

Developing patient centric, real-world digital clinical measures for Rett syndrome

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Rett Syndrome

Rare neurodevelopmental disorder

- Occurs in 1:10,000 female births
- Apparently normal early development followed by developmental delay & regression of acquired skills

Clinical diagnosis with genetic confirmation

- Clinical diagnostic criteria
- MECP2 mutations identified in over 95% of cases

Diverse life-long symptoms

- Autonomic dysfunction, sleep disturbances, GI dysmotility, nutrition issues, scoliosis, contractures, seizures, movement disorders, limited communication, repetitive hand movements, others



Biosensors can Improve Drug Development for Rare Disease

Assessment of Efficacy on Rett symptoms



- Questionnaires are subjective and indirect
- Static snapshot in time or summary based on memory
- How therapeutics are currently developed



- Biosensors are objective and direct
- Continuous data collection, even at home
- Ability to expedite development

Autonomic Dysfunction is Prevalent in Rett Syndrome

Can we quantify Rett syndrome physiology?

Advantages

- Should self-correct with curative therapeutics
- Limits variables such as learning and skill implementation
- Precedent in animal models

Autonomic dysfunctions amenable to biosensor collection

- Breathing irregularities
- Heart rate variability
- Sleep disturbances



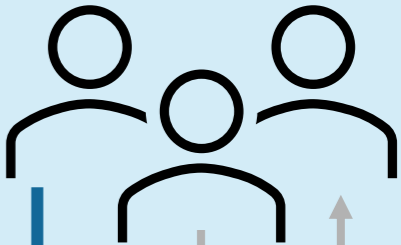
Expand to more complex symptoms?

- Mobility and gait
- Movement disorder characteristics
- Repetitive hand stereotypies
- Others

Patient Centric – Digital Measures that Matter

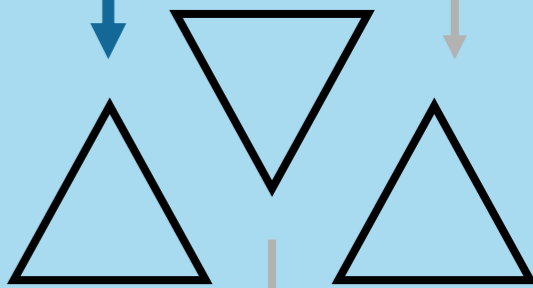
Meaningful Aspects of Health

Aspect of a disease that a person a) doesn't want to become worse, b) wants to improve, or c) wants to prevent



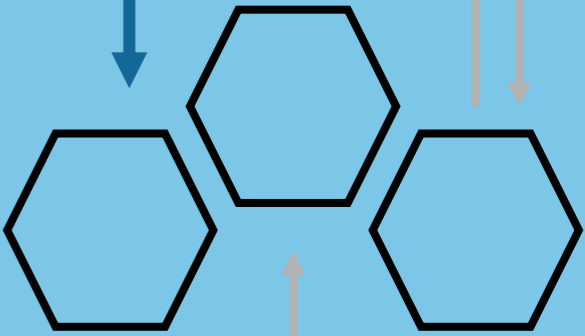
Concept of Interest

Simplified or narrowed element that can be practically measured



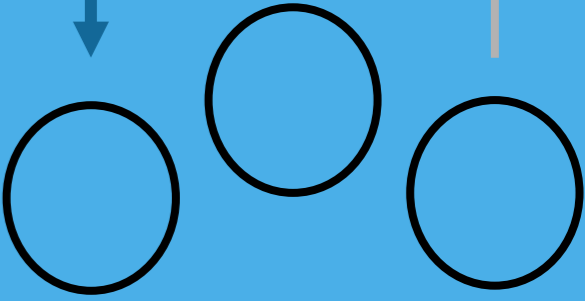
Outcome to be measured

Specific measurable characteristic



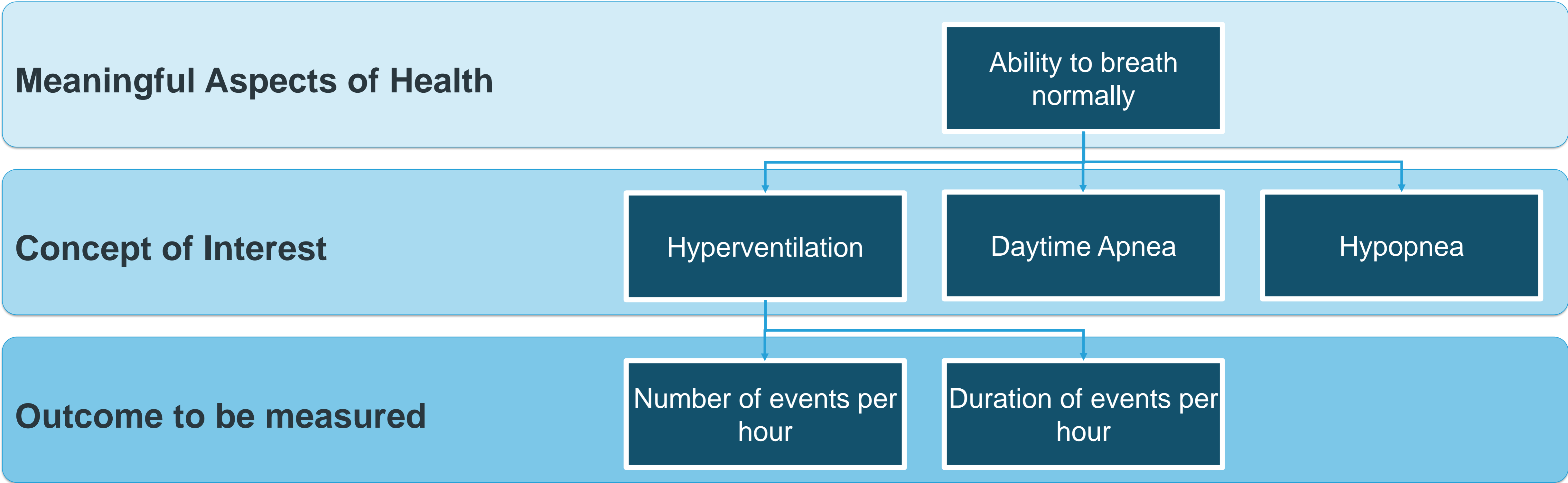
Endpoint

Precisely defined, statistically analyzed variable



Patient Centric – Digital Measures that Matter

Breathing Irregularities



Patient Centric - Meaningfulness

VOICE OF THE PATIENT REPORT

Rett Syndrome Externally-Led Patient-Focused Drug Development Meeting

Meeting Date: March 11, 2022



Breathing Irregularities are Meaningful to Parents

Explore meaningful aspects of health as defined by caregivers of individuals with Rett syndrome

- 13 Semi-structured in-depth interviews with caregivers

Meaningfulness

- “It's painful to watch her hold her breath involuntarily so long that she absolutely has a panicked look on her face. It's so difficult. It affects so much.”
- “She has indicated to us that she, you know through her communication devices, that it's hard for her to breathe and that she wishes breathing was more easy.”

