charging process	not needed	every day, but external battery	induction – every 2. day for 10 to 15 minutes
battery replacement	IPG change	no change needed, due to external battery	IPG change
programming	by telemetry	external programming	by telemetry
MRI	Under certain requirements up to 1.5 Tesla (FDA: up tp 1.5 Tesla)	whole body till 3.0 Tesla	none compatible
therapy hypothesis	**active** opening of the upper airway by **selective breathing cycle dependent (inspiration)** stimulation	**active** opening of the upper airway by **selective duty cycle dependent** stimulation	**toning** of the muscles by temporal **variation of the stimulation field vectors which is breathing cycle independent**

HNS and its evidence in the real world

A Randomized Sham-Controlled Crossover Trial

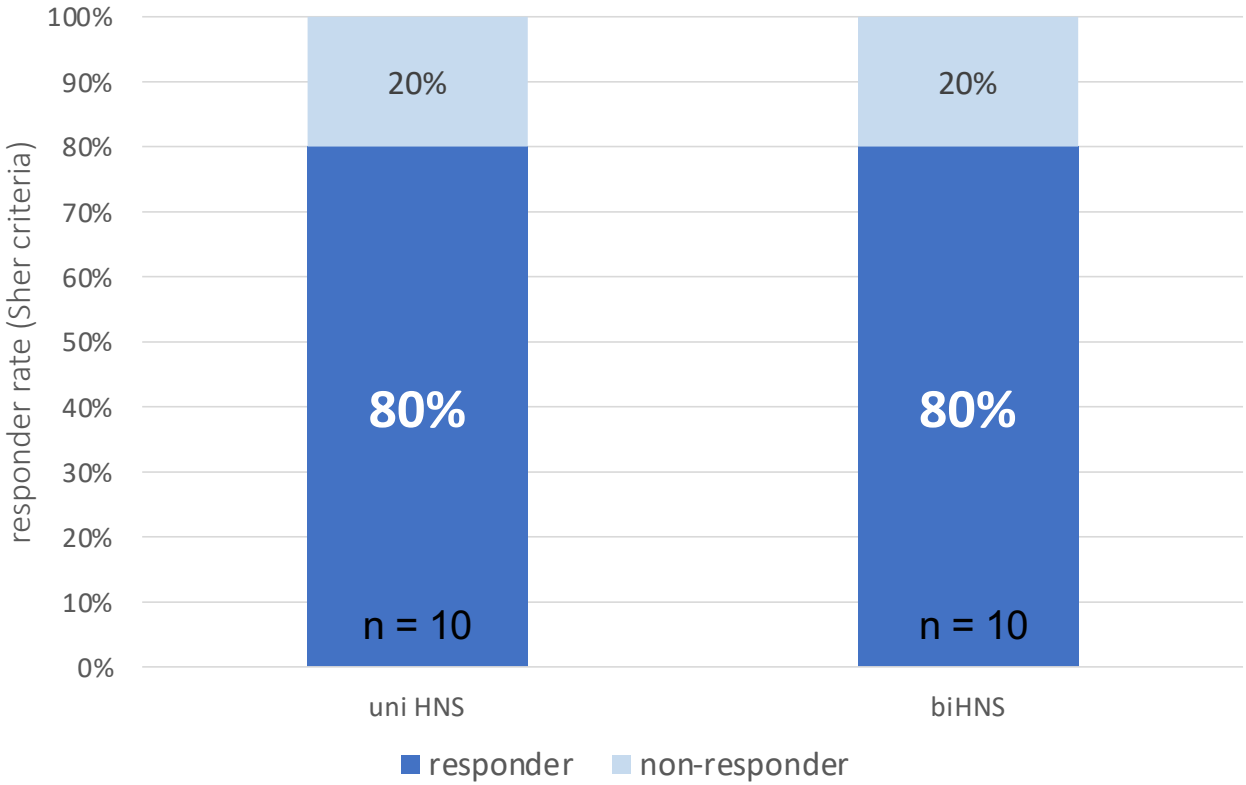




Summary: Therapeutic HNS significantly improved AHI, ODI, ESS and FOSQ compared with sham stimulation.

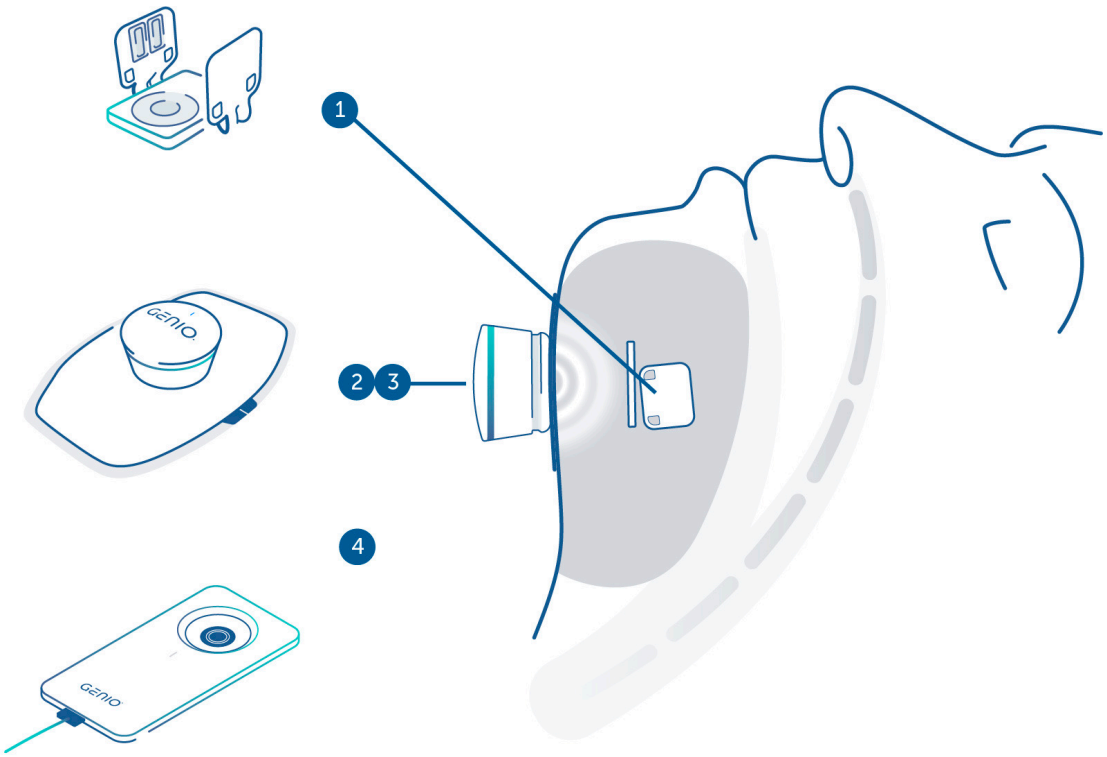
Heiser C, Steffen A, Hofauer B, Mehra R, Strollo PJ Jr, Vanderveken OM, Maurer JT. Effect of Upper Airway Stimulation in Patients with Obstructive Sleep Apnea (EFFECT): A Randomized Controlled Crossover Trial. J Clin Med. 2021 Jun 29;10(13)

bilateral vs. unilateral HNS – month 6



Partly published: Heiser C, Sommer JU, Hofauer B, de Vries N, Ravesloot MJ, Vanderveken OM, Jira D. Bilateral vs Unilateral Hypoglossal Nerve Stimulation in Patients With Obstructive Sleep Apnea. OTO Open. 2022 Jul 6;6(3):2473974X221109794.

