Inmedix
INNOVATIVE MEDICAL DISCOVERY

Stress and the immune system

University Sunrise Rotary Club
May 27, 2021

Andrew J. Holman, MD

Co-founder and CEO, Inmedix Inc. Seattle, WA, USA
Associate Clinical Professor of Medicine
University of Washington

A Pacific Northwest Legacy

- 1970's First use of weekly use of methotrexate in rheumatoid arthritis (Harborview)
- 1980's Inverted pyramid treatment strategy (Virginia Mason)
- 1990's Enbrel® First biologic treatment for rheumatoid arthritis (Immunex)
- 2000's Dopamine theory for fibromyalgia (Inmedix)

NEXT?

Inmedix
INNOVATIVE MEDICAL DISCOVERY

Stress

Scientific data showed STRESS is strongly linked to immune regulation & treatment response

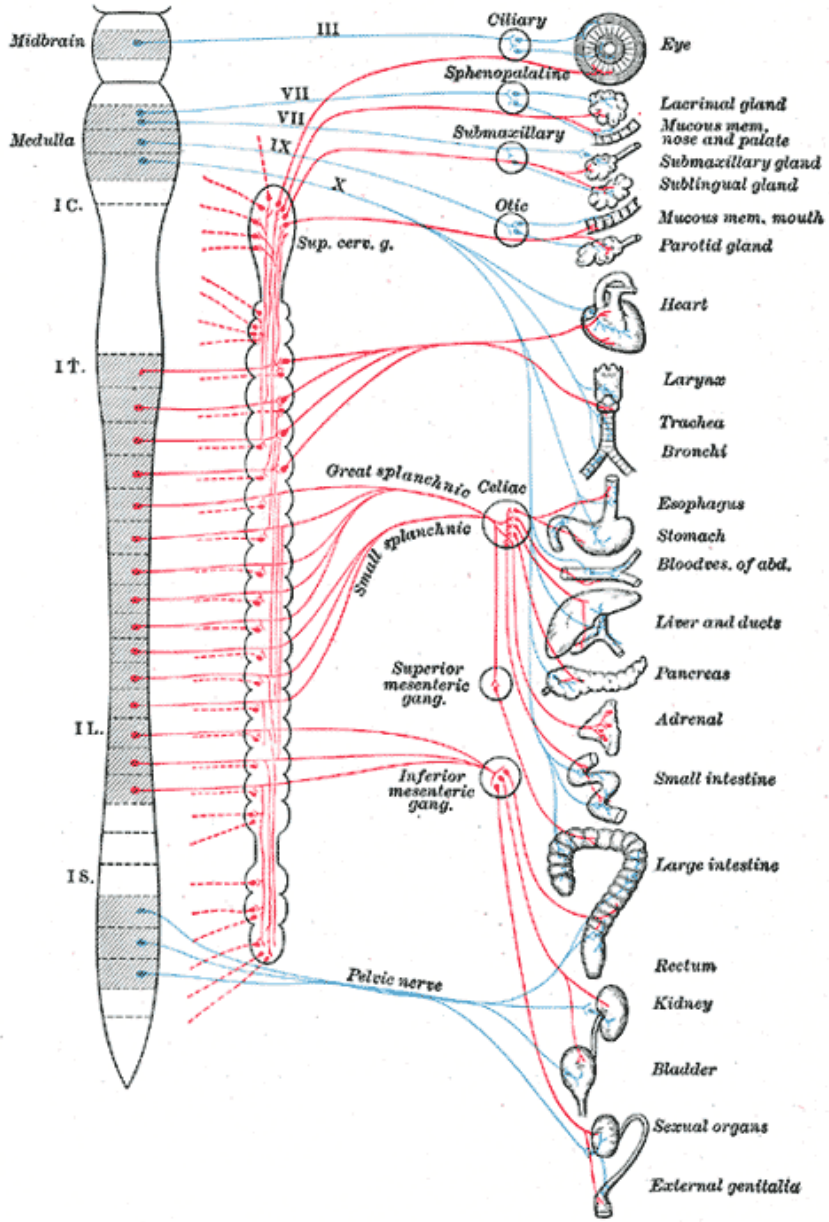
Ingegnoli F *et al*, The Link Between Autonomic Nervous System and Rheumatoid Arthritis: From Bench to Bedside. Front. Med. 2020;7:589079. doi: 10.3389/fmed.2020.589079.

The Autonomic Nervous System (ANS)

Parasympathetic

Sympathetic

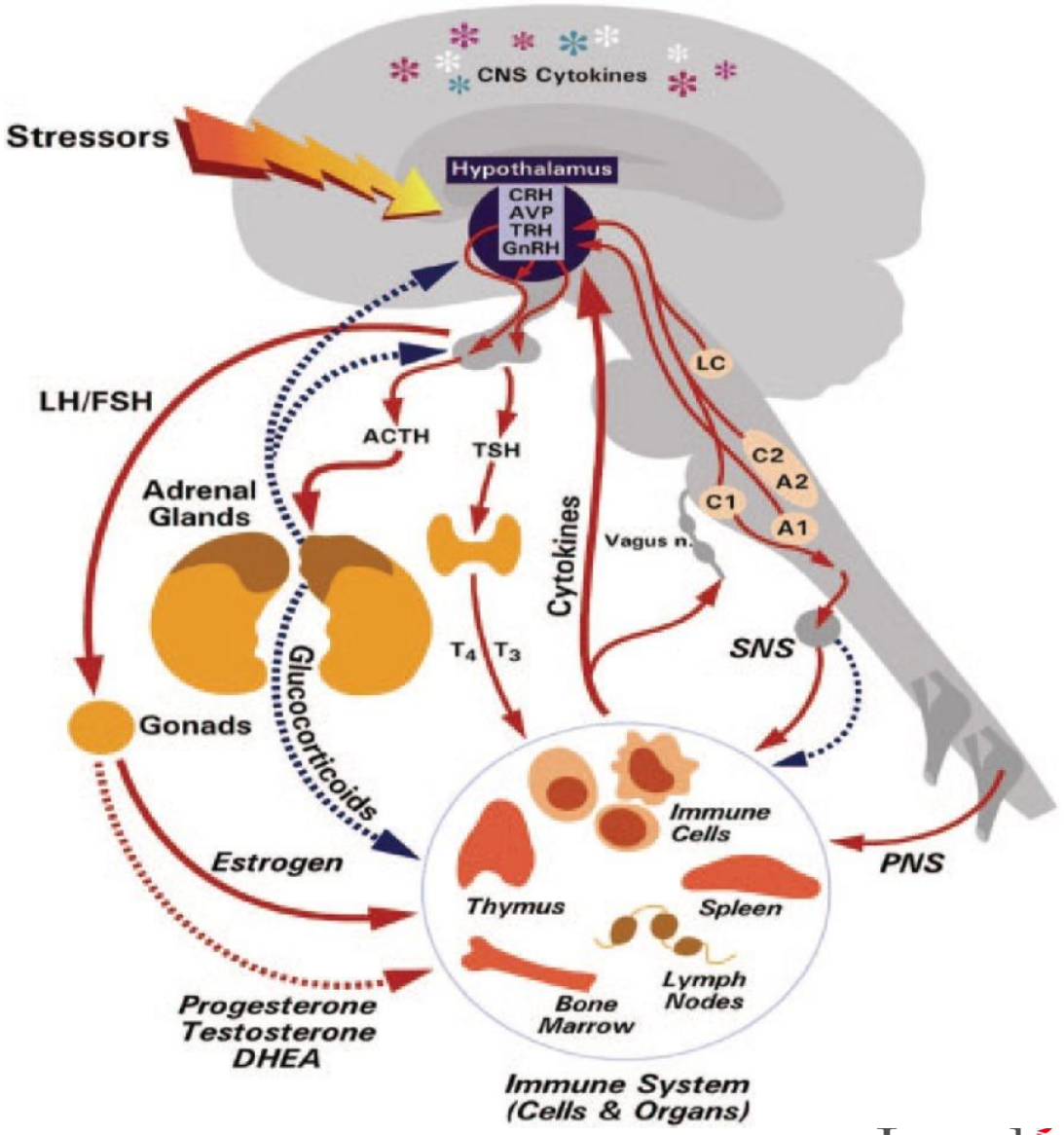
Functions: temperature, sleep, digestion, heart rate and blood pressure, breathing, pupillary, urinary, immune, fight-or-flight survival.