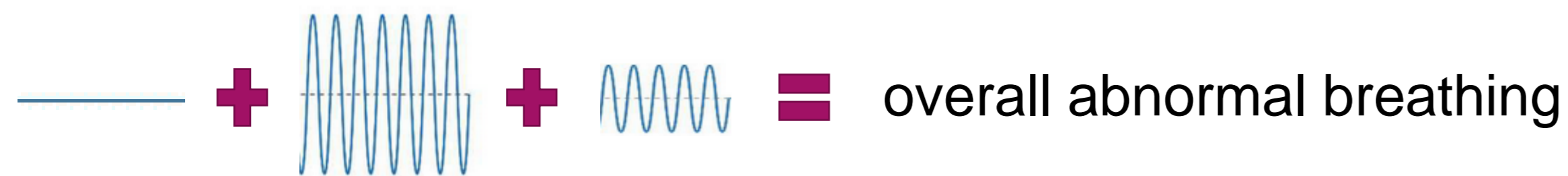
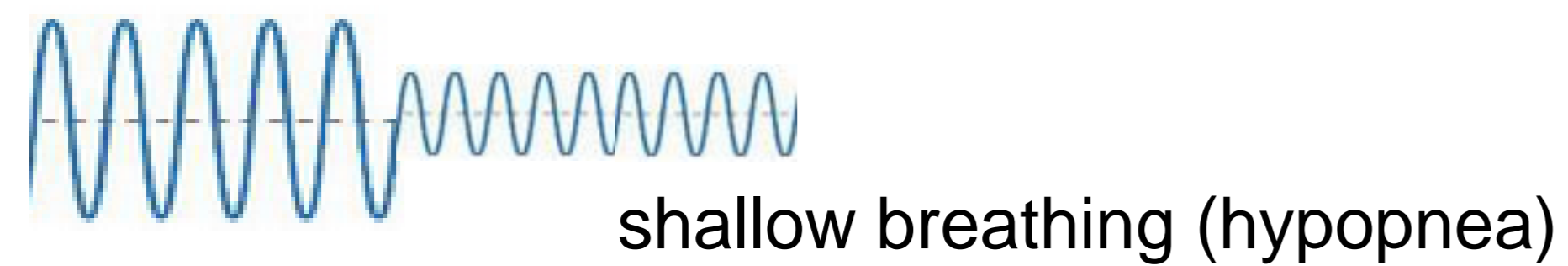
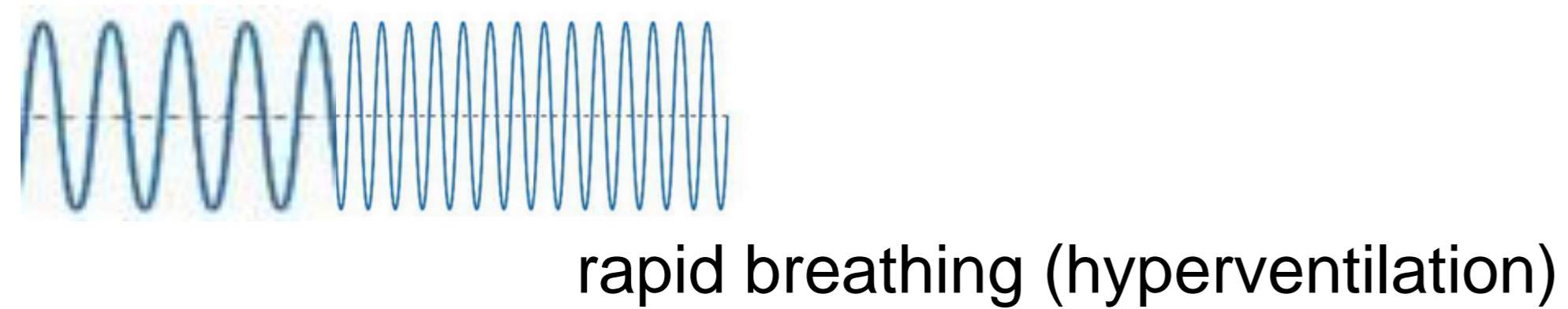
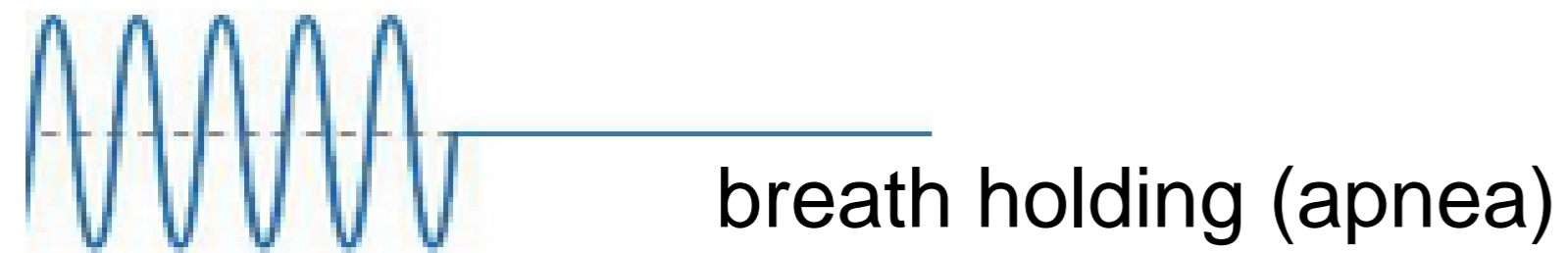
Ubiquitousness

- “That's like [breathing problems], to me that's just her.”
- “I think she has to really focus on breathing. Can you imagine having to focus on your breathing? It doesn't just happen. You have to think about it. Like you have to think to do something that you don't do on an every-day basis.”

