From EEG to PPG to ACC:

Usage of Digital Devices to Quantify Sleep in Clinical Trials

Ariel V. Dowling, PhD
Head of Sensing and Measurement
Data Sciences Institute, Takeda Pharmaceuticals

Better Health, Brighter Future

What is Sleep?

SLEEP

WAKE

- A period of rest and reduced activity
- Decreased responsiveness to external stimuli
- Associated with typical posture of lying down with eyes closed
- Typically occurs at regular, nocturnal intervals
- A physical state that is relatively easy to reverse with awakening

Medical Definition of Sleep:

Sleep is a state that is characterized by changes in **brain wave activity**, breathing, heart rate, body temperature, and other physiological functions.

Why Measure Sleep?

Sleep affects almost all major organ systems and is implicated in many disease states

>90 sleep disorders affecting 70 million people per year:

- Insomnia
- Narcolepsy
- Restless Leg Syndrome
- Sleep Apnea

Poor sleep contributes to:

- Diabetes
- Heart disease
- Dementia
- Depression
- Anxiety
- Obesity

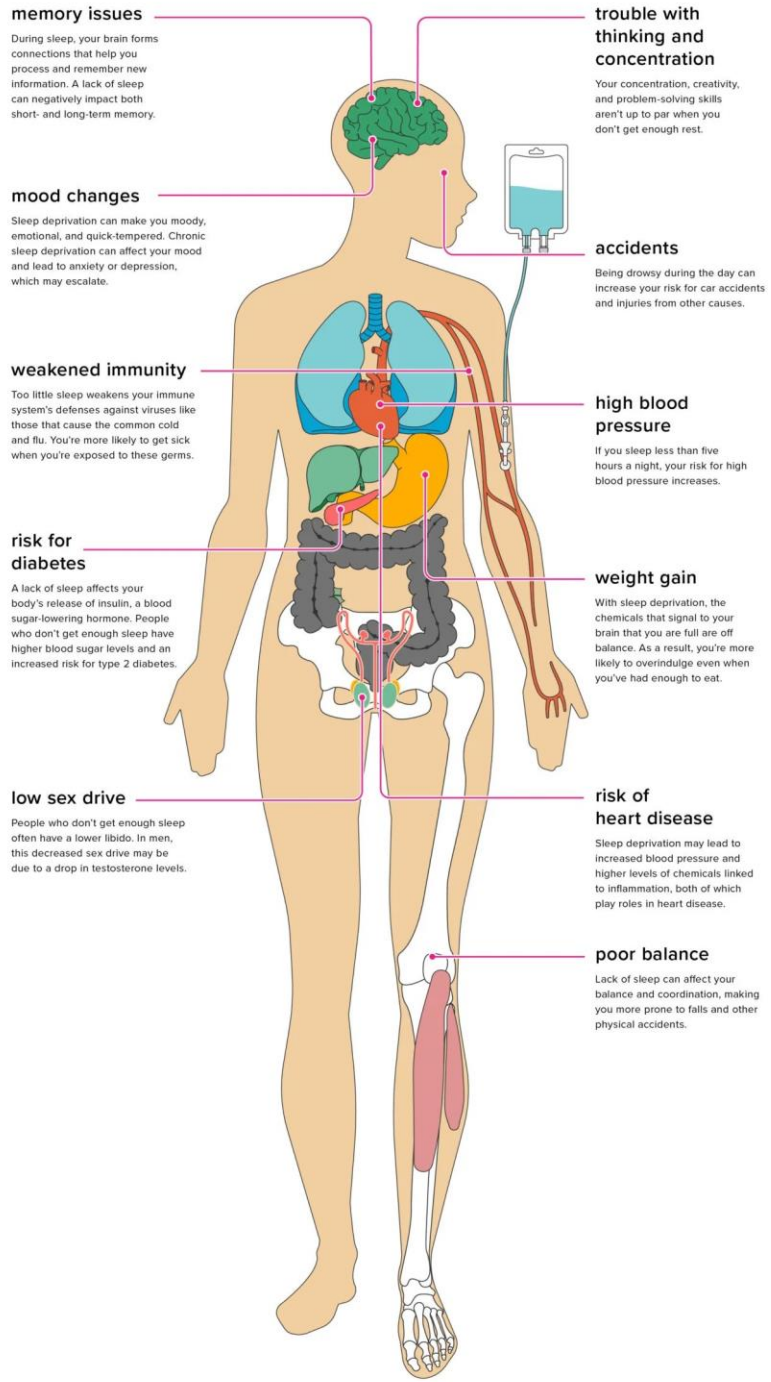


Image from Healthline.com, 2024; AASM, 2024;

Sleep Measurement – A Brief History

5000-1000 BCE: Regulation of sleep and dreams through rituals

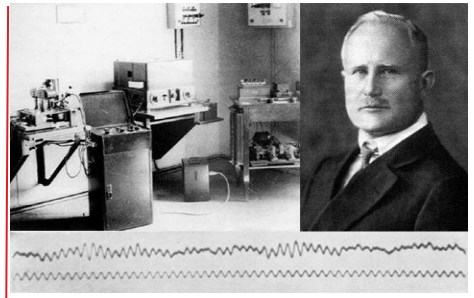
Fast forward ~2000 years

1180: 8 hrs sleep/night defined as optimal

Fast forward ~600 years

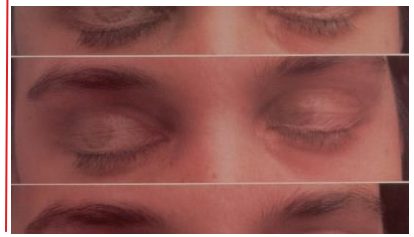
1729: Concept of circadian rhythms

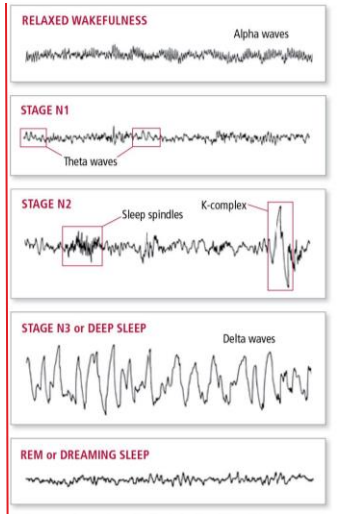
Fast forward ~200 years



1924: EEG captures neural activity in sleep

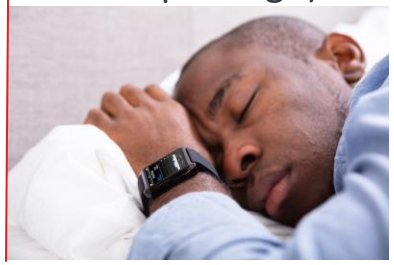
1952: Discovery of rapid eye movement (REM) sleep