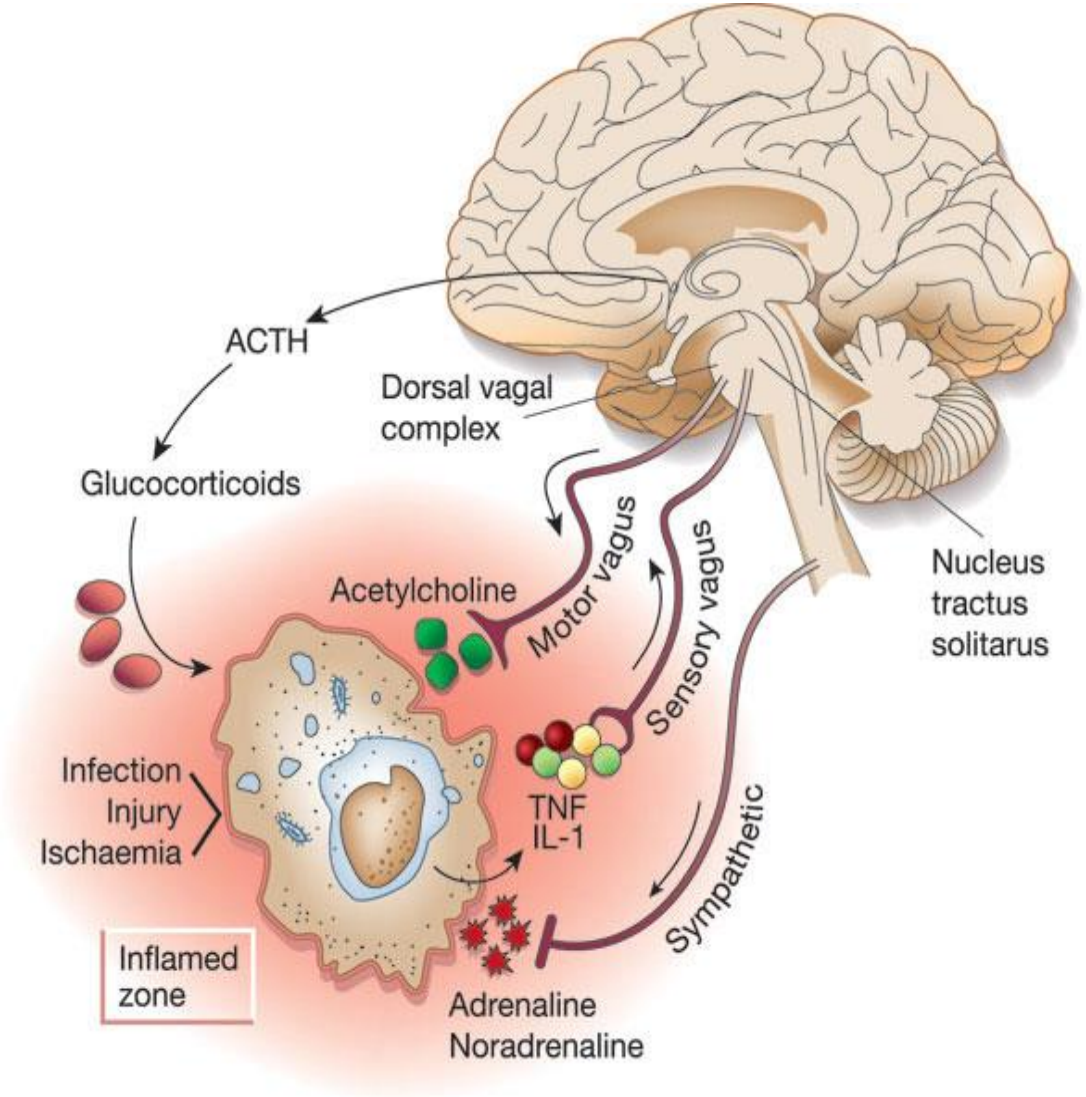
Inmedix
Innovative Medical Discovery

Biochemistry of Stress

- **Stress** exists to enhance survival
- **Stress** is controlled within the brain by an **autonomic nervous system (ANS)** coordinating hormones, cytokines and neurotransmitters



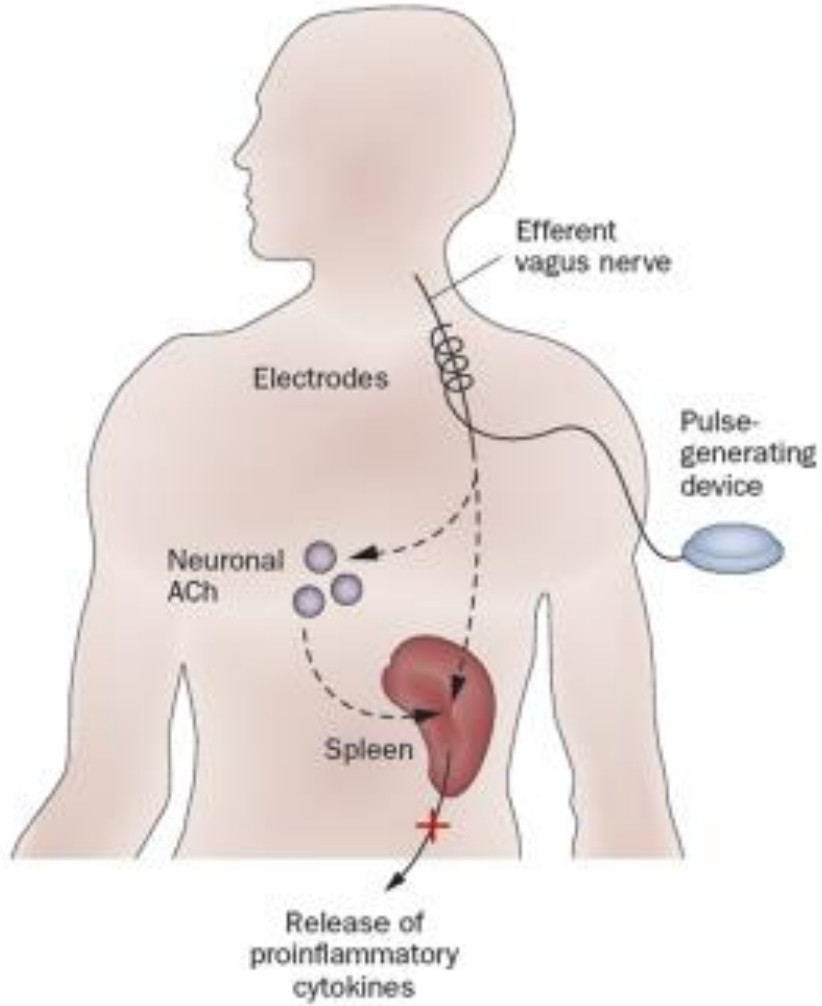
The ANS and Immune responses are hard-wired



- The discovery that cholinergic neurons inhibit acute inflammation has expanded our understanding of how the **autonomic nervous system (ANS) modulates immune responses**.