bilateral hypoglossal nerve stimulation

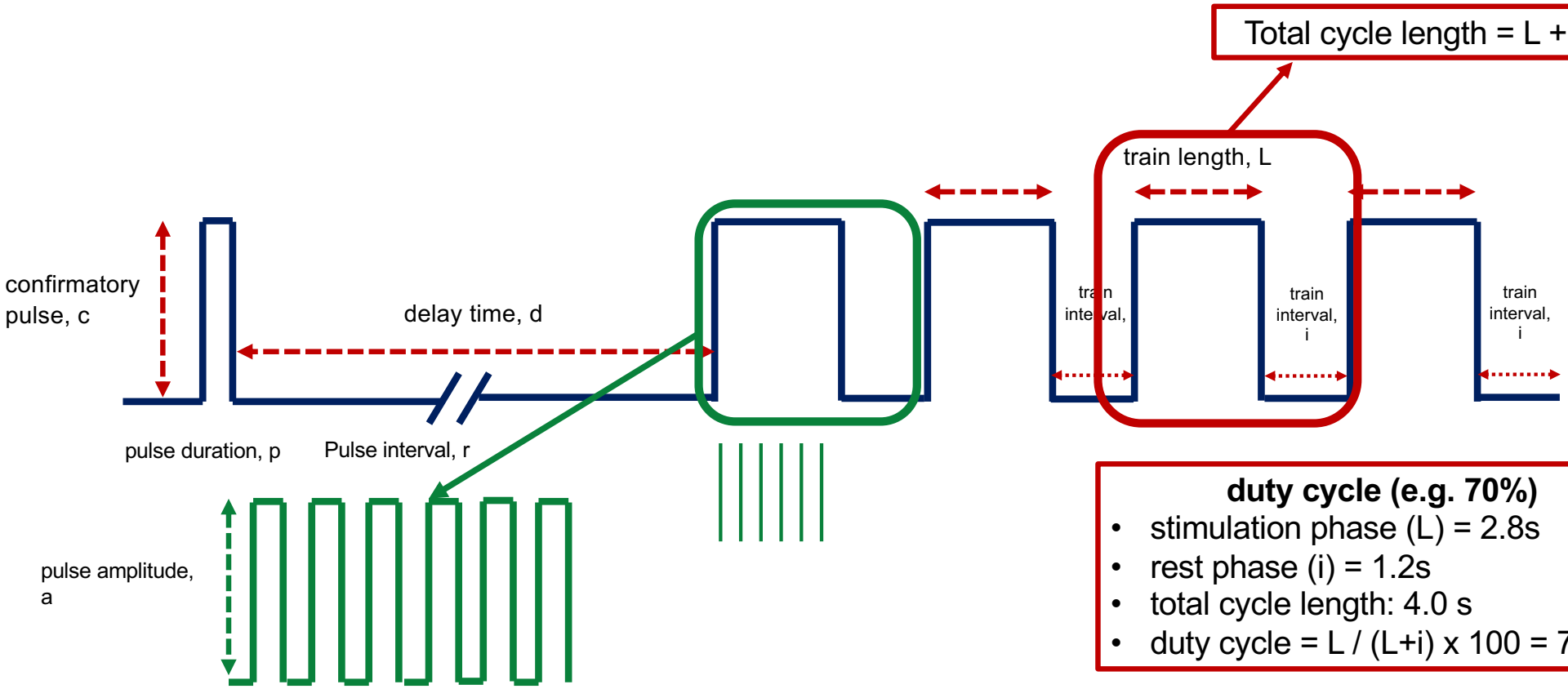


bilateral stimulation hypoglossal nerve

disposable Activation Chip (including battery)

Heiser C, deVries N: Upper Airway Stimulation in Obstructive Sleep Apnea: Best Practices in Evaluation and Surgical Management. Springer; 1st ed. 2022 Edition (1. August 2022)

