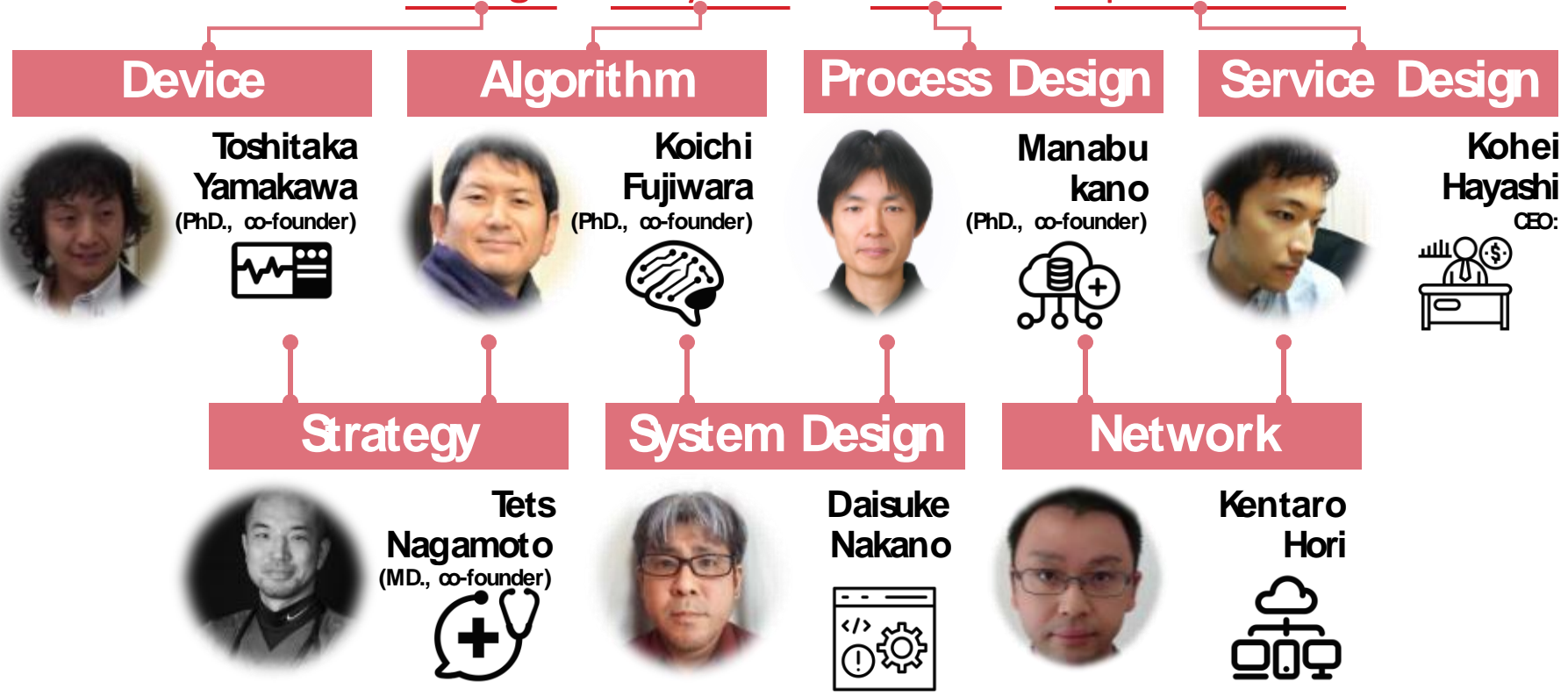


Quadlytics Inc.: a bioinformatics startup from Kyoto Univ.

SAFE = Sensing & Analytics for Future & Empowerment

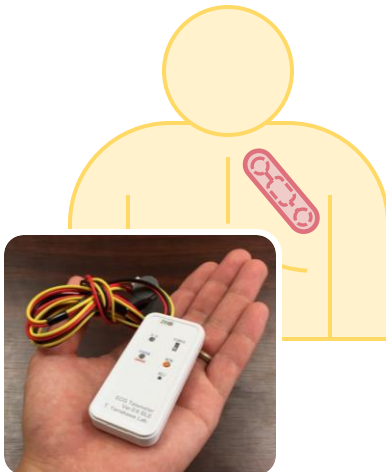


Our unique strengths and value: "SAFE"

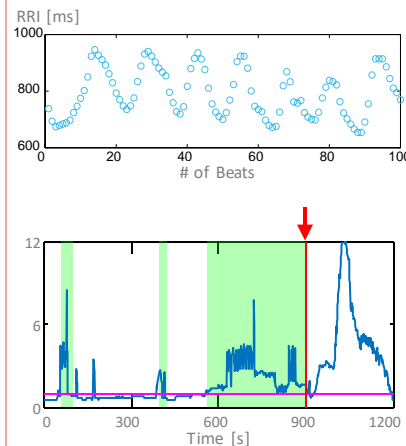
We offer truly wearable sensor technologies together with real-time physiological signal analytics to realize predictive & informative services, thus supporting safety and security of individuals and society.

SAFE = Sensing & Analytics for Foresight & Empowerment

truly wearable,
non-invasive,
multi-day sensors
for simple continuous
streaming



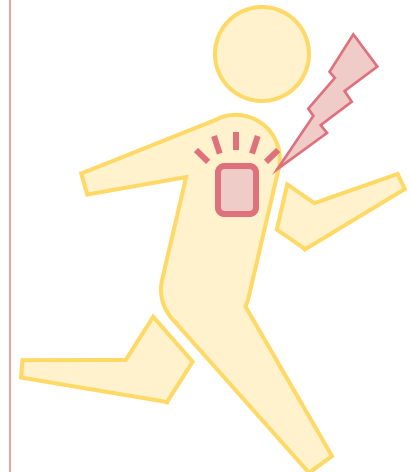
physiology analytics
AI/ML expertise
translated into
efficient real-time
edge computing



predictive algorithms
offering foresight and
time window for
protection and
prevention

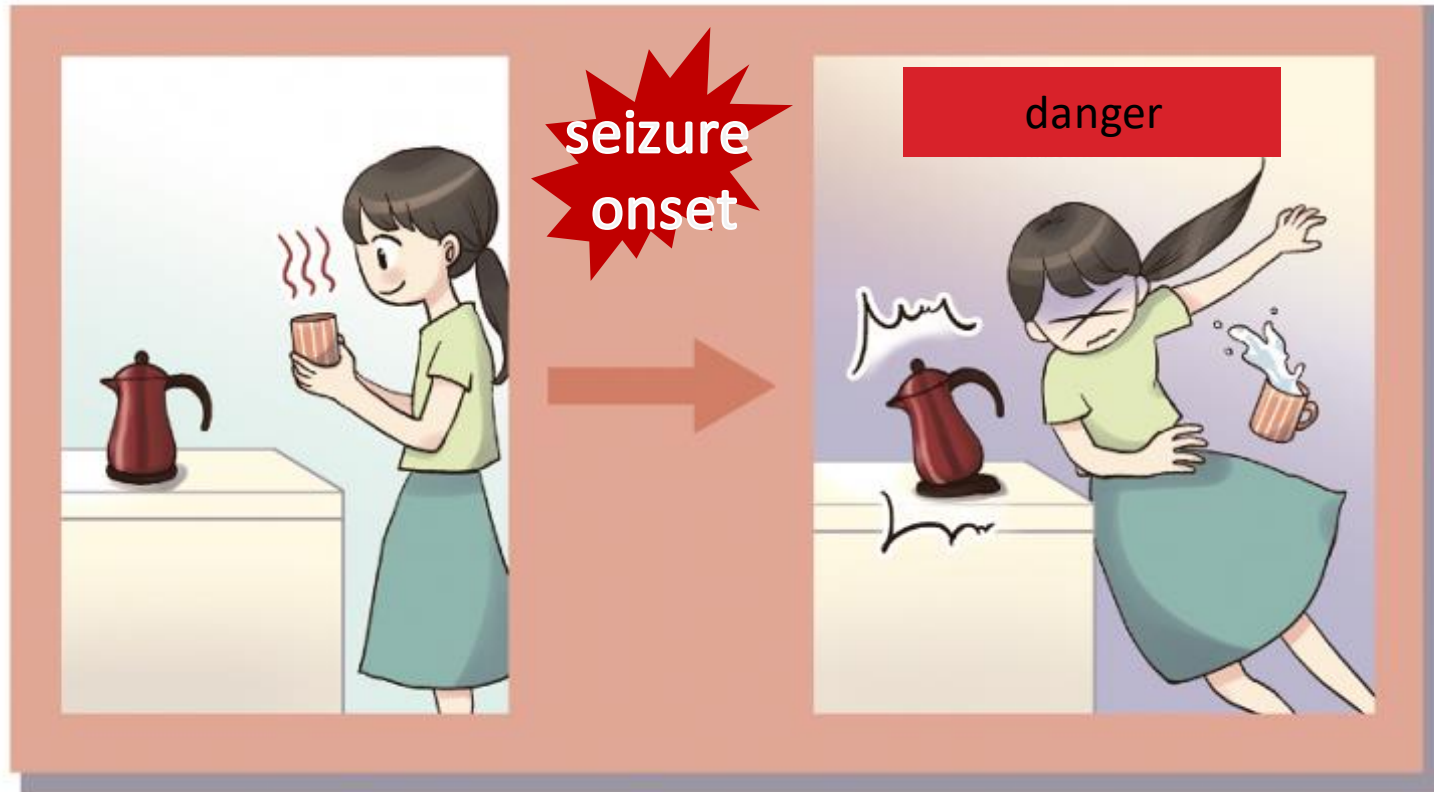


clinically relevant &
supportive feedback
for users, family
members, and
organizations