Breathing Irregularities are Detectable in Rett



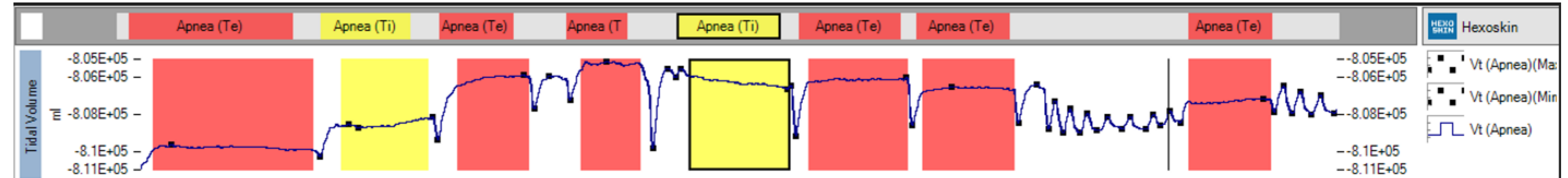
- Irregular breathing is prevalent in Rett syndrome



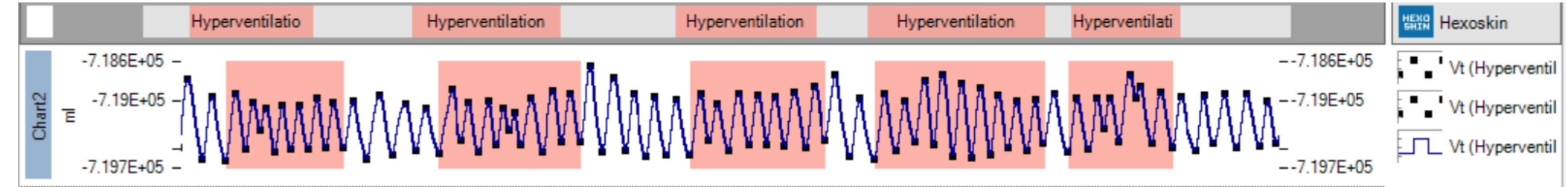
- 22 patient study (KET-101-RSRT) for feasibility and sensitivity to treatment effect

Breathing Irregularities in Rett

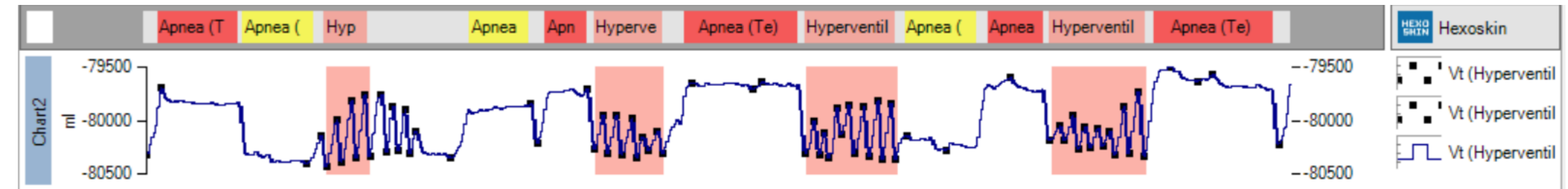
Apnea / breath holds



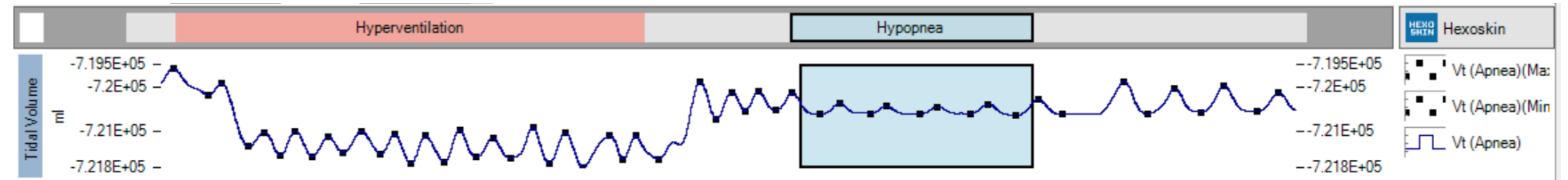
Hyperventilation (regular breath length)



Hyperventilation (variable breath length)



Hypopnea / shallow breaths



VivoSense analysis of Ket-101-RSRT Hexoskin breathing data



ECG Derived Breathing Irregularities

VivoSense analysis of SENS-101-RSRT BioStamp ECG data



Identify frequency and duration of daytime apnea and hyperventilation events



17 patients simultaneously wore a respiratory plethysmography (RP) and an ECG



Algorithm built and tested

mc10

Configure Sensor (Supervised)