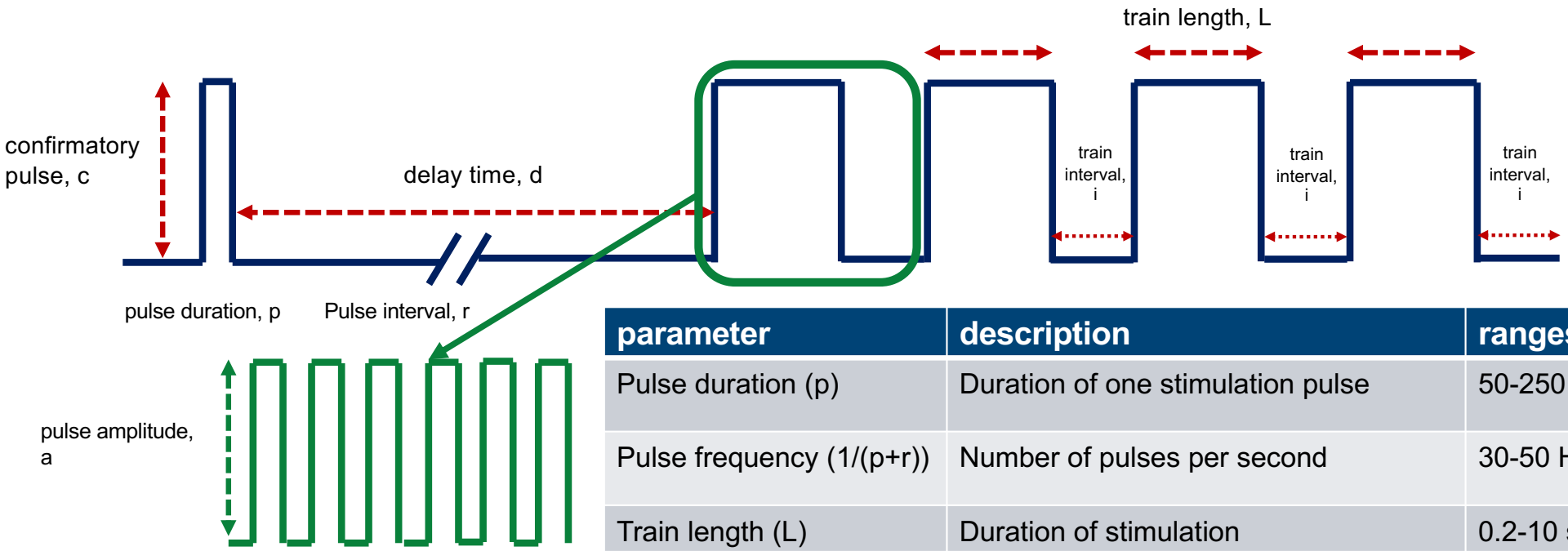
bilateral HNS – duty cycle stimulation



duty cycle (e.g. 70%)

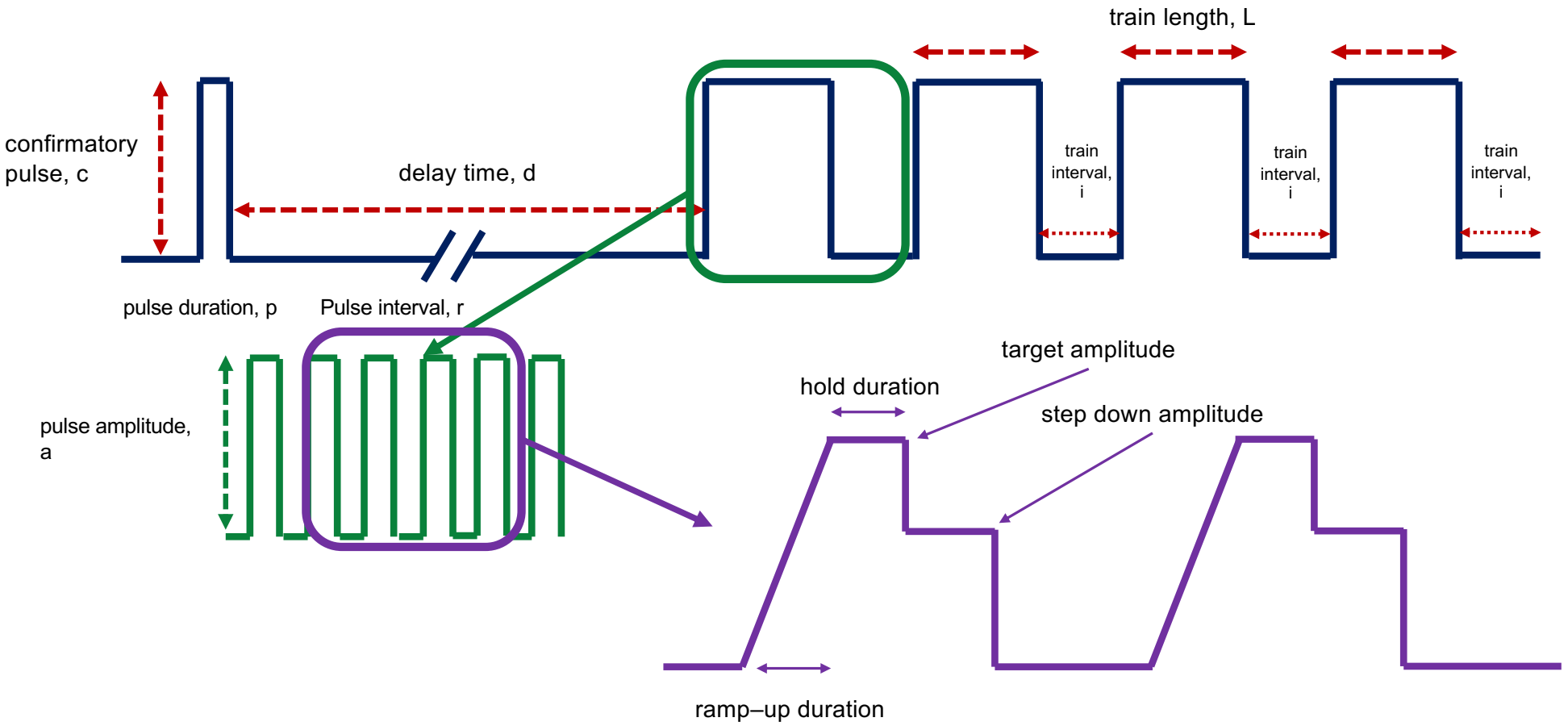
- stimulation phase (L) = 2.8s
- rest phase (i) = 1.2s
- total cycle length: 4.0 s
- duty cycle = L / (L+i) x 100 = 70%