Epileptic seizure occurs very unexpectedly

- Epileptic seizure occurs unexpectedly, frequently leading to loss of consciousness
- Patients have no way to prepare for and avoid accidents, leading to major injuries (including traffic accidents), burns/fires (while cooking), and drowning



Economic burden of epilepsy over \$10 billion

- Epilepsy is an economic burden because of losses in employment, wages. Total economic loss is estimated over \$10 billion(Charles E. Begley et al., 2000)
- Also, the very material risks, on top of the psychosocial stigma associated with seizures, disincentivizes patients' socioeconomic participation.

Patients lose job, wages

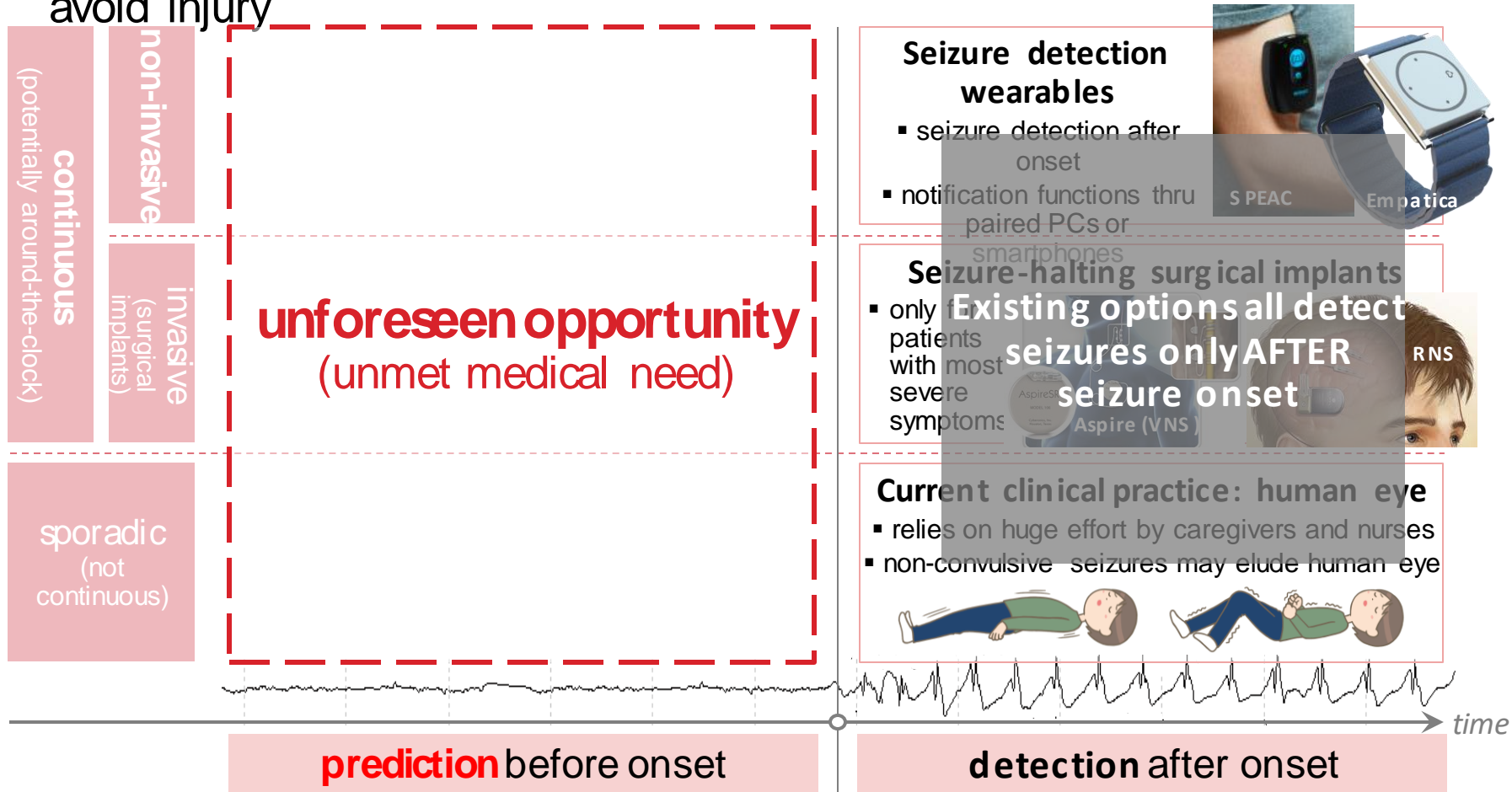


less patients' socioeconomic participation



Prediction of seizure is unforeseen opportunity

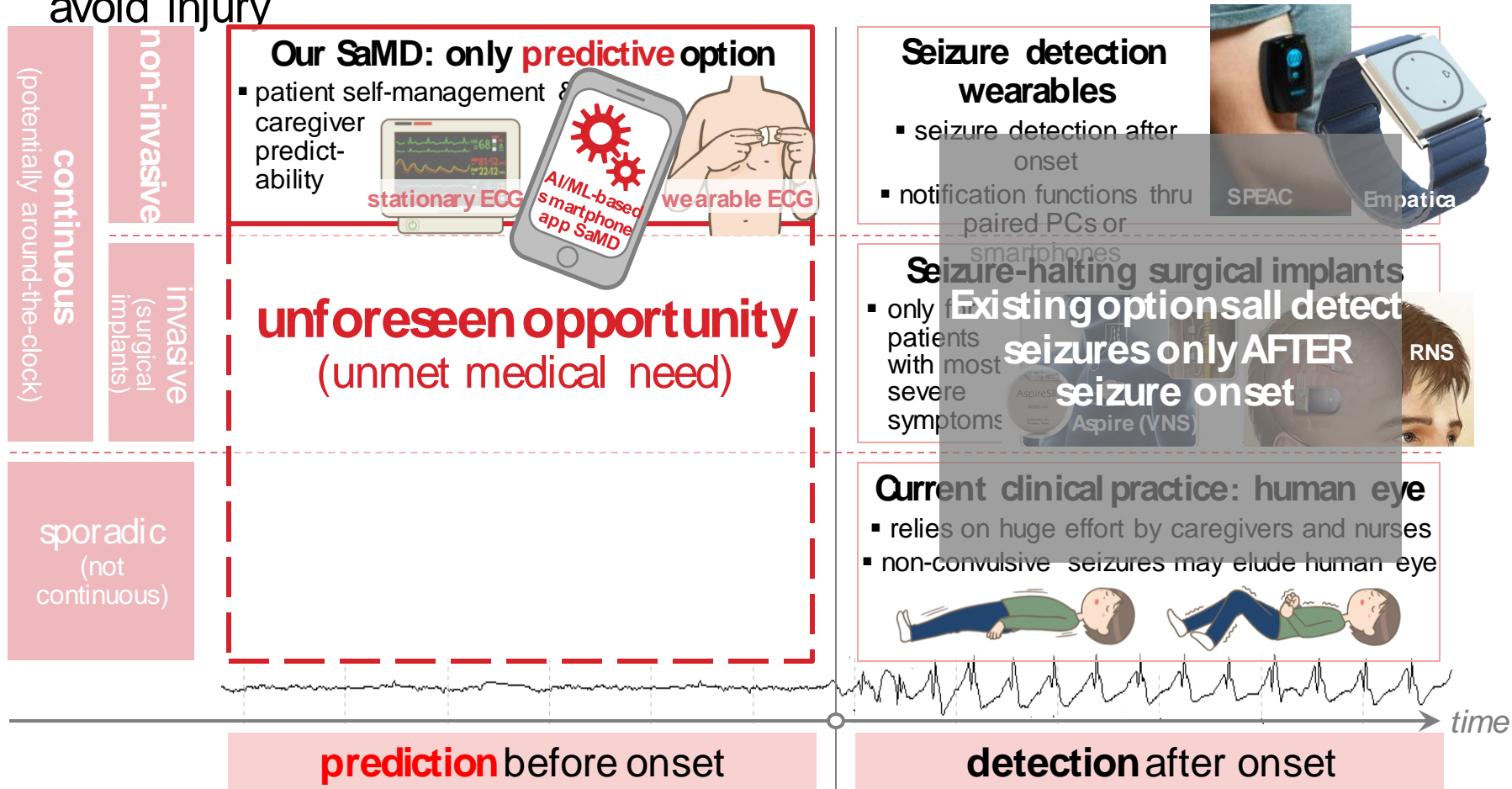
- Existing solutions that cater to epileptic seizures all detect seizures AFTER its onset, leaving almost no room for patients themselves to avoid injury



photos: www.kango-roo.com, LivaNova, RNS, Brain Sentinel, Empatica; *SaMD: software-as-medical-device