Tracey KJ. The inflammatory reflex. Nature 2002;420:853-59

Modulating the cholinergic anti-inflammatory pathway in RA: Direct electrical stimulation of the efferent vagus nerve by an external device



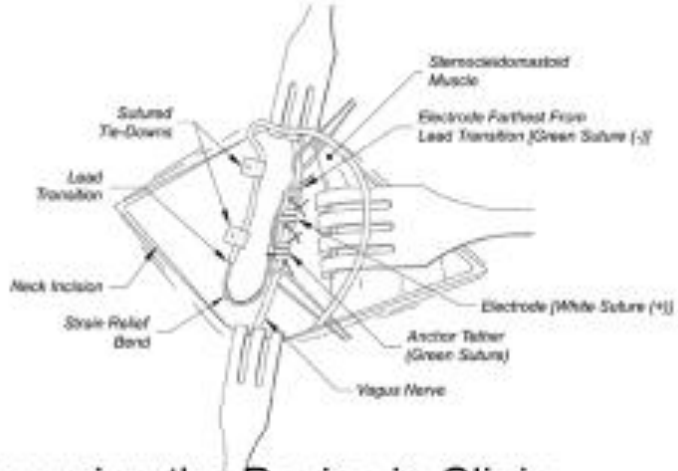
Van Maanen MA, Vervoordeldonk MJ, Tak PP. Nature Rev Rheumatol 2009;5:229-232

Standard Commercially Available Cyberonics VNS Devices Were Used In The Study

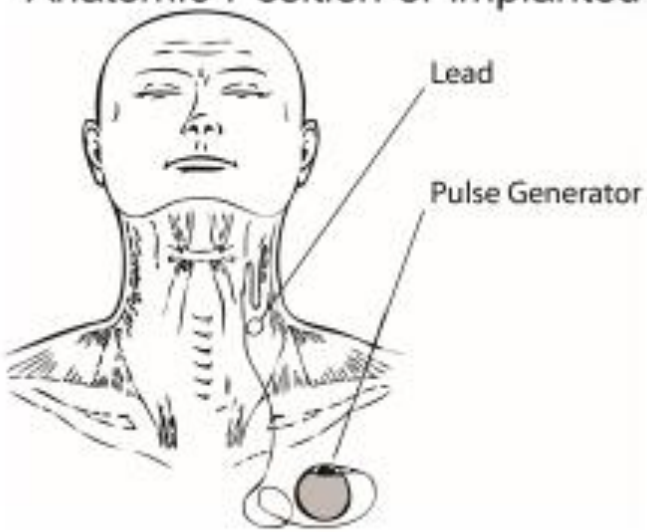
Lead

Pulse Generator

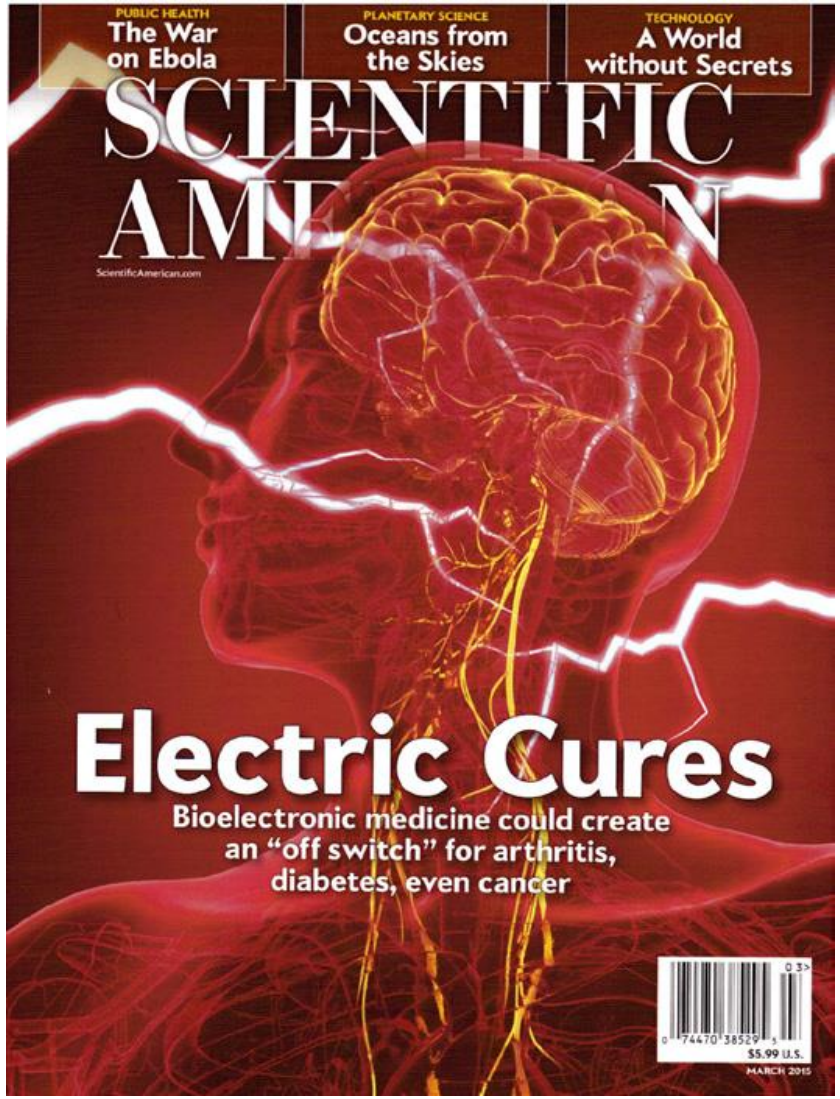
Implantation



Anatomic Position of Implanted Device



Programming the Device in Clinic

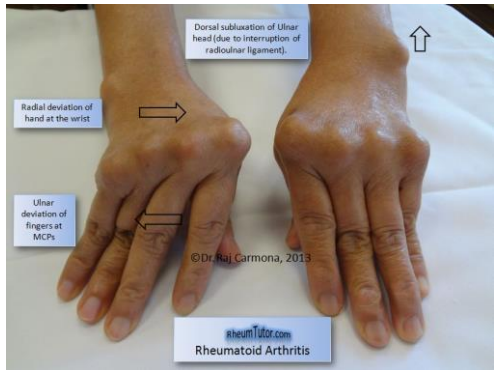

PUBLIC HEALTH
The War on Ebola
PLANETARY SCIENCE
Oceans from the Skies
TECHNOLOGY
A World without Secrets
SCIENTIFIC AMERICAN
ScientificAmerican.com
Electric Cures
Bioelectronic medicine could create an "off switch" for arthritis, diabetes, even cancer
$5.99 U.S.
MARCH 2015

March, 2015

What is rheumatology?

Common diseases:

Rheumatoid Arthritis (RA)



Psoriatic arthritis (PsA)

Systemic lupus erythematosus (SLE)

Fibromyalgia (FM)

Treatments:

- Pain medications
- Steroids
- Weekly methotrexate (MTX)
- Biologics

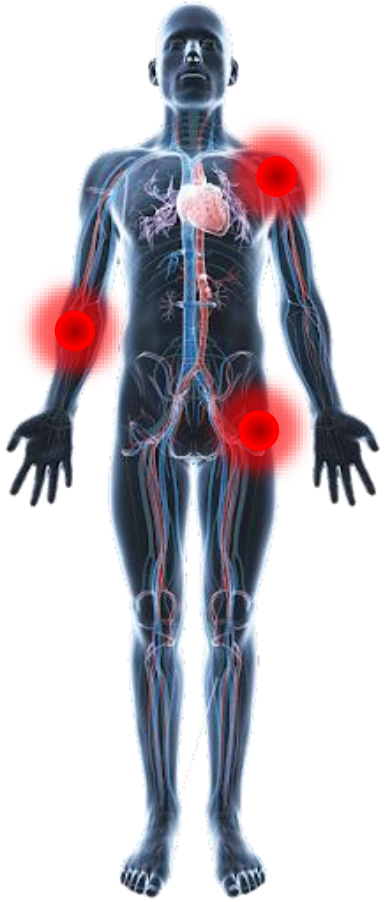
Issues:

- Poor control (25%) and cost ($30-60K)
- Toxic medications (liver, kidney, bone marrow)
- Opportunistic infections
- Treatments cause birth defects

AMGEN abbvie Pfizer MERCK AstraZeneca gsk Bristol-Myers Squibb Roche Johnson & Johnson Innovative Medical Discovery

PROBLEM: STRESS WEAKENS THE EFFECT OF INFLAMMATION TREATMENTS

Autoimmune Disease
Low Stress



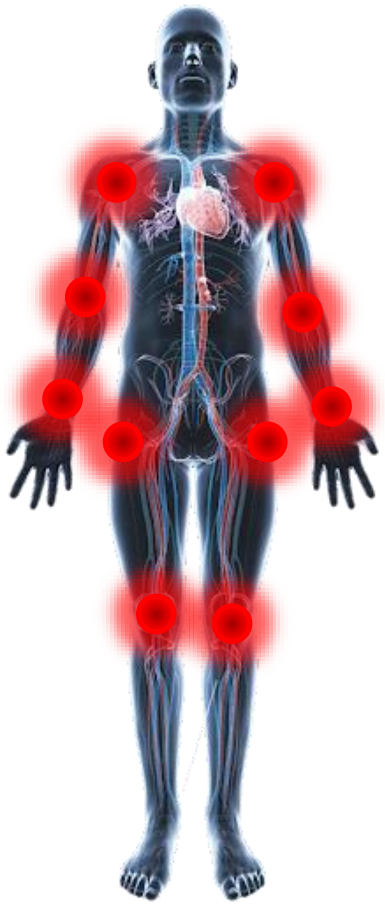
IMMUNO-AUTONOMICS

Higher stress levels increase inflammation making it harder for drugs to be effective.