Body Location: Medial Chest

Side: No Side

Mode: Accelerometer

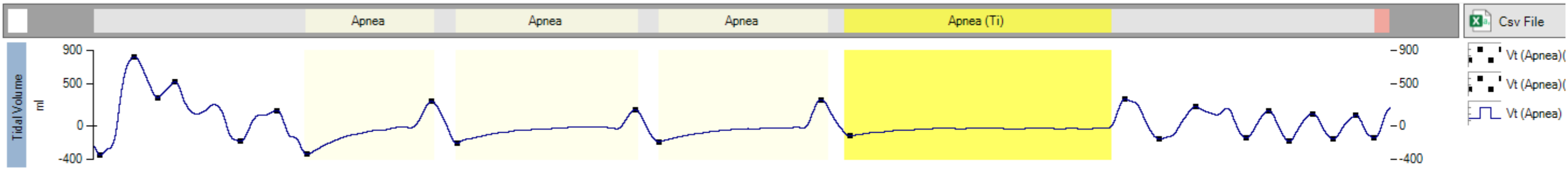
31.25Hz +/- 4G

Desired Daily Recording Time: 1 hour, 1 sensor per day

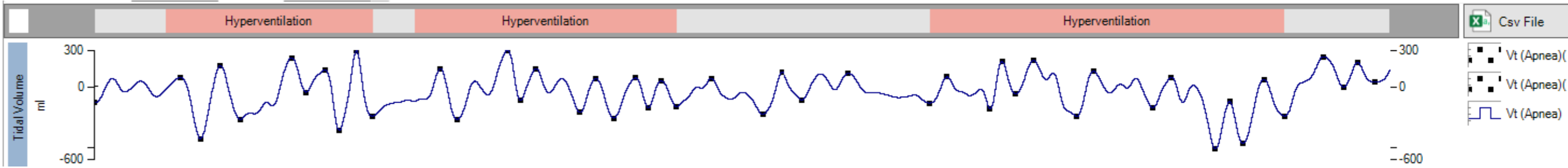
Save Cancel

ECG Derived Breathing Irregularities

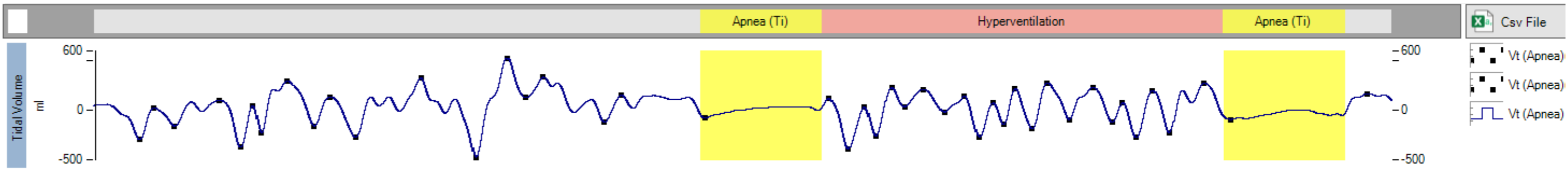
Apnea / breath holds



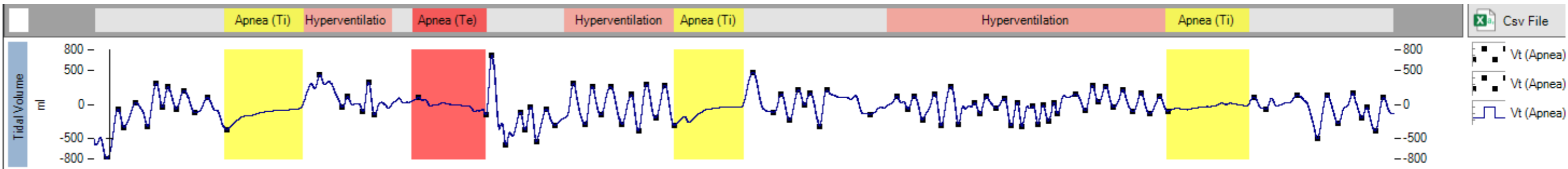
Hyperventilation



Hyperventilation & Apnea



Hyperventilation & Apnea



ECG Derived Breathing Irregularities

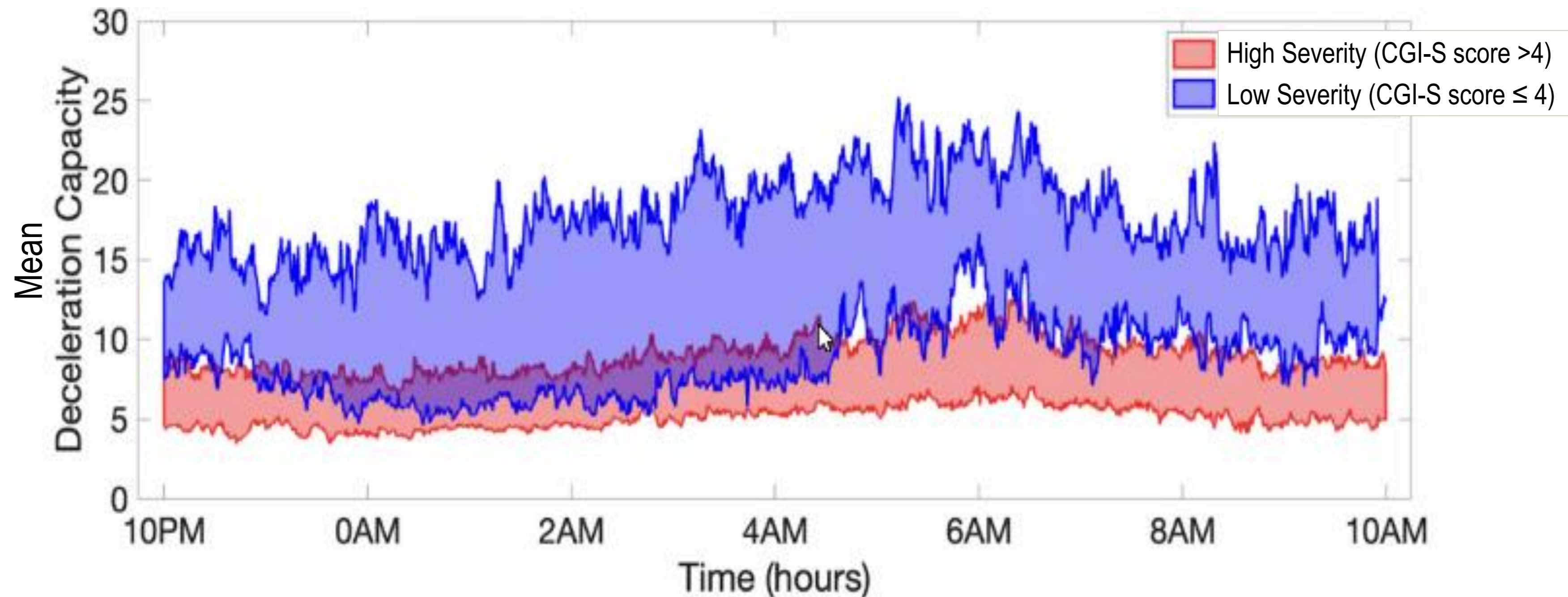
Initial feasibility

Additional studies lead to analytical validation

ECG patches improved patient experience

More robust real-world data

Deceleration capacity correlates with Rett patient severity



HRV metric pNN50 variance:
percent of adjacent beat-to-
beat intervals differing by >
50 ms

- 20 patient study
- Clinical Global Impression of Severity Scores categorized patients to High or Low Severity
- At least 48-hr ECG wear post CGI-S assessment
- Confirmatory analyses ongoing on additional completed studies



Emerald: an invisible for remote monitoring



- Touchless sensor and machine learning platform
- Uses radio frequencies less powerful than WiFi
- Used to assess gait speed and mobility, sleep staging, and pose estimation (movement)
- Validated against PSG and breathing belt in other indications