Prediction of seizure is unforeseen opportunity

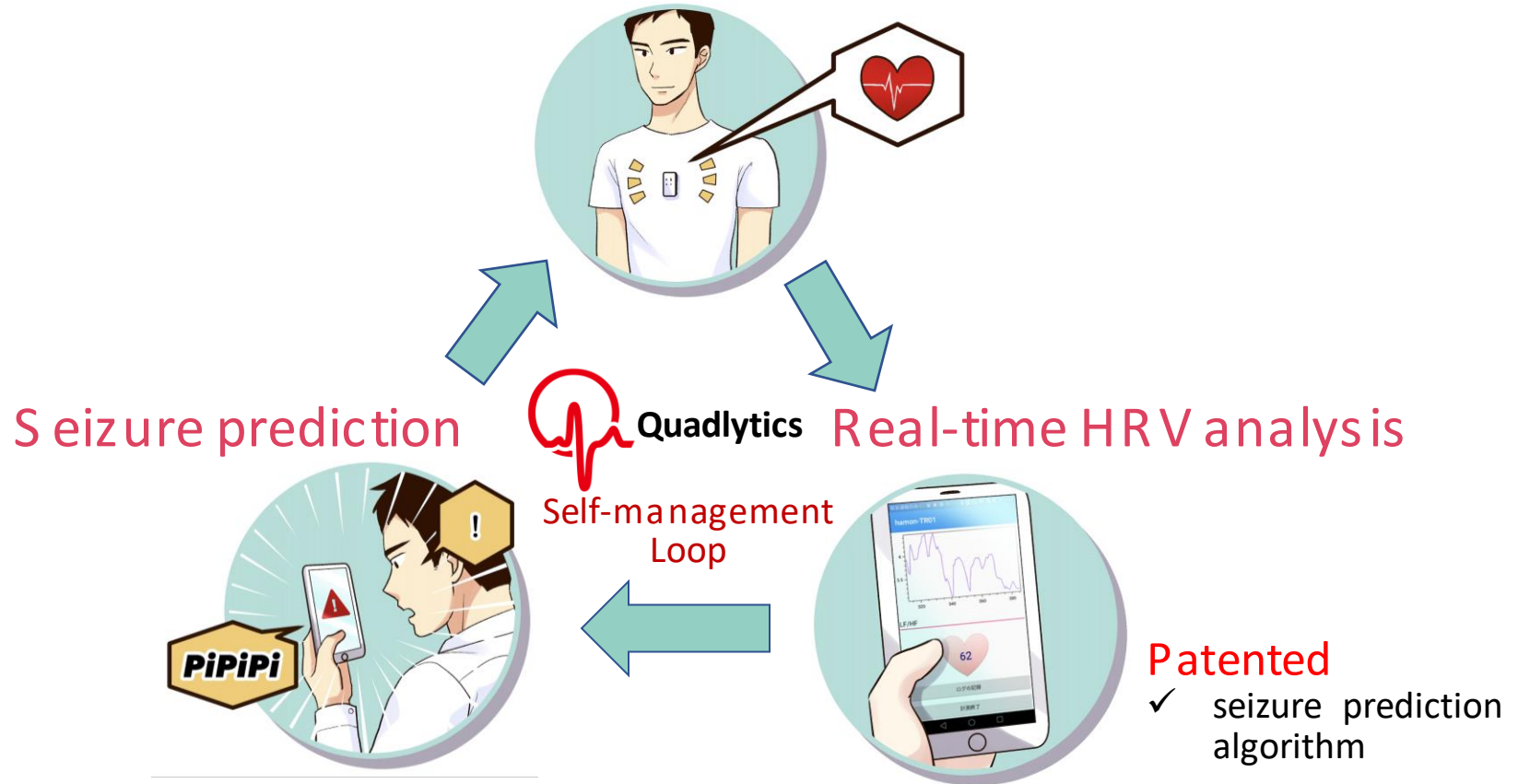
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photos: www.kango-roo.com, LivaNova, RNS, Brain Sentinel, Empatica; *SaMD: software-as-medical-device

Predictive solution by AI/ML-based algorithm

Around-the-clock ECG monitoring

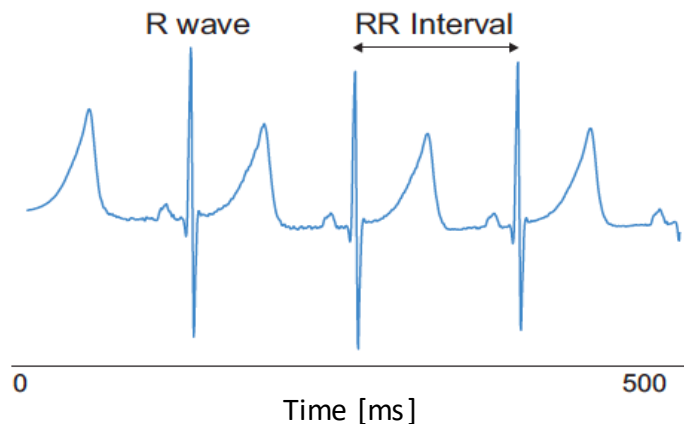


ECG: electrocardiogram
HRV: heart rate variability

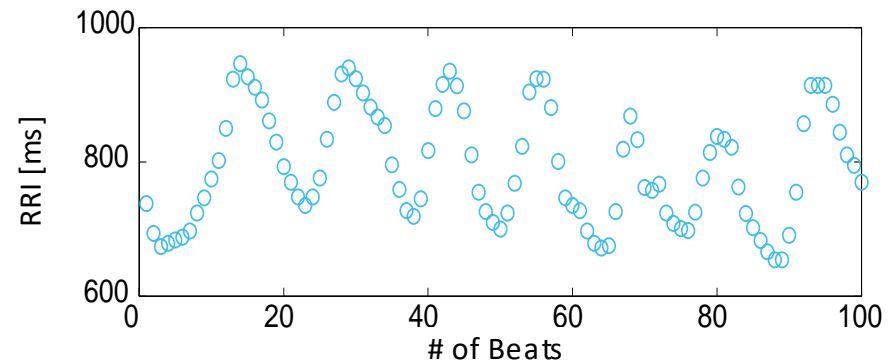
HRV analysis is tool for seizure prediction

- We can obtain fluctuation in heart rates by plot of RRI(RR Interval).
- It is called HRV (heart rate variability), is known to be affected by epileptic seizure. We use several indexes of HRV for machine learning.