In addition to a deficient immune system, drugs must fight even harder against **extra inflammation** due to stress.

Therefore, drugs are less effective for people with autoimmune disease with high stress levels.

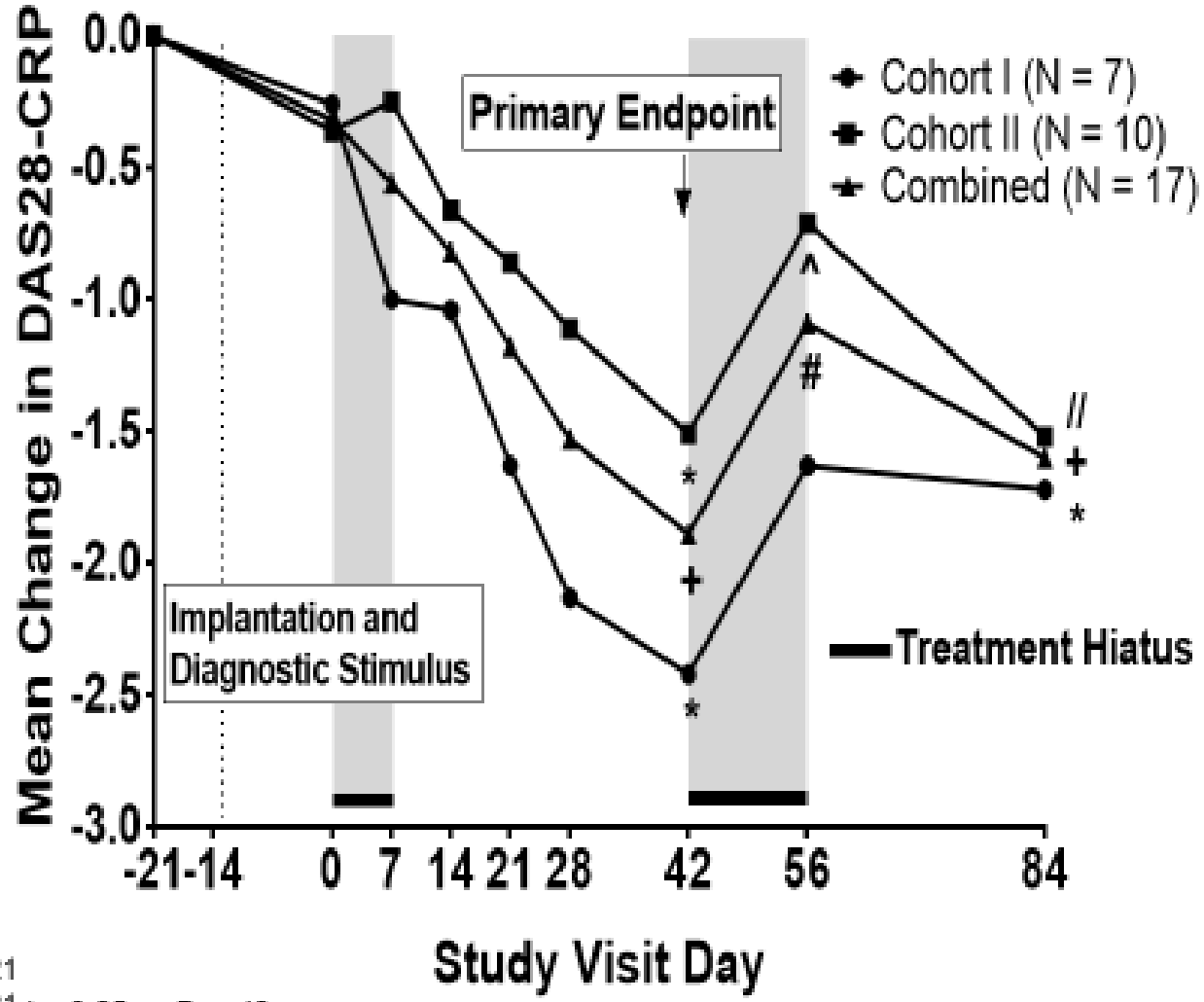
Autoimmune Disease
High Stress



Taylor PC, Holman AJ. Rheumatoid arthritis and the emergence of immuno-autonomics [editorial]. Rheumatology (Oxford). 2019 Jun 9. pii: kez216. doi: 10.1093/rheumatology/kez216.

Inmedix
INNOVATIVE MEDICAL DISCOVERY

Mean change in DAS28-CRP through day 84



*p<0.05 vs Day-21
//p<0.01 vs Day-21
+p<0.001 vs Day-21
^p<0.05 vs Day 42
#p<0.001 vs Day 42

Koopman FA et al. PNAS;2016; 113:8284-9

OUR SOLUTION:

Leverage immuno-autonomics knowledge to define and mitigate ‘stress’

We target and measure the biochemistry of stress to predict therapy response
and
enhance treatment effectiveness in reducing disease activity over time

Inmedix
INNOVATIVE MEDICAL DISCOVERY

Inmedix cloud e-laboratory

Data management & analytics

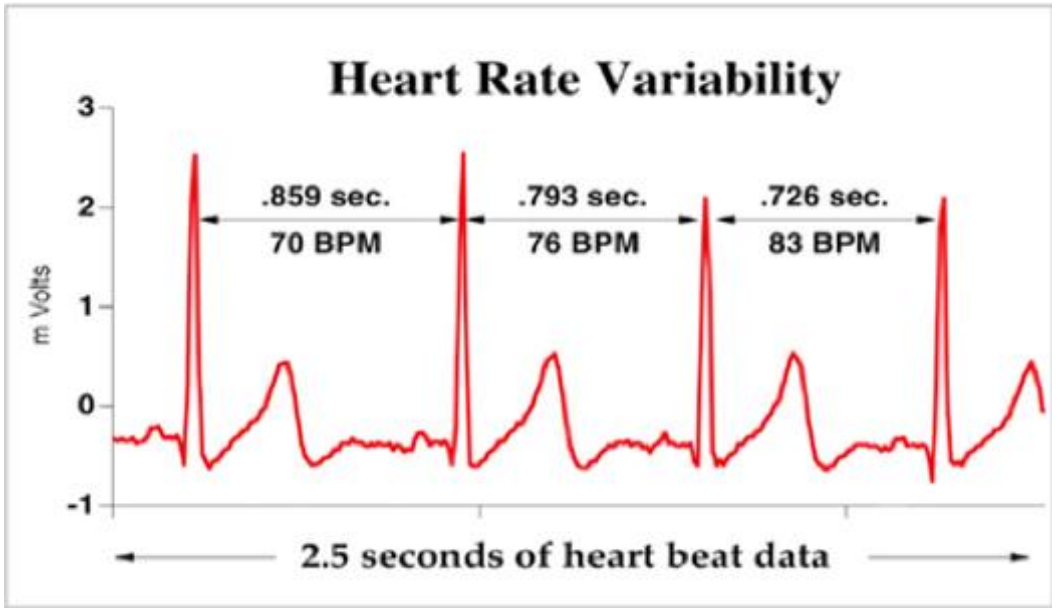
- Current partner drug label expansion
- Partner drug Discovery
- Collaboration: Corrona database, JointMan, NIH, NHS

Bloodless, scalable, clinical diagnostics

- Current Device #1
  - Current Application #1 Autoimmune disease
  - Application #2 Cancer
- Future Hardware and application #2 2023
- Future Hardware and Applications #3,4,5… 2024

15

How to measure stress?