Crohn's



COVID-19



Atopic Dermatitis



Parkinson's



Alzheimer's

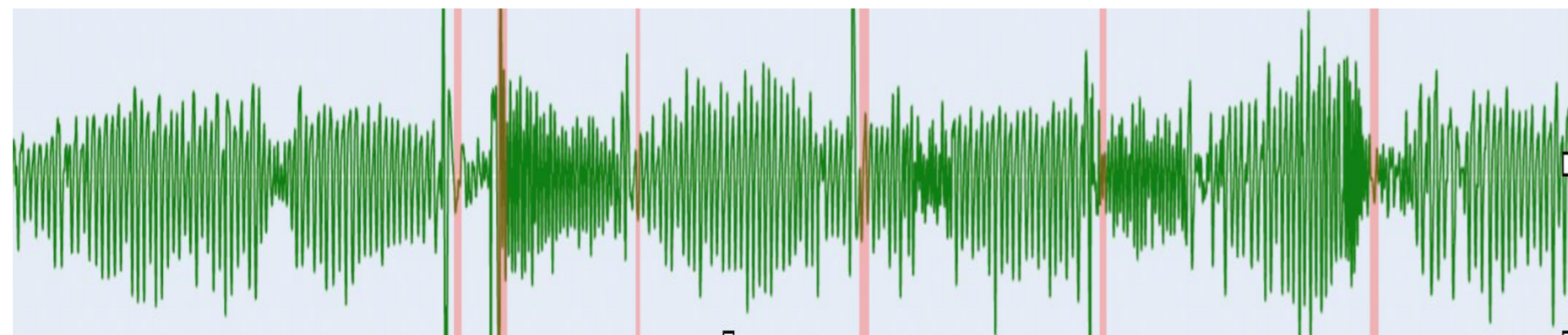


Rett Syndrome

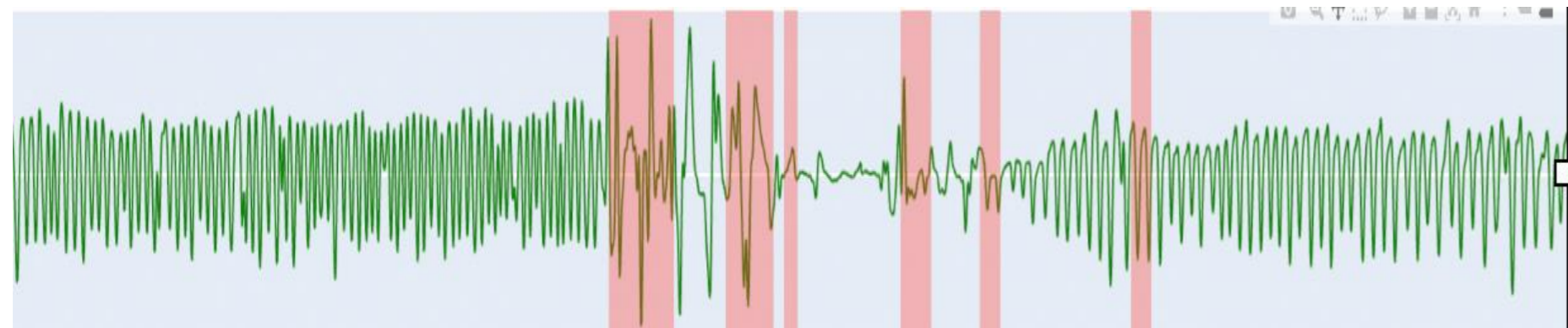


Rett patients show variable breath length and depth

Pt 01001



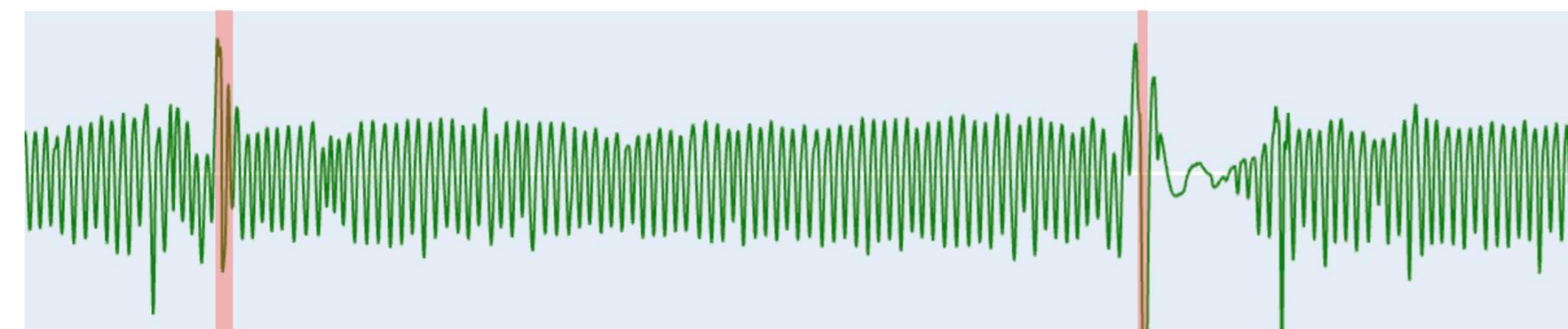
Pt 01002



