



G R E A T P L A I N S
IDeA | Clinical and
Translational Research

Sentinel: team science to create a COVID warning system

Sentinel Research Team

Great Plains IDeA-CTR Seminar Series – August 13, 2020

The Following Video Shows
the Timelapse Map of the **Coronavirus** throughout
the World since January 20, 2020

**EPIDEMICS SPREAD EXPONENTIALLY
(NON INTUITIVE)**

SPREAD BY ASYMPTOMATIC PERSONS

LONG INCUBATION TIME

PRESENTATION OVERVIEW



Problem



Approach



Team members



Current status

SENTINEL: A PHYSIOLOGIC-BASED ALERT SYSTEM FOR POPULATION-BASED HEALTH CHALLENGES

SARS-COV-2



SYMPTOM-BASED DIAGNOSES

Diagnosis requires recognition
striking pattern/severity
numbers



Difficulties for novel pathogen

SENTINEL: A PHYSIOLOGIC-BASED ALERT SYSTEM FOR POPULATION-BASED HEALTH CHALLENGES

SARS-COV-2

Homeokinesis



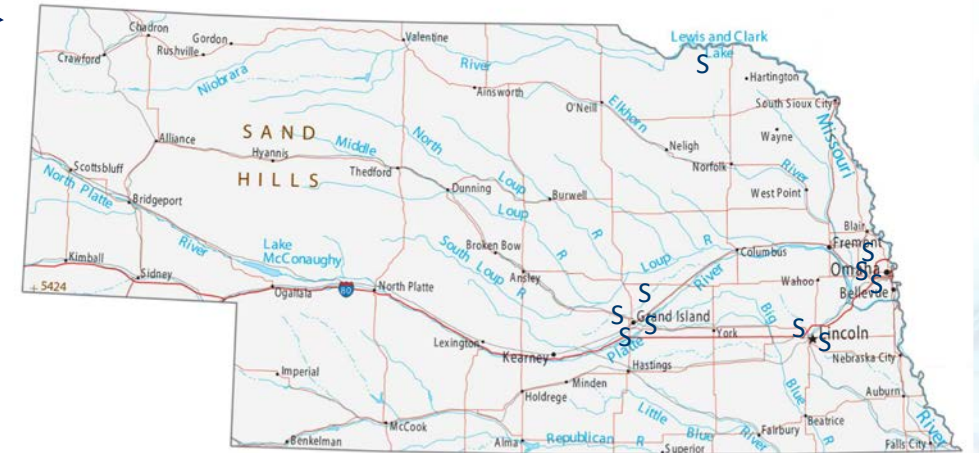
Frey et al. J. Appl. Physiol. 110: 1723, 2011

Passive wearable sensor

Loss of complexity

Transition from health

SYMPTOM-BASED DIAGNOSES



SENTINEL: A PHYSIOLOGIC-BASED ALERT SYSTEM FOR POPULATION-BASED HEALTH CHALLENGES

SARS-COV-2

Homeokinesis



Frey et al. J. Appl. Physiol. 110: 1723, 2011

Passive wearable sensor

Loss of variability and complexity;
coupling, network

Transition from health

SYMPTOM-BASED DIAGNOSES



TRANSITION-BASED DIAGNOSES (80% sensitivity)



SENTINEL: A PHYSIOLOGIC-BASED ALERT SYSTEM FOR POPULATION-BASED HEALTH CHALLENGES

Hypothesis: **A wearable sensor-based system can detect physiologic changes that indicate a transition from health to disease with SARS-CoV-2 infection**

Needed:

Sensor

Extraction of meaningful physiological parameters from sensor data

Validate parameters as diagnostics

Clinical study for data collection

Rigorous statistical analysis plan

SENTINEL: A PHYSIOLOGIC-BASED ALERT SYSTEM FOR POPULATION-BASED HEALTH CHALLENGES

Hypothesis: **A wearable sensor-based system can detect physiologic changes that indicate a transition from health to disease with SARS-CoV-2 infection**

Needed:

Dr. Markvicka	Sensor
Dr. Yentes	Extraction of meaningful physiological parameters from sensor data
	Validate parameters as diagnostics
Dr. McClay	Clinical study for data collection
Dr. Zhang	Rigorous statistical analysis plan

Eric Markvicka, PhD

Assistant Professor

Mechanical and Materials Engineering

College of Engineering

University of Nebraska-Lincoln



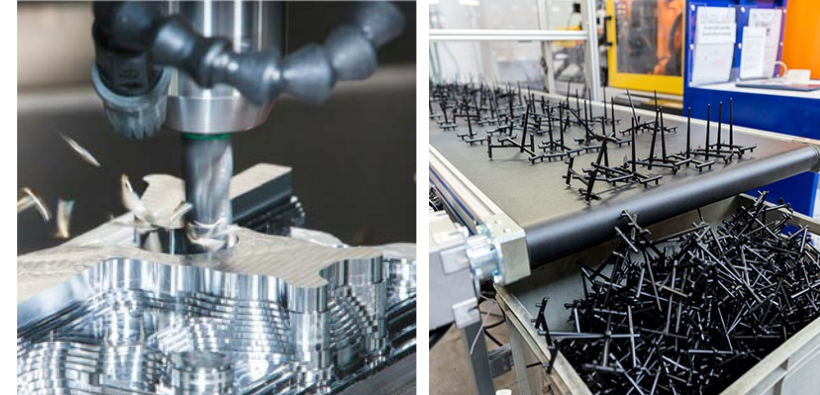
Smart Materials and Robotics Laboratory

<http://smr.unl.edu>

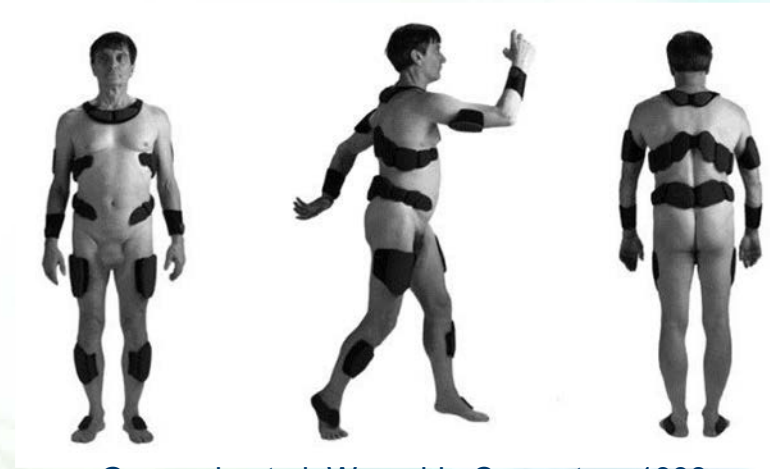
Commercial Wearable Electronics



Materials:



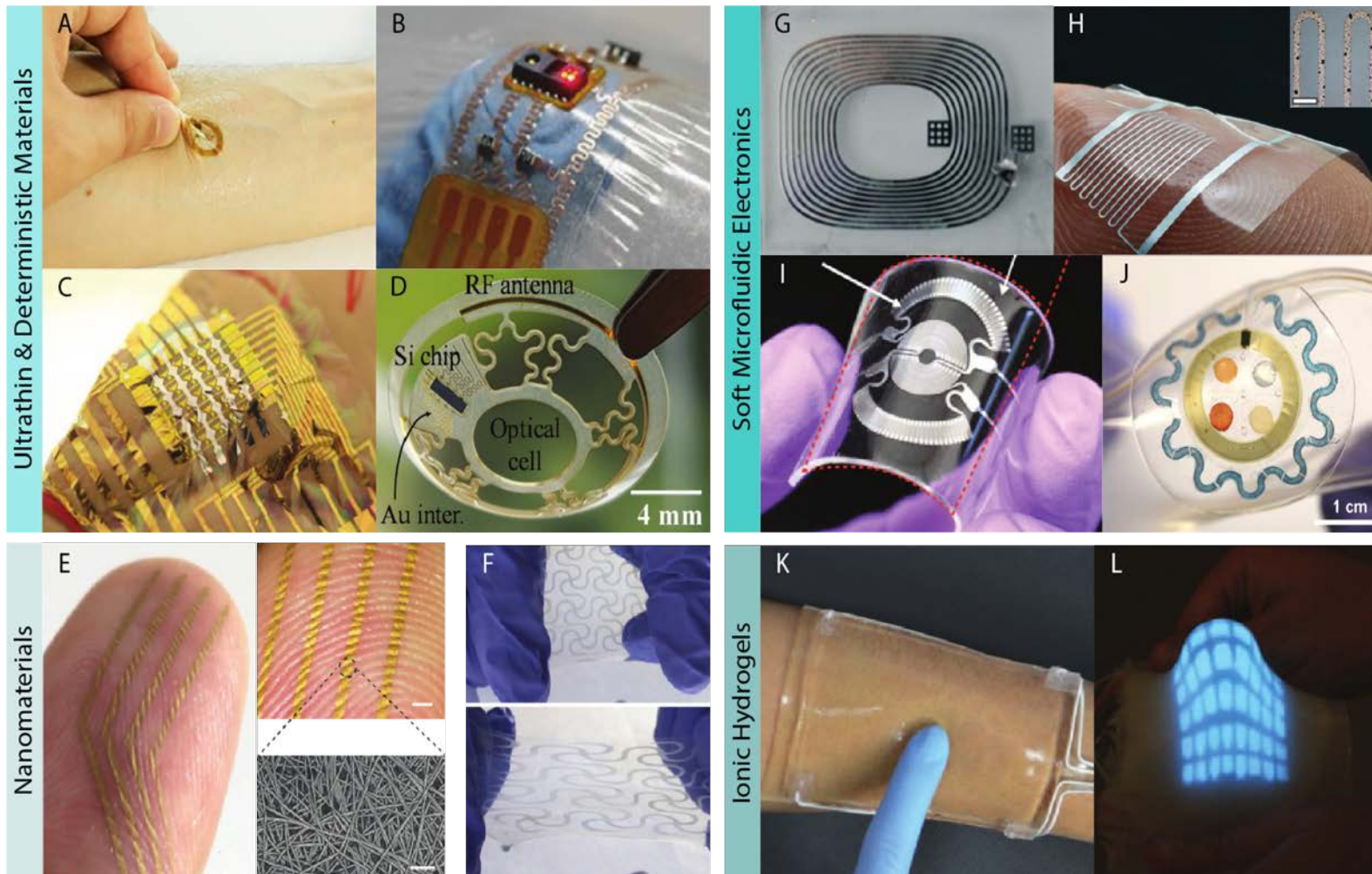
Limited placement:



Gemperle et al. Wearable Computers 1998



Stretchable Electronics



Rich, S. et al., *Nat Elec.*, 2018



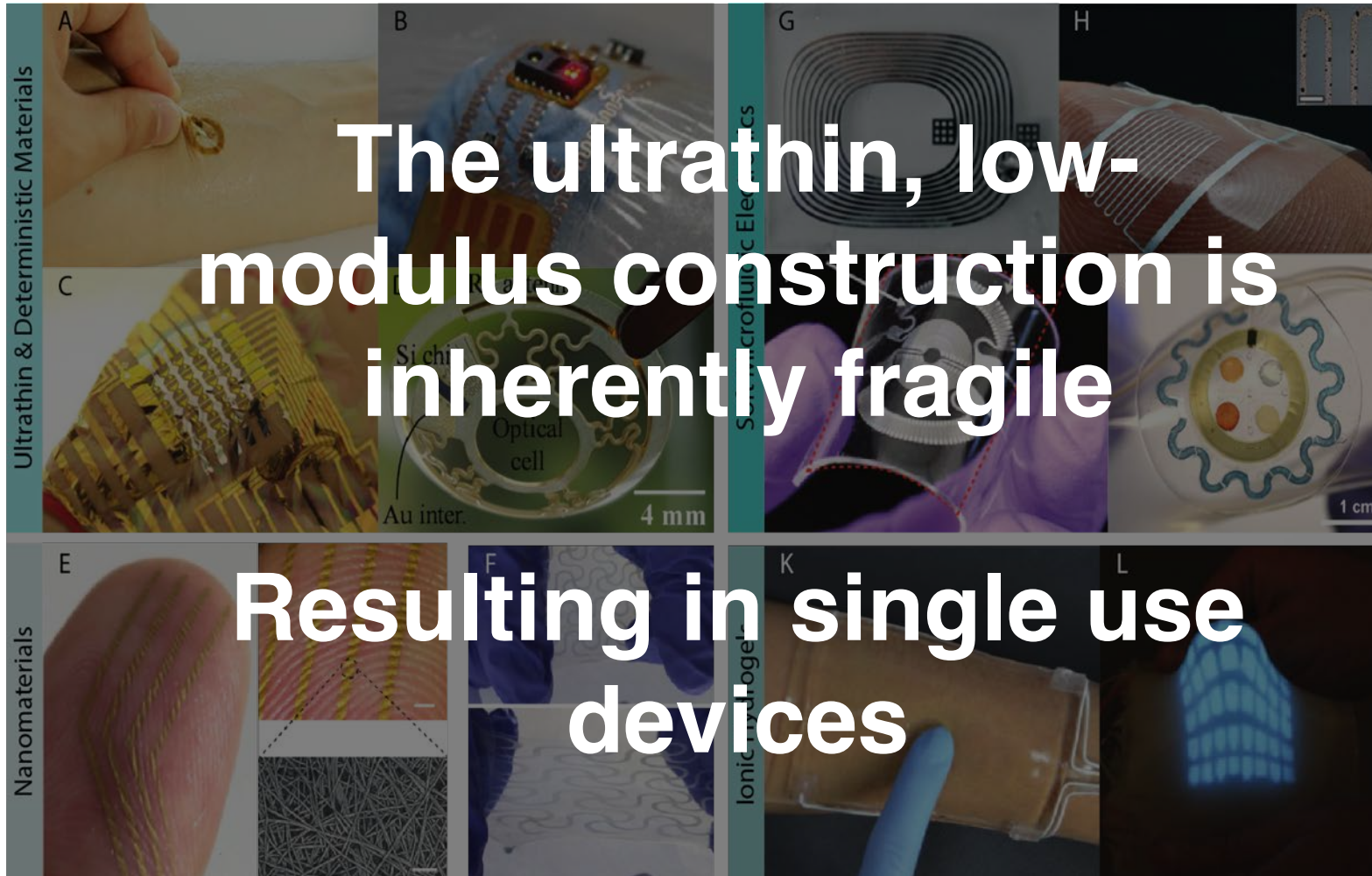
Properties:

- Thin
- Lightweight
- Soft
- Highly deformable
- Elastic

Tethers Provide:

- Power
- Data communication
- Signal processing

Stretchable Electronics



The ultrathin, low-modulus construction is inherently fragile

Resulting in single use devices

Properties:

- Thin
- Lightweight
- Soft
- Highly deformable
- Elastic

Tethers Provide:

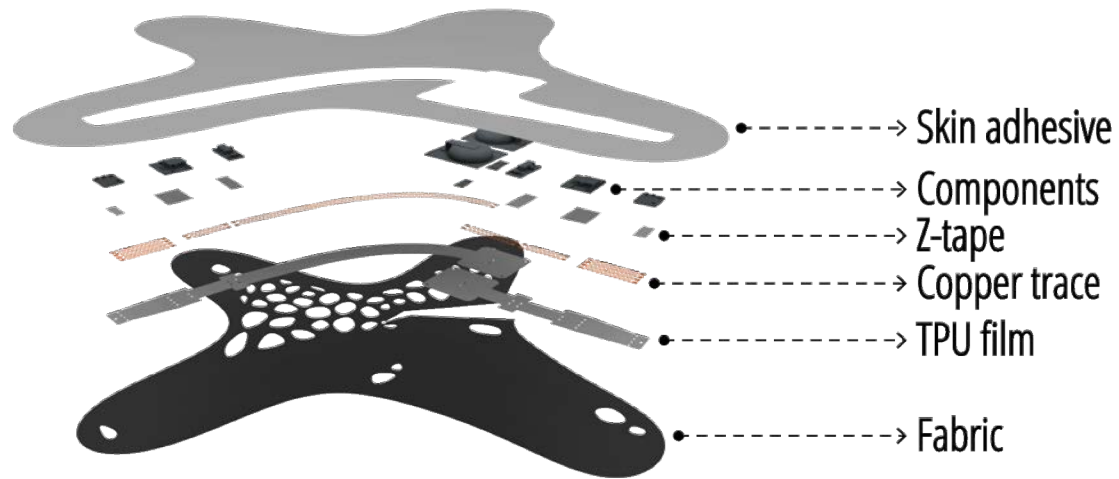
- Power
- Data communication
- Signal processing

Rich, S. et al., *Nat Elec.*, 2018



Stretchable Hybrid Electronic Architecture

Embedding advanced microelectronic circuits with high performance textiles

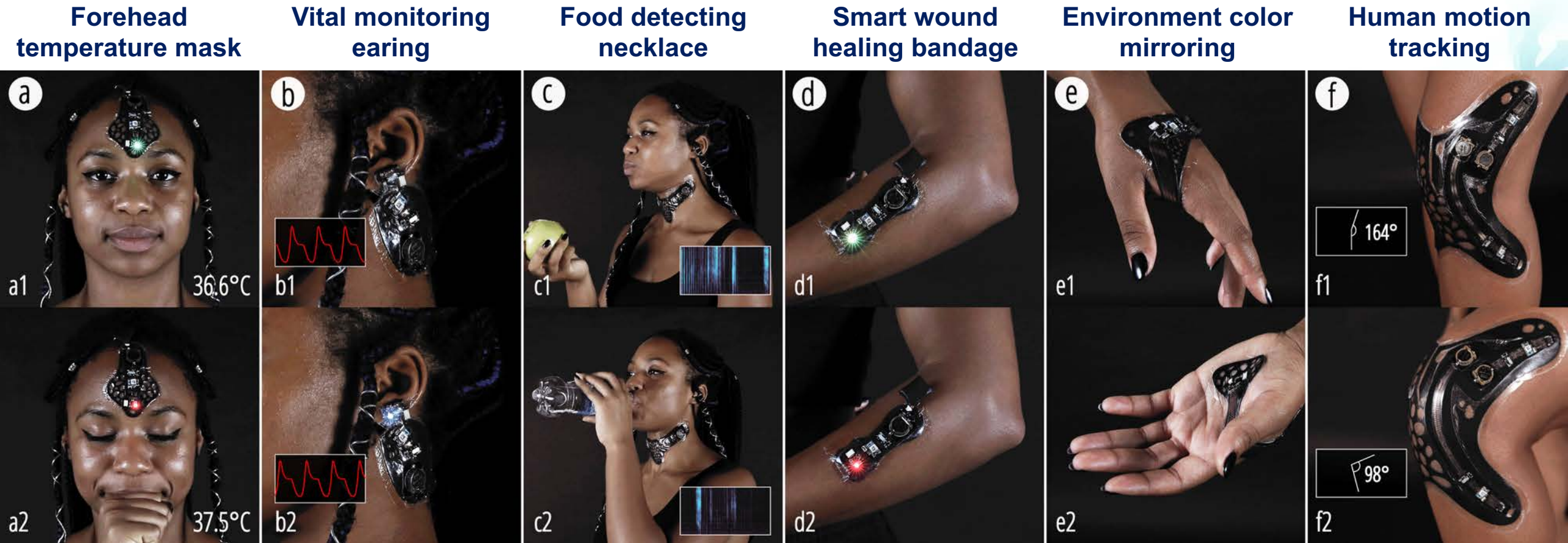


Properties:

- Thin ($< 2\text{mm}$)
- Lightweight construction ($< 30\text{g}$)
- Structural conformity
- Soft and elastic properties that match or exceed human tissue
- Untethered
- Mechanically robust
- Reusable



Prototypes



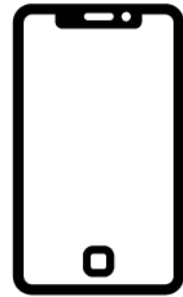
E. Markvicka, G. Wang, Y. Lee, G. Laput, C. Majidi, L. Yao, CHI 2019.

Proposed Sentinel Device

Wearable Sentinel Device



Secure
cloud storage



Smartphone

Sensors:

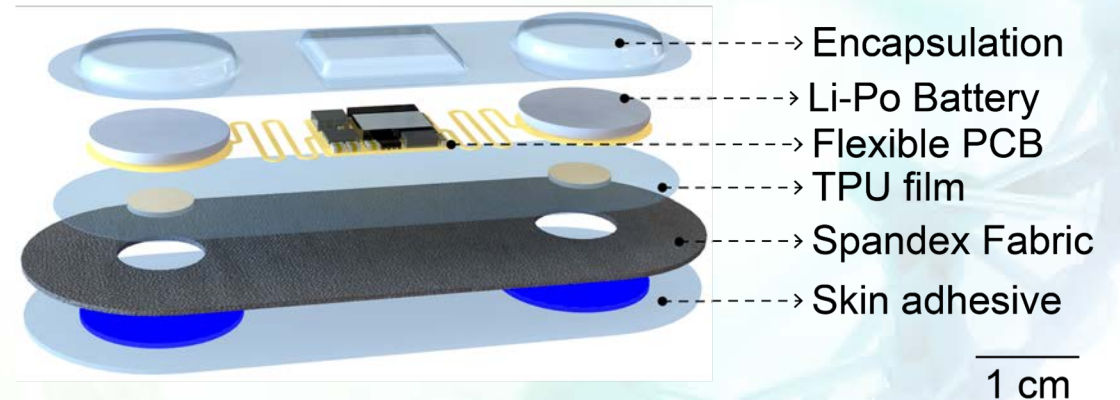
- Biopotential
- Accelerometer



Measures:

- Electrocardiogram
- Respiration
- Gait

Sealed waterproof construction



Introduction to the team

Jenna Yentes, Ph.D.