ECG: electrocardiogram

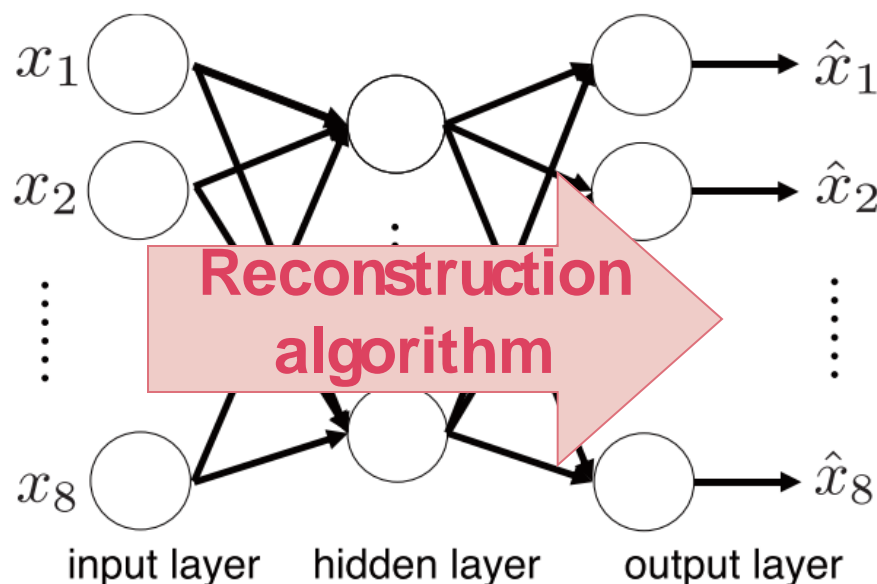


Plot of RRI



Autoencoder

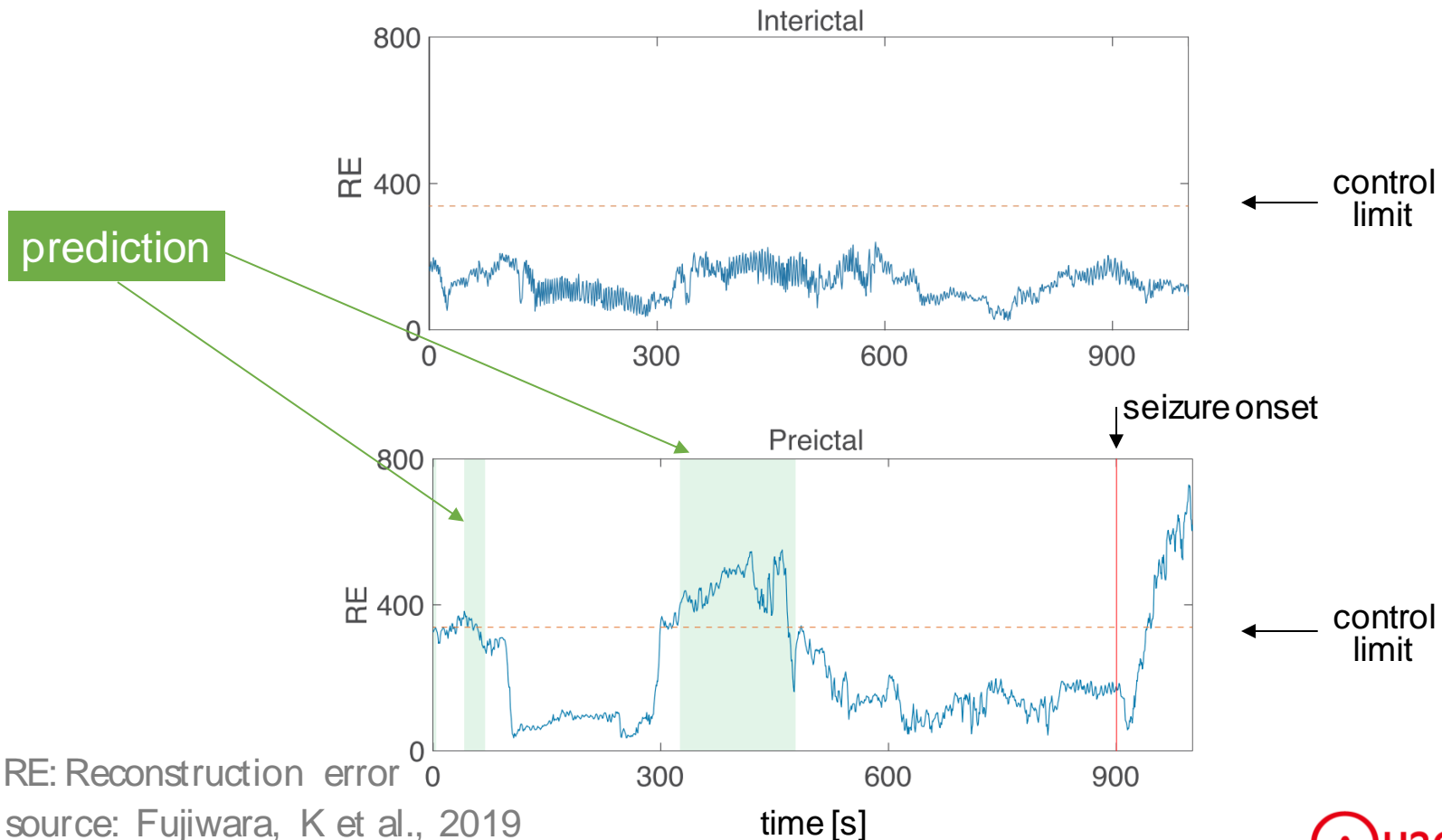
- Autoencoder is a type of neural network. Learning is performed as reconstruction so that an output equal to the input is obtained.
- It is assumed that an abnormality has occurred when the reconstruction error exceeds a predetermined control limit.



source: Fujiwara, K et al., 2019

Our algorithm predicts seizures before onset

- Our algorithm predicts seizures at around 10 minutes *prior to* seizure onset
- This opens a precious time window for patients to take preventive measures by themselves (and for family members and caregivers as well)



Predictive alarm for self-management

- Seizure prediction will offer patients the time window for self-management and injury prevention, thus confidence for socioeconomic participation
- For this to work, **it should run any time, anywhere, continuously and real-time**. Only our technology can overcome these issues.