Current weakness of HRV

Raw data noise, poor reproducibility, no measure of 'sympathetic' fight-or-flight stress

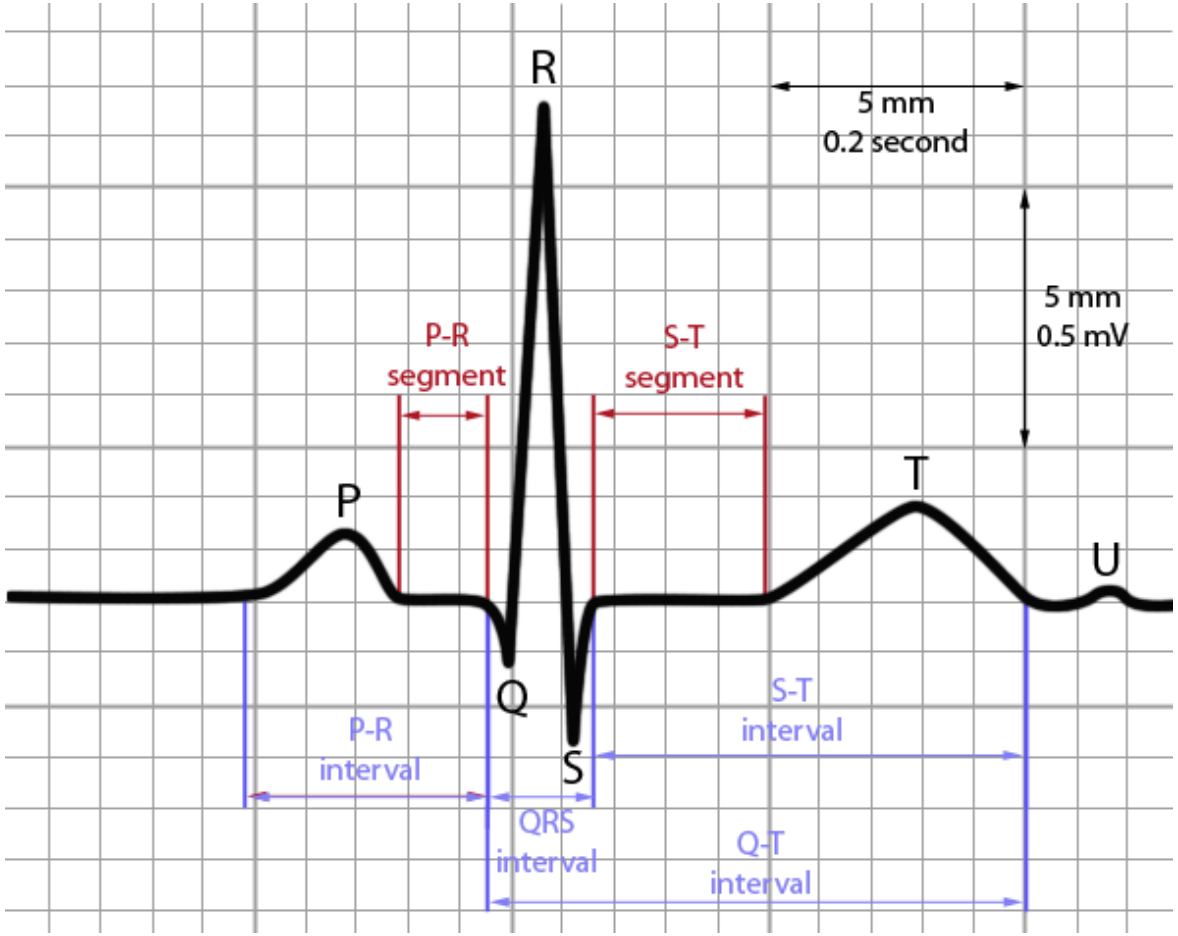
What's coming?

Next-generation HRV

Proprietary algorithm for 'fight-or-flight', precision ECG measurement, advanced filtering of raw data, clinical validation, cloud platform

Inmedix
Innovative Medical Discovery

BEAT-TO-BEAT ANALYSIS REQUIRES PRECISION



Average heartbeat takes ½ second

A-Fib apps need accuracy to 0.1 sec.

Next-gen HRV measurement is accurate to 1/1000 second

Medical grade ECG is 255-333 Hz

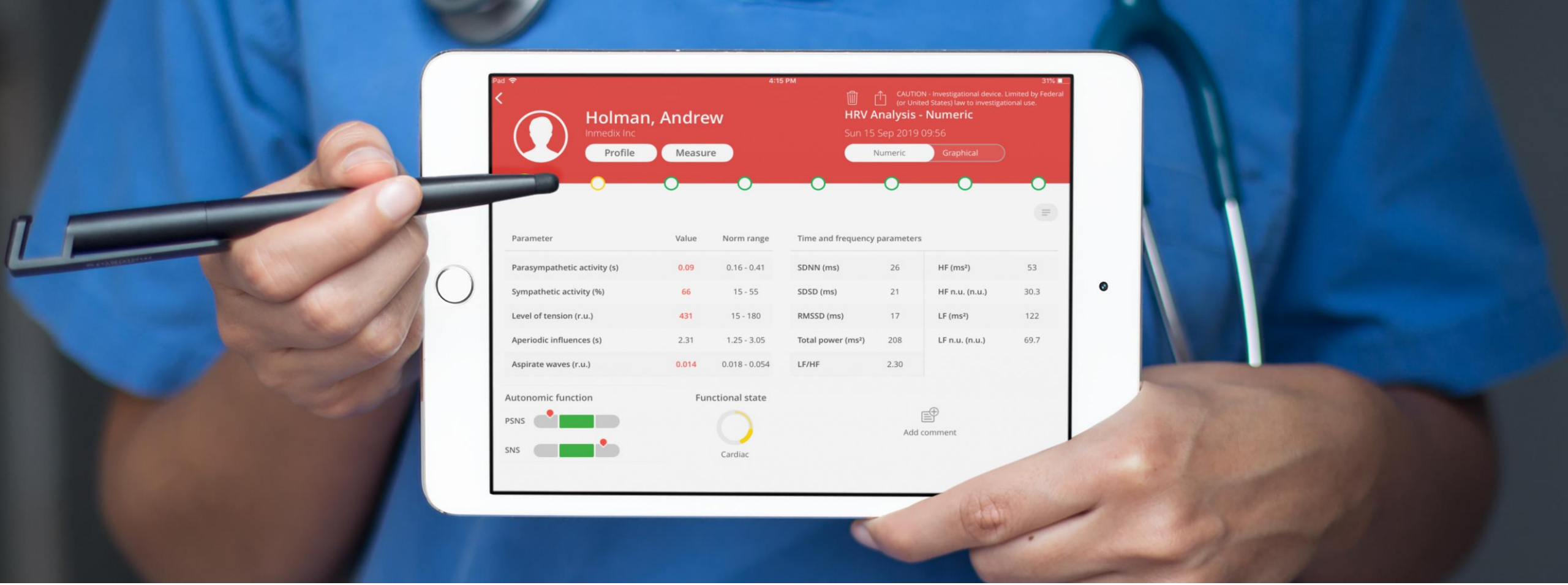
Next-gen HRV ECG sampling is 8000 Hz

Inmedix
Innovative Medical Discovery

A cardiovascular test (ECG)

to measure a brain function (ANS stress state)

to solve an immunology problem (autoimmune diseases)