Science, Engineering &
Medicine Retreat
March 2019



**Some of the most interesting research
is happening at the intersection of
engineering and medicine**

Team has Provided:

- Clinical relevance
- Access to key patient populations
- Expertise in
 - Medicine and disease
 - Clinical validation of medical devices
 - Observational human trials
 - Physiology, signal processing and data analysis



CENTER FOR RESEARCH IN HUMAN MOVEMENT VARIABILITY

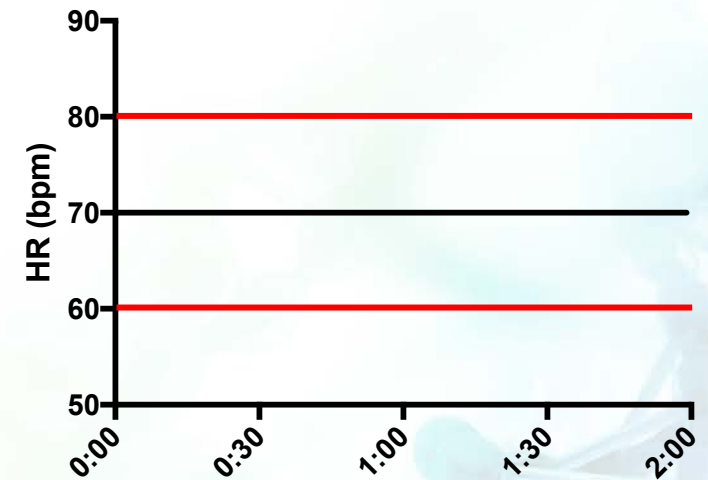
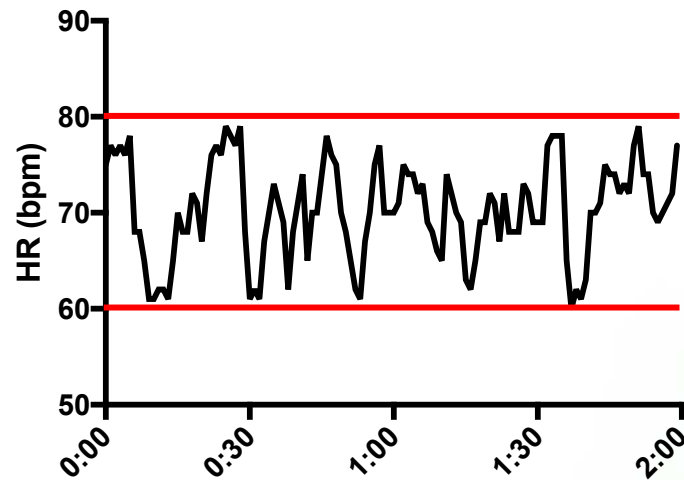
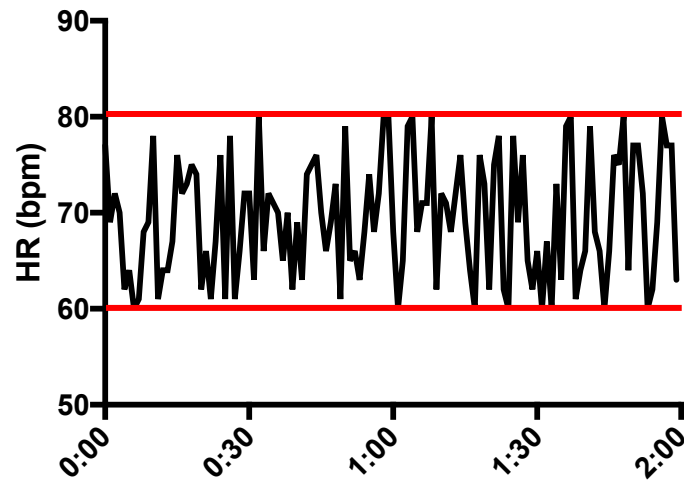


Jenna Yentes, Ph.D.
Associate Professor

Department of Biomechanics
University of Nebraska at Omaha

HOMEOKINESIS

- The ability to maintain an ordered system that fluctuates within an acceptable range^{1,2}

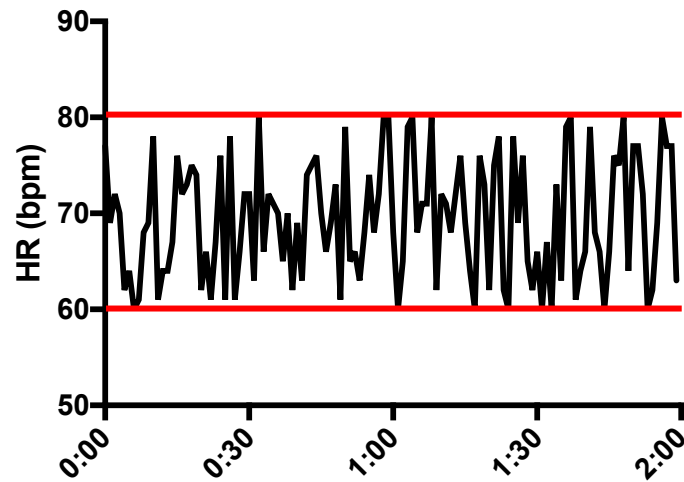


¹Iberall, A.S. & McCulloch W.S., *Homeokinesis-The organizing principle of complex living systems*. IFAC Proceedings Volumes, 1968, 2(4):39-50.

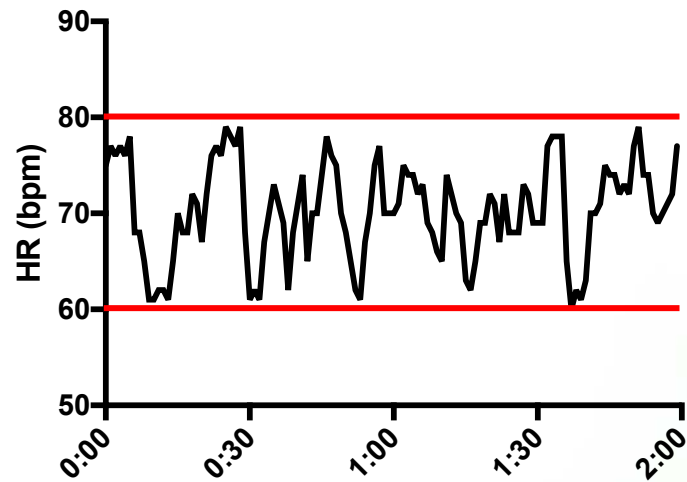
²Macklem, P.T., *Emergent phenomena and the secrets of life*. J Appl Physiol , 2008, 104(6):1844-6.

FLUCTUATIONS

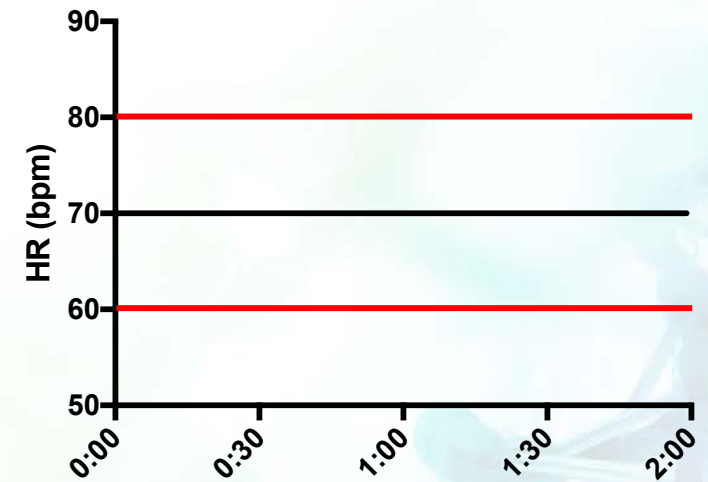
- Variability = magnitude



Mean = 69 bpm
Standard Deviation = 6 bpm



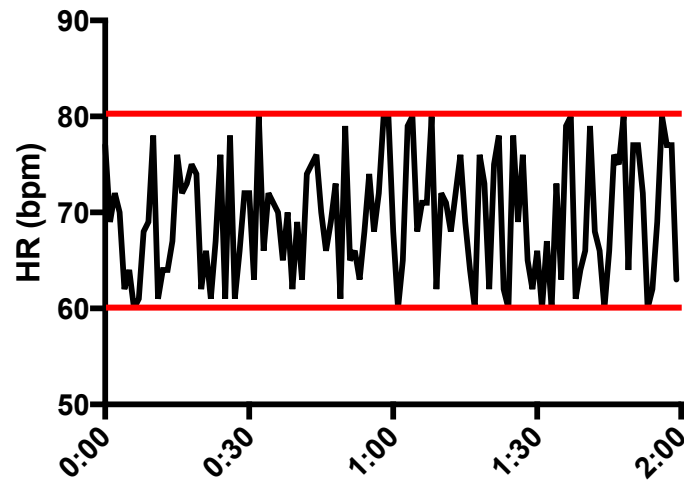
Mean = 70 bpm
Standard Deviation = 5 bpm