bilateral HNS – duty cycle stimulation

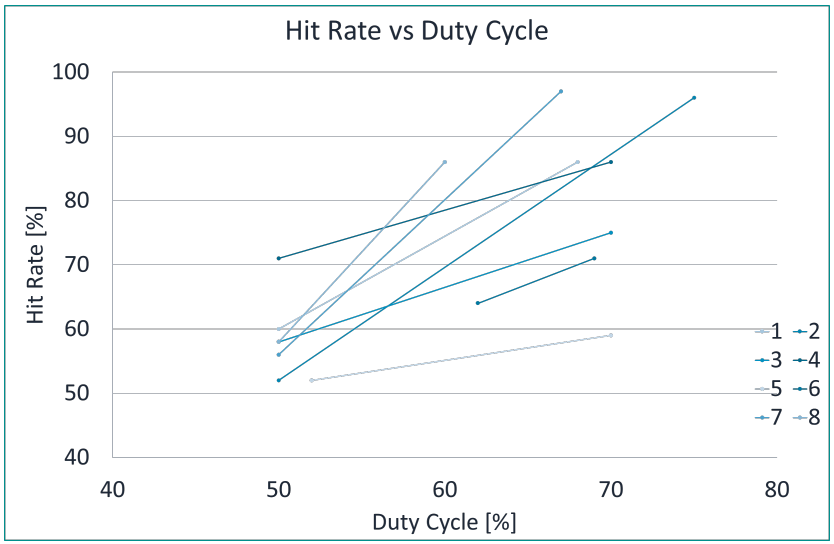


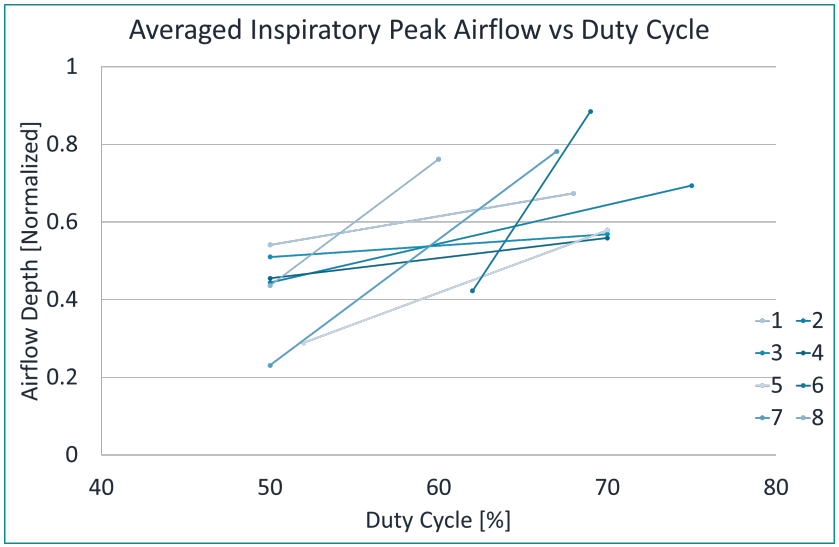
parameter	description	ranges
Pulse duration (p)	Duration of one stimulation pulse	50-250 µs
Pulse frequency (1/(p+r))	Number of pulses per second	30-50 Hz
Train length (L)	Duration of stimulation	0.2-10 s
Train interval (i)	Duration between 2 trains of stimulation	0.2 – 10 s
Pulse amplitude (a)	Stimulation amplitude	1-100 %
Delay time	Time to allow the patient to fall asleep	05-90 min

bilateral HNS – duty cycle stimulation



bilateral HNS – duty cycle stimulation





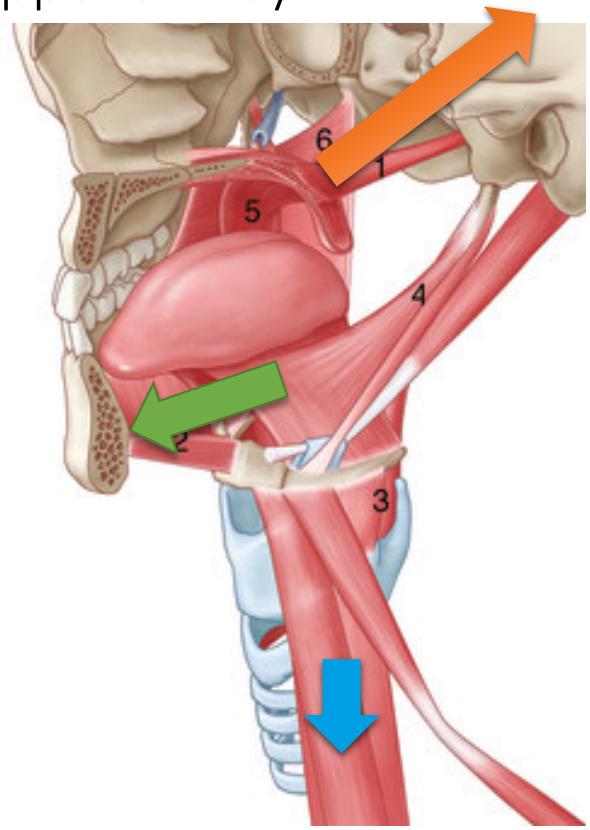
With increase in duty cycle

- the HIT rate increases in relation to inspiration
  - Increases inspiratory volume

not yet published

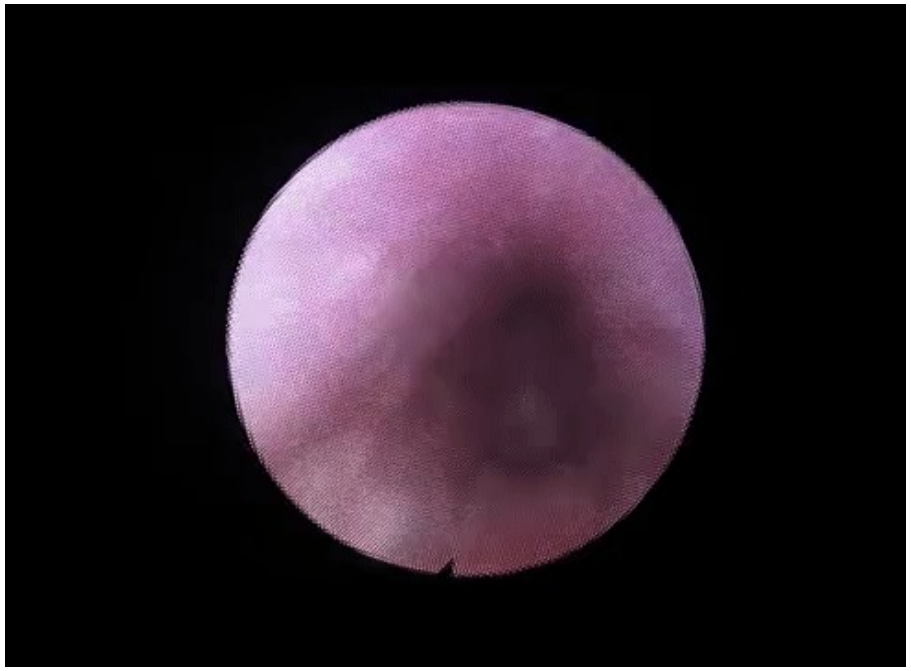
Mechanism to open the upper airway

- The pharynx: A flexible muscular tube suspended from the skull base and spine
  - Modifiable in anterior-posterior **and caudal** directions
  - **50 years of sleep surgery only modify A-P dimension**
- Three physiologic supporting mechanisms
  1. Genioglossus Tone
  2. Tracheal Traction
  3. Intrinsic Pharyngeal Muscle Tone
- **Opposing forces create synergistic effect**
  - **Reduces need for intensive tongue protrusion**



Kent, D. Ansa Cervicalis Stimulation: A New Direction in Neurostimulation for Obstructive Sleep Apnea. Chest. 2021 Mar;159(3):1212-1221