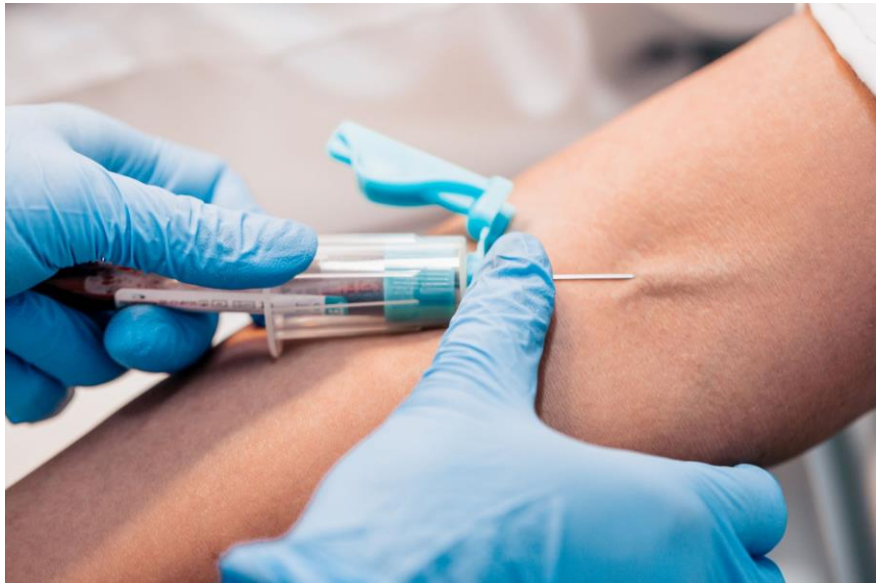


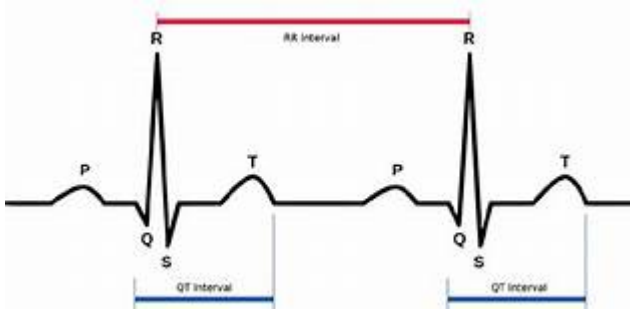
ANS Neuroscan™

Precision measurement of physiological stress can inform therapeutic selection to achieve effective disease management

Inmedix
Innovative Medical Discovery

Replacing blood with ECG math





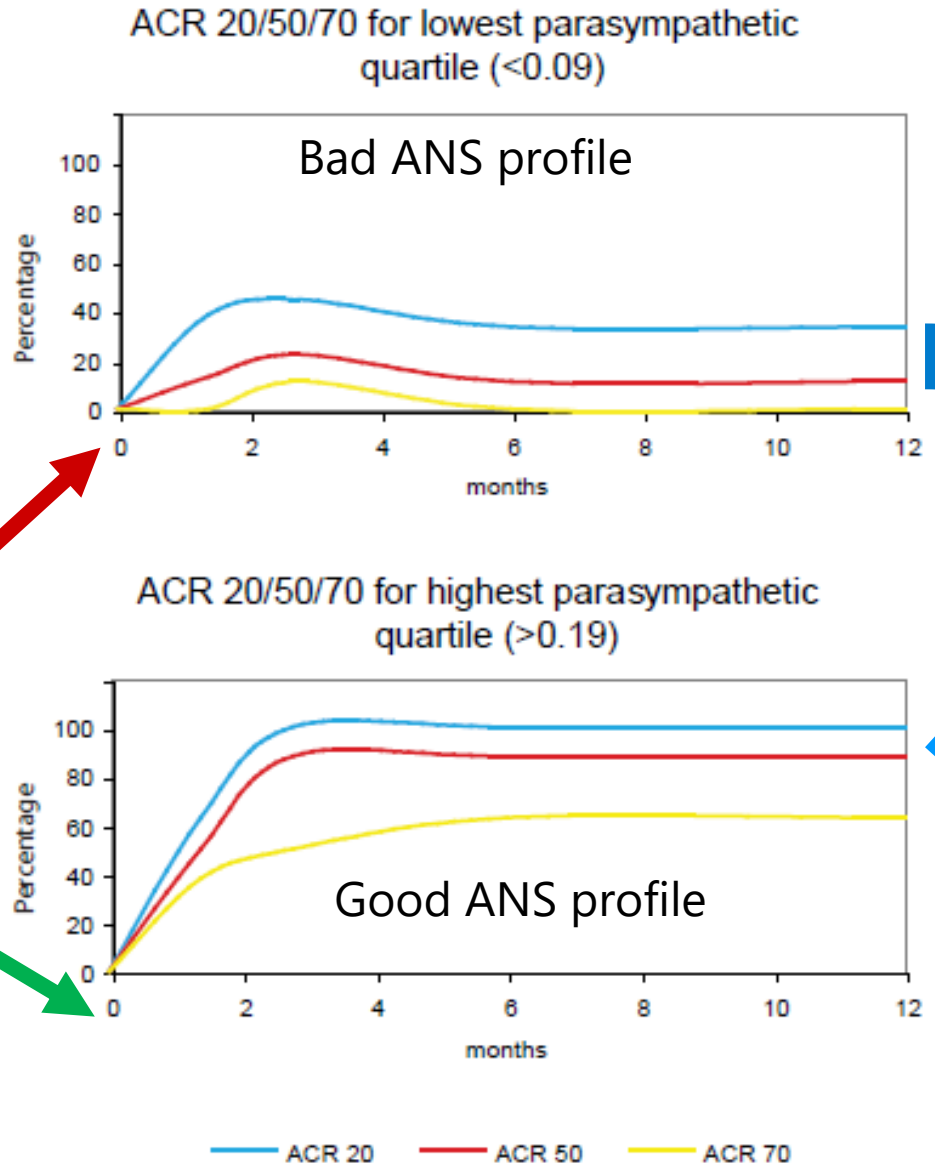
$$x_k = \frac{1}{2\pi}\left(\sum_{1=0}^{N-1} X_1 \cdot e^{-j\Delta\omega k\Delta t_{\Delta\omega}} \right), k = 0, 1, .., N-1 \quad (16)$$

PREDICT THERAPY OUTCOMES FOR INFLAMMATORY ARTHRITIS

PREDICT THERAPY RESPONSE AT BASELINE*

Parasympathetic measured at day 0 by Inmedix next-gen HRV predicts 52-wk biologics treatment outcome[1]

*: Data on both biologics and conventional DMARDs



ENABLE PHYSICIANS TO ADD MEDICATIONS TO IMPROVE ANS PROFILE OF PREDICTED POOR RESPONDERS AND IMPROVE 1YR REMISSION RATE BY 200%

ACR20: ≈ 20% improvement
ACR50: ≈ 50% improvement
ACR70: ≈ Disease remission

1. Holman AJ, Ng E. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. Autonomic Neurosci Basic Clinical 2008 Dec 5;143(1-2):58-67.

Inmedix
INNOVATIVE MEDICAL DISCOVERY

IMPROVE RA TREATMENT OUTCOME

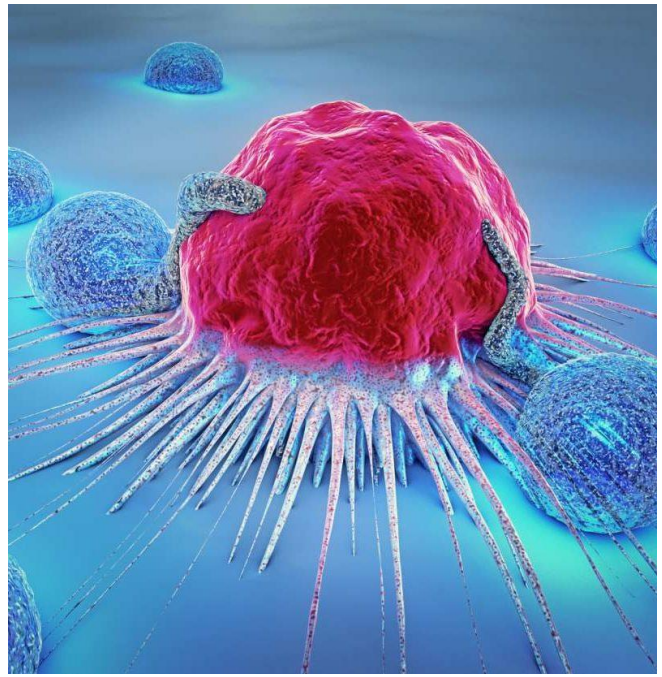
- **The only test that can PREDICT 52-week rheumatoid arthritis treatment outcome at baseline[1]**
- **Prescribing concomitant drug therapy to mitigate stress can TRIPLE remission rate[2]**
- **Health Economics study projected $35 BILLION reduction in cost for rheumatoid arthritis over 10 years[3]**