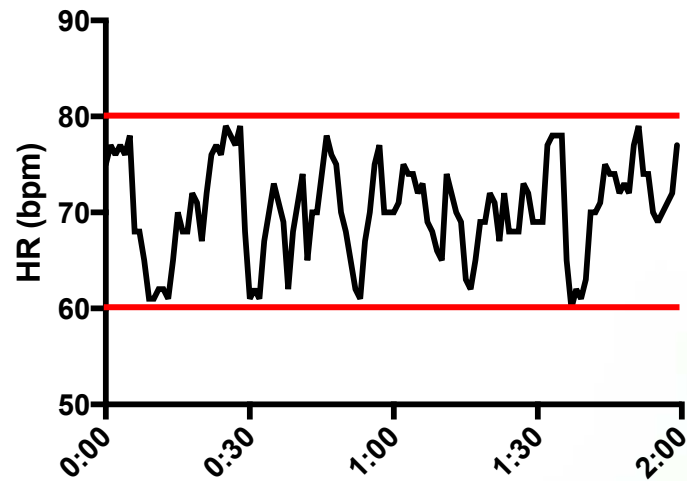
Mean = 70 bpm
Standard Deviation = 0 bpm

FLUCTUATIONS

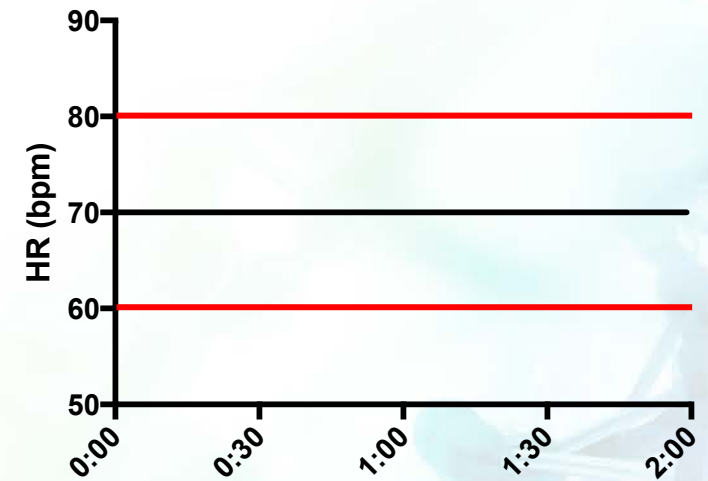
- Complexity = structure



Entropy = 2.2 bits



Entropy = 1.2 bits



Entropy = 0 bits

Coupling

Uncoupling of biological oscillators: A complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome

778

BIOL PSYCHIATRY
1992;32:778-789

Paul J. Godin, MD; Timothy G. Buchman, PhD, MD, FCCM

Cardiovascular Phase Relationships to the Cortical Event-Related Potential of Schizophrenic, Depressed, and Normal Subjects

Curt A. Sandman, Carey S. Vigor-Zierk, Robert Isenhardt,
Joseph Wu, and Mark Zetin

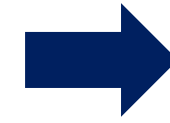
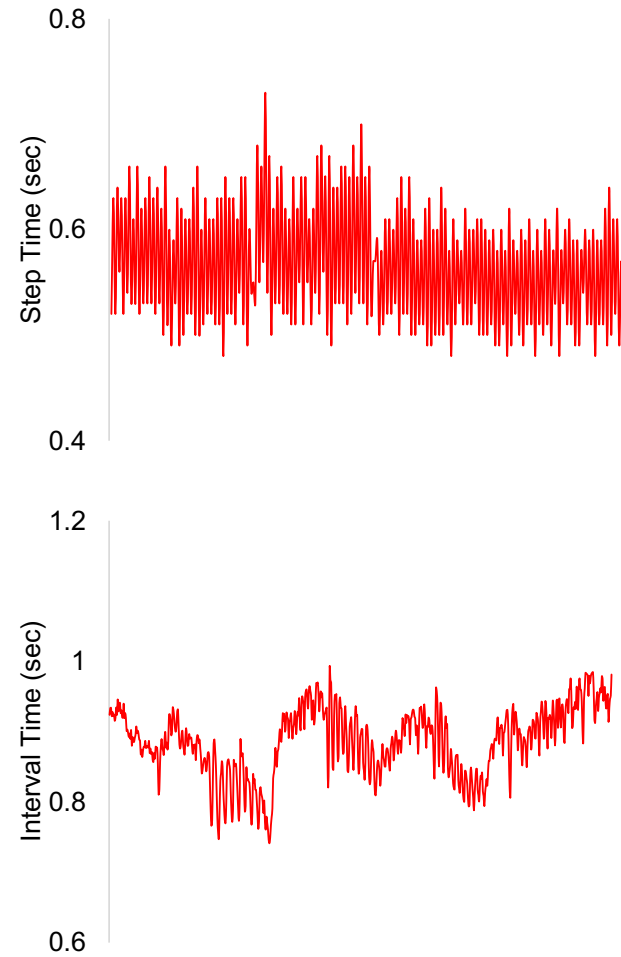
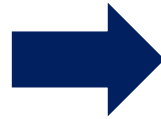
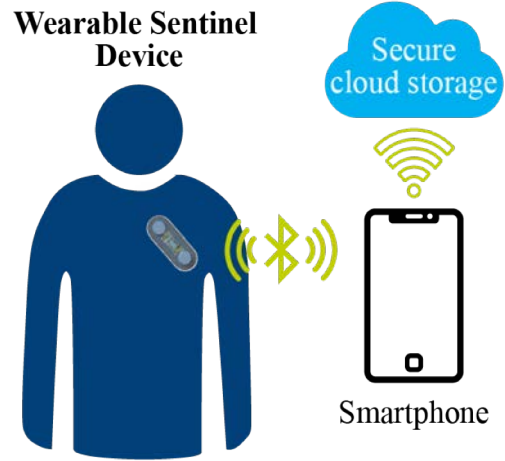
The Journal of Neuroscience, July 1, 2000, 20(13):5135-5143

Multiple Oscillators Provide Metastability in Rhythm Generation

Hong-Shiu Chang, Kevin Staras, and Michael P. Gilbey

*Autonomic Neuroscience Institute, Department of Physiology, Royal Free and University College Medical School,
University College London, London NW3 2PF, United Kingdom*