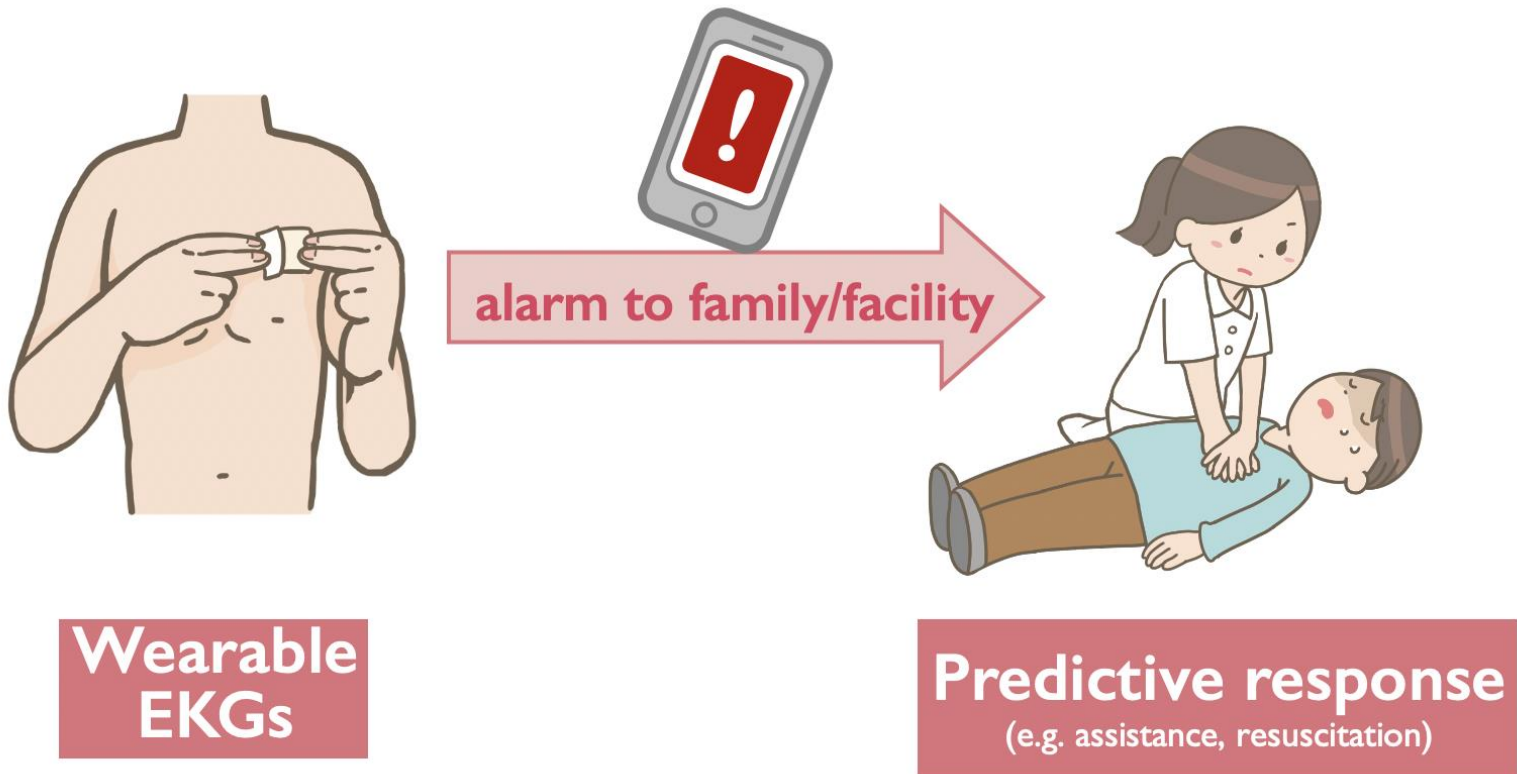
response time for self-management



Predictability is less stress for caregiver

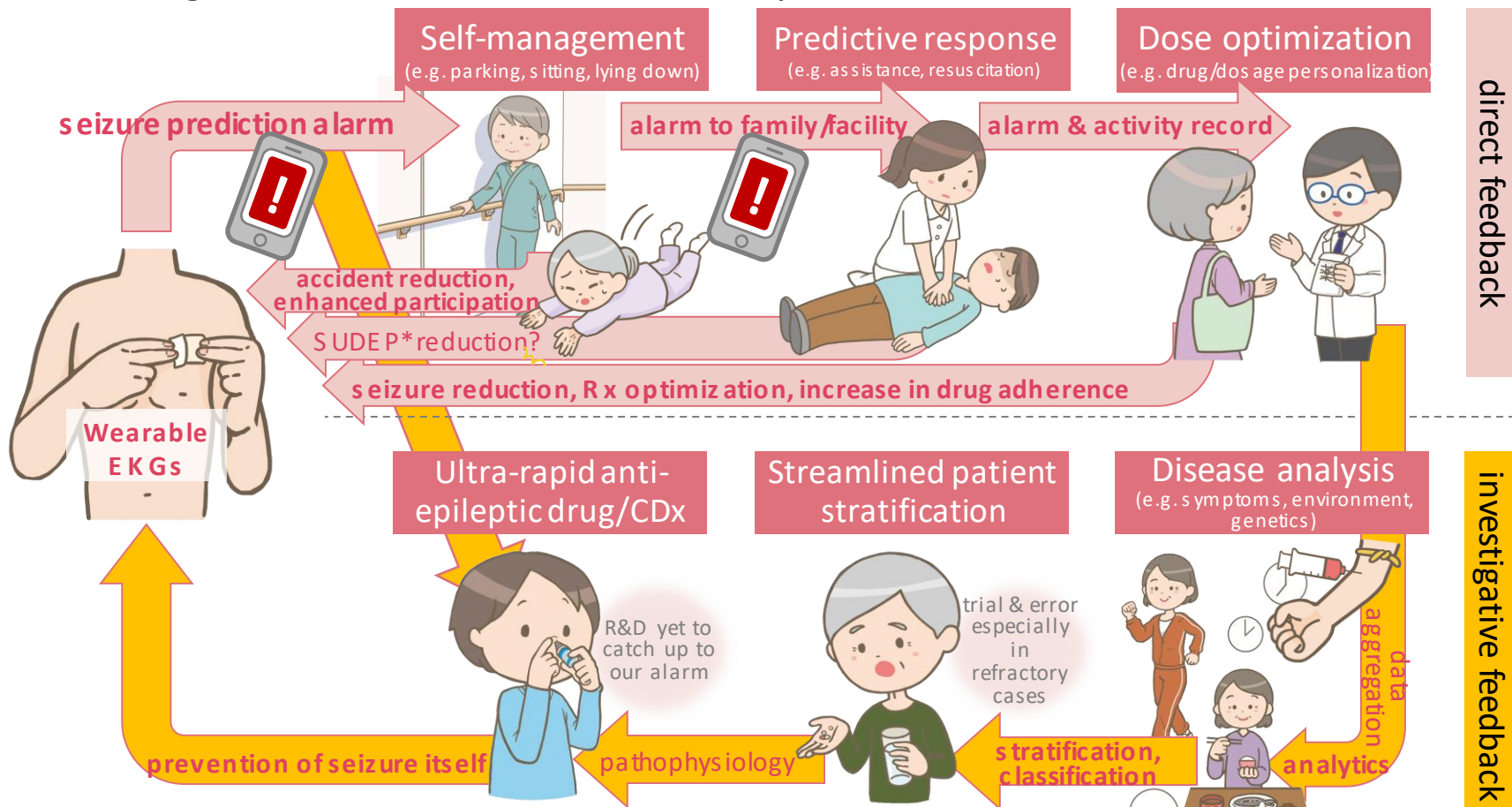
- Leading to timely responses and interventions as necessary, incl. oxygen and medication, and crucially less stress (associated with the unpredictability)

predictability save human resource



Beyond alarms: precision medicine at its best

- Direct feedback: self-management, predictive response, dose optimization
- Investigative feedback: disease analysis, stratification, CDx, R&D



source: Tets Nagamoto, Kyoto University. images: <https://www.kango-roo.com/> *SUDEP: Sudden Unexpected Death in Epilepsy

A thick red line that starts as a horizontal baseline, then rises into a sharp peak, falls into a deep trough, and then rises into a smaller peak before returning to the baseline.

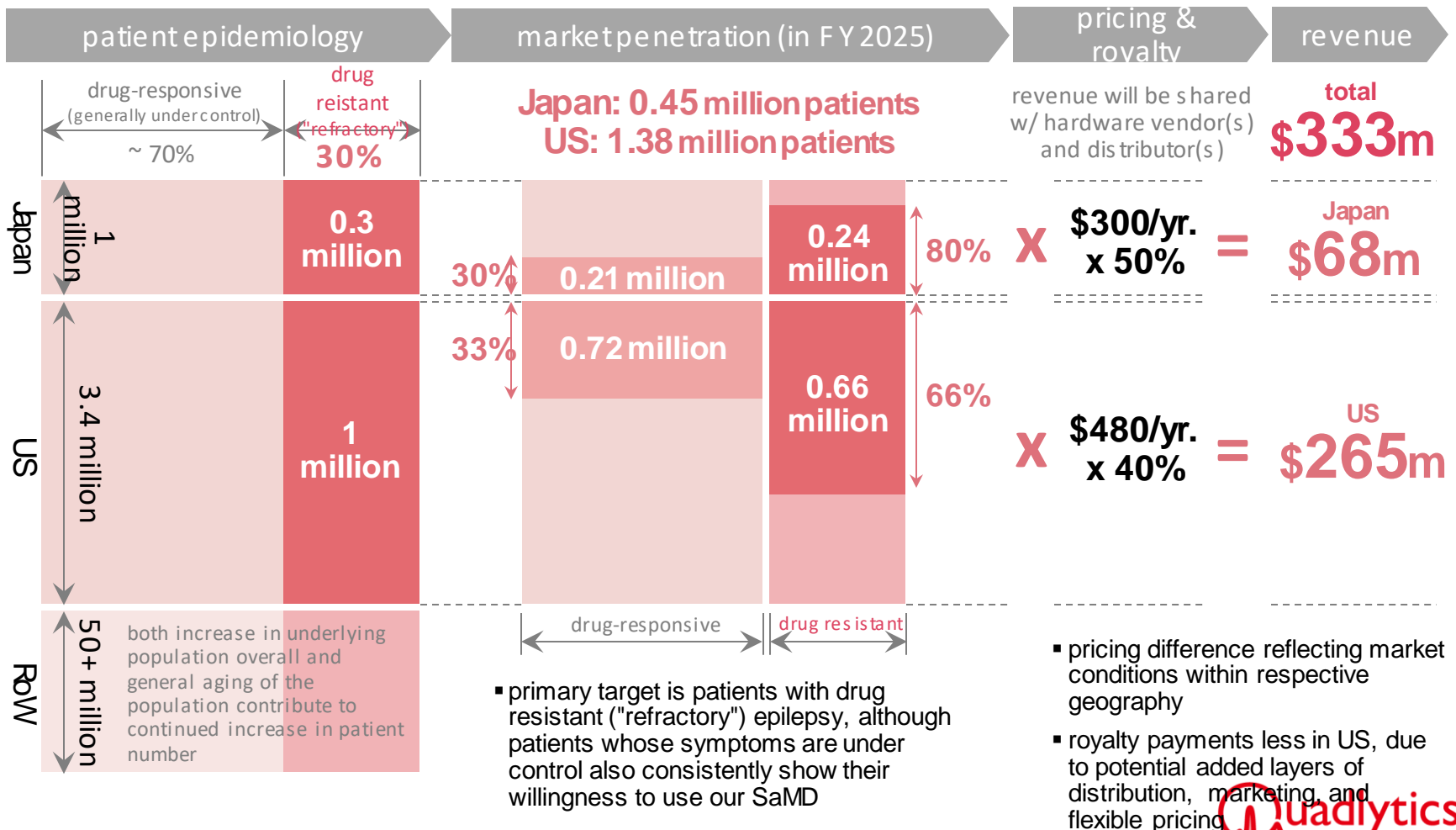
Appendix

August, 2020.



Revenue projection: Epileptic seizure prediction service

- Because epilepsy is a globally prevalent illness, we have an addressable market of 50m+ patients worldwide
- As the world's first of its kind, just focusing on Japan and US alone will offer us gross revenue of 333 mUSD
- Revenue will be shared with hardware vendors, who are likely to handle hospital relations on our behalf



Regulatory strategy: overall landscape

- Quadlytics will be primarily responsible for SaMD*, approval for which will be offered independently from hardware
- We will initially target in-hospital use where data quality will be high, then expand the label to include outpatient use
- Reimbursement coding will accelerate physicians' uptake of our service, although it will not be a prerequisite for use

S hardware (=ECG)
Kumamoto Univ. >> distributor

A software (= analytics & alerting)
Nagoya Univ. & Kyoto Univ. >> Quadlytics Inc.