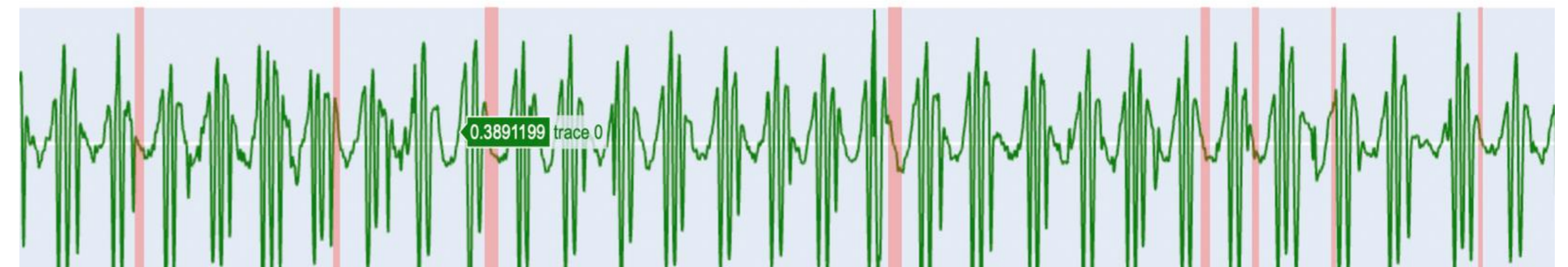
Pt 01003



Pt 01004



Pt 01005



Breathing #1

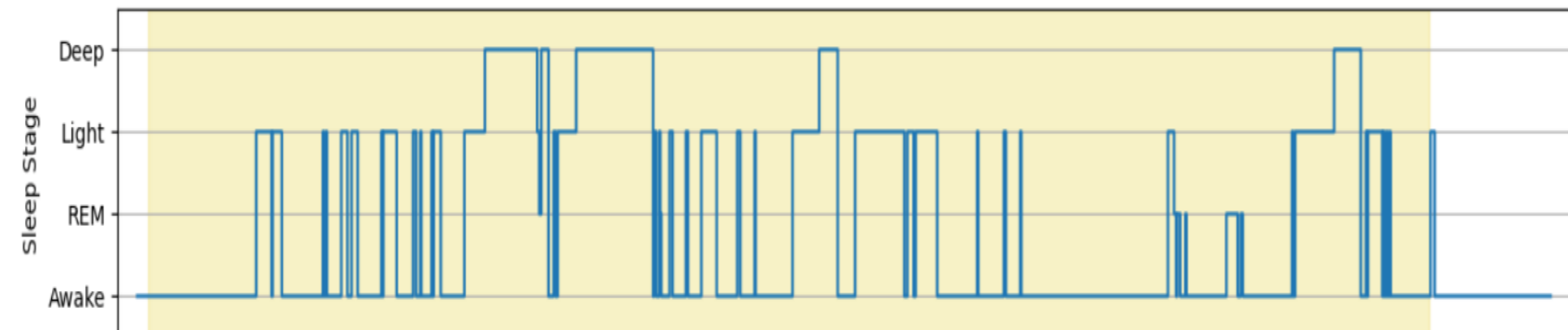


Healthy

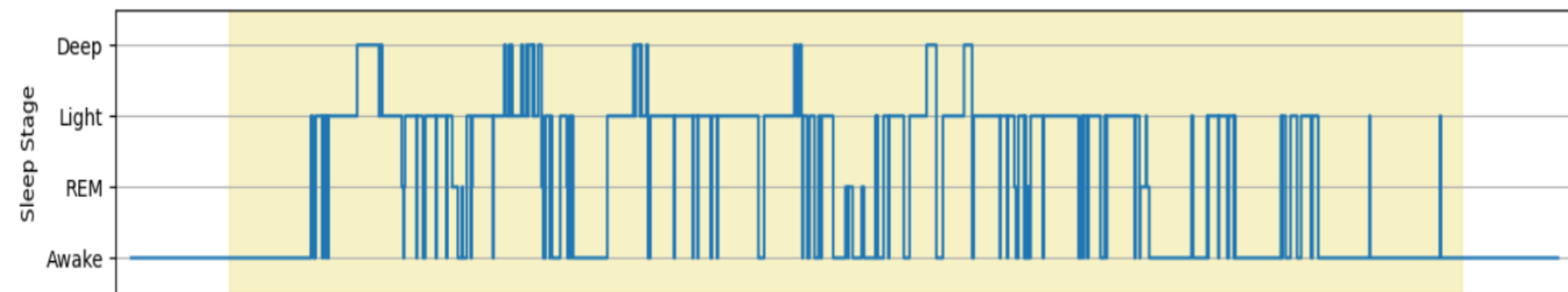


Rett patients show significant sleep disruption

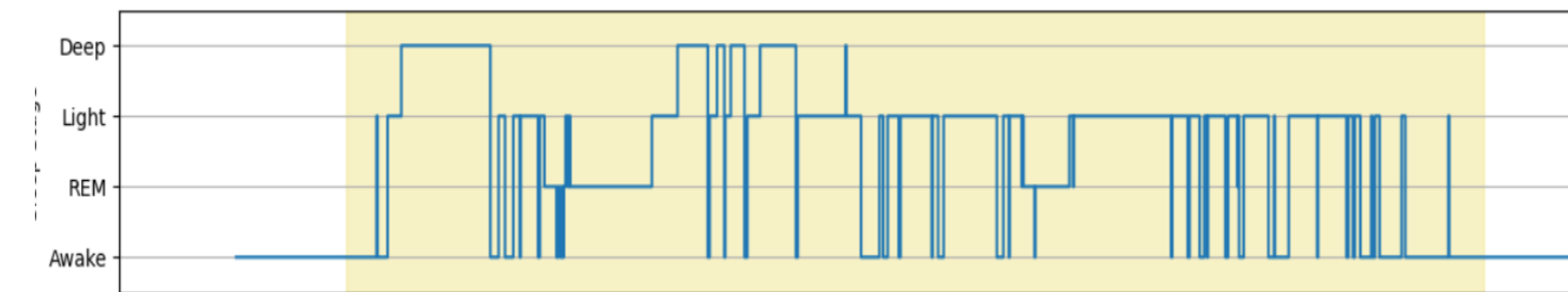