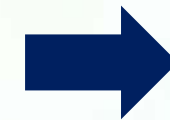
PARAMETER EXTRACTION



Variability
Complexity



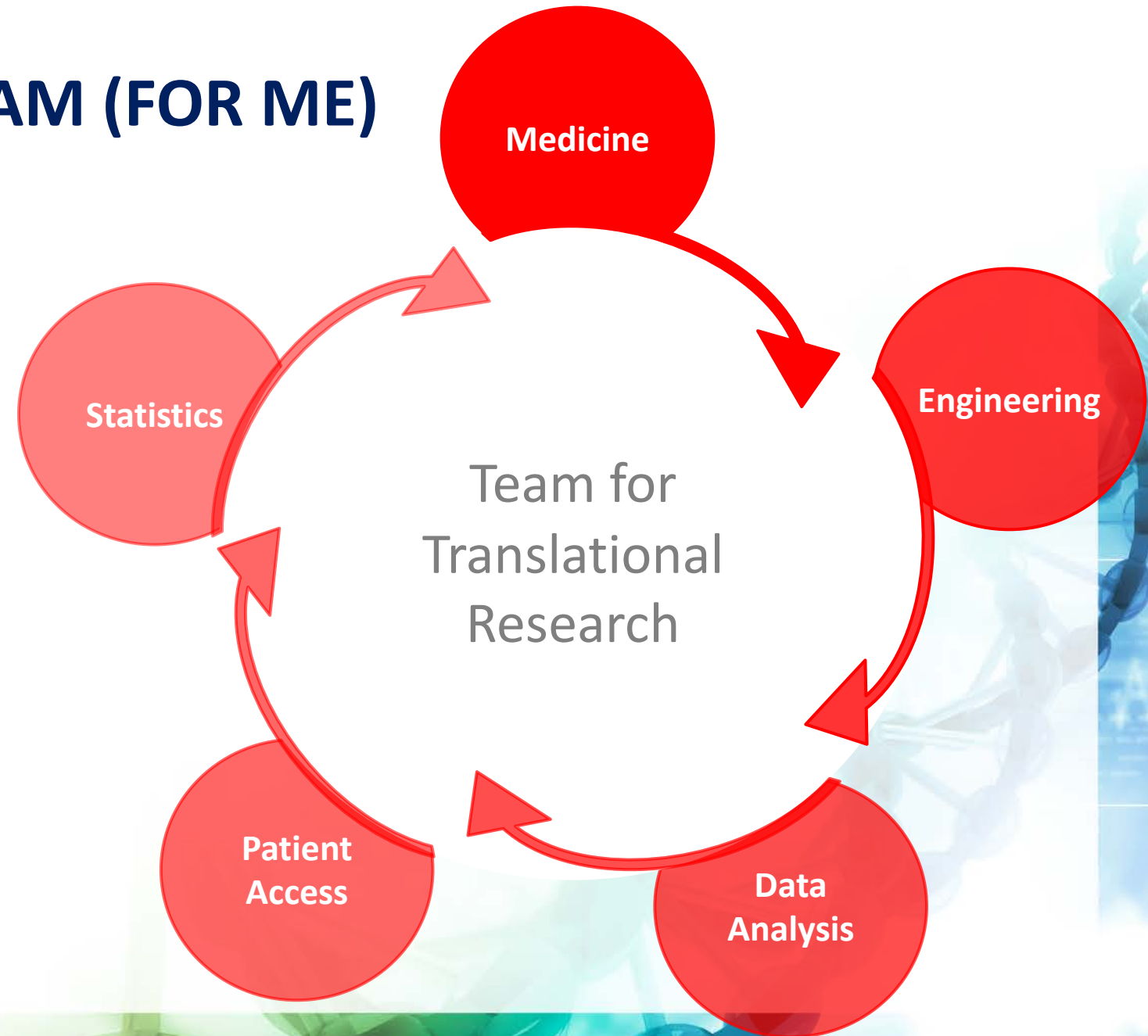
Coupling



Variability
Complexity

BENEFITS OF THE TEAM (FOR ME)

- Knowledge
- Capacity
- Contribution
- Encouragement
- Motivation



JIM MCCLAY, MD, MS, FACEP, FAMIA
PROFESSOR, EMERGENCY MEDICINE, UNMC



- Chair, UNMC Biomedical Informatics Graduate Program
#UNMCInformatics



- Co-PI, Greater Plains Collaborative Research Network
funded by PCORnet/PCORI
#GPCNetwork



- Director, Great Plains IDeA CTR Biomedical Informatics and
Cyberinfrastructure Core
#GPIDeACTR



- Chair, Emergency Care Workgroup, HL7
#HL7ECWG





ENHANCING THE EFFECTIVENESS OF **TEAM SCIENCE**

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

PLATFORMS TO ACCELERATE TRANSLATIONAL TEAM SCIENCE

- Clinical Translational Science
 - Bench – clinic – population – policy
- Supporting team science in CTR
 - Data Infrastructure
 - Policy and procedure
 - Skill sets
 - Trust
- Access to clinical data

National Research Council. 2015. *Enhancing the Effectiveness of Team Science*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/19007>.

CRANE – A COLLABORATIVE PLATFORM FOR CLINICAL TRANSLATIONAL TEAM SCIENCE



Extensive infrastructure in development since 2014

Central clinical information repository from Nebraska medicine:

Linked EHR, Registry, Social and Lab data

De-identified, mapped to national standards

Collaborations with multiple research networks

PCORnet, Greater Plains Collaborative (GPC),

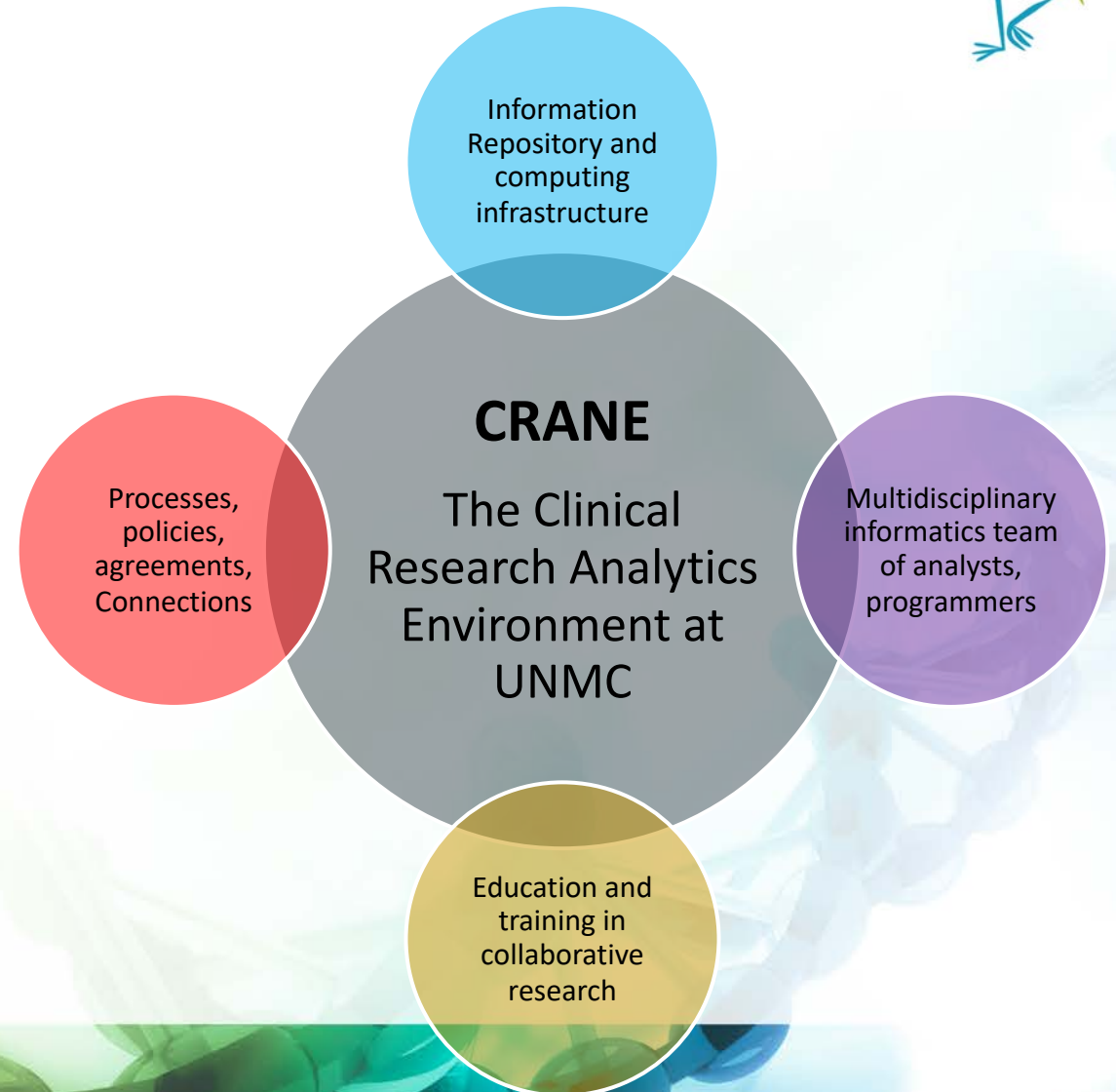
National COVID Cohort Collaborative (N3C),