1. Holman AJ, Ng E. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. Autonomic Neurosci Basic Clinical 2008 Dec 5;143(1-2):58-67.
2. Holman AJ, Ng E. Use of adjunctive neuroregulatory medication to improve etanercept treatment response for patients with inflammatory arthritis a pilot study [abstract]. Arthritis Rheumatol. 2015;67 (suppl 10) #422.
3. Zimmermann M, Vodicka E, Holman AJ, Garrison LP. Heart rate variability testing: could it change spending for rheumatoid arthritis patients in the United States? An exploratory economic analysis. J Med Econ. 2018 Jul;21(7):712-720.

Inmedix
INNOVATIVE MEDICAL DISCOVERY

NEXT FRONTIER FOR IMMUNO-AUTONOMICS:

ONCOLOGY



sophistication

- Mass detection
- Surgical removal
- Precision surgery
- Chemotherapy, radiation
- Immuno-oncology
  - block cancer defenses with check-point inhibitors
    - Merck Keytruda $14B 2020 sales
  - make tumors 'hot' with oncolytic viruses

  - **immuno-autonomics**

Inmedix
INNOVATIVE MEDICAL DISCOVERY

Advanced Pancreatic Cancer (n=272)

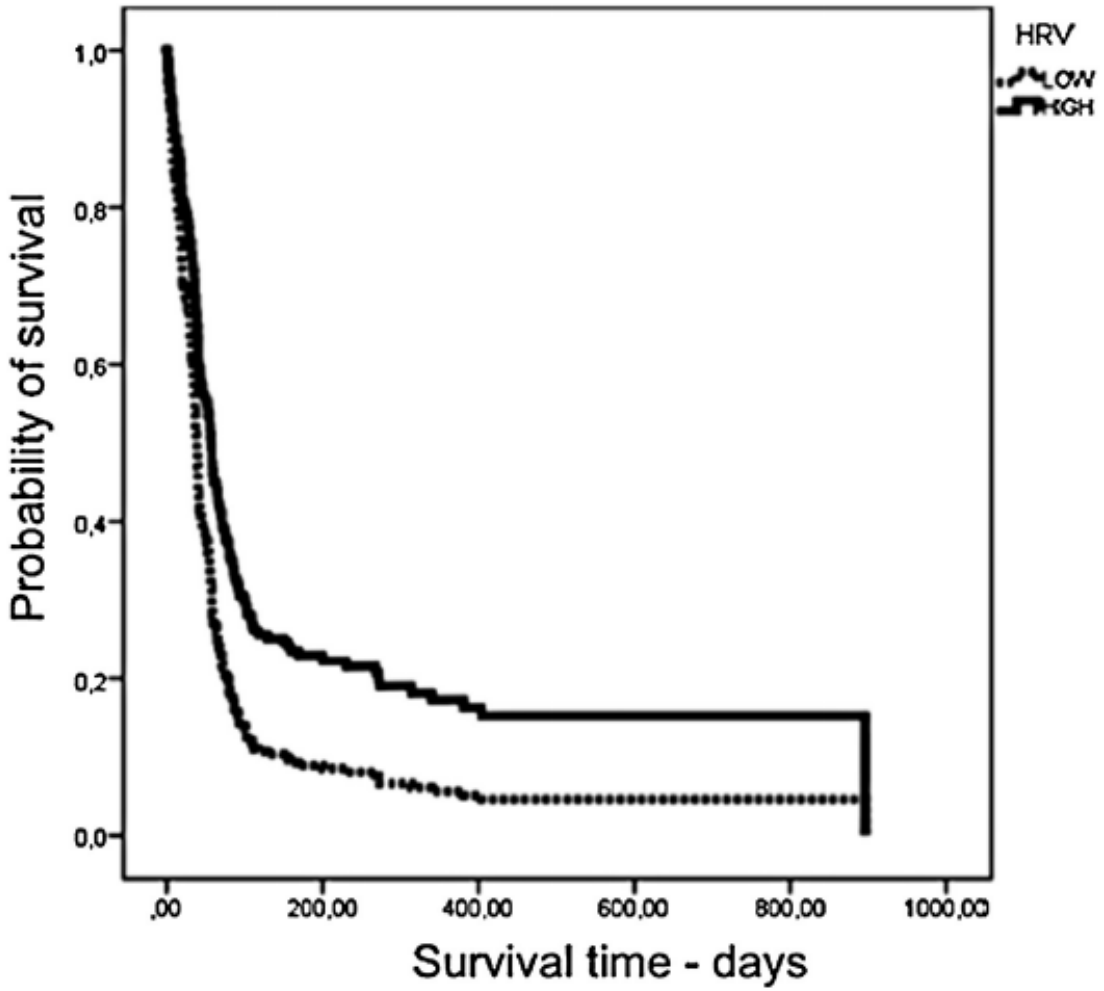
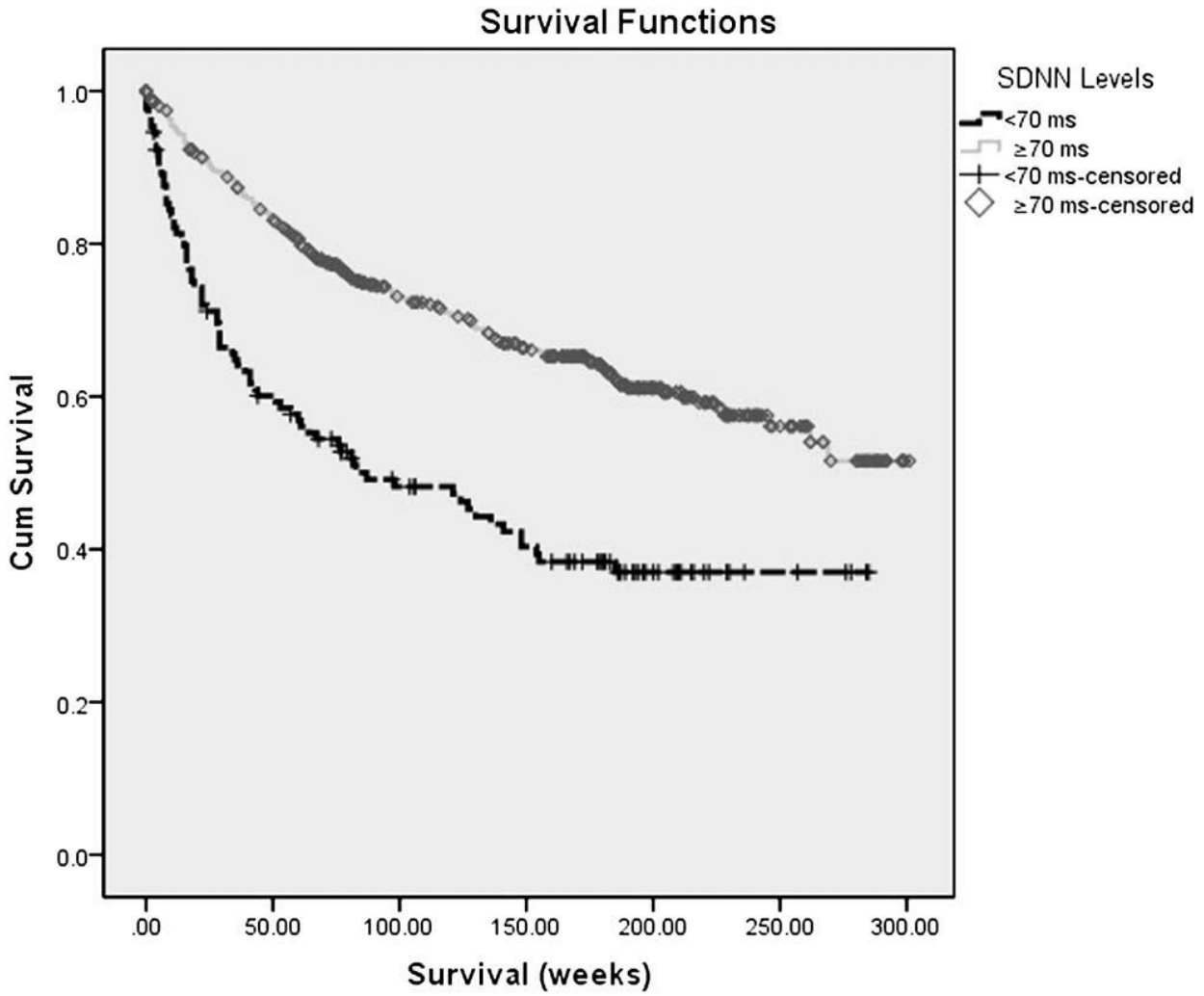