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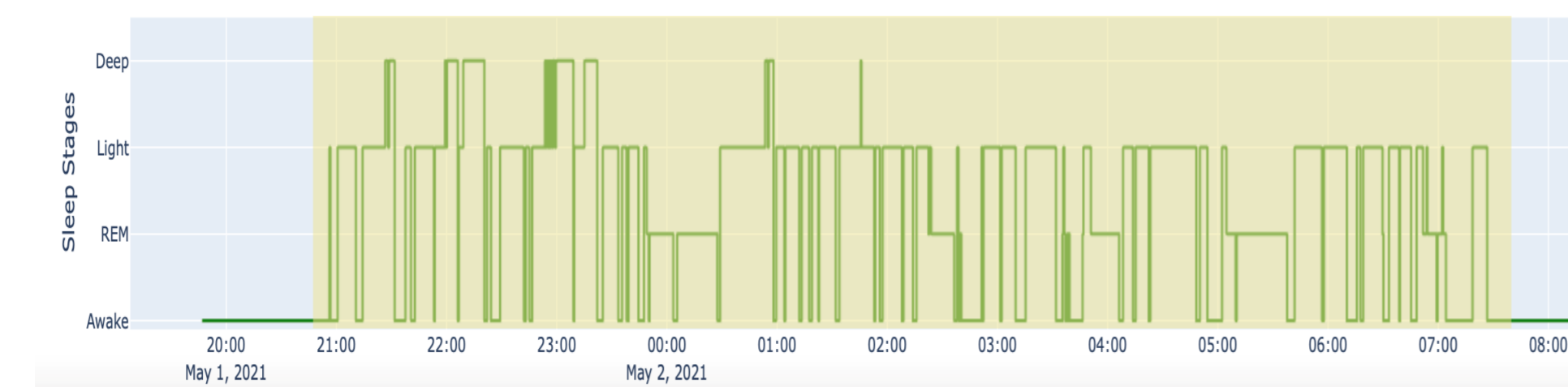
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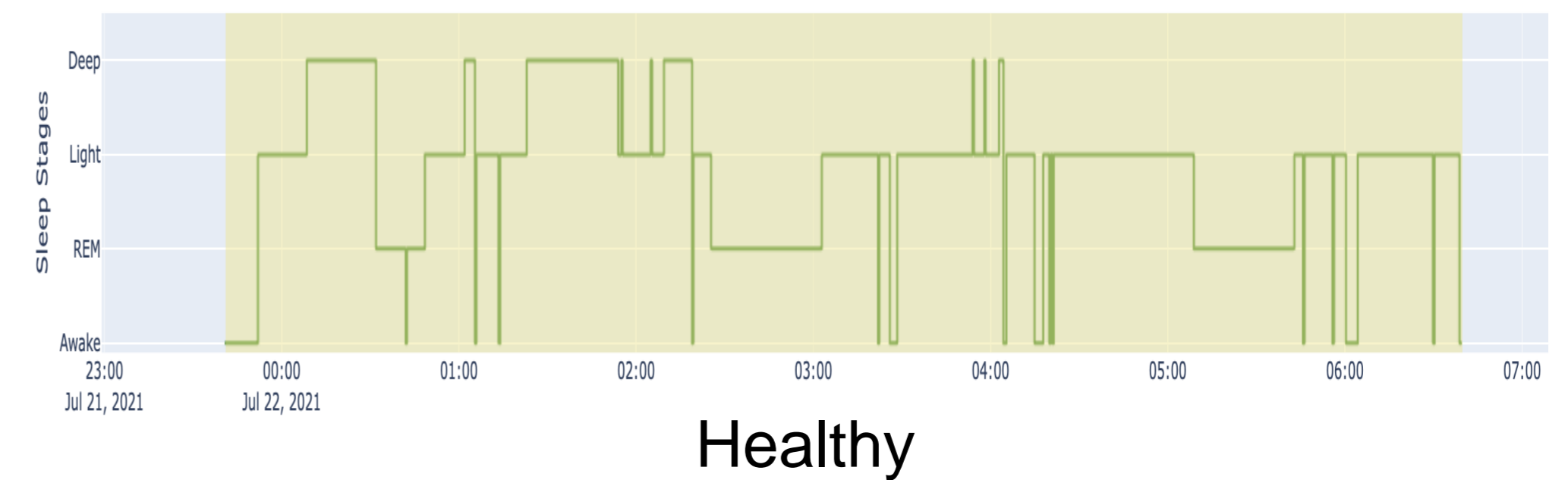
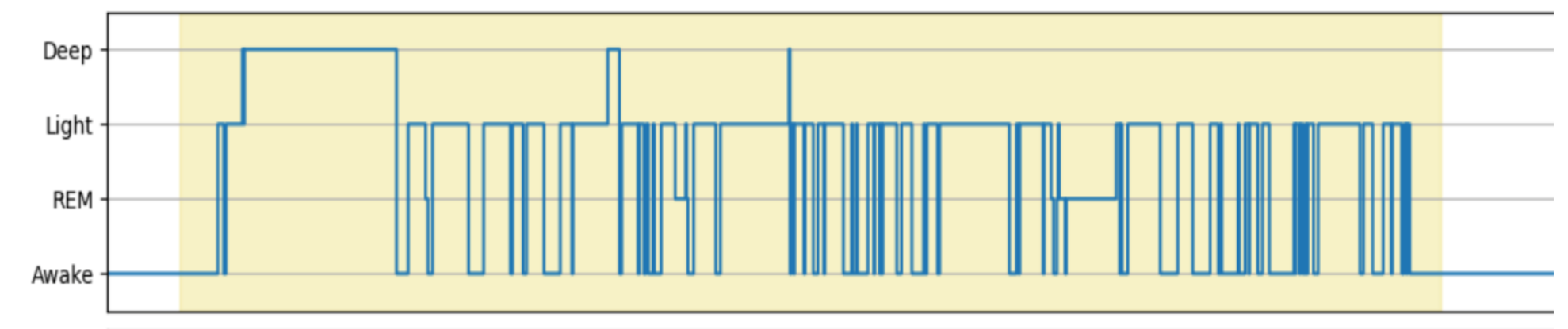
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Pt 01004