NCATS ACT Network, OHDSI

Policies and procedures for use of data in CTR in collaboration with
UNMC VCR

A dedicated team of informatics specialists

Training program with expanding cohort of users.



BRING THE CLINICAL TO CTR

- CRANE team collaborations with PCORnet
 - Data Use Agreement in place
 - Reciprocal IRB process in place
 - Shared data structure across network
- Led to involvement in Healthcare Worker Exposure Response & Outcomes (HERO) Registry
- Approached HERO team to launch ancillary study to recruit for SENTINEL trial.
 - Rapid turn around in a few days to use platform
 - Provides access to recruitment, follow up mechanism.



Healthcare Worker Exposure
Response & Outcomes

HEROESRESEARCH.ORG

The Role of the Biostatistician in Team Science

Ying Zhang, PhD

Professor & Chair

Department of Biostatistics

College of Public Health

University of Nebraska Medical Center



1. SCIENTIFIC MINDSET

- Genuine Interest in scientific research
- Willingness to be challenged
- Curiosity and desire to learn things from others
- Drive to scientific discovery

2. ENGAGEMENT IN TEAM SCIENCE

- Early participation in team discussion to stimulate
 - scientific premise for **Sentinel** project
 - testable hypotheses
 - brainstorming of technical approaches
- Development of research plan
 - identification of primary outcomes
 - literature research for the appropriate approaches
 - details of technical approaches

3. STATISTICAL ANALYSIS PLAN (SAP) FOR SENTINEL PROJECT

- Identification of most sensible physiology outcomes to power the study-sample size calculation
- Primary Analysis-unsupervised learning methods
 - Likelihood ratio methods for changing point detection
 - Cumulative sum algorithms for changing point detection
 - ROC analysis for validation
- Secondary Analysis-rare PCR+ for COVID-19
 - Consider all respiratory infections
 - Latent clustering methods to single out the trajectory for COVID-19

HOW DID THE TEAM COME TOGETHER (STEVE'S VIEW)

1. Jenna's mentor suggested she include me on her PhD thesis committee
2. Coupling of respiration and gait in COPD
3. Device (kludgy) developed to capture data
4. Jenna and Eric learn of mutual interests
5. Steve hears Jim present at infrastructure sharing meeting (not for the first time)
6. Ying is recommended by a member of his department

What it offers

1. Novel science
2. Important problem
3. Delightful collaborators
4. Reasonable grant funding opportunities



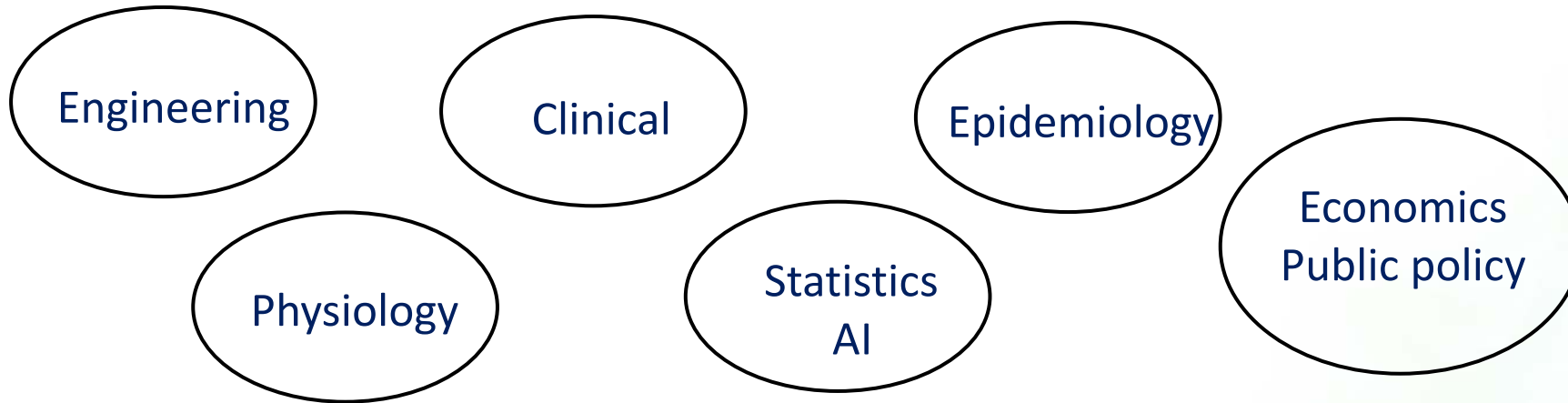
Stephen Rennard, MD
Professor, Internal Medicine
Division of Pulmonary, Critical
Care, Sleep & Allergy

Fundamental Problems with Sentinel:

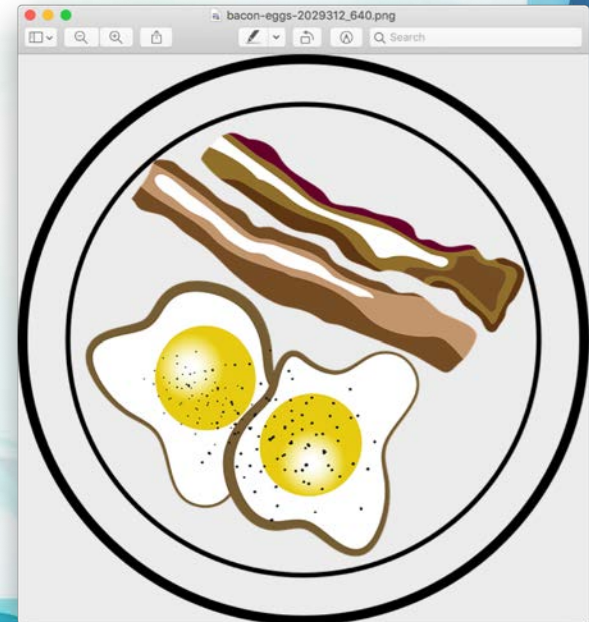
(1) *Somebody else's problem problem:* How to make your spaceship invisible: "Surround it with a somebody else's problem field. Nobody can see somebody else's problem."