Regulatory Affairs (broadly defined)	Regulatory Affairs (narrowly defined: FDA/PMDA approval)	reusable EKG (ECG)	SaMD* (i.e. stand-alone decoupled from specific hardware)	
			initial labeling: in-hospital use	label expansion: outpatient use
		<ul style="list-style-type: none"> ➤ Notified Body third-party certification (or, PMDA approval if w/ uniquely-added functionalities) <ul style="list-style-type: none"> ✓ primarily handled by partner distributor(s) ✓ QMS and validation assistance offered as needed, in particular for component technologies offered by Quadlytics ➤ functional criteria for individual indications dependent on SaMD label <ul style="list-style-type: none"> ✓ performance criteria (especially signal quality threshold) likely to be set in paired SaMD indication/label 	use in controlled environment <ul style="list-style-type: none"> ➤ use at rest: expected noise contamination minimal, allowing for high quality EKG data, thus more stable analytics result ➤ professional support and complementary testing available upon contingencies and other patient needs, allaying concerns for potentially adverse sequelae 	use in real-world environment <ul style="list-style-type: none"> ➤ use in settings w/ external environmental factors potentially adverse to signal quality ➤ used w/o immediate assistance from professionals and simultaneous tests, allowing for remote monitoring services ➤ can leverage data and clinical experience from preceding history of in-hospital use
		multiple reimbursement options <ul style="list-style-type: none"> ➤ Basic hardware fees normally not separated; reusable hardware costs included in testing/management fees ➤ Rental subscription potentially the primary option to mitigate the initial cost (for patients and/or providers) <ul style="list-style-type: none"> ✓ outright purchasing also an option, particularly if it is covered by the insurance and/or if pricing is reduced enough for easy access 	bonus reimbursement added to expert testing fee? <ul style="list-style-type: none"> ➤ "long-term vEEG recording": fee currently set at 3500 pts/day (=350USD/day) <ul style="list-style-type: none"> ✓ higher fee for specialist facilities newly established in 2016 after Japan Epilepsy Society asked the reimbursement committee ✓ target additional 200~400 pts/day (20~40 USD/day) bonus for use of our service? ✓ strong HEOR justification study desirable (nursing burden, added safety, etc.) 	new subclassification under existing management fee codes? <ul style="list-style-type: none"> ➤ monthly recurring coding as target <ul style="list-style-type: none"> ✓ candidate codes: "designated disease therapy management fee" (470 pts/month = 47 USD/mo.) or "epilepsy guidance fee" (250 pts/month = 25USD/mo.) ✓ better symptom tracking and management, and/or remote monitoring as rationale for the superior subclassification ✓ HEOR justification potentially warranted

*SaMD = software as medical device

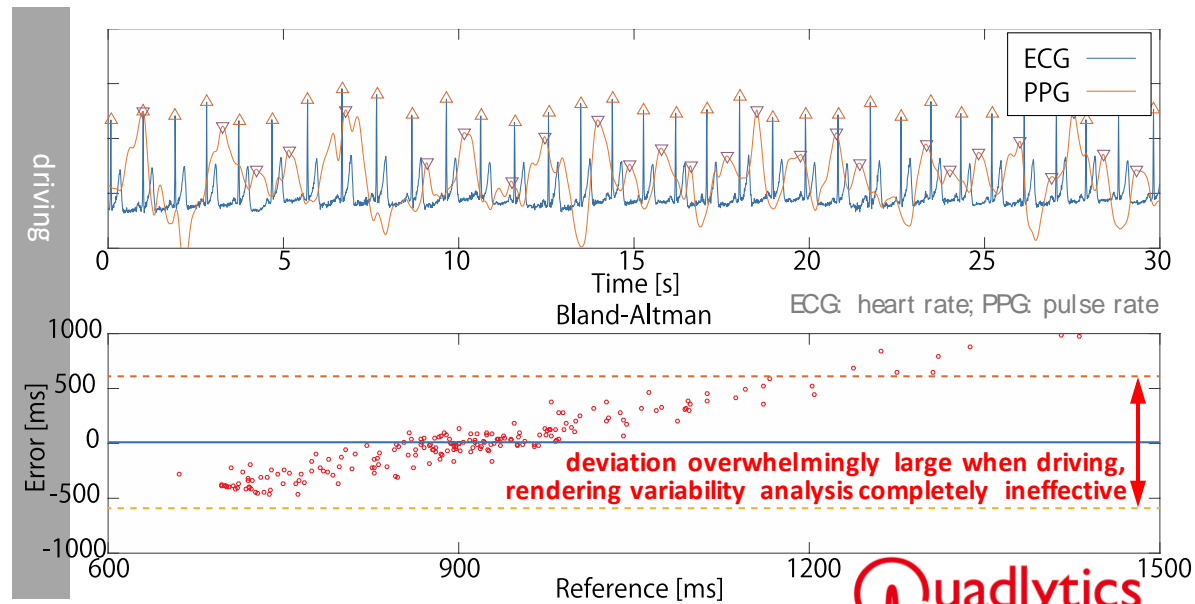
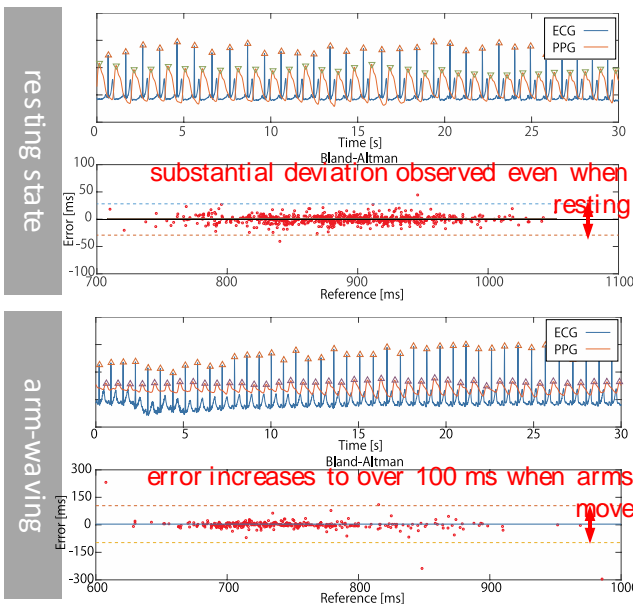
Sensor technology: proprietary IP for multi-day measurements

- Our proprietary high-efficiency electrocardiograph (EKG) technology allows for high-precision, multi-day continuous heart monitoring, which form the foundation for finely grained, very descriptive heart rate variability (HRV) analytics
- Because pulse rate variability, as can be derived from wristbands and smartwatches, are heavily influenced by physical factors such as body movement, posture, and blood vessel structures, analytic inference remains substantially inferior
- **Proprietary technology: medical-quality wearable EKG that continuously lasts for days**
 - Optimized for HRV analytics, automatically detecting Rwaves continuously with high precision (patented)
 - Highly efficient circuitry design that allows for continuous functioning lasting multiple days in one charge
 - Data transmission of physiological signals based on highly prevalent BLE (bluetooth low energy) standard
 - Precision not attainable with pulse rate variability inference seen in wristbands/smartwatches (see below)

(experimental prototype in use [patented by Yamakawa.])