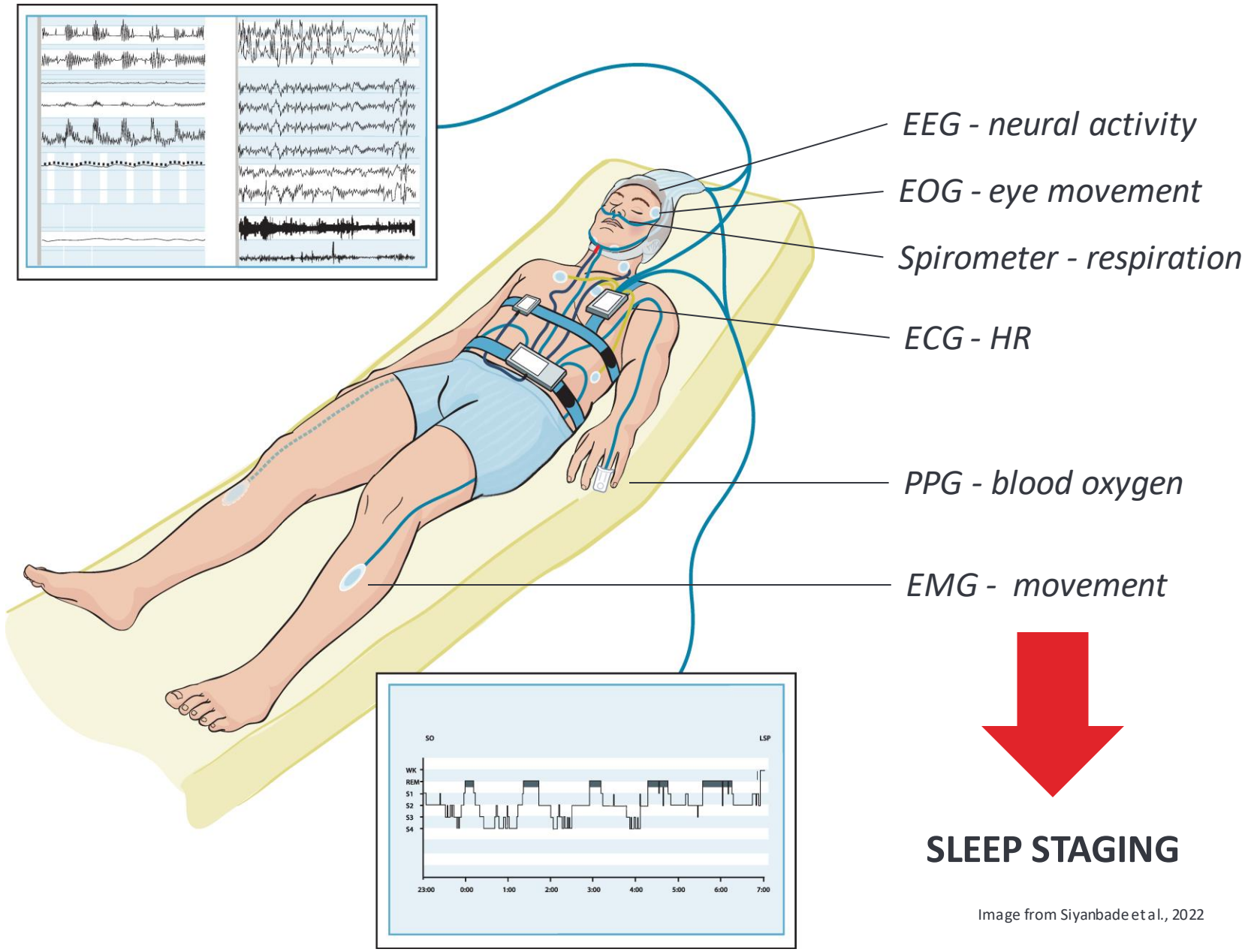
1968: Sleep stages defined from EEG

1992: Sleep tracking from activity (accelerometers and Cole-Kripke algo)



Sleep Measurement in the Clinic: Polysomnography (PSG)

Medical Definition: Sleep is a state that is characterized by changes in brain wave activity, breathing, heart rate, body temperature, and other physiological functions.



SLEEP STAGING

Image from Siyanbade et al., 2022

Sleep Measurement in the Digital Era

>600

digital devices

Source: HumanFirst, 2024

Measuring Sleep Using Digital Devices in Clinical Trials

Possible Outcome Measures in Sleep

Total Sleep Time	REM Latency	Time Asleep during the Day
Total Time in Bed	Time in Deep Sleep	Circadian Dichotomy Index
Sleep Efficiency	Time in Light Sleep	Circadian Interday Stability
Sleep Fragmentation	Time in NREM Sleep	Circadian Interday Variability
Sleep Fragmentation Index	Time in REM sleep	Circadian Intradaily Stability
Sleep Latency	Time in N1	Circadian Intraday Variability
Sleep Midpoint	Time in N2	Sleep Position
Sleep Onset	Time in N3	Sleep Quality
Device-Detected Bedtime	Number of Sleep Spindles	Number of Snoring Bouts
User-Inputted Bedtime	Number of Slow Oscillations	Time Snoring
Time Awake in Bed	Wake After Sleep Onset	Number of Nocturnal Scratches
Time Out of Bed	Wake Time	Time Scratching during Night
Sleep Stages	Number of Awakenings	Number of Active Events
Time in Sleep Stages	Number of Sleep Bouts	Time Active during Sleep
REM Density	Number of Daytime Sleep Events	Number of Bruxism Events