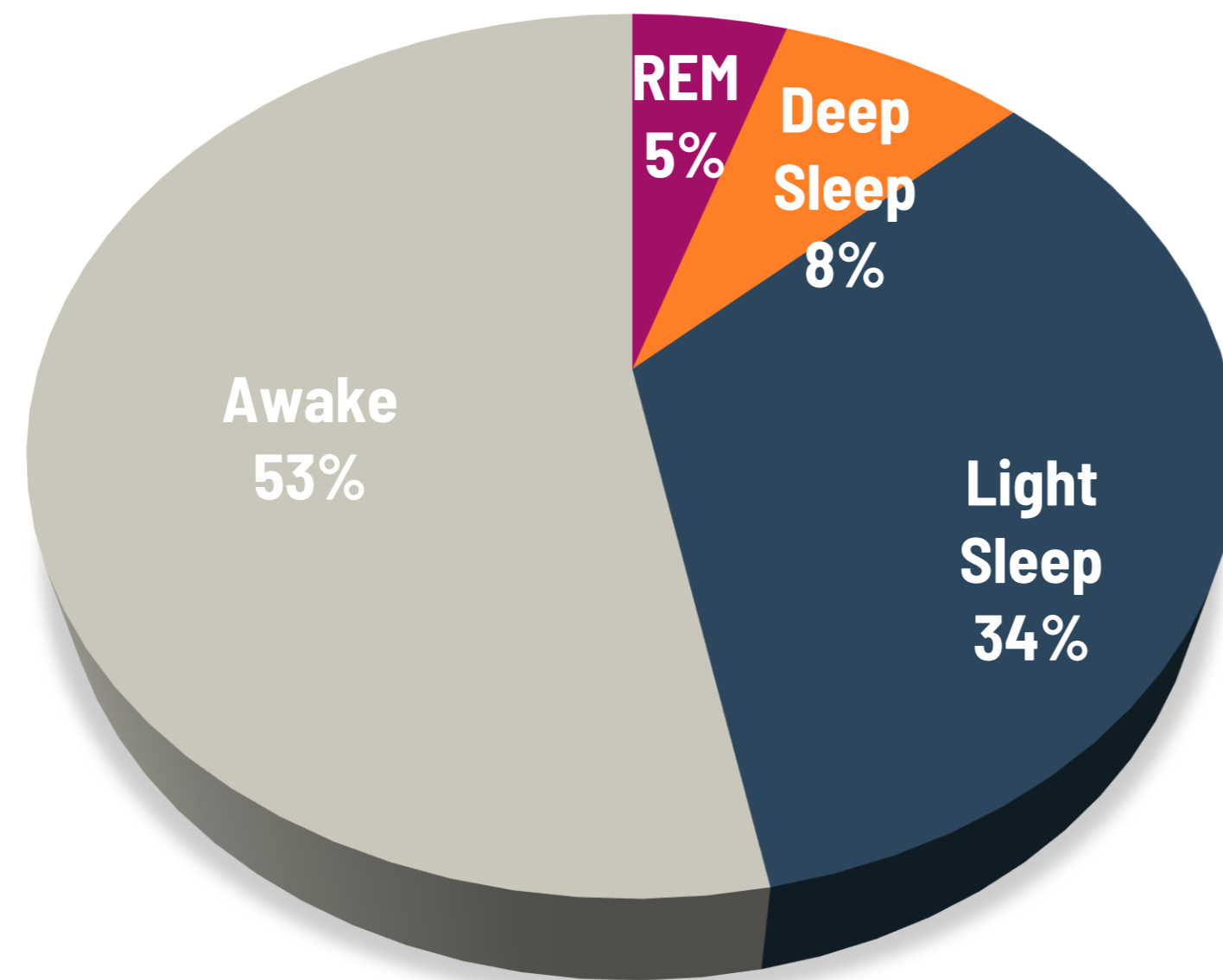


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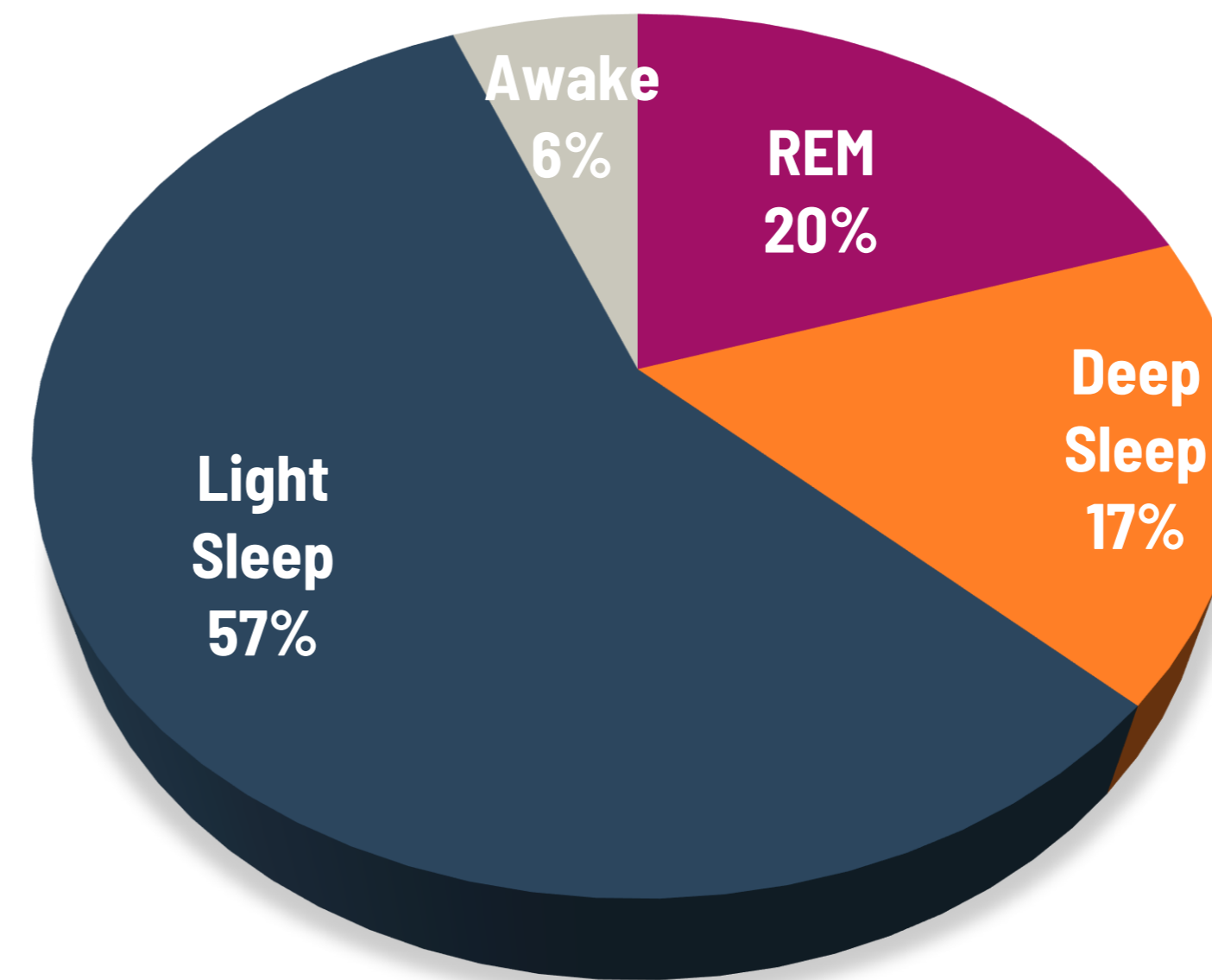


Rett patients are often awake and have reduced REM

Rett Patient Sleep
Little REM and ~50% Awake



Healthy Individual
Little Awake and ~20% REM



Objective measures of autonomic dysfunction are possible

Breathing, HRV, and sleep can be measured objectively in Rett patients

Potential to serve as biomarkers in therapeutic trials

Engaging regulators and industry partners for further development

Expansion of biosensors to assess movement disorders and other symptoms

Future Patient Centric Work

Patient centricity and co-creation

- Bi-directionality (not transactional)
 - Sensor form fit
 - Study design
 - Improving inclusivity

Move forward with formal qualification



VivoSense



rett syndrome
research trust

Thank you