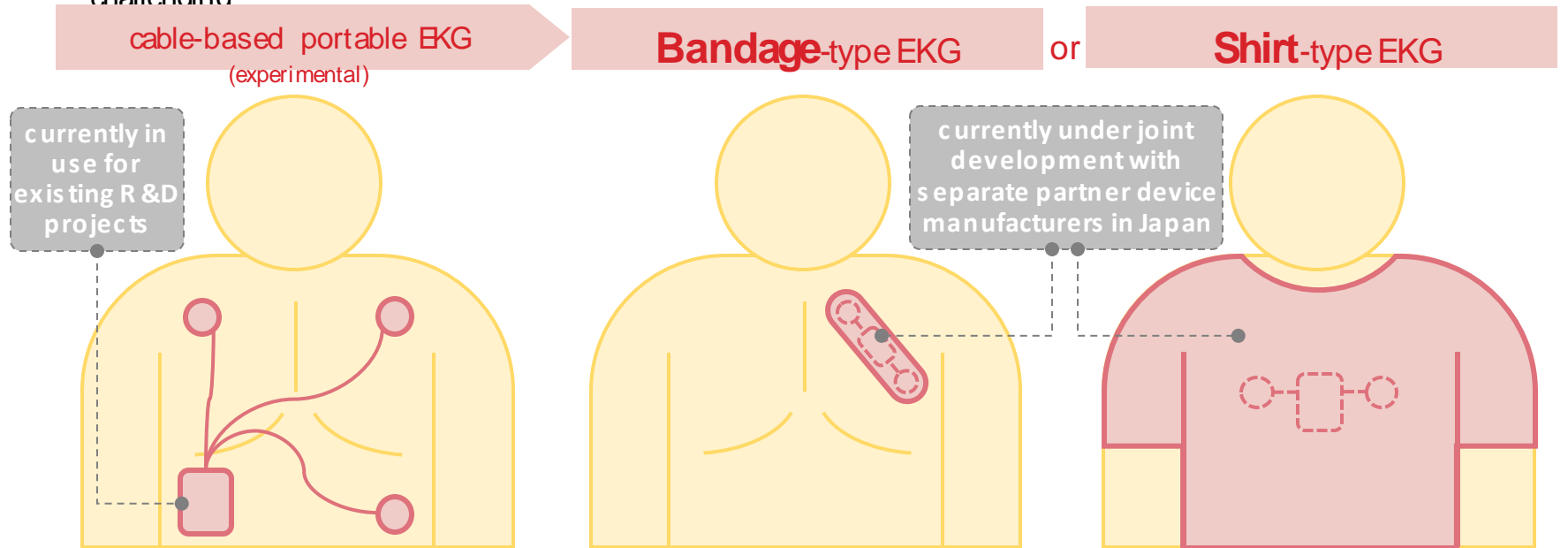


Pulse waves cannot avoid substantial noise contamination, erasing the subtle traces of HRV needed for meaningful analysis



S Sensor development: pursuit of truly 'wearable' experience

- Current R&D programs use experimental device with cables, with non-cable form factors under development
- Bandage-type EKGs has a non-bulky simplicity, but long-term continuous stability of attachment needs validation
- Shirt-type offers a 'wearing' experience, but noise contamination and size/tightness optimization remain challenging



- Only available device wearable enough but still offers sufficient and continuously stable signal quality long enough for complex HRV analysis (proprietary)
- Plan to switch over to devices on right once either/both of them become available in sufficient quantity & quality

- Adhesive and latches stable enough despite sweat and movement needed
- Adhesive area/design optimization needed to attain signal and adhesive stability and minimize risks of skin rash
- Impact assessment of differences in direction of device attachment needed

- Structural reinforcement needed to counteract deviation/detachment of electrode from arm and hip movement
- Attainment of both stable electrode attachment and shirt comfort needed
- Impact on signal quality from sweat and repeated laundry washing needed

A Analytics: rich insights from high-quality & dynamic HRV analytics

- Long & continuous waveform, when analyzed expertly, offers rich insights, unlike sporadic data points (e.g. blood draw)
- HRV analysis offers insights into autonomic dynamism from high frequency respiration to high-tl months

- We have implemented HRV analytics on smartphone apps as very portable applic
- **Proprietary visualization software based on serial data analytics know-how**



- Highly efficient algorithms based on continuous (especially waveform) analytics know-how accumulated in physiologic and inorganic subjects, by Profs. Kano & Fujiwara
- Meets all the criteria (below) demanded of HRV analysis for autonomic system assessment

(screen image of beta version app currently in use)

- Underlying HRV-related library copyrighted from Kyoto University

- Frequency-domain methods should be preferred to the time-domain methods when investigating short-term recordings. **The recording should last for at least 10 times the wavelength of the lower frequency bound of the investigated component**, and, in order to ensure the stability of the signal, should not be substantially extended. Thus, **recording of approximately 1 min is needed to assess the HF components of HRV while approximately 2 min are needed to address the LF component**. In order to standardize different studies investigating short-term HRV, 5 min recordings of a stationary system are preferred unless the nature of the study dictates another design.

- In order to standardize physiological and clinical studies, two types of recordings should be used whenever possible: **(a) short-term recordings of 5 min** made under physiologically stable conditions processed by frequency-domain methods, and/or **(b) nominal 24-h recordings** processed by time-domain methods.

continuous data longer than two minutes desirable for frequency-domain analysis (e.g. HF, LF)

at least 24 hours of recording is desirable for meaningful time-domain analysis

- Although the time-domain methods, especially the SDNN and RMS SD methods, can be used to investigate recordings of short durations, the frequency methods are usually able to provide more easily interpretable results in terms of physiological regulations. In general, the time-domain methods are ideal for the analysis of long-term recordings (the lower stability of heart rate modulations during long-term recordings makes the results of frequency methods less easily interpretable). The experiences shows **that a substantial part of the long-term HRV value is contributed by the day-night differences. Thus the long-term recording analysed by the time-domain methods should contain at least 18 h of analysable ECG data that includes the whole night.**

circadian rhythm must be incorporated by using data encompassing whole night

- Spectral analysis of 24-h recordings shows that in normal subjects LF and HF expressed in normalized units exhibit a circadian pattern and reciprocal fluctuations, with higher values of LF in the daytime and of HF at night. **These patterns become undetectable when a single spectrum of the entire 24-h period is used or when spectra of subsequent shorter segments are averaged.**

multiple frequency spectra should be analyzed in parallel for at least 24 hours

all citations from: Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Guidelines: Heart rate variability - Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996; 17: 354-381.

A Analytics: [reference] HRV as representing cardiac autonomic function

- HRV can be used to accurately and non-invasively determine cardiac autonomic neuropathy
- HRV can be a more useful marker of autonomic functions than existing tests, as it is likely to offer consistent and quantifiable metrics, free from inter-operator variances

■ Spectral analysis of heart-rate variability

- Subclinical CAN (cardiac autonomic neuropathy) can be detected through a reduction in HRV. HRV may be assessed by time-domain analysis or frequency-domain analysis, with the former looking at statistical analysis of R-R intervals (SD of all normal R-R intervals and root-mean square of the difference of successive R-R intervals) and the latter at spectral analysis.

✓ [Razanskaite-Virbickiene D. BMC Cardiovasc Disord. 2017;17(1):34.]

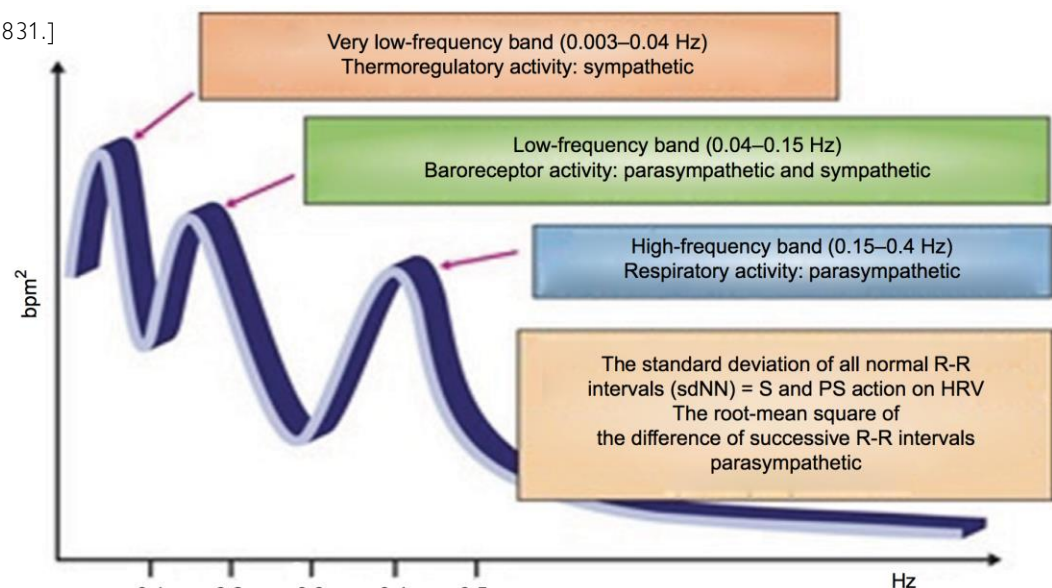
- In healthy individuals, there is normal beat-to-beat variation during inspiration and expiration, which is driven by sympathetic and para-sympathetic activity. Thus, abnormal beat-to-beat variations may be indicative of early changes to myocardial autonomic innervation.

✓ [Montano N, et al. Circulation. 1994;90(4):1826–1831.]

- Studies have shown that HRV abnormalities can be present at the time of diagnosis and that time- and frequency-domain analysis may permit more accurate evaluation of CV parasympathetic and sympathetic activity.

✓ [Kuehl M, Stevens MJ. Nat Rev Endocrinol. 2012;8(7):405–416.]