Source: HumanFirst, 2024

Your Outcome Measure Matters

Concepts of Interest Approach:

		Sleep Example
Meaningful Aspect of Health (MAH)	Aspect of the disease the patient doesn't want to get worse, wants to improve, or wants to prevent	**Patient experiencing insomnia after dosing events**
Concept of Interest (COI)	Simplified element that can be practically measured	**Sleep**
Outcome Measure	Specific measurable characteristic	**Total sleep time (TST)**
Endpoint	Precisely defined, statistically analyzed variable	**Change in TST pre- and post-drug intervention**

Manta, Patrick-Lake, and Goldsack, *Digital Biomarkers*, 2020

Your Outcome Measure Chooses Your Device

Neurological Measure: EEG-enabled Device

- Time in Sleep Stages
- Probability of Sleep Stage per Epoch
- Time in N1
- Time in N2
- Time in N3
- Time in REM
- Number of Sleep Spindles
- Number of Slow Oscillations
- Sleep Efficiency
- Sleep Fragmentation
- Sleep Fragmentation Index

Physiological Measure: Device with Other Sensors (PPG, ACC, Gyro, EDA)

- Total Sleep Time
- Total Time in Bed
- Sleep Position
- Number of Active Events
- Time Active during Sleep
- Number of Snoring Bouts
- Time Snoring
- Number of Nocturnal Scratches
- Time Scratching during Night
- Number of Bruxism Events
- Time in Bruxism

How You Measure your Outcome Matters

Quality of Evidence Required

Operational Lift & Patient Burden

Neurological Measurements of Sleep in Takeda Clinical Trials

Clinical Investigations of Wearable EEG in Narcolepsy

Challenge: Clinical validation of a wearable headband EEG device for sleep detection and staging in patients with Narcolepsy Type 1 (NT1)

- Concordance of sleep stage scoring and correlation of sleep transitions: in-clinic comparison to gold standard PSG
- Digital biomarkers of night-to-night variability in sleep patterns and sleep transitions: at-home data (wearable EEG only)

Study Design: In-clinic validation, at-home usability

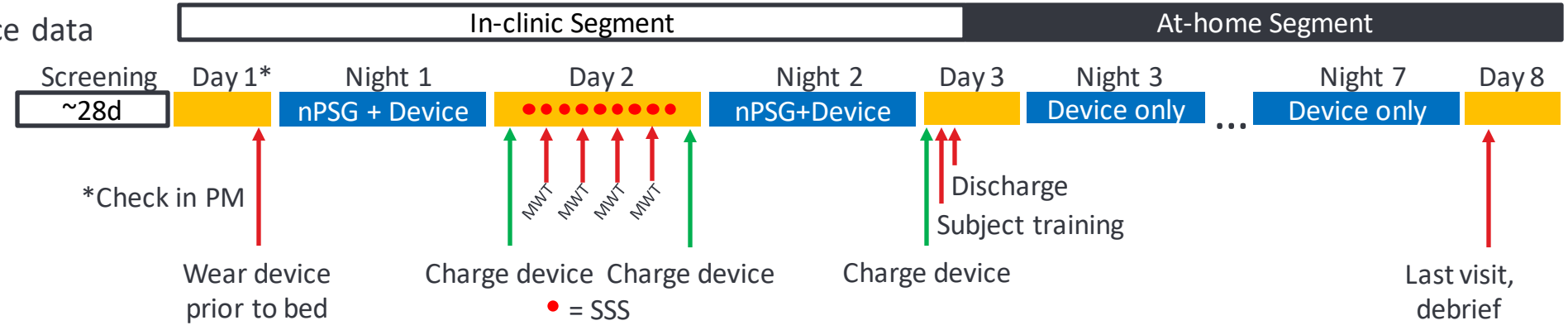
- Headband device designed for at-home nighttime use in healthy subjects
- 16 patients with narcolepsy, 16 age/gender matched controls
- 2 nights in-patient testing against gold standard, 5 nights at-home testing with ePRO diary