Mechanism to open the upper airway

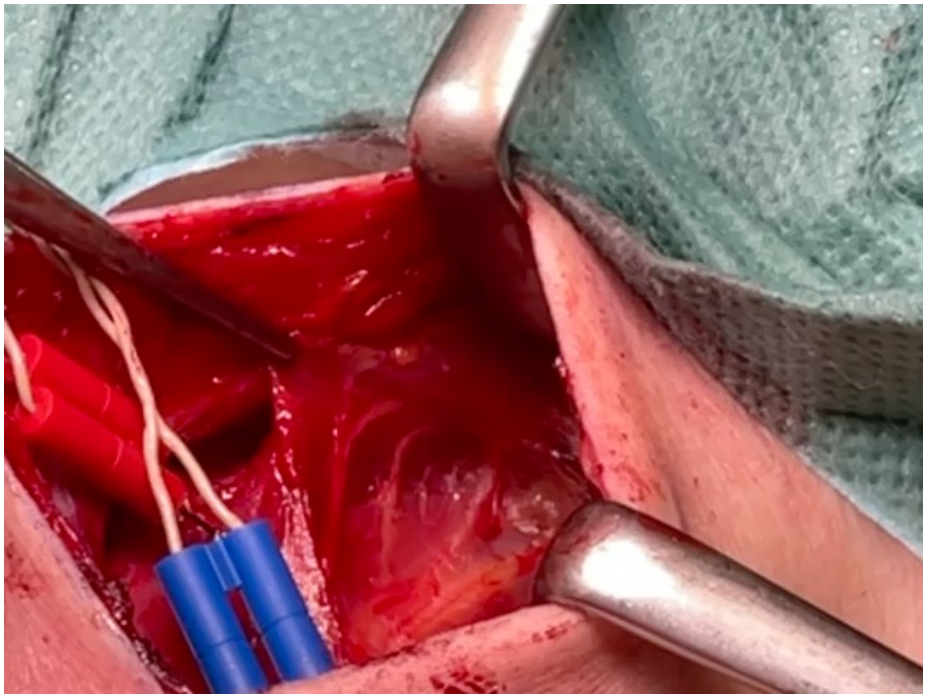


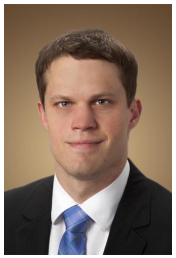
Unilateral HNS Only: Note partial R palatal movement anteriorly, persistent LW collapse

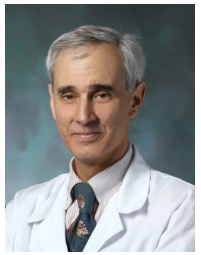
Unilateral HNS + Sternothyroid: Note improved palatal opening; LW stabilization

Kent DT, Scott WC, Zealear D, Schwartz AR. Ansa cervicalis stimulation increases pharyngeal patency in patients with obstructive sleep apnea. J Appl Physiol (1985). 2021 Aug 1;131(2):487-495

ANSA cervicalis stimulation







VANDERBILT UNIVERSITY

JOHNS HOPKINS UNIVERSITY

Nyxoah
The path to restful nights

Kent DT, Zealear D, Schwartz AR. Ansa Cervicalis and Hypoglossal Nerve Stimulation in a Patient With Obstructive Sleep Apnea. Otolaryngol Head Neck Surg. 2021 [Epub Ahead of Print]

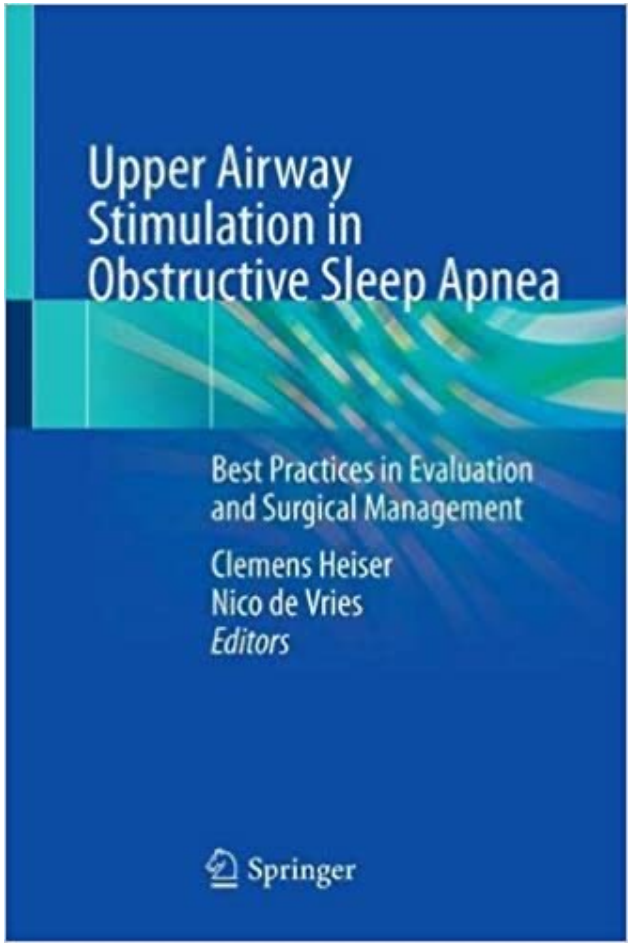
Mwachaka PM et al: Variations in the anatomy of ansa cervicalis. Folia Morphol (Warsz). 2010 Aug;69(3):160-3

Summary / Conclusion

HNS (uni- & bilateral) in the clinical routine is

- safe
- well tolerated & accepted by the patients
- shows good adherence
- And highly effective

New innovative therapeutic approaches in this field will make neurostimulation to smart neuromodulation.