Fig. 1. The relationship between HRV and overall survival.

MD Couch et al/ Cancer Epidemiology 40 (2016):47-51

Mixed cohort with solid and hematologic cancers (n=520)



Guo Y et al./ J Clin Neurophysiol 2015; 32: 516-520. 25

Lung or breast cancer brain metastasis (n=40)

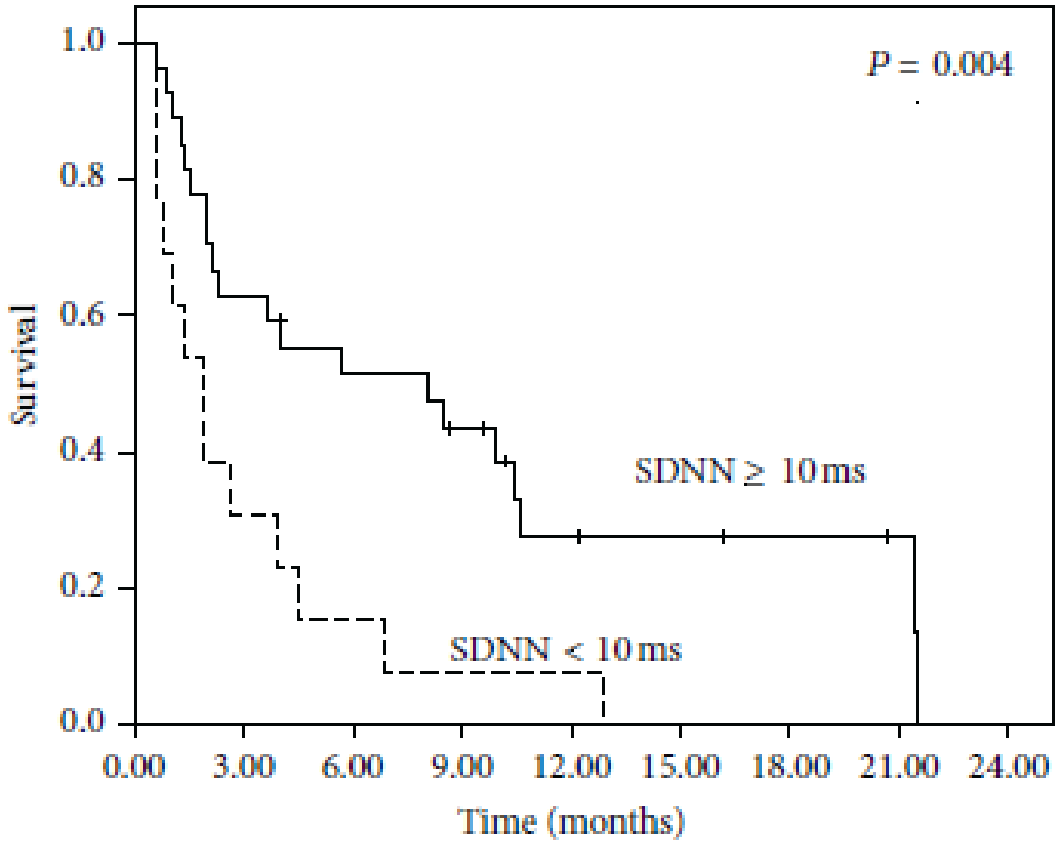


FIGURE 2: Overall survival of all patients stratified by SDNN <10 ms or SDNN ≥10 ms.

Wang YM et al. BioMed Research International 2013 Article ID 501412

1997 Zutphen Study (n=2356)

Am J Epidemiology 1997;145:899-908

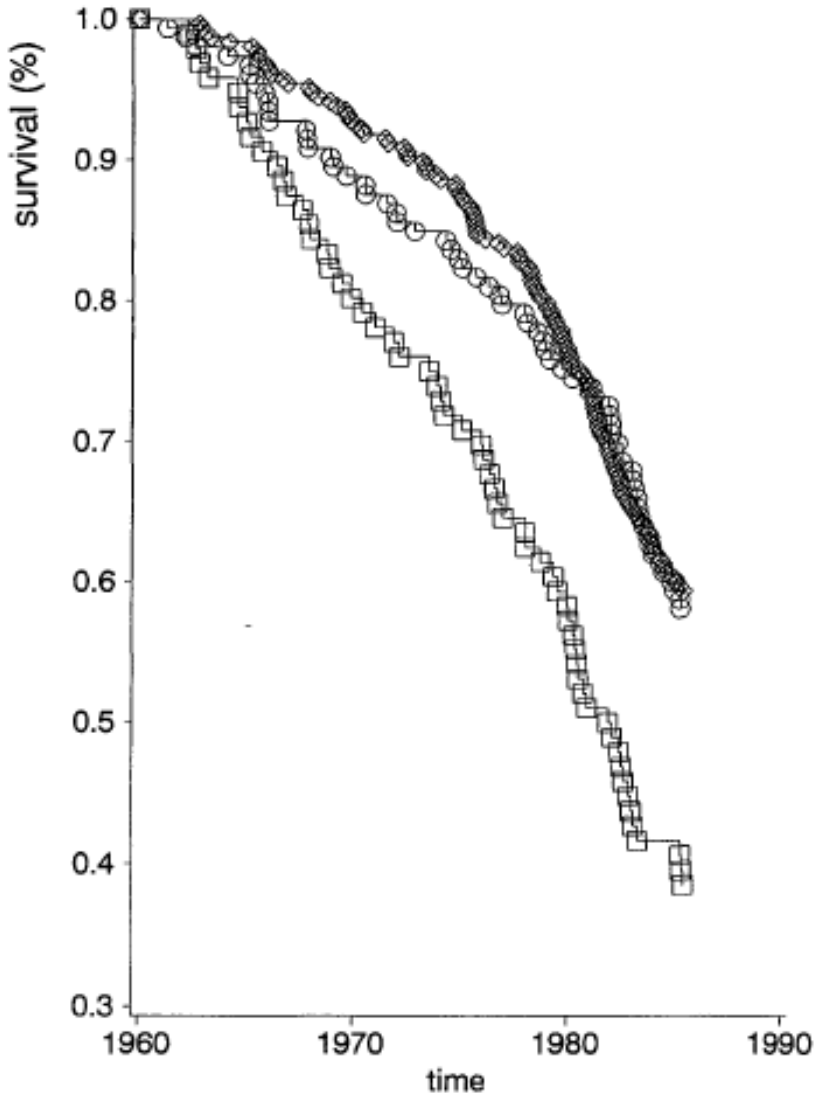


FIGURE 1. Kaplan-Meier survival curves of total mortality in categories of heart rate variability in middle-aged men: <20 milliseconds (msec) (low, □), 20–39 msec (intermediate, ◇), and ≥40 msec (high, ○), the Zutphen Study, 1960–1990.


You cannot manage...
what you do not measure.


Inmedix

iPad Mounting (Front)