Results: Primary endpoints not met in study to demonstrate acceptable equivalence to PSG

- Compliance and usability scores lower than anticipated in NT1 patients
- Accuracy of sleep staging did not meet prespecified thresholds

Next Steps: Test newer version of hardware and sleep staging algorithm focused on disturbed sleep

- Improved hardware form factor
- Addition of sleep disturbance data



Exploratory Investigations of Wearable EEG Devices

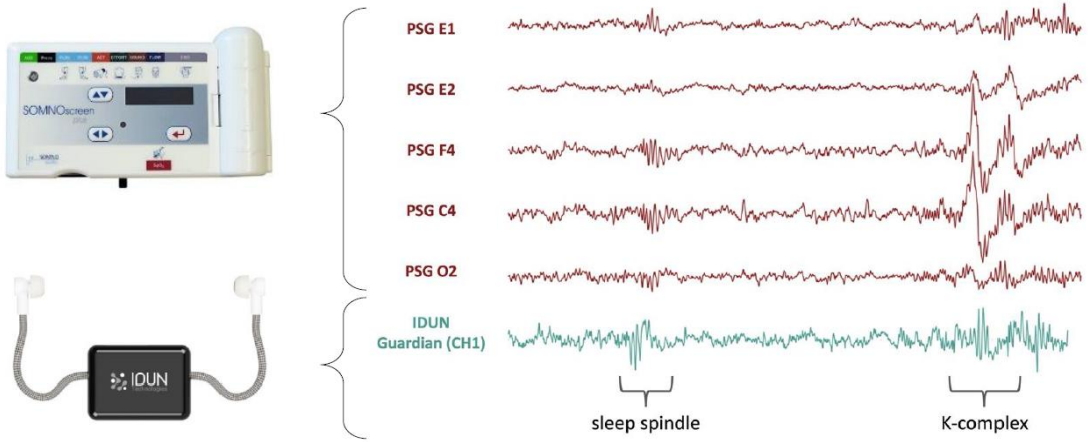
Proof-of-Concept studies of new EEG devices in advance of the clinical pipeline

DIGITAL HEALTH INNOVATION CHALLENGE

Who: IDUN Technologies

What: Pilot study to investigate 2-channel, in-ear EEG wearable device for sleep staging in healthy subjects

Results: 2-channel in-ear EEG can capture sleep waveforms for sleep stage scoring comparable to PSG



EXTERNAL PARTNERSHIP

Who: NextSense, Emory University

What: Pilot study to investigate 5-channel in-ear EEG wearable device for sleep staging in healthy controls and NT1 patients

Results: 5-channel in-ear EEG can capture sleep waveforms for sleep stage scoring and other endpoints comparable to PSG

Endpoint	Mean (95% CI) difference
MWT SOL, minutes	-0.9 (-1.7 to -0.1)
WASO, minutes (night)	3.8 (1.2-8.0)
TST, minutes (night)	-3.4 (-8.3 to -0.6)
% REM in first 2 hours (night)	0.7 (-1.2 to 3.2)