Thanks for your attention

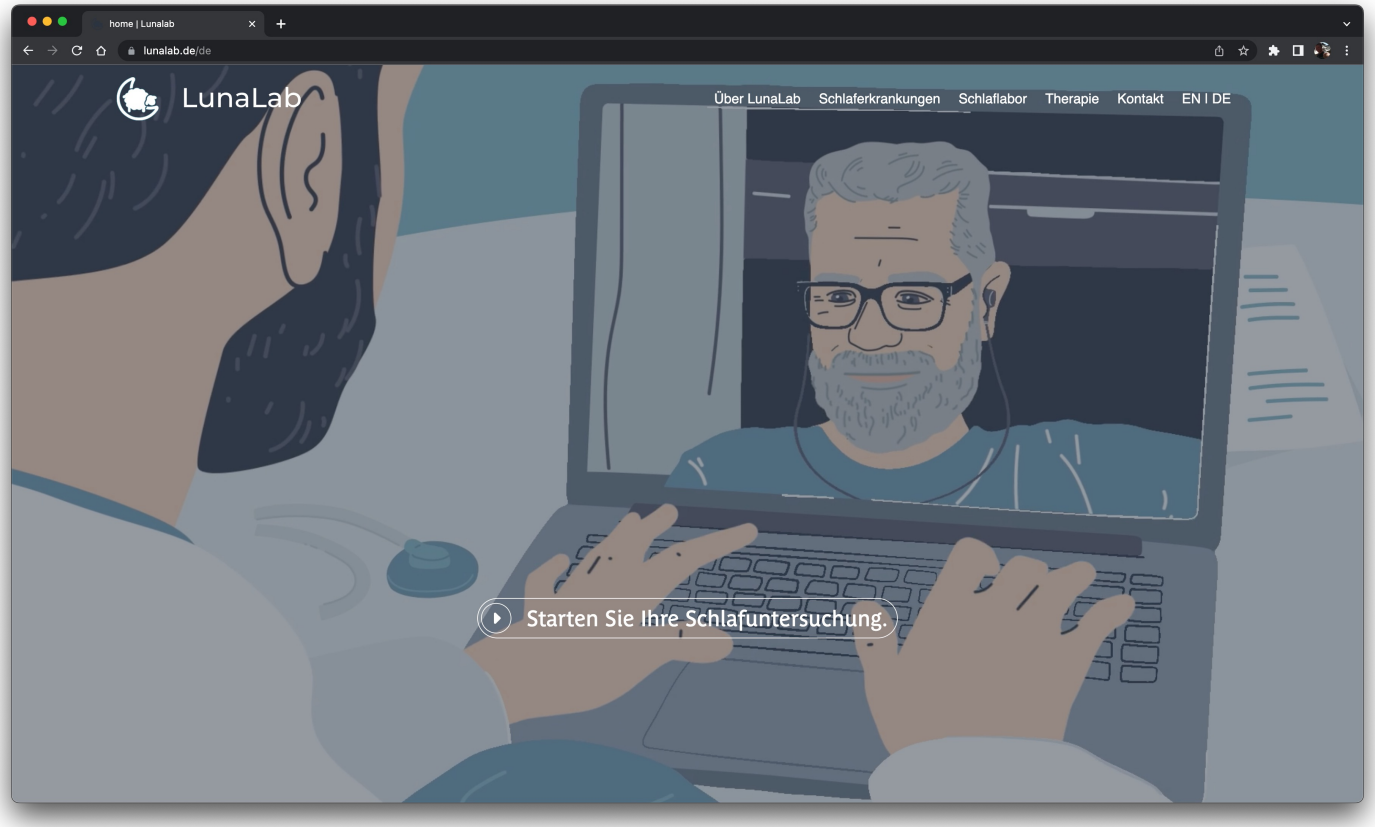
The AcuPebble Opportunity

Prof. Dr. med. J. Ulrich Sommer

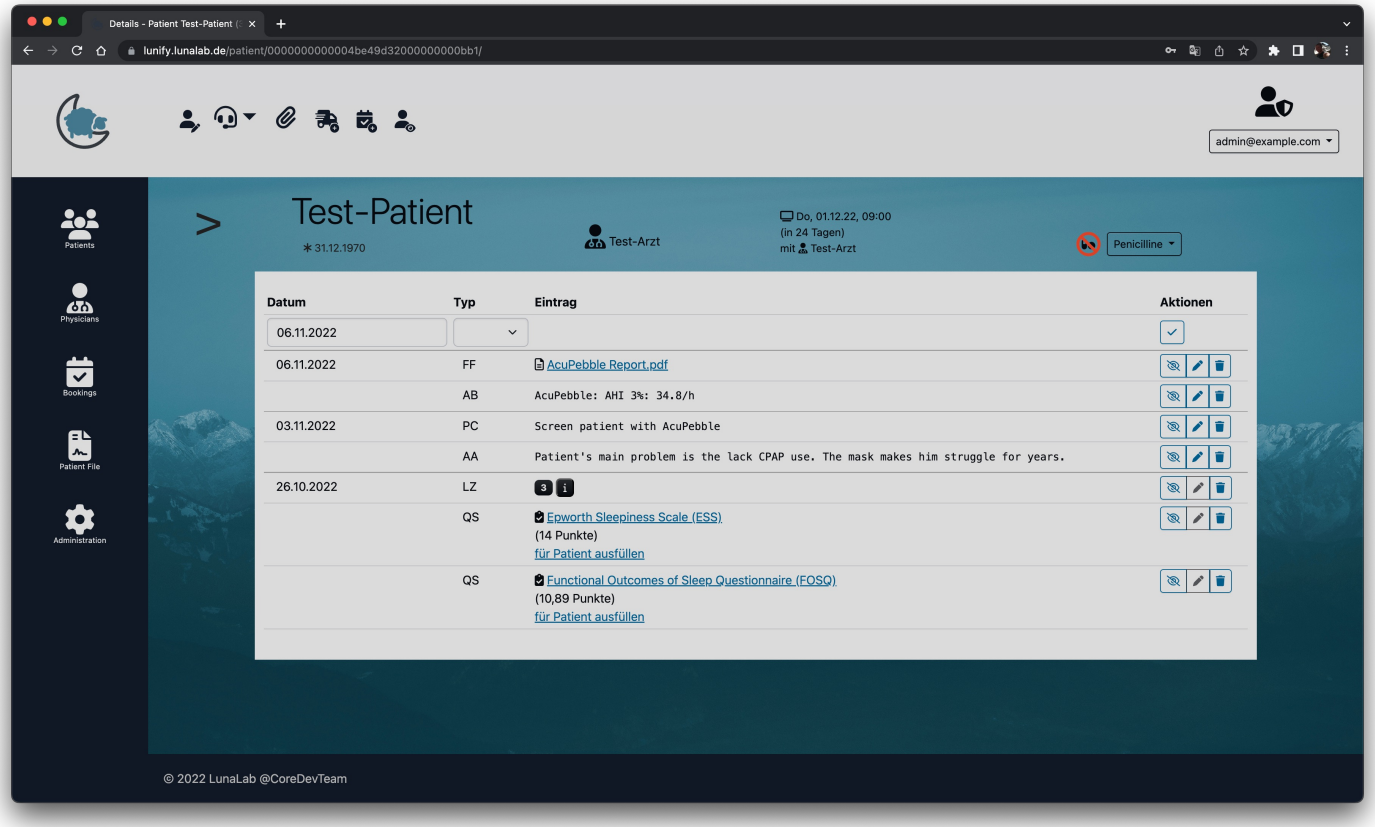
01

What is LunaLab?

LunaLab


home | Lunalab
lunalab.de/de
LunaLab
Über LunaLab
Schlaferkrankungen
Schlaflabor
Therapie
Kontakt
EN I DE
Starten Sie Ihre Schlafuntersuchung.