Douglas Adams

Domains of serious scholarly pursuit in Sentinel



(2) *Bacon and eggs problem:* If we only had eggs, we could have bacon and eggs, if we only had bacon

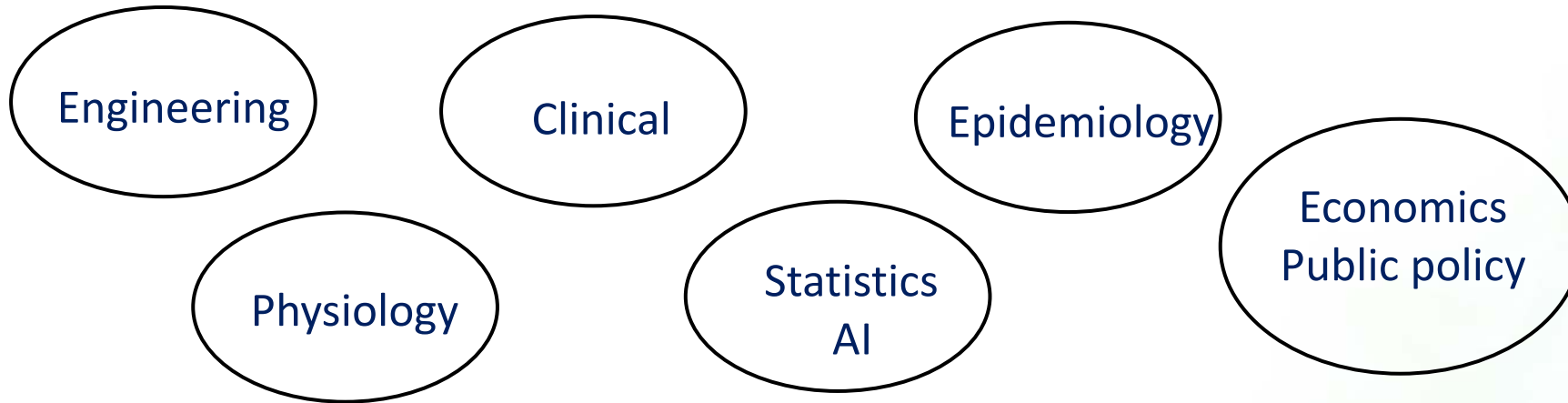


Fundamental Problems with Sentinel: \$\$\$

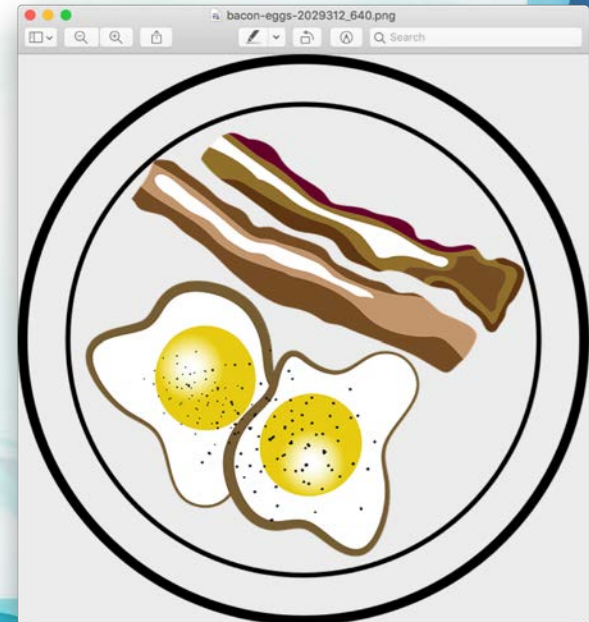
(1) *Somebody else's problem problem:* How to make your spaceship invisible: "Surround it with a somebody else's problem field. Nobody can see somebody else's problem."

Douglas Adams

Domains of serious scholarly pursuit in Sentinel



(2) *Bacon and eggs problem:* If we only had eggs, we could have bacon and eggs, if we only had bacon

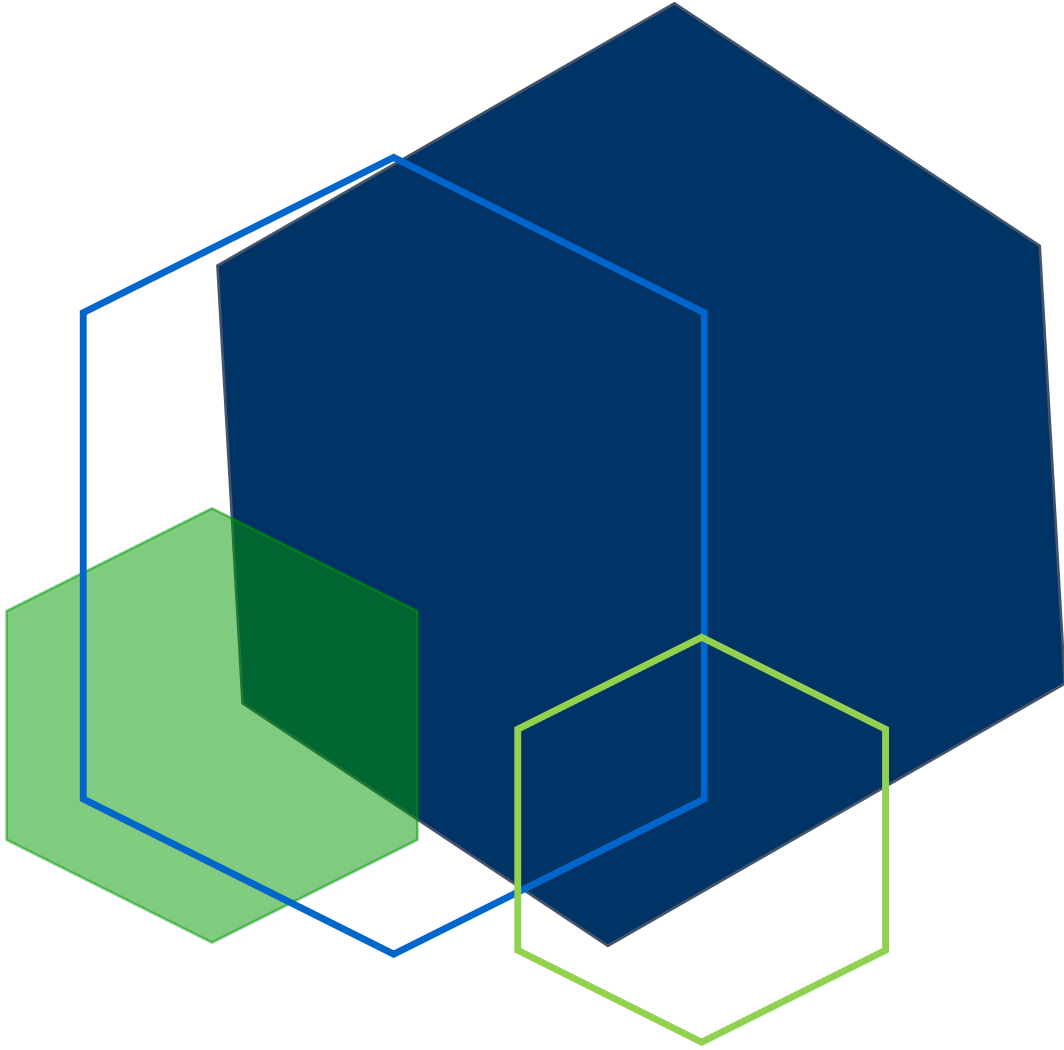


Our opportunities: grants

- University of Nebraska Collaboration
- Dept of Defense: Sentinel submitted
- NHLBI: cohort ancillary
- NIH Directors Award: COVID

- Device
- Physiology
- Clinical
- Epidemiological

		DoD Sentinel	UN Collab	NIH Directors	SBIR	NIH cohort	HEI/EPA
Device		X	X	X	X		
Physiology				??	??	X	
Clinical		X		X	??	X	X
Epidemiological				X			X



G R E A T P L A I N S
IDeA | Clinical and
Translational Research

If you aren't already a member, please consider joining. The CTR Seminar Series is one of many resource available for network members.

<https://gpctr.unmc.edu/membership/>

Questions?