Metric*	Ear-EEG	PSG-EEG
Accuracy (%)	82.7	91.0
Cohen's Kappa (%)	74.3	85.8

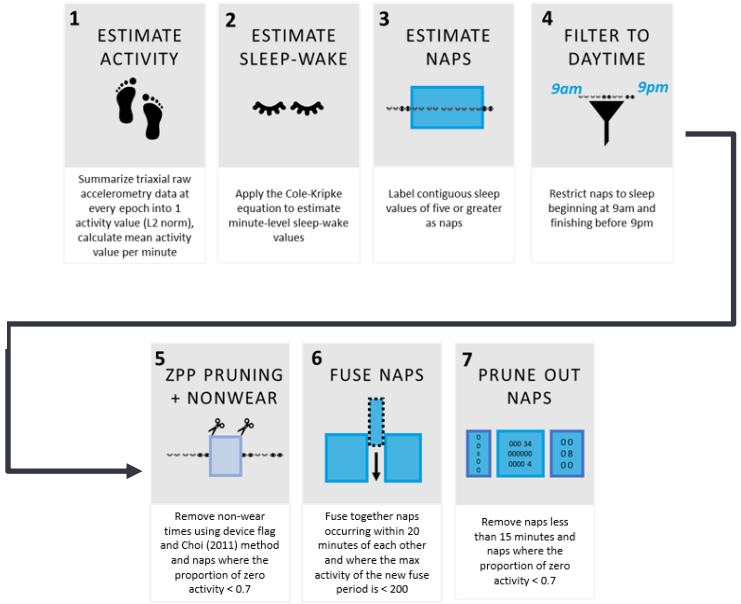
Physiological Measurements of Sleep in Takeda Clinical Trials

Actigraphy-based Digital Biomarkers for Patients with Narcolepsy

Clinical Motivation

Excessive daytime napping is a **key manifestation of narcolepsy** but is understudied. ePROs are the current standard measurement but are susceptible to recall error and bias.

Napping measured by actigraphy is an objective measurement that meaningfully quantifies excessive daytime sleepiness.

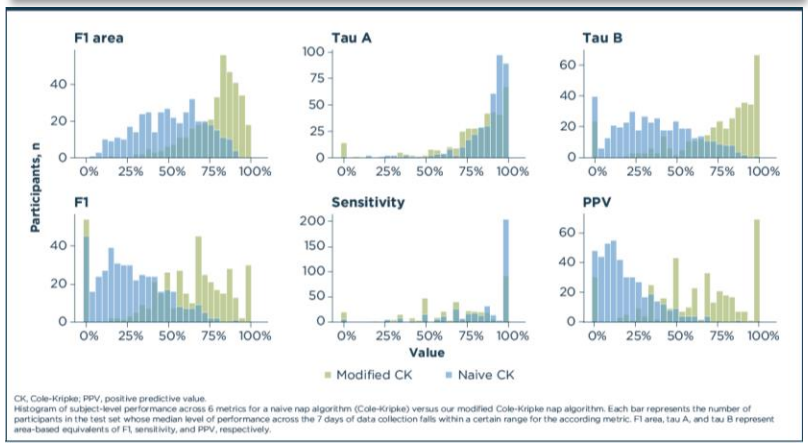


Algorithm Development

We **developed an algorithm to detect daytime naps** using annotated naps in the Multi-Ethnic Study of Atherosclerosis dataset (MESA).

- Algorithm optimized for specificity of nap detection
- Naïve algorithm classified most epochs as sleep (low specificity)
- Modified Cole-Kripke had high sensitivity (88.9%) and high F1 area (84.4%) with low false positives

Participant-level performance was improved with the modified CK nap algorithm

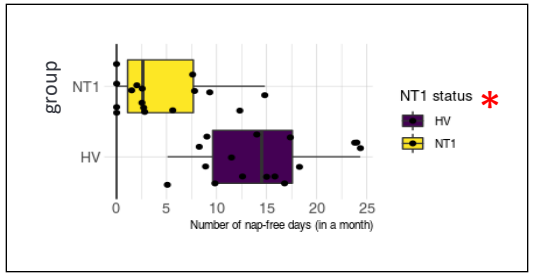


Clinical Deployment

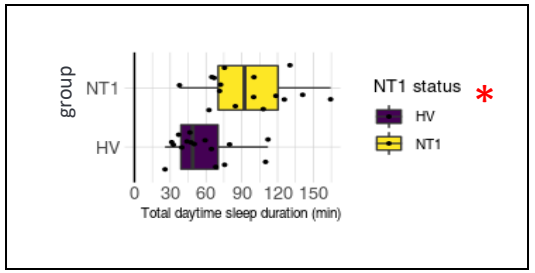
Algorithm tested in an **observational clinical trial** of NT1 and healthy participants