Solution suitable for fast paced workflows?



02

What is AcuPebble?

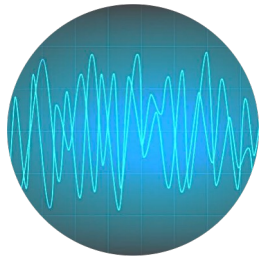
And why AcuPebble might be a perfect match for LunaLab…

“A sensor records sounds generated by respiratory and cardiac functions and blood oxygen.

How it works…

- Data transfer to a patient owned mobile device

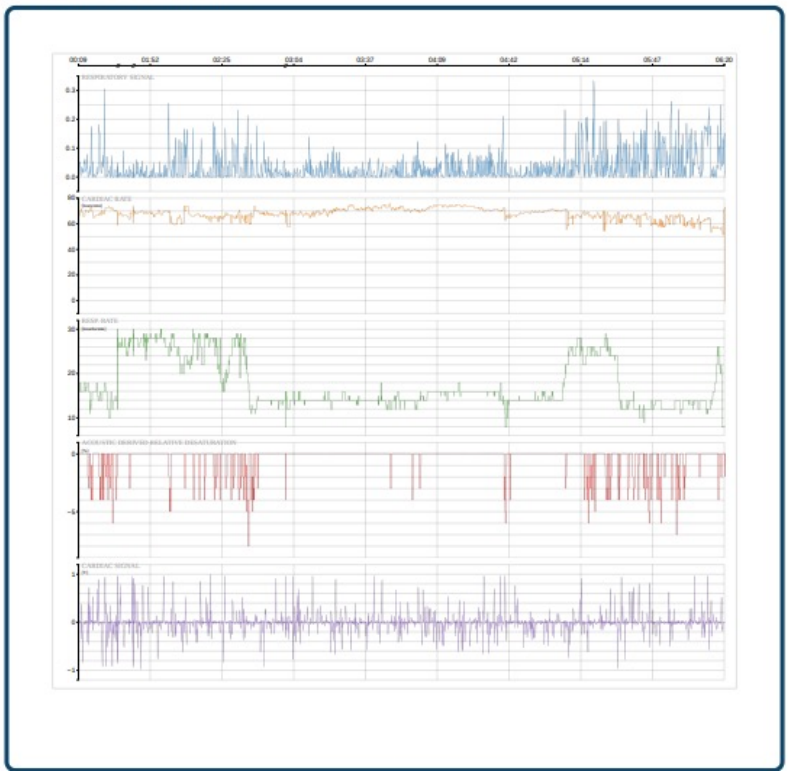
- Upload to the cloud



- Signal processing algorithms using hyperscalable cloud computing

Report

SIGNALS SUMMARY



Report

TEST RESULT

CLINICIAN COMMENTS
No comments entered

DIAGNOSIS

DIAGNOSTIC INDEX	SEVERITY	EVENTS/HOUR
3% desaturation		
AHI3	MODERATE	21
ODI3	MODERATE	17
4% desaturation		
AHI4	MODERATE	21
ODI4	MODERATE	17

DEFINITIONS

- **AHI3** Average number of events per hour with events defined as per AASM version 2.5
- **ODI3** Average number of 3% oxygen desaturation events per hour.
- **AHI4** Average number of events per hour with events defined as per AASM version 2.5 but with desaturation threshold at 4%.
- **ODI4** Average number of 4% oxygen desaturation events per hour.

EVENTS ANALYSIS

AHI3 APNOEA EVENTS ANALYSIS

TYPE OF EVENT[0]	PERCENTAGE	AVG./HOUR
CENTRAL APNOEA	2.9%	0.6
CENTRAL OR OBSTRUCTIVE APNOEA[1]	2.9%	0.6
HYPOPNOEA	9.8%	2
OBSTRUCTIVE APNOEA (100%)[2]	16.7%	3.5
OBSTRUCTIVE APNOEA (≥90%)[3]	9.8%	2
OBSTRUCTIVE APNOEA OR HYPOPNOEA[4]	57.9%	12.1

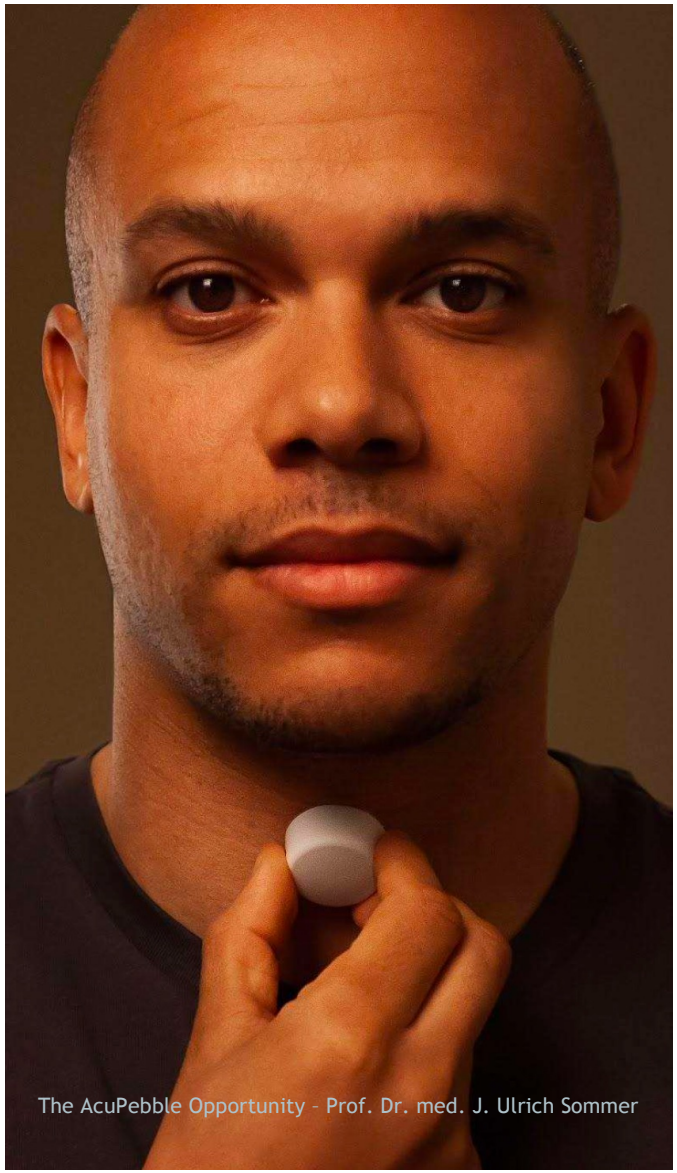
AHI4 APNOEA EVENTS ANALYSIS

TYPE OF EVENT[0]	PERCENTAGE	AVG./HOUR
CENTRAL APNOEA	2.9%	0.6
CENTRAL OR OBSTRUCTIVE APNOEA[1]	2.9%	0.6
HYPOPNOEA	9.8%	2
OBSTRUCTIVE APNOEA (100%)[2]	16.7%	3.5
OBSTRUCTIVE APNOEA (≥90%)[3]	9.8%	2
OBSTRUCTIVE APNOEA OR HYPOPNOEA[4]	57.9%	12.1