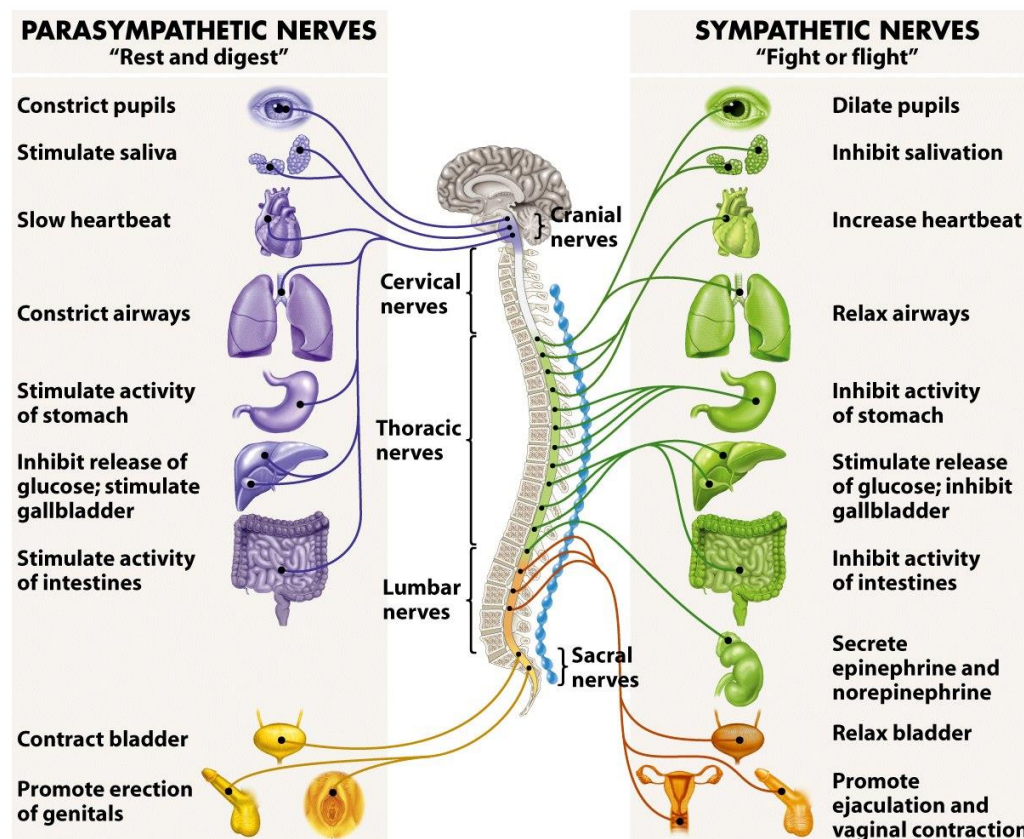
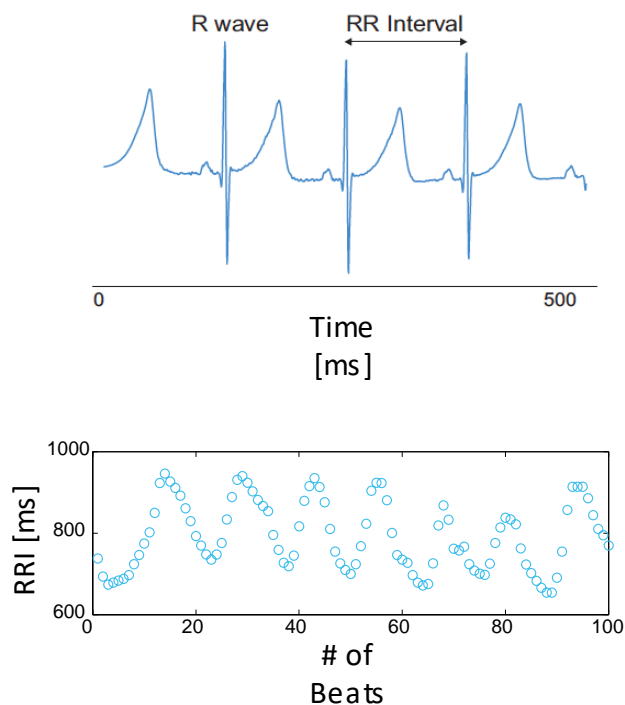
- Power spectral analysis of HRV can be carried out under resting conditions with demonstration of low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.4 Hz) components. The LF component of the power spectrum of HRV primarily reflects sympathetic activity, whereas the HF component (also termed the respiratory frequency [RF]) primarily reflects parasympathetic activity. LF:HF ratios are calculated, and provide a measure of sympathetic/parasympathetic activity.



[Vinik AI, et al.] Diabetes Investig 2013;4:4-18.]

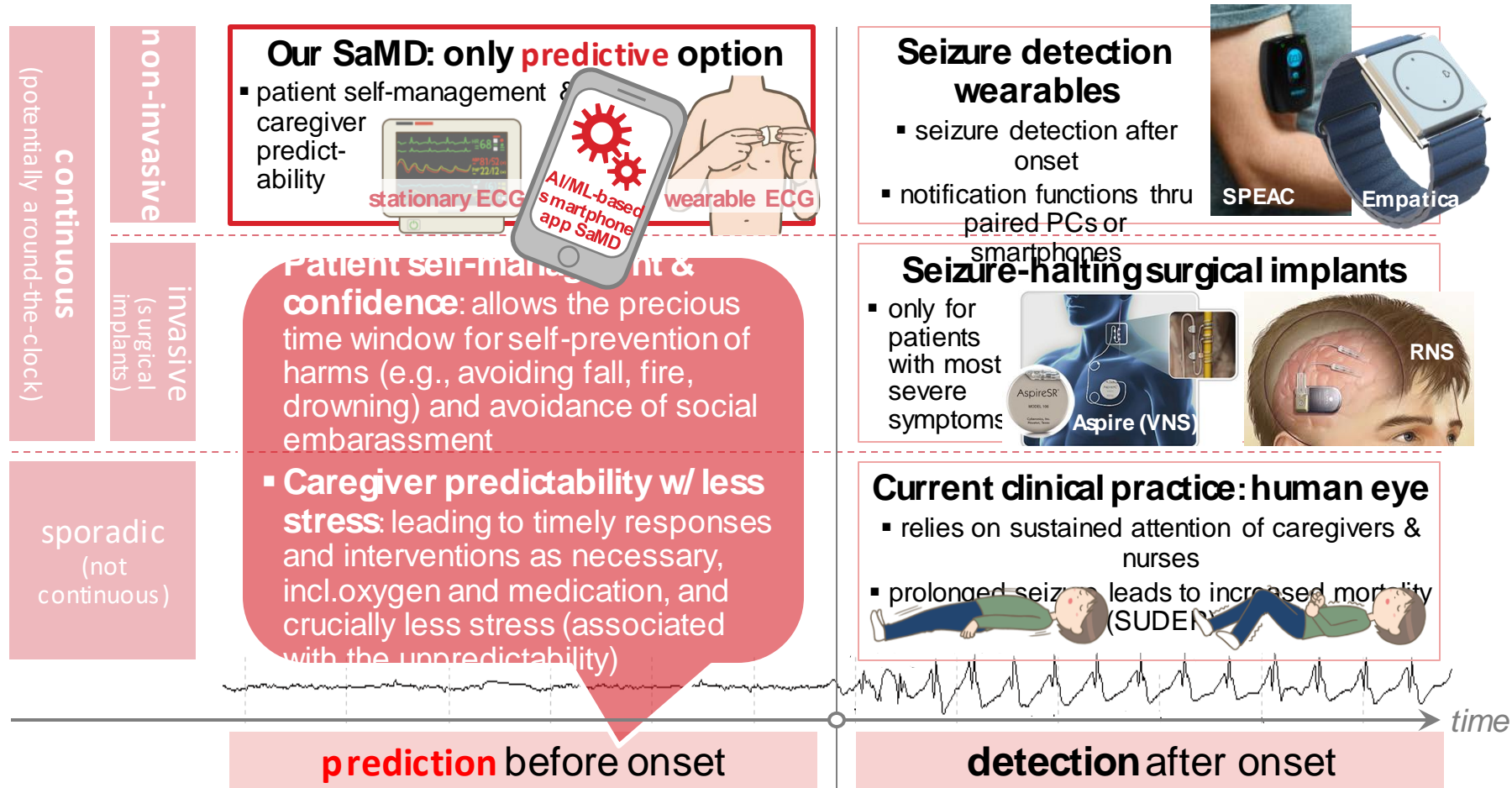
HRV analysis is tool for seizure prediction

- Fluctuation in heart rates, called HRV (heart rate variability), is known to be affected by the body-wide network of autonomic nervous system (ANS)
- The ANS is influenced by dramatic neurological changes, as in epileptic seizure



Predictive (& non-invasive) alarm system

- Our solution is the only option that allows for prediction of seizure prior to onset, thus allowing patients the crucial time window for self-management



images: www.kango-roo.com, LivaNova, RNS, Brain Sentinel, Empatica; *SUDEP: Sudden Unexpected Death in Epilepsy; **SaMD: software-as-a-medical-device

Supporting both patients and doctors

- Our front-end service and back-end data infrastructure will offer both better self-management and optimized medical engagement/intervention