- 2 digital biomarkers: nap-free days and total daytime sleep (min)
- NT1 patients had 8x lower odds of a nap-free day, and slept for 53 more daytime minutes on days they napped
- Nap detection algorithm had poor agreement with ePROs
  - F1 area = 0.20, ICC = 0.32

Nap-free days



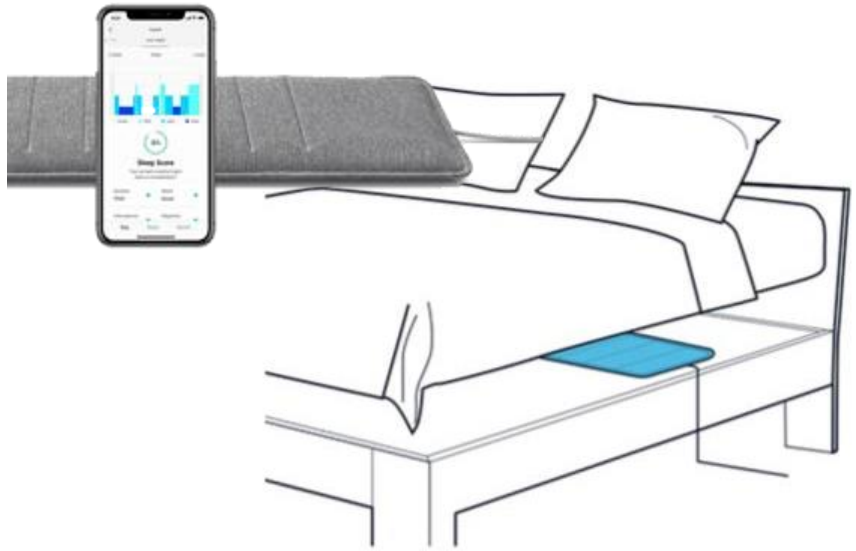
Total daytime sleep (min)



*Digital biomarker development by Raul Torres in the Quantitative Sciences group at Takeda, led by Dmitri Volfson. Results presented at World Sleep Conference 2023.

Validation and Usability of a Contactless Sleep Device

Can we improve patient compliance with contactless monitoring?



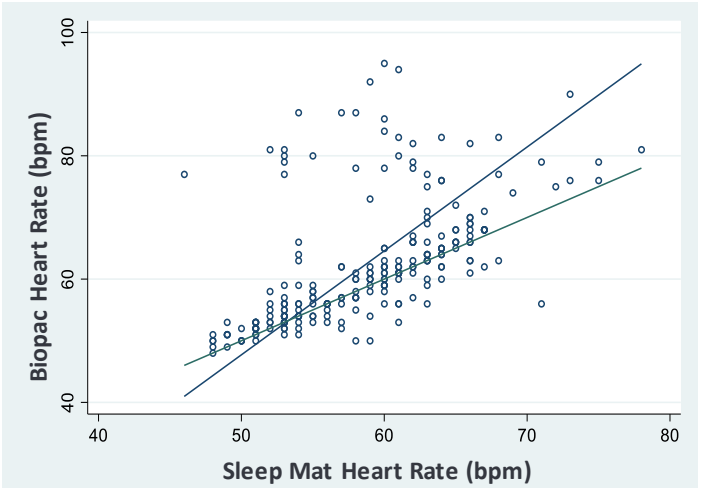
Collaborator: Exercise and Physical Activity Resource Center (UCSD): Job Godino