0 - Type of event considered in diagnosis and AHI
1 - Events with flow reduction larger than 90%, but unclear whether caused centrally or by obstruction
2 - 100% cessation of breathing
3 - Flow reduction ≥90% of pre-event baseline but not total cessation of breathing
4 - Events with estimated desaturation >4% and flow reduction >70%, but unclear whether larger or smaller than 90%

03

Clinical data



The AcuPebble Opportunity – Prof. Dr. med. J. Ulrich Sommer

Clinical data

Open access Original research

BMJ Open

Accuracy and usability of AcuPebble SA100 for automated diagnosis of obstructive sleep apnoea in the home environment setting: an evaluation study

Nikesh Devani,[1] Renard Xaviero Adhi Pramono,[2] Syed Anas Imtiaz,[2] Stuart Bowyer,[2] Esther Rodriguez-Villegas ,[2] Swapna Mandal[1]

- n=150
- AcuPebble + cardiorespiratory polygraphy simultaneously

Positive and negative predictive value

- Few diagnostic tests have both high PPV and NPV
  - Pulse Oximetry for the diagnosis of OSA [1]
    - PPV 97%
    - NPV 48%
  - Lung cancer screening test (with low dose CT) [2]
    - PPV 2.4%
    - NPV 99.9%

	3% desaturation	4% desaturation
AHI based diagnosis results	PPV: 94.4% NPV: 95.8%	PPV: 94.0% NPV: 98.0%
ODI based diagnosis results	PPV: 93.4% NPV: 90.5%	PPV: 85.7% NPV: 98.9%

[1] Chiner E, Signes-Costa J, Arriero JM, et al Nocturnal oximetry for the diagnosis of the sleep apnoea hypopnoea syndrome: a method to reduce the number of polysomnographies; Thorax 1999;54:968-971

[2] Denise R. Aberle, Sarah DeMello, Christine D. Berg, et al. , Results of the Two Incidence Screenings in the National Lung Screening Trial, N Engl J Med 2013; 369:920-931

AcuPebble vs. PG

		Diagnosis based on AHI defined by the current AASM recommended criteria[17] but with the exception of having >4% as the minimum threshold for desaturation (*K*=0.89)				Diagnosis based on current AASM recommended AHI-based criteria[17] (*K*=0.82)			
		Gold-standard diagnosis—number of patients=150							
		Normal	**Mild**	**Moderate**	**Severe**	**Normal**	**Mild**	**Moderate**	**Severe**
Acupebble diagnosis n=150	Normal	68	2	0	0	53	7	1	0
	Mild	1	28	2	0	2	31	3	0
	Moderate	0	3	20	2	0	3	19	2
	Severe	0	0	1	23	0	0	1	28

AcuPebble SA100 versus CR-PG (with manual expert marking) as reference gold-standard test.
Cells highlighted with green indicate complete agreement between AcuPebble and Gold Standard diagnosis.
AASM, American Academy of Sleep Medicine; CR-PG, cardiorespiratory polygraphy.

04

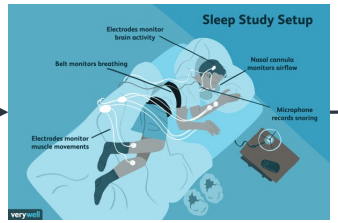
The AcuPebble Opportunity

Ensure patients most in need receive therapy ASAP

PSG Waiting List

6 Months+ for All

PSG



CPAP Therapy?

The LunaLab Paradigm

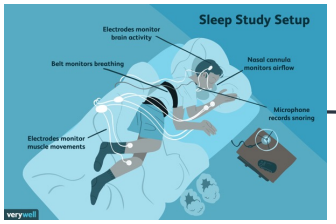
AcuPebble Sleep Test

Faster Treatment for Moderate/Severe Patients

CPAP Therapy?

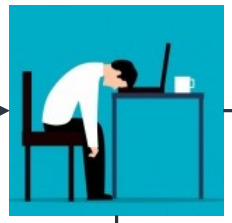
Current CPAP failure practice and shortcut

PSG



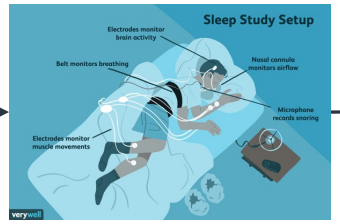
CPAP

CPAP Failure



6 Months +

PSG



Genio?

The LunaLab Paradigm

6 Days -

AcuPebble Sleep Test

Genio?

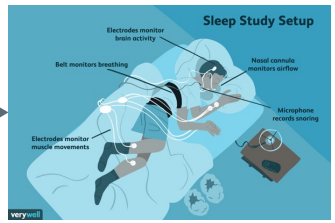
Monitoring Genio patients to ensure therapy is optimized

Genio

Genio Patient

Limitations on Routine Monitoring
Waiting Lists, Costs, Inconvenience

PSG



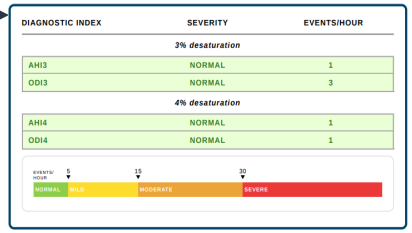
The LunaLab Paradigm

AcuPebble Sleep Test

AcuPebble for Routine Monitoring and Therapy Optimization

TEST RESULT

DIAGNOSIS



DIAGNOSTIC INDEX	SEVERITY	EVENTS/HOUR
3% desaturation		
AHI3	NORMAL	1
ODI3	NORMAL	3
4% desaturation		
AHI4	NORMAL	1
ODI4	NORMAL	1

AcuPebble Sleep Report

05

Summary

“AcuPebble enables us to provide high-quality OSA screening in a fast-paced and virtualized environment

Thank you and a wonderful evening!

Prof. Dr. med. J. Ulrich Sommer

Thank You & Enjoy the Evening

Nyxoah®