Device: Withings Sleep Mat – Contactless under-mattress air-filled mat

Goals: In-lab validation and at-home usability assessment with healthy subjects

In-Lab Validation

- 28 healthy subjects
- Heart rate compared to ECG: reasonable error of 7% MAPE



- Respiratory rate compared to capnography: high error of 23% MAPE

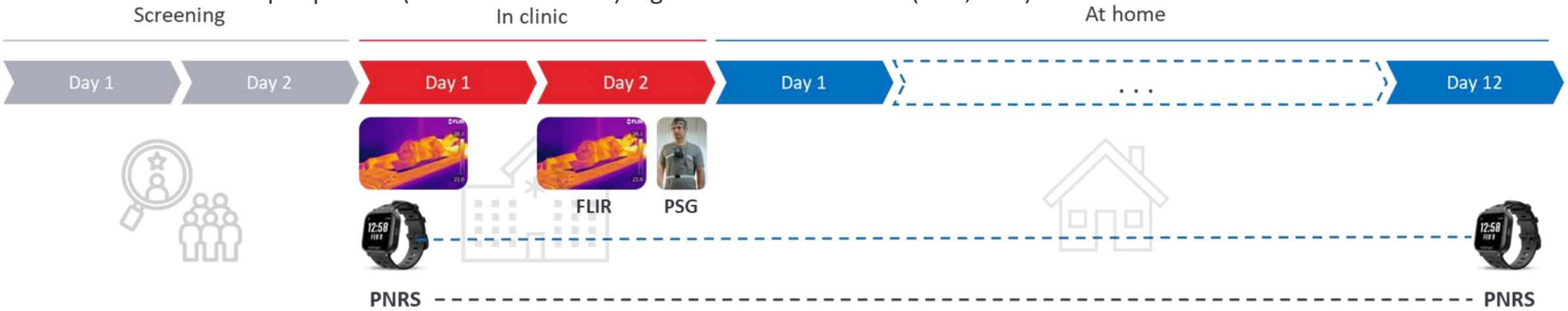
At-Home Usability

- All subjects used sleep mat at-home for 7 days:
  - Installed device by connecting to home Wi-Fi
- Usability assessed with the System Usability Scale:
  - 72.9 / 100 SUS score
- Subject compliance tracked on a nightly basis:
  - 94% compliance

High usability and patient acceptance with low burden and minimal data loss

Sleep in the Precompetitive DECODE Consortium

- **DECODE consortium** (Actigraph, Takeda, J&J, UCB) kicked off in Q4 2023 for nocturnal scratch measure development
  - 30 adult atopic dermatitis (AD) + 15 pediatric AD + 10 adult psoriasis (PsO) patients, single-center single-arm study in Europe
  - 2 LEAP devices per patient (one on each wrist) + ground truth methods (FLIR, PSG) + PROs



- In addition to scratch, the clinical trial will investigate **sleep in the target population**
  - **Primary sleep related endpoints:** Average daily 1) Total sleep time 2) Sleep efficiency 3) WASO
  - **Secondary sleep related endpoints:** Mean error of 1) Total sleep time 2) WASO 3) Major sleep interval duration
  - **Exploratory endpoints:** PRO (e.g., sleep diary) comparison to sleep metrics

- **Analytical validation of existing sleep algorithms** in the specific dermatological populations
  - Legacy count based methods[1] (e.g., Cole Kripke, Sadeh, Tudor-Locke)
  - Raw accelerometer based methods[2] (e.g., Van Hees, Deep learning)

[1] https://actigraphcorp.my.site.com/support/s/article/How-does-CentrePoint-Calculate-Sleep-Periods
[2] https://www.nature.com/articles/s41746-023-00802-1.pdf

Take Home Points for the Digital Measurement of Sleep

Best Practices for Measuring Sleep in Clinical Trials with Digital Devices

- Determine whether sleep is a **Meaningful Aspect of Health** for your patients
- Determine your primary and secondary **Outcome Measures** using the COI framework
  - Neurological or physiological measure?
  - Hierarchy of outcomes measures
- Based on your outcome measures, select a **digital device**
  - Quality of evidence required
  - Operational lift and patient burden
  - Form factor: headband, patch, watch, passive monitoring
- Conduct **feasibility testing** of device
  - Hands-on experience for digital and ops teams
  - Patient feedback (if possible)
  - Prepare for future challenges
- Ensure you have a **compliance monitoring system**
  - Real-time data uploads
  - Automatic compliance-tracking algorithm with alerting
  - Robust patient outreach protocol

Thank You

Better Health, Brighter Future